THE ROLE OF IMMUNE COMPONENTS IN PSYCHIATRIC DISORDERS

EDITED BY: Marion Leboyer, Iris E. Sommer and Michael Berk
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THE ROLE OF IMMUNE COMPONENTS IN PSYCHIATRIC DISORDERS

Topic Editors:
Marion Leboyer, Université Paris-Est Créteil Val de Marne, France
Iris E. Sommer, University Medical Center Groningen, Netherlands
Michael Berk, Deakin University, Australia

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PERSPECTIVE
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Maternal Immune Activation and Related Factors in the Risk of Offspring Psychiatric Disorders

*Fiona Conway and Alan S. Brown**

New York State Psychiatric Institute, Columbia University Medical Center, New York, NY, United States

Maternal immune activation (MIA) at the time of gestation has been linked to increased risk of neurodevelopmental psychiatric disorders. Animal and human models have been used to evaluate the relationship between MIA and these outcomes. Given that each of these two disciplines of study have their benefits and limitations, a translational perspective is expected to illuminate more than by the use of any single approach. In this article, we discuss this translational framework and explore how it may be enhanced by the utilization of epigenetic studies and by investigating the microbiome. In this perspectives piece, we focus on the impact of epidemiologic studies, animal models, and preclinical studies in the literature on MIA as well as the potential for greater integration between fields.

Keywords: autism, schizophrenia, maternal immune activation, stress, microbiome

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Edited by:
Marion Leboyer,
Université Paris-Est
Créteil Val de Marne, France

Reviewed by:
Ju Wang,
Tianjin Medical University, China
Ulrike Weber-Stadlbauer,
University of Zurich, Switzerland

***Correspondence:**
Alan S. Brown
asb11@cumc.columbia.edu

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INTRODUCTION

Fetal developmental events occurring *in utero* are implicated in the postnatal health of offspring through adulthood. Environmental exposures during gestation, including maternal infection, nutritional deficiencies, toxic exposures, and other factors that cause stress during pregnancy are particularly insidious during gestation. Central nervous system (CNS) disorders, particularly schizophrenia, autism spectrum disorder (ASD), and bipolar disorder likely result from both genetic and environmental contributions. Epidemiologic studies have revealed strong connections between conditions associated with heighted maternal immune activation (MIA), resulting from infection and stress, and schizophrenia (1, 2), ASD (3, 4), and bipolar disorder (5) in offspring. At the same time, substantial advances have been made through animal models to understand the mechanisms underlying these diagnoses. More recent studies have begun to address potential mediating pathways including epigenetics, and the role of the microbiome in these disorders.

IMPACT AND LIMITATIONS OF EPIDEMIOLOGIC STUDIES OF MIA

Epidemiologic studies offer important potential inferences into etiologic processes through the direct study of human populations. Results from early ecologic studies, which focused on the comparison of groups instead of on individuals, were consistent with associations historically found between schizophrenia and prenatal exposure to influenza outbreaks (6). Later, ecologic studies, with larger cohorts and those investigating other infectious agents, showed inconsistent results and generally weak effects. However, these types of studies are imprecise in their measurement of this exposure, as individual-level data are missing. About 70% of those who were *in utero* during the influenza

epidemic of 1957, but were unexposed, were incorrectly classified as exposed because ecologic studies are based on dates of birth to establish fetal exposure (7).

To address this limitation, individual-level information has been garnered through the use of birth cohort studies, by which exposures occurring during pregnancy can be documented with questionnaires, medical histories or biological samples. Individuals studied can then be longitudinally monitored for diagnoses such as ASD or schizophrenia. Birth cohort studies have shown that offspring of mothers with antibodies to certain infections, including influenza, and/or elevated C-reactive protein levels during pregnancy, were at increased risk for schizophrenia (1, 2, 8), ASD (3, 9, 10), and bipolar disorder (5, 11). This is discussed in a recent review [see Ref. (12)].

One key limitation of birth cohort studies is that they cannot be used to identify biological mechanisms underlying the pathology. The potential to draw causal inferences is further limited by potential bias and confounding, though our group and others have utilized epidemiologic and statistical approaches to reduce the impact of these factors. Since a myriad of infectious agents produce cytokines and other inflammatory markers, they can be used as a common indicator of these exposures and may operate as a shared mechanism by which neurodevelopment of offspring may be prenatally modified, thus increasing the risk for schizophrenia, bipolar disorder, and other psychiatric conditions (2, 13, 14).

IMPACT AND LIMITATIONS OF ANIMAL AND HUMAN MODELS OF MIA

The abovementioned epidemiological studies have inspired research on prenatal infection and MIA using rodent and primate models. Animal models have provided unique experimental tools to overcome the limitations of epidemiological studies, such as longitudinal evaluation of neurobiological processes as well as establishing causality. They also facilitate the unraveling of cellular and molecular mechanisms, which is not possible in epidemiologic studies. Through studies of animal models, cytokines were found to act on the developing fetal brain as inflammatory signaling proteins of detrimental environmental exposures. Cytokines play critical roles in normal fetal development, including neuron proliferation, and synaptogenesis (15). However, elevated maternal proinflammatory cytokine levels cause changes in these processes and have been associated with abnormal neurodevelopment (16). The MIA models in animals allow for in-depth tracking of biologically-relevant phenotypes over time from gestation to adulthood (17). These models involve triggering the maternal immune system during fetal development using a variety of immunogens, such as lipopolysaccharide (LPS) and polyinosinic:polycytidylic acid (poly I:C), and then observing changes in the brain and behavioral development of offspring for features corresponding to human neurological disorders (18, 19). It is possible that prenatal immune challenge acts as a "disease primer" which, when combined with other environmental, genetic, and epigenetic factors, alters the trajectory of fetal neurodevelopment and may ultimately result in the emergence of a number of CNS disorders (17).

Rodents have historically been the principal species utilized in animal model studies. For example, deficits in sensorimotor gating (17, 18), depression-like behaviors (20), and high levels of repetitive behaviors (18, 21, 22) have been noted in offspring of rodent MIA models. One particular mouse study (8) reported neural and behavioral abnormalities resembling those found in schizophrenia as a result of prenatal exposure to MIA interacting synergistically with traumatizing experiences in puberty (23). Studies have also included nonhuman primates, such as rhesus monkeys (24). These models have provided greater comparability with regard to biological phenotypes and neurodevelopmental processes to humans. In one rhesus monkey model, MIA produced progeny that displayed irregular social interactions, abnormal communication, and repetitive behaviors. These results extended rodent MIA findings to behaviors that more closely mirror human behaviors, such as those in both ASD and, to some degree, in schizophrenia (25). More recently, novel evidence implicating MIA exposure with alterations of nonhuman primate dendritic morphology was found (26). This may offer insight into revealing the neuropathology of CNS disorders related to MIA and pave the way for clinical investigations.

Recent clinical studies have served to help bridge the gap between non-human and human primate basic science by evaluating relationships between maternal immune function and neuroanatomic abnormalities. Maternal pro-inflammatory cytokine interleukin-6 concentrations were associated with offspring frontolimbic white matter microstructural properties, including maturational changes in the first 12 months postnatally (27). Another clinical study linked high maternal inflammatory concentration of interleukin-6, a pro-inflammatory cytokine, during pregnancy with abnormal development in offspring at 2 years of age in brain regions associated with sensory processing and impulse control (28).

STRESS AND MIA

Many studies have suggested a correlation between maternal stress during pregnancy and a myriad of negative neurodevelopmental effects in offspring (29, 30). Stressful experiences during pregnancy, including death in the family, war, natural disasters, and more recently socioeconomic disadvantage have been linked with schizophrenia in offspring (31–34). These results provide evidence for an association between maternal stress and schizophrenia in offspring. The impact of prenatal exposure to maternal stress has been investigated by several birth cohort studies. Distressing experiences while the mother was pregnant were recorded and used to anticipate potential risk of psychiatric disorders among offspring in a Danish cohort (35). There is a growing body of evidence implicating stress during prenatal development to ASD (36, 37).These results corroborate epidemiological research on birth cohorts from the Dutch Hunger Winter of 1944–45 which reported relationships between prenatal famine and offspring long-term cognitive and mental health development (38–40), including schizophrenia and affective disorders. Although nutritional deficiency is regarded as the likely cause of the findings, it is possible that maternal stress due to the exposure played a role. However, conflicting results were found

in a population-based cohort study, regarding maternal exposure to death of a relative and risk for ASD in offspring, in which no correlation was reported (41).

Although the precise mechanisms for the associations between maternal stress, immune activation, and subsequent offspring pathology are still not well known, it is thought that psychological stress, through the inflammatory response, may exert an influence on human health (42). One study has examined the cytokine profiles of umbilical cord blood, in association with prenatal stress, as a marker of their effects on the immune system. The findings suggest that both adaptive and innate immune responses were altered by prenatal stress (43). A more recent birth cohort investigation implicated maternal psychological stress in alterations of perinatal cytokine profile in offspring. In particular, prenatal maternal stress was associated with higher levels of interleukin-4, interleukin-5, interleukin-6, interleukin-8, and interleukin-1ß (44).

THE MICROBIOME AND MIA

The microbiome is a relatively new topic that has been explored as a potential etiologic factor in central nervous system disorders and the remediation of their symptoms. An imbalance in the microbiome is correlated with a variety of adverse consequences, including lasting behavioral abnormalities, neuropathology, immune dysfunction, and deficient gastrointestinal integrity. Abnormalities in immune function are reported in ASD and other psychiatric disorders, and recent studies suggest that microbiota is an important factor in this dysregulation (45, 46). The gut microbiome composition has been determined to not only be affected by neuroinflammation (46) but to reciprocally affect specific regional immune responses in the brain (47).

Animal Models

Experimental studies have shown that MIA brings about enduring changes in immune system activity as well as ubiquitous alterations in the balance of offspring microbiota in adulthood (48–50). One study reported changing the microbiome of mice using human commensal *B. fragilis* enhanced not only gastrointestinal health, but also execution of certain tasks used to measure behaviors principally associated with ASD (49). In another study, investigators found that mice that had more Th17 cells in their intestine, and in which there was more colonization with segmented filamentous bacteria (SFB), were more prone to behavioral pathology caused by MIA (50). This susceptibility was passed to other mice by induction of Th17 cells and colonization of SFB. In addition, during MIA, elevated interleukin-17a responses were caused by the activation of dendritic cells, a key cell type involved in CNS pathology, interacting with SFB colonized Th17 cells (50).

MIA and the Human Microbiome

When the maternal immune system is activated during pregnancy, the inflammatory cytokines released affect the offspring's vagal system and consequently their CNS regulation (51). MIA activation also affects maternal gut bacteria, which in turn can affect the microbiome of offspring. The microbiome of offspring has been shown to be populated and affected by the prenatal environment (52), mode of delivery (53), diet, and other aspects of postnatal care (54). The microbiome of children with ASD, when compared with controls, is less diverse, with overgrowth of certain microbes, such as *Desulfovibrio* (55), *Alistipes*, and *Akkermansia* (56), being more common.

Probiotics are hypothesized to aid autism symptoms by colonizing the gastrointestinal system with beneficial bacteria. However, clinical trials of probiotic supplementation have shown mixed results for the effectiveness of probiotics on the behavioral symptoms of ASD (57). A more recent open-label study using microbiota transfer therapy (MTT), which consists of round of an antibiotic, a colon cleanse, and fecal transplant therapy, resulted in an 80% decrease in problematic GI symptoms using the Gastrointestinal Symptom Rating Scale and increased diversity of the microbiome of participants (58). This therapy also resulted in improved ASD behavioral symptoms which continued for 8 weeks post-treatment completion. This therapy will need to be studied more extensively with larger sample sizes, but these results are promising for a potential treatment option.

It has recently been reported that oral probiotic supplementation during pregnancy reduced MIA cytokine levels and subsequent offspring ASD symptoms, such as depression, anxiety, and social deficits, in mouse models (59). Some of these results may be due to the prevention of Poly(I:C)-induced weight loss of dams, another result of the oral probiotic supplementation. Although this has yet to be studied in humans, this offers insight into potential preventative measures for expecting mothers.

EPIGENETICS AND MIA

It has been found that epigenetic modifications occur beyond early embryonic development and are dynamic throughout fetal development and over one's lifetime (60, 61). Epigenetic alterations offer possible mechanisms by which immune insults during prenatal development affect offspring outcomes. Maternal distress has been reported to be a leading cause in epigenetic alterations (61). Birth cohort studies investigating the effects of the Dutch Hunger Winter have examined whether standard DNA methylation is modified as a result of maternal famine and stress. Hypo-methylation during gestation alters the accessibility of offspring DNA to translation and therefore changes gene expression in these regions. Several genes, including ABCA1, insulin-like growth factor II, interleukin-10, GNASAS, and MEG3 have been found to have modified levels of DNA methylation in offspring, thus implicating extensive epigenetic effects of maternal famine (62, 63).

In mouse models of MIA, adult offspring have displayed hypo-methylation, and transcriptional changes, in genes related to GABAergic signaling and neural development (64). In a more recent review, maternal depression, and its associated immunological alterations in cytokines and reactive oxygen species levels, was linked to offspring DNA methylation (65). Experimental evidence from animal models has indicated that MIA can result in widespread DNA hypo-methylation in the

hypothalamus (66). This can be a potential factor for dysregulation of the hypothalamus–pituitary–adrenal gland (HPA) axis, which has been linked to the pathophysiology of schizophrenia (67). Alterations in the gray-matter composition of the hypothalamus have also been linked to ASD (68). Another study reported that, in MIA exposed mice, 80% of hypo-methylated sites were stabilized with a diet high in anti-inflammatory fats (69). Although this is yet to be studied in humans, this has profound implications for possible dietary interventions to mitigate the effects of MIA induced hypo-methylation in addition to standard treatment.

MIA also alters histone acetylation. Adult female offspring of MIA mice expressed anhedonic behavior, which was correlated with global histone acetylation changes in the hippocampus (70). Histone modification caused by MIA may alter hippocampal serotonin transporter (SERT) expression, a critical component to the etiology of depression and which may play a significant role in schizophrenia (70, 71).

FUTURE RESEARCH AND PERSPECTIVES

Great strides have been made through both epidemiologic work and basic science to explore the potential role of MIA in neuropsychiatric disorders. The addition of epigenetics to the MIA model as a mediating mechanism may shed more light on pathogenic processes that underlie these disorders. A key challenge regarding a suitable translational approach (12) is the Research Domain Criteria (RDOC) (72), which is aimed at deconstructing psychiatric disorders into their most basic psycho- and neuropathological components. Further insights for future translational research may be gleaned from standardization of immune activating agents and methods, integrating postmortem pathology, and longitudinal neuroimaging (73–75).

Although stress has been conceptualized as a teratogen, and may activate the maternal immune system in a way similar to infection, the biological framework for how it may affect offspring is still not well understood. Beyond cytokines, maternal cortisol levels have also been implicated in offspring neuropathology (76). Further elucidation of the biological mechanism by which maternal stress may act as an inflammatory agent, and influence offspring neuropathology relevant to psychiatry disorders, is necessary.

Although investigation of the microbiome offers the potential for important findings linking the immune system and psychopathology, several issues remain. For example, whether exposure to known risk factors for ASD and other psychiatric outcomes also result in microbiome alterations requires further investigation. Another question of interest relates to the cause-effect relationship between MIA and the maternal microbiota, on offspring neurodevelopment. Studies comparing psychiatric outcomes following C-section versus natural birth creates opportunities to address this question given the differences in exposure to the vaginal microbiome between the two delivery methods (77).

CONCLUSIONS

In conclusion, we propose it is vital to consider MIA in the context of not only infection but also other factors, such as maternal psychological stress, in the etiology of neurodevelopmental disorders. Epigenetic events may represent mediating or modifying factors in the putative pathogenesis of psychiatric disorders following MIA. The microbiome is another promising area of investigation in the MIA hypothesis of mental disorders. We believe that a translational approach that incorporates knowledge of these processes will be necessary to broaden our understanding of the effects of prenatal MIA on offspring susceptibility to psychiatric disorders.

AUTHOR CONTRIBUTIONS

FC wrote the first draft of the manuscript. AB contributed to the conception, editing, and research for the manuscript. Both authors contributed to manuscript revision and have read and approved the final manuscript.

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REFERENCES

1. Canetta S, Sourander A, Surcel HM, Hinkka-Yli-Salomäki S, Leiviskä J, Kellendonk C, et al. Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. *Am J Psychiatry* (2014) 171:960–8. doi: 10.1176/appi.ajp.2014.13121579
2. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry* (2010) 167:261–80. doi: 10.1176/appi.ajp.2009.09030361
3. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, Mckeague IW, Sundvall J, Surcel HM. Elevated maternal C-reactive protein and autism in a national birth cohort. *Mol Psychiatry* (2014) 19:259–64. doi: 10.1038/mp.2012.197
4. Patterson PH, Xu W, Smith SE, Devarman BE. Maternal immune activation, cytokines and autism. In: *Autism*. Totowa, NJ: Springer (2008). doi: 10.1007/978-1-60327-489-0_13
5. Parboosing R, Bao Y, Shen L, Schaefer CA, Brown AS. Gestational influenza and bipolar disorder in adult offspring. *JAMA Psychiatry* (2013) 70:677–85. doi: 10.1001/jamapsychiatry.2013.896
6. Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* (1988) 45:189–92. doi: 10.1001/archpsyc.1988.01800260109013
7. Kilbourne. ED. *Influenza*. New York, NY: Plenum Medical Book Co. (1987). doi: 10.1007/978-1-4684-5239-6
8. Debost JP, Larsen JT, Munk-Olsen T, Mortensen PB, Meyer U, Petersen L. Joint effects of exposure to prenatal infection and peripubertal psychological trauma in schizophrenia. *Schizophr Bull* (2017) 43:171–9. doi: 10.1093/schbul/sbw083
9. Jiang HY, Xu LL, Shao L, Xia RM, Yu ZH, Ling ZX, et al. Maternal infection during pregnancy and risk of autism spectrum disorders: a systematic review and meta-analysis. *Brain Behav Immun* (2016) 58:165–72. doi: 10.1016/j.bbi.2016.06.005
10. Abdallah MW, Larsen N, Grove J, Norgaard-Pedersen B, Thorsen P, Mortensen EL, et al. Amniotic fluid chemokines and autism spectrum disorder: an exploratory study utilizing a Danish Historic Birth Cohort. *Brain Behav Immun* (2012) 26:170–6. doi: 10.1016/j.bbi.2011.09.003
11. Oliveira J, Oliveira-Maia AJ, Tamouza R, AS B, Leboyer M. Infectious and immunogenetic factors in bipolar disorder. *Acta Psychiatr Scand* (2017) 136(4):409–23. doi: 10.1111/acps.12791

12. Brown AS, Meyer U. Maternal immune activation and neuropsychiatric illness: a translational research perspective. *Am J Psychiatry* (2018) 11:1073–83. doi: 10.1176/appi.ajp.2018.17121311
13. Gilmore JH, Jarskog LF. Exposure to infection and brain development: cytokines in the pathogenesis of schizophrenia. *Schizophr Res* (1997) 24:365–7. doi: 10.1016/S0920-9964(96)00123-5
14. Patterson PH. Neuroscience. Maternal effects on schizophrenia risk. *Science* (2007) 318:576–7. doi: 10.1126/science.1150196
15. Burns TM, Clough JA, Klein RM, Wood GW, Berman NEJ. Developmental regulation of cytokine expression in the mouse brain. *Growth Factors* (1993) 9:253–8. doi: 10.3109/08977199308991585
16. Gayle DA, Beloosesky R, Desai M, Amidi F, Nuñez SE, Ross MG. Maternal LPS induces cytokines in the amniotic fluid and corticotropin releasing hormone in the fetal rat brain. *Am J Physiol Regul Integr Comp Physiol* (2004) 286:R1024–R1029. doi: 10.1152/ajpregu.00664.2003
17. Meyer U. Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. *Biol Psychiatry* (2014) 75:307–15. doi: 10.1016/j.biopsych.2013.07.011
18. Meyer U, Feldon J, Fatemi SH. In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. *Neurosci Biobehav Rev* (2009) 33:1061–79. doi: 10.1016/j.neubiorev.2009.05.001
19. Meyer U, Feldon J. To poly(I:C) or not to poly(I:C): advancing preclinical schizophrenia research through the use of prenatal immune activation models. *Neuropharmacol* (2012) 62:1308–21. doi: 10.1016/j.neuropharm.2011.01.009
20. Khan D, Fernando P, Cicvaric A, Berger A, Pollak A, Monje FJ, et al. Long-term effects of maternal immune activation on depression-like behavior in the mouse. *Transl Psychiatry* (2014) 4:e363. doi: 10.1038/tp.2013.132
21. Schwartzer JJ, Careaga M, Coburn MA, Rose DR, Hughes HK, Ashwood P. Behavioral impact of maternal allergic-asthma in two genetically distinct mouse strains. *Brain Behav Immun* (2017) 63:99–107. doi: 10.1016/j.bbi.2016.09.007
22. Malkova NV, Yu CZ, Hsiao EY, Moore MJ, Patterson PH. Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. *Brain Behav Immun* (2012) 26:607–16. doi: 10.1016/j.bbi.2012.01.011
23. Giovanoli S, Engler H, Engler A, Richetto J, Voget M, Willi R, et al. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. *Science* (2013) 339:1095–9. doi: 10.1126/science.1228261
24. Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, Knickmeyer RC, et al. Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. *Biol Psychiatry* (2010) 67:965–73. doi: 10.1016/j.biopsych.2009.11.026
25. Bauman MD, Iosif AM, Smith SE, Bregere C, Amaral DG, Patterson PH. Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. *Biol Psychiatry* (2014) 75:332–41. doi: 10.1016/j.biopsych.2013.06.025
26. Weir RK, Forghany R, Smith SE, Patterson PH, Mcallister AK, Schumann CM, et al. Preliminary evidence of neuropathology in nonhuman primates prenatally exposed to maternal immune activation. *Brain Behav Immun* (2015) 48:139–46. doi: 10.1016/j.bbi.2015.03.009
27. Rasmussen JM, Graham AM, Entringer S, Gilmore JH, Styner M, Fair DA, et al. Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. *Neuroimage* (2018) 185:825–35. doi: 10.1016/j.neuroimage.2018.04.020
28. Graham AM, Rasmussen JM, Rudolph MD, Heim CM, Gilmore JH, Styner M, et al. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. *Biol Psychiatry* (2018) 83:109–19. doi: 10.1016/j.biopsych.2017.05.027
29. Class QA, Abel KM, Khashan AS, Rickert ME, Dalman C, Larsson H, et al. Offspring psychopathology following preconception, prenatal and postnatal maternal bereavement stress. *Psychol Med* (2014) 44:71–84. doi: 10.1017/S0033291713000780
30. Walder DJ, Laplante DP, Sousa-Pires A, Veru F, Brunet A, King S. Prenatal maternal stress predicts autism traits in 6(1/2) year-old children: project Ice Storm. *Psychiatry Res* (2014) 219:353–60. doi: 10.1016/j.psychres.2014.04.034
31. Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. *Arch Gen Psychiatry* (1978) 35:429–31. doi: 10.1001/archpsyc.1978.01770280039004
32. Watson JB, Mednick SA, Huttunen M, Wang X. Prenatal teratogens and the development of adult mental illness. *Dev Psychopathol* (1999) 11:457–66. doi: 10.1017/S0954579499002151
33. Malaspina D, Corcoran C, Kleinhaus KR, Perrin MC, Fennig S, Nahon D, et al. Acute maternal stress in pregnancy and schizophrenia in offspring: a cohort prospective study. *BMC Psychiatry* (2008) 8:71. doi: 10.1186/1471-244X-8-71
34. Gilman SE, Hornig M, Ghassabian A, Hahn J, Cherkerzian S, Albert PS, et al. Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood. *Proc Natl Acad Sci U S A* (2017) 114:6728–33. doi: 10.1073/pnas.1617698114
35. Khashan AS, Abel KM, Mcnamee R, Pedersen MG, Webb RT, Baker PN, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Arch Gen Psychiatry* (2008) 65:146–52. doi: 10.1001/archgenpsychiatry.2007.20
36. Beversdorf DQ, Manning SE, Hillier A, Anderson SL, Nordgren RE, Walters SE, et al. Timing of prenatal stressors and autism. *J Autism Dev Disord* (2005) 35:471–8. doi: 10.1007/s10803-005-5037-8
37. Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *J Autism Dev Disord* (2008) 38:481–8. doi: 10.1007/s10803-007-0414-0
38. Hoek HW, Brown AS, Susser E. The Dutch famine and schizophrenia spectrum disorders. *Soc Psychiatry Psychiatr Epidemiol* (1998) 33:373–9. doi: 10.1007/s001270050068
39. Brown AS, Susser ES, Lin SP, Neugebauer R, Gorman JM. Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944-45. *Br J Psychiatry* (1995) 166:601–6. doi: 10.1192/bjp.166.5.601
40. Brown AS, Van OS J, Driessens C, Hoek HW, Susser ES. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry* (2000) 157:190–5. doi: 10.1176/appi.ajp.157.2.190
41. Li J, Vestergaard M, Obel C, Christensen J, Precht DH, Lu M, et al. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics* (2009) 123:1102–7. doi: 10.1542/peds.2008-1734
42. Glover V. Prenatal stress and its effects on the fetus and the child: possible underlying biological mechanisms. *Adv Neurobiol* (2015) 10:269–83. doi: 10.1007/978-1-4939-1372-5_13
43. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* (2010) 182:25–33. doi: 10.1164/rccm.200904-0637OC
44. Andersson NW, LI Q, Mills CW, Ly J, Nomura Y, Chen J. Influence of prenatal maternal stress on umbilical cord blood cytokine levels. *Arch Womens Ment Health* (2016) 19:761–7. doi: 10.1007/s00737-016-0607-7
45. Hsiao EY. Immune dysregulation in autism spectrum disorder. *Int Rev Neurobiol* (2013) 113:269–302. doi: 10.1016/B978-0-12-418700-9.00009-5
46. Cryan JF, Dinan TG. Gut microbiota: microbiota and neuroimmune signalling-Metchnikoff to microglia. *Nat Rev Gastroenterol Hepatol* (2015) 12:494–6. doi: 10.1038/nrgastro.2015.127
47. Erny D, Hrabe de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* (2015) 18:965–77. doi: 10.1038/nn.4030
48. Mandal M, Donnelly R, Elkabes S, Zhang P, Davini D, David BT, et al. Maternal immune stimulation during pregnancy shapes the immunological phenotype of offspring. *Brain Behav Immun* (2013) 33:33–45. doi: 10.1016/j.bbi.2013.04.012
49. Hsiao EY, Mcbride SW, Hsien S, Sharon G, Hyde ER, Mccue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* (2013) 155:1451–63. doi: 10.1016/j.cell.2013.11.024
50. Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, et al. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. *Nature* (2017) 549:528–32. doi: 10.1038/nature23910
51. Yarandi SS, Peterson DA, Treisman GJ, Moran TH, Pasricha PJ. Modulatory effects of gut microbiota on the central nervous system: how gut could play

a role in neuropsychiatric health and diseases. *J Neurogastroenterol Motil* (2016) 22:201–12. doi: 10.5056/jnm15146
52. Jimenez E, Marin ML, Martin R, Odriozola JM, Olivares M, Xaus J, et al. Is meconium from healthy newborns actually sterile? *Res Microbiol* (2008) 159:187–93. doi: 10.1016/j.resmic.2007.12.007
53. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, A DL, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med* (2016) 8:343ra82. doi: 10.1126/scitranslmed.aad7121
54. Yassour M, Vatanen T, Siljander H, Hamalainen AM, Harkonen T, Ryhanen SJ, et al. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Sci Transl Med* (2016) 8:343ra81. doi: 10.1126/scitranslmed.aad0917
55. Finegold SM. Desulfovibrio species are potentially important in regressive autism. *Med Hypotheses* (2011) 77:270–4. doi: 10.1016/j.mehy.2011.04.032
56. de Angelis M, Piccolo M, Vannini L, Siragusa S, de Giacomo A, Serrazzanetti DI, et al. Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. *PLoS One* (2013) 8:e76993. doi: 10.1371/journal.pone.0076993
57. Navarro F, Liu Y, Rhoads JM. Can probiotics benefit children with autism spectrum disorders? *World J Gastroenterol* (2016) 22:10093–102. doi: 10.3748/wjg.v22.i46.10093
58. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome* (2017) 5:10. doi: 10.1186/s40168-016-0225-7
59. Wang X, Yang J, Zhang H, Yu J, Yao Z. Oral probiotic administration during pregnancy prevents autism-related behaviors in offspring induced by maternal immune activation via anti-inflammation in mice. *Autism Res* (2019) 12:576–88. doi: 10.1002/aur.2079
60. Champagne FA. Epigenetic influence of social experiences across the lifespan. *Dev Psychobiol* (2010) 52:299–311. doi: 10.1002/dev.20436
61. Monk C, Spicer J, Champagne FA. Linking prenatal maternal adversity to developmental outcomes in infants: the role of epigenetic pathways. *Dev Psychopathol* (2012) 24:1361–76. doi: 10.1017/S0954579412000764
62. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* (2008) 105:17046–9. doi: 10.1073/pnas.0806560105
63. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet* (2009) 18:4046–53. doi: 10.1093/hmg/ddp353
64. Richetto J, Massart R, Weber-Stadlbauer U, Szyf M, Riva MA, Meyer U. Genome-wide DNA Methylation Changes in a Mouse Model of Infection-Mediated Neurodevelopmental Disorders. *Biol Psychiatry* (2017) 81:265–76. doi: 10.1016/j.biopsych.2016.08.010
65. Rakers F, Rupprecht S, Dreiling M, Bergmeier C, Witte OW, Schwab M. Transfer of maternal psychosocial stress to the fetus. *Neuroscience & Biobehavioral Reviews* (2017) S0149-7635(16)30719-9. doi: 10.1016/j.neubiorev.2017.02.019
66. Basil P, Li Q, Dempster EL, Mill J, Sham PC, Wong CC, et al. Prenatal maternal immune activation causes epigenetic differences in adolescent mouse brain. *Transl Psychiatry* (2014) 4:e434. doi: 10.1038/tp.2014.80
67. Tognin S, Rambaldelli G, Perlini C, Bellani M, Marinelli V, Zoccatelli G, et al. Enlarged hypothalamic volumes in schizophrenia. *Psychiatry Res* (2012) 204:75–81. doi: 10.1016/j.pscychresns.2012.10.006
68. Kurth F, Narr KL, Woods RP, O'neill J, Alger JR, Caplan R, et al. Diminished gray matter within the hypothalamus in autism disorder: a potential link to hormonal effects? *Biol Psychiatry* (2011) 70:278–82. doi: 10.1016/j.biopsych.2011.03.026
69. Basil P, Li Q, Gui H, Hui TCK, Ling VHM, Wong CCY, et al. Prenatal immune activation alters the adult neural epigenome but can be partly stabilised by a n-3 polyunsaturated fatty acid diet. *Translational Psychiatry* (2018) 8:125. doi: 10.1038/s41398-018-0167-x
70. Reisinger SN, Kong E, Khan D, Schulz S, Ronovsky M, Berger S, et al. Maternal immune activation epigenetically regulates hippocampal serotonin transporter levels. *Neurobiol Stress* (2016) 4:34–43. doi: 10.1016/j.ynstr.2016.02.007
71. Li W, Yang Y, Lin J, Wang S, Zhao J, Yang G, et al. Association of serotonin transporter gene (SLC6A4) polymorphisms with schizophrenia susceptibility and symptoms in a Chinese-Han population. *Prog Neuropsychopharmacol Biol Psychiatry* (2013) 44:290–5. doi: 10.1016/j.pnpbp.2013.04.003
72. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* (2010) 167:748–51. doi: 10.1176/appi.ajp.2010.09091379
73. Careaga M, Murai T, Bauman MD. Maternal immune activation and autism spectrum disorder: from rodents to nonhuman and human primates. *Biol Psychiatry* (2017) 81:391–401. doi: 10.1016/j.biopsych.2016.10.020
74. Bauman MD, Schumann CM. Is 'bench-to-bedside' realistic for autism? An integrative neuroscience approach. *Neuropsychiatry (London)* (2013) 3:159–68. doi: 10.2217/npy.13.18
75. Kentner AC, Bilbo SD, Brown AS, Hsiao EY, Mcallister AK, Meyer U, et al. Maternal immune activation: reporting guidelines to improve the rigor, reproducibility, and transparency of the model. *Neuropsychopharmacology* (2018) 44:245–58. doi: 10.1038/s41386-018-0185-7
76. Ellman LM, Schetter CD, Hobel CJ, Chicz-Demet A, Glynn LM, Sandman CA. Timing of fetal exposure to stress hormones: effects on newborn physical and neuromuscular maturation. *Dev Psychobiol* (2008) 50:232–41. doi: 10.1002/dev.20293
77. Jasarevic E, Howerton CL, Howard CD, Bale TL. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. *Endocrinology* (2015) 156:3265–76. doi: 10.1210/en.2015-1177

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BRIEF RESEARCH REPORT
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Atopy Increases Risk of Psychotic Experiences: A Large Population-Based Study

Marieke J.H. Begemann[1,2], Mascha M.J. Linszen[1,2], Janna N. de Boer[2], Wytske D. Hovenga[2], Shiral S. Gangadin[1,2], Maya J.L. Schutte[1,2] and Iris E.C. Sommer[1]*

[1] Cognitive Neurosciences, Department of Biomedical Sciences of Cells & Systems, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2] Department of Psychiatry, University Medical Center Utrecht, Utrecht, Netherlands

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****Correspondence:***
Marieke J.H. Begemann
m.j.h.begemann@umcg.nl

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Introduction: Building upon the comorbidity between atopy and schizophrenia, we conducted a large cross-sectional, observational population-based study to examine if such associations also exist between atopic disorders (eczema, allergic rhinitis, and asthma) and nonclinical psychotic experiences.

Methods: We examined psychotic experiences in a Dutch population sample through an online survey (≥14 years of age). Participants filled out the Questionnaire for Psychotic Experiences, together with questions screening for atopic disorders (eczema, allergic rhinitis, and asthma). Prevalence rates were calculated; binary logistic regression was used to determine odds ratios (ORs) (age, gender, and years of education as covariates).

Results: We included 6,479 participants. Individuals diagnosed with one or more atopic disorders had an increased risk of psychotic experiences as compared with controls (OR = 1.26). Analysis of individual symptoms revealed an OR of 1.27 for hallucinations, whereas delusions only showed a trend. With each additional atopic disorder, the risk of psychotic experiences increased. This was also observed for hallucinations alone but not for delusions alone. Atopy was associated with hallucinations across all modalities (OR ranging from 1.19 to 1.40). These results did not appear to be driven specifically by any one of the atopic disorders.

Conclusion: In the largest population sample of adolescents and adults to date, we found that atopic disorders (asthma, eczema, and allergic rhinitis) increase the risk of psychotic experiences, in a dose–response fashion. These results provide further support for the role of immunological components in the predisposition for psychosis and can serve as a base for further research.

Keywords: psychotic experiences, hallucinations, delusions, atopic disorders, asthma, eczema, allergic rhinitis, immune

INTRODUCTION

During the past years, the role of immunological factors [e.g., microglia, major histocompatibility complex (MHC), and complement molecules] in the pathogenesis of psychosis is supported by an increasing amount of data (1, 2). Speculation as to how immunological processes may be linked to the development of psychotic experiences has been fueled by epidemiological studies on schizophrenia patients and their relatives, finding altered prevalence rates of various autoimmune diseases such as celiac disease, autoimmune thyrotoxicosis, psoriasis, and pernicious anemia (3). For instance, a large Danish register-based study including 7,704 schizophrenia patients (and 192,590 controls) found that the incidence of autoimmune disorders was higher both in patients and their parents (4). Notably, a history of autoimmune disorder was related to a 45% increase in risk of schizophrenia (4).

A similar association has been shown for atopic disorders (i.e. a familial group of allergic disorders including asthma, allergic rhinitis, urticaria, and atopic dermatitis). A cross-sectional study in Taiwan by Chen and colleagues (44,187 schizophrenia patients; 132,748 controls) (5) observed a 1.3-fold increased risk of concurrent asthma in patients as compared with individuals without any psychiatric disease. Similarly, Weber et al. reported a relative high prevalence of asthma and eczema in schizophrenia patients (6). A longitudinal Danish register-based study (n = 808,559) found that individuals diagnosed with an atopic disorder earlier in life had an increased relative risk of 1.45 of developing schizophrenia in adulthood (7); their results were mainly driven by asthma (relative risk = 1.59). Interestingly, this association has even been observed across the psychosis continuum, as a population-based longitudinal study (n = 6,784) showed that children diagnosed with eczema and/or asthma had an increased risk of developing psychotic experiences in their adolescence (odds ratio [OR] = 1.44) (8).

To extend these findings, we conducted the first large-scale population-based study of atopic disorders and psychotic experiences in both adolescents and adults. We investigated whether atopy (defined here as diagnosed asthma, eczema, and allergic rhinitis) increased the risk of psychotic experiences (defined as hallucinations in four sensory modalities and nine delusion subtypes) in a sample of individuals aged 14+ years (n = 6,479).

MATERIALS AND METHODS

Participants

The current study is part of a larger cross-sectional, observational project conducted in the Netherlands, entitled "Zie ik spoken" ["Do I see ghosts?"; for methodology, see Linszen et al. (9)]. Inclusion took place through the project's website (www.zieikspoken.nl). The project was promoted between September 2016 and May 2017 through national media channels and several events. The current study included participants aged 14 years and over.

Measures

Questionnaire for Psychotic Experiences

The Questionnaire for Psychotic Experiences (QPE) evaluates the presence and phenomenology of psychotic experiences, covering the full spectrum of hallucinations and delusions of any origin, severity, and duration (9, 10). As described by Linszen et al. (9), a self-survey version was used, addressing hallucinations in four sensory modalities and nine delusion subtypes. Screening questions evaluated the lifetime experience of a psychotic phenomenon. When answered affirmatively, follow-up questions regarding phenomenology were asked when this experience also occurred during the past week. Hallucinations were defined as a perception without a clear source from the environment. Delusions were considered as such if the participant reported being near to fully convinced of their truth. Prevalence rates were calculated by merging subtypes of hallucinations into one binary variable; a similar approach was used for the different delusion subtypes. The variable psychotic experiences were calculated by merging hallucinations and delusions.

Atopic Disorders

Screening questions addressed whether the participant ever suffered from asthma, eczema, or allergic rhinitis (described as hay fever) and, if so, whether the illness had been diagnosed by a doctor. Participants were divided into two different groups:

- *Atopy:* participants who reported one or more atopic disorder as diagnosed by a doctor [in line with previous register-based studies (5, 7)]. To evaluate a possible additive effect, the following subgroups were evaluated: 1) one atopic disorder; 2) two atopic disorders; 3) three atopic disorders. We also examined effects of the three atopic disorders individually.
- *Controls:* participants without any atopic disorder, including those individuals who reported having one or more atopic disorders without being diagnosed by a doctor.

Procedure

Participants submitted their data *via* the website https://zieikspoken.nl [11,601 entries, see flowchart in **Figure 1**; a detailed overview is provided by Linszen et al. (9)]. The Medical Research Ethics Committee of the University Medical Center Utrecht exempted this study from full review (local protocol number 16-408/C). All participants (including underaged subjects) confirmed their participation *via* the study website. Participants filled out demographic data (e.g., age, sex, handedness, highest level of education), followed by the QPE hallucination items. After two recognition tasks [results described by De Boer (11)], participants could progress to the QPE items on delusions and the questions evaluating atopic disorders (6,857 valid entries). The current sample was restricted by age (≥14 years), resulting in 6,479 participants with complete data.

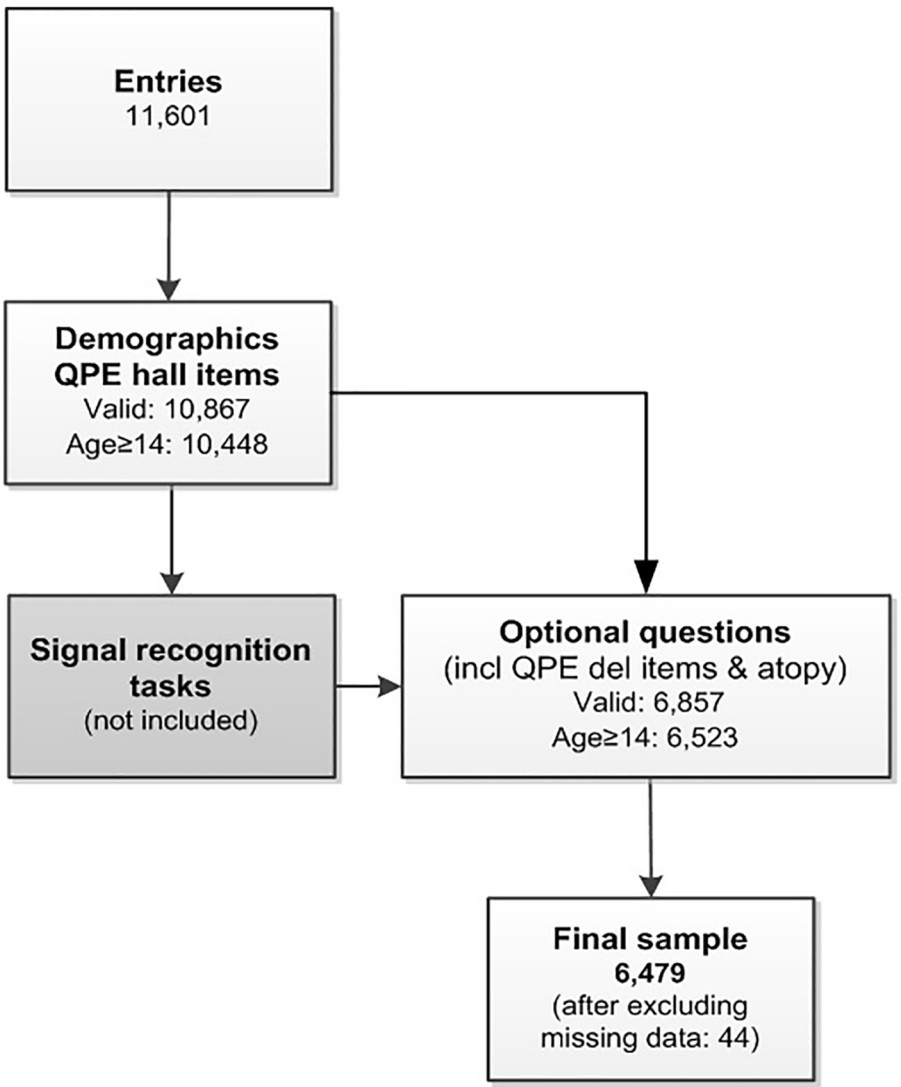

FIGURE 1 | Flow chart of the study.

Statistics

Data were analyzed using IBM SPSS statistics (25.0). Demographics and prevalence rates of psychotic experiences were calculated for each group. Binary logistic regression was used to calculate ORs for psychotic experiences for the atopy (sub)group(s) as compared with the control group (age, gender, and years of education as covariates). We also evaluated the different subtypes of hallucinations and delusions as well as the individual atopic disorders (asthma, eczema, and allergic rhinitis).

RESULTS

Baseline Group Comparisons

About one third (37.8%) of the sample (n = 6,479) reported having atopic disorders as diagnosed by a doctor (see **Figure 1** and **Table 1**). Compared with the control group, the atopy group included fewer males ($p \leq .001$). Percentage of individuals with psychotic experiences within the different groups are presented in **Table 1**.

Atopy and Psychotic Experiences

Individuals with one or more atopic disorders had a significantly increased risk of psychotic experiences as compared with those without such a diagnosis, with an OR of 1.26 (95% CI: 1.14–1.41; $p < .001$). A similar OR was observed for hallucinations (OR 1.27; 95% CI: 1.14–1.42; $p < .001$), while the association with delusions bordered on significance (OR 1.21; 95% CI: 0.99–1.48; $p = .054$).

We also evaluated the possible additive effect of multiple atopic disorders (**Figure 2**). With each additional diagnosis of atopic disorder, the odds for psychotic experiences increased (**Table 2**). This pattern was also observed for hallucinations but not for delusions.

TABLE 1 | Demographic characteristics of the study sample.

	No atopy (*n* = 4,040)	Atopy (*n* = 2,439)	*Asthma* (*n* = 954)	*Eczema* (*n* = 1,181)	*Allergic rhinitis* (*n* = 1,252)	*p* value (atopy vs. controls)[a]
Male (%)	34.0%	27.3%	26.7%	22.9%	29.2%	$p < .001$
Age, mean (SD)	36.8 (15.7)	36.5 (14.5)	35.1 (14.5)	37.0 (14.3)	36.5 (13.9)	$p = .896$
Years of education, mean (SD)	14.1 (2.1)	14.1 (2.1)	13.9 (2.1)	14.2 (2.0)	14.1 (2.0)	$p = .593$
Psychotic experiences	33.6%	39.6%	41.6%	38.4%	42.5%	
Hallucinations	31.2%	37.1%	39.2%	36.6%	39.9%	
Auditory	13.9%	18.2%	20.4%	17.5%	20.1%	
Visual	11.8%	14.0%	15.7%	13.2%	15.1%	
Tactile	10.1%	13.2%	13.4%	13.0%	14.1%	
Olfactory	9.0%	12.5%	13.4%	11.9%	13.3%	
Delusions	6.5%	7.7%	8.5%	6.8%	7.2%	
Paranoia	1.7%	2.3%	2.8%	2.1%	2.1%	
Reference	1.6%	1.8%	2.3%	1.5%	1.7%	
Guilt	1.0%	1.5%	1.9%	1.6%	1.3%	
Control	0.9%	0.7%	0.9%	0.8%	0.7%	
Religious	0.5%	0.7%	1.0%	0.5%	0.5%	
Grandeur	1.5%	2.1%	2.3%	1.7%	2.0%	
Somatic	0.8%	1.4%	1.8%	1.4%	1.1%	
Capgras	0.4%	0.5%	0.3%	0.4%	0.6%	
Cotard	0.1%	0.5%	0.2%	0.2%	0.2%	

[a]*Gender: χ^2; age and years of education: Mann–Whitney U test. n, sample size; SD, standard deviation.*

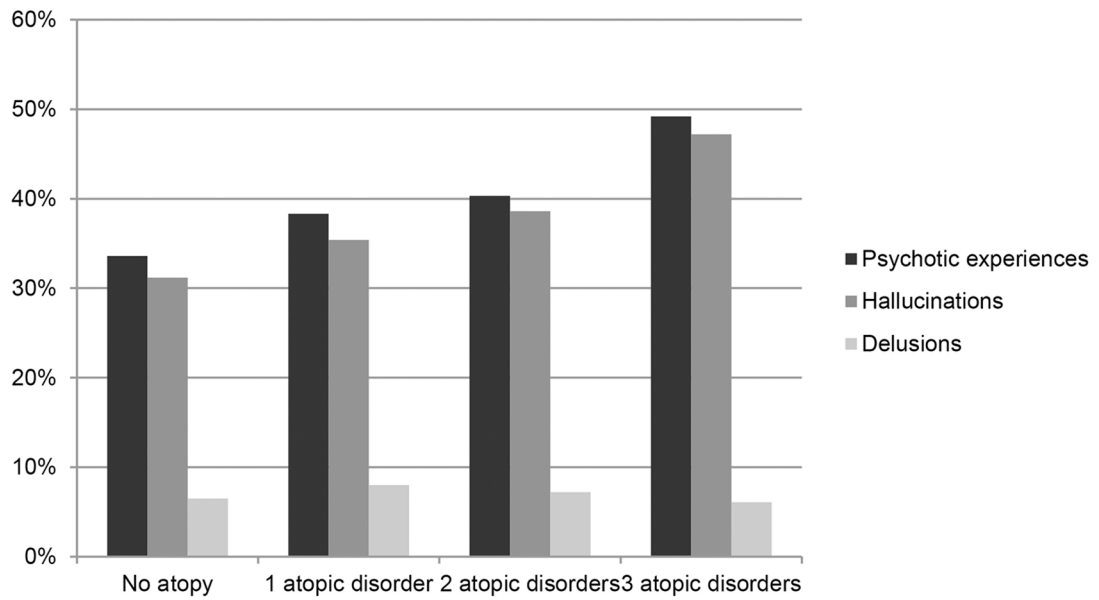

FIGURE 2 | Percentage of individuals reporting psychotic experiences, grouped by the number of diagnosed atopic disorders.

Hallucination and Delusion Subtypes

Compared to controls, atopy [≥ 1 diagnosed atopic disorder(s)] was associated with increased odds across all hallucination modalities with ORs ranging between 1.19 and 1.40 (OR for visual hallucinations was trend-level significant after Bonferroni correction), see **Table 3**. Atopy was not associated with any of the delusion subtypes.

Asthma, Eczema, and Allergic Rhinitis

Significant odd ratios for psychotic experiences were found for allergic rhinitis, asthma, and eczema as compared with those without atopic disorders (**Table 3**). The ORs were highest for allergic rhinitis (1.46), followed by asthma (1.32), and eczema (1.20). Results were similar for hallucinations, while the associations with delusions were not significant for any of the

TABLE 2 | Odds ratios (ORs) for psychotic experiences per number of diagnosed atopic disorders.

	1 atopic disorder (*n* = 1,688)	2 atopic disorders (*n* = 554)	3 atopic disorders (*n* = 197)
Psychotic experiences	**1.20 *p* = .004** (1.06–1.35)	**1.33 *p* = .003** (1.10–1.60)	**1.80 *p* < .001** (1.34–1.42)
Hallucinations	**1.18 *p* = .008** (1.05–1.34)	**1.38 *p* = .001** (1.15–1.67)	**1.85 *p* < .001** (1.38–2.48)
Delusions	**1.26 *p* = .037** (1.02–1.57)	1.17 *p* = .376 (0.83–1.66)	0.93 *p* = .810 (0.51–1.70)

*The group without (diagnosed) atopic disorders was used as reference (OR = 1.00). ORs adjusted for age, gender, and years of education (OR, 95% confidence interval). Raw percentages (noted for the 1 atopic disorder, 2 atopic disorders, and 3 atopic disorders groups): psychotic experiences 38.3, 40.3, and 49.2%; hallucinations 35.4, 38.6, and 47.2%; delusions 8.0, 7.2, and 6.1% (also see **Figure 2**).*

individual atopic disorders (asthma bordered on significance, 1.30). Regarding hallucination subtypes, all associations were significant except between asthma and tactile hallucinations and between eczema and visual hallucinations, which did not survive Bonferroni correction (**Table 3**). None of the delusion subtypes were significantly associated with asthma, eczema, or allergic rhinitis.

DISCUSSION

To our knowledge, this is the largest population-based study investigating the association between atopic disorders and psychotic experiences in an adolescent and adult sample. We observed an increased risk of psychotic experiences in individuals with atopic disorders as compared with those without, specifically for hallucinations. We found a dose–response relationship, with each additional atopic disorder diagnosis increasing the odds for psychotic experiences. This was also observed for hallucinations alone but not for delusions alone. Atopy was associated with hallucinations across all modalities, while the odds for delusions were not significant. These results did not appear to be driven specifically by allergic rhinitis, asthma, or eczema.

In comparison with findings of Khandaker and colleagues on childhood atopy and psychotic experiences in adolescence (8), we also found an increased risk of psychotic experiences in individuals with atopic disorders, both dichotomous and in a dose–response relationship. We replicated their finding that asthma and eczema are specifically associated with psychotic experiences, and extended these findings by also reporting higher odds for allergic rhinitis. In contrast to Khandaker (8), we found that atopy was associated with hallucinations across four sensory modalities, instead of auditory hallucinations alone (although the result for visual hallucinations was trend-level significant after correcting for multiple comparisons). While Khandaker found associations between atopy and two delusion subtypes (8), our results did not reach significance, which could be due to the limited number of reported delusion subtypes (percentages ranging between 0.1 and 2.8%).

Our findings are in accordance with previous studies reporting the high incidence of atopic disorders in schizophrenia patients by Chen and colleagues (5) and the increased risk of schizophrenia in individuals with atopic disorders by Pedersen et al. (7). Notably, both studies evaluated four different atopic disorders (asthma, allergic rhinitis, urticaria, and eczema) and found that their results were mainly driven by asthma. The high comorbidity between asthma and schizophrenia has also been reported by Weber et al. (6). This disorder-specific association was not evident in our sample, as the increased risk of psychotic experiences was observed for asthma, eczema, and allergic rhinitis. Moreover, our finding for allergic rhinitis does not corroborate the observation by Chen and colleagues (5), who observed that the risk for diagnosed allergic rhinitis was decreased in schizophrenia patients. However, Pederson et al. did report increased odds for allergic rhinitis but only when combined with urticaria and eczema (7).

TABLE 3 | Associations between specific psychotic experiences and atopy, including the individual atopic disorders.

	Atopy (*n* = 2,439)	*Asthma* (*n* = 954)	*Eczema* (*n* = 1,181)	*Allergic rhinitis* (*n* = 1,252)
Psychotic experiences	**1.26 *p* < .001** (1.14–1.41)	**1.32 *p* < .001** (1.14–1.53)	**1.20 *p* = .009** (1.05–1.38)	**1.46 *p* < .001** (1.28–1.67)
Hallucinations	**1.27 *p* < .001** (1.14–1.42)	**1.34 *p* < .001** (1.15–1.55)	**1.24 *p* = .002** (1.08–1.43)	**1.47 *p* < .001** (1.28–1.68)
Auditory[a]	**1.36 *p* < .001** (1.19–1.57)	**1.51 *p* < .001** (1.26–1.82)	**1.31 *p* = .003** (1.10–1.57)	**1.58 *p* < .001** (1.34–1.87)
Visual[a]	1.19 *p* = .026 (1.02–1.38)	**1.32 *p* = .006** (1.08–1.62)	1.10 *p* = .339 (0.91–1.34)	**1.31 *p* = .003** (1.10–1.58)
Tactile[a]	**1.33 *p* < .001** (1.14–1.56)	1.29 *p* = .022 (1.04–1.60)	**1.31 *p* = .010** (1.07–1.60)	**1.47 *p* < .001** (1.21–1.78)
Olfactory[a]	**1.40 *p* < .001** (1.19–1.65)	**1.51 *p* < .001** (1.21–1.87)	**1.32 *p* = .009** (1.08–1.63)	**1.53 *p* < .001** (1.26–1.87)
Delusions	1.21 *p* = .054 (0.99–1.48)	1.30 *p* = .051 (0.99–1.69)	1.07 *p* = .594 (0.83–1.40)	1.14 *p* = .304 (0.89–1.47)
Paranoia[b]	1.31 *p* = .142 (0.91–1.87)	1.55 *p* = .059 (0.98–2.43)	1.22 *p* = .402 (0.77–1.94)	1.22 *p* = .395 (0.77–1.93)
Reference[b]	1.17 *p* = .422 (0.80–1.73)	1.45 *p* = .137 (0.89–2.38)	0.96 *p* = .876 (0.56–1.63)	1.07 *p* = .794 (0.65–1.76)
Guilt[b]	1.60 *p* = .041 (1.09–2.53)	1.87 *p* = .031 (1.06–3.29)	1.71 *p* = .059 (0.98–2.99)	1.40 *p* = .264 (0.78–2.52)
Control[b]	0.87 *p* = .644 (0.49–1.55)	1.09 *p* = .828 (0.52–2.27)	0.93 *p* = .852 (0.44–1.95)	0.84 *p* = .646 (0.40–1.76)
Religious[b]	1.43 *p* = .262 (0.76–2.68)	2.02 *p* = .069 (0.95–4.29)	1.05 *p* = .913 (0.42–2.62)	0.91 *p* = .843 (0.37–2.26)
Grandeur[b]	1.44 *p* = .060 (0.99–2.11)	1.60 *p* = .062 (0.98–2.63)	1.23 *p* = .437 (0.73–2.05)	1.39 *p* = .168 (0.87–2.24)
Somatic[b]	1.67 *p* = .039 (1.03–2.70)	2.11 *p* = .013 (1.17–3.80)	1.74 *p* = .072 (0.95–3.19)	1.40 *p* = .289 (0.75–2.64)
Capgras[b]	1.24 *p* = .573 (0.59–2.61)	0.70 *p* = .567 (0.20–2.40)	1.07 *p* = .896 (0.39–2.93)	1.64 *p* = .252 (0.70–3.84)
Cotard[b]	1.72 *p* = .395 (0.49–5.96)	1.72 *p* = .521 (0.33–8.92)	1.50 *p* = .634 (0.39–7.83)	2.05 *p* = .327 (0.49–8.64)

The group without (diagnosed) atopic disorders was used as reference (OR = 1.00). ORs adjusted for age, gender, and years of education (OR, 95% confidence interval).

[a]*Alpha level was Bonferroni-corrected for hallucination subtypes (.05/4 = .0125)*

[b]*Alpha level was Bonferroni-corrected for delusion subtypes (.05/9 = .0056).*

In line with the continuum hypothesis of psychosis (12) describing psychotic symptoms along a continuous range (from isolated, nonclinical symptoms to those occurring in the context of psychotic disorders), our results contribute to the previously found associations between autoimmune disorders, atopy and schizophrenia (3–8). Current findings also corroborate previous genetic and biomedical studies that have indicated the involvement of immune-mediated pathways in the development of psychosis (1, 2). Genome-wide association studies have identified robust schizophrenia-associated risk loci involved in adaptive immunity (CD19 and CD20 B-lymphocytes) and the MHC region on chromosome six (1, 2, 13). The MHC region is best known for its involvement in antigen presentation and inflammatory mediators. It has also been suggested that asthma and schizophrenia may share genetic susceptibility (8, 14). Diverse immune alterations have been found in patients with a psychotic disorder, indicating inflammation of the central nervous system (1, 3). Cross-sectional studies have linked inflammatory parameters in the blood, including C-reactive protein as well as interleukin-6 and interleukin-8, to severity of negative symptoms and cognitive performance in schizophrenia patients (15). Furthermore, as visualized with positron electron tomography, an increased number of activated microglia cells has been found in the brains of patients with recent-onset psychosis and those at ultra-high risk of psychosis (16, 17). Excessive microglial activity potentially provides a route by which an increased pro-inflammatory state in the brain may contribute to the gray matter thinning and synapse loss observed in schizophrenia patients (18, 19). Future research should further evaluate the complex interplay between mediating factors that are relevant for both psychosis and atopy, including genetics and environmental factors such as urbanicity and childhood trauma (20–23). Importantly, more insight in the immunological components of psychosis provides new leads to improve treatment options, with anti-inflammatory drugs being viewed as potential candidates for new augmentation therapies for at least a subset of patients (24).

Strengths and Limitations

A major strength of this study is the large number of participants. Online questionnaires are suitable to evaluate common phenomena and their risk factors in large samples, which can reveal subtle associations. Given the anonymity of participation, they are also suitable for stigmatized topics such as psychotic experiences.

One important limitation is that online surveys are more prone to participation bias and skewed population samples, which prompted us to include demographic variables as covariates in our analyses (25, 26). In addition, the choice to participate is influenced by individual interests and preferences that could have contributed to the relatively high percentages of hallucinations we observed. These percentages should hence be interpreted with caution [for an elaboration on this point, see Refs. (9, 11)]. Furthermore, similar to the Khandaker et al.'s (8) study, we based the presence of atopic disorders on these self-reported data. Although we specifically asked whether these atopic disorders had been diagnosed by a doctor, these data could not be verified by making use of health records. A large systematic review by Pols et al. (27) compared self-reported prevalences from population-based studies with clinician-diagnosed prevalences in general practice (children aged 0–18 years, in the UK and the Netherlands) and concluded that the lifetime prevalence of asthma, eczema, and allergic rhinitis was lower in general practice. They also noted that individual estimates varied widely in both population-based and general practice studies. Our population-based lifetime prevalence rates of 14.7% for asthma, 18.2% for eczema, and 19.3% for allergic rhinitis were relatively low compared to those found by Pols et al. (asthma: population 19.1–35.6% vs. general practice 4.2–22.9%; eczema: population 16.5–27.1% vs. general practice 7.2–36.5%; allergic rhinitis: population 18.3–47.7% vs. general practice 1.0–11.4%). Importantly, the ORs we found for atopic disorders increasing the risk for psychotic experiences were comparable with those reported by previous studies using national-register data (5, 7). We also performed additional sensitivity analyses, as 16.8% of our control sample reported an atopic disorder that was not diagnosed by a doctor, which may have introduced some false negatives. Excluding these individuals altogether (resulting in a sample of $n = 5{,}800$) gave similar findings with overall higher ORs (atopy versus controls: psychotic experiences OR 1.34; hallucinations OR 1.34; delusions OR 1.24). Our trend association between atopy and delusions now reached significance ($p = .043$).

As mentioned above, various factors could mediate the found associations between atopy and risk for psychotic experiences. For example, our dataset did not include measurements on urbanicity. However, two previous studies that further adjusted their estimates for degree of urbanization did not find a significant change in their results without this correction (5, 7). Furthermore, it is important to note that, although our findings were statistically significant, the percentage of reported psychotic experiences was only a few percent higher in participants with atopic disorders as compared with that in the control group. However, the effects were evident in a sample taken from the general population. Our findings indicate that atopic disorders are a risk factor even for the development of nonclinical psychotic experiences. This supports the proposition that the immunological pathway may constitute an important common underlying pathway in the development of psychotic experiences across the psychosis continuum, both in healthy individuals and in patients with a psychotic disorders (8, 12).

Conclusion

In the largest population-based study in adolescents and adults to date, we found that atopic disorders (asthma, eczema, and allergic rhinitis) increased the risk of psychotic experiences in a dose–response fashion. These results provide further support for the involvement of immunological processes in the pathophysiology of psychosis.

ETHICS STATEMENT

Given the observational nature of this study, the medical ethics committee of the University Medical Center Utrecht exempted the project from further review.

AUTHOR CONTRIBUTIONS

Writing manuscript: MB. Preparation of the database: ML, JB, WH, and MS. Revising manuscript content: ML, JB, SG, IS. Approving final version of the manuscript: all authors.

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REFERENCES

1. Khandaker GM, Dantzer R. Is there a role for immune-to-brain communication in schizophrenia? *Psychopharmacol* (2016) 233(9):1559–73. doi: 10.1007/s00213-015-3975-1
2. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature* (2016) 530(7589):177. doi: 10.1038/nature16549
3. Benros ME, Eaton WW, Mortensen PB. The epidemiologic evidence linking autoimmune diseases and psychosis. *Biological psychiatry* (2014) 15(75):300–6. doi: 10.1016/j.biopsych.2013.09.023
4. Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J Psychiatry* (2006) 163(3):521–8. doi: 10.1176/appi.ajp.163.3.521
5. Chen YH, Lee HC, Lin HC. Prevalence and risk of atopic disorders among schizophrenia patients: a nationwide population based study. *Schizophr Res* (2009) 108(1-3):191–6. doi: 10.1016/j.schres.2008.12.021
6. Weber NS, Cowan DN, Millikan AM, Niebuhr DW. Psychiatric and general medical conditions comorbid with schizophrenia in the National Hospital Discharge Survey. *Psychiatr Serv* (2009) 60(8):1059–67. doi: 10.1176/ps.2009.60.8.1059
7. Pedersen MS, Benros ME, Agerbo E, Børglum AD, Mortensen PB. Schizophrenia in patients with atopic disorders with particular emphasis on asthma: a Danish population- based study. *Schizophr Res* (2012) 138(1):58–62. doi: 10.1016/j.schres.2012.02.019
8. Khandaker GM, Zammit S, Lewis G, Jones PB. A population-based study of atopic disorders and inflammatory markers in childhood before psychotic experiences in adolescence. *Schizophr Res* (2014) 152(1):139–45. doi: 10.1016/j.schres.2013.09.021
9. Linszen MMJ, de Boer JN, Schutte JL, Begemann MJH, de Vries J, Koops S, et al. Phenomenology of hallucinations in the general population: results from a large online survey. Submitted.
10. Rossell SL, Schutte MJL, Toh WL, Thomas N, Strauss C, Linszen MMJ, et al. The Questionnaire for Psychotic Experiences (QPE): an examination of the reliability and validity of the english version. *Schiz Bull* (2019) 45(S1):S78–S87. doi: 10.1093/schbul/sby148
11. De Boer JN, Linszen MMJ, de Vries J, Schutte MJL, Begemann MJH, Heringa SM, et al. Auditory hallucination-like experiences, top-down processing and language perception: a general population study. *Psychol Med* (2019) 1–9. doi: 10.1017/S003329171800380X
12. Van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychol Med* (2009) 39(2):179–95. doi: 10.1017/S0033291708003814
13. Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans PA, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* (2014) 511(7510):421. doi: 10.1038/nature13595
14. Harrison PJ, Law AJ. Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. *Biol psychiatr* (2006) 60(2):132–40. doi: 10.1016/j.biopsych.2005.11.002
15. Meyer U, Schwarz MJ, Müller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. *Pharmacol Ther* (2011) 132:96–110. doi: 10.1016/j.pharmthera.2011.06.003
16. Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo M, Owen DR, et al. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [11C] PBR28 PET brain imaging study. *Am J Psychiatry* (2015) 173(1):44–52. doi: 10.1176/appi.ajp.2015.14101358
17. Doorduin J, De Vries EF, Willemsen AT, De Groot JC, Dierckx RA, Klein HC. Neuroinflammation in schizophrenia-related psychosis: a PET study. *J Nuclear Med* (2009) 50(11):1801–7. doi: 10.2967/jnumed.109.066647
18. Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. *Science* (2018) 359(6381):1269–73. doi: 10.1126/science.aal3589
19. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* (2011) 21:1202529. doi: 10.1126/science.1202529
20. Wright RJ. Stress and atopic disorders. *J Allergy Clin Immunol* (2005) 116(6):1301–6. doi: 10.1016/j.jaci.2005.09.050
21. Schröder PC, Li J, Wong GW, Schaub B. The rural–urban enigma of allergy: what can we learn from studies around the world? *Pediatr Allergy Immunol* (2015) 26(2):95–102. doi: 10.1111/pai.12341
22. Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? a systematic review. *Br J Dermatol* (2010) 162(5):964–73. doi: 10.1111/j.1365-2133.2010.09689.x
23. Exley D, Norman A, Hyland M. Adverse childhood experience and asthma onset: a systematic review. *Eur Respir Rev* (2015) 24(136):299–305. doi: 10.1183/16000617.00004114
24. Begemann MJ, Schutte MJ, Slot MI, Doorduin J, Bakker PR, van Haren NE, et al. Simvastatin augmentation for recent-onset psychotic disorder: a study protocol. *BBA clin* (2015) 4:52–8. doi: 10.1016/j.bbacli.2015.06.007
25. Evans JR, Mathur A. The value of online surveys. *Internet Res.* (2005) 15(2):195–219. doi: 10.1108/10662240510590360
26. Wright KB. Researching Internet-based populations: advantages and disadvantages of online survey research, online questionnaire authoring software packages, and web survey services. *J Comput-mediat comm* (2005) 10(3):1034. doi: 10.1111/j.1083-6101.2005.tb00259.x
27. Pols DHJ, Wartna JB, Moed H, van Alphen EI, Bohnen AM, Bindels PJE. Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review. *Scan J Prim Health Care* (2016) 34(2):143–50. doi: 10.3109/02813432.2016.1160629

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What Is the Role of Dietary Inflammation in Severe Mental Illness? A Review of Observational and Experimental Findings

Joseph Firth[1,2], Nicola Veronese[3,4], Jack Cotter[5], Nitin Shivappa[6,7,8], James R. Hebert[6,7,8], Carolyn Ee[1], Lee Smith[9], Brendon Stubbs[10,11], Sarah E. Jackson[12] and Jerome Sarris[1,13]*

[1] NICM Health Research Institute, Western Sydney University, Westmead, NSW, Australia, [2] Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom, [3] Laboratory of Nutritional Biochemistry, Research Hospital, IRCCS "S. de Bellis", Castellana Grotte, Italy, [4] Aging Branch, Neuroscience Institute, National Research Council, Padua, Italy, [5] Cambridge Cognition, Cambridge, United Kingdom, [6] Cancer Prevention and Control Program, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States, [7] Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States, [8] Connecting Health Innovations LLC, Columbia, SC, United States, [9] Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, United Kingdom, [10] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom, [11] Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [12] Department of Behavioural Science and Health, University College London, London, United Kingdom, [13] Department of Psychiatry, University of Melbourne, The Melbourne Clinic Professorial Unit, Melbourne, VIC, Australia

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Edited by:
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***Correspondence:**
Joseph Firth
J.Firth@Westernsydney.edu.au

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Severe mental illnesses (SMI), including major depressive disorder, bipolar disorder, and schizophrenia, are associated with increased inflammation. Given diet's role in modulating inflammatory processes, excessive calorie-dense, nutrient-deficient processed food intake may contribute toward the heightened inflammation observed in SMI. This review assesses the evidence from observational and experimental studies to investigate how diet may affect physical and mental health outcomes in SMI through inflammation-related pathways. Cross-sectional studies indicate that individuals with SMI, particularly schizophrenia, consume more pro-inflammatory foods and fewer anti-inflammatory nutrients than the general population. Cohort studies indicate that high levels of dietary inflammation are associated with increased risk of developing depression, but there is currently a lack of evidence for schizophrenia or bipolar disorder. Randomized controlled trials show that dietary interventions improve symptoms of depression, but none have tested the extent to which these benefits are due to changes in inflammation. This review summarizes evidence on dietary inflammation in SMI, explores the directionality of these links, and discusses the potential use of targeted nutritional interventions for improving psychological well-being and physical health outcomes in SMI. Establishing the extent to which diet explains elevated levels of inflammatory markers observed in SMI is a priority for future research.

Keywords: nutrition, schizophrenia, bipolar disorder, nutrients, vitamin

INTRODUCTION AND AIMS

Recent meta-analyses have confirmed that severe mental illnesses (SMI), including major depressive disorder (MDD), bipolar disorder, and schizophrenia, are associated with increased levels of both peripheral inflammatory markers (1) and systemic inflammation (2). Additionally, heightened inflammation could present a novel treatment target for MDD, given that the anti-depressant efficacy of various pharmacological and lifestyle interventions appears to be associated with reductions in inflammation (3, 4). In schizophrenia, the evidence for antipsychotics altering inflammatory markers is mixed (1, 5), although there is some preliminary evidence to indicate that various adjunctive interventions may confer beneficial effects through reducing inflammatory status (6, 7).

Calorie-dense diets that are high in saturated fats and simple carbohydrates appear to increase peripheral inflammatory markers, whereas diets high in fiber and vegetables reduce inflammation (8–12). Systematic reviews of dietary patterns in people with SMI have shown elevated intakes of sugar-sweetened soft drinks, refined grains, and processed meat are common in this population (13, 14). However, the degree to which these dietary patterns heighten inflammation in SMI, and the potential impact on physical and mental health outcomes, is relatively unexplored. This comprehensive review brings together the evidence from cross-sectional, longitudinal, and experimental studies on this topic to:

(i) Examine the extent to which inflammatory potential of the diet (hereafter referred to as "dietary inflammation") is elevated in SMI populations;
(ii) Explore the directionality of the links between dietary inflammation and symptoms of SMI;
(iii) Discuss the existing evidence for the use of nutritional interventions for improving health outcomes in SMI and how these effects may act through inflammatory pathways.

FOOD INTAKE AND DIETARY INFLAMMATION IN PEOPLE WITH SEVERE MENTAL ILLNESSES

A recent large-scale study of the UK Biobank (15) compared the macro- and micro-nutrient intake of individuals with diagnosed MDD (n = 14,619), bipolar disorder (n = 952), and schizophrenia (n = 262) to healthy controls (n = 54,010), showing that people with SMI consumed significantly more carbohydrate, sugar, fat, and saturated fat than healthy controls (all $p < 0.001$), even when controlling for age, gender, education, BMI, social deprivation, and ethnicity. The study also examined the inflammatory potential of food intakes of individuals with SMI compared with the general population using the "Dietary Inflammatory Index" (DII®). The DII is a literature-derived, population-based measure, which provides an estimate of the inflammatory potential of an individual's diet from up to 45 individual food parameters (16). DII scores have been validated against various blood markers of inflammatory status across a number of different populations (17–21). The DII scores in SMI samples in the UK Biobank are displayed in **Figure 1** [derived from Firth et al. (15)], adjusted for age, gender, and total energy intake. These data show highly elevated dietary inflammation in individuals with schizophrenia, along with smaller, but significantly increased, levels of dietary inflammation in individuals with MDD (all $p < 0.01$). Although dietary inflammation in the bipolar disorder group was similarly

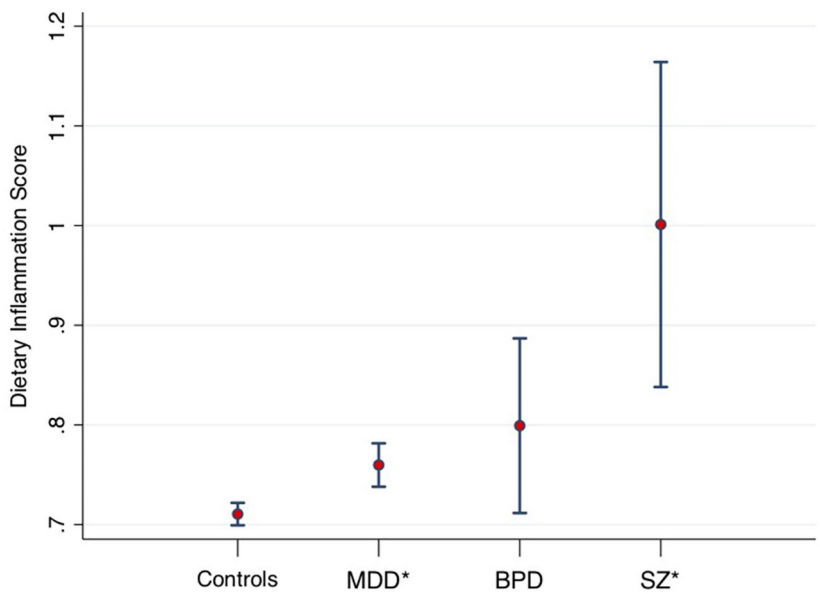


FIGURE 1 | Dietary Inflammatory Index (DII) scores from 53,270 healthy controls, compared to major depressive disorder (MDD) (n = 14,422), bipolar disorders (BPD, n = 933), and schizophrenia (SZ, n = 254). Midpoint shows adjusted means. Error bars show 95% confidence intervals. *Statistically significant difference compared to healthy controls. Data derived from Firth et al. (15).

larger than healthy controls ($p = 0.03$), this difference was reduced to a marginally non-significant trend after adjusting for BMI and socioeconomic status ($p = 0.07$).

It is interesting to note that despite the vast number of studies examining elevated levels of peripheral inflammation observed across all classes of SMI (1), none have accurately controlled for the potential confounding factor of diet. Furthermore, a priority for future research is to validate the accuracy of dietary reporting in SMI. Interestingly, previous research comparing other lifestyle factors (i.e., physical activity) using objective against self-report measures in SMI have shown that people with schizophrenia significantly overestimate health behaviors compared with the general population (22). Therefore, replication of these findings, using validated measures in SMI alongside blood markers of inflammation, is required to establish how diet may relate to inflammation in SMI.

Along with poor mental health, people with SMI experience drastic inequalities in physical health, including elevated rates of obesity, diabetes, and cardiometabolic disorders, ultimately contributing to a reduced life expectancy of around 20 years (23). Given the clear causal links between dietary inflammation and these health outcomes established in the general population (10–12), and the established benefits of dietary interventions for physical health in SMI (24), it is reasonable to explore dietary inflammation as one risk factor driving some of the physical health inequalities observed in this population. Indeed, the highest levels of dietary inflammation are observed in schizophrenia: a group that also experiences significantly worse physical health outcomes than other classes of SMI (25, 26). Poor dietary quality associated with schizophrenia may even be driven by side effects of antipsychotic medications, which may increase appetite through interfering with the "hunger hormone," ghrelin (27). Clearly, there is an urgent need for future research to determine the mechanisms through which poor diet may be driving adverse health outcomes in people with SMI. This line of investigation will provide novel insights into the etiology of the physical health inequalities observed in this population and has the potential to inform clinical care.

A key limitation of the current literature is a lack of large-scale data on dietary patterns among young people with SMI, thus making it difficult to determine whether poor diet precedes the onset of mental illness, or vice versa. In the general population, data suggest that younger people tend to have worse diets than older adults (28). This also may apply to SMI populations, as nutritional deficits in psychosis are evident even prior to antipsychotic treatment (29). Thus, in the following section, we review the prospective studies examining links between high levels of dietary inflammation and the subsequent onset of mental illness.

PROSPECTIVE ASSOCIATIONS BETWEEN DIETARY INFLAMMATION AND PSYCHIATRIC SYMPTOMS

Poor nutrition has been implicated in the onset and persistence of psychiatric disorders (30). In general, cohort studies have shown that dietary patterns, such as a Mediterranean diet, which is rich in fruits, vegetables, olive oil, and legumes, may be protective against mental health disorders (31–38). By contrast, increased risk of mental disorders has been observed with dietary patterns, such as the Western diet, characterized by high intake of saturated fat and refined carbohydrates (33, 39–41).

Inflammation presents one feasible mechanism through which diet may affect the risk of mental disorders. This is supported by multiple cohort studies showing that higher DII scores are associated with increased risk of depression (42–49). Combining all longitudinal data on this topic (including 77,420 participants from seven different studies), a recent meta-analysis confirmed that higher levels of dietary inflammation were associated with 31% increased risk of depression over the 5- to 13-year follow-up period (50). This meta-analysis also found that pro-inflammatory diets were more strongly associated with depression among females than males (50), although significant relationships were observed for both sexes.

Despite these positive findings on links between depression and dietary inflammation calculated from self-report measures, future research must establish if these relationships are mediated by biological markers of inflammatory status. Although a number of studies have found joint relationships between dietary inflammation, inflammatory markers, and depressive symptoms (51–53), those findings are inconsistent with other results showing that dietary patterns associated with heightened inflammatory markers do not consistently predict depression scores (54).

Currently, there is an urgent need for longitudinal studies to assess how dietary inflammation is related to the onset of other classes of SMI, because there is currently no strong evidence linking dietary inflammation with risk of bipolar disorder or schizophrenia. As the effects of dietary inflammation on mental health are also observed in adolescence (51), when the majority of SMIs first arise (55), the potential impact that this may have on risk of bipolar and psychotic disorders is worthy of further examination.

Along with clinical symptoms, people with SMI (and particularly schizophrenia) also display a range of cognitive deficits (56–58), which impede daily functioning (59, 60), and are not treated by psychotropic medications (61, 62). There is an emerging literature suggesting that elevated peripheral inflammatory markers are associated with deficits in cognitive function among patients with psychiatric disorders (1, 63). Though the specific mechanisms underlying this association remain unclear, chronic and acute inflammation is thought to have a number of detrimental effects on brain structure and function, which, in turn, appear to adversely affect cognitive performance (64–66).

Poor diet and obesity also have a well-established link with cognitive dysfunction (67, 68). There is mounting evidence that these associations may be mediated by inflammatory processes (69), suggesting that diet has the potential to act as a modifiable risk factor for cognitive dysfunction both in clinical and non-clinical populations. Much of the work investigating the association between diet, inflammation, and cognition has come from a series of cross-sectional and longitudinal studies in older adults, which indicate that diets with high inflammatory potential may be associated with accelerated cognitive decline and reduced brain volume (70–72). Considering the high levels

of dietary inflammation and cognitive deficits observed in SMI, along with indicated relationships between cognitive functioning and diet in other populations, this area presents a promising avenue for future research (73).

EXPERIMENTAL MANIPULATION OF DIETARY INFLAMMATION: CAN WE MAKE A DIFFERENCE TO MENTAL HEALTH?

A recent meta-analysis examined the effects of dietary interventions on mental health in 16 randomized controlled trials (RCTs) of 45,826 participants (74). Dietary improvement significantly reduced symptoms of depression [g = 0.275; 95% confidence interval (CI), 0.10–0.45; p = 0.002], with no changes in anxiety observed. Interestingly, similar degrees of benefit for depressive symptoms were observed from all the different dietary approaches trialed; dietary interventions primarily designed to improve nutrition [e.g., the Mediterranean diet, which is typically linked with anti-inflammatory effects (11)] were no more beneficial for mental health than those aimed at reducing bodyweight or decreasing dietary fat intake (74). This may be because, even without increasing anti-inflammatory nutrient intake, weight-loss and changes in energy balance can reduce inflammation through reducing excess adipose tissue, which is associated with heightened inflammation (75, 76).

However, 15 of the 16 RCTs in this meta-analysis only examined effects on depressive symptoms in samples with "sub-clinical" depression (i.e., samples without a confirmed diagnosis of MDD). However, the single trial conducted in clinically depressed participants (75) observed large reductions in depressive symptoms from a 12-week modified Mediterranean diet, with 32.3% of participants achieving remission from the dietary intervention versus 8.0% in the social support control condition (p = 0.028). Subsequent RCTs have replicated these findings of the Mediterranean diet reducing symptoms in people with moderate to severe depression (76). As a meta-analysis of 50 studies (10) has shown, the Mediterranean diet significantly reduces inflammatory markers in other (i.e., non-psychiatric) populations, and it is possible that the benefits in people with depression are linked to the anti-inflammatory effects. However, this has yet to be assessed, as no studies have measured changes in inflammation following dietary interventions in depression. Furthermore, there is currently no experimental evidence showing beneficial effects of dietary interventions on inflammation and mental health in schizophrenia or bipolar disorder.

Nonetheless, RCTs of individual nutrient-based supplements (nutraceuticals) have provided valuable insights into how nutrition can influence mental health in SMI through inflammatory pathways. For instance, in an RCT of 155 individuals with MDD, Rapaport et al. (77) found that patients with baseline elevated markers of inflammation were significantly more responsive to omega-3 treatment (mediated, in principle, *via* eicosapentenoic acid) (78). The antidepressant effects of omega-3 fatty acids working through the reduction of inflammation also were implicated in a seminal study by Su (79). This study examined depression in people with hepatitis C, undergoing interferon (IFN) alpha therapy, which commonly induces depressive symptoms due to its inflammatory effects (80). However, Su et al. (79) found that omega-3 supplementation reduced the risk of developing depression following INF-a treatment. Other nutrients, such as folate, have also been found to reduce depression in people with high levels of inflammation (81), again indicating these adjunctive treatments may confer symptomatic benefits through inflammatory pathways.

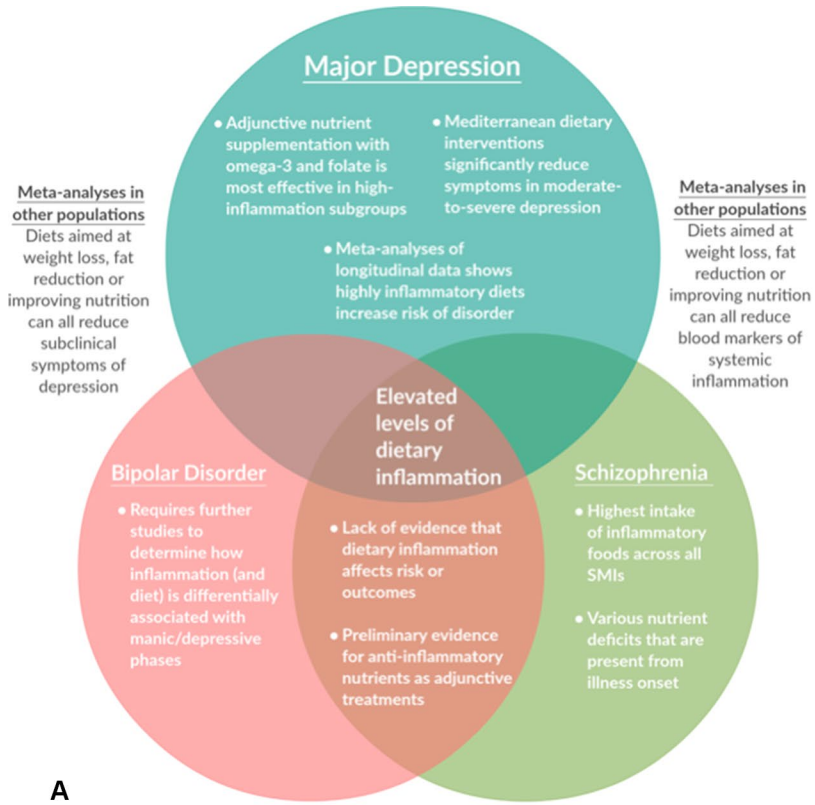
Beyond MDD, there are preliminary data from RCTs suggesting that anti-inflammatory nutrients, such as omega-3 and folate-based compounds, may also be effective for other SMIs, including bipolar disorder and schizophrenia (82). Because inflammation is particularly elevated during onset of psychotic disorders, these adjunctive treatments may have neuroprotective effects in the early stages of illness among young people (83, 84), potentially improving cognitive outcomes for some patients. However, the extent to which their effects are due specifically to their anti-inflammatory properties is not fully ascertained.

CONCLUSIONS AND FUTURE RESEARCH

The current evidence from human studies examining the role of dietary inflammation in SMI are shown in **Figure 2**. The cross-sectional literature provides consistent evidence that individuals with SMI consume more pro-inflammatory foods than the general population, and fewer anti-inflammatory nutrients—which may contribute toward the heightened levels of inflammatory markers observed in SMI. In the few studies that have compared different classes of SMI, the highest dietary risks are observed among people with schizophrenia (who also have the most severe disparities in physical health, compared with other mental disorders). However, the bulk of both the observational and experimental studies examining the links between dietary inflammation and mental health have been conducted in depression (see **Figure 2A**)—with a relative dearth of evidence in other disorders. Therefore, there is now a need for researchers and clinicians to build upon the existing evidence in MDD and give further attention to the impact of dietary inflammation in schizophrenia and bipolar disorder and explore the potential benefits of dietary modification for these populations.

The longitudinal studies now provide population-scale data showing that high levels of dietary inflammation are associated with increased the likelihood of developing depression over time. However, there is little evidence to suggest that this also applies to schizophrenia or bipolar disorder. Alongside this, a key remaining question in this field (which can only be addressed by experimental studies), is: "Can reducing dietary inflammation make a difference?" or, more specifically, "Is it possible that dietary modification can reduce inflammation and thus improve symptoms in people with SMI?"

Currently, there is no experimental evidence to show that a specific "anti-inflammatory" diet influences psychiatric symptoms of schizophrenia or bipolar disorder. Furthermore, whereas RCTs and meta-analyses have recently shown that dietary improvement reduces symptoms of depression (in both



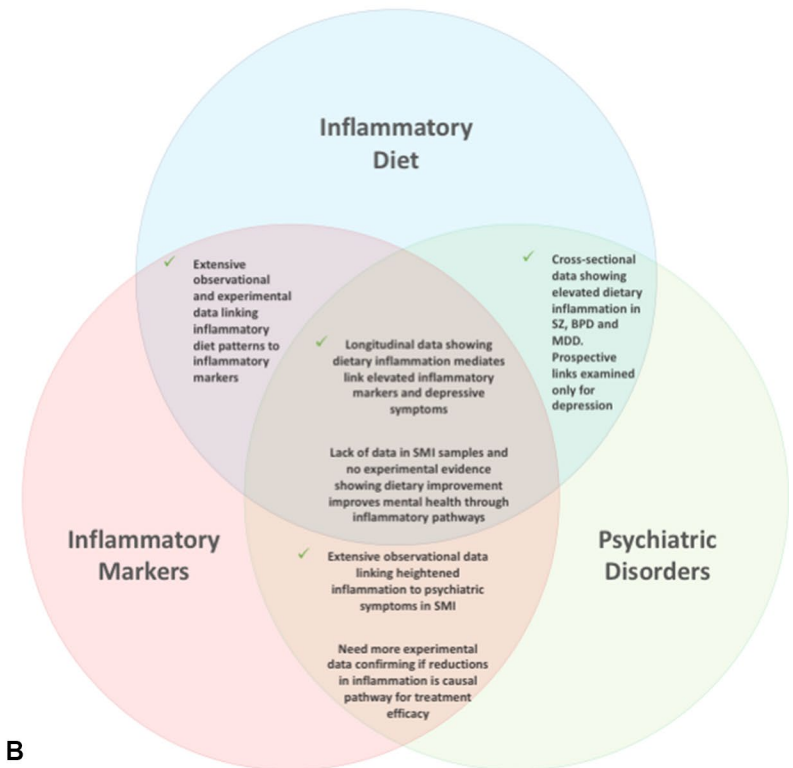


FIGURE 2 | Key Findings and Future Questions: A map of the evidence for the role of dietary inflammation in severe mental illnesses (SMI), with regard to **(A)** different conditions, and **(B)** different aspects of the interaction between dietary inflammation, inflammatory markers, and psychiatric disorders.

clinical and non-clinical populations), the extent to which this is due to anti-inflammatory effects of dietary interventions has not been assessed. Nonetheless, some evidence from nutraceutical trials suggests that certain anti-inflammatory nutrients may provide adjunctive treatments for subgroups of individuals with mental health conditions with particularly elevated levels of inflammation.

With regard to whole-diet interventions, it is interesting to consider the prevalent finding that the weight loss, fat reduction, or Mediterranean diets trialed so far all appear to confer similar beneficial effects on depressive symptoms. Whereas this may indicate a lack of specificity, it should be acknowledged that each of these interventions, although differing in stated aims, generally have some key factors in common. Specifically, all of these interventions generally involve decreasing the amount of refined, processed calorie-dense foods, while increasing intake of nutrient-dense natural-occurring fiber and vegetables. Therefore, the general equivalence across difference types of diets could ultimately produce an encouraging message, suggesting that highly specific or specialized diets are perhaps unnecessary for the average individuals, as adhering to very simple and universally accepted dietary advice appears to be equally beneficial for psychological well-being—and sufficient for avoiding the potentially deleterious effects on mental health of a "junk food" diet. To provide greater insight on this, future research should attempt to elucidate the specific mechanisms through which the dietary impacts upon inflammation to influence mental health. For instance, hyperglycemia and hyperinsulinemia after a meal of refined starches and sugars may promote inflammation by increasing production of free radicals and pro inflammatory cytokines (85, 86), whereas high levels of saturated fat intake decrease production of short chain fatty acids such as butyrate, which have anti-inflammatory properties (87). Alongside these nutritional factors, obesity and excess adipose tissue themselves directly heighten inflammation—suggesting that attenuating these adverse states of health through calorie restriction and low-fat diets could reduce inflammatory status and thus improve psychological well-being (74, 88). Along with reducing dietary patterns with inflammatory potential, the adequate intake of beneficial nutrients is another mechanism through which "healthy diets" improve inflammatory profiles and support mental health. For example, various vitamins and minerals have been shown to modulate the "kyrenuine pathway" (89), which regulates the immune system, particularly with regard neurotrophic factor production, NMDA receptor signaling, and glutamatergic neurotransmission—all of which are implicated in inflammatory hypotheses of SMI (90).

A further emerging pathway through which inflammatory potential of the diet may induce depressive symptoms is by interacting with the gut–brain axis and affecting the gut microbiome (91). However, the role of individual nutrients on modifying the microbiome is still poorly understood, as are the exact mechanisms by which the gut microbiome itself affects mental health (92).

Further investment in human trials is now required to establish the feasibility and efficacy of dietary improvement as an intervention for improving physical and mental health across different classes of SMI. Additionally, future trials should aim to measure peripheral and central inflammation before and after dietary interventions in SMI. In this way, researchers could apply subgroup and mediation analyses to examine how the potential benefits of nutrition interventions are related to changes in inflammatory status. Ultimately, this line of investigation could shed new light on the interface between physical and mental health in people with SMI, along with presenting novel interventions and adjunctive treatments for improving psychological well-being and tackling the poor cardiometabolic health observed in this underserved population.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception, development, and writing of this mini-review. All authors have approved the final paper.

REFERENCES

1. Goldsmith D, Rapaport M, Miller B. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mole Psychiatry* (2016) 21(12):1696. doi: 10.1038/mp.2016.3
2. Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. *Schizophr Bull* (2017) 44(1):75–83. doi: 10.1093/schbul/sbx035
3. Köhler CA, Freitas TH, Stubbs B, Maes M, Solmi M, Veronese N, et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: systematic review and meta-analysis. *Mol Neurobiol* (2017) 1–12. doi: 10.1007/s12035-017-0632-1
4. Schuch FB, Deslandes AC, Stubbs B, Gosmann NP, da Silva CTB, de Almeida Fleck MP. Neurobiological effects of exercise on major depressive disorder: a systematic review. *Neurosci Biobehav Rev* (2016) 61:1–11. doi: 10.1016/j.neubiorev.2015.11.012
5. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Mol Psychiatry* (2016) 21(4):554–64. doi: 10.1038/mp.2015.87
6. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophr Bul* (2013) 40(1):181–91. doi: 10.1093/schbul/sbt139
7. Firth J, Cotter J, Carney R, Yung AR. The pro-cognitive mechanisms of physical exercise in people with schizophrenia. *Br J Pharmacol* (2017). doi: 10.1111/bph.13772
8. Meyer J, Döring A, Herder C, Roden M, Koenig W, Thorand B. Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality in middle-aged men from the MONICA/KORA Augsburg cohort study. *Eur J Clin Nutr* (2011) 65(7):800. doi: 10.1038/ejcn.2011.37
9. Hlebowicz J, Persson M, Gullberg B, Sonestedt E, Wallström P, Drake I, et al. Food patterns, inflammation markers and incidence of cardiovascular disease: the Malmö Diet and Cancer study. *J Intern Med* (2011) 270(4):365–76. doi: 10.1111/j.1365-2796.2011.02382.x

10. Kastorini C-M, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* (2011) 57(11):1299–313.
11. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* (2004) 292(12):1440–6. doi: 10.1001/jama.292.12.1440
12. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol* (2006) 48(4):677–85. doi: 10.1016/j.jacc.2006.03.052
13. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. *J Psychiatr Res* (2013) 47(2):197–207. doi: 10.1016/j.jpsychires.2012.10.005
14. Molendijk M, Molero P, Sánchez-Pedreño FO, Van der Does W, Martínez-González MA. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *J Affect Disord* (2018) 226:346–54. doi: 10.1016/j.jad.2017.09.022
15. Firth J, Stubbs B, Teasdale SB, Ward PB, Veronese N, Shivappa N, et al. Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. *World Psychiatry* (2018) 17(3):365. doi: 10.1002/wps.20571
16. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* (2014) 17(8):1689–96. doi: 10.1017/S1368980013002115
17. Shivappa N, Hebert JR, Marcos A, Diaz LE, Gomez S, Nova E, et al. Association between dietary inflammatory index and inflammatory markers in the HELENA study. *Mol Nutr Food Res* (2017) 61(6). doi: 10.1002/mnfr.201600707
18. Shivappa N, Hébert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *Br J Nutr* (2015) 113(4):665–71. doi: 10.1017/S000711451400395X
19. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Pub Health Nutr* (2014) 17(8):1825–33. doi: 10.1017/S1368980013002565
20. Wirth MD, Shivappa N, Davis L, Hurley TG, Ortaglia A, Drayton R, et al. Construct validation of the dietary inflammatory index among African Americans. *J Nutr Health Aging* (2017) 21(5):487–91. doi: 10.1007/s12603-016-0775-1
21. Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. *Clin Exp Aller* (2015) 45(1):177–83. doi: 10.1111/cea.12323
22. Firth J, Stubbs B, Vancampfort D, Schuch FB, Rosenbaum S, Ward PB, et al. The validity and value of self-reported physical activity and accelerometry in people with schizophrenia: a population-scale study of the UK Biobank. *Schizophr Bull* (2018) 44(6):1293–300. doi: 10.1093/schbul/sbx149
23. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, et al. A blueprint for protecting physical health in people with mental illness: directions for health promotion, clinical services and future research. *Lancet Psychiatry* (2019).
24. Vancampfort D, Firth J, Correll C, Solmi S, De Hert M, Carney R, et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry* (2019) 18(1). doi: 10.1002/wps.20614
25. Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* (2016) 15(2):166–74. doi: 10.1002/wps.20309
26. Hayes JF, Marston L, Walters K, King MB, Osborn DP. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–14. *Br J Psychiatry* (2017) 211(3):175–81. doi: 10.1192/bjp.bp.117.202606
27. Firth J, Teasdale SB, Jackson SE, Vancampfort D, Siskind D, Sarris J, et al. Do reductions in ghrelin contribute towards antipsychotic-induced weight gain? *Schizophr Res* (2018). doi: 10.1016/j.schres.2018.12.043
28. Drewnowski A, Renderson SA, Driscoll A, Rolls BJ. The dietary variety score: assessing diet quality in healthy young and older adults. *J Am Diet Assoc* (1997) 97(3):266–71. doi: 10.1016/S0002-8223(97)00070-9
29. Firth J, Carney R, Stubbs B, Teasdale S, Vancampfort D, Ward P, et al. Nutritional deficiencies and clinical correlates in first-episode psychosis: a systematic review and meta-analysis. *Schizophr Bull* (2018) 44:1275–92. doi: 10.1093/schbul/sbx162
30. Jacka FN, Pasco JA, Mykletun A, Williams LJ, Hodge AM, O'reilly SL, et al. Association of Western and traditional diets with depression and anxiety in women. *Am J Psychiatry* (2010) 167(3):305–11. doi: 10.1176/appi.ajp.2009.09060881
31. Hoare E, Dash SR, Varsamis P, Jennings GL, Kingwell BA. Fasting plasma glucose, self-appraised diet quality and depressive symptoms: a US-representative cross-sectional study. *Nutrients* (2017) 9(12):1330. doi: 10.3390/nu9121330
32. Oddy WH, Robinson M, Ambrosini GL, O'Sullivan TA, de Klerk NH, Beilin LJ, et al. The association between dietary patterns and mental health in early adolescence. *Prev Med* (2009) 49(1):39–44. doi: 10.1016/j.ypmed.2009.05.009
33. Jacka FN, Kremer PJ, Berk M, de Silva-Sanigorski AM, Moodie M, Leslie ER, et al. A prospective study of diet quality and mental health in adolescents. *PLoS One* (2011) 6(9):e24805. doi: 10.1371/journal.pone.0024805
34. Jacka FN, Rothon C, Taylor S, Berk M, Stansfeld SA. Diet quality and mental health problems in adolescents from East London: a prospective study. *Soc Psychiatry Psychiatr Epidemiol* (2013) 48(8):1297–306. doi: 10.1007/s00127-012-0623-5
35. Rienks J, Dobson AJ, Mishra GD. Mediterranean dietary pattern and prevalence and incidence of depressive symptoms in mid-aged women: results from a large community-based prospective study. *Eur J Clin Nutr* (2013) 67(1):75–82. doi: 10.1038/ejcn.2012.193
36. Sanchez-Villegas A, Delgado-Rodriguez M, Alonso A, Schlatter J, Lahortiga F, Serra Majem L, et al. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. *Arch Gen Psychiatry* (2009) 66(10):1090–8. doi: 10.1001/archgenpsychiatry.2009.129
37. Chen YC, Jung CC, Chen JH, Chiou JM, Chen TF, Chen YF, et al. Association of dietary patterns with global and domain-specific cognitive decline in Chinese elderly. *J Am Geriatr Soc* (2017) 65(6):1159–67. doi: 10.1111/jgs.14741
38. Akbaraly TN, Brunner EJ, Ferrie JE, Marmot MG, Kivimaki M, Singh-Manoux A. Dietary pattern and depressive symptoms in middle age. *Br J Psychiatry* (2009) 195(5):408–13. doi: 10.1192/bjp.bp.108.058925
39. Le Port A, Gueguen A, Kesse-Guyot E, Melchior M, Lemogne C, Nabi H, et al. Association between dietary patterns and depressive symptoms over time: a 10-year follow-up study of the GAZEL cohort. *PLoS One* (2012) 7(12):e51593. doi: 10.1371/journal.pone.0051593
40. Granic A, Davies K, Adamson A, Kirkwood T, Hill TR, Siervo M, et al. Dietary patterns high in red meat, potato, gravy, and butter are associated with poor cognitive functioning but not with rate of cognitive decline in very old adults. *J Nutr* (2016) 146(2):265–74. doi: 10.3945/jn.115.216952
41. Sanchez-Villegas A, Ruiz-Canela M, de la Fuente-Arrillaga C, Gea A, Shivappa N, Hebert JR, et al. Dietary inflammatory index, cardiometabolic conditions and depression in the Seguimiento Universidad de Navarra cohort study. *Br J Nutr* (2015) 114(9):1471–9. doi: 10.1017/S0007114515003074
42. Shivappa N, Schoenaker DA, Hebert JR, Mishra GD. Association between inflammatory potential of diet and risk of depression in middle-aged women: the Australian Longitudinal Study on Women's Health. *Br J Nutr* (2016) 116(6):1077–86. doi: 10.1017/S0007114516002853
43. Wirth MD, Shivappa N, Burch JB, Hurley TG, Hebert JR. The Dietary Inflammatory Index, shift work, and depression: results from NHANES. *Health Psychol* (2017) 36(8):760–9. doi: 10.1037/hea0000514
44. Shivappa N, Hebert JR, Neshatbini Tehrani A, Bayzai B, Naja F, Rashidkhani B. A pro-inflammatory diet is associated with an increased odds of depression symptoms among iranian female adolescents: a cross-sectional study. *Front Psychiatry* (2018) 9:400. doi: 10.3389/fpsyt.2018.00400

45. Shivappa N, Hebert JR, Veronese N, Caruso MG, Notarnicola M, Maggi S, et al. The relationship between the dietary inflammatory index (DII((R))) and incident depressive symptoms: a longitudinal cohort study. *J Affect Disord* (2018) 235:39–44. doi: 10.1016/j.jad.2018.04.014
46. Phillips CM, Shivappa N, Hebert JR, Perry IJ. Dietary inflammatory index and mental health: a cross-sectional analysis of the relationship with depressive symptoms, anxiety and well-being in adults. *Clin Nutr* (2018) 37(5):1485–91. doi: 10.1016/j.clnu.2017.08.029
47. Adjibade M, Andreeva VA, Lemogne C, Touvier M, Shivappa N, Hebert JR, et al. The inflammatory potential of the diet is associated with depressive symptoms in different subgroups of the general population. *J Nutr* (2017) 147(5):879–87. doi: 10.3945/jn.116.245167
48. Akbaraly T, Kerlau C, Wyart M, Chevallier N, Ndiaye L, Shivappa N, et al. Dietary inflammatory index and recurrence of depressive symptoms: results from the Whitehall II Study. *Clin Psychol Sci* (2016) 4(6):1125–34. doi: 10.1177/2167702616645777
49. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: a systematic review and meta-analysis. *Clin Nutr* (2018). doi: 10.1016/j.clnu.2018.11.007
50. Oddy WH, Allen KL, Trapp GS, Ambrosini GL, Black LJ, Huang R-C, et al. Dietary patterns, body mass index and inflammation: pathways to depression and mental health problems in adolescents. *Brain Behav Immun* (2018). doi: 10.1016/j.bbi.2018.01.002
51. Milaneschi Y, Bandinelli S, Penninx B, Vogelzangs N, Corsi A, Lauretani F, et al. Depressive symptoms and inflammation increase in a prospective study of older adults: a protective effect of a healthy (Mediterranean-style) diet. *Molec Psychiatry* (2011) 16(6):589. doi: 10.1038/mp.2010.113
52. Lucas M, Chocano-Bedoya P, Shulze MB, Mirzaei F, O'Reilly ÉJ, Okereke OI, et al. Inflammatory dietary pattern and risk of depression among women. *Brain Behav Immun* (2014) 36:46–53. doi: 10.1016/j.bbi.2013.09.014
53. Vermeulen E, Brouwer IA, Stronks K, Bandinelli S, Ferrucci L, Visser M, et al. Inflammatory dietary patterns and depressive symptoms in Italian older adults. *Brain Behav Immun* (2018) 67:290–8. doi: 10.1016/j.bbi.2017.09.005
54. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry* (2007) 20(4):359. doi: 10.1097/YCO.0b013e32816ebc8c
55. Bora E, Harrison B, Yücel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol Med* (2013) 43(10):2017–26. doi: 10.1017/S0033291712002085
56. Gold JM, Harvey PD. Cognitive deficits in schizophrenia. *Psychiatr Clin North Am* (1993). doi: 10.1016/S0193-953X(18)30175-8
57. Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. In: *Novel antischizophrenia treatments*. New York: Springer (2012). p. 11–37. doi: 10.1007/978-3-642-25758-2_2
58. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* (2000) 26(1):119. doi: 10.1093/oxfordjournals.schbul.a033430
59. Evans VC, Iverson GL, Yatham LN, Lam RW. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. *J Clin Psychiatry* (2014) 75(12):1359–70. doi: 10.4088/JCP.13r08939
60. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *Am J Psychiatry* (1999) 156(9):1336–41.
61. Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC, et al. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry* (2007) 64(10):1115–22. doi: 10.1001/archpsyc.64.10.1115
62. Rosenblat JD, Brietzke E, Mansur RB, Maruschak NA, Lee Y, McIntyre RS. Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: evidence, pathophysiology and treatment implications. *J Affect Disord* (2015) 188:149–59. doi: 10.1016/j.jad.2015.08.058
63. Allison DJ, Ditor DS. The common inflammatory etiology of depression and cognitive impairment: a therapeutic target. *J Neuroinflamm* (2014) 11(1):151. doi: 10.1186/s12974-014-0151-1
64. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* (2011) 130(2):226–38. doi: 10.1016/j.pharmthera.2011.01.014
65. Majer M, Welberg LA, Capuron L, Pagnoni G, Raison CL, Miller AH. IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. *Brain Behav Immun* (2008) 22(6):870–80. doi: 10.1016/j.bbi.2007.12.009
66. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav* (2011) 103(1):59–68. doi: 10.1016/j.physbeh.2010.12.003
67. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev* (2011) 12(9):740–55. doi: 10.1111/j.1467-789X.2011.00920.x
68. Nguyen JC, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci* (2014) 8:375. doi: 10.3389/fnins.2014.00375
69. Jacka FN, Cherbuin N, Anstey KJ, Sachdev P, Butterworth P. Western diet is associated with a smaller hippocampus: a longitudinal investigation. *BMC Med* (2015) 13(1):215. doi: 10.1186/s12916-015-0461-x
70. Hayden KM, Beavers DP, Steck SE, Hebert JR, Tabung FK, Shivappa N, et al. The association between an inflammatory diet and global cognitive function and incident dementia in older women: the Women's Health Initiative Memory Study. *Alzheimers Dement* (2017) 13(11):1187–96. doi: 10.1016/j.jalz.2017.04.004
71. Kesse-Guyot E, Assmann KE, Andreeva VA, Touvier M, Neufcourt L, Shivappa N, et al. Long-term association between the dietary inflammatory index and cognitive functioning: findings from the SU.VI.MAX study. *Eur J Nutr* (2017) 56(4):1647–55. doi: 10.1007/s00394-016-1211-3
72. Joseph J, Depp C, Shih P-aB, Cadenhead KS, Schmid-Schönbein G. Modified Mediterranean diet for enrichment of short chain fatty acids: potential adjunctive therapeutic to target immune and metabolic dysfunction in schizophrenia? *Front Neurosci* (2017) 11:155. doi: 10.3389/fnins.2017.00155
73. Firth J, Marx W, Dash S, Carney R, Teasdale SB, Solmi M, et al. The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials. *Psychosom Med* (2019). doi: 10.1097/PSY.0000000000000673
74. Clément K, Viguerie N, Poitou C, Carette C, Pelloux V, Curat CA, et al. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB J* (2004) 18(14):1657–69. doi: 10.1096/fj.04-2204com
75. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med* (2017) 15(1):23. doi: 10.1186/s12916-017-0791-y
76. Parletta N, Zarnowiecki D, Cho J, Wilson A, Bogomolova S, Villani A, et al. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: a randomized controlled trial (HELFIMED). *Nutr Neurosci* (2017) 1–14. doi: 10.1080/1028415X.2017.1411320
77. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol Psychiatry* (2016) 21(1):71–9. doi: 10.1038/mp.2015.22
78. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr* (2002) 21(6):495–505. doi: 10.1080/07315724.2002.10719248
79. Su K-P, Lai H-C, Yang H-T, Su W-P, Peng C-Y, Chang JP-C, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. *Biol Psychiatry* (2014) 76(7):559–66. doi: 10.1016/j.biopsych.2014.01.008
80. Prather AA, Rabinovitz M, Pollock BG, Lotrich FE. Cytokine-induced depression during IFN-α treatment: the role of IL-6 and sleep quality. *Brain Behav Immun* (2009) 23(8):1109–16. doi: 10.1016/j.bbi.2009.07.001
81. Shelton RC, Pencina MJ, Barrentine LW, Ruiz JA, Fava M, Zajecka JM, et al. Association of obesity and inflammatory marker levels on treatment outcome: results from a double-blind, randomized study of adjunctive L-methylfolate calcium in patients with MDD who are inadequate responders to SSRIs. *J Clin Psychiatry* (2015) 76(12):1635–41. doi: 10.4088/JCP.14m09587

82. Firth J, Teasdale S, Allot K, Siskind D, Marx W, Cotter J, et al. The efficacy and safety of nutrient supplements in the treatment of mental illness: a systematic synthesis of 33 meta-analyses of randomized controlled trials. *World Psychiatry* (2019) in press.
83. Firth J, Rosenbaum S, Ward PB, Curtis J, Teasdale SB, Yung AR, et al. Adjunctive nutrients in first-episode psychosis: a systematic review of efficacy, tolerability and neurobiological mechanisms. *Early Interven Psychiatry* (2018). doi: 10.1111/eip.12544
84. Pawełczyk T, Piątkowska-Janko E, Bogorodzki P, Gębski P, Grancow-Grabka M, Trafalska E, et al. Omega-3 fatty acid supplementation may prevent loss of gray matter thickness in the left parieto-occipital cortex in first episode schizophrenia: a secondary outcome analysis of the OFFER randomized controlled study. *Schizophr Res* (2018) 195:168–75. doi: 10.1016/j.schres.2017.10.013
85. Kallio P, Kolehmainen M, Laaksonen DE, Pulkkinen L, Atalay M, Mykkänen H, et al. Inflammation markers are modulated by responses to diets differing in postprandial insulin responses in individuals with the metabolic syndrome. *Am J Clin Nutr* (2008) 87(5):1497–503. doi: 10.1093/ajcn/87.5.1497
86. Bulló M, Casas-Agustench P, Amigó-Correig P, Aranceta J, Salas-Salvadó J. Inflammation, obesity and comorbidities: the role of diet. *Pub Health Nutr* (2007) 10(10A):1164–72. doi: 10.1017/S1368980007000663
87. Singh RK, Chang H-W, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med* (2017) 15:73. doi: 10.1186/s12967-017-1175-y
88. Steckhan N, Hohmann C-D, Kessler C, Dobos G, Michalsen A, Cramer H. Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: a systematic review and meta-analysis. *Nutrition* (2016) 32(3):338–48. doi: 10.1016/j.nut.2015.09.010
89. Majewski M, Kozlowska A, Thoene M, Lepiarczyk E, Grzegorzewski W. Overview of the role of vitamins and minerals on the kynurenine pathway in health and disease. *J Physiol Pharmacol* (2016) 67(1):3–19.
90. Savitz J. The kynurenine pathway: a finger in every pie. *Mol Psychiatry* (2019). doi: 10.1038/s41380-019-0414-4
91. Dash S, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: focus on depression. *Curr Opin Psychiatry* (2015) 28(1):1–6. doi: 10.1097/YCO.0000000000000117
92. Oriach CS, Robertson RC, Stanton C, Cryan JF, Dinan TG. Food for thought: the role of nutrition in the microbiota-gut–brain axis. *Clin Nutr Exp* (2016) 6:25–38. doi: 10.1016/j.yclnex.2016.01.003
93. Sarris J, Logan AC, Akbaraly TN, Amminger GP, Balanzá-Martínez V, Freeman MP, et al. Nutritional medicine as mainstream in psychiatry. *Lancet Psychiatry* (2015) 2(3):271–4. doi: 10.1016/S2215-0366(14)00051-0

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REVIEW
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Neuroinflammation in Bipolar Depression

Francesco Benedetti[1,2*], *Veronica Aggio*[1,3], *Maria Luisa Pratesi*[4], *Giacomo Greco*[4] *and Roberto Furlan*[4]

[1] Psychiatry and Clinical Psychobiology Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele Hospital, Milano, Italy, [2] University Vita-Salute San Raffaele, Milano, Italy, [3] PhD Program in Molecular Medicine, University Vita-Salute San Raffaele, Milan, Italy, [4] Clinical Neuroimmunology Unit, Institute of Experimental Neurology, IRCCS Ospedale San Raffaele, Milano, Italy

Bipolar disorder (BD) is a leading cause of worldwide disability among mood disorders. Pathological mechanisms are still vastly unclear, and current treatments with conventional medications are often unsatisfactory in maintaining symptoms control and an adequate quality of life. Consequently, current research is focusing on shedding new light on disease pathogenesis, to improve therapeutic effectiveness. Recent evidence has suggested a prominent role of inflammation in mood disorders. Elevated levels of peripheral proinflammatory mediators have been reported in BD, as well as in other mood disorders, and people with systemic autoimmune diseases have an increased risk of developing BD. These immunological alterations are stable, and current medications are unable to alter peripheral concentrations even when clinical improvement is evident. These findings have also been replicated in the central nervous system (CNS) milieu, whereas genetic studies have shown that these immune alterations are not due to the disorder itself, being detectable before the illness onset. Moreover, these inflammatory modifications seem to be affected by and linked to other biomarkers of the disorder, such as alterations of white matter (WM) microstructure, metabolism, kynurenine pathway, and circadian rhythmicity. Finally, these immune variations seem to be useful as predictors of therapeutic responsiveness to medications, and in discriminating between clinically different outcomes. The objective of this review is to summarize available evidence on the connection between inflammation and BD, focusing on peripheral inflammatory markers and recent findings on their connection with other typical features of BD, to outline a general overview of the disorder. Moreover, it is meant to analyze the issues with data gathering and interpretation, given the partially contradictory and inconsistent nature of results.

Keywords: bipolar disorder, neuroinflammation, cytokines, neuroimaging, neurotransmitters

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Sophie E. Holmes,
Yale University, United States

***Correspondence:**
Francesco Benedetti
benedetti.francesco@hsr.it

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INTRODUCTION

At least 20% of the general population will experience a mood episode at some time in their lives or, even worse, develop a mood disorder. Within mood disorders, bipolar (BD) and major depressive disorder (MDD) are the most frequent and disabling ones. BD is a chronic recurrent mental disorder characterized by mood shifts, ranging from acute depression to mania and hypomania, and followed by a return to

euthymia. BD affects around 2% of the general population, with a typical early onset before 30 years of age (1).On the other hand, MDD is characterized by a chronic recurrence of depressive episodes with a lifetime prevalence of about 12%. Patients generally reach clinical attention only years after the illness onset, with a delay of 6–10 years for a correct diagnosis. Because of the absence of specific biomarkers, the diagnosis is made simply with a clinical interview, thus leading to possible misdiagnosis, particularly for those BD patients that experience a clear hypomanic or manic episode only after a few depressive ones. Clinical and physiological manifestations of BD are complex, heterogeneous, and severe mood changes are only the most evident sign, as it also involves neurovegetative, inflammatory, molecular, metabolic, and psychomotor alterations. Moreover, the efficacy of current medications, mainly antidepressants and mood stabilizers, is modest for both disorders and has a delayed effect. Although several risk factors have been identified, mainly genetic and environmental, the pathophysiology of these disorders is largely unknown. One of the most reported biomarkers of the disorder is a widespread alteration of white and grey matter microstructure (2–4), together with an atrophy of the hippocampus (5), but their biological underpinning still remains unclear. Following this line of reasoning, it is clear why the psychiatry research field is looking for new biomarkers that can be helpful to improve the etiology, diagnosis, and treatment understanding of BD.

THE IMMUNE SYSTEM IN BD

Evidence for possible involvement of the immune system, and in a broader sense, inflammation, in mood disorders, has been steadily accumulating in recent years. The rationale behind this relation originally arises from the observation of the so-called "sickness behavior," the complex mixture of behavioral changes observed in inflammatory states, which includes mood changes such as anxiety, depression, failure to concentrate, lethargy, and more. Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) are held responsible for these changes (6). It has also been established that these cytokines can induce MDD in physically ill patients without a previous mental illness (7). Moreover, a great percentage of patients with mood disorders show comorbidities with autoimmune pathologies, such as hypothyroidism, rheumatoid arthritis, diabetes mellitus, hepatitis, and Crohn's disease (8, 9). Patients who experience systemic autoimmune diseases also present an increased risk of developing BD (10). Consequently, these findings prompted further research into the potential role of cytokines and immunity markers on affective disorders.

Even if the data are not always convergent, the majority of the studies reported increased peripheral cytokines levels in both MDD and BD. The greater limit of these studies is the use of peripheral blood for the analysis of immune markers, thus leading to many questions about whether the same alterations could be observed in the central nervous system (CNS). This is a core point, considering the fundamental importance of CSN-specific T-cells' role in shaping brain function (11, 12). Some elegant studies have analyzed the CNS inflammatory status through microglia activation. Microglia are probably the most important innate immune cells in the brain, where they regulate cellular inflammatory response and represent the primary source of proinflammatory cytokines. Haarman and colleagues (13) firstly reported a neuroinflammatory condition *in vivo* in BD using positron emission tomography (PET). *In vivo* microglia characterization showed significantly increased activation in the hippocampus of BD patients compared to healthy controls (HC). Furthermore, in a subsequent study, the same group reported a direct association between microglia activation and neuronal damage in BD, thus suggesting a possible harmful effect of this neuroinflammatory condition (14). Previously reported findings of inflammatory markers in the periphery now seem to be supported by microglia studies, thus contributing to create more evidence supporting the neuroinflammatory theories on mood disorders.

One of the most recent theories about immune alterations in mood disorder is the one formulated from the reported findings of Grosse, Drexhage, and colleagues. This theory postulates that MDD and BD share a partial deficit at different age periods; MDD patients have an early mild T cell defect, characterized by a reduced maturation of Th2 and Th17 cells, that becomes more prominent with increasing age, also including a reduced maturation of T regulatory cells and an increased immune activation (15). On the other hand, BD could be characterized by an early T cell defect similar to those of MDD aged patients, which will become partially restored with increasing age (16). More evidence supporting this hypothesis comes from genetic studies: aberrant expression of mRNA inflammatory genes in BD and related offspring has been reported. This "genetic signature" is present before illness onset, thus underling that an inflammatory condition—due to a different genetic expression—is not the consequence of the disorder itself, but more likely one of the contributing factors (17). In a subsequent study on BD twins, the same group found that the occurrence of the previously reported gene-expression signature was principally due to shared environmental factors, demonstrating that BD itself cannot be considered as a causative factor for monocyte activation (18). The involvement of immune dysfunctions as a consequence of different genetic expressions would therefore seem a plausible etiological factor implicated in BD onset and development. In the next subheadings we will present and discuss the findings on peripheral markers in BD, and we will then proceed to link these findings to other core features of BD, such as brain structural alterations, neurotransmitter production and release, circadian alterations, and sleep disturbances.

PERIPHERAL IMMUNE SYSTEM ALTERATIONS IN BD

Innate and Adaptive Immunity Inflammatory Cytokines

During the last few years, increasing evidence for the involvement of the immune system in mood disorders has been accumulating, with many studies showing significant changes to cytokines levels. Cytokines are small molecules secreted by the immune system in response to a variety of stimuli, which are capable of affecting the behavior of other cells. More in detail, cytokines are

capable of control and promote cell and tissue growth, development, migration, differentiation, and death. In BD, significantly elevated levels of IL-1ß were detected in the serum of BD patients during manic episodes compared with HC, whereas those experiencing depressive episodes did not show variations (19). Data on IL-6 are among the most consistent in the whole literature on BD. IL6 is a pleiotropic cytokine which is known to enhance clonal expansion and activation of T cells, B cells differentiation, and to manage acute- phase response (20). A vast majority of immune system cells can produce IL-6 when driven by Toll-like receptors (TLR), prostaglandins, adipokines, stress responses, and other cytokines. IL-6 levels were found to be higher in BD patients compared with HC. Moreover, they seemed to considerably decrease after 6 weeks of treatment (21). The same study demonstrated an increase in TNF-α as well, although no significant reduction was noticed after treatment. These data were also confirmed by a recent meta-analysis (22). Evidence supporting the role of an inflammatory milieu in the pathogenesis of BD is growing. This could perhaps play a part in the increase in mortality and clinical comorbidities observed in BD patients.

Among all factors involved, TNF-α holds a key position. TNF-α has a prominent role in the regulation and preservation of immune system mechanisms, inflammation, and host defense. It has also been associated with chronic inflammation, autoimmunity, the development of cancer and the metastatic process (23). Numerous studies reported elevated TNF-α levels in BD patients, as opposed to HC, during both manic and depressive episodes(19, 22, 24).Nonetheless, some results suggest that this marker may not be significant at all (25, 26). Such inconsistencies may be related to heterogeneity in the samples, due to discrepancies in symptoms, disease duration, and treatment. Some studies explored the significance of TNF receptors (TNFR1 and TNFR2), which appear to be more stable and could, therefore, represent more dependable markers than the cytokine itself. Moreover, these receptors are likely to be involved in BD, since various studies described their alteration in other conditions, such as MDD, schizophrenia, and Parkinson's disease. In particular, the soluble isoform of TNFR1 (sTNFR1) showed a strong association with BD patients in any phase of the disease, as compared to HC, although the same did not apply to sTNFR2 (27).

A marker which gained quite some attention in this field was CRP. A recent meta-analysis (28) found that CRP concentrations are higher in BD patients, substantially during a manic episode, moderately throughout depressive episodes or euthymia. These data were partially corroborated by another meta-analysis (29), which confirmed elevated levels of CRP in manic and euthymic, but not depressed BD patients. Further findings regarded different increases in CRP concentrations in distinct mood shifts. Results showed that notwithstanding evidence of higher levels in all three phases when compared with healthy subjects, CRP rises more in the manic stage compared to depression and euthymia in BD. Furthermore, CRP concentrations seemed to be higher in patients who did not undergo any treatment. Despite great evidence for the involvement of CRP in BD, the extension of its elevation was not associated with symptoms severity or disease duration. Besides, CRP levels decreased when achieving euthymia after a manic episode, without reaching control groups concentrations. The same study also demonstrated that high concentrations of CRP raise the risk of developing BD, but do not cause neuroprogression in BD patients (30). However, other studies reported no significant differences between HC and BD patients, although trends could be observed for a reduction in CRP levels for manic and depressive periods compared with euthymia (31).

Among the adaptive immune cytokines, the most relevant ones analyzed include IL-2 and INF-γ. Results from literature were somewhat inconsistent, as a few studies reported no differences between BD patients and HC (21, 32), whereas others noted a significant reduction of IL-2 levels in BD patients (19). Some studies found INF-γ to be reduced (33) andothers reported it as increased in BD patients anda reduction in its levels was evident after a few weeks of pharmacological treatments (34).

The accumulation of a vast amount of evidence in favor of a proinflammatory activation in BD pathogenesis has led to the belief that antiinflammatory cytokines in affected subjects would be reduced or unchanged. Many studies reported no difference between IL-10 levels in BD patients and HC (24, 35). Nonetheless, there were a few contradictory reports. Other works found elevated antiinflammatory cytokines levels, similarly to findings for major depressive disease, as a compensatory response to proinflammatory mobilization (22). A meta-analysis, which included over 1,600 among healthy subjects and BD patients in various phases of the disease, demonstrated significantly higher levels of IL-4 in BD patients compared to controls (22).

It should also be considered that the immune system is deeply connected to the circadian system. The link between these two entities takes place on multiple levels. On one hand, the immune system features daily cycles, which seem to be vital for the retention of a functional apparatus. On the other hand, immune responses cause changes in circadian rhythms, disrupting their stability. Many immune cell types show daily fluctuations in human and rodents' blood. Among those are T and B cells, monocytes, macrophages, and NK cells. The same is true for various cytokines, such as IL-1ß, IL-6, INF-γ, and TNF-α. Many of the studies on this topic were performed on regular day-night and sleep-wake conditions, therefore rendering it impossible to understand if differences in concentration were due to the endogenous circadian system or cyclical environmental signals.

Chemokines

Studies exploring the association between BD and chemotactic cytokines are sparse. One of the most relevant had enrolled 70 BD patients and 50 healthy subjects (36). BD patients presented higher levels of CCL11, CCL24, and CXCL10, and reduced levels of CXCL8 compared to controls. No significant differences were noted between manic and euthymic patients. Higher CXCL10 have also been reported in a separate study (37). CXCL10 promotes activated Th1 cells mototaxis, and Th1 cells hyperactivity has already been demonstrated in BD patients. On the other hand, CCL11 and CCL24 activity is suggestive of Th2 cells hyperactivity, which is known to be associated with BD.

Lastly, CXCL8 is a chemokine produced by monocytes, macrophages, and endothelial cells. Previous research has highlighted contradictory data concerning BD, with some of the works finding an increase in its plasmatic levels for depressive and manic states, while others did not report alterations in euthymic patients.

INFLAMMATORY STATUS ACROSS MOOD STATES: A ROUNDUP

Even if quite the majority of the studies seems to point out a peripheral inflammatory markers alteration in BD (38), data available is heavily subject to interpretation, and we will now produce a brief roundup of cytokines movement throughout different mood states, extrapolated from what we already discussed.

Among the most prominent cytokines in human biology are tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These are heavily implicated in many physiological processes, and it is of huge interest to seek their potential role in BD mood swings.

As far as IL-1ß goes, a study showed that BD patients during manic episodes produce higher levels of the cytokine, whereas those experiencing depressive episodes did not show variations (19).

On the other hand, IL-6 levels were found to be elevated in BD patients, across all mood states and without significant correlation to the polarity of mood states. A crucial finding is that they were notably reduced after 6 weeks of treatment (21), something which could hold a very significant value in assessing the efficacy of pharmacological treatment in these patients, and therefore adjusting therapeutic approaches. TNF-α was also shown to be increased in BD patients in the same study, even though its levels did not significantly decrease after treatment.

Still, TNF-α was assessed in many different studies, with contrasting results. A few studies asserted that BD patients generally show higher levels of TNF-α than HC, with no significant difference between manic and depressive episodes (19, 22, 24). At the same time, some studies concluded that no such difference existed (25, 26). Such inconsistencies highlight the need for more dependable biomarkers, which could prove to be more stable and consistent across patients and mood states. TNF receptors (TNFR1 and TNFR2), are potential candidates for the role, and indeed the soluble isoform of TNFR1 (sTNFR1) demonstrated strong correlations with BD patients in any phase of the disease, as compared to HC, although the same did not apply to sTNFR2 (27). Further studies are surely needed to better assess the potential of this interesting marker in such patients.

Another very promising marker, implicated to a great extent in a number of different milieus, is CRP. Data in the field are again inconsistent and generally come from large meta-analysis, which all show higher CRP concentrations in BD patients compared with HC, but are not on the same page as it regards levels through various mood states in BD.

A few studies also looked at adaptive immunity cytokines, notably IL-2 and INF-γ, which would implicate a more complex pathological mechanism. Indeed, results showed an even higher degree of variability, although some showed promise in highlighting possible markers of response to treatment, particularly one which reported a reduction in INF-γ levels after a few weeks of pharmacological treatment. For summing up purposes, we hereby provide a table with all major findings on cytokine levels in studies included in this review (**Figure S1**).

The overall direction from the mentioned studies is in favor of a proinflammatory activation in BD pathogenesis, but these results taken together push the need to find a better way to standardize methods such as patients' selection, samples collection timing, storage and analysis, among others. Efforts shall be put towards standardizing all studies which aim to explore such correlations among peripheral cytokines, so as to compare results more objectively, and hopefully find more consistency when putting data together.

MORE THAN AUTOIMMUNITY: OTHER PROPOSED FACTORS CONTRIBUTING TO BD ETIOLOGY

Before the interest in immune alterations as a possible contributing factor to BD pathology, several decades of research have enlightened different systemic and local alterations as biomarkers of the disorder. The most-reported ones relate to brain structure, neurotransmitter release and neurocircuit functioning, circadian rhythmicity, tryptophan degradation, metabolism, and cognitive modification. These markers are both interconnected and linked to the immune system modification found in BD.

BRAIN STRUCTURAL ALTERATIONS

White matter (WM) microstructural alterations have been extensively associated with BD and have been proposed as a possible biomarker of the disorder. Neuroimaging studies on diffusion tensor imaging (DTI) consistently reported a widespread pattern of increased diffusivity perpendicular to the WM tracts' main diffusion trajectory (radial diffusivity, RD), and in the molecular diffusion rate measured by mean diffusivity (MD) (2, 39–41). These patterns of alterations are usually accompanied by a reduced diffusivity along the main WM fiber axis, or axial diffusivity (AD), and a lower coherent directionality, measured by fractional anisotropy (FA). WM alterations also concern a volumetric reduction, as described in voxel-based morphometry studies (42), and increased WM hyperintensities (43, 44). These WM modifications have been linked to possible alterations in oligodendrocytes, the axons' myelinating cells in the CNS (45). In the brain of individuals with BD, postmortem studies show a significant reduction in oligodendroglial cells density (46–48), and oligodendrocyte-specific mRNA markers were found to be downregulated (49), thus possibly impairing the homeostatic maintenance of myelinated axons and re-myelination processes (50).

Moreover, stressed oligodendrocytes can also lead to microglia activation through the release of different signaling chemokines and cytokines (51). Microglia activation, as previously reported, has been

found in postmortem and *in vivo* studies of BD patients. In physiological condition, microglia is one the major glial cell populations and is present in high density in all adult brain regions. In a "resting" condition, microglial cells are morphologically characterized by a small cell soma with several elongated processes, which scan the surrounding environment. If these cells meet harmful stimuli or pathogens, they retract the processes and become more mobile, gaining effector abilities. This microglia condition, called M1 state, has prominent proinflammatory features, with the release of cytokines, chemokines, and reactive oxygen species (ROS). On the other hand, microglial cells can move into a M2 condition to downregulate, repair, or protect the brain from inflammation (52, 53). If this physiological activation into a proinflammatory state becomes chronic, it can drive neuronal damage and synaptic alterations, thus leading to neurodegenerative diseases (54).

We investigated the hypothesis that WM microstructure alterations, that have repeatedly been found in BD, could be linked also to a neuroinflammatory condition. In their first research, higher peripheral levels of inflammatory cytokines, such as TNF-α, IFN-γ, IL-8, IL-10, IGFBP2, and PDGF-BB were positively associated with RD and MD, and negatively with FA. These initial findings seem to suggest that a higher concentration of cytokines can be negatively linked to the integrity of myelin sheaths (55). To investigate inflammation not only *via* a multiplex immunoassay but also through immune characterization, the subsequent study investigated the levels of circulating T cells characterized *via* flow cytometry analyses. Peripheral T-helper 17 cells were positively associated with FA, whereas T regulatory cells (FoxP3 positive) were positively associated with RD. These findings were found also in a control sample of healthy volunteers. This balance between regulatory and helper-17 T cells seems to be fundamental not only for the immune homeostasis but might also regulate WM microstructure (56).

Another recent study reported that reduced frequencies of circulating CD8+ effector T cells related to decreased FA and increased RD, independently from BD illness phase (57). Altogether, these studies seem to support the idea that WM alterations found in BD can be related to neuroimmunological alterations. Even if all of these studies have been conducted on peripheral quantification and/or characterization of inflammatory markers, we can hypothesize that a similar condition can also be present in the CNS. Peripheral cytokines can enter the brain by volume diffusion, or *via* active cytokine transporters at the blood-brain barrier (BBB) (7). Further research will be instrumental in clarifying this theory.

Moreover, Patel and colleagues have suggested that the BBB of BD patients can be impaired transiently or persistently, thus leading to a facilitate passage of proinflammatory molecules from the periphery and decreased CNS protection. This BBB disruption can be linked to the neuroinflammatory alterations, microglial activation, and oligodendrocytes dysfunction previously described in BD (58). The demonstrated presence of a relation between one the most recognized biomarker of the disorder, WM pathology, and an inflammatory alteration, seems to underlie that the immunological investigation of BD can lead to a novel and, maybe, completely different understanding and conceptualization of its etiology, suggesting a new field of therapeutic investigation.

Moreover, cortical grey matter (GM) volume reduction in schizophrenia has been associated with higher expression of IL-6, IL-1β, IL-8, and SERPINA3 mRNAs in the prefrontal cortex of postmortem brains (59). Unipolar and bipolar depressed patients with a family history of mood disorders showed a 48% and 39% reduction in subgenual PFC volume, respectively (60), because of a reduction of glial cell number and density and of a reduction of synapses with a preserved number, and increased density, of neurons (61–63). GM volumes in the orbitofrontal cortex of patients with BD and their healthy siblings are smaller than in unrelated HC (64), and are even smaller when BD is associated with severe symptoms such as suicide (65). It could be hypothesized that cytokines play a role in GM reductions in BD, too. In the few available studies, proinflammatory cytokines were associated with GM volumes in the orbitofrontal cortex, lingual gyrus, inferior frontal cortex, middle frontal cortex (66), but with reduced effects in BD compared with schizophrenia (67). We studied stem cell factor (SCF), which is a hematopoietic growth factor and a neurotrophic factor, involved in neuron-neuron and neuron-(micro)glia interactions, fostering neuronal growth and an antiinflammatory milieu; and correlated SCF levels with antidepressant response and with functional and structural MRI measures in cortical areas that are involved in the cognitive generation and control of affect, thus suggesting that factors affecting the inflammatory state in the brain do influence cortical structure and function in BD illness episodes (68).

NEUROTRANSMITTERS: THE KYNURENINE PATHWAY OF TRYPTOPHAN DEGRADATION

One of the first hypotheses concerning mood disorders etiology was related to neurotransmitters alterations: psychopharmaceutical development has highlighted an important role of different neurotransmitter systems into the functional and clinical aspects of mood disorders. However, although existing literature tends to emphasize specificity in drugs' mechanisms of actions, many effective treatments target multiple mechanisms and a multitarget approach to treatment could be better suited for a multifactorial illness such as MDD (69).

MDD has been initially linked to monoaminergic alterations, such as serotonin, dopamine, and norepinephrine, and the gold standard drugs specifically target monoamine neurotransmitters to augment their activity *via* reuptake inhibition mechanisms (e.g., selective serotonin reuptake inhibitors or SSRIs) (70). This monoaminergic theory has been partially rejected only decades after, due to increasing evidence, such as the absence of depressive symptoms in healthy subjects with experimentally induced monoamine depletion (71), moving towards the idea that monoaminergic alterations only partially contribute to explain MDD clinical features. On the other hand, switches between depression and manic episodes in BD patients have originally been

linked to changes in dopaminergic systems functioning. Depressive features were believed to be underlined by a hypodopaminergic condition, whereas the manic phase would have been due to a hyperdopaminergic condition (72). Dopamine antagonists and partial agonists are widely used in the pharmacological treatment of BD, the use of which range from depressive episodes to acute manic phases. These neurotransmitters systems, which are altered in BD, are also regulated by immunological modification. Under physiological conditions, cytokines are fundamental players in synaptic plasticity, neurogenesis, learning, and memory-linked mechanisms (73). Some immunological alterations, like those reported in BD, can also influence the neurotransmitters systems involved in BD.

Two of the previously described cytokines, TNF-α and IFN-γ, play a major role in influencing one fundamental biological pathway in the brain: the kynurenine pathway of tryptophan degradation. Alterations in the kynurenine pathway, that begins with tryptophan degradation, have been hypothesized in depression models; this pathway is the starting point for serotonin and melatonin biosynthesis, both quantitatively altered in BD (74–77).

Serotonin synthesis rate is determined by the bioavailability of tryptophan. Tryptophan degradation is operated by indoleamine 2,3 dioxygenase (IDO) or tryptophan 2,3 dioxygenase (TDO). The pathway regulated by IDO is particularly important for immune homeostasis and regulation, especially during infection and autoimmunity (78). In an inflammatory condition, such as those triggered by the presence of TNF-α and IFN-γ, peripheral tryptophan is converted by IDO into kynurenine. Once transported in the brain, kynurenine degradation leads to the formation of either 3- hydroxykynurenine (3-HK) and quinolinic acid (QUIN) or kynurenic acid (KA) (7). KA show a neuroprotective effect, competitively antagonizing NMDA glutamate receptors, where 3-HK and the derived QUIN seems to exert neurotoxic effects (79). Following IFN-γ activation in the IDO pathway, the kynurenine system exerts an antiinflammatory effect *via* KA releasing, to modulate immune response (78). An imbalance of the kynurenine pathway of tryptophan degradation can lead to an ineffective inflammatory counterbalance activity, and neurotoxicity.

Several studies have shown an involvement of this kynurenine pathway of tryptophan degradation in BD and MDD, which seems to be shifted towards its neurotoxic branch (80, 81). In a cutting-edge study, Myint and colleagues report that plasmatic levels of kynurenine out of tryptophan, defined as tryptophan breakdown index, was increased in BD, together with a reduction of KA concentration, thus lowering its neuroprotective effect (81). More recently, Birner and colleagues report similar data of decreased KA levels in a BD sample compared to healthy volunteers (82). Finally, kynurenine breakdown has been related also to WM microstructure, where BD show reduced concentrations of KA and 5-HIAA, a measure of serotonin levels, that are positively associated with DTI measures of WM integrity (83).

Moreover, ventral, striatal-ventrolateral, and orbitofrontal cortical reward processing circuitry have been proposed to define an endophenotype specific of BD (84), and consistent evidence associates inflammation with decreased dopamine synthesis, packaging, and release, leading to decreased dopamine and dopamine metabolites in cerebrospinal fluid, and decreased availability of striatal dopamine, which results—at the behavioral level—in depressive symptoms related to motivation and motor activity (85).

CIRCADIAN RHYTHMS AND SLEEP ALTERATIONS

Circadian rhythm alterations and sleep disruption have been closely associated with BD pathophysiology (86–88). The fundamental circadian pacemaker is located in the suprachiasmatic nucleus of the hypothalamus, based on multiple transcriptional/translational feedback loops, and it hierarchically controls the peripheral clocks (89). Immune responses cause changes in circadian rhythms, disrupting their stability. Many immune cells types show daily fluctuations in human and rodents' blood. On the other hand, both circadian rhythms and sleep plays a regulatory role on immune system: sleep is involved into the maintenance of Th1 and Th2 homeostasis, the activity of effector and regulatory t cells, and natural killer (NK) cells (90). Sleep seems also to be involved in the transcription regulation of pro and antiinflammatory factors (91).

The influence of sleep alteration of immune functions has been demonstrated also in animal models: sleep deprivation promotes an inflammatory condition *via* microglia and astrocytes activation in rats (92), thus leading to increased proinflammatory cytokines release. Another study reports that in mice with a predominant proinflammatory response, there is an increased BBB permeability and neuroinflammatory markers expression (93). It is possible to surmise that the chronic inflammatory condition that seems to characterize a subpopulation of BD patients can, therefore, also be related to sleep and circadian disturbances. Studies are lacking on the topic, but in a very small sample, major depression was associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion, resulting in the presence or absence of significant differences in respect to healthy subjects at different circadian time points (94).

ADIPOSE TISSUE INVOLVEMENT

BD patients usually present with chronic clinic comorbidities, which cause increased mortality from cardiovascular, respiratory, and endocrine disease. Although currently available treatments (mood stabilizers and antipsychotics) are associated with weight gain, some studies suggest that somatic types with significant abdominal fat carry a higher risk of developing BD (95). Recent findings suggest an association between BD and weight gain, independent from pharmacological treatment. Possible mechanisms supporting the relation between BD and obesity

include endocrine dysregulation, behavioral patterns (physical inactivity and excessive food intake), and a proinflammatory state connected to obesity (96).

Adipokines, such as adiponectin, resistin, and leptin, are cytokines released from adipose tissue, and play a key role in energetic homeostasis, insulin sensitivity, and immune response (97). Recent work has shown that BD patients present with an increase in plasmatic levels of adiponectin and leptin as opposed to HC. Moreover, antipsychotic drugs did not seem to affect concentrations of these molecules (95, 98), but contrasting findings have been reported (25). About leptin, many heterogeneous results have been described. Some have reported a diminution in leptin levels for BD patients compared with controls (99, 100), whereas others have noted similar levels between the two groups (101). On a side note, a few works suggested that physical exercise in mood disorders patients could lower proinflammatory cytokines levels (102, 103). This effect might also be explained by physical exercise enhancing cortisol release, which in turn inhibits T cells cytokines production.

Finally, an association between body mass index (BMI) and WM microstructure has been found in BD: higher BMI was negatively associated with FA and positively with MD. Moreover, serum levels of triglycerides, glucose, and cholesterol inversely correlates with FA and directly with AD, RD, and MD (104). Altogether, these last findings seem to suggest that an increased BMI could be associated with reduced structural integrity, bundle coherence, and axonal branching, and demyelination in general.

Moreover, in the obese adipose tissue, M1-polarized macrophages can secrete inflammatory cytokines (105), which are thought to play a role in metabolic dysregulation and insulin resistance (105, 106), all contributing to hamper antidepressant response (107). In agreement with this hypothesis, we showed that BMI can indirectly hamper antidepressant response by increasing the levels of proinflammatory cytokines (108). Given that an altered WM microstructure is negatively associated with antidepressant response (109), these clinical effects could also result from complex interactions between metabolism, WM integrity, and inflammatory markers.

IMMUNE MARKERS AS CLINICAL OUTCOME AND DIAGNOSTIC PREDICTORS

The immune system is involved in BD, and the data described above seem to suggest a possible role in the etiology of the disorder, but there is more. Different studies reported how inflammatory markers can also help us to differentiate between mood disorders, illness phases, and predict treatment response. The first interesting data emerged from a meta-analysis that shows how peripheral concentrations of different cytokines remain elevated after antidepressant medication (e.g., escitalopram, venlafaxine, duloxetine) (110). Even if more than 50% of patients in the studies show clinical improvement after medication, cytokines modifications are very low. This evidence seems to underlie how cytokines can be strongly related to the disorder itself, and current medications only marginally affect their concentrations. Thus, altered levels of peripheral cytokines can probably be considered a stable biomarker of the disorder. BD patients show lower levels of plasma TNF-α and IL-13 (111), and serum IL-1β (112) compared to MDD patients. On the other hand, BD patients presented higher C-reactive protein, sTNFR1, soluble IL-6 receptor (sIL-6R), and MCP-1 levels compared to MDD patients (33, 113). Another group has tried to investigate the difference in the peripheral inflammatory markers' levels between BD illness phase. BD spectrum patients have higher TNF-α, TGF-β1, and IL-8 levels than controls, even if only IL-8 levels result significantly different in the BD spectrum, with higher levels in BD type I patients compared to BD type II and other unspecified BD (114). BD type I patients also show higher levels of the sTNF-R1 compared to BD type II patients (115). Although studies on the inflammatory differences between mood disorders and BD illness phase are currently too few to reach any conclusion, we cannot fail to notice that a difference in the inflammatory profile seems to exist.

More clinically relevant are some data on significantly different inflammatory profiles based on treatment response. In MDD patients, poorer medication response seems to be related to higher levels of circulating TNF-α (116), IL-6 (117, 118), IL-1 receptor (119), and acute-phase proteins (120). As previously suggested, these effects could both be due to the ability of cytokines to sabotage and circumvent mechanisms of action of conventional antidepressant agents on neurotransmitter function (121), and to their detrimental effects on synaptic plasticity and WM structure.

Concerning BD, one of the first predictive studies was performed by our group (122), showing a poorer antidepressant response to total sleep deprivation (TSD) treatment in those patients with higher baseline IL-6 serum levels. More recently, we investigated the predictive effect of a larger panel of cytokines, thus showing higher levels of proinflammatory IL-6, IL-8, IFN-γ, TNF-α, and MCP- 1 in TSD nonresponder patients compared to responders. Moreover, using individual component scores extracted from a principal component analysis performed on the five significant cytokines, we still find a negative effect of the factor scores on response to treatment (108).These data seem to support the key role of inflammatory factors, specifically proinflammatory cytokines, as biomarkers capable to differentiate between responder and not responder patients.

As further advances are made in this direction, we can hope to become able to identify a specific pattern of inflammatory alterations that allow early identification of treatment-resistant patients, to provide an effective tailored treatment as soon as possible.

CONCLUSIONS

Recent works have thoroughly supported the association between BD and a proinflammatory state which involves both the innate and the adaptive immune system. In particular, T helper-1 cells (Th1), known to mediate cellular immune reactions, which induce production of cytokines such as IL-1, IL- 2, IL-6, TNF-α and IFN-γ, and Th2 cells, and enhance antibody-mediated reactions and the

production of IL-4, IL-5, and IL-10, are heavily implicated. These results strongly suggest the existence of an inflammatory profile in BD patients during all phases of the disease. Indeed, compared to control subjects, BD patients show an increase in serum concentration of interleukins and CRP.

In a more specific way, Drexhage and colleagues demonstrated that BD patients and offspring share an inflammatory-genes mRNA overexpression signature that is detectable before illness onset (17, 18). Moreover, they state that inflammatory alterations occur not only in the periphery but also in the CNS, as demonstrated by microglial activation found both *in vivo* and postmortem in brains of BD patients (13, 14). This inflammatory condition can trigger a cascade of negative effects on brain structure and biology. In BD patients, cytokines levels and T cells percentage has been linked to WM structure alterations (55–57). These widespread alterations can also be linked to inflammatory-related oligodendrocyte dysfunction (46–49). WM modification has been related also to the tryptophan degradation cascade, that seems to be involved into the negative effect of an inflammatory condition (83). The increased levels of cytokines reduce the tryptophan-derived serotonin, increasing the production of tryptophan catabolites, which negatively impact on the neuroprotective ratio. These imbalances have been linked to an ineffective counter-regulating effect on the proinflammatory condition, and neurotoxicity (7, 78, 79). All these data seem to suggest that the immunological alteration concerning microglial, cytokines, and T cells, can represent a common etiological marker that partially explains the majority of the different modification founded as characteristics of BD.

Recently, another possible explanation has been explored in the relationship between the inflammatory profile and the hypothalamic-pituitary-adrenal axis (HPA) axis. Cytokines are capable of crossing the BBB and to act on various CNS areas, including this axis (7). HPA axis dysfunctions, together with elevated levels of proinflammatory cytokines can influence neuronal plasticity with a negative impact on mood symptoms and cognition. Moreover, higher levels of inflammatory cytokines may act by stimulating the HPA axis as a physiological response to stress (9). Taken together, this evidence goes on to highlight once again the notion that stress and synaptic plasticity might somehow be involved in the pathogenesis of mood disturbances, and especially BD.

Perhaps more interestingly, the role of inflammation in BD pathophysiology offers a new therapeutic approach, as targeting a reduction in the proinflammatory state of these patients might prove fruitful. Indeed, some research conducted with antiinflammatory drugs on other mood disorders, particularly MDD, has already shown a moderate degree of success (123–125), and their application in BD is attractive. Recent studies show that the characterization of peripheral inflammatory markers can lead to discriminate between responding and not responding to treatment patients, with the augmented levels of peripheral proinflammatory cytokines marks poorer antidepressant response (108, 122). We can, therefore, speculate that an early inflammatory characterization of BD patients, in particular of those patients that show higher immunological imbalance, can help to address a more tailored treatment to improve therapeutic efficacy. Further research is still needed to better understand the pathophysiological relation between inflammation and BD, to find new therapeutic approaches. Ongoing and future clinical studies with antiinflammatory agents will enlighten us on their therapeutic margin and help provide more arrows in our quiver against BD.

Regarding biological findings on peripheral markers, the vast difference and inconsistency among techniques used for analysis must be taken into consideration. If cytometry immunoprofilation does provide a wider idea on the main immune system features, showing with a high degree of precision which cell type is releasing particular cytokines and chemokines, a simple quantification like those performed using commercially available Elisa or panels won't be able to provide a clear and dependable overview of a patient's immune profile. Moreover, such biological data needs to be analyzed in larger multifactorial studies, with as many biomarkers as possible, for us to be able to understand the relations between the different factors involved in BD etiology and maintenance.

AUTHOR CONTRIBUTIONS

All individuals included as authors of papers contributed substantially to the scientific process leading up to the writing of the review. FB and RF designed the paper structure. VA, MP, and GG wrote the first draft of the manuscript. FB and RF supervised and revised the final version of the manuscript. All authors take final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00071/full#supplementary-material

REFERENCES

1. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry* (2007) 64(5):543–52. doi: 10.1001/archpsyc.64.5.543
2. Dong D, Wang Y, Chang X, Chen X, Chang X, Luo C, et al. Common and diagnosis-specific fractional anisotropy of white matter in schizophrenia, bipolar disorder, and major depressive disorder: evidence from comparative voxel-based meta-analysis. *Schizophr Res* (2018) 193:456–8. doi: 10.1016/j.schres.2017.07.003
3. Benedetti F, Bollettini I. Recent findings on the role of white matter pathology in bipolar disorder. *Harv Rev Psychiatry* (2014) 22(6):338–41. doi: 10.1097/HRP.0000000000000007
4. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, et al. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Mol Psychiatry* (2017) 22(10):1455–63. doi: 10.1038/mp.2016.72

5. Chepenik LG, Wang F, Spencer L, Spann M, Kalmar JH, Womer F, et al. Structure-function associations in hippocampus in bipolar disorder. *Biol Psychol* (2012) 90(1):18–22. doi: 10.1016/j.biopsycho.2012.01.008
6. Shattuck EC, Muehlenbein MP. Towards an integrative picture of human sickness behavior. *Brain Behav Immunity* (2016) 57:255–62. doi: 10.1016/j.bbi.2016.05.002
7. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* (2008) 9(1):46–56. doi: 10.1038/nrn2297
8. Kridin K, Zelber-Sagi S, Comaneshter D, Cohen AD. Bipolar disorder associated with another autoimmune disease-pemphigus: a population-based study. *Can J Psychiatry Rev Can Psychiatr* (2018) 63(7):474–80. doi: 10.1177/0706743717740344
9. Rosenblat JD, McIntyre RS. bipolar disorder and immune dysfunction: epidemiological findings, proposed pathophysiology and clinical implications. *Brain Sci* (2017) 7(11):110–44. doi: 10.3390/brainsci7110144
10. Wang LY, Chen SF, Chiang JH, Hsu CY, Shen YC. Systemic autoimmune diseases are associated with an increased risk of obsessive-compulsive disorder: a nationwide population-based cohort study. *Soc Psychiatry Psychiatr Epidemiol* (2018). 54(4):507–16. doi: 10.1007/s00127-018-1622-y
11. Schwartz M, Baruch K. The resolution of neuroinflammation in neurodegeneration: leukocyte recruitment *via the* choroid plexus. *EMBO J* (2014) 33(1):7–22. doi: 10.1002/embj.201386609
12. Schwartz M, Baruch K. Breaking peripheral immune tolerance to CNS antigens in neurodegenerative diseases: boosting autoimmunity to fight-off chronic neuroinflammation. *J Autoimmun* (2014) 54:8–14. doi: 10.1016/j.jaut.2014.08.002
13. Haarman BC, Riemersma-Van der Lek RF, de Groot JC, Ruhe HG, Klein HC, Zandstra TE, et al. Neuroinflammation in bipolar disorder - a [(11)C]-(R)-PK11195 positron emission tomography study. *Brain Behav Immun* (2014) 40:219–25. doi: 10.1016/j.bbi.2014.03.016
14. Haarman BC, Burger H, Doorduin J, Renken RJ, Sibeijn-Kuiper AJ, Marsman JB, et al. Volume, metabolites and neuroinflammation of the hippocampus in bipolar disorder - a combined magnetic resonance imaging and positron emission tomography study. *Brain Behav Immunity* (2016) 56:21–33. doi: 10.1016/j.bbi.2015.09.004
15. Grosse L, Hoogenboezem T, Ambree O, Bellingrath S, Jorgens S, de Wit HJ, et al. Deficiencies of the T and natural killer cell system in major depressive disorder: T regulatory cell defects are associated with inflammatory monocyte activation. *Brain Behav Immun* (2016) 54:38–44. doi: 10.1016/j.bbi.2015.12.003
16. Drexhage RC, Hoogenboezem TH, Versnel MA, Berghout A, Nolen WA, Drexhage HA. The activation of monocyte and T cell networks in patients with bipolar disorder. *Brain Behav Immun* (2011) 25(6):1206–13. doi: 10.1016/j.bbi.2011.03.013
17. Padmos RC, Hillegers MH, Knijff EM, Vonk R, Bouvy A, Staal FJ, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry* (2008) 65(4):395–407. doi: 10.1001/archpsyc.65.4.395
18. Padmos RC, Van Baal GC, Vonk R, Wijkhuijs AJ, Kahn RS, Nolen WA, et al. Genetic and environmental influences on pro-inflammatory monocytes in bipolar disorder: a twin study. *Arch Gen Psychiatry* (2009) 66(9):957–65. doi: 10.1001/archgenpsychiatry.2009.116
19. Ortiz-Dominguez A, Hernandez ME, Berlanga C, Gutierrez-Mora D, Moreno J, Heinze G, et al. Immune variations in bipolar disorder: phasic differences. *Bipolar Disord* (2007) 9(6):596–602. doi: 10.1111/j.1399-5618.2007.00493.x
20. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol* (2015) 16(5):448–57. doi: 10.1038/ni.3153
21. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord* (2007) 104(1-3):91–5. doi: 10.1016/j.jad.2007.02.018
22. Munkholm K, Brauner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. *J Psychiatr Res* (2013) 47(9):1119–33. doi: 10.1016/j.jpsychires.2013.05.018
23. Balkwill F. TNF-alpha in promotion and progression of cancer. *Cancer Metastasis Rev* (2006) 25(3):409–16. doi: 10.1007/s10555-006-9005-3
24. O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. *J Affect Disord* (2006) 90(2-3):263–7. doi: 10.1016/j.jad.2005.11.015
25. Hung YJ, Hsieh CH, Chen YJ, Pei D, Kuo SW, Shen DC, et al. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. *Clin Endocrinol* (2007) 67(5):784–9. doi: 10.1111/j.1365-2265.2007.02963.x
26. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord* (2009) 116(3):214–7. doi: 10.1016/j.jad.2008.12.001
27. Barbosa IG, Huguet RB, Mendonca VA, Sousa LP, Neves FS, Bauer ME, et al. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* (2011) 261(2):139–43. doi: 10.1007/s00406-010-0116-z
28. Dargel AA, Godin O, Kapczinski F, Kupfer DJ, Leboyer M. C-reactive protein alterations in bipolar disorder: a meta-analysis. *J Clin Psychiatry* (2015) 76(2):142–50. doi: 10.4088/JCP.14r09007
29. Fernandes BS, Steiner J, Molendijk ML, Dodd S, Nardin P, Goncalves CA, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* (2016) 3 (12):1147–56. doi: 10.1016/S2215-0366(16)30370-4
30. Gibson-Smith D, Bot M, Paans NP, Visser M, Brouwer I, Penninx BW. The role of obesity measures in the development and persistence of major depressive disorder. *J Affect Disord* (2016) 198:222–9. doi: 10.1016/j.jad.2016.03.032
31. Jacoby AS, Munkholm K, Vinberg M, Pedersen BK, Kessing LV. Cytokines, brain-derived neurotrophic factor and C-reactive protein in bipolar I disorder - Results from a prospective study. *J Affect Disord* (2016) 197:167–74. doi: 10.1016/j.jad.2016.03.040
32. Liu HC, Yang YY, Chou YM, Chen KP, Shen WW, Leu SJ. Immunologic variables in acute mania of bipolar disorder. *J Neuroimmunol* (2004) 150 (1-2):116–22. doi: 10.1016/j.jneuroim.2004.01.006
33. Bai YM, Su TP, Li CT, Tsai SJ, Chen MH, Tu PC, et al. Comparison of pro-inflammatory cytokines among patients with bipolar disorder and unipolar depression and normal controls. *Bipolar Disord* (2015) 17 (3):269–77. doi: 10.1111/bdi.12259
34. Uyanik V, Tuglu C, Gorgulu Y, Kunduracilar H, Uyanik MS. Assessment of cytokine levels and hs-CRP in bipolar I disorder before and after treatment. *Psychiatry Res* (2015) 228(3):386–92. doi: 10.1016/j.psychres.2015.05.078
35. Kunz M, Cereser KM, Goi PD, Fries GR, Teixeira AL, Fernandes BS, et al. Serum levels of IL-6, IL-10 and TNF-alpha in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. *Rev Bras Psiquiatr* (2011) 33(3):268–74. doi: 10.1590/S1516-44462011000300010
36. Barbosa IG, Rocha NP, Bauer ME, de Miranda AS, Huguet RB, Reis HJ, et al. Chemokines in bipolar disorder: trait or state? *Eur Arch Psychiatry Clin Neurosci* (2013) 263(2):159–65. doi: 10.1007/s00406-012-0327-6
37. Brietzke E, Kauer-Sant'Anna M, Teixeira AL, Kapczinski F. Abnormalities in serum chemokine levels in euthymic patients with bipolar disorder. *Brain Behav Immun* (2009) 23(8):1079–82. doi: 10.1016/j.bbi.2009.04.008
38. Ghafouri-Fard S, Oskooei VK, Omrani MD, Taheri M. Dysregulation of cytokine coding genes in peripheral blood of bipolar patients. *J Affect Disord* (2019) 256:578–83. doi: 10.1016/j.jad.2019.06.028
39. Benedetti F, Bollettini I. Recent findings on the role of white matter pathology in bipolar disorder. >*Harv Rev Psychiatry* (2014) 22(6):338–41. doi: 10.1097/HRP.0000000000000007
40. Duarte JA, de Araujo ESJQ, Goldani AA, Massuda R, Gama CS. Neurobiological underpinnings of bipolar disorder focusing on findings of diffusion tensor imaging: a systematic review. *Rev Bras Psiquiatr* (2016) 38 (2):167–75. doi: 10.1590/1516-4446-2015-1793
41. Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, et al. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. *Biol Psychiatry* (2011) 69(4):309–17. doi: 10.1016/j.biopsych.2010.07.028
42. Pezzoli S, Emsell L, Yip SW, Dima D, Giannakopoulos P, Zarei M, et al. Meta-analysis of regional white matter volume in bipolar disorder with replication in an independent sample using coordinates, T-maps, and

individual MRI data. *Neurosci Biobehav Rev* (2018) 84:162–70. doi: 10.1016/j.neubiorev.2017.11.005
43. Kieseppa T, Mantyla R, Tuulio-Henriksson A, Luoma K, Mantere O, Ketokivi M, et al. White matter hyperintensities and cognitive performance in adult patients with bipolar I, bipolar II, and major depressive disorders. *Eur Psychiatry* (2014) 29(4):226–32. doi: 10.1016/j.eurpsy.2013.08.002
44. Wadhwa R, Wen W, Frankland A, Leung V, Sinbandhit C, Stuart A, et al. White matter hyperintensities in young individuals with bipolar disorder or at high genetic risk. *J Affect Disord* (2018) 245:228–36. doi: 10.1016/j.jad.2018.10.368
45. Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. *Acta Neuropathol* (2010) 119(1):37–53. doi: 10.1007/s00401-009-0601-5
46. Manji HK, Moore GJ, Rajkowska G, Chen G. Neuroplasticity and cellular resilience in mood disorders. *Mol Psychiatry* (2000) 5(6):578–93. doi: 10.1038/sj.mp.4000811
47. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res* (2004) 67(2-3):269–75. doi: 10.1016/S0920-9964(03)00181-6
48. Ongur D, Bechtholt AJ, Carlezon WAJr., Cohen BM. Glial abnormalities in mood disorders. *Harv Rev Psychiatry* (2014) 22(6):334–7. doi: 10.1097/HRP.0000000000000060
49. Konradi C, Sillivan SE, Clay HB. Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis. *Neurobiol Dis* (2012) 45(1):37–47. doi: 10.1016/j.nbd.2011.01.025
50. Bellani M, Boschello F, Delvecchio G, Dusi N, Altamura CA, Ruggeri M, et al. DTI and myelin plasticity in bipolar disorder: integrating neuroimaging and neuropathological findings. *Front Psychiatry* (2016) 7:21. doi: 10.3389/fpsyt.2016.00021
51. Scheld M, Fragoulis A, Nyamoya S, Zendedel A, Denecke B, Krauspe B, et al. Mitochondrial impairment in oligodendroglial cells induces cytokine expression and signaling. *J Mol Neurosci* (2018) 67(2):265–75. doi: 10.1007/s12031-018-1236-6
52. Kierdorf K, Prinz M. Factors regulating microglia activation. *Front Cell Neurosci* (2013) 7:44. doi: 10.3389/fncel.2013.00044
53. Cherry JD, Olschowka JA, O'Banion MK. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. *J Neuroinflammation* (2014) 11:98. doi: 10.1186/1742-2094-11-98
54. Pascual O, Ben Achour S, Rostaing P, Triller A, Bessis A. Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. *Proc Natl Acad Sci U S A* (2012) 109(4):E197–205. doi: 10.1073/pnas.1111098109
55. Benedetti F, Poletti S, Hoogenboezem TA, Mazza E, Ambree O, de Wit H, et al. Inflammatory cytokines influence measures of white matter integrity in Bipolar Disorder. *J Affect Disord* (2016) 202:1–9. doi: 10.1016/j.jad.2016.05.047
56. Poletti S, de Wit H, Mazza E, Wijkhuijs AJ, Locatelli C, Aggio V, et al. Th17 cells correlate positively to the structural and functional integrity of the brain in bipolar depression and healthy controls. *Brain Behav Immun* (2017) 61:317–25. doi: 10.1016/j.bbi.2016.12.020
57. Magioncalda P, Martino M, Tardito S, Sterlini B, Conio B, Marozzi V, et al. White matter microstructure alterations correlate with terminally differentiated CD8+ effector T cell depletion in the peripheral blood in mania: combined DTI and immunological investigation in the different phases of bipolar disorder. *Brain Behav Immunity* (2018) 73:192–204. doi: 10.1016/j.bbi.2018.04.017
58. Patel JP, Frey BN. Disruption in the blood-brain barrier: the missing link between brain and body inflammation in bipolar disorder? *Neural Plast* (2015) 2015:708306. doi: 10.1155/2015/708306
59. Zhang Y, Catts VS, Sheedy D, McCrossin T, Kril JJ, Shannon Weickert C. Cortical grey matter volume reduction in people with schizophrenia is associated with neuro-inflammation. *Transl Psychiatry* (2016) 6(12):e982. doi: 10.1038/tp.2016.238
60. Drevets WC, Price JL, Simpson JRJ, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* (1997) 38:824–7. doi: 10.1038/386824a0
61. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. *Trends Cognit Sci* (2012) 16(1):61–71. doi: 10.1016/j.tics.2011.12.011
62. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci U S A* (1998) 95(22):13290–5. doi: 10.1073/pnas.95.22.13290
63. Rajkowska G. Cell pathology in bipolar disorder. *Bipolar Disord* (2002) 4(2):105–16. doi: 10.1034/j.1399-5618.2002.01149.x
64. Eker C, Simsek F, Yilmazer EE, Kitis O, Cinar C, Eker OD, et al. Brain regions associated with risk and resistance for bipolar I disorder: a voxel-based MRI study of patients with bipolar disorder and their healthy siblings. *Bipolar Disord* (2014). 16(3):249–61. doi: 10.1111/bdi.12181
65. Benedetti F, Radaelli D, Poletti S, Locatelli C, Falini A, Colombo C, et al. Opposite effects of suicidality and lithium on gray matter volumes in bipolar depression. *J Affect Disord* (2011) 135(1-3):139–47. doi: 10.1016/j.jad.2011.07.006
66. Chen MH, Chang WC, Hsu JW, Huang KL, Tu PC, Su TP, et al. Correlation of proinflammatory cytokines levels and reduced gray matter volumes between patients with bipolar disorder and unipolar depression. *J Affect Disord* (2018) 245:8–15. doi: 10.1016/j.jad.2018.10.106
67. Lesh TA, Careaga M, Rose DR, McAllister AK, Van de Water J, Carter CS, et al. Cytokine alterations in first-episode schizophrenia and bipolar disorder: relationships to brain structure and symptoms. *J Neuroinflammation* (2018) 15(1):165. doi: 10.1186/s12974-018-1197-2
68. Benedetti F, Poletti S, Hoogenboezem TA, Locatelli C, Ambree O, de Wit H, et al. Stem Cell Factor (SCF) is a putative biomarker of antidepressant response. *J Neuroimmune Pharmacol* (2016) 11(2):248–58. doi: 10.1007/s11481-016-9672-y
69. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther* (2006) 110(2):135–370. doi: 10.1016/j.pharmthera.2005.11.006
70. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol* (2015) 23(1):1–21. doi: 10.1037/a0038550
71. Salomon RM, Miller HL, Krystal JH, Heninger GR, Charney DS. Lack of behavioral effects of monoamine depletion in healthy subjects. *Biol Psychiatry* (1997) 41(1):58–64. doi: 10.1016/0006-3223(95)00670-2
72. Ashok AH, Marques TR, Jauhar S, Nour MM, Goodwin GM, Young AH, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. *Mol Psychiatry* (2017) 22(5):666–79. doi: 10.1038/mp.2017.16
73. Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav Immunity* (2011) 25(2):181–213. doi: 10.1016/j.bbi.2010.10.015
74. Nurnberger JIJr., Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, et al. Melatonin suppression by light in euthymic bipolar and unipolar patients. *Arch Gen Psychiatry* (2000) 57(6):572–9. doi: 10.1001/archpsyc.57.6.572
75. Manji HK, Quiroz JA, Payne JL, Singh J, Lopes BP, Viegas JS, et al. The underlying neurobiology of bipolar disorder. *World Psychiatry* (2003) 2(3):136–46.
76. Mahmood T, Silverstone T. Serotonin and bipolar disorder. *J Affect Disord* (2001) 66(1):1–11. doi: 10.1016/S0165-0327(00)00226-3
77. Anderson G, Jacob A, Bellivier F, Geoffroy PA. Bipolar disorder: the role of the kynurenine and melatonergic pathways. *Curr Pharm Des* (2016) 22(8):987–1012. doi: 10.2174/1381612822666151214105314
78. Mandi Y, Vecsei L. The kynurenine system and immunoregulation. *J Neural Transm (Vienna)* (2012) 119(2):197–209. doi: 10.1007/s00702-011-0681-y
79. Davis I, Liu A. What is the tryptophan kynurenine pathway and why is it important to neurotherapeutics? *Expert Rev Neurother* (2015) 15(7):719–21. doi: 10.1586/14737175.2015.1049999
80. Erhardt S, Schwieler L, Imbeault S, Engberg G. The kynurenine pathway in schizophrenia and bipolar disorder. *Neuropharmacology* (2017) 112(Pt B):297–306. doi: 10.1016/j.neuropharm.2016.05.020
81. Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. *J Affect Disord* (2007) 98(1-2):143–51. doi: 10.1016/j.jad.2006.07.013
82. Birner A, Platzer M, Bengesser SA, Dalkner N, Fellendorf FT, Queissner R, et al. Increased breakdown of kynurenine towards its neurotoxic branch in

bipolar disorder. *PLoS One* (2017) 12(2):e0172699. doi: 10.1371/journal.pone.0172699
83. Poletti S, Myint AM, Schuetze G, Bollettini I, Mazza E, Grillitsch D, et al. Kynurenine pathway and white matter microstructure in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* (2018) 268(2):157–68. doi: 10.1007/s00406-016-0731-4
84. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry* (2014) 171(8):829–43. doi: 10.1176/appi.ajp.2014.13081008
85. Felger JC. The role of dopamine in inflammation-associated depression: mechanisms and therapeutic implications. *Curr Top Behav Neurosci* (2017) 31:199–219. doi: 10.1007/7854_2016_13
86. Dallaspezia S, Benedetti F. Chronobiology of bipolar disorder: therapeutic implication. *Curr Psychiatry Rep* (2015) 17(8):606. doi: 10.1007/s11920-015-0606-9
87. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry* (2008) 165(7):820–9. doi: 10.1176/appi.ajp.2008.08010098
88. McClung CA. How might circadian rhythms control mood? Let me count the ways. *Biol Psychiatry* (2013) 74(4):242–9. doi: 10.1016/j.biopsych.2013.02.019
89. Acuna-Castroviejo D, Rahim I, Acuna-Fernandez C, Fernandez-Ortiz M, Solera-Marin J, Sayed RKA, et al. Melatonin, clock genes and mitochondria in sepsis. *Cell Mol Life Sci* (2017) 74(21):3965–87. doi: 10.1007/s00018-017-2610-1
90. Morris G, Stubbs B, Kohler CA, Walder K, Slyepchenko A, Berk M, et al. The putative role of oxidative stress and inflammation in the pathophysiology of sleep dysfunction across neuropsychiatric disorders: focus on chronic fatigue syndrome, bipolar disorder and multiple sclerosis. *Sleep Med Rev* (2018) 41:255–65. doi: 10.1016/j.smrv.2018.03.007
91. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating human antigen presenting cells regulated by sleep. *Sleep* (2007) 30(4):401–11. doi: 10.1093/sleep/30.4.401
92. Fernandes GL, Araujo P, Tufik S, Andersen ML. The role of IL-6 and STAT in sleep and neuroinflammation. *Clin Immunol* (2017) 180:58–9. doi: 10.1016/j.clim.2017.04.004
93. Hurtado-Alvarado G, Becerril-Villanueva E, Contis-Montes de Oca A, Dominguez-Salazar E, Salinas-Jazmin N, Perez-Tapia SM, et al. The ying/yang of inflammatory status: Blood-brain barrier regulation during sleep. *Brain Behav Immun* (2017) 69:154–66. doi: 10.1016/j.bbi.2017.11.009
94. Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab* (2005) 90(5):2522–30. doi: 10.1210/jc.2004-1667
95. Barbosa IG, Rocha NP, de Miranda AS, Magalhaes PV, Huguet RB, de Souza LP, et al. Increased levels of adipokines in bipolar disorder. *J Psychiatr Res* (2012) 46(3):389–93. doi: 10.1016/j.jpsychires.2011.11.010
96. Fagiolini A, Chengappa KN, Soreca I, Chang J. Bipolar disorder and the metabolic syndrome: causal factors, psychiatric outcomes and economic burden. *CNS Drugs* (2008) 22(8):655–69. doi: 10.2165/00023210-200822080-00004
97. Soczynska JK, Kennedy SH, Woldeyohannes HO, Liauw SS, Alsuwaidan M, Yim CY, et al. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. *Neuromol Med* (2011) 13(2):93–116. doi: 10.1007/s12017-010-8140-8
98. Elmslie JL, Porter RJ, Joyce PR, Hunt PJ, Shand BI, Scott RS. Comparison of insulin resistance, metabolic syndrome and adiponectin in overweight bipolar patients taking sodium valproate and controls. *Aust New Z J Psychiatry* (2009) 43(1):53–60. doi: 10.1080/00048670802534341
99. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Weight gain and serum leptin levels in patients on lithium treatment. *Neuropsychobiology* (2002) 46(2):67–9. doi: 10.1159/000065414
100. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Bayik Y. Serum leptin and cholesterol levels in patients with bipolar disorder. *Neuropsychobiology* (2002) 46(4):176–9. doi: 10.1159/000067809
101. Tsai SY, Lee HC, Chen CC. Hyperinsulinaemia associated with beta-adrenoceptor antagonist in medicated bipolar patients during manic episode. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) 31(5):1038–43. doi: 10.1016/j.pnpbp.2007.03.003
102. Thomson D, Turner A, Lauder S, Gigler ME, Berk L, Singh AB, et al. A brief review of exercise, bipolar disorder, and mechanistic pathways. *Front Psychol* (2015) 6:147. doi: 10.3389/fpsyg.2015.00147
103. Hallberg L, Janelidze S, Engstrom G, Wisen AG, Westrin A, Brundin L. Exercise-induced release of cytokines in patients with major depressive disorder. *J Affect Disord* (2010) 126(1-2):262–7. doi: 10.1016/j.jad.2010.02.133
104. Mazza E, Poletti S, Bollettini I, Locatelli C, Falini A, Colombo C, et al. Body mass index associates with white matter microstructure in bipolar depression. *Bipolar Disord* (2017) 19(2):116–27. doi: 10.1111/bdi.12484
105. Chatzigeorgiou A, Chavakis T. Immune cells and metabolism. *Handb Exp Pharmacol* (2016) 233:221–49. doi: 10.1007/164_2015_8
106. Baldeon RL, Weigelt K, de Wit H, Ozcan B, van Oudenaren A, Sempertegui F, et al. Decreased serum level of miR-146a as sign of chronic inflammation in type 2 diabetic patients. *PLoS One* (2014) 9(12):e115209. doi: 10.1371/journal.pone.0115209
107. Calkin CV, Ruzickova M, Uher R, Hajek T, Slaney CM, Garnham JS, et al. Insulin resistance and outcome in bipolar disorder. *Br J Psychiatry* (2015) 206(1):52–7. doi: 10.1192/bjp.bp.114.152850
108. Benedetti F, Poletti S, Hoogenboezem TA, Locatelli C, de Wit H, Wijkhuijs AJM, et al. Higher baseline proinflammatory cytokines mark poor antidepressant response in bipolar disorder. *J Clin Psychiatry* (2017) 78(8):e986–e93. doi: 10.4088/JCP.16m11310
109. Bollettini I, Poletti S, Locatelli C, Vai B, Smeraldi E, Colombo C, et al. Disruption of white matter integrity marks poor antidepressant response in bipolar disorder. *J Affect Disord* (2015) 174:233–40. doi: 10.1016/j.jad.2014.11.010
110. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* (2011) 36(12):2452–9. doi: 10.1038/npp.2011.132
111. Mao R, Zhang C, Chen J, Zhao G, Zhou R, Wang F, et al. Different levels of pro- and anti-inflammatory cytokines in patients with unipolar and bipolar depression. *J Affect Disord* (2018) 237:65–72. doi: 10.1016/j.jad.2018.04.115
112. Mota R, Gazal M, Acosta BA, de Leon PB, Jansen K, Pinheiro RT, et al. Interleukin-1beta is associated with depressive episode in major depression but not in bipolar disorder. *J Psychiatr Res* (2013) 47(12):2011–4. doi: 10.1016/j.jpsychires.2013.08.020
113. Chang HH, Wang TY, Lee IH, Lee SY, Chen KC, Huang SY, et al. C-reactive protein: a differential biomarker for major depressive disorder and bipolar II disorder. *World J Biol Psychiatry* (2017) 18(1):63–70. doi: 10.3109/15622975.2016.1155746
114. Wang TY, Lee SY, Chen SL, Chung YL, Li CL, Chang YH, et al. The Differential levels of inflammatory cytokines and BDNF among bipolar spectrum disorders. *Int J Neuropsychopharmacol* (2016) 19(8):1–8. doi: 10.1093/ijnp/pyw012
115. Bai YM, Su TP, Tsai SJ, Wen-Fei C, Li CT, Pei-Chi T, et al. Comparison of inflammatory cytokine levels among type I/type II and manic/hypomanic/euthymic/depressive states of bipolar disorder. *J Affect Disord* (2014) 166:187–92. doi: 10.1016/j.jad.2014.05.009
116. Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* (2008) 32(2):445–50. doi: 10.1016/j.pnpbp.2007.09.015
117. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. *Prog Neuropsychopharmacol Biol Psychiatry* (2009) 33(4):722–6. doi: 10.1016/j.pnpbp.2009.03.020
118. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* (2000) 22(4):370–9. doi: 10.1016/S0893-133X(99)00134-7
119. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* (1997) 9(11):853–8. doi: 10.1006/cyto.1997.0238

120. Sluzewska A, Sobieska M, Rybakowski JK. Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiology*> (1997) 35(3):123–7. doi: 10.1159/000119332
121. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* (2009) 65(9):732–41. doi: 10.1016/j.biopsych.2008.11.029
122. Benedetti F, Lucca A, Brambilla F, Colombo C, Smeraldi E. Interleukine-6 serum levels correlate with response to antidepressant sleep deprivation and sleep phase advance. *Prog Neuro-Psychopharmacol Biol Psychiatry* (2002) 26 (6):1167–70. doi: 10.1016/S0278-5846(02)00255-5
123. Abbasi SH, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. *J Affect Disord* (2012) 141(2-3):308–14. doi: 10.1016/j.jad.2012.03.033
124. Muller N. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. *Curr Opin Invest Drugs* (2010) 11(1):31–42.
125. Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry* (2006) 11(7):680–4. doi: 10.1038/sj.mp.4001805

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REVIEW
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Autoimmune Diseases and Psychotic Disorders

*Rose Jeppesen and Michael Eriksen Benros**

Mental Health Centre Copenhagen, Gentofte Hospital, Copenhagen University Hospital, Hellerup, Denmark

The notion of immunological pathways playing a role in the etiology of a subset of psychotic disorders has received increased interest in the last decades. One of the findings that has spiked interest herein, is an apparent link between autoimmune diseases and psychotic disorders. This is supported by genetic findings associating immune-related genetic markers with schizophrenia and clinical studies finding increased levels of inflammatory markers in patients with psychosis. Several large-scale epidemiologic studies have found positive associations between autoimmune diseases and psychosis. Particularly, autoimmune diseases as multiple sclerosis and lupus are known to have higher frequencies of neuropsychiatric symptoms, including psychosis, compared to healthy controls. Cross sectional studies have found higher prevalence of psychiatric diagnoses among those with autoimmune diseases, and longitudinal studies have shown bidirectional associations between several autoimmune diseases and increased risks associated with schizophrenia. Moreover, a family history of autoimmune diseases has been shown to be associated with an increased risk of psychotic disorders and vice versa. In this review we will summarize the epidemiologic evidence on associations between autoimmune diseases and psychosis. Possible mechanisms accountable for the association will be discussed, amongst others the probable role of shared genetic risk factors, the impact of infections on both autoimmunity and the development of psychotic disorders, and the potential role of the microbiome. We discuss the findings on and influence of autoantibodies and dysregulation of T- and B-cells in both disease categories, and why further research hereon is needed. In addition to the potential importance of autoimmunity in etiological mechanisms of psychotic disorders, the association also brings important attention to somatic comorbidity in patients with psychotic disorders.

Keywords: autoimmune, immune system, psychosis, schizophrenia, mental illness

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Marion Leboyer,
Université Paris-Est Créteil Val de Marne, France

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Stefania Schiavone,
University of Foggia, Italy
Konrad Prasad,
University of Pittsburgh, United States

****Correspondence:***
Michael Eriksen Benros
benros@dadlnet.dk

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INTRODUCTION

The association between immunological processes and mental disorders was observed by doctors centuries before the immune system was discovered. Psychosis arising either with the occurrence or disappearance of acute fever has been described by many scientists from Hippocrates around 400 BC to Kraepelin around 1900. In the 1930s it was first hypothesized by Hermann Lehmann-Facius that schizophrenia was the product of an autoimmune reaction with antibodies attacking brain tissue (1). In the 1950s and 1960s it was noticed that celiac disease seemed to occur more often within those suffering from schizophrenia than in the general population (2), and conversely, that schizophrenia occurred less frequently within patients with rheumatoid arthritis (3, 4). Additionally, autoantibodies cross-reacting with brain antigens were found in patients

with schizophrenia back in the 1960s (5, 6), and interest in anti-neuronal antibodies in psychotic disorders has increased during the last couple of decades, with an increasing number of reports on previously unknown antibodies with brain reactivity in patients suffering from psychosis (7–9).

The amount of evidence supporting the notion of a link between immunological processes and psychotic disorders has increased. Elevated levels of inflammatory markers have been found both in the blood (10, 11) and CSF (12–14) of patients with psychosis, with even higher levels in patients in first episode psychosis or acute relapse. Furthermore, some have found association between higher levels of inflammation in childhood and adolescence and increased risk of psychotic disorders (15, 16), elevated inflammatory biomarkers has been associated with lack of treatment response (17), and anti-inflammatory treatment has been found to have especially beneficial effect in an inflamed subgroup of patients (18–21). Moreover, it has been suggested that schizophrenia could be an autoimmune disease, based on similarities such as the remitting-relapsing phenotype of the illness, as well as the above-mentioned immunological processes (22).

Research in the field of psychoneuroimmunology is still evolving, with many different aspects being investigated. The notion of a role of the immune system in psychotic disorders seems evident, and understanding the link between autoimmune diseases and mental disorders may shed light on possible etiological mechanisms herein. Understanding how the immune system and psychotic illness interact can improve our understanding of psychosis and give rise to a wide range of new treatment options in psychiatry; amongst other the possibility to identify subgroups of patients with psychotic disorders and ongoing inflammatory processes that could benefit from more targeted treatment. Additionally, it is very important for clinicians to be aware of somatic comorbidities, particularly in patients with psychotic disorders, in order to improve detection and treatment, and thus the course of illness.

EPIDEMIOLOGICAL ASSOCIATIONS

The world-wide prevalence of schizophrenia is known to be around 1% (23) and the prevalence of autoimmune diseases have been found in a Danish nationwide study to be 4% (24). The vast majority of epidemiological studies have found a general association between autoimmunity and psychotic disorders (24–29). In large-scale register-based studies from Denmark, 6% of those diagnosed with schizophrenia also had a hospital contact related to an autoimmune disease during follow-up (25, 26), and a Taiwanese study found that 3.4% of persons with a hospital contact for autoimmune diseases also had a hospital contact related to schizophrenia (29). A Danish study based on 7704 patients with schizophrenia, found an increased prevalence by about 45% of the occurrence of an autoimmune disease (28), which was later confirmed in a Taiwanese population-based study (27). Regarding the risk of psychosis after an autoimmune disease diagnosis, a Danish nationwide study found this to be increased by 45%, which diminished to a 29% increased risk when excluding the effect of infections (26), and a very recent meta-analysis by Cullen et al. (30) found that a diagnosis of a non-neurological autoimmune disease increased the risk of later being diagnosed with a psychotic disorder by 43%.

Additionally, being diagnosed with schizophrenia increases the lifetime prevalence of autoimmune diseases. Two Danish register-based studies found that individuals with psychotic disorders had a subsequently elevated risk for autoimmune diseases by around 50% (25, 28). Supporting this, the recent meta-analysis found that the risk of having an autoimmune disease was 55% higher among those with a prior diagnosis of a psychotic disorder (30).

Autoimmune diseases and psychosis are not only associated on an individual level. Having a first degree relative with schizophrenia has also been found to increase the risk of autoimmune diseases with 6% (25), and a family history of autoimmunity has been found to increase risk of both schizophrenia and non-affective psychoses with 10% (24).

The associations with psychotic disorders have been found for a broad range of autoimmune diseases. For an overview of the associations between specific autoimmune diseases with psychotic disorders, please see **Table 1** and the below sections.

Celiac Disease

The original findings from the 1950s of an association between celiac disease and schizophrenia has since been explored further. During the next decades it was noticed that populations with lower consumption of wheat had lower incidence rates of schizophrenia (34–36), and small studies have since found beneficial effect on psychotic symptoms of a gluten-free diet in patients suffering from both celiac disease and schizophrenia (37, 38). One epidemiological study found no significant correlation between celiac disease and psychosis (24). However, another large-scale study found a 2.11-times increased risk of schizophrenia (26) and the recent meta-analysis also found an association with an elevated risk of schizophrenia with 53% (30). Additionally, it has been found in a Taiwanese population, that the risk of celiac disease is increased when suffering from schizophrenia (29). When discussing epidemiological studies using health records, it is important to note that celiac disease might be majorly underdiagnosed particularly within those who have already debuted with psychotic symptoms. In summary, most studies found a positive association between celiac disease and psychotic disorders.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease associated with many neuropsychiatric symptoms, such as depression and anxiety (39). It has been found that 4% of patients with MS experiences psychosis (40), a prevalence much higher than that of the general population. Danish register-based studies have found that having MS increases the risk of schizophrenia with up to 44% (24, 26), with an even further increase in risk when having both MS and a prior hospital contact due to infection (26). Two studies found increased risk of schizophrenia with up to 30% in individuals with a family history of MS; however, they found no associations on an individual level (24, 28), and a

TABLE 1 | Associations found between autoimmune diseases and psychotic disorders.

Autoimmune disorders	Studies with positive association	Positive ass. only with concurrent infection	Studies with no significant association	Studies with negative association
Celiac disease	Chen et al (29), Cullen et al. (30), Benros et al. (26)		Benros et al. (25)	
Multiple sclerosis	Benros et al. (25), Benros et al. (26)		Wang et al. (27), Eaton et al. (28), Eaton et al. (24)	Johansson et al. (31)
Lupus	Wang et al. (27)	Benros et al. (26)	Cullen et al. (30), Benros et al. (25), Chen et al. (29), Eaton et al. (28), Eaton et al. (24)	
Graves/thyrotoxicosis	Chen et al. (29), Cullen et al. (30), Eaton et al. (28), Eaton et al. (24), Benros et al. (26)		Benros et al. (25)	
Autoimmune thyroiditis		Benros et al. (26)	Eaton et al. (28), Benros et al. (25)	
Diabetes type 1	Benros et al. (25), Eaton et al. (24), Benros et al. (26)		Chen et al. (29), Cullen et al. (30), Cremaschi et al. (32)	Juvonen et al. (33)
Rheumatoid arthritis	Wang et al. (27)	Benros et al. (26)	Eaton et al. (28), Eaton et al. (24)	Benros et al. (25), Chen et al. (29), Cullen et al. (30)
Psoriasis	Benros et al. (25), Chen et al. (29), Cullen et al. (30), Eaton et al. (24), Benros et al. (26)		Eaton et al. (28),	
Guillain-Barre	Benros et al. (25)	Benros et al. (26)	Eaton et al. (28),	
Crohns disease	Benros et al. (25)	Benros et al. (26)	Wang et al. (27), Cullen et al. (30), Eaton et al. (24)	
Autoimmune hepatitis	Benros et al. (25), Eaton et al. (28), Eaton et al. (24), Benros et al. (26)			
Pernicious anemia	Benros et al. (25), Cullen et al. (30), Chen et al. (29)			
Primary adrenocortical insufficiency	Benros et al. (25),			
Primary biliary cirrhosis	Benros et al. (25),			
Ankylosing spondylitis	Eaton et al. (24)	Benros et al. (26)	Benros et al. (25), Chen et al. (29), Eaton et al. (28)	Cullen et al. (30)
Sjögren syndrome	Eaton et al. (28)	Benros et al. (26)	Benros et al. (25), Chen et al. (29)	
Hypersensitivity vasculitis	Chen et al. (29)			
Haemolytic anemia	Eaton et al. (28)		Chen et al. (29)	
Pemphigoid	Cullen et al. (30)		Eaton et al. (28)	
Alopecia areata	Eaton et al. (28)		Benros et al. (25), Cullen et al. (30), Chen et al. (29)	
Polymylagia rheumatic	Eaton et al. (28)		Benros et al. (25), Chen et al. (29)	

study from Taiwan only found a trend toward an increased risk of schizophrenia in those with a diagnosis of MS (27). On the risk of a subsequent MS diagnosis in patients with schizophrenia, contradictory results have been found between a Danish and a Swedish nationwide study, finding the risk to be respectively increased by 57% (25) and decreased by 40% (31). Current evidence of an association between MS and psychotic disorders is limited with studies showing conflicting results. Many, especially sensory, symptoms of multiple sclerosis might be misinterpreted as part of the patients' psychotic disorders, complicating the diagnostic process, and psychotic symptoms in people with MS might not be diagnosed since they are considered to be delirium in relation to acute MS exacerbations.

Lupus

Systemic Lupus Erythematosus (SLE) is another autoimmune disease known to have a high degree of neuropsychiatric problems, such as depression and anxiety, occurring in between 21 and 95% of patients (41). However, it has been estimated that only 13–38%, are directly attributable to SLE, whereas the remaining is suggested to be due to for example treatment complications (41). Regarding psychosis in SLE, the prevalence ranges from 2.3 to 11% in studies (42–44). A study from England comprising 458 patients with SLE, found that only 2.3% experienced psychosis (42), while a higher prevalence of psychosis have been found in a black Caribbean study population (366 patients, 7% with psychosis) (43) and in a Brazilian population (520 patients, 11% with psychosis) (44). In those experiencing psychosis, this was one of the initial symptoms of SLE in up to 60% of these patients (42). In population-based studies, a nationwide Taiwanese study found an increased risk of schizophrenia among those with SLE (27), and in one Danish study the presence of both SLE and a prior hospital contact with infection resulted in an increased risk of schizophrenia (26).

None of the other epidemiological studies have found significant association between psychotic disorders and SLE (24, 25, 28, 30), but noteworthy, the number of cases available was very small in all studies, limiting the significance of possible findings. In summary, large scale studies with a greater number of cases have been able to find positive associations between SLE and psychotic disorders, while smaller studies have failed to do so.

Autoimmune Thyroid Disorders

Graves' disease, the most common cause of hyperthyroidism, is also known to be linked to neuropsychiatric issues, and some even present with psychotic disorders (45). A German study found that in a cohort of 100 patients with a schizophreniform illness, 19 had increases antithyroid autoantibodies in sera, and 13 showed signs of intrathecal synthesis hereof (46). In epidemiological studies, both Graves' disease and thyrotoxicosis have been linked with an increased risk of schizophrenia (24, 26, 30). Additionally, the prevalence hereof has been found to be increased among individuals with schizophrenia (28, 29), though this finding has not been replicated in all studies (25, 32). Hence, most studies indicate a positive association between Graves' disease/thyrotoxicosis and psychotic disorders.

No studies has been able to show a significant association between autoimmune thyroiditis and schizophrenia on an individual level (24, 28), but one Danish study found an increased incidence among parents and siblings of patients with schizophrenia (28).

Diabetes Type 1

Diabetes mellitus type 1 is a disease characterized by the presence of glutamic acid decarboxylase (GAD) antibodies. These autoantibodies have been linked with neurological problems (47), and thus have shown ability to cross the blood brain barrier, making them an interesting topic in the discussion of pathophysiological mechanisms. However, conflicting results have been found regarding the association of type 1 diabetes and psychotic disorders. Two Danish studies found an increased risk of schizophrenia when suffering from type 1 diabetes (24, 26), and one found an increased risk of type 1 diabetes after having been diagnosed with schizophrenia (25). This, however, was not replicated neither in a Swedish cohort (32), a Taiwanese cohort (29) nor in the recent meta-analysis (30), and a Finnish study even found a negative association (33). In summary, there does not seem to be a clear association between type 1 Diabetes and psychosis.

Rheumatoid Arthritis

A disease which has consistently been found to be negatively associated with schizophrenia is rheumatoid arthritis (RA). This apparent "protective" effect of schizophrenia on the development of rheumatoid arthritis was investigated as early as the 1950s (48, 49). The negative association between the two has since been backed by epidemiological studies, finding decreased risk of schizophrenia in those with RA (30) and vice versa (25, 29, 50, 51). However, some studies did not find associations (24, 52), and regarding the association on the risk of psychosis after a RA diagnosis, more controversy exist, with a Danish study finding that a combined history of a hospital contact due to infection and RA increased the risk of schizophrenia (26) and a new Taiwanese study finding an increased risk of developing schizophrenia in individuals with a history of RA (27). Moreover, a Danish study found an increased prevalence of RA in the family of those with schizophrenia (28). One explanation of the consistent finding of negative association with subsequent RA diagnosis after a schizophrenia diagnosis could be that RA tends to be underdiagnosed in those suffering from psychotic disorder, and in concordance with this, both a Swedish and Danish nationwide study has shown that the same negative association can be found with other musculoskeletal diseases (50, 51).

Autoimmune Encephalitis

Something that really spiked the interest in autoimmunity as a player in mental illness, was the discovery of autoimmune encephalitis. As a group, these diseases are characterized by the presence of neuronal surface antibodies (NSAbs) and symptoms include psychiatric and cognitive alterations, seizures and movement disorders, with the most commonly affected part of the brain being the limbic system. The most discussed antibody in psychotic disorders at the moment is the N-methyl-D-aspartate receptor (NMDA-R) antibody. It has been reported that as many as 74% of patients suffering from NMDA-R encephalitis experience psychotic symptoms (53, 54), and a recent smaller study found that 13% were initially admitted to the hospital with a psychiatric diagnosis (55). Multiple studies have investigated the frequency of NMDA-R antibodies in schizophrenia, but so far most have only had access to serum not CSF, most have had no healthy control group, and results have varied markedly (56).

Other Autoimmune Diseases

Associations have been found between psychotic disorders and other autoimmune diseases as well. The incidence of psoriasis have been found to be significantly increased in individuals with schizophrenia (25, 29), but not in all studies (28). Increased incidence of psoriasis have also been found in individuals with a family history of schizophrenia (28). In addition, the risk of developing schizophrenia has been found in multiple studies to be increased in those with a history of psoriasis (24, 26, 30), with an additional increase when combined with a prior hospital contact due to an infection (26). The risk of developing Guillain-Barré syndrome, an autoimmune disease attacking peripheral nerves, has been found to be increased markedly in individuals with schizophrenia (25), and when having both a history of a hospital contact with an infection as wells as Guillain-Barré, the risk of developing schizophrenia has also been found to be increased (26). However, one other study found no association (28). Autoimmune hepatitis has been found to be greatly associated with psychotic disorders as well, with both individual history and family history hereof increasing the risk of schizophrenia (24, 26), and schizophrenia increasing the risk of autoimmune hepatitis (25). Some evidence of an association between schizophrenia and Crohn's disease has also been found (25, 26), though no significantly increased risk was shown in two other studies (24, 27) or the recent meta-analysis (30).

POSSIBLE MECHANISMS

The potential etiological background and the many factors that can influence the association between autoimmune diseases and psychosis are numerous and not mutually exclusive as outlined in the following sections. For an overview hereof, see **Figure 1**.

Antibodies

One potential contributing factor to the link between some autoimmune diseases with mental illness, can be the presence of neuronal surface antibodies (NSAbs). GAD-antibodies have been linked with multiple neurological problems (47), and in neuropsychiatric lupus, an increased amount of antibodies was found both in serum and CSF compared to lupus with no neuropsychiatric manifestation (57). Furthermore, gliadin antibodies, associated with celiac disease, have been found to be increased in the serum of patients with recent onset schizophrenia (58). With the discovery of NMDA-receptor encephalitis, and its ability to mimic mental disorders, the interest spiked further, and with GAD-antibodies being able to induce limbic encephalitis (59, 60) and antibodies reacting with the NR2 subunit of NMDA being present in some cases of lupus (61), a possible link emerged.

Many studies have sought to evaluate the presence of multiple different NSAbs in mental illness, but so far, consistency in methods and assays have limited the generalization of the findings (56, 62). Many studies have lacked a healthy control group to compare their results with, and most studies have included serum but not CSF samples. The relevance of circulating NSAbs in serum is still unknown, and therefore comprehensive studies including healthy controls evaluating antibodies in both CSF and serum is needed to increase knowledge further.

Dysregulated Immune System

A dysregulated balance between regulatory T cells and Th17 cells have been described to be essential for immunological homeostasis and have been implicated in the development of several autoimmune disorders (63). Signs of a dysregulated immune system has also been found in mental illnesses and might play a role in the association found between the two.

A meta-analysis found that levels of several lymphocytes differed when examining patients with schizophrenia compared to healthy controls (64), and studies have linked decreased regulatory T cells with negative symptoms and cognitive deficits (65), as well as increased levels of Th17 with psychopathology (66).

In recent years, B cells have received increasing attention in the pathology of autoimmunity, and have been implicated to play a big role in for example MS, where it has also been found that anti B-cell antigen (anti-CD20) have great efficacy in the treatment hereof (67). It has been shown that oligoclonal bands (OCBs) in the CSF, something which is found in approximately 90% of patients with MS, is a sign of ongoing stimulation and maturation of antibody-expressing B-cells (68). Interestingly, a recent meta-analysis found that OCBs were found in the CSF of up to 12.5% of patients with schizophrenia (14).

Another frequent finding in patients with schizophrenia is increased levels of pro-inflammatory and decreased levels of anti-inflammatory cytokines in serum (10). Dysregulation of the anti-inflammatory cytokine IL-10 has been found to be linked with abnormal responses to common infections, and to increase the risk of developing autoimmune diseases (69).

Infections as a Common Risk Factor

It is thought that one of the most important triggers for developing autoimmune diseases is infection (70), and it is known that infectious encephalitis, specifically with herpes-simplex virus, markedly increases the risk of developing NMDA-receptor encephalitis (71). As it was shown in a large Danish nationwide study, prior infection increased the risk of developing schizophrenia in a dose-response fashion (26), and this finding has been repeated in other large studies (72, 73). The effect of infection on risk of schizophrenia was present regardless of autoimmune diseases, but additionally, a significant synergy was found in those with both a history of autoimmunity and infections (26). For many of the individual autoimmune diseases, it was seen that the effect on the risk of schizophrenia increased when a prior hospital contact due to infection was also present (26).

Being exposed to viral or bacterial infection is known to increase the permeability of the blood-brain-barrier (BBB) (74), which allows the entering into the central nervous system of immune cells and pro-inflammatory cytokines. This in itself might allow an inflammatory state in the brain, which has been theorized to play a role in the development of psychotic disorders. It may also explain the synergistic effect on risk of schizophrenia of having both an autoimmune disease and prior infections, as BBB disruption might also allow the entering of circulating antibodies. Supporting the role hereof, signs of a disrupted BBB has been found in patient with schizophrenia with evidence of increased albumin CSF:plasma ratio (75, 76) and increased levels of circulating s100-b (77).

It has also been found that infections during pregnancy increases the risk of schizophrenia in the offspring (78). On the basis hereof, it has been considered whether infections during the prenatal phase might prime the immune system, making it more vulnerable and perhaps more likely to produce abnormal responses to later infections, resulting in increased inflammation. However, a new study have shown that even maternal infections before and after pregnancy increases the risk of mental illness (79), which could also indicate a genetic susceptibility for infections associated with mental illness.

Genetics

Both schizophrenia and autoimmune diseases are known to be highly hereditable. The most consistent finding in genetic studies of patients with schizophrenia, are differences in genes known to be linked to the immune system (80), and several genetic loci that increases the risk of autoimmune diseases has been located (81). As with schizophrenia, some of the discovered genetic loci in autoimmune diseases are located in the MHC region (82). However, while one study found significant overlap in genes between MS and schizophrenia (but not MS and bipolar disorder)

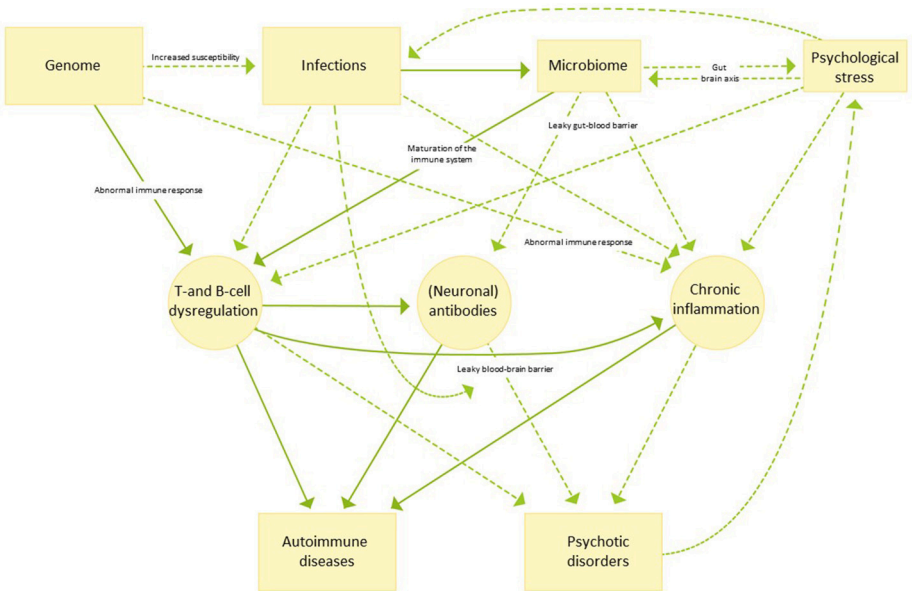

FIGURE 1 | An illustrative overview of possible etiological mechanisms linking autoimmune disease and psychotic disorders. Continuous arrows indicate pathways for which evidence is strong, while dotted arrows indicate pathways which are currently not well understood or more speculative in nature.

(83), another study found no genetic association between 25 different autoimmune diseases and schizophrenia (84). Genetic pleiotropy has also been hypothesized to account for the negative association found between RA and schizophrenia, with genes found to be associated with schizophrenia possibly decreasing the risk of RA (85).

Another possible role of genetics in the association of autoimmune diseases and psychotic disorders could be a hereditary susceptibility for shared risk factors. It has been hypothesized that some of the genetic findings associated with schizophrenia might increase the risk of having infections (86, 87), that then subsequently increase the risk of both autoimmune diseases and psychotic disorders. Additionally, it has been theorized whether some individuals with schizophrenia, might have a genetic predisposition for an abnormal immune response to common infections and foreign pathogens, for example via differences in the HLA region and complement system (88, 89), which in turn could increase the risk of developing autoimmune reactions. The complement system has also been implicated to play a role in neurodevelopment and -maturation (90), and evidence of altered complement activity in patients with schizophrenia have been found (reviewed in (88)).

The Microbiome

The gastro-intestinal tract of humans contains vast amounts of bacteria, phyla and other microorganisms, their genes collectively known as the microbiome, containing at least 100 times more genetic material than the human genome (91). This area has received great attention in the research of many different illnesses in the last years and have been implicated as a possible etiological factor in both neuropsychiatric illnesses and autoimmune diseases. As early as 1953, interest in gastro-intestinal inflammation in psychosis was raised, when a group of researchers found in an autopsy study that out of 82 patients with schizophrenia, 50% had gastritis, 88% enteritis and 92% colitis (92). This study has not since been replicated, but other signs of microbiome dysbiosis in this group of patients has been found with significant difference between cases and controls in the presence of both bacteria and fungi (93), and bacteriophages (94). Studies so far have mainly focused on the oropharyngeal microbiome due to practical limitations. One study however, has looked into fecal microbiome, finding no significant difference between healthy controls and patients, but showing associations between microbiome composition and symptom severity and outcome (95).

The composition of the microbiome has been hypothesized to be very important in the development of both the central nervous system (96) and the immune system (97, 98). Dysbiosis of the microbiome has been shown to affect both the Th1/Th2 balance and the ratio of T regulatory and Th17 cells, impacting the immune response to foreign pathogens (99). Dysbiosis have been found to influence the T-cell mediated inflammation in MS patients (100, 101), and has also been suspected to play a part in the development of celiac disease (102), as well as non-gastro-intestinal autoimmune diseases (103). In rodents, disruption of the microbiome has been found to impair social functioning (104), behavior and cognition (105), and induce neurodevelopmental disorders (106).

An important function of the microbiome, seems to be its effect on the epithelial cells in the GI wall, with evidence implicating that the composition of the microbiome is important for the tightness of the gut-blood barrier (107). Severance et al. (108) found markers in the serum of patients with schizophrenia

indicating increased permeability, also known as "leaky gut." A leaky gut allows the entrance of foreign pathogens and antigens into the blood. It has been suspected to induce systemic inflammation, and in mice it has been found to even result in neuroinflammation (109), both of which might increase the risk of mental illness and autoimmune diseases.

Interestingly, both infections and the treatment hereof with antibiotics can modulate the microbiome, linking the previously mentioned epidemiological findings of the influence of infections (26) with the microbiome theory. Additionally, it has been theorized that maternal infection might alter both the maternal and fetal microbiome (110), possibly impacting the immune system and neuropsychiatric development of the offspring.

A few studies have tried probiotic treatment in patients with schizophrenia, but no evidence of effect hereof on psychopathology has yet been found (111, 112). However, further research on the actual composition of the microbiome in patients with mental illness as well as the possibility of using probiotics as treatment hereof is warranted.

Psychological Stress

Psychological stress such as sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying, both in childhood and later on, has been associated with increased risk of psychotic disorders in multiple studies (113, 114). A Swedish register-based study found that stress-related disorders increased the risk of subsequent development of autoimmune disorders (115) and, accordingly, in many other studies, stress have been found to be associated with disease onset and disease exacerbations in several autoimmune conditions (116).

Stress can theoretically influence many of the above-mentioned possible etiological factors. Acute psychological stress, even in brief episodes, have been found in a meta-analysis to increase circulating proinflammatory cytokines such as IL-6, IL-1β, and TNF-α (117), possibly via the sympathetic nerve system and the HPA axis, and multiple adverse life events or stressful living conditions might therefore possibly contribute to a more chronic inflammatory state with dysregulation of immune response (118).

Psychological stress have been thought to influence composition of the microbiome and vice versa, as well as the microbiome's effect on peripheral inflammation (119). Additionally, it has been hypothesized to increase susceptibility to infections, with one study finding that healthy subjects with higher scores on questionnaires on psychological stress were more prone to developing clinical cold and respiratory infections after exposure to respiratory viruses (120). Acute stress, for example as a result of a psychiatric disorder or hospitalization, may also lead to exacerbation in symptoms of autoimmune diseases, leading to the discovery of a disease formerly undiagnosed.

CLINICAL IMPLICATIONS

The increasing knowledge on the potential involvement of inflammatory processes in mental disorders and the associations found between autoimmunity and psychotic disorders can help the expanding field of immuno-psychiatry and have impact on the outcome of patients. In the last couple of years, researchers have focused on the role of infections, autoantibodies and other immune components that plays a major role in autoimmune diseases. Potentially this might also be the case for mental disorders. Risk factors for both autoimmune diseases and schizophrenia includes an interaction between environmental factors, such as infections and stress, with genetic factors involving the HLA region. Autoimmune reactions with activation of immune components and the production of NSAbs can induce a broad spectrum of psychiatric symptoms, hereunder psychosis. The potential autoimmune-mediated psychosis group might only be a small part of a broader immune-related psychosis group, and an even smaller fraction of the overall psychosis group. However, identification of this subgroup might allow for precision medicine strategies where immune-based treatment could possibly improve the psychotic symptoms. A quick discovery and treatment of autoimmune encephalitis markedly reduces the neuropsychiatric sequelae, and intensive immunotherapy in lupus patients with psychosis massively benefits psychiatric symptoms (42, 121).

Focus on the association between autoimmunity and psychosis, regardless of etiology, is important, not only for researchers but also for the individual patient. It is known that patients suffering from schizophrenia have an excess early mortality, with a life expectancy up to 13.5 years shorter than the general population, primarily due to physical diseases (122). Bearing this in mind and considering that patients with psychotic disorders might struggle with reporting on somatic symptoms, it is important for clinicians to be aware of an increased prevalence of autoimmune disease in this group. Symptoms from a disease such as celiac disease or rheumatoid arthritis might very well be overlooked and cast aside as a part of the patient's psychosis, or possibly adverse events caused by their treatment. With increasingly sufficient treatment strategies in autoimmune diseases, overlooking and therefore not treating these diseases, increases the health gap between those with schizophrenia and the general population even further. Therefore, patients with a psychotic disorder need to be thoroughly and frequently examined when presenting with symptoms possibly related to autoimmunity or other health problems.

AUTHOR CONTRIBUTIONS

RJ was responsible for literature search and wrote the first draft of the manuscript. MB contributed with supervision and expert advice and revised the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

1. Steinberg H, Kirkby K, Himmerich H. The historical development of immunoendocrine concepts of psychiatric disorders and their therapy. *Int J Mol Sci.* (2015) 16:28841–69. doi: 10.3390/ijms161226136
2. Bender L. Childhood schizophrenia. *Psychiatr Q.* (1953) 27:663–81.
3. Pilkington TL. The coincidence of rheumatoid arthritis and schizophrenia. *J Nerv Ment Dis.* (1956) 124:604–6. doi: 10.1097/00005053-195612000-00007
4. Trevathan RD, Tatum JC. Rarity of concurrence of psychosis and rheumatoid arthritis in individual patients; report of a case. *J Nerv Ment Dis.* (1954) 120:83–4.
5. Fessel WJ. Autoimmunity and mental illness. *Arch Gen Psychiatry.* (1962) 6:320. doi: 10.1001/archpsyc.1962.01710220062008
6. Heath RG, Krupp IM. Schizophrenia as an immunologic disorder. *Arch Gen Psychiatry.* (1967) 16:1. doi: 10.1001/archpsyc.1967.01730190003001
7. Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol.* (2011) 258:686–8. doi: 10.1007/s00415-010-5788-9
8. Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein H-G, Vielhaber S, et al. Increased prevalence of diverse N -Methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia. *JAMA Psychiatry.* (2013) 70:271. doi: 10.1001/2013.jamapsychiatry.86
9. Pollak TA, Rogers JP, Nagele RG, Peakman M, Stone JM, David AS, et al. Antibodies in the diagnosis, prognosis, and prediction of psychotic disorders. *Schizophr Bull.* (2018) 45:233–246. doi: 10.1093/schbul/sby021
10. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry.* (2011) 70:663–71. doi: 10.1016/j.biopsych.2011.04.013
11. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry.* (2016) 21:1696–709. doi: 10.1038/mp.2016.3
12. Bechter K, Reiber H, Herzog S, Fuchs D, Tumani H, Maxeiner HG. Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: identification of subgroups with immune responses and blood–CSF barrier dysfunction. *J Psychiatr Res.* (2010) 44:321–30. doi: 10.1016/j.jpsychires.2009.08.008
13. Cavanagh J, Klados MA, Tebartz Van Elst L, Endres D, Perlov E, Baumgartner A, et al. Immunological findings in psychotic syndromes: a tertiary care hospital's CSF sample of 180 patients. (2015) 9:476. doi: 10.3389/fnhum.2015.00476
14. Orlovska-Waast S, Köhler-Forsberg O, Brix SW, Nordentoft M, Kondziella D, Krogh J, et al. Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. *Mol Psychiatry.* (2018) doi: 10.1038/s41380-018-0220-4. [Epub ahead of print].
15. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA psychiatry.* (2014) 71:1121–8. doi: 10.1001/jamapsychiatry.2014.1332
16. Metcalf SA, Jones PB, Nordstrom T, Timonen M, Mäki P, Miettunen J, et al. Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: a prospective birth cohort study. *Brain Behav Immun.* (2017) 59:253–9. doi: 10.1016/j.bbi.2016.09.008
17. Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophr Bull.* (2015) 41:1162–70. doi: 10.1093/schbul/sbv028
18. Girgis RR, Ciarleglio A, Choo T, Haynes G, Bathon JM, Cremers S, et al. A randomized, double-blind, placebo-controlled clinical trial of tocilizumab, an interleukin-6 receptor antibody, for residual symptoms in schizophrenia. *Neuropsychopharmacology.* (2018) 43:1317–23. doi: 10.1038/npp.2017.258
19. Vincenzi B, Stock S, Borba CPC, Cleary SM, Oppenheim CE, Petruzzi LJ, et al. A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: Effect on inflammation, psychopathology, cognition and lipid metabolism. *Schizophr Res.* (2014) 159:395–403. doi: 10.1016/j.schres.2014.08.021
20. Müller N, Ulmschneider M, Scheppach C, Schwarz MJ, Ackenheil M, Möller H-J, et al. COX-2 inhibition as a treatment approach in schizophrenia: Immunological considerations and clinical effects of celecoxib add-on therapy. *Eur Arch Psychiatry Clin Neurosci.* (2004) 254:14–22. doi: 10.1007/s00406-004-0478-1
21. Laan W, Grobbee DE, Selten J-P, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders. *J Clin Psychiatry.* (2010) 71:520–7. doi: 10.4088/JCP.09m05117yel
22. Al-Diwani AAJ, Pollak TA, Irani SR, Lennox BR. Psychosis: an autoimmune disease? *Immunology.* (2017) 152:388–401. doi: 10.1111/imm.12795
23. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* (2005) 2:e141. doi: 10.1371/journal.pmed.0020141
24. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar Disord.* (2010) 12:638–46. doi: 10.1111/j.1399-5618.2010.00853.x
25. Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. *Am J Psychiatry.* (2014) 171:218–26. doi: 10.1176/appi.ajp.2013.13010086
26. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry.* (2011) 168:1303–10. doi: 10.1176/appi.ajp.2011.11030516
27. Wang L-Y, Chen S-F, Chiang J-H, Hsu C-Y, Shen Y-C. Autoimmune diseases are associated with an increased risk of schizophrenia: a nationwide population-based cohort study. *Schizophr Res.* (2018). doi: 10.1016/j.schres.2018.06.033
28. Eaton WW, Byrne M, Ewald H, Mors O, Chen C-Y, Agerbo E, et al. Association of schizophrenia and autoimmune diseases: linkage of danish national registers. *Am J Psychiatry.* (2006) 163:521–8. doi: 10.1176/appi.ajp.163.3.521
29. Chen S-J, Chao Y-L, Chen C-Y, Chang C-M, Wu EC-H, Wu C-S, et al. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. *Br J Psychiatry.* (2012) 200:374–80. doi: 10.1192/bjp.bp.111.092098
30. Cullen AE, Holmes S, Pollak TA, Blackman G, Joyce DW, Kempton MJ, et al. Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis. *Biol Psychiatry.* (2018) 85:35–48. doi: 10.1016/j.biopsych.2018.06.016
31. Johansson V, Lundholm C, Hillert J, Masterman T, Lichtenstein P, Landén M, et al. Multiple sclerosis and psychiatric disorders: comorbidity and sibling risk in a nationwide Swedish cohort. *Mult Scler J.* (2014) 20:1881–91. doi: 10.1177/1352458514540970
32. Cremaschi L, Kardell M, Johansson V, Isgren A, Sellgren CM, Altamura AC, et al. Prevalences of autoimmune diseases in schizophrenia, bipolar I and II disorder, and controls. *Psychiatry Res.* (2017) 258:9–14. doi: 10.1016/j.psychres.2017.09.071
33. Juvonen H, Reunanen A, Haukka J, Muhonen M, Suvisaari J, Arajärvi R, et al. Incidence of schizophrenia in a nationwide cohort of patients with type 1 diabetes mellitus. *Arch Gen Psychiatry.* (2007) 64:894–9. doi: 10.1001/archpsyc.64.8.894
34. Dohan FC. Wheat "consumption" and hospital admissions for schizophrenia during world war II. a preliminary report. *Am J Clin Nutr.* (1966) 18:7–10. doi: 10.1093/ajcn/18.1.7
35. Dohan F. CŒLIAC DISEASE AND SCHIZOPHRENIA. *Lancet.* (1970) 295:897–8. doi: 10.1016/S0140-6736(70)91729-0
36. Dohan FC, Harper EH, Clark MH, Rodrigue RB, Zigas V. Is schizophrenia rare if grain is rare? *Biol Psychiatry.* (1984) 19:385–99.
37. Singh MM, Kay SR. Wheat gluten as a pathogenic factor in schizophrenia. *Science.* (1976) 191:401–2.
38. Jackson J, Eaton W, Cascella N, Fasano A, Warfel D, Feldman S, et al. A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies. *Schizophr Res.* (2012) 140:262–3. doi: 10.1016/j.schres.2012.06.011

39. Murphy R, O'Donoghue S, Counihan T, McDonald C, Calabresi PA, Ahmed MA, et al. Neuropsychiatric syndromes of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. (2017) 88:697–708. doi: 10.1136/jnnp-2016-315367
40. Marrie RA, Fisk JD, Tremlett H, Wolfson C, Warren S, Tennakoon A, et al. CIHR team in the epidemiology and impact of comorbidity on multiple sclerosis. differences in the burden of psychiatric comorbidity in MS vs the general population. *Neurology*. (2015) 85:1972–9. doi: 10.1212/WNL.0000000000002174
41. Tay SH, Mak A. Diagnosing and attributing neuropsychiatric events to systemic lupus erythematosus: time to untie the Gordian knot? *Rheumatology*. (2016) 56:i14–24. doi: 10.1093/rheumatology/kew338
42. Pego-Reigosa JM, Isenberg DA. Psychosis due to systemic lupus erythematosus: characteristics and long-term outcome of this rare manifestation of the disease. *Rheumatology (Oxford)*. (2008) 47:1498–502. doi: 10.1093/rheumatology/ken260
43. Flower C, Hambleton I, Corbin D, Marquez S, Edghill R. The spectrum of neuropsychiatric lupus in a black caribbean population: a report of the Barbados National Lupus Registry. *Lupus*. (2017) 26:1034–41. doi: 10.1177/0961203317692431
44. Appenzeller S, Cendes F, Costallat LTL. Acute psychosis in systemic lupus erythematosus. *Rheumatol Int*. (2008) 28:237–43. doi: 10.1007/s00296-007-0410-x
45. Golub D, Rodack V. Antipsychotics in hyperthyroid-related psychosis: case report and systematic review. *Neuro Endocrinol Lett*. (2018) 39:65–74.
46. Endres D, Dersch R, Hochstuhl B, Fiebich B, Hottenrott T, Perlov E, et al. Intrathecal thyroid autoantibody synthesis in a subgroup of patients with schizophreniform syndromes. *J Neuropsychiatry Clin Neurosci*. (2017) 29:365–74. doi: 10.1176/appi.neuropsych.16110296
47. Baizabal-Carvallo JF, Alonso-Juarez M. Cerebellar disease associated with anti-glutamic acid decarboxylase antibodies: review. *J Neural Transm*. (2017) 124:1171–82. doi: 10.1007/s00702-017-1754-3
48. Trevathan R, Tatum JC. Rarity of concurrence of psychosis and rheumatoid arthritis in individual patients; report of a case. *J Nerv Mental Dis*. (1954) 120:83–4.
49. Bender L. Childhood schizophrenia. *Psychiatr Q*. (1953) 27:663–81. doi: 10.1007/BF01562517
50. Sellgren C, Frisell T, Lichtenstein P, Landen M, Askling J. The association between schizophrenia and rheumatoid arthritis: a nationwide population-based swedish study on intraindividual and familial risks. *Schizophr Bull*. (2014) 40:1552–9. doi: 10.1093/schbul/sbu054
51. Mors O, Mortensen PB, Ewald H. A population-based register study of the association between schizophrenia and rheumatoid arthritis. *Schizophr Res*. (1999) 40:67–74.
52. Marrie RA, Hitchon CA, Walld R, Patten SB, Bolton JM, Sareen J, et al. Increased burden of psychiatric disorders in rheumatoid arthritis. *Arthritis Care Res*. (2018) 70:970–8. doi: 10.1002/acr.23539
53. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain J Neurol*. (2010) 133:1655–67. doi: 10.1093/brain/awq113
54. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti– *N* -Methyl-d -aspartate receptor encephalitis. *JAMA Neurol*. (2013) 70:1133. doi: 10.1001/jamaneurol.2013.3216
55. Baumgartner A, Rauer S, Hottenrott T, Leypoldt F, Ufer F, Hegen H, et al. Admission diagnoses of patients later diagnosed with autoimmune encephalitis. *J Neurol*. (2018) 266:124–132. doi: 10.1007/s00415-018-9105-3
56. Pollak TA, McCormack R, Peakman M, Nicholson TR, David AS. Prevalence of anti-N-methyl-d-aspartate (NMDA) receptor antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. *Psychol Med*. (2014) 44:2475–87. doi: 10.1017/S003329171300295X
57. Ho RC, Thiaghu C, Ong H, Lu Y, Ho CS, Tam WW, et al. A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus. *Autoimmun Rev*. (2016) 15:124–38. doi: 10.1016/j.autrev.2015.10.003
58. Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Leister F, et al. Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia. *Biol Psychiatry*. (2010) 68:100–4. doi: 10.1016/j.biopsych.2010.03.021
59. Matà S, Muscas GC, Naldi I, Rosati E, Paladini S, Cruciatti B, et al. Non-paraneoplastic limbic encephalitis associated with anti-glutamic acid decarboxylase antibodies. *J Neuroimmunol*. (2008) 199:155–9. doi: 10.1016/j.jneuroim.2008.05.015
60. Malter MP, Helmstaedter C, Urbach H, Vincent A, Bien CG. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. *Ann Neurol*. (2010) 67:470–8. doi: 10.1002/ana.21917
61. DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat Med*. (2001) 7:1189–93. doi: 10.1038/nm1101-1189
62. Al-Diwani A, Pollak TA, Langford AE, Lennox BR. Synaptic and neuronal autoantibody-associated psychiatric syndromes: controversies and hypotheses. *Front psychiatry*. (2017) 8:13. doi: 10.3389/fpsyt.2017.00013
63. Diller ML, Kudchadkar RR, Delman KA, Lawson DH, Ford ML. Balancing inflammation: the link between Th17 and regulatory T Cells. *Mediators Inflamm*. (2016) 2016:6309219. doi: 10.1155/2016/6309219
64. Miller BJ, Gassama B, Sebastian D, Buckley P, Mellor A. Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*. (2013) 73:993–9. doi: 10.1016/j.biopsych.2012.09.007
65. Fernandez-Egea E, Vértes PE, Flint SM, Turner L, Mustafa S, Hatton A, et al. Peripheral immune cell populations associated with cognitive deficits and negative symptoms of treatment-resistant schizophrenia. *PLoS ONE*. (2016) 11:e0155631. doi: 10.1371/journal.pone.0155631
66. Ding M, Song X, Zhao J, Gao J, Li X, Yang G, et al. Activation of Th17 cells in drug naïve, first episode schizophrenia. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2014) 51:78–82. doi: 10.1016/j.pnpbp.2014.01.001
67. Disanto G, Morahan JM, Barnett MH, Giovannoni G, Ramagopalan S V. The evidence for a role of B cells in multiple sclerosis. *Neurology*. (2012) 78:823–32. doi: 10.1212/WNL.0b013e318249f6f0
68. Bankoti J, Apeltsin L, Hauser SL, Allen S, Albertolle ME, Witkowska HE, et al. In multiple sclerosis, oligoclonal bands connect to peripheral B-cell responses. *Ann Neurol*. (2014) 75:266–76. doi: 10.1002/ana.24088
69. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Crit Rev Immunol*. (2012) 32:23–63. doi: 10.1615/CritRevImmunol.v32.i1.30
70. Getts DR, Chastain EML, Terry RL, Miller SD. Virus infection, antiviral immunity, and autoimmunity. *Immunol Rev*. (2013) 255:197–209. doi: 10.1111/imr.12091
71. Armangue T, Spatola M, Vlagea A, Mattozzi S, Cárceles-Cordon M, Martinez-Heras E, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol*. (2018) 17:760–72. doi: 10.1016/S1474-4422(18)30244-8
72. Nielsen PR, Benros ME, Mortensen PB. Hospital contacts with infection and risk of schizophrenia: a population-based cohort study with linkage of Danish national registers. *Schizophr Bull*. (2014) 40:1526–32. doi: 10.1093/schbul/sbt200
73. Nielsen PR, Laursen TM, Agerbo E. Comorbidity of schizophrenia and infection: a population-based cohort study. *Soc Psychiatry Psychiatr Epidemiol*. (2016) 51:1581–9. doi: 10.1007/s00127-016-1297-1
74. Chaudhuri JD. Blood brain barrier and infection. *Med Sci Monit*. (2016) 6:1213–22.
75. Melkersson K, Bensing S. Signs of impaired blood-brain barrier function and lower IgG synthesis within the central nervous system in patients with schizophrenia or related psychosis, compared to that in controls. *Neuro Endocrinol Lett*. (2018) 39:33–42.
76. Severance EG, Gressitt KL, Alaedini A, Rohleder C, Enning F, Bumb JM, et al. IgG dynamics of dietary antigens point to cerebrospinal fluid barrier or flow dysfunction in first-episode schizophrenia. *Brain Behav Immun*. (2015) 44:148–58. doi: 10.1016/j.bbi.2014.09.009
77. Aleksovska K, Leoncini E, Bonassi S, Cesario A, Boccia S, Frustaci A. Systematic review and meta-analysis of circulating S100B blood levels in schizophrenia. *PLoS ONE*. (2014) 9:e106342. doi: 10.1371/journal.pone.0106342

78. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med.* (2013) 43:239–57. doi: 10.1017/S0033291712000736
79. Lydholm CN, Köhler-Forsberg O, Nordentoft M, Yolken RH, Mortensen PB, Petersen L, Benros ME. Parental infections before, during, and after pregnancy as risk factors for mental disorders in childhood and adolescence: a nationwide danish study. *Biol Psychiatry.* (2018) 85:317–25. doi: 10.1016/j.biopsych.2018.09.013
80. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* (2014) 511:421–7. doi: 10.1038/nature13595
81. Feero WG, Guttmacher AE, Cho JH, Gregersen PK. Genomic medicine genomics and the multifactorial nature of human autoimmune disease. *N Engl J Med.* (2011) 365:1612–23. doi: 10.1056/NEJMra1100030
82. Lie BA, Thorsby E. Several genes in the extended human MHC contribute to predisposition to autoimmune diseases. *Curr Opin Immunol.* (2005) 17:526–31. doi: 10.1016/J.COI.2005.07.001
83. Andreassen OA, Harbo HF, Wang Y, Thompson WK, Schork AJ, Mattingsdal M, et al. Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. *Mol Psychiatry.* (2015) 20:207–14. doi: 10.1038/mp.2013.195
84. Hoeffding LK, Rosengren A, Thygesen JH, Schmock H, Werge T, Hansen T. Evaluation of shared genetic susceptibility loci between autoimmune diseases and schizophrenia based on genome-wide association studies. *Nord J Psychiatry.* (2017) 71:20–5. doi: 10.1080/08039488.2016.1198420
85. Malavia TA, Chaparala S, Wood J, Chowdari K, Prasad KM, McClain L, et al. Generating testable hypotheses for schizophrenia and rheumatoid arthritis pathogenesis by integrating epidemiological, genomic, and protein interaction data. *NPJ Schizophr.* (2017) 3:11. doi: 10.1038/s41537-017-0010-z
86. Avramopoulos D, Pearce BD, Mcgrath J, Wolyniec P, Wang R, Eckart N. Infection and inflammation in schizophrenia and bipolar disorder: a genome wide study for interactions with genetic variation. *PLoS ONE.* (2015) 10:116696. doi: 10.1371/journal.pone.0116696
87. Bamne M, Wood J, Chowdari K, Watson AM, Celik C, Mansour H, et al. Evaluation of HLA polymorphisms in relation to schizophrenia risk and infectious exposure. *Schizophr Bull.* (2012) 38:1149–54. doi: 10.1093/schbul/sbs087
88. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature.* (2016) 530:177–83. doi: 10.1038/nature16549
89. Nimgaonkar VL, Prasad KM, Chowdari KV, Severance EG, Yolken RH. The complement system: a gateway to gene–environment interactions in schizophrenia pathogenesis. *Mol Psychiatry.* (2017) 22:1554–61. doi: 10.1038/mp.2017.151
90. Prasad KM, Chowdari KV, D'Aiuto LA, Iyengar S, Stanley JA, Nimgaonkar VL. Neuropil contraction in relation to complement C4 gene copy numbers in independent cohorts of adolescent-onset and young adult-onset schizophrenia patients–a pilot study. *Transl Psychiatry.* (2018) 8:134. doi: 10.1038/s41398-018-0181-z
91. Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. *Science.* (2006) 312:1355–9. doi: 10.1126/science.1124234
92. Buscaino VM. "Patologia extraneurale della schizofrenia : fegato, tubo digerente, sistema reticolo-endoteliale," in *Acta Neurologica VIII.*, 1–60.
93. Castro-Nallar E, Bendall ML, Pérez-Losada M, Sabuncyan S, Severance EG, Dickerson FB, et al. Composition, taxonomy and functional diversity of the oropharynx microbiome in individuals with schizophrenia and controls. *PeerJ.* (2015) 3:e1140. doi: 10.7717/peerj.1140
94. Yolken RH, Severance EG, Sabunciyan S, Gressitt KL, Chen O, Stallings C, et al. Metagenomic sequencing indicates that the oropharyngeal phageome of individuals with schizophrenia differs from that of controls. *Schizophr Bull.* (2015) 41:1153–61. doi: 10.1093/schbul/sbu197
95. Schwarz E, Maukonen J, Hyytiäinen T, Kieseppä T, Orešič M, Sabunciyan S, et al. Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. *Schizophr Res.* (2018) 192:398–403. doi: 10.1016/j.schres.2017.04.017
96. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. *Cell.* (2016) 167:915–32. doi: 10.1016/j.cell.2016.10.027
97. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. *Nature.* (2011) 474:327–36. doi: 10.1038/nature10213
98. Rook G, Bäckhed F, Levin BR, Mcfall-Ngai MJ, Mclean AR. Evolution, human-microbe interactions, and life history plasticity. *Evolut Pub Health.* (2017) 390:521–30. doi: 10.1016/S0140-6736(17)30566-4
99. Lee YK, Mazmanian SK. Has the microbiota played a critical role in the evolution of the adaptive immune system? *Science.* (2010) 330:1768–73. doi: 10.1126/science.1195568
100. Cekanaviciute E, Yoo BB, Runia TF, Debelius JW, Singh S, Nelson CA, et al. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. *Proc Natl Acad Sci USA.* (2017) 114:10713–18. doi: 10.1073/pnas.1711235114
101. Cekanaviciute E, Pröbstel A-K, Thomann A, Runia TF, Casaccia P, Katz Sand I, et al. Multiple sclerosis-associated changes in the composition and immune functions of spore-forming bacteria. *mSystems.* (2018) 3:e00083. doi: 10.1128/mSystems.00083-18
102. Elson CO, Alexander KL. Host-microbiota interactions in the intestine. *Dig Dis.* (2015) 33:131–6. doi: 10.1159/000369534
103. Opazo MC, Ortega-Rocha EM, Coronado-Arrázola I, Bonifaz LC, Boudin H, Neunlist M, et al. Intestinal microbiota influences non-intestinal related autoimmune diseases. *Front Microbiol.* (2018) 9:432. doi: 10.3389/fmicb.2018.00432
104. Desbonnet L, Clarke G, Shanahan F, Dinan TG, Cryan JF. Microbiota is essential for social development in the mouse. *Mol Psychiatry.* (2014) 19:146–148. doi: 10.1038/mp.2013.65
105. Desbonnet L, Clarke G, Traplin A, O'sullivan O, Crispie F, Moloney RD, et al. Gut microbiota depletion from early adolescence in mice: implications for brain and behaviour.*Brain Behav Immun.* (2015) 48:165–73. doi: 10.1016/j.bbi.2015.04.004
106. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell.* (2013) 155:1451–63. doi: 10.1016/j.cell.2013.11.024
107. Burger-Van Paassen N, Vincent A, Puiman PJ, Van Der Sluis M, Bouma J, Boehm G, et al. The regulation of intestinal mucin MUC2 expression by short-chain fatty acids: implications for epithelial protection. *Biochem J.* (2009) 420:211–9. doi: 10.1042/BJ20082222
108. Severance EG, Alaedini A, Yang S, Halling M, Gressitt KL, Stallings CR, et al. Gastrointestinal inflammation and associated immune activation in schizophrenia. *Schizophr Res.* (2012) 138:48–53. doi: 10.1016/j.schres.2012.02.025
109. Alhasson F, Das S, Seth R, Dattaroy D, Chandrashekaran V, Ryan CN, et al. Altered gut microbiome in a mouse model of Gulf War Illness causes neuroinflammation and intestinal injury via leaky gut and TLR4 activation. *PLoS ONE.* (2017) 12:e0172914 doi: 10.1371/JOURNAL.PONE.0172914
110. Romano-Keeler J, Weitkamp J-H. Maternal influences on fetal microbial colonization and immune development. *Pediatr Res.* (2015) 77:189–95. doi: 10.1038/pr.2014.163
111. Severance EG, Gressitt KL, Stallings CR, Katsafanas E, Schweinfurth LA, Savage CLG, et al. Probiotic normalization of candida albicans in schizophrenia: a randomized, placebo-controlled, longitudinal pilot study. *Brain Behav Immun.* (2017) 62:41–5. doi: 10.1016/j.bbi.2016.11.019
112. Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CLG, Schweinfurth LAB, et al. Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning. *Prim Care Companion CNS Disord.* (2014) 16:13m01579. doi: 10.4088/PCC.13m01579
113. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull.* (2012) 38:661–71. doi: 10.1093/schbul/sbs050

114. Lataster J, Myin-Germeys I, Lieb R, Wittchen H-U, van Os J. Adversity and psychosis: a 10-year prospective study investigating synergism between early and recent adversity in psychosis. *Acta Psychiatr Scand.* (2012) 125:388–99. doi: 10.1111/j.1600-0447.2011.01805.x
115. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, et al. Association of stress-related disorders with subsequent autoimmune disease. *JAMA*. (2018) 319:2388. doi: 10.1001/jama.2018.7028
116. Sharif K, Watad A, Coplan L, Lichtbroun B, Krosser A, Lichtbroun M, et al. The role of stress in the mosaic of autoimmunity: an overlooked association. *Autoimmun Rev.* (2018) 17:967–83. doi: 10.1016/j.autrev.2018.04.005
117. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav Immun.* (2017) 64:208–19. doi: 10.1016/j.bbi.2017.01.011
118. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res.* (2014) 58:193–210. doi: 10.1007/s12026-014-8517-0
119. Gur TL, Bailey MT. Effects of stress on commensal microbes and immune system activity. *Adv Exp Med Biol.* (2016) 874:289–300. doi: 10.1007/978-3-319-20215-0_14
120. Cohen S, Tyrrell DAJ, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med.* (1991) 325:606–12. doi: 10.1056/NEJM199108293250903
121. Paholpak P, Rangseekajee P, Foocharoen C. Characteristics, treatments and outcome of psychosis in Thai SLE patients. *J Psychosom Res.* (2012) 73:448–51. doi: 10.1016/j.jpsychores.2012.08.006
122. Laursen TM, Plana-Ripoll O, Andersen PK, McGrath JJ, Toender A, Nordentoft M, et al. Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse? *Schizophr Res.* (2018) doi: 10.1016/j.schres.2018.11.003. [Epub ahead of print]

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BRIEF RESEARCH REPORT
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Human Autoantibodies Against N-Methyl-D-Aspartate Receptor Modestly Alter Dopamine D1 Receptor Surface Dynamics

*Hélène Gréa[1,2], Delphine Bouchet[1,2], Véronique Rogemond[3,4,5], Nora Hamdani[6,7,8,9], Emmanuel Le Guen[6,7,8,9], Ryad Tamouza[6,7,8,9], Estelle Darrau[7], Christine Passerieux[9,10,11], Jérôme Honnorat[3,4,5], Marion Leboyer[6,7,8,9] and Laurent Groc[1,2]**

[1] Université de Bordeaux, Interdisciplinary Institute for Neuroscience, UMR 5297, Bordeaux, France, [2] CNRS, IINS UMR 5297, Bordeaux, France, [3] NeuroMyoGene Institute, INSERM U1217/CNRS UMR 5310, Lyon, France, [4] French Reference Center of Paraneoplastic Neurological Syndrome, Hospices Civils de Lyon, Hôpital Neurologique, Lyon, France, [5] Université de Lyon - Université Claude Bernard Lyon 1, Lyon, France, [6] Université Paris Est Créteil, Psychiatry Department, Groupe Hospitalier Universitaire Henri Mondor, AP-HP, DHU PePSY, Créteil, France, [7] Université Paris Est Créteil, Life Science and Health Department, INSERM IMRB U955, Créteil, France, [8] INSERM, IMRB U955, Translational Psychiatry laboratory, Créteil, France, [9] FondaMental foundation, Créteil, France, [10] Université de Versaillles Saint Quentin en Yvelines, HandiRESP laboratory (EA4047), Health Science Department Simone Veil, Montigny le Bretonneux, France, [11] Versailles Hospital, Department of Adult Psychiatry, Le Chesnay, France

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Filippo Drago, University of Catania, Italy

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***Correspondence:**
Laurent Groc
laurent.groc@u-bordeaux.fr

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Circulating autoantibodies directed against extracellular domains of the glutamatergic N-methyl-D-aspartate receptors (NMDAR-Ab) elicit psychotic symptoms in humans and behavioral deficits in animal models. Recent advances suggest that NMDAR-Ab exert their pathogenic action by altering the trafficking of NMDAR, which results in a synaptic NMDAR hypofunction consistent with the consensual glutamatergic hypothesis of psychotic disorders. Yet, dysfunction in the dopaminergic signaling is also proposed to be at the core of psychotic disorders. Since NMDAR and dopamine D1 receptors (D1R) form membrane signaling complexes, we investigated whether NMDAR-Ab purified from patients with NMDAR-encephalitis or schizophrenia impaired D1R surface dynamics. As previous data demonstrated that NMDAR-Ab, at least from NMDAR-encephalitis patients, mainly bind to hippocampal NMDAR, we used single nanoparticle imaging to track D1R specifically at the surface of hippocampal neurons that were exposed to either purified G type immunoglobulins (IgGs) from NMDAR-Ab seropositive patients suffering from NMDAR-encephalitis or schizophrenia, or control IgGs from healthy NMDAR-Ab seropositive or seronegative subjects. We report that overnight incubation with NMDAR-Ab from patients, but not from healthy carriers, decreased the surface dynamics of D1R compared with NMDAR-Ab seronegative IgGs. This decrease was abolished, and even reversed, in D1R mutant that cannot physically interact with NMDAR. Overall, our data indicate that NMDAR-Ab from patients with psychotic symptoms alter the trafficking of D1R, likely through the surface crosstalk between NMDAR and D1R.

Keywords: autoimmunity, encephalitis, schizophrenia, autoimmune psychosis, dopamine, single molecule imaging, hippocampal neurons

INTRODUCTION

Psychotic disorders, such as schizophrenia, are major mental illnesses with multiple etiologies. During the past decades, accumulating evidence suggests that dysregulations of the immune system, such as the presence of autoantibodies directed against neurotransmitter receptors, play a major role in psychosis (1–5), paving the way for the recognition of an autoimmune psychosis subclass (6). The discovery of the well-characterized N-methyl-D-aspartate receptor (NMDAR)-encephalitis demonstrated that circulating autoantibodies targeting the NMDAR (i.e., NMDAR-Ab) play an instrumental and pathogenic role (7). Indeed, the presence of NMDAR-Ab in the sera of NMDAR-encephalitis patients correlates, in a titer-dependent manner, with psychotic-like symptoms that appear at early stage of the illness. At the molecular level, autoantibodies from NMDAR-encephalitis patients laterally displace synaptic NMDAR toward the extrasynaptic membrane, in which they are physically cross-linked and internalized, leading to the downregulation of NMDAR-mediated signaling (8, 9). Recently, NMDAR-Ab have also been found in the sera of a significant proportion of patients diagnosed with schizophrenia (10) but also in a very few healthy carriers (11). Similarly to NMDAR-Ab from encephalitis patients, NMDAR-Ab from psychotic patients, but not from healthy subjects, laterally displace synaptic NMDAR toward the extrasynaptic membrane (12). Thus, different molecular cascades are triggered by NMDAR-Ab from different origins, calling for caution in generalizing the impact of these autoantibodies. Although the identification of NMDAR-Ab has further fueled the hypothesis of a NMDAR hypofunction in psychosis (13), gold-standard treatments of psychotic disorders remain composed of antagonists of the dopamine receptors and other monoamine systems (e.g., serotonin) (14–16). Understanding how the glutamatergic and dopaminergic systems influence each other and likely participate to the etiology of psychotic disorders is still obviously a major challenge in the field of psychiatry. The fact that NMDAR physically interacts with dopamine receptors [e.g., dopamine D1 receptor (D1R)] in an agonist-dependent manner indicates that, already at the plasma membrane level, a functional interplay between dopaminergic and NMDAR signaling exists (17). We here hypothesize that the altered surface trafficking of NMDAR triggered by NMDAR-Ab from patients with NMDAR-encephalitis or schizophrenia, but not from healthy carriers, could then modify the surface dynamics of D1R. As NMDAR-Ab from patients with NMDAR-encephalitis mainly bind to NMDAR in the hippocampus (18), we investigated the molecular impact of NMDAR-Ab on D1R surface dynamics in a model of cultured hippocampal neurons. A former investigation revealed that a short incubation (2 h) of hippocampal cell networks with NMDAR-Ab from encephalitis patients did not alter D1R surface trafficking (8). Herein, we used a single molecule-based imaging approach to assess the D1R surface dynamics in hippocampal neurons exposed for a longer incubation period (overnight) to NMDAR-Ab [purified G type immunoglobulins (IgGs)] from either healthy seropositive carriers (Healthy+), patients with NMDAR-encephalitis (Enceph), or schizophrenia (SCZ+), or seronegative matched-healthy subjects (Healthy-). In order to assess if the expected alteration of D1R surface dynamics is a direct consequence of the physical interaction between D1R and NMDAR-Ab-targeted NMDAR, we investigated the surface diffusion of a truncated exogenous D1R, which prevents its physical interaction with NMDAR, expressed in hippocampal neurons exposed to purified IgGs from a patient with schizophrenia compared with an healthy seronegative subject.

Abbreviations: NMDAR-Ab, N-methyl-D-aspartate receptor autoantibodies; CFP, cyan fluorescent protein; D1R, dopamine D1 receptor; D1R-Δt2, intracellular t2 segment truncated dopamine D1 receptor; IgGs, type G immunoglobulins; QD, quantum dot; Healthy-, healthy subjects seronegative for NMDAR-Ab; Healthy +, healthy subjects seropositive for NMDAR-Ab; Enceph, NMDAR-encephalitis patients (inherently seropositive for NMDAR-Ab); SCZ+, patients with schizophrenia seropositive for NMDAR-Ab; MSD, mean square displacement.

METHODS

Participants

Five patients with NMDAR-encephalitis (Enceph) and three patients with schizophrenia (SCZ+) (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria), all seropositive for NMDAR-Ab, were included in this study after approval by a French ethical committee (**Table 1**). Patients with NMDAR-encephalitis had no psychiatric history and were recruited from a cohort of 400 NMDAR-encephalitis patients (French National Reference Centre for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis, Bron, France). Patients with schizophrenia were recruited after admission to two university-affiliated psychiatric departments (Mondor Hospital, Créteil, University of Paris-Est, and Fernand Widal Hospital, Paris, University of Diderot, Paris), and any history of stroke, multiple sclerosis, epilepsy, or encephalitis constituted exclusion criteria. The clinical state of both type of patients could assure their total capacity to understand the aims and the procedures of the study and finally to express their will to participate in a written informed consent. Two seropositive (Healthy+) and five seronegative (Healthy-) for NMDAR-Ab healthy matched for age, gender, and years of education subjects with no personal or familial history of psychosis were included in the study as controls.

Purified Type G Immunoglobulins From Participants

All experiments were conducted using purified IgGs containing (Healthy+, SCZ+, Enceph) or not containing (Healthy-) NMDAR-Ab from subjects' sera. In all experiments, purified IgGs were used from separate individuals, except for three out of the five NMDAR-encephalitis patients and three out of the five healthy seronegative subjects for whom pooled IgGs were available.

Detection of NMDAR Autoantibodies in Participants' Sera

For patients with NMDAR-encephalitis or schizophrenia, sera were collected at symptom presentation, before any treatment and stored at -80°C. The presence of NMDAR-Ab in sera of either patients or control subjects was assessed using a classic cell-based assay. Briefly, exogenous NMDAR were ectopically expressed in human embryonic kidney cells (HEK) 293 transfected with GluN1-NMDAR subunit fused to the green fluorescent protein (GFP)

TABLE 1 | Clinical features of seropositive for NMDAR-Ab patients with either NMDAR-encephalitis (Enceph) or schizophrenia (SCZ+).

	Age at onset/sex	Clinical symptoms*	Treatments			
Patients with NMDAR-encephalitis (Enceph)				**ICU**	**Cancer**	**Outcome**
1	18/F	Hallucinations, abnormal behavior, abnormal movements	PE, C, IvIg, Cyclophosphamide	No	No	Cured after 24 months
2	29/F	Hallucinations, abnormal behavior, abnormal movements, epilepsy	C, IvIg, Cyclophosphamide Rituximab Micophenolate mophetyl	Yes 10 days	Ovarian teratoma	Cured after 24 months
3	21/F**	Hallucinations, abnormal behavior, abnormal movements	Cyclophosphamide Rituximab Micophenolate mophetyl	No	No	Cured after 24 months
4	18/F**	Hallucinations, epilepsy, abnormal behavior, abnormal movements	C, IvIg, Azathioprine	No	No	Cured after 18 months
5	22/F**	Hallucinations, abnormal behavior, abnormal movements, epilepsy, dysautonomia	C, IvIg, Cyclophosphamide Micophenolate mophetyl	Yes 1 month	No	Cured after 9 months
Patients with schizophrenia (SCZ+)				**PANSS Total (>60)** Positive scale score Negative scale score	**MRI**	**Other medical history**
1	22/M	Blunted affects Disorganization Suicidal thoughts	Risperidone (4 mg/day) Cyamemazine (75 mg/day) Oxazepam (30 mg/day) Duloxetine (60 mg/day)	66 Positive scale : 7 Negative scale : 26	normal	Dyslipidemia Type 2 diabetes mellitus
2	34/F	Cognitive impairment Delusions Attention deficits Blunted affects	Aripiprazole (30 mg/day) Escitaloprame (10 mg/day) Hydroxyzine (300 mg/day)	132 Positive scale : 26 Negative scale : 42	none	none
3	25/M	Blunted affects Cognitive impairment Delusions Disorganization	Clozapine (100 mg/day) Loxapine (150 mg/day)	76 Positive scale : 14 Negative scale : 19	normal	Epilepsia Head trauma Hepatic colic

*ICU, intensive care unit; C, corticosteroids; PE, plasma exchange; IvIg, intravenous immunoglobulines. PANSS total, Positive and Negative Syndrome Scale total score. *Symptoms at presentation for patients with NMDAR-encephalitis and residual/active symptoms for patients with schizophrenia. **Purified G type immunoglobulins (IgGs) from patients with NMDAR-encephalitis #3, #4, and #5 were available pooled together.*

along with GluN2B-NMDAR subunit to promote the insertion of functional NMDAR at the cell surface. After a 48-h expression period, live HEK cells were incubated with subjects' sera (3 h, 1/20 in saturation buffer). Then, fixed HEK cells were incubated with anti-human IgG coupled to Alexa 555. Using a fluorescence microscope, the observation of an overlap of both green and red staining led to the assessment of the subject seropositivity for NMDAR-Ab.

Primary Cell Culture and Single Quantum Dot Tracking

As NMDAR-Ab from NMDAR-encephalitis patients mainly bind to NMDAR in the hippocampus both in humans and rodents despite their brain widespread distribution (18), we assessed the impact of autoantibodies on D1R surface dynamics on hippocampal cultured neurons prepared from E18 Sprague-Dawley rats. At 7–11 days of development *in vitro*, neurons were co-transfected with D1R fused to the cyan fluorescent protein (D1R-CFP) and Homer1C fused to DsRed protein DNAs to specifically track and concentrate our analysis on the extrasynaptic D1R pool, as we previously demonstrated that the vast majority of D1R are located outside hippocampal synapses (19, 20). In addition, since NMDAR-Ab could alter the surface dynamics of D1R through a domino effect due to the physical interaction between NMDAR and D1R, we assessed the impact of autoantibodies from one patient with schizophrenia on D1R surface dynamics in neurons in which this physical interaction was genetically prevented by expressing the intracellular C-terminus t2 segment-truncated D1R-CFP (D1RΔt2-CFP; see **Figure 1D**). Quantum dot (QD) tracking of D1R-CFP (or D1RΔt2-CFP) was performed on live hippocampal neurons at 12–15 days of development *in vitro*. Neurons were first incubated overnight (14 ± 2 h) with NMDAR-Ab containing purified IgGs (5 μg/ml) from either patients with

NMDAR-encephalitis (Enceph), schizophrenia (SCZ+), or healthy carriers (Healthy+), or with purified IgG (5 µg/ml) from healthy seronegative subjects (Healthy-) (**Figure 1A**, top). Incubation time was increased compared with that in previous report that failed to reveal any effect of NMDAR-Ab on D1R surface dynamics when using a shorter exposure (2 h) (8). For QD labeling and microscopy, hippocampal neurons were then incubated (10 min) with anti-GFP antibodies (Molecular Probes A6455, 1/10,000 to 1/20,000 dilution). Neurons were then washed and incubated (10 min) with QDs coupled to an anti-Rabbit F(ab) fragment (Life Technologies Q11421MP, 1/100,000 dilution). Images were obtained with an acquisition time of 50 ms with up to 500 consecutive frames. The instantaneous diffusion coefficient, D, was calculated for each trajectory, from linear fits of the first four points of the mean square displacement (MSD) versus time (t) function using $MSD(t) = < r2>(t) = 4Dt$.

Statistical Analysis

Comparisons between conditions were made running nonparametric Kruskall–Wallis tests followed by Dunn's multiple comparisons. Analyses were performed using GraphPad Prism 8 for Windows software (version 8.0.2, GraphPad Software, Inc) with a statistical significance of 0.05.

RESULTS

As D1R physically interacts with NMDAR, we explored the possibility that circulating NMDAR-Ab from patients with NMDAR-encephalitis or schizophrenia alter as a mechanical consequence the lateral dynamics of D1R. Hippocampal neurons expressing exogenous D1R were exposed to either NMDAR-Ab-containing IgGs (overnight, 5 µg/ml) from patients (Enceph or SCZ+), healthy carriers (Healthy+), or IgGs from seronegative

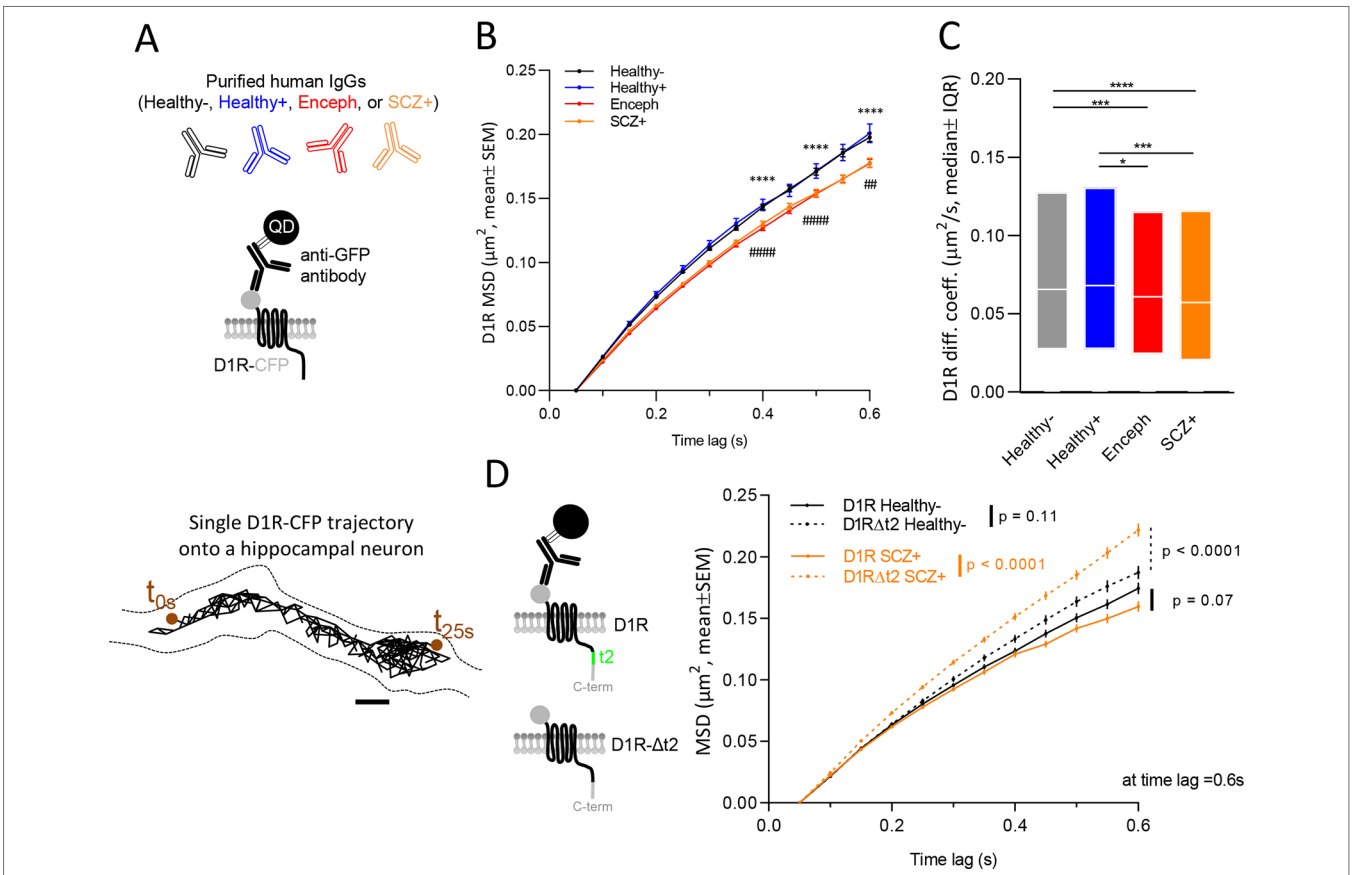

FIGURE 1 | NMDAR-Ab from patients with NMDAR-encephalitis (Enceph) or schizophrenia (SCZ+), but not from healthy carriers (Healthy+), alter the surface dynamics of D1R compared with healthy seronegative subjects (Healthy-). **(A)** Schematic representation of the experimental design. Before tracking, D1R-CFP-antiGFPAb-QD complexes, hippocampal cultures (12 to 15 days *in vitro*) were incubated overnight with different purified type G immunoglobulins (IgGs, 5 µm/ml) samples from either patients with NMDAR-encephalitis (Enceph), schizophrenia (SCZ+), healthy carriers (Healthy+), or healthy seronegative subjects (Healthy-) (top panel). Representative trajectory of a single D1R-CFP-antiGFPAb-QD complex (500 frames, 50 ms acquisition) on the dendritic shaft (dashed lines). Scale bar: 500 nm (bottom panel). **(B)** Comparison of D1R-CFP-antiGFPAb-QD complexes mean square displacements (MSD, mean ± SEM) in the absence (Healthy-) or presence of NMDAR-Ab from healthy carriers (Healthy+), or from patients with NMDAR-encephalitis (Enceph) or schizophrenia (SCZ+). ****SCZ+ vs Healthy- $p < 0.0001$, ####Enceph vs Healthy- $p < 0.0001$, ##Enceph vs Healthy- $p = 0.0048$. **(C)** Comparison of D1R-CFP-antiGFPAb-QD complexes instantaneous diffusion coefficients (median ± interquartile range 25–75%) in the absence (Healthy-) or the presence of NMDAR-Ab from healthy carriers (Healthy+) or patients with NMDAR-encephalitis (Enceph) or schizophrenia (SCZ+). ****$p < 0.0001$, ***$p = 0.0006$, *$p = 0.0119$. **(D)** Representation of full D1R containing t2 segment enabling the physical interaction with NMDAR (top) and the mutated D1R (D1RΔt2-CFP) preventing its binding to NMDAR (bottom) (left). Comparison of D1R-CFP-antiGFPAb-QD/D1RΔt2-CFP-antiGFPAb-QD complexes surface dynamics (MSD, mean ± SEM) in the absence (Healthy-) or presence (SCZ+) of NMDAR-Ab from patient #2 with schizophrenia (right).

controls (Healthy-). Single nanoparticle tracking of D1R was then performed to investigate the impact of NMDAR-Ab on D1R membrane dynamics (**Figure 1A**). As D1R being mostly located outside glutamatergic synapses (19, 20), we specifically analyzed the extrasynaptic diffusion. Surface dynamics of D1R was assessed by measuring their MSD curves and instantaneous diffusion coefficients (21). NMDAR-Ab from patients with NMDAR-encephalitis or schizophrenia, but not from healthy carriers, decrease the explored areas and instantaneous diffusion coefficients of D1R when compared with the Healthy- condition (**Figures 1B**, **C**, **Table 2**). Noteworthy, NMDAR-Ab from healthy carriers did not differ from healthy seronegative controls. These data suggest that only NMDAR-Ab from patients have the potency to alter the dynamics of D1R, likely through a "domino effect" in which the physical interplay between NMDAR and D1R controls the single molecule behavior of each partner. To directly address this possibility, we investigated the impact of NMDAR-Ab from one patient with schizophrenia on D1R that were genetically prevented to interact with GluN1-NMDAR (D1RΔt2-CFP): the intracellular t2 segment is a major binding sequence to the GluN1 subunit (17) (**Figure 1D**, left). Remarkably, the surface dynamics (MSD) of the D1R mutant was not decreased by NMDAR-Ab from the patient but instead significantly increased (**Figure 1D**, right), indicating that the alteration of D1R trafficking by NMDAR-Ab patients is regulated, at least in part, by the physical interaction with NMDAR.

DISCUSSION

Dopamine is a powerful modulator of the glutamatergic neurotransmission, acting mostly through the metabotropic actions, e.g., intracellular cascades, of its receptor family (22, 23). However, the physical interaction of membrane dopamine receptors with several other receptors, such as the NMDAR (17), provides an additional way to modulate the synaptic activity through the

TABLE 2 | Statistical analysis and values. MSD, mean square displacement; N, number of trajectories.

Fig	Parameter	Conditions	Values Median ± 25–75% IQR	N	Statistical test α = 0.05	P value
1B	MSD (at time lag = 0.4 s)	Healthy- Healthy+ Enceph SCZ+	0.1060 ± 0.05160–0.1900 μm² 0.1100 ± 0.05100–0.1950 μm² 0.1010 ± 0.04678–0.1710 μm² 0.09405 ± 0.04120–0.1770 μm²	4,505 891 3,750 3,498	Kruskal–Wallis ($p < 0.0001$) followed by Dunn's multiple comparison test	Healthy+ vs Healthy- > 0.9999 ns Enceph vs Healthy- < 0.0001 SCZ+ vs Healthy- < 0.0001 Enceph vs SCZ+ > 0.9999 ns
	MSD (at time lag = 0.5 s)	Healthy- Healthy+ Enceph SCZ+	0.1240 ± 0.06030–0.2270 μm² 0.1305 ± 0.05940–0.2350 μm² 0.1200 ± 0.05488–0.2070 μm² 0.1110 ± 0.04725–0.2080 μm²	3,761 728 2,998 3,113		Healthy+ vs Healthy- > 0.9999 ns Enceph vs Healthy- < 0.0001 SCZ+ vs Healthy- < 0.0001 Enceph vs SCZ+ > 0.9999 ns
	MSD (at time lag = 0.6 s)	Healthy- Healthy+ Enceph SCZ+	0.1420 ± 0.06805–0.2630 μm² 0.1545 ± 0.06995–0.2733 μm² 0.1371 ± 0.06000–0.2380 μm² 0.1240 ± 0.05000–0.2430 μm²	3,380 646 2,723 2,747		Healthy+ vs Healthy- > 0.9999 ns Enceph vs Healthy- = 0.0048 SCZ+ vs Healthy- < 0.0001 Enceph vs SCZ+ = 0.3976 ns
1C	Instantaneous diffusion coefficient	Healthy- Healthy+ Enceph SCZ+	0.06546 ± 0.02720–0.1276 μm²/s 0.06801 ± 0.02735–0.1306 μm²/s 0.06080 ± 0.02430–0.1153 μm²/s 0.05715 ± 0.02015–0.1160 μm²/s	5,127 1,000 4,321 4,003	Kruskal–Wallis ($p < 0.0001$) followed by Dunn's multiple comparison test	Healthy+ vs Healthy- > 0.9999 ns Enceph vs Healthy- =0.0006 SCZ+ vs Healthy- < 0.0001 Enceph vs SCZ+ = 0.4711 ns Enceph vs Healthy+ = 0.0119 SCZ+ vs Healthy+ = 0.0002
1D	MSD (at time lag = 0.4 s)	D1R Healthy- D1RΔt2 Healthy- D1R SCZ+ D1RΔt2 SCZ+	0.09415 ± 0.04065–0.1740 μm² 0.1070 ± 0.05130–0.1820 μm² 0.08990 ± 0.04260–0.1590 μm² 0.1280 ± 0.05940–0.2170 μm²	1,664 1,287 1,869 1,615		D1R Healthy- vs D1RΔt2 Healthy- = 0.0537 ns D1R Healthy- vs D1R SCZ+ > 0.9999 ns D1RΔt2 SCZ+ vs others <0.0001
	MSD (at time lag = 0.5 s)	D1R Healthy- D1RΔt2 Healthy- D1R SCZ+ D1RΔt2 SCZ+	0.1150 ± 0.04888–0.2110 μm² 0.1320 ± 0.06150–0.2250 μm² 0.1070 ± 0.04840–0.1860 μm² 0.1560 ± 0.07135–0.2670 μm²	1,410 1,103 1,555 1,381	Kruskal–Wallis ($p < 0.0001$) followed by Dunn's multiple comparison test	D1R Healthy- vs D1RΔt2 Healthy- = 0.0586 ns D1R Healthy- vs D1R SCZ+ = 0.2643 ns D1RΔt2 SCZ+ vs D1RΔt2 Healthy- = 0.0008 D1RΔt2 SCZ+ vs D1R Healthy- < 0.0001 D1RΔt2 SCZ+ vs D1R SCZ+ < 0.0001
	MSD (at time lag = 0.6 s)	D1R Healthy- D1RΔt2 Healthy- D1R SCZ+ D1RΔt2 SCZ+	0.1325 ± 0.05323–0.2450 μm² 0.1520 ± 0.06730–0.2550 μm² 0.1190 ± 0.05275–0.2145 μm² 0.1840 ± 0.08320–0.3150 μm²	1,256 975 1,377 1,223		D1R Healthy- vs D1RΔt2 Healthy- = 0.1109 ns D1R Healthy- vs D1R SCZ+ = 0.0703 ns D1RΔt2 SCZ+ vs others <0.0001

presence of receptor hetero-complexes (24). For instance, the activation of D1R disrupts the D1R-NMDAR interaction, increases NMDAR synaptic content through a fast lateral redistribution, and favors NMDAR-dependent long-term potentiation of glutamatergic synapses in a model of cultured hippocampal neurons (19). Here, we investigated, in the same model, whether the well-defined alteration of the NMDAR surface dynamics by NMDAR-Ab from patients sharing psychotic-like symptoms also perturbs, as a consequence, D1R dynamics. We demonstrate that an overnight incubation of hippocampal neurons with NMDAR-Ab from patients with NMDAR-encephalitis or schizophrenia, but not from healthy carriers, alters the surface dynamics of D1R. The fact that a shorter incubation (2 h) did not alter D1R surface dynamics supports the notion that the NMDAR-Ab effect is time dependent and likely indirect. Furthermore, the magnitude of NMDAR-Ab effects on D1R (~10%) is, by far, weaker than the one on NMDAR (~3-fold) (8, 12), likely due to the fact that only a fraction of D1R interacts with NMDAR and is thus prone to destabilization by NMDAR-Ab (19).

Both NMDAR-Ab from patients with encephalitis and schizophrenia were found to slowdown D1R surface dynamics. This is likely a mechanical consequence of the NMDAR immobilization triggered by autoantibodies in the extrasynaptic compartment where D1R is mainly located. Indeed, when the physical D1R-NMDAR interaction was genetically prevented, the D1R dynamics downregulation by NMDAR-Ab from patient with schizophrenia was abolished. To note, D1R surface dynamics was even upregulated in this condition, as expected from the NMDAR-Ab-induced NMDAR crosslinking and internalization (8, 9).

Collectively, we here demonstrated that NMDAR-Ab, which primarily target and alter NMDAR surface organization, also disorganize its membrane partner D1R. However, we highlighted that the effect of the NMDAR-Ab is relatively weaker on D1R when compared with that on NMDAR. Importantly, NMDAR-Ab from different origins (patients versus healthy carriers) do not necessarily share the same molecular impact on the glutamatergic and dopaminergic receptor trafficking. This is consistent with previous finding demonstrating that NMDAR-Ab from healthy carriers or patient with autism spectrum disorder without history of psychosis do not alter NMDAR surface trafficking (12, 25). Our data further highlight that NMDAR-Ab are diverse in their mechanisms of action and call for further investigations to decrypt the alterations on the targeted NMDAR and its membrane partners.

ETHICS STATEMENT

Patients with NMDAR encephalitis and schizophrenic (DSM-IV criteria) were included in this study after approval by a French ethical committee and written informed consent for their participation.

AUTHOR CONTRIBUTIONS

HG and LG designed the study. VR, NH, EG, RT, ED, CP, ML, and JH performed clinical analysis. HG performed single nanoparticle experiments. DB performed molecular biology and cell biology preparation. HG analyzed the data. HG and LG wrote the paper.

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REFERENCES

1. Benros ME, Eaton WW, Mortensen PB. The epidemiologic evidence linking autoimmune diseases and psychosis. *Biol Psychiatry* (2014) 75:300–6. doi: 10.1016/j.biopsych.2013.09.023
2. Coutinho E, Harrison P, Vincent A. Do neuronal autoantibodies cause psychosis ? A neuroimmunological perspective. *Biol Psychiatry* (2014) 75:269–75. doi: 10.1016/j.biopsych.2013.07.040
3. Pollak TA, Beck K, Irani SR, Howes OD, David AS, McGuire PK. Autoantibodies to central nervous system neuronal surface antigens: psychiatric symptoms and psychopharmacological implications. *Psychopharmacol (Berl)* (2016) 233:1605–21. doi: 10.1007/s00213-015-4156-y
4. Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. *Schizophr Res* (2016) 176:36–40. doi: 10.1016/j.schres.2014.10.007
5. Deakin J, Lennox BR, Zandi MS. Antibodies to the N-Methyl-D-Aspartate receptor and other synaptic proteins in psychosis. *Biol Psychiatry* (2013) 75:284–91. doi: 10.1016/j.biopsych.2013.07.018
6. Ellul P, Groc L, Tamouza R, Leboyer M. The clinical challenge of autoimmune psychosis: learning from anti-NMDA receptor autoantibodies. *Front Psychiatry* (2017) 8:1–6. doi: 10.3389/fpsyt.2017.00054
7. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* (2008) 7:1091–8. doi: 10.1016/S1474-4422(08)70224-2
8. Mikasova L, De Rossi P, Bouchet D, Georges F, Rogemond V, Didelot A, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain* (2012) 135:1606–21. doi: 10.1093/brain/aws092
9. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* (2010) 30:5866–75. doi: 10.1523/JNEUROSCI.0167-10.2010
10. Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol* (2011) 258:686–8. doi: 10.1007/s00415-010-5788-9
11. Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein H-G, Vielhaber S, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. *JAMA Psychiatry* (2013) 70:271–8. doi: 10.1001/2013.jamapsychiatry.86
12. Jézéquel J, Johansson EM, Dupuis JP, Rogemond V, Gréa H, Kellermayer B, et al. Dynamic disorganization of synaptic NMDA receptors triggered by

autoantibodies from psychotic patients. *Nat Commun* (2017) 8:1791–1805. doi: 10.1038/s41467-017-01700-3
13. Kantrowitz J, Javitt DC. Glutamatergic transmission in schizophrenia: from basic research to clinical practice. *Curr Opin Psyhiatry* (2012) 25:96–102. doi: 10.1097/YCO.0b013e32835035b2
14. Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* (2001) 41:237–60. doi: 10.1146/annurev.pharmtox.41.1.237
15. Iversen SD, Iversen LL. Dopamine: 50 years in perspective. *Trends Neurosci* (2007) 30:188–93. doi: 10.1016/j.tins.2007.03.002
16. Morrison PD, Murray RM. The antipsychotic landscape: dopamine and beyond. *Ther Adv Psychopharmacol* (2018) 8:127–35. doi: 10.1177/2045125317752915
17. Lee FJS, Xue S, Pei L, Vukusic B, Chéry N, Wang Y, et al. Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. *Cell* (2002) 111:219–30. doi: 10.1016/S0092-8674(02)00962-5
18. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med* (2018) 378:840–51. doi: 10.1056/NEJMra1708712
19. Ladepeche L, Dupuis JP, Bouchet D, Doudnikoff E, Yang L, Campagne Y, et al. Single-molecule imaging of the functional crosstalk between surface NMDA and dopamine D1 receptors. *Proc Natl Acad Sci U S A* (2013) 110:18005–10. doi: 10.1073/pnas.1310145110
20. Ladepeche L, Yang L, Bouchet D, Groc L. Regulation of dopamine D1 receptor dynamics within the postsynaptic density of hippocampal glutamate synapses. *PLoS One* (2013) 8:1–8. doi: 10.1371/journal.pone.0074512
21. Choquet D, Triller A. The dynamic synapse. *Neuron* (2013) 80:691–703. doi: 10.1016/j.neuron.2013.10.013
22. Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci* (2004) 5:483–94. doi: 10.1038/nrn1406
23. Beaulieu J-M, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* (2011) 63:182 LP– 217. doi: 10.1124/pr.110.002642
24. Borroto-Escuela DO, Carlsson J, Ambrogini P, Narváez M, Wydra K, Tarakanov AO, et al. Understanding the role of GPCR heteroreceptor complexes in modulating the brain networks in health and disease. *Front Cell Neurosci* (2017) 11:37. doi: 10.3389/fncel.2017.00037
25. Gréa H, Scheid I, Gaman A, Rogemond V, Gillet S, Honnorat J, et al. Clinical and autoimmune features of a patient with autism spectrum disorder seropositive for anti-NMDA-receptor autoantibody. *Dialogues Clin Neurosci* (2017) 19:65–70. doi: 10.1097/QAI.0000000000001168

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REVIEW
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Emerging Roles of Complement in Psychiatric Disorders

Mélanie Druart[1,2,3] *and Corentin Le Magueresse*[1,2,3]*

[1] INSERM UMR-S 1270, Paris, France, [2] Science and Engineering Faculty, Sorbonne Université, Paris, France, [3] Institut du Fer à Moulin, Paris, France

The complement system consists of more than 30 proteins that have long been known to participate to the immune defence against pathogens and to the removal of damaged cells. Their role, however, extends beyond immunity and clearance of altered "self" components in the periphery. In particular, complement proteins can be induced by all cell types in the brain. Recent discoveries highlight the role of complement in normal and pathological brain development. Specifically, the complement system mediates synaptic pruning, a developmental process whereby supernumerary synapses are eliminated in the immature brain. The complement system has been implicated in pathological synapse elimination in schizophrenia, West Nile virus infection, and lupus, all of which are associated with psychiatric manifestations. Complement also contributes to synapse loss in neurodegenerative conditions. This review provides a brief overview of the well-studied role of complement molecules in immunity. The contribution of complement to embryonic and adult neurogenesis, neuronal migration, and developmental synaptic elimination in the normal brain is reviewed. We discuss the role of complement in synapse loss in psychiatric and neurological diseases and evaluate the therapeutic potential of complement-targeting drugs for brain disorders.

Keywords: brain development, schizophrenia, synapse elimination, synaptic pruning, microglia

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University of Foggia, Italy

***Correspondence:**
Corentin Le Magueresse
corentin.le-magueresse@inserm.fr

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INTRODUCTION

The link between immunogenetics, inflammation, and several major psychiatric disorders such as Schizophrenia (SZ), Bipolar Disorder (BD), and Autism Spectrum Disorder (ASD) is now well substantiated (1–5). The molecular and cellular mechanisms that mediate immunity-related neurodevelopmental alterations in psychiatric diseases are gradually coming to light, and the complement system appears to be a key player in these complex processes. The complement system is an ensemble of proteins that collectively participate to host defense against infections by opsonizing antigens, promoting inflammation, and lysing pathogens, and has been well characterized in the periphery. Unexpectedly, complement was shown to control synaptic pruning, a development process whereby supernumerary synapses are eliminated during the course of normal brain maturation (6). Recently, the complement system has received much attention in the field of psychiatry after Sekar et al. demonstrated that distinct genetic variants of C4, a gene encoding a protein of the classical complement pathway, predispose to SZ (7). This landmark study provided a solid basis for establishing a causal relationship between complement-mediated synaptic pruning and cortical thinning frequently associated with SZ. Furthermore, complement-mediated synapse loss was also implicated in Lupus and West Nile virus infection, two immune disorders that can induce psychosis and cognitive impairment, respectively. In this review, we briefly summarize the

known functions of the complement system in the periphery and highlight its newly discovered roles in brain maturation and in psychiatric disorders.

The Three Complement Cascades in Innate and Acquired Immunity

The complement system consists of more than 30 proteins present in the blood plasma or on the cell surface. These proteins are mainly produced by the liver, although multiple cell types in different organs, including the brain, express and secrete complement molecules (8). The complement system has been extensively studied, and numerous reviews cover complement pathways in depth (9–12). Complement molecules have three major functions in the immune system: i) opsonization of "foreign" molecules, bacteria, or damaged cells, i.e., promotion of their phagocytosis by neutrophils or monocytes, ii) increase of the inflammatory response via short peptides called anaphylatoxins (C3a, C4a, and C5a) resulting from enzymatic cleavage of complement proteins, and iii) lysis of pathogenic micro-organisms via the formation of a pore in the lipid membrane.

Complement proteins are soluble and circulate in the blood in an inactive form. In response to an activating mechanism, some complement proteins are transformed into proteases and cleave other specific complement members, initiating amplification cascades (**Figure 1**). Complement activation results from the activation of one or several of three distinct pathways: the classical pathway, the lectin pathway, and the alternative pathway. The three pathways converge to cause cleavage of C3, which is the most abundant complement protein, resulting in the formation of the anaphylatoxin C3a and the C3b fragment. Factor I, in the presence of its co-factor and C3b receptor CR1, cleaves C3b into iC3b and a small peptide of 17 amino-acids (C3f). The resulting conformational rearrangement of iC3b generates binding surfaces for the interaction with complement receptors CR2 (CD21), CR3 (CD11b/CD18), and CR4 (CD11c/CD18) located on leukocytes, which down-regulates inflammation and increases B cell sensitivity, thus forming a link between the innate and adaptive immune systems (13, 14). The C3b fragment can also directly label antigens for opsonization or bind to other complement peptides to form the C5 convertase. The resulting cleavage of C5 is the beginning of the terminal pathway of the complement: C5 is cleaved into C5a, the most potent anaphylatoxin, and C5b. The latter forms a complex with C6 and C7, which then binds with C8. The resulting change in C8 conformation allows the insertion of an alpha chain and anchoring in the target membrane. The combination of the C5b678 complex with one to 18 C9 molecules, termed membrane attack complex, forms a pore that lyses the target pathogen.

The Classical Pathway

The classical pathway is activated by the C1 complex, composed of the C1q protein recognizing antibodies bound to their antigen, associated with the C1r and C1s proenzymes. Through C1q, the complex can also recognize non-immunoglobulin activators, particularly surface proteins of bacteria and viruses. The binding of C1q to its target results in a conformational change of C1q which activates C1r, which in turn cleaves and activates the two C1s molecules of the C1 complex to form the activated C1s serine protease. Activated C1s cleaves C4 and C2, whose cleavage products combine to form the C3 convertase C4b2b which activates C3.

The Lectin Pathway

The lectin pathway is activated by the binding of pattern recognition receptors such as mannose-binding lectins, ficolins, or collectin 11 to specifically arranged carbohydrates present on damaged cell surfaces or on invading pathogens. This results in the activation of associated serine proteinases (MASP1/2) and cleavage of C4 and C2. The formation of the C3 convertase C4b2b then cleaves C3 as in the classical pathway.

The Alternative Pathway

Unlike the other two pathways, the alternative pathway is not initiated by binding of complement molecules to antigens or antibodies. Spontaneous hydrolysis of C3 results in the cleavage of an intramolecular thioester bond and leads to the formation of reactive molecules C3(H_2O) and C3b. When C3(H_2O) or C3b binds to positively charged surfaces present in microorganisms, it reacts with Factor B in the presence of Factor D to form a C3 convertase (C3(H_2O)Bb or C3bBb) that is strongly stabilized by properdin (Factor P). The convertase then generates additional C3b molecules, initiating a positive feedback loop amplification.

Complement Proteins in Normal Brain Development

Expression of Complement Components in the Brain

Studies conducted since the 1990s have shown extrahepatic production of complement proteins by several organs and cell types (8) and, in particular, by neurons and glial cells (15). This local production in the CNS is all the more important as the brain-blood barrier prevents circulating macromolecules, including complements proteins, to penetrate into the brain tissue (16).

In the past two decades, expression of complement components has been documented in primary cultures of astrocytes, microglia, oligodendrocytes, and neurons (17–20). More recent studies have shown that neural cells express complement molecules throughout embryonic and postnatal development in rodent and human brain tissue (**Table 1**) (25, 33–35). Importantly, complement components are released into the extracellular space, suggesting that a given brain cell type can participate to complement activation without expressing the full range of complement molecules (7).

Complement expression by neural cells was first demonstrated using immunoprecipitation in cultured astrocytes (17). This observation was compatible with the macrophagic function of astrocytes and their role in the brain's immune system (36). Astrocytes express components of the classical pathway (C1q, C1r, C1s, C2, C3, C4), the alternative pathway (factors B, D, I, H, P), and the terminal pathway (C5-C9) (19, 21, 26, 28). They also express complement receptors CR1, CR2, C3aR, and C5aR (29, 30). These initial studies relied on cultured cell lines. In the mouse brain, astrocytes are the main source of C3 (37). Like astrocytes, microglia are considered part of the immune system of the brain

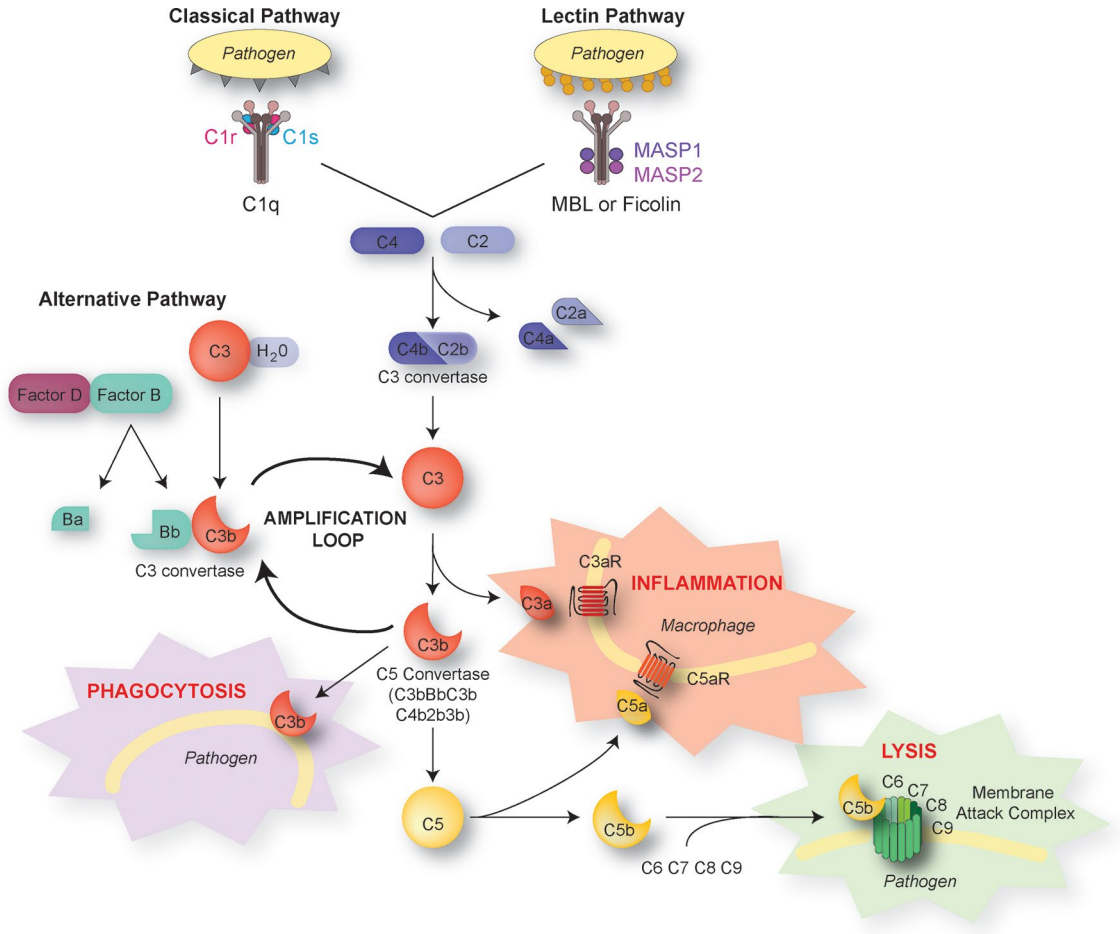

FIGURE 1 | The complement pathways. There are three distinct activation pathways in the complement system: the classical and lectin pathway that are activated by pathogens or damaged cells, and the alternative pathway that is activated by the spontaneous hydrolysis of C3. All lead to the sequential recruitment of complement components to form a C3 convertase (C4bC2b or C3bBb). The C3 convertase cleaves C3 into C3a and C3b. The C3b fragment binds to the surface of antigens, targeting them for opsonization (phagocytosis). C3b also induces a positive-feedback loop ("amplification loop") leading to the generation of additional C3 convertase. C3b can also be recruited to become part of the C5 convertase, which cleaves C5 into C5a and C5b. The short C3a and C5a fragments, also known as anaphylatoxins, foster immune responses and inflammation. C5b initiates the assembly of C6, 7, 8, and 9 into the membrane attack complex, which forms a membrane pore resulting in the lysis of the pathogen.

because of their ability to secrete pro-inflammatory factors such as chemokines and cytokines and for their macrophagic function (38, 39). Microglial cells express classical pathway components (C1q, C1r, C1s, C2, C3, C4) and complement receptors C1qR, CR2, C3aR, and C5aR (19, 22, 40–43). Microglial cells have been shown to be the dominant source of C1q in the mouse brain (44). Oligodendrocytes also express members of the classical pathway (C1q, C2, C3, C4), factor H, as well components of the terminal pathway (C5-C9) (23, 24).

Finally, neurons also express complement molecules. In culture, they can produce a complete complement system (20). mRNA coding for C1q, C2, C3, C4, and terminal complement components (C5-C9) was also detected in human neurons using *in situ* hybridization in *post mortem* brain tissue (25). Immunohistochemical experiments using human cortical neurons in culture showed the presence of the C4 protein in neurons and in the extracellular medium, confirming that neurons express and release C4 (7). Altogether, these results suggest that both neurons and glial cells express complement components and their receptors. Given the pro-inflammatory role of anaphylatoxins C3a and C5a, the expression of their receptors by glial cells was not surprising. In contrast, expression of these receptors in neurons was more unexpected. Yet, neuronal expression of C3aR and C5aR at a low level has been shown in the cortex, cerebellum, and hippocampus in the adult mouse brain (31, 32, 45).

Complement expression varies according to the brain's inflammatory status. In response to infection or inflammation such as in bacterial meningitis, elevated levels of complement proteins are detected in the cerebro-spinal fluid (46). Regulation of complement receptor expression was shown in an ischemic brain model where C3aR and C5aR are more expressed in both neurons and glial cells following blood vessel occlusion (47). Interestingly, a cell type-specific upregulation of complement expression has been observed in a model of transient ischemia where C1q expression increases specifically in microglia but not

TABLE 1 | Complement molecules expressed by brain cells.

	Astrocytes	References	Microglia	References	Oligodendrocytes	References	Neurons	References
Classical pathway	C1q, C1r, C1s, C2, C3, C4	Barnum et al. (21) Veerhuis et al. (19)	C1q, C1r, C1s, C2, C3, C4	Walker et al. (18) Haga et al. (22) Veerhuis et al. (19)	C1q, C1r, C1s, C2, C3, C4	Hosokawa et al. (23) Gasque and Morgan (24)	C1q, C1r, C1s, C2, C3, C4	Shen et al. (25) Thomas et al. (20)
Alternative pathway	C3, Factors B, D, I, H	Barnum et al. (21) Gordon et al. (26)	C3	Veerhuis et al. (19)	C3, Factor H	Hosokawa et al. (23) Gasque and Morgan (24)	C3, Factors B and D	Thomas et al. (20)
Lectin pathway							(embryonic neurons) MASP1, MASP2	Gorelik et al. (27)
Terminal pathway	C5,C6,C7,C8,C9	Gasque et al. (28)			C5, C6, C7, C8, C9	Hosokawa et al. (23) Gasque and Morgan (24)	C5, C6, C7, C9	Shen et al. (25) Thomas et al. (20)
Receptors	CR1, CR2, C3aR, C5aR	Gasque and Morgan (24) Gasque et al. (29) Gasque et al. (30)	CR2, C3aR, C5aR	Gasque et al. (30) Davoust et al. (31)			C3aR, C5aR	Davoust et al. (31) Stahel et al. (32) Benard et al. (33)

in neurons (48). Expression of complement components and receptors also varies during the course of brain development (33). For example in the mouse hippocampus, C3 expression is much lower at postnatal day 30 (P30) than at P2 (35). In the rat cerebellum, C3aR and C5aR expression in granule cells peaks around postnatal day 12 (33). This fine developmental regulation of complement expression has led to the study of its role in brain maturation.

Embryogenesis and Neuronal Proliferation

A study conducted in *Xenopus larves* highlighted the expression of complement components already during gastrula/early neurula stage. In particular, properdin, C1qA, C3, and C9 are expressed in the neural plate and in neural precursors, while C1qR and C6 are expressed at the periphery of the neural plate, in the presumptive neural crest (49). Based on the observation that there is a chronological and tissue specification of complement expression, the hypothesis of the complement's involvement in developmental processes independently of inflammation has been put forward. In mammals, C5 and C5aR are also expressed early in development. C5 and C5aR are located in neuroepithelium in mice in the early stages of neurulation and also in human neuroepithelium. C5aR-deficient mice do not display overt congenital anomalies but have more neural tube malformations than wild-type controls after maternal folate deficiency (50). These observations suggest a degree of functional redundancy of developmentally expressed complement proteins, with the role of C5aR in neurulation only becoming apparent under conditions of environmental stress.

The C5a-C5aR axis is involved in neurogenesis, but only at embryonic stages of development. A recent study showed that C5aR activation increases neural recursor cell (NPC) proliferation *in vivo* in the embryonic ventricular zone through PKCζ/ERK signaling and that conversely, pharmacological blockade of C5aR decreases proliferation (51). In contrast, mice lacking C5aR do not show altered adult neurogenesis (52). Similarly, C5aR antagonists do not alter neural NPC proliferation within the external granular layer of the early postnatal rat cerebellum. However, C5aR agonists promote the proliferation of NPCs in the granular layer at the same developmental stage, suggesting that C5aR is expressed but not activated (53). The effect of C5aR activation at embryonic, but not postnatal stages, can be explained by the developmental time course of C5a expression. Indeed, the concentration of C5a is higher in embryonic than in adult cerebro-spinal fluid, suggesting that neuroepithelium secretes high quantities of C5a to promote NPC proliferation (51). The transient disruption of C5a-C5aR signaling during embryonic development alters adult cerebral organization and causes behavioral deficits (51), highlighting the crucial role of this pathway for the establishment of functional neuronal circuits. Interestingly, *Serping1*, a gene encoding a C1 inhibitor known to block the initiation of the classical and lectin pathways, negatively regulates neural proliferation in the embryonic ventricular zone by decreasing C5aR activation (54). Thus, C5aR activation must be precisely balanced for adequate NPC proliferation in the embryonic ventricular zone.

Complement molecules other than C5a are also involved in the control of adult neurogenesis. Thus, complement receptor CR2 is expressed by neural progenitors in the adult dentate gyrus (DG) and its activation by C3d or interferon-alpha reduces NPC proliferation and decreases the formation of new neurons in the adult hippocampus. Conversely, $Cr2^{-/-}$ mice exhibit increased neurogenesis in the adult DG (55). C3a is also implicated in normal and ischemia-induced adult neurogenesis. C3aR is expressed by neural progenitor cells (NPC) in adult mice. Basal adult neurogenesis is decreased both in C3-deficient mice and

in mice lacking C3aR. Furthermore, C3-deficient mice have impaired ischemia-induced neurogenesis in the subventricular zone, the main source of neural progenitor cells in the adult mouse brain (56).

Neuronal Migration

The complement system also plays a role in neuronal migration. During brain development, cells can migrate in a coordinated way in the same direction, a process termed collective migration that requires chemoattraction between cells. In neural ridge cells from Xenopus laevis and zebrafish, collective migration is dependent on the C3a fragment and its receptor C3aR. Disruption of the interaction between the ligand and its receptor prevents proper cellular migration and causes neuronal dispersion (57). A possibly related mechanism has been reported in adult brain-derived NPCs in which C3a and SDF-1 induce ERK phosphorylation, which in turn causes differentiation and neuronal migration in vitro (58).

Furthermore, knockdown of C1q inhibitor-encoding *Serping 1* impairs radial migration. Interestingly, *Serping 1* affects both cell autonomous and non-cell autonomous radial migration in mouse embryos, indicating that C1q inhibitor is secreted and influences neighboring neurons. This effect can be rescued C3aR agonists, demonstrating that C3aR signaling is required for the proper migration of cortical plate neurons (54). Further experiments have shown that the lectin pathway controls neuronal migration in the developing neocortex. Indeed, in mouse embryos knocking down C3, but also MASP1 or MASP2, which are critically involved in the lectin pathway, impairs migration of neuroblasts derived from the ventricular zone. This effect can be reversed by co-electroporating molecular mimics of C3 cleavage products, suggesting that the activity of the complement pathway, and not only the presence of the C3 protein, is required for proper migration of neuroblasts in the developing cortex (27).

Synaptic Pruning

In the past decade, a key role of the complement in the postnatal maturation of brain circuits has been uncovered. At birth, the mammalian brain is characterized by an excess of synaptic connections. Over the course of postnatal development, extra synapses are eliminated to establish functional mature neuronal networks (59, 60). This process called synaptic pruning is activity-dependent and has been documented in different regions such as the cortex (61, 62), cerebellum (63), retinogeniculate system (59), and neuromuscular junction (64).

The role of complement in synaptic pruning has been first demonstrated in the retinogeniculate system (**Figure 2A**, **B**). Early in development, retinal ganglion cells (RGC) project exuberant axons onto neurons in the dorsal lateral geniculate nucleus (dLGN) of the thalamus. During postnatal development, retinogeniculate synapses are eliminated to ensure a good segregation between ipsi and contralateral inputs to dLGN neurons. Activity-dependent pruning that occurs in the first postnatal week in mice is necessary to provide a functional binocular vision in adults (65, 66). Using array tomography on thin brain sections, Stevens and colleagues showed that C1q and C3 are abundantly expressed and colocalize with excitatory synapses in the dLGN at P5 but not at P30. Consistent with a role of complement in synaptic pruning, C1q-, C3-, and C4-deficient mice display higher densities of excitatory synapses in the dLGN and abnormalities in eye-specific segregation (6, 7). The colocalization between C3 and excitatory synapses suggests that C3 or its cleavage products act like tags of synapses to be eliminated by microglia. Indeed, if the interaction between iC3b and its receptor CR3 is blocked, synaptic pruning is impaired (67). CR3 is selectively expressed by microglial cells during postnatal development and anterograde tracer injection in the retina showed that presynaptic elements are engulfed by microglial cells in the developing dLGN, indicating that microglial cells are key players in complement-mediated synaptic pruning (67). C1q and C4 also colocalize at synapses in the developing dLGN (6, 7). However, it is unclear whether they directly participate in microglia-dependent synaptic elimination by tagging synapses, or whether they indirectly promote synapse elimination by allowing the cleavage of C3 and the generation of iC3b.

Consistent with numerous studies highlighting that synaptic pruning is activity-dependent, microglia-mediated engulfment of RGC inputs is regulated by the activity of presynaptic neurons (67). This further suggests that inactive synapses are those that are tagged by complement molecules and targeted for microglia-mediated pruning, although the mechanisms underlying activity-dependent complement binding remain unknown.

The role of complement in synaptic pruning has also been demonstrated in other brain regions. Thus, the complement system contributes to pruning of axonal boutons in layer V pyramidal neurons of the somatosensory cortex (68). A role of microglia in synaptic pruning has also been demonstrated in the hippocampus (69, 70), suggesting that complement-dependent synaptic pruning may be widespread in the developing brain. A recent study shed light on microglia-neuron interactions in the developing hippocampus at the ultrastructural level, showing that presynaptic structures in developing hippocampal neurons are not entirely phagocytosed by microglia but rather "trogocytosed," a term originally used to describe membrane transfer in immune cells and later extended to refer to partial phagocytosis (71). Of note, microglia-independent processes also participate to synaptic pruning. Thus, astrocytes contribute to synapse elimination in the developing and adult dLGN through the MEGF10 and MERTK phagocytic pathways (72). The contribution of complement to astrocyte-mediated pruning is unclear, but the identification of MEGF10 as an astrocytic receptor for C1q in the developing mouse cerebellum (73) raises the possibility that astrocytes recognize C1q-tagged synapses for elimination.

C1q Family

Interestingly, proteins that have homology with C1q but are not involved in the leptin, classical, or alternative pathways are expressed in the brain and participate in synapse formation, maintenance, and function. These proteins of the C1q family include precerebellin (Cbln1), which is released by cerebellar granule cells. Cbln1 promotes synapse formation between granule cell axons (parallel fibers) and Purkinje cells through binding to glutamate receptor delta 2 (GluRD2) on postsynaptic site and to Neurexin on presynaptic sites. C1q-like (C1ql) proteins, another subtype of C1q family proteins, also regulate synapse formation and function in the cerebellum and in the forebrain. For example, in the cerebellum, C1ql1 controls

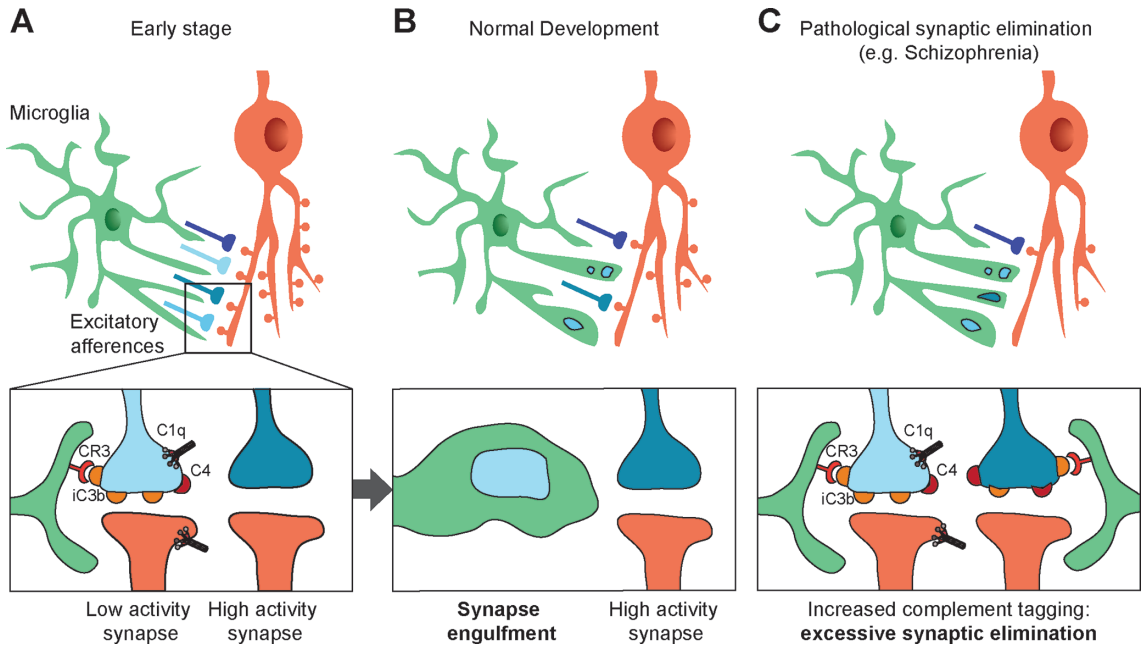

FIGURE 2 | Synapses elimination by microglia in normal and pathologic development. **(A, B)** During the course of postnatal development, supernumerary synapses are eliminated by microglia (upper panels). Complement components C1q, C4, and the C3 fragment iC3b tag inactive synapses. Microglial cells bind iC3b through their CR3 receptors and partially phagocyte tagged synapses, resulting in selective synapse elimination. High-activity synapses appear to be protected from synaptic pruning by an activity-dependent signal (bottom panels). **(C)** Synaptic pruning hypothesis in schizophrenia: high C4A expression in the schizophrenic human brain and the associated decrease in synapse density suggest increased complement activity resulting in an excess of iC3b-marked synapses and faulty synapse elimination **(C)**.

the formation and maintenance of synapses between axons of the inferior olivary nucleus (climbing fibers) and Purkinje cells through binding to the postsynaptic receptor Bai3 (74–76). Two other C1ql proteins, C1ql2 and C1ql3, are strongly expressed by dentate granule cells in the hippocampus and recruit postsynaptic kainate receptors at mossy fiber-CA3 synapses (77). However, proteins of the C1q family other than C1q do not participate in the molecular cascades resulting in the cleavage of C3, and hence are not part of the complement system per se.

The Complement System in Psychiatric Diseases

Schizophrenia

Compelling evidence links the complement system and SZ (**Figure 2C**). Following the demonstration that synaptic density in neocortex peaks in early childhood, then decreases before reaching a plateau in adolescence (61), Feinberg proposed that SZ may result from faulty synapse elimination in the postnatal period based in particular on age at onset (78). Several observations corroborated Feinberg's hypothesis. First, spine density is decreased in upper cortical layers in SZ patients (79, 80). Second, MRI studies revealed that cortical thinning that takes place during normal postnatal development in humans is exacerbated in SZ patients, possibly reflecting an excess of pruning (81, 82). Given the now well-established role of complement in developmental synaptic pruning, it is not surprising, in retrospect, that alterations in complement genetics or complement expression have been associated with SZ. Early studies of the complement system in SZ showed altered expression or activity of complement molecules in SZ, although the results were inconsistent. In particular, increased hemolytic activity of the complement Cl, C2, C4 components in SZ had been reported by several studies (83, 84) [for a thorough review, see (85)]. However, the small scale of these studies prevented firm conclusions. A more robust association between the complement system and SZ has been made possible by large-scale genome-wide association studies of SZ. A significant association was found on chromosome 8 near *CSMD1* (86, 87), which encodes a complement-regulating protein (88). CSMD1-deficient mice display behaviors that are reminiscent of SZ-associated blunted emotional responses, anxiety, and depression (89). Furthermore, several GWAS have indicated that the Major Histocompatibility Complex (MHC) genomic region on chromosome 6 is implicated in SZ. Given that the strongest association within the MHC lies near the genomic region encoding complement component 4 (*C4*), Sekar et al. explored in detail the C4 complement cluster of the MHC in SZ patients and control individuals. They demonstrated a strong relationship between the C4 region and SZ (7). The tandemly arranged C4A and C4B genes in the MHC class III region are polymorphic in terms of copy number variation (CNV) and structure. They have over 95% sequence homology but encode functionally distinct proteins with different molecular targets. Further complexity stems from the fact that both C4A and C4B can be found in either "long" or "short" forms depending on the presence of human endogenous retroviral (HERV) indels (6.5 kb in size) in the intron 9 of the C4 genes. High copy number and the presence of HERV elements increase the mRNA levels of C4A and C4B. Importantly, the presence of multiple copies of C4A and of long forms of C4A was shown to increase the risk for SZ, suggesting that higher C4A expression predisposes to SZ.

Indeed, in a separate set of experiments Sekar et al. used postmortem expression analysis to demonstrate that C4A is significantly more expressed in the brain of SZ patients than in the brain of control individuals (7). A subsequent brain imaging study using phosphorus magnetic resonance spectroscopy directly confirmed the association between C4A gene repeats and neuropil contraction in two cohorts of SZ patients. Increased neuropil contraction was observed in the prefrontal and parietal regions among adult-onset schizophrenia patients with high C4A gene copy numbers, whereas adolescent-onset SZ patients showed increased neuropil contraction in the prefrontal cortex and thalamus (90).

Immune Disorders With Psychiatric Manifestations

Systemic lupus erythematosus (SLE) is a relatively rare chronic autoimmune disease. In most patients with SLE, anti-nuclear autoantibodies cause chronic inflammation which damages tissues, leading to a variety of symptoms. Lupus can affect many organs such as the kidneys, heart, lungs, blood vessels, and brain. Neuropsychiatric manifestations are present in two-thirds of the patients with SLE and include anxiety, depression, and psychosis, the latter being present in about 5% of patients (91). Gray matter atrophy was reported in SLE patients (92), which may be an indicator of synapse loss. In the 564Igi mouse model of SLE, a B-cell-receptor insertion model with known autoantibody specificity, behavioral phenotypes including anxiety, cognitive alterations, and social deficits correlate with synapse loss and the presence of reactive microglia. Treating 564Igi mice with an antibody against type I interferon receptor prevented reactive microglia, synapse loss, and behavioral phenotypes, suggesting that microglia-dependent synaptic elimination is involved in the behavioral alterations in SLE (93). Since the classical complement pathway is involved in microglia-dependent synaptic pruning in the healthy brain, it has been proposed that the complement system may directly or indirectly stimulate the type I interferon pathway to promote synapse engulfment and elimination by microglia in SLE (94).

The complement system has also been implicated in neuroinvasive infection with West Nile Virus. Cognitive decline including memory dysfunction is present in at least 50% of patients that survive following West Nile virus infection (95, 96). Using a mouse model of West Nile virus neuroinvasive infection, Vasek et al. showed that several complement proteins are significantly upregulated in the hippocampus, including C1q, C2, C3, and C4b (97). West Nile virus infection was accompanied by synaptic terminal elimination, which was blocked in C3-deficient mice and C3aR-deficient mice. Surprisingly, virus-induced synaptic elimination was still present in CR3-deficient mice, in which developmental synaptic pruning is strongly decreased (67). These results suggest that several distinct complement-dependent mechanisms may promote pathological pruning.

Neurodegenerative Disorders

While this review's emphasis is on psychiatric disorders, it is noteworthy that the complement has also been implicated in neuron and synapse loss in neurodegenerative disorders. Increased expression of the complement has been noted in the brain following injury and neurodegeneration (98, 99). In Alzheimer's disease (AD), the accumulation of extracellular Amyloid-beta (Aβ) peptides contributes to pathogenesis (100). Aggregated Aβ binds to C1q and C3b/iC3b and activates both the classical and alternative complement pathways in vitro (101, 102). Transcriptome studies showed that complement gene expression is increased in the disease, indicating activation of the complement system (103). Furthermore, several studies have demonstrated that the membrane attack complex colocalizes with amyloid plaques and tangle-bearing neurons, suggesting that complement activation in AD contributes to neurotoxicity (104–107). Indeed, C1q-deficient mouse models of AD display decreased levels of activated glia surrounding amyloid plaques, and slower decline of synaptic markers (108). Aged C3-deficient mice also show reduced age-dependent synapse and neuronal loss in hippocampal CA3, together with enhanced long-term potentiation and cognition (35). A recent study investigated in detail the role of the complement in synapse loss in the familial AD-mutant human amyloid precursor protein transgenic mouse model. In this model, C1q expression increases and C1q localizes to synapses before amyloid plaque deposition. Moreover, C1q-deficient mice are protected from Aβ-dependent synapse loss. These data suggested that the developmental pruning pathway is re-activated at the preplaque in AD, prompting the authors to test whether Aβ-dependent synapse loss is present in mice lacking CR3, a complement receptor only expressed by microglia in the brain. Synapse loss and microglial engulfment are prevented in CR3 KO mice (109). Another study has uncovered the contribution of C3aR, another complement receptor mainly expressed by microglia. Expression of C3 and C3aR is positively correlated with cognitive decline in human AD brains. In the PS19 mouse model, which is used to study neurofibrillary tangles in neurodegenerative taupathies like AD, a significant increase in C3 and C3aR expression correlates with synapse loss and microglial activation. Crossing PS19 mice with C3aR KO mice attenuates both synaptic impairment and microglial activation (110). Altogether, these results demonstrate the role of microglia and complement axis C3/CR3 and C3/C3aR in pathological synapse elimination. While research on complement activation in the AD brain has focused primarily on the classical complement pathway, it should be noted that mRNA for a critical alternative pathway component, Factor B, is present in the cortex of AD patients and that split products of Factor B, Bb and Ba, are significantly increased, indicating alternative pathway activation (111).

Pathological complement-mediated synapse loss is involved not only in AD but also in other neurogenerative disorders. In a progranulin-deficient mouse model of frontotemporal dementia, increased complement production and synaptic pruning activity by microglia preferentially eliminate inhibitory synapses in the ventral thalamus, which is prevented in progranulin-deficient C1q KO mice (112). C1q upregulation and C1q-dependent synapse loss were also observed in a mouse model of glaucoma, a neurodegenerative disease characterized by the progressive dysfunction and loss of retinal ganglion cells (113).

Complement molecules also participate indirectly in synapse loss and neurodegeneration in disorders such Alzheimer's, Huntington's, Parkinson's, Amyotrophic lateral sclerosis, and Multiple Sclerosis by inducing reactive astrocytes. Upon microglial activation, C1q is released by microglial cells together with Il-1α and TNFα. The combined action of these three factors is sufficient to convert resting

astrocytes into reactive "A1" astrocytes with impaired ability to promote synapse formation, decreased phagocytic capacity, and neurotoxicity (114).

It is remarkable that complement molecules participate to synapse loss in animal models of several distinct neurodegenerative disorders. While the neurotoxic effect of the complement may be less relevant for psychiatric disorders than for neurodegenerative disorders, similar complement-dependent mechanisms appear to induce synapse loss in both types of diseases (**Table 2**). Deciphering the underlying mechanisms in animal models of neurological disorders will help understand complement-dependent synaptic alterations in neurodevelopmental psychiatric disorders.

Perspectives

Is the Complement System Involved in Bipolar Disorder and Autism Spectrum Disorder?

Collectively, the studies discussed above have identified the classical complement pathway as a key contributor to pathological synapse elimination in the context of SZ and other disorders with psychosis or cognitive dysfunction. While the main emphasis has been on SZ, other psychiatric disorders such as BD and ASD are also associated with immune activation/inflammation (2–5) and altered synaptic pruning. Increased cortical thinning during adolescence has been observed in BD patients (115) and may reflect excessive synaptic pruning. Conversely, ASD has been associated with decreased synaptic pruning. Thus, in postmortem brain tissue, dendritic spine density was found to be increased in the cortex of ASD patients (116), which appears to result from decreased synaptic pruning as another study confirmed these results and showed that spine density decreased by ∼45% in control subjects from childhood through adolescence, but only by ∼16% in ASD patients (117).

Given the well-established role of complement molecules in both immune processes and synaptic pruning, these observations raise the question of whether the complement system may be causally involved in BD or ASD but with a different phenotypic expression than in SZ. The answer to this intriguing question may be multifold. First, clinically distinct psychiatric disorders sometimes display partly overlapping symptoms, which may reflect shared cellular endophenotypes including complement-mediated alterations at the synaptic level. Second, synaptic dysfunctions in SZ, BD, and ASD may rely on distinct mechanisms. The MHC region, which includes the C2, C4, and Factor B complement genes, has been associated with BD in genome-wide association studies (118), although the link between complement expression and BP is not straightforward (119). In contrast, preliminary results from a genome-wide association study on about 6500 ASD patients, a number that was sufficient to associate the MHC region in SZ (118), failed to reveal an association between the MHC and ASD (120). These results suggest that the MHC, which includes complement genes, might contribute to synapse elimination in BD, but seems less likely to be involved in ASD. Other mechanisms controlling spine density, such as autophagy, may underlie connectivity defects in some forms of ASD (117). Third, immune activation during brain development interacts with a genetic program that varies from one individual to another. Thus, genetic predisposition leading to strong expression of *C4A* could interact with brain inflammation to induce excessive synaptic pruning in SZ and possibly BD, while other variants, or other predisposition genes, would promote a different consequence of inflammation in ASD.

Types of Synapses Subject to Complement-Mediated Elimination

It is unclear whether complement-mediated synapse elimination targets both glutamatergic synapses and other synapses, such as GABAergic synapses, or even sites of neuromodulator (e.g., dopamine, acetylcholine, serotonin, noradrenaline) release. Microglia- and complement-mediated pruning has been extensively studied in hippocampal and thalamic excitatory neurons that bear dendritic spines (6, 7, 67, 69, 71). Moreover, developmental

TABLE 2 | Complement pathways involved in selected brain disorders.

	Neurodevelopmental disorder		**Neuro-immune disorder**	**Neurodegenerative disorder**	
	Schizophrenia		**West Nile Virus**	**Alzheimer's disease**	
Complement pathway	Classical	Lectin	Classical	Classical	Alternative
Putative complement activation	Increased expression of C4A	Unknown	C1q binds to WNV antigen-positive neurons	C1q binds to Aβ	C3b/iC3b binds to Aβ
Changes in complement components	Increased C4 mRNA expression (human brain)	Increased MBL/ MASP-2 complex activation (human serum)	Increased C1q, C2, C3 and C4b mRNA expression in the brain (mouse model)	Increased C1q, C3, C4, C9 mRNA expression (human brain) and increased C1q, C3, C3aR protein expression in the brain (mouse models)	Increased expression of split products of Factor B (Ba and Bb) (human brain)
Cellular mechanisms involved	Excess of microglia-dependent synaptic pruning	Unknown	Excess of C3/C3aR-dependent synaptic pruning	Excess of microglia-dependent synaptic pruning through the C3/ CR3 and C3/C3aR axis	Unknown
References	Sekar et al. (7)	Mayilyan et al. (84)	Vasek et al. (97)	Jiang et al. (101) Blalock et al. (103) Hong et al. (109) Litvinchuk et al. (110)	Bradt et al. (102) Strohmeyer et al. (111)

synaptic pruning in the primate cortex as well as excessive synaptic pruning in the schizophrenic cortex have been mostly studied, at the cellular level, using spine density as a readout (61, 79). Does this mean that dendritic spines are the physical substrate for complement-mediated pruning? Accumulating evidence shows that complement-mediated synapse pruning involves the elimination of presynaptic elements, but not postsynaptic material, by microglia (67, 71), although microglial engulfment of postsynaptic structures has also been reported (121). Thus, the disappearance of dendritic spines may follow the elimination of presynaptic elements, but is unlikely to be directly caused by complement-mediated microglial trogocytosis. Is complement-mediated synaptic pruning limited to glutamatergic synapses on dendritic spines? In this case, glutamatergic afferences onto GABAergic interneurons, which are almost deprived of dendritic spines, should be spared by complement-mediated pruning. Conversely, medium spiny neurons in the striatum, which bear numerous spines, may be particularly prone to undergo elevated synaptic pruning. This is important in the context of SZ, since typical antipsychotics primarily exert their function by blocking dopamine D2 receptors which are strongly expressed in medium spiny neurons. Interestingly, there is evidence that hippocampal GABAergic synapses are not affected by genetic manipulations altering microglia-neuron communication, suggesting that the mechanisms of pruning are different at excitatory and inhibitory synapses (70). In line with these findings, early electron microscopy studies in the macaque cortex showed a decrease in asymmetric (glutamatergic) synapse density, but not in symmetric (mostly GABAergic) synapse density during postnatal development (122). Furthermore C1q-deficient mice, which display alterations of synaptic pruning at excitatory synapses, show no significant change in inhibitory connectivity to layer V cortical pyramidal neurons (68). These studies supported the concept that complement- and microglia-dependent pruning preferentially affects excitatory synapses during postnatal development. However, C1q-dependent pruning of inhibitory, but not excitatory, synapses was recently demonstrated in the thalamus of progranulin-deficient mice (112). Moreover, the density of excitatory synapses on parvalbumin interneurons is lower in postpubertal relative to prepubertal monkeys, suggesting some degree of pruning at excitatory synapses onto aspiny neurons, although the role of complement was not investigated (123). Thus, different types of synapses may undergo complement-dependent pruning. Further studies are now needed to evaluate normal and pathological synaptic pruning in different neuronal types, brain areas, and neurotransmitter systems. If specific types of synapses are predominantly targeted by complement-mediated elimination, it will be important to decipher the molecular mechanisms that underlie this selectivity.

Effect on the Brain of Complement Molecules Generated Outside the Brain

Do complement molecules from outside the brain influence the central nervous system? Since most complement proteins do not cross the blood-brain barrier (BBB), it is likely that only complement molecules generated locally by neurons and glial cells shape normal brain development and function. Moreover, in SZ and AD, changes in complement levels in the brain are associated with upregulated complement expression by brain cells (7, 34). Nevertheless, pathological activation of complement in the periphery, for example, following immune challenges, may indirectly contribute to inflammation and physio-pathological processes in the brain by i) increasing the production of cytokines that cross the BBB and ii) compromising the BBB, which allows complement molecules of the periphery to enter the brain. Thus, BBB disruption is present in patients with SLE and the elevated level of C3 in the patients' cerebro-spinal fluid was suggested to be, at least in part, attributable to the transfer of C3 from the systemic circulation (124). On the contrary, complement activation in the periphery can protect against brain-damaging infections. For example, the complement system controls West Nile virus infection by inducing a protective antibody response (125).

The Complement System as a Target for Therapeutic Intervention in Psychiatric Disorders

The first anti-complement drug used in the clinic, eculizumab, is the humanized form of a C5-specific monoclonal antibody. As early as 2004, clinical trials demonstrated its efficacy in treating paroxysmal nocturnal haemoglobinuria (PNH), a heamatological disorder that involves complement-dependent intravascular hemolysis (126). Chronic eculizumab treatment substantially reduces mortality and improves quality of life for patients with PNH (127). After the US Food and Drug Administration (FDA) approval of eculizumab for PNH treatment in 2007, eculizumab also received FDA approval for the kidney disease atypical haemolytic uraemic syndrome in 2011. In addition, four C1 inhibitors (Berinert, Ruconest, Cetor, and Cinryze) are currently approved for the treatment of hereditary angioedema (128). These successes renewed interest in complement-targeted drug discovery. Given the role of complement in innate immunity, the use of complement-targeting drugs has raised concerns about potential adverse side-effects. Indeed, patients with complement deficiencies are more likely to suffer from serious infections (129, 130). The infectious risk decreases when patients with complement deficiencies reach adulthood, suggesting that complement therapeutics may be safer past adolescence (131). Moreover, the long-term clinical use of eculizumab has allowed to gather favourable safety data, which has contributed to enhance the interest for complement therapeutics. Thus, several anti-complement drugs are in advanced-stage clinical trials, and many more are in development (128, 132). These compounds target several distinct complement proteins, including C1q, C1s, C2, Factor B, Factor D, C3, C5, C5a, and C5aR. Few target the central nervous system, for the role of complement in brain disorders has been established relatively recently and because of specific requirements for brain-targeting drugs. In particular, crossing the blood-brain barrier requires small lipophilic molecules, or molecules that can access carrier-mediated transport systems within the blood-brain barrier. A few recently developed anti-complement molecules have been shown to be effective in crossing the blood-brain barrier (133). Preclinical studies support the use of anti-complement drugs to prevent synapse loss in brain trauma and neurological disorders, but these findings have yet to translate into

the clinic (134). Nevertheless, these investigations may pave the way for complement-based therapies in psychiatric disorders.

CONCLUSIONS

In conclusion, our review outlines recent discoveries that link the complement system and psychiatric disorders. In the brain, the role of complement appears fundamentally different from its role in innate immunity, although key elements of the signaling cascades well described in the immune system are preserved. Indeed, most complement molecules of the three complement pathways, including those that form the membrane attack complex, are expressed in the brain. The specificity of complement actions in the brain seems to result from the specificity of the neural mechanisms involved, such as synaptic pruning, and from the expression of molecular targets that may not exist outside the brain, such as those located at synapses. These complement-binding molecules remain to be fully identified.

Early studies into the antibacterial action of serum complement can be traced back to the early 1790s and were continued by generations of scientific luminaries including Ilya Metchnikoff and Jules Bordet, as discussed by Sim et al. in a recent historical review (135). It is striking that research on the complement is still a source of major discoveries today and will provide exciting insight into normal and pathological brain development, a research area that might have seemed unlikely to the pioneers of the 18th, 19th, and 20th centuries.

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REFERENCES

1. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry* (2015) 2(3):258–70. doi: 10.1016/S2215-0366(14)00122-9
2. Meltzer A, Van de Water J. The role of the immune system in autism spectrum disorder. *Neuropsychopharmacology* (2017) 42(1):284–98. doi: 10.1038/npp.2016.158
3. Oliveira J, Oliveira-Maia AJ, Tamouza R, Brown AS, Leboyer M. Infectious and immunogenetic factors in bipolar disorder. *Acta Psychiatr Scand* (2017) 136(4):409–23. doi: 10.1111/acps.12791
4. Rosenblat JD, McIntyre RS. Bipolar disorder and immune dysfunction: epidemiological findings, proposed pathophysiology and clinical implications. *Brain Sci* (2017) 7(11):144. doi: 10.3390/brainsci7110144
5. Siniscalco D, Schultz S, Brigida AL, Antonucci N. Inflammation and neuro-immune dysregulations in autism spectrum disorders. *Pharmaceuticals (Basel)* (2018) 11(2):56. doi: 10.3390/ph11020056
6. Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, et al. The classical complement cascade mediates CNS synapse elimination. *Cell* (2007) 131(6):1164–78. doi: 10.1016/j.cell.2007.10.036
7. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature* (2016) 530(7589):177–83. doi: 10.1038/nature16549
8. Li K, Sacks SH, Zhou W. The relative importance of local and systemic complement production in ischaemia, transplantation and other pathologies. *Mol Immunol* (2007) 44(16):3866–74. doi: 10.1016/j.molimm.2007.06.006
9. Walport MJ. Complement. first of two parts. *N Engl J Med* (2001) 344(14):1058–66. doi: 10.1056/NEJM200104053441406
10. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. *Nat Immunol* (2010) 11(9):785–97. doi: 10.1038/ni.1923
11. Carroll MV, Sim RB. Complement in health and disease. *Adv Drug Deliv Rev* (2011) 63(12):965–75. doi: 10.1016/j.addr.2011.06.005
12. Merle NS, Church SE, Fremeaux-Bacchi V, Roumenina LT. Complement system part I - molecular mechanisms of activation and regulation. *Front Immunol* (2015) 6:262. doi: 10.3389/fimmu.2015.00262
13. Alcorlo M, Martinez-Barricarte R, Fernandez FJ, Rodriguez-Gallego C, Round A, Vega MC, et al. Unique structure of iC3b resolved at a resolution of 24 A by 3D-electron microscopy. *Proc Natl Acad Sci U S A* (2011) 108(32):13236–40. doi: 10.1073/pnas.1106746108
14. Kieslich CA, Morikis D. The two sides of complement C3d: evolution of electrostatics in a link between innate and adaptive immunity. *PLoS Comput Biol* (2012) 8(12):e1002840. doi: 10.1371/journal.pcbi.1002840
15. Woodruff TM, Ager RR, Tenner AJ, Noakes PG, Taylor SM. The role of the complement system and the activation fragment C5a in the central nervous system. *Neuromolecular Med* (2010) 12(2):179–92. doi: 10.1007/s12017-009-8085-y
16. Alexander JJ. Blood-brain barrier (BBB) and the complement landscape. *Mol Immunol* (2018) 102:26–31. doi: 10.1016/j.molimm.2018.06.267
17. Levi-Strauss M, Mallat M. Primary cultures of murine astrocytes produce C3 and factor B, two components of the alternative pathway of complement activation. *J Immunol* (1987) 139(7):2361–6.
18. Walker DG, McGeer PL. Complement gene expression in neuroblastoma and astrocytoma cell lines of human origin. *Neurosci Lett* (1993) 157(1):99–102. doi: 10.1016/0304-3940(93)90652-2
19. Veerhuis R, Janssen I, De Groot CJ, Van Muiswinkel FL, Hack CE, Eikelenboom P. Cytokines associated with amyloid plaques in Alzheimer's disease brain stimulate human glial and neuronal cell cultures to secrete early complement proteins, but not C1-inhibitor. *Exp Neurol* (1999) 160(1):289–99. doi: 10.1006/exnr.1999.7199
20. Thomas A, Gasque P, Vaudry D, Gonzalez B, Fontaine M. Expression of a complete and functional complement system by human neuronal cells in vitro. *Int Immunol* (2000) 12(7):1015–23. doi: 10.1093/intimm/12.7.1015
21. Barnum SR, Ishii Y, Agrawal A, Volanakis JE. Production and interferon-gamma-mediated regulation of complement component C2 and factors B and D by the astroglioma cell line U105-MG. *Biochem J* (1992) 287(Pt 2): 595–601. doi: 10.1042/bj2870595
22. Haga S, Aizawa T, Ishii T, Ikeda K. Complement gene expression in mouse microglia and astrocytes in culture: comparisons with mouse peritoneal macrophages. *Neurosci Lett* (1996) 216(3):191–4. doi: 10.1016/0304-3940(96)13040-8
23. Hosokawa M, Klegeris A, Maguire J, McGeer PL. Expression of complement messenger RNAs and proteins by human oligodendroglial cells. *Glia* (2003) 42(4):417–23. doi: 10.1002/glia.10234
24. Gasque P, Morgan BP. Complement regulatory protein expression by a human oligodendrocyte cell line: cytokine regulation and comparison with astrocytes. *Immunology* (1996) 89(3):338–47. doi: 10.1046/j.1365-2567.1996.d01-756.x

25. Shen Y, Li R, McGeer EG, McGeer PL. Neuronal expression of mRNAs for complement proteins of the classical pathway in Alzheimer brain. *Brain Res* (1997) 769(2):391–5. doi: 10.1016/S0006-8993(97)00850-0
26. Gordon DL, Avery VM, Adrian DL, Sadlon TA. Detection of complement protein mRNA in human astrocytes by the polymerase chain reaction. *J Neurosci Methods* (1992) 45(3):191–7. doi: 10.1016/0165-0270(92)90076-P
27. Gorelik A, Sapir T, Haffner-Krausz R, Olender T, Woodruff TM, Reiner O. Developmental activities of the complement pathway in migrating neurons. *Nat Commun* (2017a) 8:15096. doi: 10.1038/ncomms15096
28. Gasque P, Fontaine M, Morgan BP. Complement expression in human brain. Biosynthesis of terminal pathway components and regulators in human glial cells and cell lines. *J Immunol* (1995) 154(9):4726–33.
29. Gasque P, Chan P, Mauger C, Schouft MT, Singhrao S, Dierich MP, et al. Identification and characterization of complement C3 receptors on human astrocytes. *J Immunol* (1996) 156(6):2247–55.
30. Gasque P, Singhrao SK, Neal JW, Gotze O, Morgan BP. Expression of the receptor for complement C5a (CD88) is up-regulated on reactive astrocytes, microglia, and endothelial cells in the inflamed human central nervous system. *Am J Pathol* (1997) 150(1):31–41.
31. Davoust N, Jones J, Stahel PF, Ames RS, Barnum SR. Receptor for the C3a anaphylatoxin is expressed by neurons and glial cells. *Glia* (1999) 26(3):201–11. doi: 10.1002/(SICI)1098-1136(199905)26:3<201::AID-GLIA2>3.0.CO;2-M
32. Stahel PF, Kariya K, Shohami E, Barnum SR, Eugster H, Trentz O, et al. Intracerebral complement C5a receptor (CD88) expression is regulated by TNF and lymphotoxin-alpha following closed head injury in mice. *J Neuroimmunol* (2000) 109(2):164–72. doi: 10.1016/S0165-5728(00)00304-0
33. Benard M, Gonzalez BJ, Schouft MT, Falluel-Morel A, Vaudry D, Chan P, et al. Characterization of C3a and C5a receptors in rat cerebellar granule neurons during maturation. Neuroprotective effect of C5a against apoptotic cell death. *J Biol Chem* (2004) 279(42):43487–96. doi: 10.1074/jbc.M404124200
34. Yasojima K, Schwab C, McGeer EG, McGeer PL. Up-regulated production and activation of the complement system in Alzheimer's disease brain. *Am J Pathol* (1999) 154(3):927–36. doi: 10.1016/S0002-9440(10)65340-0
35. Shi Q, Colodner KJ, Matousek SB, Merry K, Hong S, Kenison JE, et al. Complement C3-deficient mice fail to display age-related hippocampal decline. *J Neurosci* (2015) 35(38):13029–42. doi: 10.1523/JNEUROSCI.1698-15.2015
36. Verkhratsky A, Parpura V. Recent advances in (patho)physiology of astroglia. *Acta Pharmacol Sin* (2010) 31(9):1044–54. doi: 10.1038/aps.2010.108
37. Lian H, Litvinchuk A, Chiang AC, Aithmitti N, Jankowsky JL, Zheng H. Astrocyte-microglia cross talk through complement activation modulates amyloid pathology in mouse models of Alzheimer's disease. *J Neurosci* (2016) 36(2):577–89. doi: 10.1523/JNEUROSCI.2117-15.2016
38. Thomas WE. Brain macrophages: evaluation of microglia and their functions. *Brain Res Brain Res Rev* (1992) 17(1):61–74. doi: 10.1016/0165-0173(92)90007-9
39. Dong Y, Benveniste EN. Immune function of astrocytes. *Glia* (2001) 36(2):180–90. doi: 10.1002/glia.1107
40. Walker DG, Kim SU, McGeer PL. Complement and cytokine gene expression in cultured microglial derived from postmortem human brains. *J Neurosci Res* (1995a) 40(4):478–93. doi: 10.1002/jnr.490400407
41. Walker DG, Yasuhara O, Patston PA, McGeer EG, McGeer PL. Complement C1 inhibitor is produced by brain tissue and is cleaved in Alzheimer disease. *Brain Res* (1995b) 675(1-2):75–82. doi: 10.1016/0006-8993(95)00041-N
42. Gasque P, Singhrao SK, Neal JW, Wang P, Sayah S, Fontaine M, et al. The receptor for complement anaphylatoxin C3a is expressed by myeloid cells and nonmyeloid cells in inflamed human central nervous system: analysis in multiple sclerosis and bacterial meningitis. *J Immunol* (1998) 160(7):3543–54.
43. Webster SD, Park M, Fonseca MI, Tenner AJ. Structural and functional evidence for microglial expression of C1qR(P), the C1q receptor that enhances phagocytosis. *J Leukoc Biol* (2000) 67(1):109–16. doi: 10.1002/jlb.67.1.109
44. Fonseca MI, Chu SH, Hernandez MX, Fang MJ, Modarresi L, Selvan P, et al. Cell-specific deletion of C1qa identifies microglia as the dominant source of C1q in mouse brain. *J Neuroinflammation* (2017) 14(1):48. doi: 10.1186/s12974-017-0814-9
45. Stahel PF, Kossmann T, Morganti-Kossmann MC, Hans VH, Barnum SR. Experimental diffuse axonal injury induces enhanced neuronal C5a receptor mRNA expression in rats. *Brain Res Mol Brain Res* (1997a) 50(1-2):205–12. doi: 10.1016/S0169-328X(97)00189-7
46. Stahel PF, Nadal D, Pfister HW, Paradisis PM, Barnum SR. Complement C3 and factor B cerebrospinal fluid concentrations in bacterial and aseptic meningitis. *Lancet* (1997b) 349(9069):1886–7. doi: 10.1016/S0140-6736(05)63877-9
47. Van Beek J, Bernaudin M, Petit E, Gasque P, Nouvelot A, MacKenzie ET, et al. Expression of receptors for complement anaphylatoxins C3a and C5a following permanent focal cerebral ischemia in the mouse. *Exp Neurol* (2000) 161(1):373–82. doi: 10.1006/exnr.1999.7273
48. Schafer MK, Schwaeble WJ, Post C, Salvati P, Calabresi M, Sim RB, et al. Complement C1q is dramatically up-regulated in brain microglia in response to transient global cerebral ischemia. *J Immunol* (2000) 164(10):5446–52. doi: 10.4049/jimmunol.164.10.5446
49. McLin VA, Hu CH, Shah R, Jamrich M. Expression of complement components coincides with early patterning and organogenesis in Xenopus laevis. *Int J Dev Biol* (2008) 52(8):1123–33. doi: 10.1387/ijdb.072465v
50. Denny KJ, Coulthard LG, Jeanes A, Lisgo S, Simmons DG, Callaway LK, et al. C5a receptor signaling prevents folate deficiency-induced neural tube defects in mice. *J Immunol* (2013) 190(7):3493–9. doi: 10.4049/jimmunol.1203072
51. Coulthard LG, Hawksworth OA, Li R, Balachandran A, Lee JD, Sepehrband F, et al. Complement C5aR1 signaling promotes polarization and proliferation of embryonic neural progenitor cells through PKCzeta. *J Neurosci* (2017) 37(22):5395–407. doi: 10.1523/JNEUROSCI.0525-17.2017
52. Bogestal YR, Barnum SR, Smith PL, Mattisson V, Pekny M, Pekna M. Signaling through C5aR is not involved in basal neurogenesis. *J Neurosci Res* (2007) 85(13):2892–7. doi: 10.1002/jnr.21401
53. Benard M, Raoult E, Vaudry D, Leprince J, Falluel-Morel A, Gonzalez BJ, et al. Role of complement anaphylatoxin receptors (C3aR, C5aR) in the development of the rat cerebellum. *Mol Immunol* (2008) 45(14):3767–74. doi: 10.1016/j.molimm.2008.05.027
54. Gorelik A, Sapir T, Woodruff TM, Reiner O. Serping1/C1 inhibitor affects cortical development in a cell autonomous and non-cell autonomous manner. *Front Cell Neurosci* (2017b) 11:169. doi: 10.3389/fncel.2017.00169
55. Moriyama M, Fukuhara T, Britschgi M, He Y, Narasimhan R, Villeda S, et al. Complement receptor 2 is expressed in neural progenitor cells and regulates adult hippocampal neurogenesis. *J Neurosci* (2011) 31(11):3981–9. doi: 10.1523/JNEUROSCI.3617-10.2011
56. Rahpeymai Y, Hietala MA, Wilhelmsson U, Fotheringham A, Davies I, Nilsson AK, et al. Complement: a novel factor in basal and ischemia-induced neurogenesis. *EMBO J* (2006) 25(6):1364–74. doi: 10.1038/sj.emboj.7601004
57. Carmona-Fontaine C, Theveneau E, Tzekou A, Tada M, Woods M, Page KM, et al. Complement fragment C3a controls mutual cell attraction during collective cell migration. *Dev Cell* (2011) 21(6):1026–37. doi: 10.1016/j.devcel.2011.10.012
58. Shinjyo N, Stahlberg A, Dragunow M, Pekny M, Pekna M. Complement-derived anaphylatoxin C3a regulates in vitro differentiation and migration of neural progenitor cells. *Stem Cells* (2009) 27(11):2824–32. doi: 10.1002/stem.225
59. Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. *Science* (1996) 274(5290):1133–8. doi: 10.1126/science.274.5290.1133
60. Neniskyte U, Gross CT. Errant gardeners: glial-cell-dependent synaptic pruning and neurodevelopmental disorders. *Nat Rev Neurosci* (2017) 18(11):658–70. doi: 10.1038/nrn.2017.110
61. Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res* (1979) 163(2):195–205. doi: 10.1016/0006-8993(79)90349-4
62. Walhovd KB, Fjell AM, Giedd J, Dale AM, Brown TT. Through thick and thin: a need to reconcile contradictory results on trajectories in human cortical development. *Cereb Cortex* (2017) 27(2):1472–81. doi: 10.1093/cercor/bhv301
63. Hashimoto K, Kano M. Synapse elimination in the developing cerebellum. *Cell Mol Life Sci* (2013) 70(24):4667–80. doi: 10.1007/s00018-013-1405-2
64. Darabid H, Perez-Gonzalez AP, Robitaille R. Neuromuscular synaptogenesis: coordinating partners with multiple functions. *Nat Rev Neurosci* (2014) 15(11):703–18. doi: 10.1038/nrn3821
65. Hooks BM, Chen C. Distinct roles for spontaneous and visual activity in remodeling of the retinogeniculate synapse. *Neuron* (2006) 52(2):281–91. doi: 10.1016/j.neuron.2006.07.007

66. Huberman AD, Feller MB, Chapman B. Mechanisms underlying development of visual maps and receptive fields. *Annu Rev Neurosci* (2008) 31:479–509. doi: 10.1146/annurev.neuro.31.060407.125533
67. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* (2012) 74(4):691–705. doi: 10.1016/j.neuron.2012.03.026
68. Chu Y, Jin X, Parada I, Pesic A, Stevens B, Barres B, et al. Enhanced synaptic connectivity and epilepsy in C1q knockout mice. *Proc Natl Acad Sci U S A* (2010) 107(17):7975–80. doi: 10.1073/pnas.0913449107
69. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* (2011) 333(6048):1456–8. doi: 10.1126/science.1202529
70. Zhan Y, Paolicelli RC, Sforazzini F, Weinhard L, Bolasco G, Pagani F, et al. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nat Neurosci* (2014) 17(3):400–6. doi: 10.1038/nn.3641
71. Weinhard L, di Bartolomei G, Bolasco G, Machado P, Schieber NL, Neniskyte U, et al. Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. *Nat Commun* (2018) 9(1):1228. doi: 10.1038/s41467-018-03566-5
72. Chung WS, Clarke LE, Wang GX, Stafford BK, Sher A, Chakraborty C, et al. Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. *Nature* (2013) 504(7480):394–400. doi: 10.1038/nature12776
73. Iram T, Ramirez-Ortiz Z, Byrne MH, Coleman UA, Kingery ND, Means TK, et al. Megf10 is a receptor for C1Q that mediates clearance of apoptotic cells by astrocytes. *J Neurosci* (2016) 36(19):5185–92. doi: 10.1523/JNEUROSCI.3850-15.2016
74. Bolliger MF, Martinelli DC, Sudhof TC. The cell-adhesion G protein-coupled receptor BAI3 is a high-affinity receptor for C1q-like proteins. *Proc Natl Acad Sci U S A* (2011) 108(6):2534–9. doi: 10.1073/pnas.1019577108
75. Lanoue V, Usardi A, Sigoillot SM, Talleur M, Iyer K, Mariani J, et al. The adhesion-GPCR BAI3, a gene linked to psychiatric disorders, regulates dendrite morphogenesis in neurons. *Mol Psychiatry* (2013) 18(8):943–50. doi: 10.1038/mp.2013.46
76. Sigoillot SM, Iyer K, Binda F, Gonzalez-Calvo I, Talleur M, Vodjdani G, et al. The secreted protein C1QL1 and its receptor BAI3 control the synaptic connectivity of excitatory inputs converging on cerebellar Purkinje cells. *Cell Rep.* (2015) 10(5):820–32. doi: 10.1016/j.celrep.2015.01.034
77. Matsuda K, Budisantoso T, Mitakidis N, Sugaya Y, Miura E, Kakegawa W, et al. Transsynaptic modulation of kainate receptor functions by C1q-like proteins. *Neuron* (2016) 90(4):752–67. doi: 10.1016/j.neuron.2016.04.001
78. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res* (1982) 17(4):319–34. doi: 10.1016/0022-3956(82)90038-3
79. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry* (2000) 57(1):65–73. doi: 10.1001/archpsyc.57.1.65
80. Sweet RA, Henteleff RA, Zhang W, Sampson AR, Lewis DA. Reduced dendritic spine density in auditory cortex of subjects with schizophrenia. *Neuropsychopharmacology* (2009) 34(2):374–89. doi: 10.1038/npp.2008.67
81. McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, et al. MRI anatomy of schizophrenia. *Biol Psychiatry* (1999) 45(9):1099–119. doi: 10.1016/S0006-3223(99)00018-9
82. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry* (2005) 162(12):2233–45. doi: 10.1176/appi.ajp.162.12.2233
83. Hakobyan S, Boyajyan A, Sim RB. Classical pathway complement activity in schizophrenia. *Neurosci Lett* (2005) 374(1):35–7. doi: 10.1016/j.neulet.2004.10.024
84. Mayilyan KR, Arnold JN, Presanis JS, Soghoyan AF, Sim RB. Increased complement classical and mannan-binding lectin pathway activities in schizophrenia. *Neurosci Lett* (2006) 404(3):336–41. doi: 10.1016/j.neulet.2006.06.051
85. Mayilyan KR, Weinberger DR, Sim RB. The complement system in schizophrenia. *Drug News Perspect* (2008) 21(4):200–10. doi: 10.1358/dnp.2008.21.4.1213349
86. Havik B, Le Hellard S, Rietschel M, Lybaek H, Djurovic S, Mattheisen M, et al. The complement control-related genes CSMD1 and CSMD2 associate to schizophrenia. *Biol Psychiatry* (2011) 70(1):35–42. doi: 10.1016/j.biopsych.2011.01.030
87. Ripke S, Neale BM, Corvin A, Walters, JT, Farh K, et al., et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* (2014) 511(7510):421–7. doi: 10.1038/nature13595
88. Escudero-Esparza A, Kalchishkova N, Kurbasic E, Jiang WG, Blom AM. The novel complement inhibitor human CUB and Sushi multiple domains 1 (CSMD1) protein promotes factor I-mediated degradation of C4b and C3b and inhibits the membrane attack complex assembly. *FASEB J* (2013) 27(12):5083–93. doi: 10.1096/fj.13-230706
89. Steen VM, Nepal C, Ersland KM, Holdhus R, Naevdal M, Ratvik SM, et al. Neuropsychological deficits in mice depleted of the schizophrenia susceptibility gene CSMD1. *PLoS One* (2013) 8(11):e79501. doi: 10.1371/journal.pone.0079501
90. Prasad KM, Chowdari KV, D'Aiuto LA, Iyengar S, Stanley JA, Nimgaonkar VL. Neuropil contraction in relation to Complement C4 gene copy numbers in independent cohorts of adolescent-onset and young adult-onset schizophrenia patients-a pilot study. *Transl Psychiatry* (2018) 8(1):134. doi: 10.1038/s41398-018-0181-z
91. Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stallworth CL, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. *Neurology* (2002) 58(8):1214–20. doi: 10.1212/WNL.58.8.1214
92. Cagnoli PC, Sundgren PC, Kairys A, Graft CC, Clauw DJ, Gebarski S, et al. Changes in regional brain morphology in neuropsychiatric systemic lupus erythematosus. *J Rheumatol* (2012) 39(5):959–67. doi: 10.3899/jrheum.110833
93. Bialas AR, Presumey J, Das A, van der Poel CE, Lapchak PH, Mesin L, et al. Microglia-dependent synapse loss in type I interferon-mediated lupus. *Nature* (2017) 546(7659):539–43. doi: 10.1038/nature22821
94. Presumey J, Bialas AR, Carroll MC. Complement system in neural synapse elimination in development and disease. *Adv Immunol* (2017) 135:53–79. doi: 10.1016/bs.ai.2017.06.004
95. Sadek JR, Pergam SA, Harrington JA, Echevarria LA, Davis LE, Goade D, et al. Persistent neuropsychological impairment associated with West Nile virus infection. *J Clin Exp Neuropsychol* (2010) 32(1):81–7. doi: 10.1080/13803390902881918
96. Petersen LR, Carson PJ, Biggerstaff BJ, Custer B, Borchardt SM, Busch MP. Estimated cumulative incidence of West Nile virus infection in US adults, 1999-2010. *Epidemiol Infect* (2013) 141(3):591–5. doi: 10.1017/S0950268812001070
97. Vasek MJ, Garber C, Dorsey D, Durrant DM, Bollman B, Soung A, et al. A complement-microglial axis drives synapse loss during virus-induced memory impairment. *Nature* (2016) 534(7608):538–43. doi: 10.1038/nature18283
98. D'Ambrosio AL, Pinsky DJ, Connolly ES. The role of the complement cascade in ischemia/reperfusion injury: implications for neuroprotection. *Mol Med* (2001) 7(6):367–82. doi: 10.1007/BF03402183
99. Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. *Cold Spring Harb Perspect Med* (2012) 2(1):a006346. doi: 10.1101/cshperspect.a006346
100. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* (2016) 8(6):595–608. doi: 10.15252/emmm.201606210
101. Jiang H, Burdick D, Glabe CG, Cotman CW, Tenner AJ. beta-Amyloid activates complement by binding to a specific region of the collagen-like domain of the C1q A chain. *J Immunol* (1994) 152(10):5050–9.
102. Bradt BM, Kolb WP, Cooper NR. Complement-dependent proinflammatory properties of the Alzheimer's disease beta-peptide. *J Exp Med* (1998) 188(3):431–8. doi: 10.1084/jem.188.3.431
103. Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, Landfield PW. Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proc Natl Acad Sci U S A* (2004) 101(7):2173–8. doi: 10.1073/pnas.0308512100
104. Eikelenboom P, Hack CE, Rozemuller JM, Stam FC. Complement activation in amyloid plaques in Alzheimer's dementia. *Virchows Arch B Cell Pathol Incl Mol Pathol* (1989) 56(4):259–62. doi: 10.1007/BF02890024

105. Itagaki S, Akiyama H, Saito H, McGeer PL. Ultrastructural localization of complement membrane attack complex (MAC)-like immunoreactivity in brains of patients with Alzheimer's disease. *Brain Res* (1994) 645(1-2):78–84. doi: 10.1016/0006-8993(94)91640-3
106. Webster S, Lue LF, Brachova L, Tenner AJ, McGeer PL, Terai K, et al. Molecular and cellular characterization of the membrane attack complex, C5b-9, in Alzheimer's disease. *Neurobiol Aging* (1997) 18(4):415–21. doi: 10.1016/S0197-4580(97)00042-0
107. Shen Y, Lue L, Yang L, Roher A, Kuo Y, Strohmeyer R, et al. Complement activation by neurofibrillary tangles in Alzheimer's disease. *Neurosci Lett* (2001) 305(3):165–8. doi: 10.1016/S0304-3940(01)01842-0
108. Fonseca MI, Zhou J, Botto M, Tenner AJ. Absence of C1q leads to less neuropathology in transgenic mouse models of Alzheimer's disease. *J Neurosci* (2004) 24(29):6457–65. doi: 10.1523/JNEUROSCI.0901-04.2004
109. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* (2016) 352(6286):712–6. doi: 10.1126/science.aad8373
110. Litvinchuk A, Wan YW, Swartzlander DB, Chen F, Cole A, Propson NE, et al. Complement C3aR inactivation attenuates tau pathology and reverses an immune network deregulated in tauopathy models and Alzheimer's disease. *Neuron* (2018) 100(6):1337–1353 e5. doi: 10.1016/j.neuron.2018.10.031
111. Strohmeyer R, Shen Y, Rogers J. Detection of complement alternative pathway mRNA and proteins in the Alzheimer's disease brain. *Brain Res Mol Brain Res* (2000) 81(1-2):7–18. doi: 10.1016/S0169-328X(00)00149-2
112. Lui H, Zhang J, Makinson SR, Cahill MK, Kelley KW, Huang HY, et al. Progranulin deficiency promotes circuit-specific synaptic pruning by microglia via complement activation. *Cell* (2016) 165(4):921–35. doi: 10.1016/j.cell.2016.04.001
113. Williams PA, Tribble JR, Pepper KW, Cross SD, Morgan BP, Morgan JE, et al. Inhibition of the classical pathway of the complement cascade prevents early dendritic and synaptic degeneration in glaucoma. *Mol Neurodegener* (2016) 11:26. doi: 10.1186/s13024-016-0091-6
114. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* (2017) 541(7638):481–7. doi: 10.1038/nature21029
115. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA bipolar disorder working group. *Mol Psychiatry* (2018) 23(4):932–42. doi: 10.1038/mp.2017.73
116. Hutsler JJ, Zhang H. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Res* (2010) 1309:83–94. doi: 10.1016/j.brainres.2009.09.120
117. Tang G, Gudsnuk K, Kuo SH, Cotrina ML, Rosoklija G, Sosunov A, et al. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. *Neuron* (2014) 83(5):1131–43. doi: 10.1016/j.neuron.2014.07.040
118. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* (2009) 460(7256):748–52. doi: 10.1038/nature08185
119. Akcan U, Karabulut S, Ismail Kucukali C, Cakir S, Tuzun E. Bipolar disorder patients display reduced serum complement levels and elevated peripheral blood complement expression levels. *Acta Neuropsychiatr* (2018) 30(2):70–8. doi: 10.1017/neu.2017.10
120. Ruzzo EK, Geschwind DH. Schizophrenia genetics complements its mechanistic understanding. *Nat Neurosci* (2016) 19(4):523–5. doi: 10.1038/nn.4277
121. Tremblay ME, Lowery RL, Majewska AK. Microglial interactions with synapses are modulated by visual experience. *PLoS Biol* (2010) 8(11):e1000527. doi: 10.1371/journal.pbio.1000527
122. Bourgeois JP, Rakic P. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. *J Neurosci* (1993) 13(7):2801–20. doi: 10.1523/JNEUROSCI.13-07-02801.1993
123. Chung DW, Wills ZP, Fish KN, Lewis DA. Developmental pruning of excitatory synaptic inputs to parvalbumin interneurons in monkey prefrontal cortex. *Proc Natl Acad Sci U S A* (2017) 114(4):E629–37. doi: 10.1073/pnas.1610077114
124. Asano T, Ito H, Kariya Y, Hoshi K, Yoshihara A, Ugawa Y, et al. Evaluation of blood-brain barrier function by quotient alpha2 macroglobulin and its relationship with interleukin-6 and complement component 3 levels in neuropsychiatric systemic lupus erythematosus. *PLoS One* (2017) 12(10):e0186414. doi: 10.1371/journal.pone.0186414
125. Mehlhop E, Whitby K, Oliphant T, Marri A, Engle M, Diamond MS. Complement activation is required for induction of a protective antibody response against West Nile virus infection. *J Virol* (2005) 79(12):7466–77. doi: 10.1128/JVI.79.12.7466-7477.2005
126. Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med* (2004) 350(6):552–9. doi: 10.1056/NEJMoa031688
127. Hillmen P, Muus P, Roth A, Elebute MO, Risitano AM, Schrezenmeier H, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* (2013) 162(1):62–73. doi: 10.1111/bjh.12347
128. Ricklin D, Mastellos DC, Reis ES, Lambris JD. The renaissance of complement therapeutics. *Nat Rev Nephrol* (2018) 14(1):26–47. doi: 10.1038/nrneph.2017.156
129. Falcao DA, Reis ES, Paixao-Cavalcante D, Amano MT, Delcolli MI, Florido MP, et al. Deficiency of the human complement regulatory protein factor H associated with low levels of component C9. *Scand J Immunol* (2008) 68(4):445–55. doi: 10.1111/j.1365-3083.2008.02152.x
130. Audemard-Verger A, Descloux E, Ponard D, Deroux A, Fantin B, Fieschi C, et al. Infections revealing complement deficiency in adults: a French nationwide study enrolling 41 patients. *Medicine (Baltimore)* (2016) 95(19):e3548. doi: 10.1097/MD.0000000000003548
131. Lachmann PJ, Smith RA. Taking complement to the clinic-has the time finally come? *Scand J Immunol* (2009) 69(6):471–8. doi: 10.1111/j.1365-3083.2009.02258.x
132. Morgan BP, Harris CL. Complement, a target for therapy in inflammatory and degenerative diseases. *Nat Rev Drug Discov* (2015) 14(12):857–77. doi: 10.1038/nrd4657
133. Ricklin D, Lambris JD. New milestones ahead in complement-targeted therapy. *Semin Immunol* (2016) 28(3):208–22. doi: 10.1016/j.smim.2016.06.001
134. Brennan FH, Lee JD, Ruitenberg MJ, Woodruff TM. Therapeutic targeting of complement to modify disease course and improve outcomes in neurological conditions. *Semin Immunol* (2016) 28(3):292–308. doi: 10.1016/j.smim.2016.03.015
135. Sim RB, Schwaeble W, Fujita T. Complement research in the 18th-21st centuries: Progress comes with new technology. *Immunobiology* (2016) 221(10):1037–45. doi: 10.1016/j.imbio.2016.06.011

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REVIEW
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The Anti-Inflammatory Role of Omega-3 Polyunsaturated Fatty Acids Metabolites in Pre-Clinical Models of Psychiatric, Neurodegenerative, and Neurological Disorders

Juliette Giacobbe[1†], *Bonnie Benoiton*[2†], *Patricia Zunszain*[1], *Carmine M. Pariante*[1] *and Alessandra Borsini*[1*]

[1] *Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom,* [2] *Guy's King's and St. Thomas' School of Life Science and Medicine, King's College London, London, United Kingdom*

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***Correspondence:**
Alessandra Borsini
alessandra.borsini@kcl.ac.uk

[†] *These authors have contributed equally to this work*

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Inflammation has been identified as one of the main pathophysiological mechanisms underlying neuropsychiatric and neurodegenerative disorders. Despite the role of inflammation in those conditions, there is still a lack of effective anti-inflammatory therapeutic strategies. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) can reduce depressive symptoms and exert anti-inflammatory action putatively by the production of distinct n-3 PUFA-derived metabolites, such as resolvins D (RvD) and E (RvE) series, maresins (MaR) and protectins (PD), which are collectively named specialized pro-resolving mediators (SPMs) and act as strong anti-inflammatory agents. In this review we summarize evidence showing the effects of treatment with those metabolites in pre-clinical models of psychiatric, neurodegenerative and neurological disorders. A total of 25 pre-clinical studies were identified using the PubMed database. Overall, RvD and RvE treatment improved depressive-like behaviors, whereas protectins and maresins ameliorated neurological function. On a cellular level, RvDs increased serotonin levels in a model of depression, and decreased gliosis in neurodegenerative disorders. Protectins prevented neurite and dendrite retraction and apoptosis in models of neurodegeneration, while maresins reduced cell death across all studies. In terms of mechanisms, all SPMs down-regulated pro-inflammatory cytokines. Resolvins activated mTOR and MAP/ERK signaling in models of depression, while resolvins and maresins activated the NF-κB pathway in models of neurodegeneration and neurological disorders. Our review indicates a potential promising approach for tailored therapy with n-3 PUFAs-derived metabolites in the treatment of psychiatric, neurodegenerative, and neurological conditions.

Keywords: resolvin, protectin, maresin, neuroinflammation, omega-3, polyunsaturated fatty acid

INTRODUCTION

Over the last few decades, inflammation has been identified as one of the main pathophysiological mechanisms underlying psychiatric conditions (1, 2). Indeed, over-expression of distinct pro-inflammatory cytokines, including interleukin 1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α), has been associated with several neuropsychiatric disorders, such as depression (3, 4), as well as neurodegenerative diseases, like Alzheimer's (AD) and Parkinson's (PD) (5, 6). In particular, patients with major depressive disorder (MDD) exhibit both increased immune activation and aberrant regulation of brain plasticity (7), which has been linked with abnormal cellular immunity (8). Similar abnormalities have also been reported in PD and AD, which are characterized by a dysregulated immune response, due to hyper-stimulation of microglia to activate distinct inflammatory signaling pathways (9) related to aggregates of alpha-synuclein and beta-amyloid protein, respectively (10, 11). In all these conditions, the presence of pro-inflammatory cytokines leads to the impairment of microglial function, including phagocytosis of debris, and propagation of inflammation (12). This is accompanied by an insufficient compensatory and regulatory function of anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, which are produced by alternatively activated M2 microglia (13). Conversely, classically activated M1 microglia have been shown to be increased in the brain of patients (13, 14). Despite the role of inflammation in the context of both psychiatric and neurodegenerative disorders (15, 16), there is still a lack of effective anti-inflammatory strategies that are safe for everyday use and display a clear mechanism of action.

Recently, increasing attention has been given to potentially anti-inflammatory nutritional interventions, particularly omega-3 polyunsaturated fatty acids (n-3 PUFAs), like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have been known to reduce depressive symptoms in patients (17, 18) and animal models (19), as well as cognitive symptoms (20). EPA has been found to be present at lower levels in patients with interferon-alpha-induced depression (21), the development of which has been shown to be prevented by EPA treatment (22), supporting n-3 PUFAs anti-inflammatory properties (23). Although the exact mechanisms underlying their mode of action remain unknown, n-3 PUFAs are important in regulating immune responses by inhibiting activation of pro-inflammatory pathways and reducing cytokine expression (24). This function has been suggested to be mediated by the production of distinct n-3 PUFAs-derived metabolites, defined as specialized pro-resolving mediators (SPMs), including resolvins D (RvD) and E (RvE) series, maresins (MaR) and protectins (PD), which become elevated upon exposure to an inflammatory challenge in order to re-establish internal immune homeostasis (25). In particular, SPMs are produced upon metabolism of n-3 PUFAs by specific enzymes including lipoxygenases, 5-lipoxygenase-1 (5-LOX), 12-LOX, and 15-LOX, cyclooxygenases, primarily COX-2, and cytochrome P450 enzymes (**Figure 1**). These enzymatic transformations occur rapidly within the organism and genetic variants of the involved enzymes have been associated with increased risk of developing interferon-alpha-induced depression (26), which suggests that the anti-inflammatory effects of n-3 PUFAs may indeed stem from SPMs actions.

Research into the effectiveness of SPMs treatment has been carried out in various models of peripheral and central inflammation. For example, RvDs and protectins have been shown to improve inflammatory outcomes in animal models of colitis and obesity-induced diabetes, where a reduction in cytokine levels, including IL-6, were reported in macrophages derived from bone marrow tissue (27, 28), as well as in adipose tissue (29). With respect to the CNS, evidence has shown that protectins and resolvins are produced in the brain, as shown

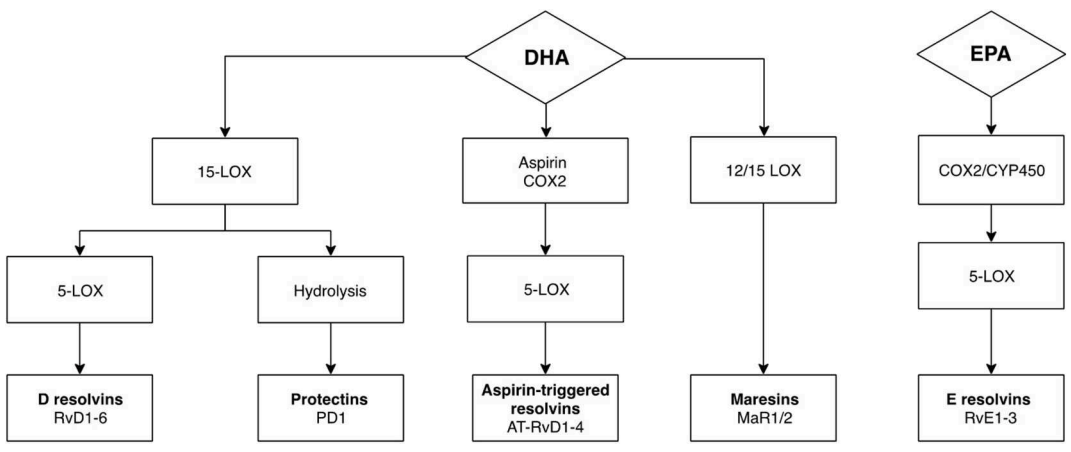

FIGURE 1 | Metabolism of DHA and EPA to SPMs through enzymatic transformation. SPMs are produced upon metabolism of n-3 PUFAs by specific lipoxygenase and cyclooxygenase enzymes. Respectively, the enzymes 15-lipoxygenase-1 (15-LOX) and 12-lipoxygenase (12-LOX) are responsible for initiating the conversion of DHA to protectin-1 (PD1), and maresin 1 and 2 (MaR1, MaR2), whereas 15-LOX, cyclooxygenase 2 (COX-2) and cytochrome P450 are responsible for the conversion of DHA to resolvins D series (RvD), and of EPA to resolvins E series (RvE). Downstream, metabolism of RvD and RvE are dependent on 5-lipoxygenase (5-LOX). Aspirin-acetylated COX-2 followed by 5-lipoxygenase (5-LOX) transformation generates aspirin-triggered isomers of RvDs (AT-RvD).

by studies using brain tissue homogenates (30, 31), neuron-glia cultures or hippocampal tissue (32). In a model of inflammatory pain, RvDs and RvEs were found to reduce pain behaviors through central actions (33). Additionally, maresins have been demonstrated to attenuate mechanical allodynia (34, 35), a process involving central sensitization, and decreased levels of IL-1β, IL-6, and TNF-α in spinal cord tissue in models of neuropathic pain. Taken together, these findings therefore suggest the potential involvement of SPMs in other disorders within the CNS.

Given the need to elucidate the mechanisms whereby n-3 PUFAs-derived metabolites exert their anti-inflammatory actions and the potential role of SPMs in reducing CNS inflammation, it appears relevant to summarize the evidence provided thus far on their effects in the context of psychiatric, neurodegenerative, and neurological disorders, in addition to uncovering mechanisms specific to these conditions. Overall, 25 articles were obtained from the PubMed database, including *ex vivo*, *in vivo*, and *in vitro* studies investigating resolvins (RvD1, RvD2, RvE1, RvE2, RvE3), protectins (PD1, NPD1), and maresins (MaR1, MaR2) in relation to psychiatric, neurodegenerative, and neurological disorders affecting cognition, and in which neuroinflammation is part of the pathophysiology. Studies excluded from the search were or contained one or more of the following: not published in English language, did not look at the specific effects of treatment with resolvin, proctectin, or maresin, were not measuring psychiatric, neurological, neuroinflammatory, or cognitive outcomes.

BEHAVIORAL, CELLULAR AND MOLECULAR OUTCOMES IDENTIFIED UPON TREATMENT WITH SPMs

In this section of the review we summarize behavioral, cellular, and molecular outcomes identified in *ex vivo*, *in vivo*, and *in vitro* studies which used treatment with resolvins, protectins and maresins in the context of psychiatric, neurodegenerative, and neurological disorders (**Table 1**).

Resolvin D

RvD1

Behavioral findings

Models of depression. While depression has a wide range of symptoms, from persistent sad mood to appetite or sleep changes (60), it was assessed by behavioral despair, measured using the immobility time in the forced swim test (FST) or tail suspension test (TST) in most of the studies. In a mouse chronic unpredictable stress (CUS) model (39) intracranial RvD1 administration decreased behavioral despair in the FST. This was also found in a rat post-myocardial infarct model of depression, where depression-like behaviors are increased after occlusion of the left anterior descending coronary artery (37). However, neither peripheral nor central RvD1 administration improved FST immobility in a mouse fibromyalgia-induced depression model (38), where mice develop depression-like behavior after reserpine injection. In the TST, intracranial RvD1 also reduced behavioral despair in both CUS (39) and lipopolysaccharide (LPS)-induced mouse models of depression (36). Social behavior, commonly affected in depression, was enhanced by intracranial injection of RvD1 in a rat model of depression (37).

Models of neurodegenerative and neurological disorders. The behavioral outcomes of aspirin-triggered isomer of RvD1 (AT-RvD1) administration were investigated in two *in vivo* studies. Peripheral AT-RvD1 injection ameliorated sensorimotor function and memory after traumatic brain injury (TBI) in mice, confirming the hypothesis that reducing the prolonged inflammation caused by TBI would in consequence limit the impact seen in neurological functions (43). Peripheral AT-RvD1 administration was also beneficial on cognitive impairment and fear-associated freezing in mice with surgery-induced cognitive decline, mimicking the cognitive dysfunctions observed in some patients after orthopedic surgery (44).

Cellular findings

Models of depression. Only one of the studies previously mentioned investigated the cellular effects of AT-RvD1 in the context of depression. *In vivo,* intravenous AT-RvD1 administration increased levels of cortical dopamine and glutamate, and limited serotonin depletion in a mouse model of fibromyalgia-associated depression, suggesting a positive effect of treatment on neurotransmitter imbalance in depression (38).

Models of neurodegenerative and neurological disorders. Three studies investigated the effects of RvD1 in macrophages isolated from peripheral blood mononuclear cells (PBMC) of AD patients treated with n-3 PUFAs supplementation. In one study, RvD1 incubation of PBMC from AD patients improved phagocytosis of Aβ peptides on a trend level (41). In another, RvD1 significantly increased phagocytosis and decreased apoptosis in PBMC (42). In the third paper treatment with RvD1 decreased the M1/M2 macrophage ratio in PBMC from AD patients with the apolipoprotein E (APoE) ε3/ε3 genotype, while RvD1 increased it in cells with the APoE ε3/ε4 genotype (40).

In vivo, peripheral AT-RvD1 administration prevented astrogliosis and improved short and long-term potentiation in the hippocampus of mice with cognitive decline (44). *In vitro*, embryonic human microglia incubated with $A\beta_{42}$ peptides and exposed to RvD1 had decreased expression of microglia pro-inflammatory markers CD11b and CD40 (46). In an *in vitro* model of PD using the toxin 1-methyl-4-phenyl pyridinium (MPP+) to target dopaminergic cells, RvD1 treatment of rat adrenal phaeochromocytoma cells rescued them from apoptosis (45).

Mechanisms of action

Models of depression. In the selected papers, only one *in vivo* study using a mouse model of depression examined the mechanisms underlying the actions of RvD1. The anti-depressant effects of intracranial administration of RvD1 were shown to be mediated by the activation of the N-formyl peptide receptor 2 (ALX/FPR2). Downstream, RvD1 was shown to act through activation of mammalian target of rapamycin complex

TABLE 1 | Behavioral, cellular and molecular outcomes identified upon treatment with SPMs.

Treatment	Type of study	Pathology	Model	Main findings			References
				Behavioral	Cellular	Mechanism	
				Resolvin D			
RvD1							
Models of depression							
RvD1	*In vivo*	Depression	LPS-induced, mice. I.c.v. RvD1 treatment and pathway antagonists	↘ TST immobility		Effects dependent on ALX/FPR2 rec., mTORC, MAP/ERK, AMPAR, PI3K/Akt	Deyama et al. (36)*
RvD1	*In vivo*	Myocardial infarct-associated depression	Rats I.c.v. RvD1 before or after ischemia	↗ social interaction ↘FST			Gilbert et al. (37)
RvD1 and AT-RvD1	*In vivo*	Fibromyalgia-associated depression	Resperine induced, mice. I.v. or i.c. RvD1 or AT-RvD1 treatment	AT-RvD1: ↘ mechanical allodynia (acute), nociception (chronic) ↘ FST immobility (chronic) RvD1: NS effect	AT-RvD1: ↗ dopamine (cortex), serotonin (thalamus), glutamate RvD1: NS effect		Klein et al. (38)*
RvD1	*In vivo*	Depression	Chronic unpredictable stress, mice. I.c.v. RvD1	↘FST, TST immobility			Ishikawa et al. (39)*
Models of neurocognitive and neurological disorders							
RvD1	*Ex vivo*	AD/MCI	PBMC of patients taking DHA+EPA supplements RvD1 treatment		RvD1 ↘ M1/M2 ratio in ApoE ε3/ε3 cells but ↗ M1/M2 ratio in ApoE ε3/ε4 cells		Famenini et al. (40)
RvD1	*Ex vivo*	AD	Macrophages from PBMC of patients taking DHA+EPA supplements Cells: DHA+EPA or RvD1 treatment Aβ incubation		RvD1 treatment: NS ↗ of phagocytosis compared with placebo	RvD1 treatment: NS ↗ of p-PERK expression NS ↘ caspase 3 expression in MCI patients	Olivera-Perez et al. (41)
RvD1	*Ex vivo*	AD	PBMC of AD patients. RvD1 treatment Aβ incubation Pre-treated with GPR32, EGTA, MEK1/2, PI3, or PKI antagonists		↗ phagocytosis ↘ caspase-3 dependent apoptosis	↗ phagocytosis dependent on GPR32, EGTA, MEK1/2, PI3, and PKI ↘ cytokines and chemokine transcription ↘ IL-1β, IL-6, IL-10, GMCSF, and TNF-α secretion	Mizwicki et al. (42)
AT-RvD1	*In vivo*	Traumatic brain injury	Midline perfusion injury, mice. I.p. AT-RvD1	↗ sensorimotor functions ↗ NOR task			Harrison et al. (43)*
AT-RvD1	*In vivo*	Surgery-induced cognitive decline	Open stabilized tibia fracture model, mice. Fear conditioning pre-surgery I.p. pre-treatment or delayed AT-RvD1	↗ memory ↗ impaired freezing behavior	Prevention of astrogliosis and prevention of ramification and ↘ cell area	↘ IL-6, LXA4 in plasma	Terrando et al. (44)
			Hippocampal slices from mice, post-surgery, and post-AT-RvD1 treatment		Pre-treatment ↗ short-term plasticity and LTP Delayed treatment ↗LTP		
RvD1	*In vitro*	Parkinson	Rat adrenal phaeochromocytoma cells, MPP+ -induced RvD1 treatment		↘ apoptosis, cellular damage ↗viability	↘ p-p38 MAPK, p-ERK ↘ NF-κB p50 ↘ TNF-α, not IL-6	Xu et al. (45)

(Continued)

TABLE 1 | Continued

Treatment	Type of study	Pathology	Model	Main findings			References
				Behavioral	Cellular	Mechanism	
RvD1	*In vitro*	AD	Human bone-marrow derived neuroblastoma cells RvD1 treatment		↘ apoptosis ↗viability	GPR32 expressed	Zhu et al. (46)*
			Embryonic human microglial cells RvD1 treatment Aβ42 incubation		↗ CD11b	GPR32 and ALX/FPR2 expressed	
RvD2							
Models of depression							
RvD2	*In vivo*	Fibromyalgia-associated depression	Resperine induced, mice. I.v. or i.c., acute or chronic.	↘ mechanical allodynia (acute), nociception (chronic) ↘ FST immobility (chronic)	↗ serotonin, glutamate		Klein et al. (38)*
RvD2	*In vivo*	Depression	Chronic unpredictable stress, mice. I.c.v. RvD2	↘ FST, TST immobility			Ishikawa et al. (39)*
RvD2	*In vivo*	Depression	LPS-induced, mice. I.c.v. RvD2 + pathway antagonists	↘ FST, TST immobility		Effects dependent on GPR18 rec., mTORC, MEK/ERK	Deyama et al. (36)*
Models of neurocognitive and neurological disorders							
RvD2	*In vivo*	Parkinson	LPS-induced, rats. I.c.v. RvD2	↗ motor behavior	↗ ramified microglia	↘ NF-κB ↘ IL-18, IL-6, NO, TNF-α, and IL-1β	Tian et al. (47)
	Ex vivo	Parkinson	Primary cortical microglia culture, rats LPS-induced RvD2 (5 ≠ concentrations)		↘ activated microglia	↘ NF-κB p65, iNOS, IkBa, IKKb ↘ IL-18, IL-6, NO, TNF-α, and IL-1β	

Treatment	Type of study	Pathology	Model	Main findings			References
				Behavioral	Cellular	Mechanism	
				Resolvin E			
Models of depression							
RvE1	*In vivo*	Depression	LPS-induced, mice. I.c.v. RvE1, pathway antagonists	↘ FST, TST		Effects similar to ChemR23 agonist, dependent on mTORC1	Deyama et al. (48)
RvE2	*In vivo*	Depression	LPS-induced, mice. I.c.v. RvE2, pathway antagonists	↘ FST, TST		Effects similar to ChemR23 agonist	
RvE3	*In vivo*	Depression	LPS-induced, mice. I.c.v. RvE3	↘ TST			Deyama et al. (49)
Models of neurocognitive and neurological disorders							
RvE1	*In vivo*	Traumatic brain injury	Midline perfusion injury, mice. I.p. RvE1	↗ sleep	↗ ramified microglia, ↘ M1		Harrison et al. (43)*

(Continued)

TABLE 1 | Continued

Treatment	Type of study	Pathology	Model	Main findings			References
				Behavioral	Cellular	Mechanism	
RvE1	*In vivo*	AD	5xFAD mice. I.p. RvE1, LXA4, or RvE1+LXA4		RvE1+LXA4 ↘ microgliosis and astrogliosis RvE1+LXA4 ↘ Aβ40 RvE1 ↘ Aβ42 ↘ RvE1 and RvD2 in AD vs. WT, ↗ after RvE1 treatment	All ↘ GMCSF, IL-1β, IL-6, IL-10	Kantarci et al. (50)

Treatment	Type of study	Pathology	Model	Main findings			References
				Behavioral	Cellular	Molecular/mechanism	
PROTECTIN							
Models of neurocognitive and neurological disorders							
AT-PD1-SS AT-PD1-ME	*In vivo*	Ischemic stroke	Right middle cerebral artery occlusion, rats. I.v. AT-PD1-SS or AT-PD1-ME	↗ neurological recovery	↘ activated microglia/macrophages ↗ blood vessel + GFAP-rich scar density		Bazan et al. (51)
PD1	*In vivo*	TBI	Skull thinning in *fat-1* mice Normal or high n-6 diet I.v. DHA or i.c.v. PD1		↗ parenchymal cell survival in WT PD1 ↗ PD1 in fat-1 mice vs. WT		Ren et al. (52)
PD1	*In vivo*	Ischemic stroke	Right middle cerebral artery occlusion, rats. I.v. DHA, saline, PD1, or CSF treatment	↗ neurological score	↗ neuro- and angiogenesis ↘ IgG immunoreactivity ↗ axonal sprouting		Belayev et al. (53)
PD1 $_{n-3}$ DPA–ME	*In vivo*	Epilepsy	Kainic acid epilepsy model, mice. I.c.v. PD1 after status epilepticus	Rescued ORT exploration time ↘ number of seizures	↘ astro- and microgliosis ↘ ectopic DCX cells No neuroprotection	↘ IL-1β, TNF-α mRNA	Frigerio et al. (54)
PD1	*In vitro*	PD	Primary rat dopaminergic mesencephalic neurons MPP+, MPTP, or rotenone induced PD1 treatment		↘ apoptosis in MPP+ and rotenone cells ↗ arborization (MPP+ cells only) ↘ dendrite retraction (MPP+, MPTP)		Calandria et al. (55)
PD1	*In vitro*	AD	Cortical human neuron-glia co-culture		↘ $A\beta_{42}$-induced apoptosis ↘ neurite retraction	↗ Bcl-xl, Bcl-2, Blf(A1) ↘ Bax, Bik	Lukiw et al. (32)
PD1	*In vitro*	AD	Human neuronal-glial cells Challenged with Aβ42 oligomeric peptide or transfected with beta amyloid precursor protein $(\beta APP)_{SW}$ PD1 treatment		↘ $A\beta_{42}$-induced apoptosis PD1 ↘ viability and ↗ apoptosis and cytotoxicity ↘ BACE1 ↗m-ADAM10 ↘ sAPPβSW ↗sAPPα	NPD1 mimics PPARγ receptor effects ↘ COX-2, TNF-α, B94 ↘ caspase-3	Zhao et al. (56)
PDX	*In vitro*	Ischemia	Mouse subventricular zone NSC Healthy or glucose-deprived PDX or DHA treatment		PDX ↘ proliferation in healthy NSC, ↗ proliferation in OGD NSC ↗ differentiation in healthy NSC (trend level) and OGD cells		Lo Van et al. (57)
PDX	*In vitro*	AD	Human bone-marrow derived neuroblastoma cells PDX treatment		↘ apoptosis ↗viability		Zhu et al. (46)*

(Continued)

TABLE 1 | Continued

Treatment	Type of study	Pathology	Model	Main findings			References
				Behavioral	Cellular	Mechanism	
				MARESIN			
Models of neurocognitive and neurological disorders							
MaR1	*In vivo*	Stroke	MCAO, mice. I.c.v. MaR1 administration	↗ neurological score	↘ neurodegeneration, cell death (PSD95, synapsin1) ↘ gliosis	↘ NF-κB p65 ↘ TNF-α, IL-1β, MCP-1	Xian et al. (58)
MaR1	*In vitro*	ALS	SOD1 or TDP-43 expression in human neuroblastoma spinal cord cells H_2O_2 stress-induced cell death model DHA or MaR1 treatment		↘ cell death (MaR1 stronger than DHA) in SOD1/TDP-43 model ↘ oxidative stress-induced cell death	Caspase 3/7 inhibition by MaR1 ↘ ROS, ↘ p-NF-κB	Ohuchi et al. (59)
MaR1	*In vitro*	AD	Human bone-marrow derived neuroblastoma cells MaR1 treatment Embryonic human microglial cells Aβ42 incubation MaR1 treatment		↘ apoptosis ↗phagocytosis	↘ CD11b, MHC-II, CD86, CD40, and CD33	Zhu et al. (46)*

15-LOX, 15-lipoxygenase; 5-LOX, 5-lipoxygenase; AD, Alzheimer's disease; ALX/FPR2, N-formyl peptide receptor 2; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ApoE, Apolipoprotein E; AT-PD1-ME, aspirin-triggered protectin D1 methyl-ester; AT-PD1-SS, aspirin- triggered protectin D1 sodium-salt; AT-RvD1, aspirin-triggered resolvin D; Aβ, beta amyloid; BACE1, beta-secretase 1; CCL, CC chemokine ligand; ChemR23, chemokine-like receptor 1; CNS, central nervous system; COX-2, cyclooxygenase 2; CSF, cerebrospinal fluid; CXCL, chemokine C-X-C motif ligand; DCX, doublecortin; DHA, docosahexaenoic acid; EAE, experimental autoimmune encephalitis; EGTA, ethylene glycol tetraacetic acid; FST, forced swim test; GFAP, glial fibrillary acidic protein; GPR18, G protein-coupled receptor 18; GPR32, G protein-coupled receptor 32; GSH, glutathione; GSMCSF, granulocyte-macrophage colony-stimulating factor; Hcb, hemicerebellectomy; i.c., intrathecal; i.c.v., intracerebroventricular; IFN-γ, interferon gamma; IgG, immunoglobulin; IKK, IκB kinase; IL-1β, interleukin 1 beta; IL-6, interleukin 6; i.p., intraperitoneal; i.v., intravenous; LPS, lipopolysaccharide; LTP, long term potentiation; LXA4, lipoxin 4; MAPK, mitogen-activated protein kinase; MaR1, maresin 1; MCI, mild cognitive impairment; MCP-1, monocyte chemoattractant protein 1; MEK, mitogen-activated protein kinase; MHC-II, majoe histocompatibility complex class II; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTORC, mammalian target of rapamycin complex; n-3 PUFA, omega-3 polyunsaturated fatty acid; NF-κB, Nuclear factor-kappa B; NO, nitric oxide; NOR, novel object recognition task; NOS, nitric oxide synthases; NSC, neural stem cells; PBMC, peripheral blood mononuclear cells; PD1, protectin 1; PDX, protectin DX; p-ERK, phosphorylated extracellular signal–regulated kinase; PI3, phosphatidylinositide 3-kinase; PKI, protein kinase inhibitor; p-p38, phosphorylated p38; PPARγ, peroxisome proliferator-activated receptor gamma; p-PERK, phosphorylated protein kinase-like endoplasmic reticulum kinase; PSD95, postsynaptic density protein 95; RvD1, resolvin D 1; RvD2, resolvin D 2; RvE1, resolvin E 1; SCI, spinal cord injury; SOD-1, superoxide dismutase 1; SMNΔ7, survival motor neuron gene lacking exon 7; SPM, specialized pro-resolving mediators; TDP-43, TAR DNA-binding protein 43; TH+, tyrosine hydroxylase positive; TNF-α, tumor necrosis factor alpha; TST, tail suspension test; WT, wild type; βAPP_{sw}, beta amyloid precursor protein swedish double mutation.

*↗ increase; ↘ decrease; * article appearing several times.*

1(mTORC1), MAP/ERK, PI3K/Akt signaling, as well as by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (36).

Models of neurodegenerative and neurological disorders. Out of the five studies investigating the mechanisms of RvD1 in neurodegenerative and neurological disorders, two were *ex vivo*, one was *in vivo* and two were *in vitro*. In PBMC from AD patients, RvD1 treatment decreased the transcription of immune genes and the secretion of cytokines, such as IL-1β, IL-10, or IL-6 (42). In the same study, inhibition of the G protein-coupled receptor 32 (GRP32) prevented RvD1-induced phagocytosis of Aβ (42). In another study using PBMC from AD patients receiving oral nutritional intervention with n-3 PUFAs, cell treatment with RvD1 lowered p-PERK and caspase-3 expression on a trend level (41).

In vivo, IL-6 was decreased by peripheral RvD1 injection, along with the n-6 PUFAs-derived SPM lipoxin (LXA_4) in the plasma of mice with surgery-induced cognitive decline (44). *In vitro*, RvD1 reduced TNF-α protein expression, but not IL-6, and prevented high levels of NF-κB p50 in a PD model of rat adrenal phaeochromocytoma cells (45). The expression of GRP32 was also confirmed in human bone-marrow derived neuroblastoma cells (46).

RvD2

Behavioral and cellular findings

Models of depression. In three mouse models of depression, RvD2 was shown to have positive effects on depressive-like behavior, however, only one study also investigated cellular outcomes. Central RvD2 administration was reported to improve FST and TST scores in LPS-induced (36) and in a CUS model of depression (39). Similarly, in a model of fibromyalgia-associated depression, intravenous RvD2 prevented immobility in the FST (38). With respect to cellular findings, RvD2 administration partially prevented total brain serotonin loss and increased glutamate levels (38).

Models of neurodegenerative and neurological disorders. To our knowledge, only one study described findings on the behavioral and cellular effects of RvD2 administration in neurodegenerative disorders. In a LPS-induced PD model, intracranial addition of RvD2 to apomorphine, a non-selective dopamine receptor agonist, improved motor function of rats more efficiently, when compared with apomorphine alone (47). Regarding cellular findings, RvD2 effectively reduced the number of activated microglia and increased the ramified phenotype in the substantia nigra of rats with PD. This was also shown in a primary culture of cortical microglia from neonatal rats (47).

Mechanisms of action

Models of depression. Among the studies previously mentioned, only one investigated the mechanisms underlying the effects of treatment with RvD2 in a model of depression. In particular, they showed that improvement in depressive-like behavior was observed in mice after intracranial RvD2 administration, which was independently mediated by GPR18, a G-protein-coupled receptor activated by cannabinoids (61) and RvD2, mTORC1, and MAP/ERK signaling (36).

Models of neurodegenerative and neurological disorders. In one study, RvD2 was reported to exert its beneficial actions through microglia in LPS-induced PD models. Specifically, RvD2 decreased transcription of several cytokines such as IL-18, IL-6, TNF-α, and IL-1β in the cytoplasm in an *in vitro* model of PD using rat primary cortical microglia. The expression of these cytokines was also reduced in the plasma of PD rats after central injection of RvD2. Moreover, RvD2 effectively prevented an up-regulation of NF-κB p65 subunit and IκBα in ventral mesencephalon microglia of PD rats (47).

The evidence summarized in this section highlights the role of RvDs in reducing depression-like behavior in models of depression, and in decreasing glial inflammatory processes in neurogenerative models.

Resolvin E

Behavioral and Cellular Findings

Models of depression

RvE series were shown to have beneficial effects in mice when injected centrally. Administration of RvE1, RvE2, and RvE3 improved behavioral despair in the TST in a LPS-induced model of depression (48, 49). This was also demonstrated in the FST, but only in respects of intracranial RvE1 and RvE2 injection (49).

Models of neurodegenerative and neurological disorders

One *in vivo* study investigated the behavioral effects of RvE1, and two *in vivo* studies investigated the cellular effects. In a mouse model of TBI, peripheral RvE1 administration affected sleep during the first 12 h post-injury. Specifically, an overall increase in number, but not length, of sleep bouts in both light and dark periods was seen upon RvE1 administration (43). On a cellular level, RvE1 administration increased the number of ramified microglia and decreased the number of rod microglia in the primary somatosensory cortex of mice (43). In addition, intraperitoneal injection of RvE1 with LXA_4 decreased microgliosis and astrogliosis in the cortex and hippocampus of AD mice (50).

Mechanisms of Action

Models of depression

One *in vivo* study proposed two different mechanisms of actions for RvEs using a model of LPS-induced depression in mice. Firstly, intracranial injection of RvE1 and RvE2 produced anti-depressant effects similar to those observed by activating ChemR23, a G-coupled receptor activated by chemerin (62) and RvE1 (63), suggesting the involvement of this receptor in depression. Secondly, inhibition of the mTORC1 pathway was able to prevent the anti-depressant effects of RvE1 (49).

Models of neurodegenerative and neurological disorders

In an *in vivo* transgenic mouse model of AD, RvE1 was shown to exert its effects through down-regulation of various pro-inflammatory factors. Specifically, peripheral RvE1 injection reduced levels of IL-6, IL-1β, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, TNF-α, monocyte

chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP)-1a, and MIP1b in the prefrontal cortex (50).

The evidence summarized in this section supports the potential of RvEs, similar to RvDs, to alleviate depression-like behavior, which would occur via mTORC1 activation. In terms of neurodegenerative disorders, studies clearly present RvEs as beneficial agents against the increased levels of cytokines and pro-inflammatory factors present in those conditions.

Protectins

Behavioral Findings

Models of neurodegenerative and neurological disorders

Behavioral effects of PD1 administration were measured in three *in vivo* studies, one in the context of epilepsy and two in the context of stroke, both conditions which are associated with increased central inflammation affecting neurogenesis-related cognitive processes. Intracranial PD1 administration improved cognitive function, specifically non-spatial recognition memory, in the novel object recognition task in kainic acid-induced epilepsy in mice (54). PD1 also reduced frequency and seizure duration and prevented weight loss (54). Additionally, intravenous injection of PD1 and its aspirin-triggered isomer (AT-PD1) improved neurological recovery in rat models of ischemic stroke using middle cerebral artery occlusion (51, 53).

Cellular Findings

Models of neurodegenerative and neurological disorders

Cellular outcomes were investigated in nine studies both *in vivo* and *in vitro*, predominantly using models of AD and ischemia. Intravenous administration of PD1 *in vivo* reduced immunoglobulin G (IgG) immunoreactivity in the cortex, subcortex, and whole right hemisphere of rats subject to ischemic stroke (53). It also inhibited astrocyte and microglia activation in the penumbra of ischemic rats (51). Likewise, intracranial infusion of PD1 in epileptic mice decreased astrogliosis and microgliosis in the hippocampus, and increased neuroblasts migration in the hilus (54). In a mouse model of TBI, intracranial administration of PD1 also improved parenchymal cell survival (52).

In vitro, PD1 treatment decreased $A\beta_{42}$ production (56) and prevented $A\beta_{42}$-induced apoptosis and increased cell viability in two human models of AD, both using cortical neuron-glia co-culture (32, 56). This was also observed upon treatment with protectin isomer, PDX, in a human bone-marrow derived neuroblastoma cell model of AD (46). In a rat dopaminergic mesencephalon neurons model of PD, PD1 treatment decreased dendritic retraction and increased neuronal survival (55). Finally, in an *in vitro* model of ischemia, PDX also increased proliferation of mice subventricular zone neural progenitors (57).

Mechanisms of Action

Models of neurodegenerative and neurological disorders

One *in vivo* and two *in vitro* studies investigated the mechanisms of PD1. *In vivo,* transcription and expression of IL-1β and TNF-α were reduced in the hippocampus upon PD1 intracranial administration in a murine model of epilepsy (54). In an *in vitro* model of AD, PD1 administration reduced $A\beta_{42}$ production through repression of pro-inflammatory molecules, including COX-2 and TNF-α (56). Furthermore, PD1 enhanced expression of anti-apoptotic proteins of the B-cell lymphoma 2 (Bcl-2) gene family (32) and reduced caspase-3 activity in cortical human neuronal cells *in vitro* (56).

Based on the evidence summarized in this section, protectins are especially useful in reducing behavioral deficits observed in neurological disorders, most likely via reducing microgliosis and pro-inflammatory cytokines levels.

Maresins

Behavioral and Cellular Findings

Models of neurodegenerative and neurological disorders

One *in vivo* study investigated the behavioral effects of treatment with MaR1, whereas three *in vitro* studies assessed cellular outcomes. In an *in vivo* mouse model of stroke, intracranial administration of MaR1 reduced neurological impairments over time (58). On a cellular level, administration of MaR1 protected against brain cell death and inhibited the degradation of postsynaptic density protein 95 (PSD95) and synapsin. Furthermore, MaR1 administration also inhibited neutrophil infiltration and glial activation in the cortex (58). *In vitro,* MaR1 treatment prevented cell death in human bone-marrow derived neuroblastoma cell models of ALS and AD (46, 59). MaR1 also stimulated an increase of $A\beta_{42}$ phagocytosis in embryonic human microglial cells (46).

Mechanisms of Action

Models of neurodegenerative and neurological disorders

All three studies previously mentioned investigated the mechanisms of action of PD1. In an *in vivo* mouse model of stroke, expression of TNF-α, IL-1β, and MCP-1 in the cortex was reduced by intracranial administration of MaR1. Furthermore, MaR1 decreased NF-κB activation through down-regulation of p65 phosphorylation (58). Similar effects were seen *in vitro*, with MaR1 treatment decreasing levels of phosphorylated NF-κB in human bone-marrow derived neuroblastoma cells (59). MaR1 treatment of embryonic human microglia also induced a reduction in pro-inflammatory markers including CD11b, major histocompatibility complex class II (MHC-II), CD86, CD40, and CD33 (46).

The limited evidence available on maresins suggests that they might benefit neurological conditions, specifically by reducing cell death and inflammatory factors, which may be related to decreased NF-κB pathway activation.

OVERALL DISCUSSION OF THE EVIDENCE

This review summarizes evidence on the beneficial effects of resolvins, protectins and maresins, in the treatment of psychiatric, neurodegenerative, and neurological disorders (**Figure 2**). Overall, treatment with both RvD and RvE improved depressive-like behaviors in various animal models of depression, whereas PD1 and MaR1 ameliorated neurological function. On a cellular level, RvD1 and RvD2 increased serotonin levels in a model of depression, and decreased gliosis in neurodegenerative disorders. In contrast, PD1 and PDX

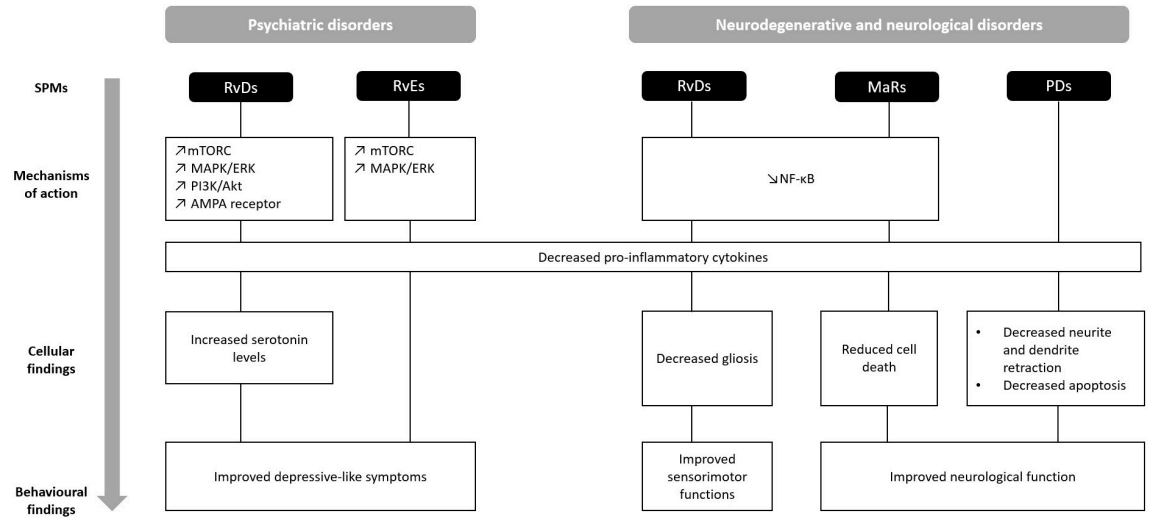

FIGURE 2 | Comparison of behavioral, cellular, and molecular findings upon treatment with SPMs in the context of psychiatric, neurodegenerative, and neurological disorders. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MAP/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; MaR, maresin; mTORC, mammalian target of rapamycin complex; NF-κB, Nuclear factor-kappa B; PD, protectin; PI3K/Akt, Phosphoinositide 3-kinases/Protein kinase B; RvD, resolvins D series; RvE, resolvins E series. ↗ increase; ↘ decrease.

prevented neurite and dendrite retraction and apoptosis in models of neurodegeneration, while MaR1 reduced cell death across all studies. In terms of mechanisms, all SPMs down-regulated pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. RvD1, RvD2, and RvE1 exerted their effects through mTOR and MAP/ERK signaling in models of depression, while RvD1, RvD2, and MaR1 through the NF-κB pathway in models of neurodegeneration and neurological disorders. These findings suggest that not only do SPMs have anti-inflammatory properties across different models, but also possess characteristic therapeutic effects depending on the condition.

Despite the scarce number of studies conducted in psychiatric disorders, differences among specific SPMs could be drawn on several levels. In particular, RvD1 and RvEs were the most effective in improving depressive symptoms across several mouse models (36, 39, 48, 49). This could be explained by their mechanistic actions, which were notably distinct between psychiatric and neurological conditions. The mTORC1 pathway, which is a key signaling pathway in the effectiveness of antidepressants (64), was found to underlie the behavioral effects of resolvins (36, 49). Similar findings were presented for the MAPK/ERK pathway and PI3K/Akt and AMPA signaling (36), which are involved in cell growth and proliferation and can influence the expression of proteins associated with gene × environment interactions in depression (65). Moreover, all of these are key elements involved in neurogenesis (66), which is impaired by pro-inflammatory cytokines (67) and has been shown to be rescued by n-3 PUFAs treatment after IL-1β challenge *in vitro* (68).

With respect to neurodegenerative disorders, none of the SPMs could be distinguished in terms of better therapeutic effects. While apoptosis or gliosis were equally reduced by RvD1, RvE1, PD1, and MaR1 in *in vivo* and *in vitro* models, the benefits observed in *ex vivo* studies using patient-derived cells remained on a trend level (41) or were restricted to specific sub-groups (40). Although it is difficult to disentangle the underlying cause of these seemingly puzzling findings, the situation can be closely related to the reality of research into AD therapy. Many anti-inflammatory drugs appear promising at pre-clinical stages but are not effective in clinical trials, presumably due to the complexity of the disorder and the number of interacting factors (11). Further investigation is thus necessary to achieve a clearer understanding of SPMs in neurodegenerative disorders.

Although, maresins and protectins have not been examined in the context of depression, the evidence was conclusive in neurological disorders, where they appear to have a greater potential. PD1, PDX, and MaR1 improved neurological function in animal models of ischaemia, and TBI (51, 53, 58). In line with this, PD1 limited cell death, highlighting its neuroprotective abilities. MaR1 likely had a greater effect in these conditions due to its presence in macrophages and its more potent role in dampening the activation of microglia (69), which are more acutely and severely triggered in those conditions. Additionally, MaR1 promotes tissue regeneration, which could be of increased therapeutic value in ischemic stroke (35).

Thus, the ability of specific metabolites to improve behavioral, cellular and mechanistic components differentially in psychiatric and neurodegenerative disorders could be a basis for new personalized therapeutic strategies. Although current pharmacotherapies for AD and PD appear to slow the progression of cognitive impairment, the benefits have often found to be marginal and non-sustained (70). Additionally, up to one third of MDD patients fail to respond to first-line pharmacological treatment (71), which has been associated

with elevated plasma pro-inflammatory factors expression (72). With AD projected to hit 131 million people by 2050 (73) and depression affecting about 5% of the world's population (74), new treatment avenues are needed more than ever. N-3 PUFAs have been approved as safe when administered in doses up to 3 g per day and minor side-effects are rare (75). Recent reviews and meta-analysis have reported a clinical efficacy of n-3 PUFAs treatment, which might be partly attributable to SPMs, in MDD and AD patients (76, 77). More interestingly, the majority of the animal studies so far only used males, which have recently been shown to have higher baseline levels of n-3 PUFAs metabolites than females in brain tissue (78). The single study using female mice reported positive effects of RvE1 on inflammatory factors, however, this does not allow for direct comparison between sexes (50). With women being at increased risk of developing MDD and AD (79, 80), further insight into this question is necessary as they might even more particularly benefit from this type of intervention.

Based on the findings from our review, personalized SPMs treatment could be a therapeutic possibility. RvD1, RvD2, or RvE1 could prove to be beneficial in psychiatric conditions, like depression, while MaR1 or PD1 would be optimally targeted toward neurological conditions. Although more studies are required to determine their exact influence and production in the brain, our review indicates a potential promising approach for tailored therapy with SPMs. With further research, this could lead to subsequent dietary recommendations and nutritional interventions in the treatment of psychiatric, neurodegenerative or neurological conditions, as n-3 PUFAs have been demonstrated to raise specific SPMs levels (81).

This review has few limitations that must be considered, such as the number of studies meeting the inclusion criteria and the prominence of cognitive and neurological compared with psychiatric studies. Additionally, dosage and route of administration between metabolites was also variable. Nonetheless, this is the first review to compare the effects of SPMs in the context of psychiatric, neurodegenerative and neurological disorders and sheds light on the differential mechanisms mediating their beneficial properties. Further research is needed to elucidate the exact mechanisms of action of these metabolites, as well as the extent of their anti-inflammatory properties, in order to discern which disorder they should optimally target.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REFERENCES

1. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflammation*. (2013) 10:43. doi: 10.1186/1742-2094-10-43
2. Pariante CM. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. *Eur Neuropsychopharmacol*. (2017) 27:554–9. doi: 10.1016/j.euroneuro.2017.04.001
3. Zunszain PA, Hepgul N, Pariante CM. Inflammation and depression. *Curr Top Behav Neurosci*. (2013) 14:135–51. doi: 10.1007/7854_2012_211
4. Sawyer KM, Zunszain PA, Dazzan P, Pariante CM. Intergenerational transmission of depression: clinical observations and molecular mechanisms. *Mol Psychiatry*. (2019) 24:1157–77. doi: 10.1038/s41380-018-0265-4
5. Nuzzo D, Picone P, Caruana L, Vasto S, Barera A, Caruso C, et al. Inflammatory mediators as biomarkers in brain disorders. *Inflammation*. (2014) 37:639–48. doi: 10.1007/s10753-013-9780-2
6. Monson NL, Ireland SJ, Ligocki AJ, Chen D, Rounds WH, Li M, et al. Elevated CNS inflammation in patients with preclinical Alzheimer's disease. *J Cereb Blood Flow Metab*. (2014) 34:30–3. doi: 10.1038/jcbfm.2013.183
7. Joshi SH, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, et al. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. *Biol Psychiatry*. (2016) 79:282–92. doi: 10.1016/j.biopsych.2015.02.029
8. Innes S, Pariante CM, Borsini A. Microglial-driven changes in synaptic plasticity: a possible role in major depressive disorder. *Psychoneuroendocrinology*. (2018) 102:236–47. doi: 10.1016/j.psyneuen.2018.12.233
9. Das S, Basu A. Inflammation: a new candidate in modulating adult neurogenesis. *J Neurosci Res*. (2008) 86:1199–208. doi: 10.1002/jnr.21585
10. Vivekanantham S, Shah S, Dewji R, Dewji A, Khatri C, Ologunde R. Neuroinflammation in Parkinson's disease: role in neurodegeneration and tissue repair. *Int J Neurosci*. (2015) 125:717–25. doi: 10.3109/00207454.2014.982795
11. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. (2015) 14:388–405. doi: 10.1016/S1474-4422(15)70016-5
12. Hurley LL, Tizabi Y. Neuroinflammation, neurodegeneration, and depression. *Neurotox Res*. (2013) 23:131–44. doi: 10.1007/s12640-012-9348-1
13. Tang Y, Le W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Mol Neurobiol*. (2016) 53:1181–94. doi: 10.1007/s12035-014-9070-5
14. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain Behav Immun*. (2014) 42:50–9. doi: 10.1016/j.bbi.2014.05.007
15. Amor S, Peferoen LAN, Vogel DYS, Breur M, van der Valk P, Baker D, et al. Inflammation in neurodegenerative diseases - an update. *Immunology*. (2014) 142:151–66. doi: 10.1111/imm.12233
16. Pariante CM. The year of immunopsychiatry: a special issue that foresaw the future. *Psychoneuroendocrinology*. (2019) 103:49–51. doi: 10.1016/j.psyneuen.2019.01.002

17. Su K-P, Huang S-Y, Chiu T-H, Huang K-C, Huang C-L, Chang H-C, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. (2008) 69:644–51. doi: 10.4088/JCP.v69n0418
18. Su K-P, Yang H-T, Chang JP-C, Shih Y-H, Guu T-W, Kumaran SS, et al. Eicosapentaenoic and docosahexaenoic acids have different effects on peripheral phospholipase A2 gene expressions in acute depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. (2018) 80(Pt C):227–33. doi: 10.1016/j.pnpbp.2017.06.020
19. Huang S-Y, Yang H-T, Chiu C-C, Pariante CM, Su K-P. Omega-3 fatty acids on the forced-swimming test. *J Psychiatr Res*. (2008) 42:58–63. doi: 10.1016/j.jpsychires.2006.09.004
20. Chang JP-C, Su K-P, Mondelli V, Pariante CM. Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder: a systematic review and meta-analysis of clinical trials and biological studies. *Neuropsychopharmacology*. (2018) 43:534–45. doi: 10.1038/npp.2017.160
21. Chang JP-C, Lai H-C, Yang H-T, Su W-P, Peng C-Y, Galecki P, et al. Polyunsaturated fatty acids levels and initial presentation of somatic symptoms induced by interferon-alpha therapy in patients with chronic hepatitis C viral infection. *Nutr Neurosci*. (2017) 20:291–6. doi: 10.1080/1028415X.2015.1123378
22. Su K-P, Lai H-C, Yang H-T, Su W-P, Peng C-Y, Chang JP-C, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. *Biol Psychiatry*. (2014) 76:559–66. doi: 10.1016/j.biopsych.2014.01.008
23. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans*. (2017) 45:1105–15. doi: 10.1042/BST20160474
24. Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta Mol Cell Biol Lipids*. (2015) 1851:469–84. doi: 10.1016/j.bbalip.2014.08.010
25. Serhan CN, Krishnamoorthy S, Recchiuti A, Chiang N. Novel anti-inflammatory–pro-resolving mediators and their receptors. *Curr Top Med Chem*. (2011) 11:629–47. doi: 10.2174/1568026611109060629
26. Su K-P, Huang S-Y, Peng C-Y, Lai H-C, Huang C-L, Chen Y-C, et al. Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry*. (2010) 67:550–7. doi: 10.1016/j.biopsych.2009.11.005
27. Bento AF, Claudino RF, Dutra RC, Marcon R, Calixto JB. ω-3 fatty acid-derived mediators 17R-hydroxy docosahexaenoic acid, aspirin-triggered resolvin D1 and resolvin D2 prevent experimental colitis in mice. *J Immunol*. (2011) 187:1957–69. doi: 10.4049/jimmunol.1101305
28. Gobbetti T, Dalli J, Colas RA, Federici Canova D, Aursnes M, Bonnet D, et al. Protectin D1(n-3 DPA) and resolvin D5(n-3 DPA) are effectors of intestinal protection. *Proc Natl Acad Sci USA*. (2017) 114:3963–8. doi: 10.1073/pnas.1617290114
29. Hellmann J, Tang Y, Kosuri M, Bhatnagar A, Spite M. Resolvin D1 decreases adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice. *FASEB J*. (2011) 25:2399–407. doi: 10.1096/fj.10-178657
30. Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J Biol Chem*. (2003) 278:14677–87. doi: 10.1074/jbc.M300218200
31. Hong S, Lu Y, Yang R, Gotlinger KH, Petasis NA, Serhan CN. Resolvin D1, protectin D1, and related docosahexaenoic acid-derived products: analysis via electrospray/low energy tandem mass spectrometry based on spectra and fragmentation mechanisms. *J Am Soc Mass Spectrom*. (2007) 18:128–44. doi: 10.1016/j.jasms.2006.09.002
32. Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, et al. A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J Clin Invest*. (2005) 115:2774–83. doi: 10.1172/JCI25420
33. Xu Z-Z, Zhang L, Liu T, Park JY, Berta T, Yang R, et al. Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. *Nat Med*. (2010) 16:592. doi: 10.1038/nm.2123
34. Gao J, Tang C, Tai LW, Ouyang Y, Li N, Hu Z, et al. Pro-resolving mediator maresin 1 ameliorates pain hypersensitivity in a rat spinal nerve ligation model of neuropathic pain. *J Pain Res*. (2018) 11:1511–9. doi: 10.2147/JPR.S160779
35. Serhan CN, Dalli J, Karamnov S, Choi A, Park C-K, Xu Z-Z, et al. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. *FASEB J*. (2012) 26:1755–65. doi: 10.1096/fj.11-201442
36. Deyama S, Ishikawa Y, Yoshikawa K, Shimoda K, Ide S, Satoh M, et al. Resolvin D1 and D2 reverse lipopolysaccharide-induced depression-like behaviors through the mtorc1 signaling pathway. *Int J Neuropsychopharmacol*. (2017) 20:575–84. doi: 10.1093/ijnp/pyx023
37. Gilbert K, Bernier J, Godbout R, Rousseau G. Resolvin D1, a metabolite of omega-3 polyunsaturated fatty acid, decreases post-myocardial infarct depression. *Mar Drugs*. (2014) 12:5396–407. doi: 10.3390/md12115396
38. Klein CP, Sperotto ND, Maciel IS, Leite CE, Souza AH, Campos MM. Effects of D-series resolvins on behavioral and neurochemical changes in a fibromyalgia-like model in mice. *Neuropharmacology*. (2014) 86:57–66. doi: 10.1016/j.neuropharm.2014.05.043
39. Ishikawa Y, Deyama S, Shimoda K, Yoshikawa K, Ide S, Satoh M, et al. Rapid and sustained antidepressant effects of resolvin D1 and D2 in a chronic unpredictable stress model. *Behav Brain Res*. (2017) 332:233–6. doi: 10.1016/j.bbr.2017.06.010
40. Famenini S, Rigali EA, Olivera-Perez HM, Dang J, Chang MT, Halder R, et al. Increased intermediate M1-M2 macrophage polarization and improved cognition in mild cognitive impairment patients on omega-3 supplementation. *FASEB J*. (2017) 31:148–60. doi: 10.1096/fj.201600677RR
41. Olivera-Perez HM, Lam L, Dang J, Jiang W, Rodriguez F, Rigali E, et al. Omega-3 fatty acids increase the unfolded protein response and improve amyloid-beta phagocytosis by macrophages of patients with mild cognitive impairment. *Faseb J*. (2017) 31:4359–69. doi: 10.1096/fj.201700290R
42. Mizwicki MT, Liu G, Fiala M, Magpantay L, Sayre J, Siani A, et al. 1α,25-dihydroxyvitamin D3 and resolvin D1 retune the balance between amyloid-β phagocytosis and inflammation in Alzheimer's disease patients. *J Alzheimer Dis*. (2013) 34:155–70. doi: 10.3233/JAD-121735
43. Harrison JL, Rowe RK, Ellis TW, Yee NS, O'Hara BF, Adelson PD, et al. Resolvins AT-D1 and E1 differentially impact functional outcome, post-traumatic sleep, and microglial activation following diffuse brain injury in the mouse. *Brain Behav Immun*. (2015) 47:131–40. doi: 10.1016/j.bbi.2015.01.001
44. Terrando N, Gómez-Galán M, Yang T, Carlström M, Gustavsson D, Harding RE, et al. Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. *FASEB J*. (2013) 27:3564–71. doi: 10.1096/fj.13-230276
45. Xu J, Gao X, Yang C, Chen L, Chen Z. Resolvin D1 attenuates Mpp+-induced Parkinson disease via inhibiting inflammation in PC12 cells. *Med Sci Monit*. (2017) 23:2684–91. doi: 10.12659/MSM.901995
46. Zhu M, Wang X, Hjorth E, Colas RA, Schroeder L, Granholm AC, et al. Pro-resolving lipid mediators improve neuronal survival and increase Aβ42 phagocytosis. *Mol Neurobiol*. (2016) 53:2733–49. doi: 10.1007/s12035-015-9544-0
47. Tian Y, Zhang Y, Zhang R, Qiao S, Fan J. Resolvin D2 recovers neural injury by suppressing inflammatory mediators expression in lipopolysaccharide-induced Parkinson's disease rat model. *Biochem Biophys Res Commun*. (2015) 460:799–805. doi: 10.1016/j.bbrc.2015.03.109
48. Deyama S, Shimoda K, Ikeda H, Fukuda H, Shuto S, Minami M. Resolvin E3 attenuates lipopolysaccharide-induced depression-like behavior in mice. *J Pharmacol Sci*. (2018) 138:86–8. doi: 10.1016/j.jphs.2018.09.006
49. Deyama S, Shimoda K, Suzuki H, Ishikawa Y, Ishimura K, Fukuda H, et al. Resolvin E1/E2 ameliorate lipopolysaccharide-induced depression-like behaviors via ChemR23. *Psychopharmacol*. (2018) 235:329–36. doi: 10.1007/s00213-017-4774-7
50. Kantarci A, Aytan N, Palaska I, Stephens D, Crabtree L, Benincasa C, et al. Combined administration of resolvin E1 and lipoxin A4 resolves inflammation in a murine model of Alzheimer's disease. *Exp Neurol*. (2018) 300:111–20. doi: 10.1016/j.expneurol.2017.11.005
51. Bazan NG, Eady TN, Khoutorova L, Atkins KD, Hong S, Lu Y, et al. Novel aspirin-triggered neuroprotectin D1 attenuates cerebral ischemic injury after experimental stroke. *Exp Neurol*. (2012) 236:122–30. doi: 10.1016/j.expneurol.2012.04.007
52. Ren H, Yang Z, Luo C, Zeng H, Li P, Kang JX, et al. Enriched endogenous omega-3 fatty acids in mice ameliorate parenchymal cell death after

traumatic brain injury. *Mol Neurobiol*. (2017) 54:3317–26. doi: 10.1007/s12035-016-9931-1
53. Belayev L, Hong SH, Menghani H, Marcell SJ, Obenaus A, Freitas RS, et al. Docosanoids promote neurogenesis and angiogenesis, blood-brain barrier integrity, penumbra protection, and neurobehavioral recovery after experimental ischemic stroke. *Mol Neurobiol*. (2018) 55:7090–106. doi: 10.1007/s12035-018-1136-3
54. Frigerio F, Pasqualini G, Craparotta I, Marchini S, van Vliet EA, Foerch P, et al. n-3 Docosapentaenoic acid-derived protectin D1 promotes resolution of neuroinflammation and arrests epileptogenesis. *Brain*. (2018) 141:3130–43. doi: 10.1093/brain/awy247
55. Calandria JM, Sharp MW, Bazan NG. The docosanoid neuroprotectin D1 induces TH-positive neuronal survival in a cellular model of Parkinson's disease. *Cell Mol Neurobiol*. (2015) 35:1127–36. doi: 10.1007/s10571-015-0206-6
56. Zhao Y, Calon F, Julien C, Winkler JW, Petasis NA, Lukiw WJ, et al. Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase- and PPARγ-mediated mechanisms in Alzheimer's disease models. *PLoS ONE*. (2011) 6:e15816. doi: 10.1371/journal.pone.0015816
57. Lo Van A, Sakayori N, Hachem M, Belkouch M, Picq M, Fourmaux B, et al. Targeting the Brain with a Neuroprotective Omega-3 Fatty Acid to Enhance Neurogenesis in Hypoxic Condition in Culture. *Mol Neurobiol*. (2019) 56:986–99. doi: 10.1007/s12035-018-1139-0
58. Xian W, Wu Y, Xiong W, Li L, Li T, Pan S, et al. The pro-resolving lipid mediator Maresin 1 protects against cerebral ischemia/reperfusion injury by attenuating the pro-inflammatory response. *Biochem Biophys Res Commun*. (2016) 472:175–81. doi: 10.1016/j.bbrc.2016.02.090
59. Ohuchi K, Ono Y, Joho M, Tsuruma K, Ogami S, Yamane S, et al. A docosahexaenoic acid-derived pro-resolving agent, Maresin 1, protects motor neuron cells death. *Neurochem Res*. (2018) 43:1413–23. doi: 10.1007/s11064-018-2556-1
60. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. *BMC Med*. (2013) 17:133–7. doi: 10.1176/appi.books.9780890425596
61. Reyes-Resina I, Navarro G, Aguinaga D, Canela EI, Schoeder CT, Załuski M, et al. Molecular and functional interaction between GPR18 and cannabinoid CB2 G-protein-coupled receptors. Relevance in neurodegenerative diseases. *Biochem Pharmacol*. (2018) 157:169–79. doi: 10.1016/j.bcp.2018.06.001
62. Wittamer V, Franssen J-D, Vulcano M, Mirjolet J-F, Le Poul E, Migeotte I, et al. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. *J Exp Med*. (2003) 198:977–85. doi: 10.1084/jem.20030382
63. Arita M, Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, et al. Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *J Exp Med*. (2005) 201:713. doi: 10.1084/jem.20042031
64. Abelaira HM, Réus GZ, Neotti M V, Quevedo J. The role of mTOR in depression and antidepressant responses. *Life Sci*. (2014) 101:10–4. doi: 10.1016/j.lfs.2014.02.014
65. Cattaneo A, Cattane N, Malpighi C, Czamara D, Suarez A, Mariani N, et al. FoxO1, A2M, and TGF-β1: three novel genes predicting depression in gene X environment interactions are identified using cross-species and cross-tissues transcriptomic and miRNomic analyses. *Mol Psychiatry*. (2018) 23:2192–208. doi: 10.1038/s41380-017-0002-4
66. Ignacio ZM, Reus GZ, Arent CO, Abelaira HM, Pitcher MR, Quevedo J. New perspectives on the involvement of mTOR in depression as well as in the action of antidepressant drugs. *Br J Clin Pharmacol*. (2016) 82:1280–90. doi: 10.1111/bcp.12845
67. Borsini A, Cattaneo A, Malpighi C, Thuret S, Harrison NA, Zunszain PA, et al. Interferon-alpha reduces human hippocampal neurogenesis and increases apoptosis via activation of distinct STAT1-dependent mechanisms. *Int J Neuropsychopharmacol*. (2018) 21:187–200. doi: 10.1093/ijnp/pyx083
68. Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su KP, et al. Rescue of IL-1β-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. *Brain Behav Immun*. (2017) 65:230–8. doi: 10.1016/j.bbi.2017.05.006
69. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. (2014) 510:92. doi: 10.1038/nature13479
70. Szeto JY, Lewis SJ. Current treatment options for Alzheimer's disease and Parkinson's disease dementia. *Curr Neuropharmacol*. (2016) 14:326–38. doi: 10.2174/1570159X14666151208112754
71. Nierenberg AA, Katz J, Fava M. A critical overview of the pharmacologic management of treatment-resistant depression. *Psychiatr Clin North Am*. (2007) 30:13–29. doi: 10.1016/j.psc.2007.01.001
72. Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DNC, Drevets WC, et al. Treatment-resistant depression and peripheral C-reactive protein. *Br J Psychiatry*. (2019) 214:11–9. doi: 10.1192/bjp.2018.66
73. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. *Alzheimer's Disease International: World Alzheimer Report 2015: The Global Impact of Dementia: an Analysis of Prevalence, Incidence, Cost and Trends 2015*. Alzheimer's Disease International, London, United Kingdom (2019).
74. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol*. (2014) 43:476–93. doi: 10.1093/ije/dyu038
75. DeFilippis AP, Sperling LS. Understanding omega-3's. *Am Heart J*. (2006) 151:564–70. doi: 10.1016/j.ahj.2005.03.051
76. Song C, Shieh CH, Wu YS, Kalueff A, Gaikwad S, Su KP. The role of omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids in the treatment of major depression and Alzheimer's disease: acting separately or synergistically? *Prog Lipid Res*. (2016) 62:41–54. doi: 10.1016/j.plipres.2015.12.003
77. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS ONE*. (2014) 9:e96905. doi: 10.1371/journal.pone.0096905
78. Ferdouse A, Leng S, Winter T, Aukema HM. The brain oxylipin profile is resistant to modulation by dietary n-6 and n-3 polyunsaturated fatty acids in male and female rats. *Lipids*. (2019) 54:67–80. doi: 10.1002/lipd.12122
79. Kuehner C. Why is depression more common among women than among men? *Lancet Psychiatry*. (2017) 4:146–58. doi: 10.1016/S2215-0366(16)30263-2
80. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol*. (2014) 35:385–403. doi: 10.1016/j.yfrne.2014.01.002
81. Hashimoto M, Katakura M, Tanabe Y, Al Mamun A, Inoue T, Hossain S, et al. n-3 fatty acids effectively improve the reference memory-related learning ability associated with increased brain docosahexaenoic acid-derived docosanoids in aged rats. *Biochim Biophys Acta*. (2015) 1851:203–9. doi: 10.1016/j.bbalip.2014.10.009

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Low-Grade Inflammation as a Predictor of Antidepressant and Anti-Inflammatory Therapy Response in MDD Patients: A Systematic Review of the Literature in Combination With an Analysis of Experimental Data Collected in the EU-MOODINFLAME Consortium

Gara Arteaga-Henríquez[1,2,3†], Maria S. Simon[1†], Bianka Burger[4], Elif Weidinger[1], Annemarie Wijkhuijs[5], Volker Arolt[6], Tom K. Birkenhager[7], Richard Musil[1], Norbert Müller[1,4‡] and Hemmo A. Drexhage[2‡]*

[1] Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilian-University, Munich, Germany, [2] Department of Immunology, Erasmus Medical Center, Rotterdam, Netherlands, [3] Psychiatry, Mental Health and Addictions Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain, [4] Marion von Tessin Memory-Center, Munich, Germany, [5] RMS, Rotterdam, Netherlands, [6] Department of Psychiatry and Psychotherapy, University Hospital of Muenster, Muenster, Germany, [7] Department of Psychiatry, Erasmus Medical Center, Rotterdam, Netherlands

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***Correspondence:**
Hemmo A. Drexhage
h.drexhage@erasmusmc.nl

†These authors share first authorship.

‡These authors share last authorship.

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Low-grade inflammation plays a role not only in the pathogenesis of major depressive disorder (MDD) but probably also in the poor responsiveness to regular antidepressants. There are also indications that anti-inflammatory agents improve the outcomes of antidepressants.

Aim: To study whether the presence of low-grade inflammation predicts the outcome of antidepressants, anti-inflammatory agents, or combinations thereof.

Methods: We carried out a systematic review of the literature on the prediction capability of the serum levels of inflammatory compounds and/or the inflammatory state of circulating leukocytes for the outcome of antidepressant/anti-inflammatory treatment in MDD. We compared outcomes of the review with original data (collected in two limited trials carried out in the EU project MOODINFLAME) on the prediction capability of the inflammatory state of monocytes (as measured by inflammatory gene expression) for the outcome of venlafaxine, imipramine, or sertraline treatment, the latter with and without celecoxib added.

Results: Collectively, the literature and original data showed that: 1) raised serum levels of pro-inflammatory compounds (in particular of CRP/IL-6) characterize an inflammatory form of MDD with poor responsiveness to predominately serotonergic agents, but a better responsiveness to antidepressant regimens with a) (add-on)

noradrenergic, dopaminergic, or glutamatergic action or b) (add-on) anti-inflammatory agents such as infliximab, minocycline, or eicosapentaenoic acid, showing—next to anti-inflammatory—dopaminergic or lipid corrective action; 2) these successful anti-inflammatory (add-on) agents, when used in patients with low serum levels of CRP/IL-6, decreased response rates in comparison to placebo. Add-on aspirin, in contrast, improved responsiveness in such "non-inflammatory" patients; 3) patients with increased inflammatory gene expression in circulating leukocytes had a poor responsiveness to serotonergic/noradrenergic agents.

Conclusions: The presence of inflammation in patients with MDD heralds a poor outcome of first-line antidepressant therapies. Immediate step-ups to dopaminergic or glutamatergic regimens or to (add-on) anti-inflammatory agents are most likely indicated. However, at present, insufficient data exist to design protocols with reliable inflammation parameter cutoff points to guide such therapies, the more since detrimental outcomes are possible of anti-inflammatory agents in "non-inflamed" patients.

Keywords: major depression, inflammation, antidepressant therapy, anti-inflammatory therapy, therapy prediction

INTRODUCTION

It is well accepted that immune dysregulation plays an important role in the pathogenesis of at least a proportion of patients with major depressive disorder (MDD) (1–16). Genetic defects and/or polymorphisms, childhood trauma, and chronic stress are all capable of eliciting such immune dysregulations (17–19). In the last decades, special interest has been raised for the role of low-grade inflammation in the immune system dysregulation of MDD. Low-grade inflammation is characterized by an increase in the level of circulating pro-inflammatory compounds, such as acute phase proteins [e.g., C-reactive protein (CRP)] and cytokines [e.g., interleukin (IL)-6], and/or by a pro-inflammatory activity of circulating or tissue resident immune cells (20–23).

A wide range of medications is currently available for the treatment of MDD. First-line agents are the well-known serotonin reuptake inhibitors (SSRIs; e.g., sertraline, escitalopram, or citalopram), which show a predominantly serotonergic action (24). First-line agents are also the serotonin-noradrenaline reuptake inhibitors (SNRIs), which show a predominantly serotonergic action at low doses and a combined serotonergic–noradrenergic action at moderate to high doses (25). Tricyclic antidepressants (TCAs) show a similar mechanism of action as SNRIs regarding the dual serotonergic-noradrenergic action, but because of more side effects, they are actually used as second-line agents. Third-line agents are drugs with a predominantly noradrenergic/dopaminergic action, such as mirtazapine or bupropion, or agents with other mechanisms of action, such as ketamine [i.e., an *N*-methyl-D-aspartate (NMDA) receptor antagonist, elevating glutamate levels]. Despite this wide range of medications, response rates to treatment are still insufficient, with about half of the patients not responding adequately to an installed treatment (26, 27).

Since most of the antidepressant drugs have—next to their neurotransmission modulatory effects—also immune modulating capacities (28, 29), it is thought that the inflammatory state of patients might play a role in non-responsiveness. To enforce the mood-regulating effects of antidepressants, and being aware of the notion that low-grade inflammation plays a role, various studies have been undertaken to use anti-inflammatory agents as add-ons to regular antidepressant therapies. In this way, acetylsalicylic acid (i.e., aspirin, a COX1 and COX2 inhibitor), selective COX-2 inhibitors (e.g., celecoxib), minocycline (a tetracyclin with anti-inflammatory effects), and anti-TNF monoclonal antibodies (e.g., infliximab) have been used experimentally (30–33). Besides these anti-inflammatory agents, agents such as cholesterol-lowering fish oil (eicosapentaenoic acid) and anti-oxidative *n*-acetylcysteine have also been used (33, 34). These agents also have anti-inflammatory actions, since both the cholesterol metabolism and the anti-oxidative machinery are linked to inflammation (35, 36). Though it seems that anti-inflammatory agents did show limited beneficial effects in most of the reported studies (30–34), there is still doubt on the real validity of such interventions, particularly due to the paucity and preliminary character of the studies, while there is also the feeling that such anti-inflammatory agents might only work in a proportion of patients.

Collectively, the abovementioned notions lead to the view that there is a need for a personalized medicine approach to select patients who, in particular, will respond to first-line agents and those needing immediate step-up therapies to drugs other than the first-line drugs and/or an add-on of a first-line agent with an anti-inflammatory agent. In such an approach, it is the question whether a pre-existent state of enhanced low-grade inflammation (present in around one-third of patients) (37) indeed plays a role in non-responsiveness to antidepressants and whether such a state

is capable of predicting the outcome of the abovementioned antidepressant therapy regimens.

For this report, we have carried out a systematic review searching for the relevant literature on the prediction capability of soluble inflammatory compounds/cytokines in serum/plasma/CSF and/or the inflammatory state of circulating leukocytes for the outcome of antidepressant/anti-inflammatory treatments in MDD. We combined the outcomes of the systematic review with experimental data collected in the EU-MOODINFLAME consortium on the prediction capability of the inflammatory state of circulating monocytes (as measured by inflammatory gene expression). Two EU-MOODINFLAME trials could be evaluated, a trial carried out on patients with MDD collected at the Rotterdam site and treated in first line with venlafaxine or imipramine (38), and a small trial carried out on patients with MDD collected at the Munich site and treated with sertraline *plus* add-on celecoxib or placebo.

MATERIALS AND METHODS

Search Strategy for Systematic Review

We conducted a systematic literature search in the PubMed/MEDLINE and Web of Science databases to identify immune-inflammatory predictors for treatment response to antidepressants, anti-inflammatory agents, and/or their combination with anti-inflammatory agents (or anti-inflammatory agents alone) in MDD from inception (for anti-inflammatory) and from 2008 (for antidepressant) until August 16, 2018. To find additional relevant studies, citation lists of included articles were tracked in Google Scholar (39) or citation lists of topic-related reviews and meta-analyses were checked. The last author of a significant paper concerning celecoxib and an expert in the field (NM) was also contacted and asked of awareness of any additional studies.

The following search terms were used: (mdd OR major depressive disorder OR depression) AND (inflammation) AND (therapy OR treatment OR antidepressant drugs OR sertraline OR venlafaxine OR escitalopram OR citalopram OR tricyclic OR ssri OR snri) AND (biomarker OR cytokines OR il-6 OR t cells OR nk cells OR th17 OR leukocytes OR macrophages OR crp OR genes) AND (response OR prediction), (mood disorder OR depression OR bipolar) AND (anti-inflammatory OR inflammation) AND (therapy OR treatment OR medication OR drugs OR add-on OR adjunct OR anti TNF OR infliximab OR CRP OR aspirin OR ASA OR acetyl salicylic acid OR minocycline OR omega 3 fatty acids OR NAC OR acetylcysteine OR cox 2 inhibitor OR celecoxib) AND (biomarker OR cytokines OR macrophages OR t cells OR NK cells OR leukocytes OR CRP OR genes).

The initial search of 7,047 studies resulted in 174 relevant studies selected by title. Inclusion criteria for further selection were:

(1) publications written in the English language;
(2) human clinical trials;
(3) the diagnosis of MDD. Because of the paucity of studies in unipolar depression, both unipolar and bipolar depression were included for the studies on (add-on) anti-inflammatory agents. To make comparisons possible, we indicate in the result section (**Table 1C**, marked with **B** and **C**) which studies included bipolar depressed patients, and we discuss in the Discussion section putative differences stemming from this inclusion.
(4) the absence of severe somatic diseases (especially inflammation-related);
(5) the assessment of immune biomarkers;
(6) the use of first-line or other antidepressant agents or the use of an anti-inflammatory agent added to antidepressant treatment or alone;
(7) the assessment of symptom reduction with standardized measure [e.g., Hamilton Rating Scale for Depression (HAMD), Montgomery–Asberg Depression Rating Scale (MADRS), Beck's depression inventory (BDI)] and
(8) the analysis of responder and non-responder subgroups.

By reading the abstracts, methods, and results sections and applying the inclusion criteria and by removing duplicate records, 36 studies were selected. Further exclusion criteria were:

(1) no predictive information provided;
(2) use of parameters that are not inflammatory biomarkers in a narrower sense [e.g., serotonin and kynurenine metabolites, brain-derived neurotrophic factor (BDNF), calcium-binding protein B (S100B), macrophage-derived chemokine (MDC), platelet-derived growth factor (PDGF), and Eotaxin-1/CCL11];
(3) genetic studies were excluded except for leukocyte gene expression level studies;
(4) the use of agents whose anti-inflammatory mechanisms are not direct and even questionable (e.g., l-methylfolate, pioglitazone, modafinil).

By applying these exclusion criteria, we finally included 24 reports in the systematic review.

With the purpose of providing a comprehensive presentation, we decided to split the remaining studies into studies concerning circulating inflammatory compounds/cytokines (n = 19, see **Tables 1A–C**) and gene expression in circulating leukocytes (n = 5; see **Table 2**). For detailed information about the study selection, see **Figure 1**.

Experimental Clinical Studies

Details on the inclusion and exclusion criteria, as well as on the clinical instruments and characteristics of patients, have been published before (38, 64). In short, in- and outpatients were recruited from the Departments of Psychiatry at the Erasmus Medical Centre (ErasmusMC) in Rotterdam (The Netherlands) and at the University Hospital of the Ludwig Maximilian University (LMU) in Munich (Germany). All patients were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Text Revision* (*DSM-IV-TR*) (65) and confirmed by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (66). Included were patients with a minimum score of 17 (Rotterdam) or 22 (Munich) on

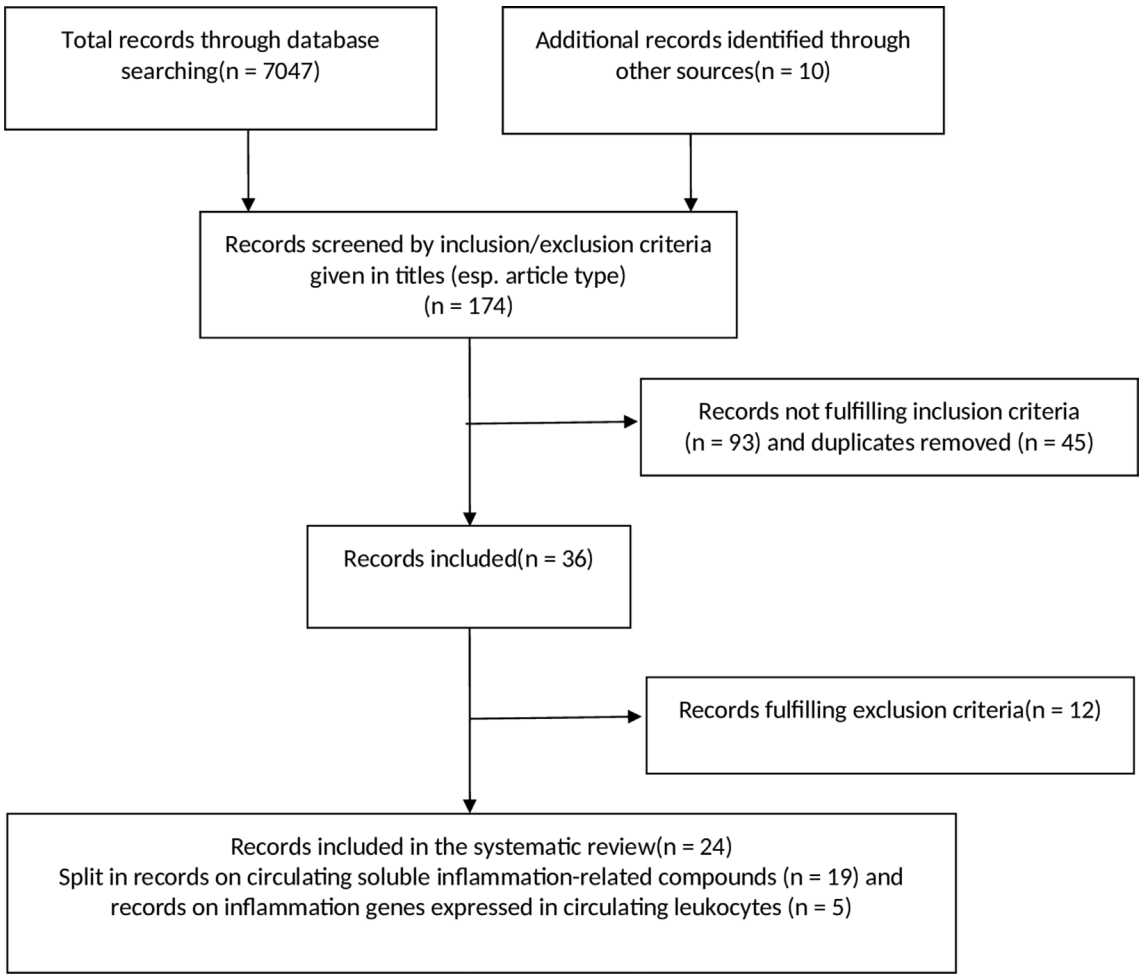

FIGURE 1 | Flow diagram of the systematic research. See materials and methods section for further explanation.

the Hamilton Rating Scale for Depression (HAMD, 17-item-version) (67).

Studies had been approved by the ethics committee of the medical faculty at the LMU, Munich (Germany), and the medical ethics committee of the ErasmusMC, Rotterdam (the Netherlands). The study was conducted in compliance with standards of Good Clinical Practice (CGP), assuring that the rights, safety, and well-being of patients were protected in accordance with the principles that have their origin in the Declaration of Helsinki (June 1964, last amendment Fortaleza 2013). Additionally, the relevant national and European regulations were adhered, too. After study procedures had been fully explained, all subjects provided written informed consent.

Healthy Controls

Healthy controls (HCs) were recruited from the same communities (Rotterdam and Munich). Details on the HC can be found in Refs. (64) and (68). In short, the inclusion criteria for HC were the absence of major *DSM-IV-TR* Axis I disorders including schizophrenia, psychotic disorders, mood disorders, anxiety disorders, or substance-related disorders according to *DSM-IV* criteria; the absence of usage of psychiatric drugs; and the absence of severe medical illness. HC had to be in self-proclaimed good health and free of any obvious medical illness for at least 2 weeks prior to the blood withdrawal, including acute infections and allergic reactions.

Treatment Protocols

Being both double-blind studies, subjects, investigators, and study staff had been blinded to the treatment assignment for the duration of the study.

Venlafaxine/Imipramine Study (Rotterdam)

Prior to the start of antidepressants, patients with MDD underwent a wash-out period for at least 1 week. The use of benzodiazepines was allowed up to a maximum daily dose of 3 mg lorazepam or the corresponding equivalent. Subsequently, patients were randomly assigned to a 7-week monotherapy with either the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine

(mean daily dose 371 mg, range dose of 300–375 mg/day) or with the TCA imipramine (mean dose 206 mg, range dose of 50–450 mg/day). The duration of the treatment trial was 7 weeks to ensure that patients treated with imipramine had adequate plasma levels for at least 4 weeks. Response to treatment was defined as ≥50% reduction of the initial HAM-D score.

Sertraline Plus Placebo/Celecoxib Study (Munich)

Prior to the start of treatment, patients with MDD underwent a washout period for 3 days. The use of lorazepam or zopiclon was allowed in this period and also during the study, up to a maximum daily dose of 3 or 15 mg, respectively. Subsequently, patients were randomly assigned in a 1:1 ratio to a 6-week therapy with either the selective serotonin reuptake inhibitor (SSRI) sertraline *plus* placebo, or with sertraline *plus* the selective COX-2 inhibitor celecoxib. The dose of sertraline was flexible and ranged between 50 and 100 mg/day. A daily dose higher than 100 mg was not recommended, but in the expectation of more clinical benefit, a daily dose of 150 mg sertraline was allowed. The daily dose of celecoxib was 400 mg (200 mg in the morning and 200 mg in the evening). Patients from the placebo group received two identical capsules (morning and evening). As in the Rotterdam cohort, response to treatment was defined as ≥50% reduction of the initial HAM-D score.

Numbers of Patients With MDD and HC

Only patients and HC with full data regarding the expression levels of all key genes for monocyte inflammatory activation could be used for the present study. The Rotterdam sample therefore consisted of 34 MDD patients and 45 HC. Of the patient group, 14 patients were treated with venlafaxine and 20 patients were treated with imipramine. The Munich sample consisted therefore of 35 MDD patients and 42 HC. Of the patient group, 19 patients were treated with sertraline *plus* placebo, and 16 patients were treated with sertraline *plus* celecoxib.

Blood Collection

Blood was collected in sodium-heparin tubes (36 ml) for immune cell preparation just prior to treatment. From the heparinized blood, peripheral blood mononuclear cell (PBMC) suspensions were prepared by low-density gradient centrifugation *via* Ficoll-Paque PLUS (GE Healthcare, Uppsala, Sweden) within 8 h to avoid erythrophagy-related activation of the monocytes. PBMCs were frozen in 10% dimethylsulfoxide and stored in liquid nitrogen. This enabled us to test immune cells of patients and controls together at a later stage. Tests were done at ErasmusMC.

Monocyte Inflammatory Gene Expression

$CD14^+$ monocytes were isolated from aliquots of the frozen and thawed PBMCs by a magnetic cell sorting system (auto MACS Pro, Miltenyi Biotec, B.V., Bergisch Gladbach, Germany). The average viability was 86.3 ± 10.4 (Trypan blue staining) and the purity of monocytes was 95.1 ± 3.0% (flow cytometry). RNA was isolated from the purified monocytes using RNA easy mini kit according to the manufacturer's instructions (Qiagen, Hilden, Germany). On average, monocytes cell yield after isolation was $2.0 \pm 1.6 \times 10^6$/subject and the quantity of RNA in monocytes was 3.2 ± 1.8 μg. One microgram of RNA was reverse-transcribed using the cDNA high capacity reverse transcription kit (Applied Biosystems, Foster City, CA, USA). qPCR was performed using Taqman Arrays, format 48 (Applied Biosystems), according to the manufacturer's protocol and validated against the single RT-qPCR method. Per fill port, 400 ng of cDNA (converted from total RNA) was loaded. PCR amplification was performed using an Applied Biosystems Prism 7900HT sequence detection system with TaqMan Array block. Thermal cycler conditions were 2 min at 50°C, 10 min at 94.5°C, 30 s at 97°C, and 1 min at 59.7°C for 40 cycles.

Based on several previous studies on mood disorders (21, 64, 69), we decided to include in our panel the most consistently abnormally expressed inflammatory genes in the studies. Therefore, relative to the housekeeping gene ABL1, the expression of a total of up to 49 genes was determined (also because of the maximum of fill ports in the Taqman assay) and expression values were calculated using the comparative threshold cycle (CT) method [see, for technical details, Refs. (21, 64, 69)]. The mentioned earlier studies also carried out a hierarchical clustering of these genes and found two main distinct clusters of gene expression. The first cluster is found consistently in virtually all of our monocyte inflammatory gene expression studies (also besides disease conditions such as mood disorders), and this cluster is composed of well-known pro-inflammatory cytokines and chemokines and important enzymes or transcription factors to produce these compounds. For the calculation of the "positivity of this inflammatory compound cluster", we took the expression level of the top 10 genes [the most consistently overexpressed genes in all our studies thus far; see Ref. (64)] of this cluster into consideration, i.e., *IL1β*, *CCL20*, *EREG*, *IL6*, *TNFAIP3*, *CXCL2*, *PDE4B*, *ATF3*, *PTX3*, and *IL1A*. These genes accounted for 70–99% of the inflammatory cluster response. For each of the 10 genes, we determined a range of the HC gene expression (using the $2^{-\Delta Ct}$ values). The range was defined by the mean of the values for that gene in HC monocytes ± 1 standard deviation (SD). Then, we used this range as a standard of comparison for the MDD patients' gene expression. We decided to refer to a patient's top gene as upregulated, if the patient's gene expression was higher than HC's mean plus 1×SD, or downregulated when it was lower than HC's mean minus 1×SD. This was done for all 10 above given genes. Then, we declared the monocyte population of a given patient as "pro-inflammatory positive" if 6 of these 10 top inflammatory genes (or more) were upregulated. These data are given in **Table 3** in the Results section. Similar calculations/algorithms for monocyte inflammatory positivity have been used by us before (21, 69–71). Further methodological details of the calculation can be found in these publications. Original Q-PCR data have been uploaded and can be retrieved *via* the GEO repository ref number GSE132315: http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE132315

Statistics

Statistical analyses were performed using IBM SPSS v.21 for Mac. Continuous sample characteristics are reported as mean (± standard deviation). Group comparisons (e.g., MDD vs. HC, responders vs. non-responders) were analyzed using analysis of

variance (ANOVA) tests for continuous data (e.g., age) and using Pearson's chi-square (χ^2) tests for categorical data (e.g., gender). For group comparisons of positivity of monocyte gene expression (e.g., MDD vs. HC, responders/non-responders vs. HC, responders vs. non-responders), Pearson's chi-square (χ^2) tests were applied, too. All hypotheses were tested with $\alpha \leq 0.05$ (two-sided).

RESULTS

Systematic Review Data on the Usefulness of Circulating Serum Inflammatory Compounds

Tables 1A, **1B**, and **1C** show the data of the systematic review of the 19 selected articles (see the section Search Strategy for Systematic Review) regarding the predictive capability of inflammatory state [assessed by serum/plasma immune compounds (mainly CRP and cytokines) (only one study used CSF)] in patients with MDD for the response rates to various classes of antidepressant drugs and to anti-inflammatory agents added to an antidepressant regimen (except for one study, in which the anti-inflammatory agent was used as monotherapy) (52). For comprehensibility, we have grouped the outcomes in **Table 1** according to the regimen used.

Table 1A shows that, in three out of three studies (40–42), antidepressants with a predominant serotonergic action [i.e., escitalopram (SSRI)] induced a better response in patients with low inflammatory markers as compared to patients with high inflammatory markers in the same study. On the contrary, when inflammatory markers were high, five out of seven of the studies (40, 45–48) showed that drugs with a predominant serotonergic action (i.e., SSRIs, SNRIs, and TCAs) induced reduced response rates as compared to patients with low inflammatory markers in the same study. Cutoff points for low and high levels were defined for CRP in the reviewed studies at 1 mg/L; for IL-6 and TNFα, values depended on the actual sensitivity of the assay used in the report. Two studies formed an exception. Manoharan et al. (44) did not find any effect of pre-selection of the inflammatory state. However, this study was special in that treatment duration was of only 6 weeks, and patients had a relatively low to moderate depression severity (HAMD score ≥ 13). The other study (43) showed the opposite message (i.e., an improved response to SSRIs in patients with a high inflammatory state as compared to a low inflammatory state). This study was special, in that many patients were treated with paroxetine (SSRIs), which—apart from its serotonergic action—also exerts a considerable dopaminergic action (72).

Taken together, predominantly serotonergic agents showed, in general, insufficient response rates in those patients with signs of moderate to high inflammation as measured by circulating inflammatory compounds.

The review also delivered that, in such conditions of moderate to high signs of inflammation, drugs with another mechanism of action than primarily serotonergic do show an effect. Using nortriptyline, mirtazapine, or ketamine alone, or combinations of an SSRI with nortriptyline or bupropion resulted, in 5 out of 5 studies, in improved responses rates (40, 41, 49–51) as compared to the patients with low inflammatory markers (**Table 1B**).

Similar beneficial effects existed for combinations of antidepressant drugs with anti-inflammatory agents. **Table 1C**

TABLE 1A | Predominantly serotonergic action: higher response rates in low inflammatory state vs. moderate–high inflammatory state (prior to treatment).

INFLAMMATORY STATE	STUDY	DRUG	INFLAMMATORY TEST	RESPONSE
LOW	Jha et al., 2017 (40)	Escitalopram (SSRI) + Placebo	CRP < 1 mg/L	**Higher** response rates compared to m–h IS *
	Uher et al., 2014[a] (41)	Escitalopram (SSRI)	CRP < 1 mg/L	**Higher** response rates compared to m–h IS ***
	Eller et al., 2008 (42)	Escitalopram (SSRI)	TNFα	**Higher** response rates compared to m–h IS *
MODERATE–HIGH	Yoshimura et al., 2013 (43)	Paroxetine, Sertraline (SSRI)	IL-6	**Higher** response rates compared to low IS *
	Manoharan et al., 2016 (44)	Fluoxetine (SSRI)	IL-6	**No associations** between biomarker values and response rates
	Jha et al., 2017 (40)	Escitalopram (SSRI) + Placebo	CRP ≥ 1 mg/L	**Lower** response rate compared to low IS *
	Chang et al., 2012 (45)	Fluoxetine (SSRI), Venlafaxine (SNRI)	CRP ≥ 1 mg/L	**Lower** response rate compared to low IS *
	Haroon et al., 2018 (46)	SSRIs, SNRIs, TCA	CRP, IL-6, TNFα, sTNF-R2	**Lower** response rate compared to low IS *
	Yoshimura et al., 2009 (47)	Paroxetine, Sertraline, Fluvoxamine, Milnacipran (SSRI, SSNRI)	IL-6	**Lower** response rate compared to low IS *
	Martinez et al., 2012 (48)	Venlafaxine (SNRI)	TNFα (CSF)	**Lower** response rate compared to low IS *

SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; TNFα, tumor necrosis factor alpha; IL, interleukin; CSF, cerebrospinal fluid; CRP, C-reactive protein; m–h, moderate–high; IS, inflammatory state.

**p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.*

[a]*Improvement on Montgomery–Asberg Depression Rating Scale (MADRS) score 3 points higher with nortriptyline when CRP ≥ 1 mg/L and 3 points higher with escitalopram when CRP < 1 mg/L.*

TABLE 1B | Predominantly noradrenergic, predominantly dopaminergic, and glutamatergic action: higher response rates in moderate–high inflammatory state vs. low inflammatory state (prior to treatment).

INFLAMMATORY STATE	STUDY	DRUG	INFLAMMATORY TEST	RESPONSE
LOW	Jha et al., 2017 (40)	Escitalopram (SSRI) + Bupropion (NDRI)	CRP < 1 mg/L	**Lower** response rate compared to m–h IS *
MODERATE–HIGH	Jha et al.,2 017 (40)	Escitalopram (SSRI) + Bupropion (NDRI)	CRP ≥ 1 mg/L	**Higher** response rates compared to low IS *
	Uher et al., 2014[a] (41)	Nortriptyline (TCA)	CRP ≥ 1 mg/L	**Higher** response rates compared to low IS ***
	Harley et al., 2010 (49)	Fluoxetine (SSRI) + Nortriptyline (TCA)	CRP ≥ 1 mg/L	**Higher** response rates compared to low IS ***
	Yang et al., 2015 (50)	Ketamine (NMDA Receptor Antagonist)	IL-6	**Higher** response rates compared to low IS ***
	Gupta et al., 2016 (51)	Mirtazapine (NaSSA)	TNFα	**Higher** response rates compared to low IS *

SSRI, selective serotonin reuptake inhibitors; NDRI, norepinephrine dopamine reuptake inhibitor; TCA, tricyclic antidepressant; NaSSA, noradrenergic and specific serotonergic antidepressant; TNFα, tumor necrosis factor alpha; IL, interleukin; CRP, C-reactive protein; m–h, moderate–high; IS, inflammatory state.
**p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.*
[a]Improvement on Montgomery–Asberg Depression Rating Scale (MADRS) score 3 points higher with nortriptyline when CRP ≥ 1 mg/L and 3 points higher with escitalopram when CRP < 1 mg/L.

TABLE 1C | Anti-inflammatory agents (added to an antidepressant regimen, except for one study): lower response rates in low inflammatory state (prior to treatment) versus placebo and higher response rates in moderate–high inflammatory state versus low inflammatory state (prior to treatment).

INFLAMMATORY STATE	STUDY	DRUG	INFLAMMATORY TEST	RESPONSE
LOW	Rapaport et al., 2016 (52)	Monotherapy eicosapentaenoic acid (EPA)	e.g., IL-1ra, hs-CRP	**Lower** response rate **compared to placebo** of low inflammatory state *
	Raison et al., 2013[b] (53)	Infliximab (anti-TNFα)	CRP ≤ 5mg/L	**Lower** response rate **compared to** placebo of low inflammatory state **
	Savitz et al., 2018[c] (54)	Minocycline	IL-6	**Lower** response rate **compared to placebo** of low inflammatory state [d]
	Savitz et al., 2018[c] (54)	Aspirin (NSAID)	IL-6	**Higher** response rates compared to m–h IS [d]
MODERATE–HIGH	Rapaport et al., 2016 (52)	Monotherapy eicosapentaenoic acid (EPA)	e.g., IL-1ra, hs-CRP	**Higher** response rates compared to low IS *
	Raison et al., 2013[b] (53)	Infliximab (anti-TNFα)	CRP > 5mg/L, TNFα, sTNFR I and II	**Higher** response rates compared to low IS **
	Savitz et al., 2018[c] (54)	Minocycline	IL-6	**Higher** response rates compared to low IS **[d]
	Husain et al., 2017 (55)	Minocycline	CRP > 5 mg/L	**Higher** response rates compared to low IS
	Porcu et al., 2018[c] (56)	*N*-acetylcysteine	CRP > 5 mg/L	**Higher** response rates compared to low IS *
	Hasebe et al., 2017 (57)	*N*-acetylcysteine	IL-6	**No associations** between biomarker values and response rates
	Panizzutti et al., 2018[c] (58)	*N*-acetylcysteine	CRP, IL-6, TNFα, BDNF, IL-8, IL-10	**No associations** between biomarker values and response rates
	Savitz et al., 2018[c] (54)	Aspirin (NSAID)	CRP	**No associations** between biomarker values and response rates
	Savitz et al., 2018[c] (54)	Aspirin (NSAID)	IL-6	**Lower** response rate compared to low IS [d]

TNFα, tumor necrosis factor alpha; IL, interleukin; CRP, C-reactive protein; m–h, moderate–high; IS, inflammatory state.
**p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, reported effects without significance were not tested for significance but showed a clear descriptive trend and were therefore considered noteworthy.*
[b]Mixed sample with MDD and bipolar depressed patients, [c]Bipolar depressed sample (type I/II and unspecified), [d]Personal communication.

shows that five out of seven studies (52–56) found a significant improvement of an (add-on) anti-inflammatory therapy, when patients with high signs were compared to patients with low signs of inflammation. The anti-inflammatory agents used in these studies were infliximab, minocycline, *n*-acetylcysteine, and fish oil (the latter as monotherapy, and compared to placebo).

It must be mentioned that the study of Savitz et al. (54) only noted such improving effect with minocycline; aspirin had no such effect in their study. Aspirin did work in their "non-inflamed" patients, yet had no effect or even a reduced effect in patients with high signs of inflammation, depending on the inflammatory serum marker used to determine the state of low-grade inflammation (CRP or IL-6, see **Table 1C**). The study of Savitz was also special in that both unipolar and bipolar depressed patients were included.

Table 1C additionally shows that there are also two out of three studies (57, 58) that showed that in the case of add-on *n*-acetyl cysteine, it was of no use to stratify the patients in low- or high-grade inflammation prior to therapy. Two of the studies of add-on *n*-acetyl cysteine (one showing and one not showing an effect of prior determination of the inflammatory state) involved both unipolar and bipolar depressed patients.

It was remarkable that when an add-on anti-inflammatory agent was given to patients with low signs of inflammation, reduced responses were obtained as compared to patients with high signs of inflammation and even to placebo (two out of three of such studies) (53, 54). Also, when fish oil (an agent with both lipid-correcting and anti-inflammatory properties) was given as a monotherapy to patients with a low inflammatory state, reduced responses were seen as compared to placebo (52) (**Table 1C**). As mentioned above, add-on aspirin did induce an increased response in patients with low signs of inflammation in the study of Savitz et al. (54).

Taking these literature data together, it is difficult to draw a simple conclusion on the usefulness of a prior measurement of serum inflammatory markers for the determination of the effect of (add-on) anti-inflammatory agents. There is a clear trend that (add-on) anti-inflammatory agents, such as infliximab, minocycline, and fish oil are effective if inflammatory markers are clearly present, but this does not apply to aspirin and *n*-acetylcysteine. However, it is also safe to say that special caution must be given when there is an absence of circulating inflammatory markers in patients with MDD: the chances are high that the use of the effective anti-inflammatory agents (such as infliximab, minocycline, and fish oil) in states of moderate–high inflammation actually has an opposite effect than expected in such patients, namely, a reduced responsiveness.

Systematic Review Data on Gene Expression in Circulating Leukocytes

Table 2 shows the studies we selected that dealt with the gene message for pro-inflammatory cytokine production in the circulating leukocyte pool prior to treatment and predictive for treatment outcome. We found five relevant articles.

In 2013, Powell et al. (59) described a significantly increased baseline expression of *TNF* in escitalopram non-responders (n = 21) compared to responders (n = 25) taken from the GENDEP study. In the same year, Cattaneo et al. (61) reported on data of the GENDEP study and found higher baseline mRNA levels for *IL1β*, macrophage inhibiting factor (*MIF*), and *TNF* in antidepressant (escitalopram or nortriptyline) non-responders compared to responders, the three cytokine expressions together explaining 46% of the variance of treatment response.

Belzeaux et al. (63) identified an algorithm of four mRNAs, including two cytokine genes (TNF and *IL1β*, together with *PPT1* and *HIST1H1E*) to be predictive of the treatment response in MDD. However, the weakness of their study was that a whole scale of antidepressants was used, while numbers of patients and HC were limited (16 vs. 13). Guilloux et al. (60) predicted non-remission following escitalopram treatment in MDD with an accuracy of 79.4% using a 13-gene model including four genes associated with immune and inflammatory activation (however, *TNF* was not part of the 13 genes). Mediation of cell proliferation was another important function of the remaining genes, but not exclusively. In 2016, Cattaneo et al. (62) took the data of the GENDEP study further and reported that absolute values of the message for *IL1β* and *MIF* together could predict non-responsiveness to escitalopram or nortriptyline in over 99%. These outcomes were confirmed in an independent, naturalistic replication sample.

Taken together, it is clear that non-responsiveness to an SSRI or to a TCA (nortriptyline) can likely be predicted by determining the expression level of combinations of important immune genes (*IL1β*, *MIF*, *TNF*, and *CD3*) in preparations of circulating leukocytes of patients with MDD.

TABLE 2 | The predictive capability of inflammatory state prior to therapy measured by circulating leukocyte gene expression for the response to various antidepressant regimens in MDD.

ANTIDEPRESSANT AGENT	GENE TRANSCRIPT	EFFECT	STUDY
Escitalopram (SSRI)	TNF	Higher levels in non-responders	Powell et al., 2013 (59)
Escitalopram (SSRI)	13-gene model, including immune/inflammatory genes (CD3D, CD97, IFITM3, and GZMA)	Predicting non-remission with 79.4% accuracy	Guilloux et al., 2015 (60)
Escitalopram(SSRI) or Nortriptyline (TCA)	IL1β, TNF, and MIF (relative mRNA values)	Higher levels in non-responders	Cattaneo et al., 2013 (61)
Escitalopram (SSRI) or Nortriptyline (TCA)	IL1β and MIF (absolute mRNA values)	Algorithm predictive of non-response with probability of over 99%	Cattaneo et al., 2016 (62)
Antidepressant treatment, not specified	IL1β, TNF, PPT1, and HIST1H1E	Algorithm predictive of treatment response	Belzeaux et al., 2012 (63)

SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; TNF, tumor necrosis factor; IL, interleukin; CD, cluster of differentiation; mRNA, messenger ribonucleic acid; PPT1, palmitoyl-protein thioesterase 1; HIST1H1E, histone cluster 1 H1 family member E; MIF, macrophage inhibition factor; IFITM3, interferon-inducible transmembrane protein 3; GZMA, granzyme A.

Experimental Data on Inflammation-Related Gene Expression in Circulating Monocytes as a Predictor of Treatment Response

Prior to treatment, we could test 34 patients with MDD [mean age: 52.2 (±9.9) years, 59% females, collected at the ErasmusMC, Rotterdam] for inflammatory gene expression in their circulating monocytes. As a control group, we tested 45 HC of comparable age [mean age: 49.1 (±9.4) years] and gender (44% females). Of the 34 patients, 14 were treated with venlafaxine and 20 were treated with imipramine. An overall response rate of 11% was found in this trial, with 11/34 patients responding to treatment. The difference between the response rates for both treatment arms were not statistically significant, i.e., a response rate of 36% (5/14) for patients treated with venlafaxine and of 30% (6/20) for patients treated with imipramine. Vermeiden et al. (38) have reported extensively on this study and described that in the entire group of patients (n = 85), 45% of the patients responded to this first line of drug treatment (measured as 50% HAM-D reduction).

The other series of patients involved 35 patients with MDD [mean age: 41.4 (±10.8) years, 46.7% females, collected at the LMU, Munich] and 42 HC of comparable age [mean age: 37.9 (±11.9) years] and gender (61.9% females). Of the 35 patients, 19 were treated with sertraline *plus* placebo and 16 were treated with sertraline *plus* celecoxib. A high overall response rate was found in this trial, i.e., 26/35 (74.3%) of patients responded to treatment. The difference between the response rates for both treatment arms was not statistically significant, i.e., a response rate of 68.4% (13/19) for patients treated with sertraline *plus* placebo and 81.3% (13/16) for patients treated with sertraline *plus* celecoxib.

We determined with an already published algorithm [see the Section Monocyte Inflammatory Gene Expression and Ref. (45)] the inflammatory state of the monocytes using the top 10 cluster 1 inflammatory genes (*IL1β*, *CCL20*, *EREG*, *IL6*, *TNFAIP3*, *CXCL2*, *PDE4B*, *ATF3*, *PTX3*, and *IL1A*). We controlled the patient monocyte tests with the outcomes of the same tests carried out in HC. **Table 3** shows that, in each study group, a significant larger proportion of patients had—prior to therapy—circulating monocytes with a positive inflammatory gene signature as compared to the respective HC. Taking all patients from the four study groups together, 25 of the 69 (36%) patients with MDD had circulating monocytes with a pro-inflammatory gene signature, while only 9 of 87 (10%) HC had such monocyte signature ($p < 0.05$). This observation is in accord with earlier observations that monocytes of part of the patients with MDD show signs of a high inflammatory state (21).

For the purpose of this study, we divided the total patient group in those with a negative monocyte inflammatory gene score and those with a positive score. The data in **Table 3** show that in the response rates in three out of four patient groups, patients with a positive inflammatory gene score had a lower response rate than those without a positive score. This, however, did not apply to the sertraline *plus* placebo group, and also significant differences were not reached in any of the groups. The phenomenon of better responsiveness in "non-inflamed" MDD patients could also be seen in the total MDD patient group; patients with a positive inflammatory gene score had a lower response rate than patients without a positive inflammatory gene score (i.e., 44% vs. 59%); however, a statistical significance was not reached in the total group of patients.

DISCUSSION

The Predictive Capability of the Inflammatory State for Anti-Depressive and Anti-Inflammatory Treatment and Potential Mechanisms

The data of the systematic review and experimental monocyte data, as presented in this study, collectively point in the direction that the state of so-called low-grade inflammation does play a role in the outcome of antidepressant therapy of patients with MDD.

Low-grade inflammation is characterized by an increase in the serum level of pro-inflammatory compounds (e.g., CRP, IL-1 β, IL-6, and TNF-α) and/or an activation state of circulating or tissue resident immune cells, including the brain microglia. Both an increase in pro-inflammatory compounds in the blood of patients with MDD and a pro-inflammatory activation

TABLE 3 | Proportions of patients with a positive inflammatory gene signature of circulating monocytes prior to therapy measured in total and by response.

Predominantly serotonergic agents	HC	MDD	Inflammatory negatives		Inflammatory positives	
	Positive	Positive	Responders	Non-responders	Responders	Non-responders
Sertraline *plus* Placebo (SSRI)	5/42 (12%)	7/19 (37%)	8/12 (67%)	4/12 (33%)	5/7 (71%)	2/7 (29%)
Sertraline *plus* Celecoxib (COX-2 inhibitor)	idem	3/16 (19%)	11/13 (85%)	2/13 (15%)	2/3 (67%)	1/3 (33%)
Venlafaxine (SNRI)	2/22 (9%)	6/14 (43%)	3/8 (38%)	5/8 (62%)	2/6 (33%)	4/6 (66%)
Imipramine (TCA)	2/23 (9%)	9/20 (45%)	4/11 (36%)	7/11 (64%)	2/9 (22%)	7/9 (78%)
SUM	9/87 (10%)	25/69 (36%)*	26/44 (59%)*	18/44 (41%)*	11/25 (44%)*	14/25 (56%)*

SSRI, selective serotonin reuptake inhibitors; SNRI, sertraline–noradrenaline reuptake inhibitors; TCA, tricyclic antidepressant; COX-2, cyclooxygenase 2; HC, healthy controls; MDD, major depressive disorder.

**$p \leq 0.05$ compared to HC.*

Positivity was defined by an upregulation of 6 (or more) of the 10 cluster 1 genes.

Original Q-PCR data have been uploaded and can be retrieved via the GEO repository ref number GSE132315: http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE132315

of microglia and/or of myeloid cells in the periphery (i.e., monocytes) have been documented in a considerable (≈30–40%) proportion of patients with MDD (20, 73, 74). Moreover, imaging and histological techniques have shown microglial activation in the hippocampus of depressed patients (75).

By producing an array of neurotrophic factors, pro- and anti-inflammatory cytokines (e.g., IL-6), as well as axon guidance molecules, non-inflammatory activated microglia has been implicated both in white matter integrity and in the adequate development and function of important stress-regulating systems in the healthy brain (76, 77). On the contrary, inflammatory activated microglia (and/or a transfer of peripheral pro-inflammatory cytokines to the brain) is thought to hamper the normal development, growth, and synaptic function of stress-regulating systems and brain connections important for mood regulation, such as the white matter tracts between the forebrain and the limbic system. To illustrate this, raised serum pro-inflammatory cytokine levels have been associated in mood disorder patients with increased activation of threat- and anxiety-related neuro-circuits (78), reduced neural responses to negative stimuli in frontal brain regions involved in cognitive and emotional functions (79), and compromised integrity of myelin sheaths in cortico-limbic networks involved in mood regulation (80).

Importantly, low-grade inflammation has been shown to influence not only brain development and function but also neurotransmission, with excellent reviews on the inhibitory effects of pro-inflammatory cytokines, such as IL-1β and TNF-α, on the synaptic availability of monoamines and BDNF, while the same cytokines have been shown to increase extracellular glutamate, all important molecular determinants in MDD pathogenesis and response to treatment (15).

The data from the here presented systematic review on circulating inflammatory compounds indicate that patients with MDD with an activated inflammatory state (as measured by, e.g., moderate to high levels of circulating CRP, IL-6, and/or TNF-α) show reduced response rates to antidepressant regimens with a primarily serotonergic action (e.g., escitalopram), while showing improved response rates to antidepressant regimens with a primarily noradrenergic (e.g., nortriptyline), dopaminergic (e.g., bupropion, mirtazapine), or glutamatergic action (i.e., ketamine).

The systematic review data on the inflammatory gene expression in circulating leukocytes confirmed this phenomenon, showing that patients with a high gene expression level of *IL1β*, *TNF*, and/or *MIF* did not respond well to interventions with an SSRI in comparison to MDD patients with a low expression of these genes. However, gene data in circulating leukocytes disagreed with the data reported for circulating inflammatory compounds regarding TCA. While the primarily noradrenergic TCA nortriptyline did not give a satisfactory response in patients with MDD with a high gene expression level in circulating leukocytes (see **Table 2**), nortriptyline did in patients with high levels of circulating inflammatory compounds (see **Table 1B**).

Apparently, inflammatory gene expression in leukocytes does not measure the same level of inflammation than the measurement of circulating inflammatory compounds in serum/plasma; a high inflammatory gene expression might typify a state of "stronger/other" inflammation in MDD needing a treatment with drugs beyond the serotonergic and noradrenergic drugs. In other studies, we have also noted that inflammatory gene expression in circulating cells does not correlate one to one with the circulating protein gene product in serum/plasma (81). We explained this phenomenon by assuming that resident cells, such as the endothelial cells and resident macrophages in the tissues, also contribute to the level of circulating inflammatory compounds.

Although the data of our experiments on inflammatory gene expression levels in circulating monocytes (a subset of the circulating leukocytes) did not deliver statistically significant results, they were, by and large, in agreement with the above-described findings for the gene expression in all circulating leukocytes and showed that patients with "inflammatory" monocytes showed reduced response rates to predominantly serotonergic drug interventions and patients with "non-inflammatory" monocytes showed higher response rates to these type of agents.

Collectively, we deduce from these data that MDD patients with an activated inflammatory state (as measured by moderate to high circulating levels of, e.g., CRP, TNF-α, and IL-6, or a high gene expression of, e.g., *IL1β*, *TNF*, and *MIF* in circulating leukocytes) need more than a monotherapy with a predominantly serotonergic agent to improve clinically in a satisfactory way. An option then seems to be an immediate step up to agents with also a strong dopaminergic or glutamatergic action.

The reason for a better response to dopaminergic or glutamatergic drugs in the case of signs of enhanced inflammation can only be speculated on. It is possible that these drugs are needed because they also have clear anti-inflammatory actions, counteracting the detrimental effects of the high inflammatory state on the signs and symptoms of depression. There is ample evidence that dopamine and ketamine can reduce the production of pro-inflammatory cytokines and enhance that of anti-inflammatory cytokines (82, 83). On the other hand, the pro-inflammatory state itself may lead to an altered neurotransmitter metabolism, necessitating more than a primarily serotonin reuptake inhibition, but also an intervention in the dopamine or glutamate metabolism. Pro-inflammatory cytokines have been reported to activate neuronal mitogen-activated protein kinase (MAPK) pathways, increasing monoamine transporter expression and activity in general, which leads to an increased pre-synaptic reuptake of not only serotonin but also other neuroactive amines (84, 85). Furthermore, the state of enhanced inflammation is thought to lead to an enhanced tryptophan breakdown *via* the kynurenine pathway, resulting in various neuroactive compounds, among which NMDA agonists and antagonists, aggravating glutamatergic neurotransmitter imbalances (86, 87). This might also necessitate more than only a serotonin reuptake inhibition to be effective.

A step up to dopaminergic and glutamatergic antidepressants was more effective in "inflammatory" MDD patients than in "non-inflammatory" patients, and a combination of an antidepressant with an anti-inflammatory agent increased the response rates in

these "inflammatory" patients with MDD as compared to "non-inflammatory" MDD patients. Though the reviewed literature data are scarce, the best prediction results seem to be obtained for infliximab (anti-TNF-α agent), minocycline (tetracycline), and eicosapentaenoic acid (fish oil). For *n*-acetylcysteine, the inflammatory state did show conjectural prediction effects, while for aspirin (acetylsalicylic acid), a reduced response was actually seen in "inflammatory" patients as compared to "non-inflammatory" patients.

The strength or character of the anti-inflammatory agents may have played a role in this variation of predictability of the state of inflammation for the (add-on) anti-inflammatory agents. Both anti-TNF agents and minocycline are in clinical practice and are considered stronger anti-inflammatory drugs than *n*-acetylcysteine and aspirin. However, for fish oil, a high inflammatory state was also predictive for a better effect in MDD patients, while fish oil is considered a relatively weak anti-inflammatory agent. Interestingly, fish oil exerts its anti-inflammatory effects *via* changing the "bad" pro-inflammatory lipid state of individuals (88), and perhaps the high state of inflammation in MDD patients is primarily driven by a bad lipid profile, which is then best corrected by fish oil.

Also, direct or indirect neurotransmitter effects of the anti-inflammatory agents may have played a role in the success or failure to predict their improved responsiveness in "inflammatory" MDD patients. Interestingly, two of the three add-on anti-inflammatory agents (minocycline and fish oil) that worked better in "inflammatory" than in "non-inflammatory" patients possess dopaminergic activities (89, 90). *N*-acetylcysteine, of which it is conjectural whether it works better as add-on in "inflammatory" than in "non-inflammatory" MDD patients, influences both dopamine and glutamate levels in the brain (91). Add-on aspirin, in contrast, had fewer effects in "inflammatory" MDD patients as compared to "non-inflammatory" patients; interestingly, aspirin has anti-glutamatergic actions (92, 93). These varying neuro-modulating actions of anti-inflammatory drugs make complex interactions in the neuro-immune network possible, inducing varying outcomes of combinations of antidepressants and anti-inflammatory agents. Of note also is that three of the reviewed studies of add-on anti-inflammatory agents had included bipolar depressed patients (54, 56, 58). This applies in particular to the study on aspirin (54), in which a reducing effect was found in "inflammatory" versus "non-inflammatory" patients. Intrinsic differences between bipolar and unipolar depression, such as differences in the immune and the glutamate state (94–98), may have played a role here.

Despite the above-listed uncertainties, it is nevertheless tempting to postulate—based on the outcomes of the literature review—that when MDD patients are "inflammatory", (add-on) anti-inflammatory drugs are also an option to improve responsiveness and then the best results are probably obtained when anti-inflammatory agents are potent, influence lipid metabolism, and/or influence primarily dopaminergic synaptic transmission.

Regarding the use of (add-on) anti-inflammatory agents, another important message emerges from our systematic review of the literature. Interestingly, three out of four reports (52–54) indicated that "non-inflammatory" MDD patients showed a reduced response rate as compared to even placebo to the effective (add-on) intervention with an anti-inflammatory agent. In other words, the addition of the anti-inflammatory drugs effective in "inflammatory" patients was detrimental, and the anti-inflammatory drugs inhibited the effect of the antidepressants or delayed natural recovery. Such an outcome of an anti-inflammatory regimen is counterintuitive, if one assumes that inflammation contributes to depressive symptomatology (see before). The authors of one of the papers describing this phenomenon (53) explain their finding, that perhaps a small activation of the inflammatory system is needed for mental well-being and that both an extreme low and an extreme high activity of the inflammatory response system is disadvantageous for mental health. In other words, there would be an optimal set point for the inflammatory state of an individual for mental health. Downregulating this optimal state with an effective anti-inflammatory agent would, in such a view, be counterproductive and would open the way for the development of depressive symptoms.

Another explanation is that there exists a form of MDD that is non-immune and characterized by absent serological markers of immune activation. As indicated, (add-on) aspirin has a beneficial effect in patients and it can be hypothesized that it is in particular the neuro-modulating effect (anti-glutamatergic) of aspirin that induces this effect.

Based on this literature review, what appears to be the best and easiest assay system to measure the inflammatory state of MDD patients? The systematic review data on the gene expression level of cytokines in circulating leukocytes showed that two of the leukocyte gene expression studies resulted in very good accuracy rates of prediction of non-responsiveness, and algorithms could be developed, which showed high accuracies from 75% to even a 100% to predict non-responsiveness to an SSRI/TCA drug intervention (60, 62). Apparently, high levels of inflammatory cytokine gene message in circulating leukocytes are a precise sign of poor (treatment) outcome, and perhaps even better than high levels of inflammatory compounds/cytokines in serum/plasma. Nevertheless, it is technically less demanding to measure inflammatory compounds/cytokines in serum/plasma than to perform a gene expression assay in circulating leukocytes. Regarding the inflammatory markers best to be measured in serum/plasma to determine a raised inflammatory state in patients with MDD, it is worthy to note that the most consistent effects were found in our literature analysis with circulating CRP and/or IL-6 levels. These inflammatory compounds were tested in a large proportion of the here reviewed studies on serum inflammatory compounds (15/19), and outcomes and conclusions were congruent between these studies regarding these two inflammation markers.

Circulating TNF-α was measured in only six studies; hence, sufficient information on the validity of this parameter is lacking. Importantly, one of the studies showed that circulating TNF-α levels were not in agreement with the general rule, finding that a high TNF-α level was not predictive of a decreased responsiveness to an SSRI/SNRI (while a high IL-6 level in the same study was)

(43). Other circulating inflammatory compounds (e.g., IL-8, IL-10, and IL-1) have also been tested in the here reported studies, but in only very few studies, and therefore data cannot be reliably evaluated. They nevertheless showed the general trend for serum/plasma factors that, in a state of inflammation, more than a monotherapy with a predominantly serotonergic agent might be needed.

Collectively, it seems that for predicting responsiveness to regular antidepressants, the avenue exploring the usefulness of serum/plasma CRP and IL-6 determination is the easiest and clinically the most feasible and promising approach. High levels of CRP/IL-6 would indicate that treatment with a serotonergic drug is not effective enough. However, the data reviewed here also indicate that the gene expression in circulating leukocytes cannot be neglected as a predicting parameter due to the reported high levels of accuracy to predict non-responsiveness to SSRI/SNRI and TCA therapy.

Limitations

In this article, we only focused on inflammation parameters as determinants for the outcome of treatment. The various other determinants important for treatment outcome have recently been reviewed by Perlman et al. (99). The authors described not only that inflammation-related determinants are important but also that a whole array of genetic, endocrine, neuroimaging, sociodemographic, and symptom-based predictors turn out to influence outcome. However, due to heterogeneous sample sizes, effect sizes, publication biases, and methodological disparities across reviews, Perlman et al. (99) concluded that they could not accurately assess the strength and directionality of the predictors, and the authors therefore highlighted the importance of large-scale research initiatives and the use of clinically easily accessible biomarkers, as well as the need for replication studies of current findings. Clearly, we support such view and underscore the notion that our review data are also affected by the heterogeneous sample sizes, effect sizes, publication biases, and methodological disparities and that the data do not yet give a clear-cut picture. Also, our own experimental data on monocyte gene expression were underpowered and too limited to obtain clear-cut results and significances. Thus, clearly more studies are needed using standardized add-on anti-inflammatory treatments to standardized single antidepressant medications to develop a clearer picture of the actual response rates in immune and otherwise stratified patients with MDD.

Conclusions

There are excellent recent reviews on the discovered signs of low-grade inflammation in psychiatric patients that have transformed our understanding of neuropsychiatric diseases and urge for new diagnostic and therapeutic criteria in the emerging field of immuno-psychiatry (100). There are, however, at present, insufficient data and reliable concepts on the inflammation pathogenesis of MDD to design clinically applicable treatment drug protocols with reliable cutoff points for inflammatory parameters to guide therapy regimens.

Despite this limitation, a few generalizations can nevertheless be made from our study regarding inflammation as a predictor. Of the inflammation parameters, the serum CRP and IL-6 seem to be the most promising parameters for further clinical development. They are relatively easy to determine and, thus, useful in clinical studies. Using these parameters, a state of raised inflammation (as evidenced by raised serum CRP and IL-6 levels) characterizes a form of MDD with a relatively poor outcome and a non-responsiveness to agents with a predominant serotonergic action. Such cases might need a faster step-up to drug regimens with agents with dopaminergic (e.g., mirtazapine and bupropion) or glutamatergic (e.g., ketamine) effects, or a combination of a first-line antidepressant with an anti-inflammatory agent such as infliximab, minocycline, or fish oil (but not aspirin), most of them showing dopaminergic action. Varying anti-inflammatory properties of antidepressants as well as varying neuro-modulatory effects of anti-inflammatory agents (and/or complex interactions thereof) may play a role in the therapeutic success or failure of the step-ups.

A word of caution is needed regarding the regimens using as add-on the successful anti-inflammatory agents infliximab, minocycline, and fish oil: There must indeed be laboratory signs of inflammation (i.e., raised serum levels of CRP or IL-6) for this addition to be effective. If not, even response rates lower than the non-add-on situation might be obtained.

ETHICS STATEMENT

These studies were carried in compliance with standards of CGP, assuring that the rights, safety, and well-being of patients were protected in accordance with the principles that have their origin in the Declaration of Helsinki (June 1964, last amendment Fortaleza 2013). Additionally, the relevant national and European regulations were adhered, too. After study procedures had been fully explained, all subjects provided written informed consent.

AUTHOR CONTRIBUTIONS

GA and MS designed the strategy of the present review. BB and EW collected part of the study cohort, GA, AW and HD evaluated the data. GAH and MS wrote the first draft of the paper, HD and NM contributed with supervision and expert advice and critically revised the draft. All other authors contributed to the manuscript revision and approved the submitted version.

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REFERENCES

1. Müller N, Hofschuster E, Ackenheil M, Mempel W, Eckstein R. Investigations of the cellular immunity during depression and the free interval: evidence for an immune activation in affective psychosis. *Prog Neuropsychopharmacol Biol Psychiatry* (1993) 17(5):713–30. doi: 10.1016/0278-5846(93)90055-W
2. Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci* (1998) 62(7):583–606. doi: 10.1016/S0024-3205(97)00990-9
3. Anisman H, Merali Z. Anhedonic and anxiogenic effects of cytokine exposure. *Adv Exp Med Biol* (1999) 461:199–233. doi: 10.1007/978-0-585-37970-8_12
4. Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *Eur Neuropsychopharmacol* (2001) 11(3):203–8. doi: 10.1016/S0924-977X(01)00081-5
5. Myint A-M, Leonard BE, Steinbusch HWM, Kim Y-K. Th1, Th2, and Th3 cytokine alterations in major depression. *J Affect Disord* (2005) 88(2):167–73. doi: 10.1016/j.jad.2005.07.008
6. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav Immun* (2007) 21(4):374–83. doi: 10.1016/j.bbi.2007.01.010
7. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* (2008) 9(1):46–56. doi: 10.1038/nrn2297
8. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* (2009) 71(2):171–86. doi: 10.1097/PSY.0b013e3181907c1b
9. Miller AH. Depression and immunity: a role for T cells? *Brain Behav Immun* (2010) 24(1):1–8. doi: 10.1016/j.bbi.2009.09.009
10. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry* (2010) 67(5):446–57. doi: 10.1016/j.biopsych.2009.09.033
11. Drexhage RC, Weigelt K, van Beveren N, Cohen D, Versnel MA, Nolen WA, et al. Immune and neuroimmune alterations in mood disorders and schizophrenia. *Int Rev Neurobiol* (2011) 101:169–201. doi: 10.1016/B978-0-12-387718-5.00007-9
12. Eyre HA, Stuart MJ, Baune BT. A phase-specific neuroimmune model of clinical depression. *Prog Neuropsychopharmacol Biol Psychiatry* (2014) 54:265–74. doi: 10.1016/j.pnpbp.2014.06.011
13. Müller N. Immunology of major depression. *NIM* (2014) 21(2–3):123–30. doi: 10.1159/000356540
14. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimäki M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun* (2015) 49:206–15. doi: 10.1016/j.bbi.2015.06.001
15. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* (2016) 16(1):22–34. doi: 10.1038/nri.2015.5
16. Grosse L, Hoogenboezem T, Ambrée O, Bellingrath S, Jörgens S, de Wit HJ, et al. Deficiencies of the T and natural killer cell system in major depressive disorder: T regulatory cell defects are associated with inflammatory monocyte activation. *Brain Behav Immun* (2016) 54:38–44. doi: 10.1016/j.bbi.2015.12.003
17. Gibney SM, Drexhage HA. Evidence for a dysregulated immune system in the etiology of psychiatric disorders. *J Neuroimmune Pharmacol* (2013) 8(4):900–20. doi: 10.1007/s11481-013-9462-8
18. Bergink V, Gibney SM, Drexhage HA. Autoimmunity, inflammation, and psychosis: a search for peripheral markers. *Biol Psychiatry* (2014) 75(4):324–31. doi: 10.1016/j.biopsych.2013.09.037
19. Poletti S, de Wit H, Mazza E, Wijkhuijs AJM, Locatelli C, Aggio V, et al. Th17 cells correlate positively to the structural and functional integrity of the brain in bipolar depression and healthy controls. *Brain Behav Immun* (2017) 61:317–25. doi: 10.1016/j.bbi.2016.12.020
20. Beumer W, Gibney SM, Drexhage RC, Pont-Lezica L, Doorduin J, Klein HC, et al. The immune theory of psychiatric diseases: a key role for activated microglia and circulating monocytes. *J Leukoc Biol* (2012) 92(5):959–75. doi: 10.1189/jlb.0212100
21. Grosse L, Carvalho LA, Wijkhuijs AJM, Bellingrath S, Ruland T, Ambrée O, et al. Clinical characteristics of inflammation-associated depression: monocyte gene expression is age-related in major depressive disorder. *Brain Behav Immun* (2015) 44:48–56. doi: 10.1016/j.bbi.2014.08.004
22. Gałecki P, Talarowska M. Inflammatory theory of depression. *Psychiatr Pol* (2018) 52(3):437–47. doi: 10.12740/PP/76863
23. Medina-Rodriguez EM, Lowell JA, Worthen RJ, Syed SA, Beurel E. Involvement of innate and adaptive immune systems alterations in the pathophysiology and treatment of depression. *Front Neurosci* (2018) 12. doi: 10.3389/fnins.2018.00547
24. Pundiak TM, Case BG, Peselow ED, Mulcare L. Discontinuation of maintenance selective serotonin reuptake inhibitor monotherapy after 5 years of stable response: a naturalistic study. *J Clin Psychiatry* (2008) 69(11):1811–7. doi: 10.4088/JCP.v69n1117
25. Dell'Osso B, Palazzo MC, Oldani L, Altamura AC. The noradrenergic action in antidepressant treatments: pharmacological and clinical aspects. *CNS Neurosci Ther* (2011) 17(6):723–32. doi: 10.1111/j.1755-5949.2010.00217.x
26. Furukawa TA, Salanti G, Atkinson LZ, Leucht S, Ruhe HG, Turner EH, et al. Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. *BMJ Open* (2016) 6(7):e010919. doi: 10.1136/bmjopen-2015-010919
27. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* (2009) 373(9665):746–58. doi: 10.1016/S0140-6736(09)60046-5
28. Frick LR, Rapanelli M. Antidepressants: influence on cancer and immunity? *Life Sci* (2013) 92(1):525–32. doi: 10.1016/j.lfs.2013.01.020
29. Gałecki P, Mossakowska-Wójcik J, Talarowska M. The anti-inflammatory mechanism of antidepressants—SSRIs, SNRIs. *Prog Neuropsychopharmacol Biol Psychiatry* (2018) 80(Pt C):291–94. doi: 10.1016/j.pnpbp.2017.03.016
30. Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. *Acta Psychiatrica Scandinavica* (2014) 123(3):163–79. doi: 10.1111/acps.12211
31. Müller N. Immunological aspects of the treatment of depression and schizophrenia. *Dialogues Clin Neurosci* (2017) 19:1.
32. Husain MI, Strawbridge R, Stokes PR, Young AH. Anti-inflammatory treatments for mood disorders: systematic review and meta-analysis. *J Psychopharmacol (Oxford)* (2017) 31(9):1137–48. doi: 10.1177/0269881117725711
33. Adzic M, Brkic Z, Mitic M, Francija E, Jovicic MJ, Radulovic J, et al. Therapeutic strategies for treatment of inflammation-related depression. *Curr Neuropharmacol* (2018) 16(2):176–209. doi: 10.2174/1570159X15666170828163048
34. Fernandes BS, Dean OM, Dodd S, Malhi GS, Berk M. Acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis. *J Clin Psychiatry* (2016) 77(4):e457-66. doi: 10.4088/JCP.15r09984
35. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol* (2015) 15(2):104–16. doi: 10.1038/nri3793

36. Palacio JR, Markert UR, Martínez P. Anti-inflammatory properties of N-acetylcysteine on lipopolysaccharide-activated macrophages. *Inflamm Res* (2011) 60(7):695–704. doi: 10.1007/s00011-011-0323-8
37. Raison CL, Miller AH. Is depression an inflammatory disorder? *Curr Psychiatry Rep* (2011) 13(6):467–75. doi: 10.1007/s11920-011-0232-0
38. Vermeiden M, Mulder PG, van den Broek WW, Bruijn JA. Birkenhäger TK. A double-blind randomized study comparing plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients. *J Psychiatr Res* (2013) 47(10):1337–42. doi: 10.1016/j.jpsychires.2013.05.029
39. Bakkalbasi N, Bauer K, Glover J, Wang L. Three options for citation tracking: Google Scholar, Scopus and Web of Science. *Biomed Digit Libr* (2006) 3:7. doi: 10.1186/1742-5581-3-7
40. Jha MK, Minhajuddin A, Gadad B, Greer T, Grannemann B, Soyombo A, et al. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology* (2017) 78:105–13. doi: 10.1016/j.psyneuen.2017.01.023
41. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am J Psychiatry* (2014) 171(12):1278–86. doi: 10.1176/appi.ajp.2014.14010094
42. Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* (2008) 32(2):445–50. doi: 10.1016/j.pnpbp.2007.09.015
43. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Katsuki A, Atake K, et al. Plasma levels of interleukin-6 and selective serotonin reuptake inhibitor response in patients with major depressive disorder: IL-6 and SSRI response. *Hum Psychopharmacol* (2013) 28(5):466–70. doi: 10.1002/hup.2333
44. Manoharan A, Rajkumar RP, Shewade DG, Sundaram R, Muthuramalingam A, Paul A. Evaluation of interleukin-6 and serotonin as biomarkers to predict response to fluoxetine. *Hum Psychopharmacol* (2016) 31(3):178–84. doi: 10.1002/hup.2525
45. Chang HH, Lee IH, Gean PW, Lee S-Y, Chi MH, Yang YK, et al. Treatment response and cognitive impairment in major depression: association with C-reactive protein. *Brain Behav Immun* (2012) 26(1):90–5. doi: 10.1016/j.bbi.2011.07.239
46. Haroon E, Daguanno AW, Woolwine BJ, Goldsmith DR, Baer WM, Wommack EC, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology* (2018) 95:43–9. doi: 10.1016/j.psyneuen.2018.05.026
47. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. *Prog Neuropsychopharmacol Biol Psychiatry* (2009) 33(4):722–6. doi: 10.1016/j.pnpbp.2009.03.020
48. Martinez JM, Garakani A, Yehuda R, Gorman JM. Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. *Depress Anxiety* (2012) 29(1):32–8. doi: 10.1002/da.20876
49. Harley J, Luty S, Carter J, Mulder R, Joyce P. Elevated C-reactive protein in depression: a predictor of good long-term outcome with antidepressants and poor outcome with psychotherapy. *J Psychopharmacol* (2010) 24(4):625–6. doi: 10.1177/0269881109102770
50. Yang J, Wang N, Yang C, Shi J, Yu H, Hashimoto K. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. *Biol Psychiatry* (2015) 77(3):e19–e20. doi: 10.1016/j.biopsych.2014.06.021
51. Gupta R, Gupta K, Tripathi AK, Bhatia MS, Gupta LK. Effect of mirtazapine treatment on serum levels of brain-derived neurotrophic factor and tumor necrosis factor-α in patients of major depressive disorder with severe depression. *Pharmacology* (2016) 97(3–4):184–8. doi: 10.1159/000444220
52. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof of concept study. *Mol Psychiatry* (2016) 21(1):71–9. doi: 10.1038/mp.2015.22
53. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression. *JAMA Psychiatry* (2013) 70(1):31–41. doi: 10.1001/2013.jamapsychiatry.4
54. Savitz JB, Teague TK, Misaki M, Macaluso M, Wurfel BE, Meyer M, et al. Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2×2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. *Transl Psychiatry* (2018) 8(1):27. doi: 10.1038/s41398-017-0073-7
55. Husain MI, Chaudhry IB, Husain N, Khoso AB, Rahman RR, Hamirani MM, et al. Minocycline as an adjunct for treatment-resistant depressive symptoms: a pilot randomised placebo-controlled trial. *J Psychopharmacol* (2017) 31(9):1166–75. doi: 10.1177/0269881117724352
56. Porcu M, Urbano MR, Verri WA, Barbosa DS, Baracat M, Vargas HO, et al. Effects of adjunctive N-acetylcysteine on depressive symptoms: modulation by baseline high-sensitivity C-reactive protein. *Psychiatry Res* (2018) 263:268–74. doi: 10.1016/j.psychres.2018.02.056
57. Hasebe K, Gray L, Bortolasci C, Panizzutti B, Mohebbi M, Kidnapillai S, et al. Adjunctive N-acetylcysteine in depression: exploration of interleukin-6, C-reactive protein and brain-derived neurotrophic factor. *Acta Neuropsychiatrica* (2017) 29(6):337–46. doi: 10.1017/neu.2017.2
58. Panizzutti B, Bortolasci C, Hasebe K, Kidnapillai S, Gray L, Walder K, et al. Mediator effects of parameters of inflammation and neurogenesis from a N-acetyl cysteine clinical-trial for bipolar depression. *Acta Neuropsychiatrica* (2018) 30(6):334–41. doi: 10.1017/neu.2018.13
59. Powell TR, Schalkwyk LC, Heffernan AL, Breen G, Lawrence T, Price T, et al. Tumor necrosis factor and its targets in the inflammatory cytokine pathway are identified as putative transcriptomic biomarkers for escitalopram response. *Eur Neuropsychopharmacol* (2013) 23(9):1105–14. doi: 10.1016/j.euroneuro.2012.09.009
60. Guilloux J-P, Bassi S, Ding Y, Walsh C, Turecki G, Tseng G, et al. Testing the predictive value of peripheral gene expression for nonremission following citalopram treatment for major depression. *Neuropsychopharmacology* (2015) 40(3):701–10. doi: 10.1038/npp.2014.226
61. Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline "predictors" and longitudinal "targets". *Neuropsychopharmacology* (2013) 38(3):377–85. doi: 10.1038/npp.2012.191
62. Cattaneo A, Ferrari C, Uher R, Bocchio-Chiavetto L, Riva MA, Pariante CM. Absolute measurements of macrophage migration inhibitory factor and interleukin-1-β mRNA levels accurately predict treatment response in depressed patients. *Int J Neuropsychopharmacol* (2016) 19(10):pyw045. doi: 10.1093/ijnp/pyw045
63. Belzeaux R, Bergon A, Jeanjean V, Loriod B, Formisano-Tréziny C, Verrier L, et al. Responder and nonresponder patients exhibit different peripheral transcriptional signatures during major depressive episode. *Transl Psychiatry* (2012) 2(11):e185. doi: 10.1038/tp.2012.112
64. Carvalho LA, Bergink V, Sumaski L, Wijkhuijs J, Hoogendijk WJ, Birkenhager TK, et al. Inflammatory activation is associated with a reduced glucocorticoid receptor alpha/beta expression ratio in monocytes of inpatients with melancholic major depressive disorder. *Transl Psychiatry* (2014) 4(1):e344. doi: 10.1038/tp.2013.118
65. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (4th ed., text rev)*. Washington, DC: American Psychiatric Association (2000).
66. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I disorders (SCID I)*. New York: Biometric Research Department (1997).
67. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi: 10.1037/t04100-000
68. Müller N, Krause D, Barth R, Myint AM, Weidinger E, Zill P, et al. Childhood adversity and current stress are related to pro- and anti-inflammatory cytokines in major depression. *J Affect Disord* (2019) 253:270–76. doi: 10.1016/j.jad.2019.04.088
69. Vogels RJ, Koenders MA, van Rossum EF, Spijker AT. Drexhage HA. T Cell Deficits and overexpression of hepatocyte growth factor in anti-inflammatory circulating monocytes of middle-aged patients with bipolar disorder characterized by a high prevalence of the metabolic syndrome. *Front Psychiatry* (2017) 8(34):1–11. doi: 10.3389/fpsyt.2017.00034
70. Mesman E, Hillegers MH, Ambree O, Arolt V, Nolen WA, Drexhage HA. Monocyte activation, brain-derived neurotrophic factor (BDNF), and S100B

in bipolar offspring: a follow-up study from adolescence into adulthood. *Bipolar Disord* (2015) 17(1):39–49. doi: 10.1111/bdi.12231
71. Snijders G, Schiweck C, Mesman E, Grosse L, De Wit H, Nolen WA, et al. A dynamic course of T cell defects in individuals at risk for mood disorders. *Brain Behav Immun* (2016) 58:11–7. doi: 10.1016/j.bbi.2016.05.007
72. Nakayama K. Effect of paroxetine on extracellular serotonin and dopamine levels in the prefrontal cortex. *Naunyn Schmiedebergs Arch Pharmacol* (2002) 365(2):102–5. doi: 10.1007/s00210-001-0497-7
73. Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand* (2017) 135(5):373–87. doi: 10.1111/acps.12698
74. Hanisch UW. Microglia as a source and target of cytokines. *Glia* (2002) 40(2):140–55. doi: 10.1002/glia.10161
75. Czéh B, Nagy SA. Clinical findings documenting cellular and molecular abnormalities of glia in depressive disorders. *Front Mol Neurosci* (2018) 11(56):1–16. doi: 10.3389/fnmol.2018.00056
76. Sato K. Effects of microglia on neurogenesis. *Glia* (2015) 63(8):1394–1405. doi: 10.1002/glia.22858
77. Hökfelt T, Stanic D, Sanford SD, Gatlin JC, Nilsson I, Paratcha G, et al. NPY and its involvement in axon guidance, neurogenesis, and feeding. *Nutrition* (2008) 24(9):860–68. doi: 10.1016/j.nut.2008.06.010
78. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proc Natl Acad Sci USA* (2010) 107(33):14817–22. doi: 10.1073/pnas.1009164107
79. Poletti S, Leone G, Hoogenboezem TA, Ghiglino D, Vai B, de Wit H, et al. Markers of neuroinflammation influence measures of cortical thickness in bipolar depression. *Psychiatry Res Neuroimaging* (2019) 285:64–6. doi: 10.1016/j.pscychresns.2019.01.009
80. Benedetti F, Poletti S, Hoogenboezem TA, Mazza E, Ambree O, de Wit H, et al. Inflammatory cytokines influence measures of white matter integrity in bipolar disorder. *J Affect Disord* (2016) 202:1–9. doi: 10.1016/j.jad.2016.05.047
81. Baldeón Rojas L, Weigelt K, de Wit H, Ozcan B, van Oudenaren A, Sempértegui F, et al. Study on inflammation-related genes and microRNAs, with special emphasis on the vascular repair factor HGF and miR-574-3p, in monocytes and serum of patients with T2D. *Diabetol Metab Syndr* (2016) 8(6):1–12. doi: 10.1186/s13098-015-0113-5
82. Beck G, Brinkkoetter P, Hanusch C, Schulte J, van Ackern K, van der Woude FJ, et al. Clinical review: immunomodulatory effects of dopamine in general inflammation. *Crit Care* (2004) 8(6):485–91. doi: 10.1186/cc2879
83. Loix S, KocK MD, Henin P. The anti-inflammatory effects of ketamine: state of the art. *Acta Anaesthesiol Belg* (2011) 62(1):47–58..
84. Zhu C-B, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology* (2006) 31(10):2121–31. doi: 10.1038/sj.npp.1301029
85. Zhu C-B, Lindler KM, Owens AW, Daws LC, Blakely RD, Hewlett WA. Interleukin-1 receptor activation by systemic lipopolysaccharide induces behavioral despair linked to MAPK regulation of CNS serotonin transporters. *Neuropsychopharmacology* (2010) 35(13):2510–20. doi: 10.1038/npp.2010.116
86. Müller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry* (2007) 12(11):988–1000. doi: 10.1038/sj.mp.4002006
87. Walker FR. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology* (2013) 67:304–17. doi: 10.1016/j.neuropharm.2012.10.002
88. Brooks JD, Norris PC, Dennis EA. Effects of omega-3 fatty acids on lipid metabolism and signaling using lipidomic analyses. *FASEB J* (2010) 24:475.1-475.1. doi: 10.1096/fasebj.24.1_supplement.475.1
89. Du Y, Ma Z, Lin S, Dodel RC, Gao F, Bales KR, et al. Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. *Proc Natl Acad Sci* (2001) 98(25):14669–74. doi: 10.1073/pnas.251341998
90. Shin SS, Dixon CE. Oral fish oil restores striatal dopamine release after traumatic brain injury. *Neurosci Lett* (2011) 496(3):168–71. doi: 10.1016/j.neulet.2011.04.009
91. Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci* (2013) 34(3):167–77. doi: 10.1016/j.tips.2013.01.001
92. De Cristóbal J, Moro MA, Dávalos A, Castillo J, Leza JC, Camarero J, et al. Neuroprotective effect of aspirin by inhibition of glutamate release after permanent focal cerebral ischaemia in rats. *J Neurochem* (2001) 79(2):456–9. doi: 10.1046/j.1471-4159.2001.00600.x
93. De Cristóbal J, Cárdenas A, Lizasoain I, Leza JC, Fernández-Tomé P, Lorenzo P, et al. Inhibition of glutamate release *via* recovery of ATP levels accounts for a neuroprotective effect of aspirin in rat cortical neurons exposed to oxygen-glucose deprivation. *Stroke* (2002) 33(1):261–7. doi: 10.1161/hs0102.101299
94. Becking K, Haarman BCM, Grosse L, Nolen WA, Claes S, Arolt V, et al. The circulating levels of CD4+ t helper cells are higher in bipolar disorder as compared to major depressive disorder. *J Neuroimmunol* (2018) 319:28–36. doi: 10.1016/j.jneuroim.2018.03.004
95. Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, et al. Brain metabolic alterations in medication-free patients with bipolar disorder. *Arch Gen Psychiatry* (2004) 61(5):450–8. doi: 10.1001/archpsyc.61.5.450
96. Yüksel C, Öngür D. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry* (2010) 68(9):785–94. doi: 10.1016/j.biopsych.2010.06.016
97. Gigante AD, Bond DJ, Lafer B, Lam RW, Young LT, Yatam LN. Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. *Bipolar Disord* (2012) 14(5):478–87. doi: 10.1111/j.1399-5618.2012.01033.x
98. Jun C, Choi Y, Lim SM, Bae S, Hong YS, Kim JE, et al. Disturbance of the glutamatergic system in mood disorders. *Exp Neurobiol* (2014) 23(1):28–35. doi: 10.5607/en.2014.23.1.28
99. Perlman K, Benrimoh D, Israel S, Rollins C, Brown E, Tunteng J-F, et al. A systematic meta-review of predictors of antidepressant treatment outcome in major depressive disorder. *J Affect Disord* (2019) 243:503–15. doi: 10.1016/j.jad.2018.09.067
100. Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsychiatry—Novel perspectives on brain disorders. *Nat Rev Neurol* (2019) 15(6):317–28. doi: 10.1038/s41582-019-0174-4

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REVIEW
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COX-2 Inhibitors, Aspirin, and Other Potential Anti-Inflammatory Treatments for Psychiatric Disorders

Norbert Müller[1,2]*

[1] Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität Munich, Munich, Germany,
[2] Marion von Tessin Memory Center, Munich, Germany

Inflammatory processes associated with persistent (chronic) infection have long been discussed as etiological factors in psychiatric disorders. Studies have found that people with major depression have higher levels of pro-inflammatory cytokines, for example, IL-1, IL-6, and tumor necrosis factor-alpha, and C-reactive protein. In schizophrenia, many reports have described raised levels of cytokines, for example, IL-6; and meta-analyses have confirmed these findings. Microglia cells are important in inflammatory processes, and positron emission tomography studies have shown microglia activation in both depression and schizophrenia.As a consequence of the above findings, immunomodulation is widely discussed as a potential treatment approach in both major depression and schizophrenia. The COX-2 inhibitor celecoxib was found to have a significant positive effect on major depression, not only in single studies but also in meta-analyses. Celecoxib has also been studied in schizophrenia and has shown efficacy, in particular, in early disease stages. The mixed COX inhibitor aspirin (acetylsalicylic acid) seems to have both protective and therapeutic effects on schizophrenia.This paper discusses the hypothesized role of inflammation in major depression and schizophrenia, including markers of inflammation; pertinent studies on celecoxib and aspirin; and additional immunomodulatory therapeutic strategies.

Keywords: Inflammation, major depression, psychoneuroimmunology, COX-2 inhibition, aspirin, psychiatry, schizophrenia

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***Correspondence:**
Norbert Müller
N.Mueller@mvt-zentrum.de

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INTRODUCTION

Studies in animal models have provided evidence that both early infection and immune activation can affect several neurodevelopmental processes, including serotonergic (1) and dopaminergic and glutamatergic neurotransmission (2, 3). Human studies on infections (4) and a cohort study on bacterial infections (5) also indicated that infection and activation of the immune system are associated with neurodevelopment. Furthermore, studies found that higher cytokine and C-reactive protein (CRP) levels in childhood increased the risk to develop depression (6) and schizophrenia (7). In meta-analyses, cytokine levels were altered in adults with major depression (MD), schizophrenia, and bipolar disorder (8, 9).

MAJOR DEPRESSION

Inflammation and Depression Risk

A population-based, prospective cohort study in Denmark followed a total of 3.56 million people for 24 years and found that those who were hospitalized for an infection or visited a hospital for treatment of an autoimmune disease had a significantly higher risk for developing a depressive disorder (10). If people were hospitalized for infection, the risk increased by 62% [incidence rate ratio (IRR) 1.62]; and if they visited the hospital because of an autoimmune disease, it increased by 45% (IRR 1.45). People with a history of both risk factors had an even higher risk of developing mood disorders (IRR 2.35), indicating that the two factors interact. In this study, the risk for later mood disorders was lower after infections of the central nervous system (CNS; IRR 1.65) than after peripheral infections, for example, hepatitis (IRR 2.82) and sepsis (IRR 2.06). Interesting findings were that the shorter the time since the infection, the greater the risk of developing a mood disorder and that the highest risk was found in the 12 months after the infection (IRR 2.70). If the study had assessed all kinds of infections—not only those for which people visited a hospital—the risk of developing a mood disorder might have been even higher (10).

Another Danish population-based register study evaluated whether the use of anti-inflammatory agents, including aspirin (acetylsalicylic acid [ASA], an inhibitor of both COX-1 and COX-2), is associated with a lower rate of depression (11). The study found a dose-dependent risk; that is, continued use of low-dose aspirin reduced the risk for incident depression, whereas the use of non-steroidal anti-inflammatory drugs (NSAIDs) and high-dose aspirin increased the rate.

Anti-Inflammatory Treatment Approaches in Major Depression

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs act by inhibiting COX-1 and COX-2. These cyclooxygenase enzymes are necessary for the synthesis of some of the prostaglandins involved in inflammation. COX-2 inhibitors have direct effects on the CNS serotonergic system and can also affect it indirectly *via* immune processes in the CNS. A study in rats showed higher serotonin levels in both the frontal and temporoparietal cortices after administration of rofecoxib, a COX-2 selective NSAID (12). Consequently, the authors hypothesized that COX-2 inhibitors may have antidepressant effects. In a study in bulbectomized rats (a model for depression), chronic administration of the COX-2 inhibitor celecoxib decreased cytokine levels and changed the animals' behavior (13). Brunello et al. (14) studied ASA in rats with the chronic escape deficit model and found that ASA accelerated the antidepressant effect of fluoxetine. In people with MD, a randomized, double-blind pilot study compared reboxetine plus celecoxib with reboxetine plus placebo and found a significant therapeutic effect of celecoxib (15). One interesting finding of this study was that the kynurenine/tryptophan ratio, which reflects the activity of indoleamine 2,3-dioxygenase (IDO), a pro-inflammatory, cytokine-driven enzyme, predicted the antidepressant response to celecoxib; that is, celecoxib had better effects on patients with a high level of IDO activity (16). A double-blind, randomized controlled trial (RCT) in MD (n = 50 patients) compared fluoxetine plus celecoxib with fluoxetine plus placebo and found a significantly better outcome in the group receiving adjunctive celecoxib (17). Similar results were found in two studies of sertraline plus celecoxib or placebo in MD (n = 40 and n = 30) (18, 19), where Hamilton Depression Rating Scale scores decreased significantly more in the celecoxib group; in one of the studies (18), serum IL-6, a pleiotropic immune-activating cytokine that primarily promotes innate and B- and T-cellular immunity and plays an important role in inflammation, correlated with the decrease in the depression rating score.

The efficacy of adjunctive treatment with an NSAID in MD was evaluated in a meta-analysis of four celecoxib studies in a total of 150 patients (20). The analysis concluded that celecoxib may be a potential treatment in this disorder, although the authors stated the benefit and safety of celecoxib and other NSAIDs need to be confirmed in larger studies of longer duration (20).

The findings of another meta-analysis on inflammation-related therapeutic approaches in MD are also of great interest (21). This analysis evaluated data from 14 studies (10 on NSAIDs, n = 4,258; 4 on cytokine inhibitors, n = 2,004) and found that the anti-inflammatory treatments had positive effects compared with placebo [standardized mean difference (SMD), −0.34; 95% confidence interval (CI), −0.57 to −0.11; I^2 = 90%], both in depression (SMD, −0.54; 95% CI, −1.08 to −0.01; I^2 = 68%) and in depressive symptoms (SMD, −0.27; 95% CI, −0.53 to −0.01; I^2 = 68%). The type of depression (clinical depression vs. depressive symptoms) or the agent (NSAID vs. cytokine inhibitor) did not explain the heterogeneity of the studies with respect to differences in treatment regimens and patient populations. Sub-analyses provided support for the positive effects of celecoxib (SMD, −0.29; 95% CI, −0.49 to −0.08; I^2 = 73%) on both remission [odds ratio (OR), 7.89; 95% CI, 2.94 to 21.17; I^2 = 0%] and response (OR, 6.59; 95% CI, 2.24 to 19.42; I^2 = 0%). Six of the studies reported adverse effects but found no difference in the rate of gastrointestinal or cardiovascular side effects at 6 weeks or infections at 12 weeks between the active treatments and placebo. The meta-analysis suggested that treatment with an anti-inflammatory agent, particularly celecoxib, can ameliorate symptoms of depression but does not carry a higher risk of side effects (21). Other studies, however, reported higher rates of adverse cardiovascular events with COX-2 inhibitors (22).

ASA has also been studied in depression. In an 8-week RCT in MD, patients were assigned to 160 mg of aspirin add-on to sertraline (n = 50) or placebo add-on (n = 50); the groups were matched for age, gender, and severity of depression (23). After 4 and 8 weeks of treatment, depression scores were significantly lower than at baseline only in the sertraline plus aspirin group. These results indicate that aspirin has positive effects on depression, although the unusually low responder rate in the sertraline (plus placebo) group may indicate that treatment resistance affected the results. A complex, placebo-controlled study of patients with bipolar depression found a significantly higher response rate in the aspirin group; however, the comparison of the mean values found no significant difference between aspirin and placebo (24).

Another recent meta-analysis included additional studies on NSAIDs and differentiated between studies on patients with a diagnosis of MD and patients with "classical" inflammatory diseases, such as arthritis or psoriasis, who also had depressive symptoms (25). The analysis found highly significant effects on both MD and depressive symptoms and a highly significant overall effect on the combined analysis of both indications. In the analysis of different substance classes and mechanisms of action of the anti-inflammatory agents, classical NSAIDs were significantly superior to placebo. Other anti-inflammatory compounds, such as cytokine inhibitors, glucocorticoids (two RCTs), and minocycline, also showed a significant advantage than did placebo. The overall effect of all anti-inflammatory substances was $p = 0.00001$.

Table 1 gives an overview of studies on selective COX-2 inhibitors and ASA in MD. Despite the limitations of the studies described above, they provide important information on the effects of anti-inflammatory treatment and, in particular, COX-2 inhibition in MD. Additional studies are needed in larger samples. Furthermore, studies need to consider the high

TABLE 1 | Clinical studies of selective COX-2 inhibitors and the mixed COX-1/COX-2 inhibitor acetyl salicylic acid (ASA) in major depression.

Authors	Diagnosis	Duration of trial	N	Study design	Concomitant drug	COX-2 inhibitor	Outcome
Abbasi et al. (18)	Major depression	6 weeks	40	Randomized, double-blind, placebo-controlled	Sertraline 200 mg	Celecoxib 400 mg/day	Significantly better response and remission rates in celecoxib group
Akhondzadeh et al. (17)	Major depression	6 weeks	40	Randomized, double-blind, placebo-controlled add-on	Fluoxetine (flexible dose)	Celecoxib 400 mg/day	Significant superiority of celecoxib
Begemann et al. (26)	Bipolar depression, rapid cycling	>5 months	1	Open	Not specified	Celecoxib 400 mg/day	Significant improvement of depressed and manic symptoms
Castillo et al. (27)	Bipolar depression	8 weeks	41	Randomized, double-blind, placebo-controlled	Escitalopram 20 mg/day	Celecoxib 400 mg/day	Celecoxib showed significantly better response and higher remission rate
Collantes-Estevez and Fernandez-Perez (28)	Depressive syndrome, comorbid to osteoarthritis	Mean 33 days	343 (with depressive syndrome)	Open	Not specified	Rofecoxib 12.5 or 25 mg/day	Significant reduction of self-reported depression
Majd et al. (19)	Major depression	8 weeks	30 (women only)	Randomized, double-blind, placebo controlled	Sertraline (25–50 mg)	Celecoxib 200 mg/day	Significant superiority of celecoxib after 4 weeks; no difference after 8 weeks
Muller et al. (15)	Major depression	6 weeks	40	Randomized double-blind, placebo-controlled, add-on	Reboxetine (flexible dose)	Celecoxib 400 mg/day	Significant superiority of the COX-2 inhibitor
Nery et al. (29)	Bipolar disorder, depressive or mixed episode	6 weeks	28	Randomized, double-blind, placebo-controlled	Mood stabilizer or atypical antipsychotics	Celecoxib 400 mg/day	Significant superiority after 1 week, no difference at end-point
Savitz et al. (24)	Bipolar depression	6 weeks	99	Randomized, double-blind, placebo-controlled	Minocycline (200 mg/day)	ASA 162 mg/day	Main effect of ASA on treatment response
Sepehrmanesh et al. (23)	Major depression	8 weeks	100	Randomized, double-blind, placebo-controlled	Sertraline (50–200 mg)	ASA 160 mg/day	Significantly greater reduction in Beck Depression Inventory scores after 4 and 8 weeks

placebo response, particularly in add-on studies with an effective antidepressant, and the severity of depression.

Drugs Targeting Cytokines

Tumor necrosis factor-alpha (TNF-a) promotes the activation of the innate and adaptive immune response and is a key molecule in inflammation. The anti-TNF-a antibody infliximab prevents the cytokine TNF-a from interacting with receptors on the cell surface and has an anti-inflammatory effect. TNF-a was initially designed as a treatment for inflammatory joint disorders and psoriasis but was then found to significantly improve symptoms of depression in patients with psoriasis (30).

In a random-effect meta-analysis of seven placebo-controlled RCTs, anti-cytokine treatment had significantly greater effects on depressive symptoms than had placebo (anti-cytokine drug: n = 1,309; placebo: n = 1,061; SMD = 0.40, 95% CI, 0.22 to 0.59) (31). Five of the seven studies were on anti-TNF-a agents, that is, adalimumab, etanercept, and infliximab (SMD = 0.33; 95% CI, 0.06 to 0.60). Similar, small-to-medium effect sizes for anti-cytokine therapy were obtained in the analyses of the two RCTs on adjunctive anti-cytokine treatment (SMD = 0.19; 95% CI, 0.00 to 0.37) and the eight non-randomized and/or non-placebo studies (SMD = 0.51; 95% CI, 0.34 to 0.67). The three anti-TNF-a drugs and the anti-IL-6 antibody (tocilizumab) significantly improved symptoms of depression. A meta-regression showed that baseline symptom severity was a predictor of antidepressant effect (p = 0.018), but sex, age, study duration, and improvement in the primary physical illness were not. An important limitation of these studies was that besides having an inflammatory disease, such as atopic dermatitis, psoriasis, Crohn's disease, or rheumatoid arthritis, the patients had concomitant symptoms of anxiety or depression or both. In addition, their overall symptoms of depression were mild to moderate, and they did not have a formal diagnosis of depression.

To my knowledge, only one 12-week, placebo-controlled study has evaluated an anti-TNF-a antibody in treatment-resistant MD (n = 60). The participants, who were either taking an antidepressant (n = 37) or partly medication free (n = 23), received three infusions of infliximab (n = 30) or placebo (n = 30). Infliximab was not superior to placebo, but the study found a significant interaction between time, treatment, and baseline levels of CRP (≤5 mg/L); that is, the response rate to infliximab (62%) was higher than that to placebo (33%) in patients who had higher CRP levels at baseline. In addition, participants who responded to infliximab had significantly higher baseline concentrations of TNF-a, sTNFR1, and sTNFR2 ($p \leq 0.01$) and significantly larger decreases in CRP ($p \leq 0.01$) than had those who did not respond (32). This study is encouraging, in particular because treatment-resistant patients with MD represent a negative selection for treatment outcome, and it indicates that CRP—the most widespread clinical marker for inflammation—may be a biomarker of anti-TNF-a antibody treatment outcome.

Drugs Targeting the IL-6 Complex

As mentioned above, studies have found that in patients with depression, IL-6 levels in the peripheral blood and cerebrospinal fluid (CSF) are higher. Consequently, the IL-6 complex has been proposed as a target for anti-cytokine treatment. The above-mentioned random-effect meta-analysis of seven RCTs (31) included two open studies of the anti-IL-6 antibody tocilizumab (33, 34), both of which showed improvements in patients with concomitant anxiety and depression. Despite these findings, we still need valid, reliable data on the effects of anti-IL-6 treatment in MD and the correct target for such treatment. Because higher levels of IL-6 are found in the CSF than in the blood and in patients with depression than in controls, IL-6 in the CSF was hypothesized to be the most promising therapeutic target. Further support for this hypothesis was given by the finding that IL-6 is overexpressed in the pre-clinical model of chronically stressed rats (35). However, IL-6 levels in the periphery are not completely independent of those in the CSF or brain but are closely connected to them. For this reason, researchers have proposed that targeting peripheral IL-6 may be a potential treatment approach in depression (35). This proposal is supported by the findings in an animal model of depression that significantly higher serum IL-6 levels were found in learned helplessness rats, which were susceptible to chronic inescapable electric stress, than in control and non-learned helplessness rats, which were resilient to the same stress (36). Supporting evidence was also provided by the finding that in depression, serum levels of IL-6 predict patients' response to ketamine (37). As an alternative, more promising strategy to inhibit IL-6, Maes et al. (38) proposed that administering soluble glycoprotein 130 (sgp 130), a component of the IL-6 complex, would increase inhibition of IL-6 trans-signaling and consequently maintain IL-6 receptor (IL-6R) signaling. In addition to tocilizumab, sirukumab, another monoclonal antibody to IL-6, has also been proposed as a potential treatment for depression (39). It acts on the signaling pathway of IL-6 and can inhibit its pro-inflammatory and anti-inflammatory effects; studies have shown beneficial effects of sirukumab in the inflammatory diseases lupus erythematosus and rheumatoid arthritis, among others (39).

Other Immune-Related Substances

Microglia cells act as macrophages in the brain and are important in inflammatory processes in the CNS. Positron emission tomography (PET) studies showed activation of microglia in MD (40, 41). Minocycline, an antibiotic, can cross the blood–brain barrier into the CNS, where it inhibits the activation of microglia. Consequently, it was proposed as a potential treatment in MD. A recent meta-analysis identified 18 clinical studies (a case report, RCTs, and open and ongoing trials) on minocycline in depression; however, only three RCTs (in a total of 158 participants) were suitable for analysis (42). The analysis observed a large, statistically significant antidepressant effect of minocycline compared with placebo, although limitations of the study included the small number and sample size of the trials included, their heterogeneity, and potential publication bias.

Although statins are primarily used to lower cholesterol, they also have direct anti-inflammatory effects (43, 44). For example, a population-based study in users of selective serotonin reuptake inhibitors (SSRIs; N = 872,216), n = 113,108 of whom were also taking a statin, found that the risk for (a relapse to) depression

was clearly lower in participants using both SSRIs and statins than in those using an SSRI alone (43).

Methodological Issues

Although a "gold standard" study in MD would be an RCT that directly compares the anti-inflammatory agent, for example, a COX-2 inhibitor or an anti-cytokine antibody, with placebo, it would not be ethical. Therefore, in almost all RCTs, the anti-inflammatory agent is administered as an adjunct to an antidepressant. As a result of this approach, the anti-inflammatory agent must have a large effect to show an advantage over the antidepressant alone or in combination with placebo. This problem is further exacerbated by the high placebo rate of up to 40% that is commonly seen in studies of antidepressants. Nevertheless, although diverse anti-inflammatory therapeutic approaches show a statistically significant beneficial effect, much further research is needed, and possible subgroups of responders and non-responders have to be identified.

It is well known that in more severe cases of depression, antidepressants show more efficacy than does placebo. This might also be true for anti-inflammatory agents. If possible, clinical studies should therefore include more severely depressed patients.

The pathology of depression is unlikely to be identical in every patient, and, consequently, an inflammatory process is probably not always present, although this hypothesis requires further research. Patients with treatment-resistant MD had higher levels of pro-inflammatory cytokines, which was taken as an indication that these patients' depression might have an inflammatory origin (45). If a clinical study of anti-inflammatory compounds has a large proportion of patients with an inflammatory pathology, it is more likely to find a positive treatment effect. A goal for future research is to identify a valid, reliable marker for an inflammatory process in depression so that we can apply targeted anti-inflammatory treatment in those patients who would benefit from it.

SCHIZOPHRENIA

Inflammation and the Rrisk for Schizophrenia

Numerous studies, including recent genetic data (46), show that an immune process and inflammation play a role in at least a subgroup of patients with schizophrenia. The results of these studies gave rise to the vulnerability–stress–inflammation hypothesis of schizophrenia (see **Figure 1**). One study in Denmark linked population-based registers nationwide and identified autoimmune disorders and severe infections that required admission to hospital as risk factors for schizophrenia and schizophrenia spectrum disorders; the risk was greatest in patients who had an autoimmune disorder and a severe infection (47). No evidence was found, however, that parental infections increased risk in the offspring (47, 48). Although the study was large, it did not have high sensitivity, and the authors consequently described the identified risk factors for schizophrenia as only the "tip of the iceberg" (48).

Another population-based study in Denmark identified all incident patients receiving antipsychotics for schizophrenia (n = 16,235) (49). Of these patients, n = 1480 (9.1%) were using concomitant NSAIDs, and n = 767 (4.7%) were using concomitant paracetamol. The risk of relapse was higher in the patients using NSAIDs [hazard rate ratio (HRR) = 1.21; 95% CI, 1.11 to 1.31], particularly ASA and diclofenac, but not in those using paracetamol (HRR = 0.97; 95% CI, 0.87 to 1.08). The authors analyzed subgroups of patients and found that among patients taking NSAIDs, the relapse risk was higher in those with a comorbid physical illness and lower in those who had been diagnosed with musculoskeletal disease (HRR = 0.82; 95% CI, 0.71 to 0.94) (49).

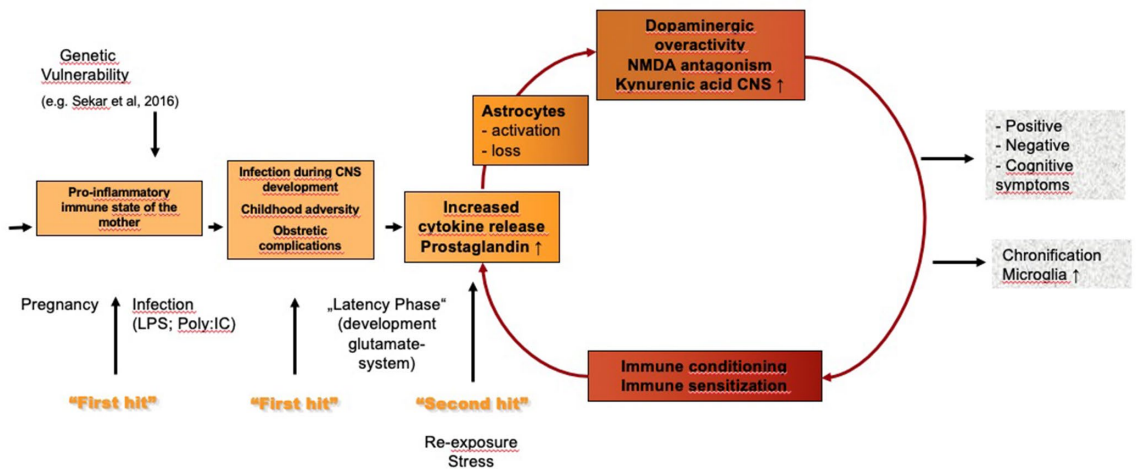

FIGURE 1 | Vulnerability–stress–inflammation hypothesis of schizophrenia. LPS, lipopolysaccharides; poly:IC, polyinosinic–polycytidylic acid.

Anti-Inflammatory Treatment in Schizophrenia

Non-Steroidal Anti-Inflammatory Drugs

Perhaps the most convincing evidence for an involvement of inflammation in schizophrenia is provided by the finding that anti-inflammatory medication is useful in schizophrenia (see **Table 2**). Noteworthy in this context is the paper by Sommer et al. (50), which reviews the effects of various anti-inflammatory treatments, including celecoxib, in schizophrenia.

My group performed a 6-week double-blind RCT in acute schizophrenia to compare risperidone plus celecoxib with risperidone alone and risperidone plus placebo (54). Outcome was significantly better in the celecoxib add-on group ($n = 25$) than in the group receiving risperidone alone ($n = 25$) (54), particularly regarding cognition (58). Data from this study and another 6-week risperidone/celecoxib study were pooled (total $N = 90$), and the analysis found a benefit of celecoxib add-on if the illness duration was 24 months or less but no such benefit in more chronic cases. A large study that included a broad spectrum of schizophrenia patients found no advantage of celecoxib over placebo (57), whereby the disease duration of up to 10 years in many patients, some of whom had chronic schizophrenia, may have contributed to the negative result. Another study in chronic schizophrenia showed no advantage of add-on celecoxib in patients with chronic schizophrenia (56), providing further support for differential effects of COX-2 inhibitors in acute and chronic phases of the disease. To further test this hypothesis, my group performed a double-blind study of amisulpride with adjunct celecoxib or placebo in first-episode schizophrenia (55); the celecoxib group showed more improvement than did the placebo group on the positive, negative, total, and general psychopathology scores of the Positive and Negative Syndrome Scale (PANSS) (55, 59).

Similar benefits have been found for ASA in schizophrenia spectrum disorders. A double-blind RCT studied 70 inpatients

TABLE 2 | Clinical studies of the selective COX-2 inhibitor celecoxib and the mixed COX-1/COX-2 inhibitor acetyl salicylic acid (ASA) in schizophrenia.

Authors	Diagnosis	Course and duration	Duration of trial	N	Study design	Concomitant drug	Substance	Outcome
Akhondzadeh et al. (51)	Schizophrenia	Chronic type (active phase)	8 weeks	60	Double-blind, randomized placebo-controlled add-on	Risperidone (fixed dose)	Celecoxib 400 mg/day	Significant advantage of the COX-2 inhibitor
Attari et al. (52)	Schizophrenia	>2 years	6 weeks treatment follow-up after 10 weeks	60	Double-blind, randomized placebo-controlled add-on	Mixed antipsychotics	ASA 325 or 500 mg	Significant benefit of ASA after 10 weeks, better effect of higher ASA after 6 weeks
Laan et al. (53)	Schizophrenia spectrum	≤5 years	3 months	70	Double-blind randomized placebo-controlled add-on	Mixed antipsychotics	ASA 1,000 mg	Significant, larger decrease in PANSS total in ASA group
Muller et al. (54)	Schizophrenia	Not specified Mean 5.9 years	5 weeks	50	Double-blind, randomized placebo-controlled add-on	Risperidone (flexible dose)	Celecoxib 400 mg/day	Significant advantage of the COX-2 inhibitor
Muller et al. (55)	Schizophrenia	First manifestation	6 weeks	50	Double-blind, randomized placebo-controlled add-on	Amisulpride (flexible dose)	Celecoxib 400 mg/day	Significant advantage of the COX-2 inhibitor on PANS total, positive, negative, and global scores
Rapaport et al. (56)	Schizophrenia	Continuously ill Mean 20 years	8 weeks	38	Double-blind, randomized placebo-controlled add-on	Risperidone or olanzapine (constant dose)	Celecoxib 400 mg/day	No advantage on the COX-2 inhibitor
Rappard and Muller (57)	Schizophrenia	≤10 years	11 weeks	270	Double-blind, randomized placebo-controlled add-on	Risperidone (flexible dose)	Celecoxib 400 mg/day	No advantage of the COX-2 inhibitor

PANSS, Positive and Negative Syndrome Scale.

and outpatients with schizophrenia spectrum disorders treated with antipsychotics and add-on aspirin 1 g/day or placebo (53). The total and positive PANSS scores decreased significantly more in patients taking aspirin add-on than in those taking placebo, and the more altered the immune function, the greater the effect on the total PANSS score. Another double-blind, placebo-controlled study evaluated 6-week adjunctive treatment with ASA in 60 inpatients with schizophrenia (52): In addition to their antipsychotic, one group (n = 20) received aspirin 325 mg/day; one (n = 20), aspirin 500 mg/day; and one (n = 20), placebo. At the end of the study, the PANSS positive and negative symptom scores and general psychopathology score were significantly lower in the aspirin groups than in the placebo group.

A meta-analysis of data from n = 264 patients from five double-blind, randomized, placebo-controlled studies on NSAIDs (celecoxib, four studies; ASA, one study) in schizophrenia found that the drugs had significant positive effects on total symptom severity and positive and negative symptom severity (60). A meta-analysis of data from n = 774 patients from eight studies (celecoxib, six; ASA, two) found that the drugs had significant effects only in patients with a first manifestation of schizophrenia and not in those with chronic schizophrenia and in inpatients but not outpatients (61).

Other Immune-Related Treatment

PET studies have shown that microglia cells are also activated in schizophrenia (62). As mentioned in the section Other Immune-Related Substances, the antibiotic minocycline can inhibit microglia activation, and studies in animal models of schizophrenia found that minocycline improves cognition (63). Double-blind, placebo-controlled, add-on studies of minocycline in schizophrenia patients found positive effects on negative and cognitive symptoms (64), and case reports described benefits for symptoms overall (65).

Other potential anti-inflammatory agents have shown some benefit in schizophrenia. For example, a meta-analysis of 26 double-blind RCTs found significant effects for *N*-acetylcysteine and estrogen (50). Positive effects were also found for interferon-gamma (IFN-γ), a cytokine responsible for the monocytic type 1 immune response (66). IFN-γ can have severe side effects, such as hallucinations, seizures, and immunosuppression, so patients must be monitored carefully.

The initial studies on monoclonal antibodies against pro-inflammatory cytokines indicate that they may also be a potential treatment approach in schizophrenia, but more studies are needed (67).

Two interesting case reports shed light on a theoretical concept that is interesting but will probably never become an alternative for schizophrenia treatment: In one case, schizophrenia seems to have transferred by bone marrow transplantation to a leukemia patient (68); and in another contrasting case, schizophrenia was remitted by bone marrow transplantation to a patient with schizophrenia (69).

Special Issues Regarding Anti-Inflammatory Treatment in Schizophrenia

On the basis of the above, we can conclude that anti-inflammatory agents may be beneficial in schizophrenia, but their usefulness depends on the stage of the disease; that is, their efficacy is lower in chronic than in acute schizophrenia; this difference may be associated with the neuroprogression of the disease. In schizophrenia, chronification is known to negatively impact outcome. Long-term treatment with anti-inflammatory agents has not yet been studied, although it may have more beneficial effects (51). This is the case in chronic inflammatory diseases, where short-term treatment with anti-inflammatory agents has only weak effects.

Further research is required on predictors of better response to anti-inflammatory treatment in schizophrenia. In all studies to date, response to antipsychotics was worse if levels of inflammation were higher (70, 71). The question whether the outcome of anti-inflammatory treatment is better in patients with high levels of inflammation, as was shown for anti-TNF-α treatment and celecoxib in MD (18, 32), remains open. As in MD, in schizophrenia, no markers have been identified that could help predict the outcome of treatment with anti-inflammatory agents.

Studies have shown probable non-immune-mediated effects for several NSAIDs, including COX-2 inhibitors (72), although their effects on schizophrenia are most likely due to their anti-inflammatory effects. Clearer evidence that inflammation is involved in the pathophysiology of schizophrenia is provided by studies on monoclonal antibodies, which do not affect neurotransmitters in any other way. However, further research is needed on this topic.

CONCLUSION

Studies and meta-analyses showing increased levels of pro-inflammatory cytokines and CRP, for example, indicate that the development of some psychiatric disorders, including MD and schizophrenia, may involve inflammation. Further support is provided by the positive effects of immunomodulatory agents in treating these disorders. Statistically significant therapeutic effects have been shown for the COX-2 inhibitor celecoxib in MD and early-stage schizophrenia, and protective and therapeutic effects have been shown for the mixed COX-1 and COX-2 inhibitor ASA (aspirin) in schizophrenia. Statistical significance, however, does not necessarily equate to clinical significance and high effect sizes. Therefore, further studies are warranted, including stand-alone studies with immunomodulators. A further limitation is that studies of these compounds in psychiatric indications lasted only several weeks, and these agents have not been evaluated in long-term studies. Celecoxib is known to be associated with an increase in cardiovascular side effects after treatment lasting about 18 months. ASA and, to a lesser extent, COX-2 inhibitors can have gastrointestinal side effects, including gastrointestinal bleeding. Nevertheless, celecoxib and, in particular, ASA are well described and, in general, are well tolerated, in a dose-dependent manner, in many different clinical indications. Another limitation is that no specific dose–response relationship studies have so far been performed in psychiatric indications, and doses have been chosen on the basis of those used in non-psychiatric indications. Different dose regimens may optimize the benefits of these substances in psychiatric indications. Many other interesting substances, such

as anti-cytokines, anti-Il-6 complex substances, minocycline, and statins, that target various components of the immune system may be beneficial in MD or schizophrenia or both.

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NM is the sole author of this review and performed all tasks related to preparation of the manuscript.

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REFERENCES

1. Goeden N, Velasquez J, Arnold KA, Chan Y, Lund BT, Anderson GM, et al. Maternal inflammation disrupts fetal neurodevelopment *via* increased placental output of serotonin to the fetal brain. *J Neurosci* (2016) 36(22):6041–9. doi: 10.1523/JNEUROSCI.2534-15.2016
2. Kabiersch A, Furukawa H, del Rey A, Besedovsky HO. Administration of interleukin-1 at birth affects dopaminergic neurons in adult mice. *Ann N Y Acad Sci* (1998) 840:123–7. doi: 10.1111/j.1749-6632.1998.tb09556.x
3. Meehan C, Harms L, Frost JD, Barreto R, Todd J, Schall U, et al. Effects of immune activation during early or late gestation on schizophrenia-related behaviour in adult rat offspring. *Brain Behav Immun* (2017) 63:8–20. doi: 10.1016/j.bbi.2016.07.144
4. Brown AS, Schaefer CA, Wyatt RJ, Goetz R, Begg MD, Gorman JM, et al. Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: a prospective birth cohort study. *Schizophr Bull* (2000) 26(2):287–95. doi: 10.1093/oxfordjournals.schbul.a033453
5. Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. *Schizophr Bull* (2009) 35(3):631–7. doi: 10.1093/schbul/sbn121
6. Cattaneo A, Macchi F, Plazzotta G, Veronica B, Bocchio-Chiavetto L, Riva MA, et al. Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. *Front Cell Neurosci* (2015) 9:40. doi: 10.3389/fncel.2015.00040
7. Metcalf SA, Jones PB, Nordstrom T, Timonen M, Maki P, Miettunen J, et al. Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: a prospective birth cohort study. *Brain Behav Immun* (2017) 59:253–9. doi: 10.1016/j.bbi.2016.09.008
8. Goldsmith DR, Rapaport MH. Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry* (2016) 21(12):1696–709. doi: 10.1038/mp.2016.3
9. Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. *Schizophr Bull* (2018) 44(1):75–83. doi: 10.1093/schbul/sbx035
10. Benros ME, Waltoft BL, Nordentoft M, Ostergaard SD, Eaton WW, Krogh J, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* (2013) 70(8):812–20. doi: 10.1001/jamapsychiatry.2013.1111
11. Kessing LV, Rytgaard HC, Gerds TA, Berk M, Ekstrom CT, Andersen PK. New drug candidates for depression—a nationwide population-based study. *Acta Psychiatr Scand* (2019) 139(1):68–77. doi: 10.1111/acps.12957
12. Sandrini M, Vitale G, Pini LA. Effect of rofecoxib on nociception and the serotonin system in the rat brain. *Inflamm Res* (2002) 51(3):154–9. doi: 10.1007/PL00000287
13. Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. *J Affect Disord* (2007) 98(1–2):143–51. doi: 10.1016/j.jad.2006.07.013
14. Brunello N, Alboni S, Capone G, Benatti C, Blom JM, Tascedda F, et al. Acetylsalicylic acid accelerates the antidepressant effect of fluoxetine in the chronic escape deficit model of depression. *Int Clin Psychopharmacol* (2006) 21(4):219–25. doi: 10.1097/00004850-200607000-00004
15. Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry* (2006) 11(7):680–4. doi: 10.1038/sj.mp.4001805
16. Krause D, Myint AM, Schuett C, Musil R, Dehning S, Cerovecki A, et al. High kynurenine (a tryptophan metabolite) predicts remission in patients with major depression to add-on treatment with celecoxib. *Front Psychiatry* (2017) 8:16. doi: 10.3389/fpsyt.2017.00016
17. Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. *Depress Anxiety* (2009) 26(7):607–11. doi: 10.1002/da.20589
18. Abbasi SH, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. *J Affect Disord* (2012) 141(2–3):308–14. doi: 10.1016/j.jad.2012.03.033
19. Majd M, Hashemian F, Hosseini SM, Vahdat Shariatpanahi M, Sharifi A. A randomized, double-blind, placebo-controlled trial of celecoxib augmentation of sertraline in treatment of drug-naive depressed women: a pilot study. *Iran J Pharm Res* (2015) 14(3):891–9.
20. Na KS, Lee KJ, Lee JS, Cho YS, Jung HY. Efficacy of adjunctive celecoxib treatment for patients with major depressive disorder: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* (2014) 48:79–85. doi: 10.1016/j.pnpbp.2013.09.006
21. Kohler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* (2014) 71(12):1381–91. doi: 10.1001/jamapsychiatry.2014.1611
22. Walker C, Biasucci LM. Cardiovascular safety of non-steroidal anti-inflammatory drugs revisited. *Postgrad Med* (2018) 130(1):55–71. doi: 10.1080/00325481.2018.1412799
23. Sepehrmanesh Z, Fahimi H, Akasheh G, Davoudi M, Gilasi H, Ghaderi A. The effects of combined sertraline and aspirin therapy on depression severity among patients with major depressive disorder: a randomized clinical trial. *Electron Physician* (2017) 9(11):5770–7. doi: 10.19082/5770
24. Savitz JB, Teague TK, Misaki M, Macaluso M, Wurfel BE, Meyer M, et al. Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2 × 2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. *Transl Psychiatry* (2018) 8(1):27. doi: 10.1038/s41398-017-0073-7
25. Kohler-Forsberg O, N Lydholm C, Hjorthoj C, Nordentoft M, Mors O, Benros ME. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr Scand* (2019) 39(5):404–19. doi: 10.1111/acps.13016
26. Begemann M, Sargin D, Rossner MJ, Bartels C, Theis F, Wichert SP, et al. Episode-specific differential gene expression of peripheral blood mononuclear cells in rapid cycling supports novel treatment approaches. *Mol Med* (2008) 14(9–10):546–52. doi: 10.2119/2008-00053.Begemann
27. Castillo MFR, Murata S, Schwarz MJ, Schutze G, Moll N, Weidinger E, et al. Celecoxib augmentation of escitalopram in treatment-resistant bipolar depression and effects of quinolinic acid. *Neurol Psychiat Br* (2019) 32:22–9. doi: 10.1016/j.npbr.2019.03.005

28. Collantes-Estevez E, Fernandez-Perez C. Improved control of osteoarthritis pain and self-reported health status in non-responders to celecoxib switched to rofecoxib: results of PAVIA, an open-label post-marketing survey in Spain. *Curr Med Res Opin* (2003) 19(5):402–10. doi: 10.1185/030079903125001938
29. Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol* (2008) 23(2):87–94. doi: 10.1002/hup.912
30. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* (2006), 367(9504):29–35. doi: 10.1016/S0140-6736(05)67763-X
31. Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry* (2018) 23(2):335–43. doi: 10.1038/mp.2016.167
32. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* (2013) 70(1):31–41. doi: 10.1001/2013.jamapsychiatry.4
33. Gossec L, Steinberg G, Rouanet S, Combe B. Fatigue in rheumatoid arthritis: quantitative findings on the efficacy of tocilizumab and on factors associated with fatigue. The French multicentre prospective PEPS Study. *Clin Exp Rheumatol* (2015) 33(5):664–70.
34. Traki L, Rostom S, Tahiri L, Bahiri R, Harzy T, Abouqal R, et al. Responsiveness of the EuroQol EQ-5D and Hospital Anxiety and Depression Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. *Clin Rheumatol* (2014) 33(8):1055–60. doi: 10.1007/s10067-014-2609-z
35. Yang C, Hashimoto K. Peripheral IL-6 signaling: a promising therapeutic target for depression? *Expert Opin Investig Drugs* (2015) 24(7):989–90. doi: 10.1517/13543784.2015.1055669
36. Yang C, Shirayama Y, Zhang JC, Ren Q, Hashimoto K. Peripheral interleukin-6 promotes resilience versus susceptibility to inescapable electric stress. *Acta Neuropsychiatr* (2015) 27(5):312–6. doi: 10.1017/neu.2015.36
37. Yang JJ, Wang N, Yang C, Shi JY, Yu HY, Hashimoto K. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. *Biol Psychiatry* (2015) 77(3):e19–20. doi: 10.1016/j.biopsych.2014.06.021
38. Maes M, Anderson G, Kubera M, Berk M. Targeting classical IL-6 signalling or IL-6 trans-signalling in depression? *Expert Opin Ther Targets* (2014) 18(5):495–512. doi: 10.1517/14728222.2014.888417
39. Zhou AJ, Lee Y, Salvadore G, Hsu B, Fonseka TM, Kennedy SH, et al. Sirukumab: a potential treatment for mood disorders? *Adv Ther* (2017) 34(1):78–90. doi: 10.1007/s12325-016-0455-x
40. Holmes SE, Hinz R, Conen S, Gregory CJ, Matthews JC, Anton-Rodriguez JM, et al. Elevated translocator protein in anterior cingulate in major depression and a role for inflammation in suicidal thinking: a positron emission tomography study. *Biol Psychiatry* (2018) 83(1):61–9. doi: 10.1016/j.biopsych.2017.08.005
41. Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miler L, Rajkowska G, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry* (2015) 72(3):268–75. doi: 10.1001/jamapsychiatry.2014.2427
42. Rosenblat JD, McIntyre RS. Efficacy and tolerability of minocycline for depression: a systematic review and meta-analysis of clinical trials. *J Affect Disord* (2018) 227:219–25. doi: 10.1016/j.jad.2017.10.042
43. Kohler O, Gasse C, Petersen L, Ingstrup KG, Nierenberg AA, Mors O, et al. The effect of concomitant treatment with SSRIs and statins: a population-based study. *Am J Psychiatry* (2016) 173(8):807–15. doi: 10.1176/appi.ajp.2016.15040463
44. Weitz-Schmidt G. Statins as anti-inflammatory agents. *Trends Pharmacol Sci* (2002) 23(10):482–6. doi: 10.1016/S0165-6147(02)02077-1
45. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* (2000) 22(4):370–9. doi: 10.1016/S0893-133X(99)00134-7
46. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature* (2016) 530(7589):177–83. doi: 10.1038/nature16549
47. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry* (2011) 168(12):1303–10. doi: 10.1176/appi.ajp.2011.11030516
48. Benros ME, Mortensen PB, Eaton WW. Autoimmune diseases and infections as risk factors for schizophrenia. *Ann N Y Acad Sci* (2012) 1262:56–66. doi: 10.1111/j.1749-6632.2012.06638.x
49. Kohler O, Petersen L, Benros ME, Mors O, Gasse C. Concomitant NSAID use during antipsychotic treatment and risk of 2-year relapse—a population-based study of 16,253 incident patients with schizophrenia. *Expert Opin Pharmacother* (2016) 17(8):1055–62. doi: 10.1517/14656566.2016.1168400
50. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophr Bull* (2014) 40(1):181–91. doi: 10.1093/schbul/sbt139
51. Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. *Schizophr Res* (2007) 90(1–3):179–85. doi: 10.1016/j.schres.2006.11.016
52. Attari A, Mojdeh A, Soltani FASK, Najarzadegan MR. Aspirin inclusion in antipsychotic treatment on severity of symptoms in schizophrenia: a randomized clinical trial. *Iran J Psychiatry Behav Sci* (2017) 11(1):e5848. doi: 10.5812/ijpbs.5848
53. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* (2010) 71(5):520–7. doi: 10.4088/JCP.09m05117yel
54. Muller N, Riedel M, Scheppach C, Brandstatter B, Sokullu S, Krampe K, et al. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. *Am J Psychiatry* (2002) 159(6):1029–34. doi: 10.1176/appi.ajp.159.6.1029
55. Muller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M, et al. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. *Schizophr Res* (2010) 121(1–3):118–24. doi: 10.1016/j.schres.2010.04.015
56. Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Celecoxib augmentation of continuously ill patients with schizophrenia. *Biol Psychiatry* (2005) 57(12):1594–6. doi: 10.1016/j.biopsych.2005.02.024
57. Rappard F, Muller N. Celecoxib add-on therapy does not have beneficial antipsychotic effects over risperidone alone in schizophrenia. *Neuropsychopharmacology* (2004) 29(Suppl 1):S222.
58. Muller N, Riedel M, Schwarz MJ, Engel RR. Clinical effects of COX-2 inhibitors on cognition in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* (2005) 255(2):149–51. doi: 10.1007/s00406-004-0548-4
59. Muller N. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. *Curr Opin Investig Drugs* (2010) 11(1):31–42.
60. Sommer IE, de Witte L, Begemann M, Kahn RS. Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. *J Clin Psychiatry* (2012) 73(4):414–9. doi: 10.4088/JCP.10r06823
61. Nitta M, Kishimoto T, Muller N, Weiser M, Davidson M, Kane JM, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. *Schizophr Bull* (2013) 39(6):1230–41. doi: 10.1093/schbul/sbt070
62. De Picker LJ, Morrens M, Chance SA, Boche D. Microglia and brain plasticity in acute psychosis and schizophrenia illness course: a meta-review. *Front Psychiatry* (2017) 8:238.
63. Mizoguchi H, Takuma K, Fukakusa A, Ito Y, Nakatani A, Ibi D, et al. Improvement by minocycline of methamphetamine-induced impairment of recognition memory in mice. *Psychopharmacology (Berl)* (2008) 196(2):233–41. doi: 10.1007/s00213-007-0955-0
64. Chaudhry IB, Hallak J, Husain N, Minhas F, Stirling J, Richardson P, et al. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. *J Psychopharmacol* (2012) 26(9):1185–93. doi: 10.1177/0269881112444941
65. Ahuja N, Carroll BT. Possible anti-catatonic effects of minocycline in patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) 31(4):968–9. doi: 10.1016/j.pnpbp.2007.01.018

66. Gruber L, Bunse T, Weidinger E, Reichard H, Muller N. Adjunctive recombinant human interferon gamma-1b for treatment-resistant schizophrenia in 2 patients. *J Clin Psychiatry* (2014) 75(11):1266–7. doi: 10.4088/JCP.14l09005
67. Miller BJ, Buckley PF. The case for adjunctive monoclonal antibody immunotherapy in schizophrenia. *Psychiatr Clin North Am* (2016) 39(2):187–98. doi: 10.1016/j.psc.2016.01.003
68. Sommer IE, van Bekkum DW, Klein H, Yolken R, de Witte L, Talamo G. Severe chronic psychosis after allogeneic SCT from a schizophrenic sibling. *Bone Marrow Transplant* (2015) 50(1):153–4. doi: 10.1038/bmt.2014.221
69. Miyaoka T, Wake R, Hashioka S, Hayashida M, Oh-Nishi A, Azis IA, et al. Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation: a case report. *Front Psychiatry* (2017) 8:174. doi: 10.3389/fpsyt.2017.00174
70. Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophr Bull* (2015) 41(5):1162–70. doi: 10.1093/schbul/sbv028
71. Zhang XY, Zhou DF, Cao LY, Wu GY, Shen YC. Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. *Neuropsychopharmacology* (2005) 30(8):1532–8. doi: 10.1038/sj.npp.1300756
72. Strauss KI, Marini AM. Cyclooxygenase-2 inhibition protects cultured cerebellar granule neurons from glutamate-mediated cell death. *J Neurotrauma* (2002) 19(5):627–38. doi: 10.1089/089771502753754091

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REVIEW
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Statins and Inflammation: New Therapeutic Opportunities in Psychiatry

Sung-Wan Kim[1], Hee-Ju Kang[1], Min Jhon[1], Ju-Wan Kim[1], Ju-Yeon Lee[1], Adam J. Walker[2], Bruno Agustini[2], Jae-Min Kim[1] and Michael Berk[2,3,4,5]*

[1] Department of Psychiatry, Chonnam National University Medical School, Gwangju, South Korea, [2] IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia, [3] Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia, [4] The Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia, [5] Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, VIC, Australia

Statins, which are widely used to treat hypercholesterolemia, have anti-inflammatory and anti-oxidant effects. These are thought to be responsible for the potential effects of statins on various psychiatric disorders. In this study, we comprehensively review the literature to investigate the effects of statins on various psychiatric disorders including depression, schizophrenia, and dementia. In addition, we review adverse effects and drug interactions of statins to give clinically useful information guiding statin use in the psychiatric field. Statins seem useful in reducing depression, particularly in patients with physical disorders such as cardiovascular disease. In patients with schizophrenia, negative symptoms may be reduced by adjuvant statin therapy. Studies on cohorts at risk for dementia have generally shown protective effects of statins, while those on treatment for dementia show inconsistent results. In conclusion, statins used in combination with conventional psychotropic medications may be effective for various psychiatric disorders including depression, schizophrenia, and dementia. Further study is required to determine optimal doses and duration of statin use for the treatment of psychiatric disorders.

Keywords: statin, depression, schizophrenia, dementia, inflammation

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***Correspondence:**
Jae-Min Kim
jmkim@chonnam.ac.kr

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INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) are widely used to prevent cardiac and cerebrovascular events by treating hypercholesterolemia. Statins also have anti-inflammatory effects, including reducing C-reactive protein (CRP) concentrations (1). The effects of lowering low-density lipoprotein (LDL) cholesterol with statins may lead to anti-inflammatory actions because LDL cholesterol itself strongly promotes inflammation (2). Furthermore, statins reduce tumor necrosis factor alpha (TNF-α) and interferon gamma (IFNγ) production in stimulated T-lymphocytes, and inhibit the T helper cell (Th-1) immune response (3). Addition of statins to human hepatocytes reduces the levels of C-reactive protein induced by circulating interleukin 6 (IL-6), suggesting that the anti-inflammatory effects of statins are hepatic in nature (4). These anti-inflammatory and anti-oxidant effects of statins are potential mechanisms for the effects of statins on various psychiatric disorders.

Many kinds of statins have been approved for treatment of hypercholesterolemia. Statins can be broadly classified as lipophilic or hydrophilic, which affect their ability to permeate the brain

(5). Hydrophilic statins, such as pravastatin, rosuvastatin, and fluvastatin are not able to easily cross the blood brain barrier (BBB), and are also less efficient at permeating cell membranes. Conversely, lipophilic statins, such as simvastatin, lovastatin, pitavastatin, and atorvastatin (6) are more likely to cross the BBB. Moreover, lipophilic statins enter cells via passive diffusion and are thus widely distributed in various tissues, whereas hydrophilic statins are more liver-specific. Cellular uptake features a variety of carrier-mediated mechanisms (5, 7). These distinct characteristics of hydrophilic and lipophilic statins may lead to differential effects of statins in terms of efficacy, or could lead to neuropsychiatric adverse events. What remains unclear is if the beneficial effects of statins require brain penetrance, or are mediated by peripheral or hepatic suppression of circulating cytokines, as is best evidenced for rosuvastatin (8), or especially in the elderly are predicated by vascular improvements in domains such as plaque stability and vessel inflammation (9).

Most psychotropic medications currently used in depression and schizophrenia act on monoamine neurotransmitters. However, certain proportions of patients with depression and schizophrenia do not respond to the conventional medications currently available. Curiously, patients with higher levels of peripheral cytokines may be less likely to respond to antidepressants (10). Therefore, clinicians require other medications with different mechanisms. Growing evidence indicates that inflammation is a key mechanisms of pathogenesis in many psychiatric disorders including depression, schizophrenia, and neurocognitive disorders. In addition, medications that act on inflammation have shown potential as alternative treatment methods. Therefore, many researchers have measured the effects of statins on these psychiatric disorders. In this study, we comprehensively reviewed clinical trials and epidemiological studies to investigate the effects of statins on various psychiatric disorders including depression, psychosis, and dementia. In addition, this study aimed to give clinical information on the implications for statin for use in clinical psychiatry.

MECHANISMS AND MEDICAL COMORBIDITY

The "classic" mechanism of action of statins involves the reduction of endogenous cholesterol biosynthesis via the inhibition of HMG-CoA reductase, a rate limiting enzyme integral to the mevalonate pathway. The corresponding reduction in hepatic cholesterol synthesis instigates translocation of membrane-bound sterol regulatory element-binding proteins to the nucleus, subsequent upregulation of LDL receptors on the surface of hepatocytes, leading to elevated clearance of LDL cholesterol from the blood (11, 12). These effects make statins effective for treating hypercholesterolemia. However, brain cholesterol metabolism is largely independent of dietary lipid intake because of the BBB. Brain cholesterol is synthesized in the central nervous system (CNS), unlike peripheral cholesterol (13). Not all statins are equally effective in terms of lowering brain cholesterol levels (14).

Interestingly, statins also have a range of so-called "pleiotropic" effects (e.g., suppressing inflammation, reducing oxidative stress, reducing T-cell activation) that have implications for extrahepatic systems including the cardiovascular system, the CNS, and the immune system (15–17). Statins are thought to exert many of these pleiotropic effects by suppressing the downstream synthesis of molecules in the mevalonate pathway, mediated through the inhibition of small GTPase prenylation and thus, isoprenoid production. Importantly, such small GTPases play essential roles in regulating a number of signaling pathways and cellular processes which are dependent on isoprenylation (18, 19). For example Ras plays a key role in cellular growth and proliferation; Rac in reactive oxygen species generation; and Rho in the proinflammatory cytokines. This inhibition of isoprenoids leads to a host of anti-inflammatory, immunomodulatory, anti-oxidative, and anti-atherosclerotic effects, including but not limited to: downregulation of transcription factors (e.g., Nuclear Factor-κB, Activator Protein-1), reduced expression of SOCS3 and CD40, suppression of cytokine (IL-1β, TNFα, IL-6), chemokine (IL-8, Monocyte Chemotactic Protein-1) and CRP production, attenuated induction of adhesion molecules (P-selectin, Very Late Antigen-4, Intercellular Adhesion Molecule-1), suppression of IFN-γ dependent co-stimulation of MHC Class II expression, as well as downregulation of T cell and monocyte activation.

Statins also reduce negative regulation of nitric oxide, lower NADPH oxidase and superoxide formation, and increasing oxygen free radical scavenging, decrease inflammatory cell infiltration, macrophage accumulation, reduce metalloproteinase activity, and expression, and attenuate activation of the NLRP3 Inflammasome (18–23). Notably, evidence also suggests statins facilitate PI3K-Akt signaling (24, 25), and crosstalk with peroxisome proliferator-activated receptor (PPAR) signaling (26) Collectively, these resultant cardioprotective, immunoprotective, and neuroprotective benefits of the aforementioned pleiotripic effects make statins worthy of investigation for treating neuropsychiatric disorders with diffuse etiologies.

Several neuroimaging studies have explored the effects of brain statins. Serial volumetric magnetic resonance imaging of patients with multiple sclerosis, a chronic inflammatory/neurodegenerative disorder, revealed significantly less whole-brain atrophy in a high-dose (80 mg daily) simvastatin group than in a placebo group (27). Studies using positron emission tomography or diffusion tensor imaging to evaluate dementia patients have yielded conflicting results in terms of the effects of statins on neurodegeneration and white matter integrity (28). Further research is required to explore whether statins control brain atrophy and functional connectivity.

Psychiatric disorders are often associated with several somatic consequences, including hypertension, heart disease, stroke, cancer, obesity, diabetes mellitus, and osteoporosis (29). It is known that individuals with psychiatric disorders tend to have unhealthier lifestyle habits, such as drinking excessive amounts of alcohol, are more likely to smoke, eat an unhealthy diet and be more physically inactive than their peers, be less compliant with medication regimens and have poorer self-care (30). All

these factors significantly contribute to the development and maintenance of the above-mentioned comorbidities.

Also, shared immunometabolic pathways have been implicated in the link between psychiatric and physical disease. Psychiatric conditions are consistently linked to disruptions in the body's stress response system (mainly the Autonomic Nervous System (ANS) and the Hypothalamic-Pituitary-Adrenal (HPA) axis (31) and are often associated with a pro-inflammatory profile (32). The chronicity of these processes might lead to several somatic consequences, including elevated blood pressure, abdominal obesity, dyslipidaemia and increased blood glucose. These conditions constitute important risk factors for cardiovascular disease (CVD), diabetes (33), cognitive impairment and even cancer (34), among others.

A recent review suggests that abdominal obesity and lipid disturbances are one of the driving forces behind the relationship between psychiatric disorders, in this case depression, and inflammation (35). Abdominal obesity gives rise to multiple immunometabolic dysregulations. White adipose tissue, especially in the abdominal area, plays as an active endocrine organ producing inflammatory cytokines and hormones (especially leptin) that disrupt important immunometabolic pathways (36). Increased leptin is a risk pathway for depression (37). Increased inflammatory activity interferes with HPA axis regulation, altering cortisol secretion and feedback, leading to a progressive feedforward loop of inflammation-related conditions (38).

Statins, with their lipid lowering, immunomodulatory, anti-inflammatory, and antioxidant properties, may act to slow or indeed prevent some of these alterations, potentially leading to interruption of the neuroprogressive cascade in these disorders (39) and decreased morbidity and mortality for individuals with psychiatric conditions. Notably, the main cause of death in psychiatric disorders remains CVD (40), where statins have its most definitive proved role (41). The possible therapeutic benefits of statins in each psychiatric disorder are described individually in this paper.

STATINS FOR DEPRESSIVE DISORDER

The pathogenesis of depression is both complex and heterogeneous. Inflammation and immune dysfunction are major contributors to the development of depression (42, 43). Inflammatory markers have been associated both with the prognosis of depression (44) and the risks of associated cardiac events and cancer (45). Peripheral pro-inflammatory cytokine signals are transmitted to the CNS via both humoral and neural pathways and may trigger depression by increasing oxidative stress (46); interacting with the hypothalamic–pituitary–adrenal axis; causing impairments in neurotransmitter systems involving glutamate, serotonin, dopamine, and noradrenaline (47–49); disrupting mitochondrial biogenesis (50); decreasing neurogenesis (51); and causing persistent and detrimental changes in the brain.

The monoaminergic theory of depression has failed to deliver novel therapeutic agents. Drugs with anti-inflammatory properties are important potential alternatives for the treatment of depression (52). Antidepressant effects of anti-inflammatory agents were noted in earlier epidemiology studies and clinical trials, including celecoxib, pioglitazone, N-acetylcysteine and statins. Besides their lipid-lowering properties, statins possess direct anti-inflammatory effects as noted above (53), which led researchers to investigate the potential impact of statins on depression. The present study summarizes previous studies focusing on the prospective association between statins and depression in **Table 1**.

To date, there has been one meta-analysis including seven observational studies (four cohort, two nested case-control, and one cross-sectional study), which found that statin users were less likely to develop depression than non-users (69). In addition to this meta-analysis, four prospective studies including large populations (n = 26,852–4,607,990) using national register data reported that statin use was associated with a reduced risk of depression (59–61, 64). Meanwhile, two prospective studies found that statin use was not associated with worsening of depression in acute myocardial infarction (AMI) patients (58) or with depression risk in a community population (n = 1,631) (63). Another study reported that statin use in stroke patients was associated with heightened depression risk (62). However, this study on stroke patients (62) did not adjust for significant covariates, limiting our ability to interpret the results (70). The study of AMI patients assessed changes in depression scale scores, which were at non-significant levels at baseline (58). Moreover, the community studies that reported potential beneficial effects of statins on depression (59, 60, 64) included larger numbers of participants and younger populations compared to the study that reported a detrimental effect of statins on depression (63). We hypothesize that the direction of associations may depend on the characteristics of the participants. In healthy populations without inflammatory loading, statins may not have beneficial anti-inflammatory effects. This finding is concordant with the findings of Miller and Raison, who found that levels of inflammation predicted response to infliximab; those with high levels benefitted, and those that had low levels worsened. The cholesterol-lowering effects of statins may make fragile people (e.g., the elderly) who are likely to already have low cholesterol levels vulnerable to depression via lowered serotonin levels. Therefore, the risks and benefits of statin use may depend on patient characteristics.

Statin use could be helpful in reducing the risk of depression in populations who are experiencing excess inflammation due to physical diseases such as CVD–highly comorbid across major psychiatric disorders. Additionally, statin use could be beneficial for depression prevention in populations with balanced nutrition who, therefore, have a plentiful reserve cholesterol, in whom lowering cholesterol does not impact the onset of depression. Although further research is needed to confirm the type of statins that would be most beneficial for depression prevention, lipophilic statins (including simvastatin) that have better brain penetrance may have greater protective effects against depression than hydrophilic statins (including rosuvastatin and pravastatin) (59). Equally statins that most robustly suppress peripheral

TABLE 1 | Studies investigating the associations between statin use and depression.

References	Study design	Subjects number (mean age)	F/U duration	Assessment	Diagnosis	Statin name and dosage	Main findings
EPIDEMIOLOGICAL STUDY							
Young-Xu et al. (54)	Prospective	606 CAD patients (67 yrs)	4–7 years	Kellner Symptom Questionnaire	Psychological well-being	Any use	Reduced risk of abnormal depression scores in CAD patients: aOR (95% CI) = 0.63 (0.43–0.93)
Stafford et al. (52)	Prospective	193 heart disease patients (64 yrs)	9 months	3M-MINI 9M-HADS	Major and minor depression dysthymia	Atorvastain, Pravastatin, Simvastatin	Reduced risk of dysthymia, minor depression, or major depression both at 3 and 9 months 3 mo: aOR (95% CI) = 0.31 (0.10–0.97) 9 mo: aOR (95% CI) = 0.21 (0.05–0.88)
Otte et al. (55)	Prospective	965 CAD patients (67 ± 11 yrs)	6 years	PHQ	PHQ ≥10 depression	Any use	Reduced risk of depression aOR (95% CI) = 0.62 (0.41–0.95)
Yang et al. (56)	Retrospective	458 depression and 1,830 controls (55 ± 9 yrs)	NA	Recorded diagnosis of depression	Depression Suicidal behavior	Any use	Reduced risk of depression aOR (95% CI) = 0.4 (0.2–0.9)
Pasco et al. (57)	Retrospective	22 Women with MDD and 323 Control (72 ± 9 yrs)	10 years	SCID using DSM-IV	MDD	Not reported	Reduced risk for MDD. Hazard ratio [HR] (95% CI) = 0.20 (0.04–0.85)
Al Badarin et al. (58)	Prospective	3,050 statin user and 625 statin nonuser (58 ± 12 yrs)	1 year	PHQ-8	PHQ-8≥10 depression	NA	No significant association in myocardial infarction patients
Redlich et al. (59)	Retrospective	4,607,990 National register data (63 ± 17 yrs)	2 years	ICD-10 codes F30–F39	Depressive disorder	Any use	Lipophilic agents- reduction in risk aOR(95% CI) = 0.92 (0.88–0.96) Hydrophilic agents-no association aOR(95% CI) = 0.85 (0.70–1.03)
Chuang et al. (60)	Retrospective (health insurance)	26,852 hyperlipidemia patients (52 ± 14 yrs)	NA	Insurance claim	Depressive disorder	NA	Reduced risk of depression in hyperlipidemia patients; HR (95% CI) = 0.81 (0.69–0.96)
Kim et al. (61)	Prospective	423 stroke patients (65 ± 10 yrs)	1 year	MINI (DSM-IV) HDRS	Major or minor depression	Any use	Reduced risk of depression in stroke patients; aOR (95% CI) = 0.54 (0.49–0.87)
Kang et al. (62)	Retrospective (health insurance)	11,218 stroke patients (71 ± 12 yrs)	1 year	ICD-9-CM 296.2, 296.3, 300.4, or 311	Depression	NA	Increased risk of depressive disorder following stroke: aHR(95% CI) = 1.65 (1.34–2.03)
Glaus et al. (63)	Prospective cohort	1,631 community population (52 ± 9 yrs)	5.2 ± 1.2 years	DIGS	DSM-IV MDD	NA	No association of MDD risk aHR(95% CI) = 1.25(0.73–2.14)
Kohler et al. (64)	Prospective (Danish Civil Registration)	872,216 SSRI users (48 [33-68] yrs)	3 years	ICD-10 F32 or F33; suicide attempt	NA	Any use	Adjunctive stain use with SSRI -Reduced risk for psychiatric hospital contacts due to depression: aHR(95% CI) = 0.64 (0.55–0.75)
INTERVENTIONAL STUDY							
Ghanizadeh et al. (65)	DB RCT	68 statin use and placebo (32 ± 10 yrs)	6 weeks	HDRS	DSM-IV MDD, (HDRS > 17)	Fluoxetine up to 40 mg/d + Lovastatin 30 mg/d	"Lovastatin + fluoxetine" improved depressive symptoms HDRS reduction 12.8(6.3) vs. 8.2(4.0), $P < 0.001$ No adverse effect
Haghighi et al. (66)	DB RCT	60 statin use and Placebo (32 ± 8 yrs)	12 weeks	HDRS	DSM-5 MDD, (HDRS ≥ 25)	Citalopram 40 mg/d + Atorvastatin 20 mg/d	"Atorvastatin + SSRI" improved depressive symptoms Partial remission OR 8.83(1.02–76.96): Statin user vs. non-user

(Continued)

TABLE 1 | Continued

References	Study design	Subjects number (mean age)	F/U duration	Assessment	Diagnosis	Statin name and dosage	Main findings
Gougol et al. (67)	DB RCT	48 statin use and Placebo (35 ± 10 yrs)	6 weeks	HDRS	DSM-IV MDD, (HDRS > 17)	Fluoxetine 40 mg/d + Simvastatin 20 mg/d	"Simvastatin + fluoxetine" improved depressive symptoms No adverse effect
Abbasi et al. (68)	DB RCT	46 patients received CABG (57 ± 7 yrs)	6 weeks	HDRS	DSM-IV MDD, (HDRS ≥ 19)	Simvastatin 20 mg/d Atorvastatin 20 mg/d	Earlier and superior effect of improving depressive symptoms; simvastatin > atorvastatin No serious adverse effect
Kim et al. (7)	Naturalistic prospective observation study	446 patients with CAD (59 ± 11 yrs)	24 weeks & 1 year	HDRS, BDI	MINI: MDD or minor depressive Dis	Any use lipophilic vs. hydrophilic statins	Improved depressive symptoms and response rate: Escitalopram + statin > statin > escitalopram > none Response rate: lipophilic statins > hydrophilic statins, OR (95% CI) 3.91 (1.21–12.59)

yrs, years; aOR, Adjusted odd ratio; CAD, coronary artery disease; MINI, Mini International Neuropsychiatric Interview; HADS, Hospital Anxiety and Depression Scale; PHQ, Patients Health Questionnaire; NA, not assessed; MDD, major depressive disorder; Dis, disorder; SCID, Structured Clinical Interview for DSM-; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases 10th revision; HDRS, Hamilton Depression Rating Scale; DIGS, Diagnostic Interview for Genetic Studies; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; BDI, Beck Depression Inventory.

inflammation, such as rosuvastatin, evidenced in the JUPITER study, may have advantages (8).

Because epidemiological studies showed that statins have beneficial effects on mood, randomized controlled trials (RCTs) have been conducted to examine the efficacy of statins in treating depression (65–67). A meta-analysis including three double-blind RCTs in subjects with depression found that adjunctive therapy with statins in addition to antidepressants could be useful for the treatment of depression without any serious adverse effects, although this finding is limited by the small number of studies and short-term follow-up periods (6–12 weeks) (71). In addition to this meta-analysis, a 6-weeks double-blind RCT of simvastatin and atorvastatin without antidepressants was conducted in depressive patients after a coronary artery bypass graft (68). Although response rates by treatment were not significantly different, simvastatin tended to improve depressive symptoms earlier and more effectively than did atorvastatin, probably because the former drug can penetrate the BBB.

A non-randomized, 1-year prospective study of depressive patients after acute coronary syndrome (ACS) demonstrated that statins were effective for the treatment of depression independently of medical status and escitalopram use. In this study, the combination of statins and escitalopram had larger effects than either drug alone. In addition, lipophilic statins showed greater potential to improve depression than hydrophilic statins (7). Further analysis of this study population (72) found that levels of pro-inflammatory cytokines, including IL-6 and IL-18, predicted subsequent depression in patients with ACS. However, the trigger effects of IL-6 and IL-18 on depression were attenuated in patients receiving statins, suggesting that the antidepressant effects of such drugs are attributable to reductions in the actions of pro-inflammatory cytokines. These recent publications suggest that statins have independent effects with regard to improving depression (7, 68), but further research is needed with larger sample sizes and well-designed randomized trials in to clarify the potential benefits of statins alone in depression treatment.

In summary, both epidemiological and interventional studies show that statins are useful in reducing depression risk in patients with physical disorders such as CVD. However, caution is warranted before prescribing statins in the general population without higher inflammation loads or in populations with poor nutritional states and low cholesterol stores, because the cholesterol-lowering effects of statins could theoretically at least increase the risk of depression in these populations. Furthermore, in depressive patients, statins have been shown to be beneficial for improving depressive symptoms when used as an adjunctive therapy to antidepressants, but the independent effects of statins are yet to be confirmed.

STATINS FOR SCHIZOPHRENIA

Schizophrenia is a severe chronic mental disorder characterized by delusions, hallucinations, cognitive impairment, avolition, reduced emotional expression, social withdrawal, and marked functional decline (73). Immune dysfunction and inflammation

have been implicated in the pathogenesis of schizophrenia by numerous epidemiological and clinical studies (74, 75). Specifically, people with schizophrenia show increased levels of pro-inflammatory cytokines, and the vulnerability-stress-inflammation model also supports the role of inflammation in schizophrenia (76). Patients with schizophrenia have elevated blood levels of IL-1β, IL-6, and transforming growth factor-β (77), and they have elevated microglia activation in the brain compared to normal controls (78). As the associations between inflammation and schizophrenia have been found repeatedly, anti-inflammatory agents including non-steroidal anti-inflammatory drugs and acetylcysteine have been used as adjunctive therapies for improving symptoms of schizophrenia (79–81).

An important consideration for understanding schizophrenia is that 50–75% of deaths among patients with schizophrenia are due to CVD, while about 33% of deaths in the general population are due to CVD (82). Metabolic syndrome and dyslipidemia are associated with second generation antipsychotics and have very high prevalence rates in patients with schizophrenia. Statins effectively manage dyslipidaemia in patients with schizophrenia (83). As statins also exert anti-inflammatory actions, they are useful in preventing cardiovascular conditions in such patients and are employed to augment schizophrenia treatment.

To date, there have been six RCTs investigating the efficacy of statins as an adjuvant treatment for schizophrenia (**Table 2**). Five of these RCTs had small sample sizes of 12–36 patients in each treatment arm, and short treatment durations of 6–12 weeks. Only one study (86) had a larger sample size of 65 patients in each treatment arm, and investigated Positive and Negative Syndrome Scale (PANSS) negative symptom score over 6 months. Most of the studies followed patients who were outpatients in a stable state (e.g., stable on medication for several weeks prior to baseline assessment), whereas one study included inpatients in the active phase of the disease (89). Three studies used simvastatin 40 mg, while other studies used lovastatin 20 mg, atorvastatin 20 mg, or pravastatin 40 mg.

One study (84) showed that statin add-on therapy for schizophrenia patients was superior to placebo in terms of improving negative symptoms as measured by the PANSS subscale evaluating blunted affect, emotional withdrawal, apathetic social withdrawal, and poverty of speech. Although negative symptoms constitute the major barrier to functional recovery in patients with schizophrenia, the current antipsychotics exert only modest effects on negative symptoms (90, 91). Therefore, studies showing effects of statins on negative symptoms in patients with schizophrenia could have important clinical implications. Another study (89) did not show any effect of statins. The four remaining studies (85, 87, 88) reported non-significant benefits of statins. Most studies noted no significant differences in the adverse event rates between the statin user and non-user groups.

The participants of the study that reported a significant reduction in PANSS negative scores had the lowest baseline PANSS score among the six RCTs (84). This implies that the effect of statins may be more pronounced in stabilized patients than acutely ill patients. Another consideration is the type of

TABLE 2 | Clinical trials investigating the efficacy of statins in patients with schizophrenia.

References	Study design	Subject number (mean age)	F/U duration	Assessment	Diagnosis	Statin Name and Dosage	Main findings
POSITIVE FINDINGS							
Tajik-Esmaeeli et al. (84)	DB RCT	36 statin and 36 placebo (44 ± 9 yrs)	8 weeks	PANSS	DSM-IV SPR, clinically stable	Simvastatin 40 mg/d + Risperidone 4~6 mg/d	"Simvastatin + risperidone" improved PANSS total and negative score at week 8
POSITIVE ASSOCIATION WITHOUT SIGNIFICANCE							
Chaudhry et al. (85)	RB RCT	12 statin and 12 placebo (18~35 yrs)	12 weeks	PANSS	DSM-IV Psychotic dis., stable	Simvastatin 40 mg/d + APs	"Simvastatin + Aps" improved PANSS total score without significant difference; little effect on PANSS negative score
Deakin et al. (86)	RB RCT	130	6 months	PANSS	NA	Simvastatin 40 mg/d + APs	"Simvastatin + Aps" improved PANSS negative score at 3 and 6 months without main effects of simvastatin
Vincenzi et al. (87)	DB RCT	30 statin and 30 placebo (44 ± 12 yrs)	12 weeks	PANSS	DSM-IV SPR, outpatients	Pravastatin 40 mg/d + APs	"Pravastatin + Aps" improved PANSS positive score at week 6, but failed to remain significant at week 12
Sayyah et al. (88)	DB RCT	21 statin (35 ± 7 yrs) and 23 placebo (40 ± 10 yrs)	6 weeks	SANS	DSM-IV SPR, chronic	Atorvastatin 20 mg/d + Risperidone 6 mg/d	"Atorvastatin + risperidone" improved SANS score without significant difference (at 4 and 6 weeks, $p = 0.074$ and 0.068, respectively).
NEGATIVE FINDINGS							
Ghanizadeh et al. (89)	DB RCT	20 statin and 16 placebo (30±8 yrs)	8 weeks	PANSS	DSM-IV SPR, inpatients	Lovastatin 20 mg/d + Risperidone 2~8 mg/d	No difference of PANSS score changes No serious adverse effect

Yrs, years; APs, antipsychotics; DB, double-blinded; RB, rater-blinded; RCT, randomized, placebo-controlled trial; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; PANSS, Positive and Negative Syndrome Scale, dis., disorder; SANS, Scale for the Assessment of Negative Symptoms; SPR, Schizophrenia; NA, not applicable.

antipsychotic medication used. There may be interactions of statins and antipsychotics, because some antipsychotics also have anti-inflammatory actions (92). Appropriate statin use may also affect the results since lipophilic statins, which can cross the BBB more readily, are more likely to interact with central brain regions (7). Simvastatin, which is the most lipophilic statin, was the most commonly used statin type in RCTs. Whether lipophilic statins improve inflammatory markers in patients with schizophrenia should be studied further.

Although there has been no study of the optimal dose and duration of statin therapy in schizophrenia, a few studies suggested the advantages of high dosage and long duration of statin therapy for CVD (93, 94). An animal study showed that hyper-locomotive activity and reduced anxiety-like behavior via NMDA receptor upregulation were initiated after high-dose simvastatin, which was higher than clinical dosages (95). Previous studies on N-acetylcysteine, which inhibits oxidative and inflammatory pathways, reported clear evidence of efficacy only after 6 months (96, 97), and a replication study noted benefits only after 9 and 12 months (98). Therefore, long-term treatment with high-dose statins may better alleviate psychotic and negative symptoms in patients with schizophrenia.

The lipid-lowering effects of statins may alleviate symptoms of schizophrenia, because studies have suggested associations between hyperlipidemia and the pathophysiology of schizophrenia (99, 100). One study found that pravastatin significantly decreased the PANSS positive subscale scores, commencing at week 6, in schizophrenia patients, but the decrease failed to remain significant to 12 weeks (87). Interestingly, the similar pattern of decrease at 6 weeks and increase at 12 weeks was found with levels of triglycerides, LDL-cholesterol, and total cholesterol. This suggests a link between lipid levels and the psychopathology of schizophrenia. However, we should consider that reduced efficacy for both psychotic symptoms and cholesterol levels could be due to poor adherence to statin medications. Additionally, a study on patients taking clozapine revealed that increases in the serum total cholesterol and triglyceride levels significantly predicted reductions in the PANSS total and/or negative subscale scores (101, 102). Furthermore, a positive longitudinal association was evident between changes in cholesterol levels and improved global cognition, particularly in verbal memory (103). Thus, further study is required to understand how changes in the serum levels of lipids and inflammatory reactions relate to changes in the symptoms of schizophrenia during statin use, and how these relationships vary with different antipsychotic drugs.

In summary, the anti-inflammatory actions of statins are expected to alleviate symptoms of schizophrenia as an augmentation to other drugs, and they have the added benefits of treating metabolic abnormalities such as hyperlipidemia to prevent CVD. We recommend the use of a sufficient dose of statins for at least 12 weeks in stable patients with schizophrenia for functional recovery as well as liberal use of statins in those with high levels of cardiovascular risk. Further studies are required in various populations and stages of illness.

STATINS FOR NEUROCOGNITIVE DISORDERS

Dementia has complex and heterogenous etiologies, including cerebrovascular disease, amyloid plaques, and tauopathy (104). Alzheimer disease (AD) is the most common cause of dementia and represents one of the largest burdens of disease in elderly persons (105). Evidence suggests that the deposition of ß-amyloid plaques and inflammatory processes in the CNS play important roles in the development and progression of AD (106, 107). Excessive amyloid beta (Aβ) accumulation is a hallmark feature of the AD neurodegenerative cascade (108). The dysregulation of the Aβ clearance process is characterized by elevated levels of pro-inflammatory cytokines, and this induces Aβ accumulation and continuous immune activation (109).

Defects in brain cholesterol homeostasis have been implicated in neurodegenerative diseases including AD and cognitive deficits typical of old age (13). Most brain cholesterol is synthesized in astrocytes; ApoE shuttles cholesterol (in a lipoprotein complex) from these cells to neurons. Therefore, ApoE may play an important role in cholesterol homeostasis in aging and diseased brains (110). Furthermore, cholesterol homeostasis may significantly affect the synthesis, deposition, and clearance of β-amyloid plaques (111, 112). The major brain cholesterol metabolite 24S-hydroxycholesterol (24S-OHC) may affect the NMDA receptor, in turn triggering cell death associated with AD (113). Statins exert anti-inflammatory and cholesterol-lowering effects in the brain, and also reduce the levels of oxysterols such as 24S-OHC (114). Statins may thus be useful in preventing/managing AD. Previous research on the association between statin use and AD, derived from cardiovascular studies, suggested that elective statin use has a beneficial effect on AD (115).

Table 3 summarizes previous studies investigating the associations between statin use and AD. Epidemiological cross-sectional and case-control studies have generally found that statins usefully prevent AD (119, 120, 125). Several prospective studies on the incidence of statin use and AD have also shown a protective association, although these studies have limitations. The Adult Changes in Thought (ACT) study was a prospective study that found that statin use may be associated with reduced risk of AD, particularly in those younger than 80 (118). The 2-year follow-up of the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) found reduced risk of AD in people taking statins, but it is important to note that participants regularly using NSAIDs were excluded, but non-statin lipid lowering agent use was permitted (117). Conversely, the Cache County Study found no association between statin use and the risk of AD over 72 weeks (116). There was no randomized clinical trial assessing statin use and risk of developing AD. A large primary prevention study of statins in the elderly, STAREE will explore this outcome (126).

There have been four published RCTs of statins as an intervention in patients with mild to moderate AD. The Lipitor's Effect in Alzheimer's Dementia (LEADe) study was the largest with 640 patients, and found that a regimen of atorvastatin

TABLE 3 | Studies investigating the associations between statin use and Alzheimer disease (AD).

References	Study design	Subject number (mean age)	F/U duration	Assessment	Diagnosis	Statin Name and Dosage	Main findings
EPIDEMIOLOGICAL STUDY							
Zandi et al. (116)	Prospective	4,895 (statin = 73 ± 5 yrs, nonuser = 76 ± 7 yrs)	3 years	DSM-III-R	AD	Any use	No association with subsequent onset of AD; aHR(95% CI) = 1.19 (0.35–2.96)
Sparks et al. (117)	Prospective	2,528 (75 ± 4 yrs)	5 years	DSM-IV NINCDS-ADRDA	AD	Any use	Reduced risk of AD; aHR(95% CI) = 0.33 (0.11–0.98)
Li et al. (118)	Prospective	3,099 (statin = 74 ± 6, non-user=76±6 yrs)	6 years	NINCDS-ADRDA, DSM-IV	AD	Any use	Reduced risk of AD; aHR(95% CI) = 0.62 (0.40–0.97) Strength of the statin diminished with age
Zissimopoulos et al. (119)	Retrospective	399,979 (women 76 and men 75 yrs)	5 years	ICD-9	AD	atorvastatin, pravastatin, rosuvastatin	Reduced risk of AD diagnosis for women: aHR(95% CI) = 0.85 (0.82–0.89) for men: aHR(95% CI) = 0.88 (0.83–0.93)
Zamrini et al. (120)	Case control	505 AD-paired patients (73 yrs)		ICD-9	AD	Any use	Reduced risk of AD; aOR (95% CI) = 0.61 (0.42–0.87)
INTERVENTIONAL STUDY							
Simons et al. (121)	RCT	44 statin and 68 placebo (68 ± 8 yrs)	26 weeks	NINCDS-ADRDA	mild-to-moderate AD	Simvastatin 80 mg	A small but significant reduction of Abeta40 in the CSF of mild but not moderate AD patients.
Sparks et al. (122)	RCT	32 statin and 31 placebo (78 ± 1 yrs)	1 year	DSM-IV NINCDS-ADRDA	mild-to-moderate AD	Atorvastatin 80 mg	Atorvastatin may slow the progression of mild to-moderate AD
Feldman et al. (123)	RCT	297 statin and 317 placebo (74 ± 8 yrs)	72 weeks	ADAS-Cog	mild-to-moderate AD	Atorvastatin 80 mg	No significant clinical benefit
Sano et al. (124)	RCT	204 statin and 202 placebo (75 ± 9 yrs)	18 months	ADAS-Cog	mild-to-moderate AD	Simvastatin 40 mg	No benefit on the progression of symptoms despite significant lowering of cholesterol.
Lin et al. (125)	Case control	719 AD-paired patients	≥ 1 year	ICD-9 DSM-IV	mild-to-moderate AD	Any use	Early stain use exhibited a 0.85-risk (95% CI = 0.76–0.95) to have AD progression than those without.

Yrs, years; RCT, randomized controlled trial; DSM, Diagnostic and Statistical Manual of Mental Disorders; aHR, Adusted Hazard Ratio; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale test; ICD-9, International Classification of Diseases, Ninth Revision.

(80 mg/day) plus donepezil was not associated with significant benefits for treatment over 72 weeks (123). Similarly, a medium-sized, placebo-controlled, double-blind, randomized study found that simvastatin (20∼40 mg) had no benefit for the progression of symptoms in individuals with mild to moderate AD (124). In contrast, a RCT showed that AD progressed more slowly (as measured by the Mini-Mental State Examination) in patients treated with simvastatin (80 mg/day) than placebo, over 26 weeks (121). Furthermore, this study showed that statins also decreased levels of beta-amyloid in the cerebrospinal fluid of patients with mild AD. In the 1-year follow-up of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial study, there were also positive effects for treatment outcomes between 32 patients receiving 1 year of atorvastatin (80 mg/day) and 31 receiving placebo (122). Atorvastatin significantly improved memory performance as measured by the ADAS-Cog instrument after 6 months of treatment in patients with mild to moderate AD. These inconsistent results may be attributed by differences in sample size, statin dosage, characteristics of the statin used (lipophilic vs. hydrophilic), baseline lipid level, and assessment tools used for cognitive function.

In summary, statins may reduce the incidence of AD (126). However, RCTs assessing cognition in AD patients have yielded inconsistent results (127). A key point emerging from this research is the importance of the timing of statin treatment for achieving benefits in AD. Because AD progresses over long periods of time, future studies should include long-term follow-up periods to enable detection of any effects of statin treatment and might usefully focus early in the illness course, such as mild cognitive impairment.

STATINS FOR OTHER PSYCHIATRIC DISORDERS

There have been several clinical trials of statins for delirium prevention or treatment in critically ill patients. Based on the neuroinflammatory hypothesis of delirium, which is characterized by acute release of inflammatory mediators during critical illness, the pleiotropic effects of statins may prevent or attenuate delirium due to their effects on neutrophil migration, BBB injury, and inflammation (94, 128). However, a review of the literature regarding the use of statins for delirium prevention or treatment reveals no clear overall conclusions. Differential effects of statins on neuroinflammation during delirium may be due to treatment with lipophilic vs. hydrophilic statins. The current study demonstrated that the use of a hydrophilic statin (pravastatin) was associated with reduced delirium incidence compared with a lipophilic statin (atorvastatin), but the reverse has also been found (129). A recent comprehensive meta-analysis found that statins did not reduce the incidence of delirium in physically ill patients (130). There are many confounding factors that might account for these inconsistent results, including heterogeneity of study designs, variability of patient populations, the multifactorial nature of delirium, inconsistent delirium assessments, limited study power and lack of information on co-administration of other neuropsychiatric medications. Therefore, well-designed studies on delirium are still needed.

When considering bipolar disorder as a multisystemic inflammatory disease (131), it is important to examine the effect of statins on the manic phase as well as the depressive phase. An RCT evaluating lovastatin as an adjuvant to lithium in patients in the manic phase of bipolar disorder found that lovastatin neither exacerbated nor improved manic symptoms (132). That study suggested that the combination of statins with lithium is well-tolerated in patients with bipolar disorder, without evidence of exacerbation of mania by the antidepressant effects of statins.

ADVERSE EVENTS ASSOCIATED WITH STATINS

The usual doses of statins are generally safe, being rarely associated with clinically significant adverse events (133). However, clinicians should know the general adverse events when prescribing statins. Statin-associated muscle symptoms (SAMs) are clinically important side effects of statins. SAMs are the most common side effects, reported by 10–25% of patients undergoing statin therapy, and are also the most common cause of statin discontinuation (134–136). SAMs range in severity from muscle cramps and weakness to creatine kinase (CK) elevation and rhabdomyolysis. Severe muscle damage is relatively rare among SAMs, but rhabdomyolysis should be distinguished from neuroleptic malignant syndrome (NMS), which is a rare but life-threatening disease that can occur with antipsychotic medication (137). Recent studies have found that patients who experienced non-severe SAMs can tolerate statins upon blinded re-challenge (138–140). Many reported adverse events can be predicated on expectancy and nocebo phenomena (141, 142). Therefore, it is necessary to consider a comprehensive approach and management such as patient assessment, treatment according to severity, re-assessment and considering other treatment options for SAMs (143). Neuropathy is most likely to develop after long-term treatment, and it generally resolves after the discontinuation of statins (144).

Statin use increased diabetes risk by 9–13% in a meta-analysis of randomized trials (145). Additionally, high-dose statins increased the risk of diabetes compared to that associated with standard-dose statins (146). Predictors of new-onset diabetes in patients treated with atorvastatin were baseline fasting blood glucose level, body mass index, hypertension, and fasting triglyceride level (147). However, a study on diabetes risks associated with statin therapy showed that patients lacking baseline risk factors (metabolic syndrome, impaired fasting glucose level, body mass index >30 kg/m^2, or HbA1c $>6\%$) did not develop diabetes (148). In addition, several studies have suggested that statin-mediated prevention of cardiovascular disease should receive more emphasis than the risk of diabetes (149–151). Risk factors for diabetes should be routinely evaluated before prescribing statins. L-carnitine (500–1,000 mg twice daily) may prevent any increase in blood sugar levels (152).

Although the serum levels of hepatic transaminases may increase in patients taking statins, routine measurement of liver enzyme levels is not required (153). Other possible physical side effects of statins are hemorrhagic stroke, decreased renal

function, tendon rupture, interstitial lung disease, and low testosterone levels (154).

Risk for potential neuropsychiatric adverse events may also be increased in the use of long-term high doses of statins. Mood disturbance, sleep changes, cognitive impairment, and suicide have been reported in patients taking statins, although casual links are uncertain (69, 155–157). Clinicians should assess neuropsychiatric adverse events associated with statin use.

The US Food and Drug Administration recently issued a warning stating that statins could cause mild cognitive impairment (158). Some case reports and several studies have reported small cognitive decreases in patients on statin therapy (159–161); other studies have found that statins reduced cognitive decline in older adults (117, 162, 163). A recent systematic review and meta-analysis found no significant association between statin use and cognitive impairment (164, 165). Neurocognitive impairment following the initiation of statins appears to depend on statin type; lipophilic statins are associated with more cognitive impairments (159, 166), while clinical trials using hydrophilic statins, which are less likely to cross the blood brain barrier, did not show any significant cognitive impairment.

It seems biologically plausible that lowering cholesterol levels with statins could cause several changes in the serotonergic system, which might lead to increased irritability and violent ideation (167–169). Despite some case reports of mood disturbance with statin use (170, 171), evidence of any relationship between statins and mood is conflicting. It has been suggested that statins might be associated with a higher rate of sleep disturbance, especially for lipophilic statins (172, 173). Multi-methodological approaches using different databases suggest that statin use was associated with an increased risk of sleep disturbances (including sleep initiation and maintenance) and parasomnias (173). However, there is no conclusive evidence that any particular statin is more likely to cause sleep disturbances than other statins, and a recent meta-analysis found that statins exerted no significant adverse effects on sleep duration or efficiency (155).

The literature regarding statin-associated suicide risk remains limited, and there is no proven association between statin use and increase in suicide (56). A Danish population-based study ($n = 642{,}058$) showed that the SSRI-statin (citalopram 57.2%, simvastatin 92%) group was associated with fewer psychiatric hospital contacts and no increase in suicidal behavior compared to populations who used SSRI alone (174). Overall, even if the cholesterol-lowering effects of statins could be associated with potential adverse events, there has been little conclusive evidence of statins causing serious side effects that would outweigh the advantages of this medication. Furthermore, the advantageous anti-inflammatory actions of statins may alleviate any potential negative effects of lower cholesterol.

DRUG INTERACTIONS OF STATINS

Metabolism of statins is complex, and begins with absorption, followed by hepatic uptake, metabolism, and elimination (175). Individual characteristics and multiple transporters acting on each phase interact with concomitant medications, leading to changes in serum concentrations of statins, may change. Among multiple pathways, the role of the cytochrome P-450 (CYP) system has been most commonly described (133). Most statins are metabolized by CYP 3A4. Exceptions include fluvastatin and rosuvastatin, which are largely metabolized by CYP 2C9 (176), and pravastatin, which is mainly metabolized by renal clearance (177). Antidepressants, antipsychotics, anxiolytics, and cognitive enhancers that are metabolized by CYP isoenzymes can increase serum statin concentrations by competing for catabolism and vice versa (176). Also, inhibition and enhancement of the CYP isoenzymes by psychotropic medications can increase or decrease serum concentrations of statins. One case report described a 79-year-old female prescribed nefazodone 300 mg daily for 8 years, who then took simvastatin 40 mg daily, and subsequently developed rhabdomyolysis, perhaps attributable to potent inhibition of CYP 3A4 by nefazodone (178). CYP status must be evaluated when combining antidepressants and statins (178).

Drug interactions between statins and antipsychotics may influence the efficacy of antipsychotics through P-glycoprotein 1 (P-gp), which is a transporter in the BBB and regulates brain tissue for access of centrally acting drugs. Both statins and some antipsychotic drugs are substrates of P-gp (179). Thus, statins and antipsychotic agents may act synergistically in terms of CNS access (180). The increased CNS levels may improve psychotic symptoms in schizophrenia patients (180).

DISCUSSION AND CONCLUSIONS

The degree of lipophilicity required to cross the BBB may be associated with direct effects of statins on the brain, as might their capacity to suppress peripheral cytokines. Neuropsychiatric side effects of statins including neuropathy and cognitive impairment may be more closely associated with the lipophilic statins, probably because they are more likely to cross the BBB. However, lipophilic statins such as simvastatin have demonstrated effectiveness for improving depression as well as the negative symptoms of schizophrenia. Clinicians should be aware of these contradictory findings that lipophilic statins are associated with a higher potential for neuropsychiatric adverse events as well as increased efficacy for psychiatric symptoms when selecting the type of statin to prescribe.

The half-life of cholesterol in the adult brain ranges from 6 months to 5 years; in contrast, the half-life of plasma cholesterol is only a few days. Thus, any brain lipid-lowering effect of statins may be very slow (13, 181). Statins exert anti-inflammatory and anti-oxidant effects, which may explain their benefits in patients with various psychiatric disorders. Therefore, for psychiatric patients, high-dose long-term statin therapy may be required. Future long-term

studies should explore the effects of statins in various psychiatric disorders.

In conclusion, statin therapy appears to be safe in the majority of patients, and the benefits of statin use far outweigh the potential risks. Statins used with conventional psychotropic medications may be effective in various psychiatric disorders including depression, schizophrenia, and the risk for dementia. Statins seem useful in reducing depression, particularly in patients with physical disorders. In patients with schizophrenia, negative symptoms may be reduced by adjuvant statin therapy. Studies on cohorts at risk for dementia have generally shown protective effects of statins, while those on treatment for dementia show inconsistent results. Further study is required to investigate optimal statin dose and duration of use. In addition, population studies using statins are ideal candidates for further investigations of the efficacy of statins in mitigating the risk and prevention of psychiatric conditions and their cardiovascular comorbidities.

AUTHOR CONTRIBUTIONS

SWK, JMK, and MB designed the strategy for the present review. SWK, HJK, MJ, JWK, JYL, AW, and BA wrote the first outlined of the review. SWK, JMK, and MB critically revised the draft. All authors read and approved the submitted version.

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REFERENCES

1. Montecucco F, Burger F, Pelli G, Poku NK, Berlier C, Steffens S, et al. Statins inhibit C-reactive protein-induced chemokine secretion, ICAM-1 upregulation and chemotaxis in adherent human monocytes. *Rheumatology.* (2009) 48:233–42. doi: 10.1093/rheumatology/ken466
2. Quist-Paulsen P. Statins and inflammation: an update. *Curr Opin Cardiol.* (2010) 25:399–405. doi: 10.1097/HCO.0b013e3283398e53
3. Link A, Ayadhi T, Bohm M, Nickenig G. Rapid immunomodulation by rosuvastatin in patients with acute coronary syndrome. *Eur Heart J.* (2006) 27:2945–55. doi: 10.1093/eurheartj/ehl277
4. Mayer C, Gruber HJ, Landl EM, Pailer S, Scharnagl H, Truschnig-Wilders M, et al. Rosuvastatin reduces interleukin-6-induced expression of C-reactive protein in human hepatocytes in a STAT3- and C/EBP-dependent fashion. *Int J Clin Pharmacol Ther.* (2007) 45:319–27. doi: 10.5414/CPP45319
5. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol.* (2005) 19:117–25. doi: 10.1111/j.1472-8206.2004.00299.x
6. Rojas-Fernandez CH, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. *Ann Pharmacother.* (2012) 46:549–57. doi: 10.1345/aph.1Q620
7. Kim SW, Bae KY, Kim JM, Shin IS, Hong YJ, Ahn Y, et al. The use of statins for the treatment of depression in patients with acute coronary syndrome. *Transl Psychiatry.* (2015) 5:e620. doi: 10.1038/tp.2015.116
8. Mora S, Ridker PM. Justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER)–can C-reactive protein be used to target statin therapy in primary prevention? *Am J Cardiol.* (2006) 97:33a—41a. doi: 10.1016/j.amjcard.2005.11.014
9. Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. *Cardiovasc Res.* (2000) 47:648–57. doi: 10.1016/S0008-6363(00)00146-2
10. Haroon E, Daguanno AW, Woolwine BJ, Goldsmith DR, Baer WM, Wommack EC, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology.* (2018) 95:43–9. doi: 10.1016/j.psyneuen.2018.05.026
11. Bedi O, Dhawan V, Sharma PL, Kumar P. Pleiotropic effects of statins: new therapeutic targets in drug design. *Naunyn Schmiedebergs Arch Pharmacol.* (2016) 389:695–712. doi: 10.1007/s00210-016-1252-4
12. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest.* (2002) 109:1125–31. doi: 10.1172/jci15593
13. Zhang J, Liu Q. Cholesterol metabolism and homeostasis in the brain. *Protein Cell.* (2015) 6:254–64. doi: 10.1007/s13238-014-0131-3
14. Gibson Wood W, Eckert GP, Igbavboa U, Muller WE. Amyloid beta-protein interactions with membranes and cholesterol: causes or casualties of Alzheimer's disease. *Biochim Biophys Acta.* (2003) 1610:281–90. doi: 10.1016/S0005-2736(03)00025-7
15. Babelova A, Sedding DG, Brandes RP. Anti-atherosclerotic mechanisms of statin therapy. *Curr Opin Pharmacol.* (2013) 13:260–4. doi: 10.1016/j.coph.2013.01.004
16. Koskinas KC, Windecker S, Raber L. Regression of coronary atherosclerosis: current evidence and future perspectives. *Trends Cardiovasc Med.* (2016) 26:150–61. doi: 10.1016/j.tcm.2015.05.004
17. Sirtori CR. The pharmacology of statins. *Pharmacol Res.* (2014) 88:3–11. doi: 10.1016/j.phrs.2014.03.002
18. Greenwood J, Mason JC. Statins and the vascular endothelial inflammatory response. *Trends Immunol.* (2007) 28:88–98. doi: 10.1016/j.it.2006.12.003
19. Liao JK. Isoprenoids as mediators of the biological effects of statins. *J Clin Invest.* (2002) 110:285–8. doi: 10.1172/jci16421
20. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The Anti-inflammatory effects of statins on coronary artery disease: an updated review of the literature. *Curr Cardiol Rev.* (2017) 13:209–16. doi: 10.2174/1573403x13666170426104611
21. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol.* (2006) 6:358–70. doi: 10.1038/nri1839
22. Morris G, Fernandes BS, Puri BK, Walker AJ, Carvalho AF, Berk M. Leaky brain in neurological and psychiatric disorders: Drivers and consequences. *Aust N Z J Psychiatry.* (2018) 52:924–48. doi: 10.1177/0004867418796955
23. Wang S, Xie X, Lei T, Zhang K, Lai B, Zhang Z, et al. Statins attenuate activation of the NLRP3 inflammasome by oxidized LDL or TNFalpha in vascular endothelial cells through a PXR-dependent mechanism. *Mol Pharmacol.* (2017) 92:256–64. doi: 10.1124/mol.116.108100
24. Ampuero J, Romero-Gomez M. Prevention of hepatocellular carcinoma by correction of metabolic abnormalities: role of statins and metformin. *World J Hepatol.* (2015) 7:1105–11. doi: 10.4254/wjh.v7.i8.1105
25. Ma Y, Chen Z, Zou Y, Ge J. Atorvastatin represses the angiotensin 2-induced oxidative stress and inflammatory response in dendritic cells via the PI3K/Akt/Nrf 2 pathway. *Oxid Med Cell Longev.* (2014) 2014:148798. doi: 10.1155/2014/148798
26. Balakumar P, Mahadevan N. Interplay between statins and PPARs in improving cardiovascular outcomes: a double-edged sword? *Br J Pharmacol.* (2012) 165:373–9. doi: 10.1111/j.1476-5381.2011.01597.x

27. Chataway J, Schuerer N, Alsanousi A, Chan D, MacManus D, Hunter K, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet.* (2014) 383:2213–21. doi: 10.1016/s0140-6736(13)62242-4
28. Ramanan VK, Przybelski SA, Graff-Radford J, Castillo AM, Lowe VJ, Mielke MM, et al. Statins and brain health: Alzheimer's disease and cerebrovascular disease biomarkers in older adults. *J Alzheimers Dis.* (2018) 65:1345–52. doi: 10.3233/jad-180446
29. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med.* (2013) 11:129. doi: 10.1186/1741-7015-11-129
30. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* (2000) 160:2101–7. doi: 10.1001/archinte.160.14.2101
31. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci.* (2009) 10:434–45. doi: 10.1038/nrn2639
32. Reus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience.* (2015) 300:141–54. doi: 10.1016/j.neuroscience.2015.05.018
33. Sattar NA, Ginsberg H, Ray K, Chapman MJ, Arca M, Averna M, et al. The use of statins in people at risk of developing diabetes mellitus: evidence and guidance for clinical practice. *Atheroscler Suppl.* (2014) 15:1–15. doi: 10.1016/j.atherosclerosissup.2014.04.001
34. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care.* (2012) 35:1171–80. doi: 10.2337/dc11-2055
35. Delgado I, Huet L, Dexpert S, Beau C, Forestier D, Ledaguenel P, et al. Depressive symptoms in obesity: Relative contribution of low-grade inflammation and metabolic health. *Psychoneuroendocrinology.* (2018) 91:55–61. doi: 10.1016/j.psyneuen.2018.02.030
36. Horowitz MA, Zunszain PA. Neuroimmune and neuroendocrine abnormalities in depression: two sides of the same coin. *Ann N Y Acad Sci.* (2015) 1351:68–79. doi: 10.1111/nyas.12781
37. Pasco JA, Jacka FN, Williams LJ, Henry MJ, Nicholson GC, Kotowicz MA, et al. Leptin in depressed women: cross-sectional and longitudinal data from an epidemiologic study. *J Affect Disord.* (2008) 107:221–5. doi: 10.1016/j.jad.2007.07.024
38. Nikkheslat N, Zunszain PA, Horowitz MA, Barbosa IG, Parker JA, Myint AM, et al. Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav Immun.* (2015) 48:8–18. doi: 10.1016/j.bbi.2015.02.002
39. Anderson G, Berk M, Dodd S, Bechter K, Altamura AC, Dell'osso B, et al. Immuno-inflammatory, oxidative and nitrosative stress, and neuroprogressive pathways in the etiology, course and treatment of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* (2013) 42:1–4. doi: 10.1016/j.pnpbp.2012.10.008
40. Grigoletti L, Perini G, Rossi A, Biggeri A, Barbui C, Tansella M, et al. Mortality and cause of death among psychiatric patients: a 20-year case-register study in an area with a community-based system of care. *Psychol Med.* (2009) 39:1875–84. doi: 10.1017/s0033291709005790
41. Heart Protection Study Collaborative G. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet.* (2011) 378:2013–20. doi: 10.1016/s0140-6736(11)61125-2
42. Anderson G, Berk M, Dean O, Moylan S, Maes M. Role of immune-inflammatory and oxidative and nitrosative stress pathways in the etiology of depression: therapeutic implications. *CNS Drugs.* (2014) 28:1–10. doi: 10.1007/s40263-013-0119-1
43. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol Psychiatry.* (2013) 18:595–606. doi: 10.1038/mp.2012.33
44. Vogelzangs N, Beekman AT, van Reedt Dortland AK, Schoevers RA, Giltay EJ, de Jonge P, et al. Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. *Neuropsychopharmacology.* (2014) 39:1624–34. doi: 10.1038/npp.2014.9
45. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med.* (2009) 71:171–86. doi: 10.1097/PSY.0b013e3181907c1b
46. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-Gonzalez A, Esquivel-Chirino C, et al. Inflammation, oxidative stress, and obesity. *Int J Mol Sci.* (2011) 12:3117–32. doi: 10.3390/ijms12053117
47. Anisman H. Stress, immunity, cytokines and depression. *Acta Neuropsychiatr.* (2002) 14:251–61. doi: 10.1034/j.1601-5215.2002.140601.x
48. Prossin AR, Koch AE, Campbell PL, Barichello T, Zalcman SS, Zubieta JK. Acute experimental changes in mood state regulate immune function in relation to central opioid neurotransmission: a model of human CNS-peripheral inflammatory interaction. *Mol Psychiatry.* (2016) 21:243–51. doi: 10.1038/mp.2015.110
49. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiol Rev.* (1999) 79:1–71. doi: 10.1152/physrev.1999.79.1.1
50. Hunter RL, Dragicevic N, Seifert K, Choi DY, Liu M, Kim HC, et al. Inflammation induces mitochondrial dysfunction and dopaminergic neurodegeneration in the nigrostriatal system. *J Neurochem.* (2007) 100:1375–86. doi: 10.1111/j.1471-4159.2006.04327.x
51. Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. *Proc Natl Acad Sci USA.* (2003) 100:13632–7. doi: 10.1073/pnas.2234031100
52. Stafford L, Berk M. The use of statins after a cardiac intervention is associated with reduced risk of subsequent depression: proof of concept for the inflammatory and oxidative hypotheses of depression? *J Clin Psychiatry.* (2011) 72:1229–35. doi: 10.4088/JCP.09m05825blu
53. Weitz-Schmidt G. Statins as anti-inflammatory agents. *Trends Pharmacol Sci.* (2002) 23:482–6. doi: 10.1016/S0165-6147(02)02077-1
54. Young-Xu Y, Chan A, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being in the elderly. *J Am Coll Cardiol.* (2003) 42:690–7. doi: 10.1016/S0735-1097(03)00785-X
55. Otte C, Zhao S, Whooley MA. Statin use and risk of depression in patients with coronary heart disease: longitudinal data from the Heart and Soul Study. *J Clin Psychiatry.* (2012) 73:610–5. doi: 10.4088/JCP.11m07038
56. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med.* (2003) 163:1926–32. doi: 10.1001/archinte.163.16.1926
57. Pasco JA, Jacka FN, Williams LJ, Henry MJ, Nicholson GC, Kotowicz MA, et al. Clinical implications of the cytokine hypothesis of depression: the association between use of statins and aspirin and the risk of major depression. *Psychother Psychosom.* (2010) 79:323–5. doi: 10.1159/000319530
58. Al Badarin FJ, Spertus JA, Gosch KL, Buchanan DM, Chan PS. Initiation of statin therapy after acute myocardial infarction is not associated with worsening depressive symptoms: insights from the prospective registry evaluating outcomes after myocardial infarctions: events and recovery (PREMIER) and translational research investigating underlying disparities in acute myocardial infarction patients' health status (TRIUMPH) registries. *Am Heart J.* (2013) 166:879–86. doi: 10.1016/j.ahj.2013.09.001
59. Redlich C, Berk M, Williams LJ, Sundquist J, Sundquist K, Li X. Statin use and risk of depression: a Swedish national cohort study. *BMC Psychiatry.* (2014) 14:348. doi: 10.1186/s12888-014-0348-y
60. Chuang CS, Yang TY, Muo CH, Su HL, Sung FC, Kao CH. Hyperlipidemia, statin use and the risk of developing depression: a nationwide retrospective cohort study. *Gen Hosp Psychiatry.* (2014) 36:497–501. doi: 10.1016/j.genhosppsych.2014.05.008
61. Kim JM, Stewart R, Kang HJ, Bae KY, Kim SW, Shin IS, et al. A prospective study of statin use and poststroke depression. *J Clin Psychopharmacol.* (2014) 34:72–9. doi: 10.1097/jcp.0000000000000051
62. Kang JH, Kao LT, Lin HC, Tsai MC, Chung SD. Statin use increases the risk of depressive disorder in stroke patients: a population-based study. *J Neurol Sci.* (2015) 348:89–93. doi: 10.1016/j.jns.2014.11.013

63. Glaus J, Vandeleur CL, Lasserre AM, Strippoli MP, Castelao E, Gholam-Rezaee M, et al. Aspirin and statin use and the subsequent development of depression in men and women: Results from a longitudinal population-based study. *J Affect Disord.* (2015) 182:126–31. doi: 10.1016/j.jad.2015.03.044
64. Kohler O, Gasse C, Petersen L, Ingstrup KG, Nierenberg AA, Mors O, et al. The effect of concomitant treatment with SSRIs and statins: a population-based study. *Am J Psychiatry.* (2016) 173:807–15. doi: 10.1176/appi.ajp.2016.15040463
65. Ghanizadeh A, Hedayati A. Augmentation of fluoxetine with lovastatin for treating major depressive disorder, a randomized double-blind placebo controlled-clinical trial. *Depress Anxiety.* (2013) 30:1084–8. doi: 10.1002/da.22195
66. Haghighi M, Khodakarami S, Jahangard L, Ahmadpanah M, Bajoghli H, Holsboer-Trachsler E, et al. In a randomized, double-blind clinical trial, adjuvant atorvastatin improved symptoms of depression and blood lipid values in patients suffering from severe major depressive disorder. *J Psychiatr Res.* (2014) 58:109–14. doi: 10.1016/j.jpsychires.2014.07.018
67. Gougol A, Zareh-Mohammadi N, Raheb S, Farokhnia M, Salimi S, Iranpour N, et al. Simvastatin as an adjuvant therapy to fluoxetine in patients with moderate to severe major depression: a double-blind placebo-controlled trial. *J Psychopharmacol.* (2015) 29:575–81. doi: 10.1177/0269881115578160
68. Abbasi SH, Mohammadinejad P, Shahmansouri N, Salehiomran A, Beglar AA, Zeinoddini A, et al. Simvastatin versus atorvastatin for improving mild to moderate depression in post-coronary artery bypass graft patients: a double-blind, placebo-controlled, randomized trial. *J Affect Disord.* (2015) 183:149–55. doi: 10.1016/j.jad.2015.04.049
69. Parsaik AK, Singh B, Murad MH, Singh K, Mascarenhas SS, Williams MD, et al. Statins use and risk of depression: a systematic review and meta-analysis. *J Affect Disord.* (2014) 160:62–7. doi: 10.1016/j.jad.2013.11.026
70. Huang J. Letter by Huang regarding the article, "Statin use increases the risk of depressive disorder in stroke patients: A population-based study". *J Neurol Sci.* (2015) 358:471. doi: 10.1016/j.jns.2015.08.023
71. Salagre E, Fernandes BS, Dodd S, Brownstein DJ, Berk M. Statins for the treatment of depression: A meta-analysis of randomized, double-blind, placebo-controlled trials. *J Affect Disord.* (2016) 200:235–42. doi: 10.1016/j.jad.2016.04.047
72. Kim SW, Kang HJ, Bae KY, Shin IS, Hong YJ, Ahn YK, et al. Interactions between pro-inflammatory cytokines and statins on depression in patients with acute coronary syndrome. *Prog Neuropsychopharmacol Biol Psychiatry.* (2018) 80:250–4. doi: 10.1016/j.pnpbp.2017.07.003
73. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet.* (2016) 388:86–97. doi: 10.1016/S0140-6736(15)01121-6
74. Miller BJ, Culpepper N, Rapaport MH. C-reactive protein levels in schizophrenia: a review and meta-analysis. *Clin Schizophr Relat Psychoses.* (2014) 7:223–30. doi: 10.3371/csrp.micu.020813
75. Najjar S, Pearlman DM. Neuroinflammation and white matter pathology in schizophrenia: systematic review. *Schizophr Res.* (2015) 161:102–12. doi: 10.1016/j.schres.2014.04.041
76. Muller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation in schizophrenia. *Front Neurosci.* (2015) 9:372. doi: 10.3389/fnins.2015.00372
77. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry.* (2011) 70:663–71. doi: 10.1016/j.biopsych.2011.04.013
78. van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. *Biol Psychiatry.* (2008) 64:820–2. doi: 10.1016/j.biopsych.2008.04.025
79. Keller WR, Kum LM, Wehring HJ, Koola MM, Buchanan RW, Kelly DL. A review of anti-inflammatory agents for symptoms of schizophrenia. *J Psychopharmacol.* (2013) 27:337–42. doi: 10.1177/0269881112467089
80. Nitta M, Kishimoto T, Muller N, Weiser M, Davidson M, Kane JM, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. *Schizophr Bull.* (2013) 39:1230–41. doi: 10.1093/schbul/sbt070
81. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophr Bull.* (2014) 40:181–91. doi: 10.1093/schbul/sbt139
82. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J.* (2005) 150:1115–21. doi: 10.1016/j.ahj.2005.02.007
83. Hanssens L, De Hert M, Kalnicka D, van Winkel R, Wampers M, Van Eyck D, et al. Pharmacological treatment of severe dyslipidaemia in patients with schizophrenia. *Int Clin Psychopharmacol.* (2007) 22:43–9. doi: 10.1097/YIC.0b013e3280113d3b
84. Tajik-Esmaeeli S, Moazen-Zadeh E, Abbasi N, Shariat SV, Rezaei F, Salehi B, et al. Simvastatin adjunct therapy for negative symptoms of schizophrenia: a randomized double-blind placebo-controlled trial. *Int Clin Psychopharmacol.* (2017) 32:87–94. doi: 10.1097/yic.0000000000000159
85. Chaudhry IB, Husain N, Drake R, Dunn G, Husain MO, Kazmi A, et al. Add-on clinical effects of simvastatin and ondansetron in patients with schizophrenia stabilized on antipsychotic treatment: pilot study. *Ther Adv Psychopharmacol.* (2014) 4:110–6. doi: 10.1177/2045125313511487
86. Deakin J HN, Parkier JJ, Husain MO, Kazmi A, Rahman R. Efficacy of ondansetron and simvastatin on cognition and negative symptoms in established schizophrenia. *Neuropsychopharmacology.* (2014) 39:S355–6.
87. Vincenzi B, Stock S, Borba CP, Cleary SM, Oppenheim CE, Petruzzi LJ, et al. A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: effect on inflammation, psychopathology, cognition and lipid metabolism. *Schizophr Res.* (2014) 159:395–403. doi: 10.1016/j.schres.2014.08.021
88. Sayyah M, Boostani H, Ashrafpoori M, Pakseresht S. Effects of atorvastatin on negative sign in chronic schizophrenia: a double blind clinical trial. *Iran J Pharm Res.* (2015) 14:1269–74.
89. Ghanizadeh A, Rezaee Z, Dehbozorgi S, Berk M, Akhondzadeh S. Lovastatin for the adjunctive treatment of schizophrenia: a preliminary randomized double-blind placebo-controlled trial. *Psychiatry Res.* (2014) 219:431–5. doi: 10.1016/j.psychres.2014.06.039
90. Kim SW, Stewart R, Park WY, Jhon M, Lee JY, Kim SY, et al. Latent iron deficiency as a marker of negative symptoms in patients with first-episode schizophrenia spectrum disorder. *Nutrients.* (2018) 10:E1707. doi: 10.3390/nu10111707
91. Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol Psychiatry.* (2009) 14:429–47. doi: 10.1038/sj.mp.4002136
92. Kato TA, Monji A, Mizoguchi Y, Hashioka S, Horikawa H, Seki Y, et al. Anti-Inflammatory properties of antipsychotics via microglia modulations: are antipsychotics a 'fire extinguisher' in the brain of schizophrenia? *Mini Rev Med Chem.* (2011) 11:565–74. doi: 10.2174/138955711795906941
93. Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP. High-intensity statin therapy and regression of coronary atherosclerosis in patients with diabetes mellitus. *J Diabetes Compl.* (2015) 29:142–5. doi: 10.1016/j.jdiacomp.2014.10.004
94. Khemasuwan D, Chae YK, Gupta S, Carpio A, Yun JH, Neagu S, et al. Dose-related effect of statins in venous thrombosis risk reduction. *Am J Med.* (2011) 124:852–9. doi: 10.1016/j.amjmed.2011.04.019
95. Wang Q, Zengin A, Deng C, Li Y, Newell KA, Yang GY, et al. High dose of simvastatin induces hyperlocomotive and anxiolytic-like activities: The association with the up-regulation of NMDA receptor binding in the rat brain. *Exp Neurol.* (2009) 216:132–8. doi: 10.1016/j.expneurol.2008.11.016
96. Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia–a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry.* (2008) 64:361–8. doi: 10.1016/j.biopsych.2008.03.004
97. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder–a double-blind randomized placebo-controlled trial. *Biol Psychiatry.* (2008) 64:468–75. doi: 10.1016/j.biopsych.2008.04.022
98. Breier A, Liffick E, Hummer TA, Vohs JL, Yang Z, Mehdiyoun NF, et al. Effects of 12-month, double-blind N-acetyl cysteine on symptoms, cognition and brain morphology in early phase schizophrenia spectrum disorders. *Schizophr Res.* (2018) 199:395–402. doi: 10.1016/j.schres.2018.03.012

99. Correll CU, Kane JM. Schizophrenia: mechanism of action of current and novel treatments. *J Clin Psychiatry.* (2014) 75:347–8. doi: 10.4088/JCP.13078co8c
100. Wysokinski A, Strzelecki D, Kloszewska I. Levels of triglycerides, cholesterol, LDL, HDL and glucose in patients with schizophrenia, unipolar depression and bipolar disorder. *Diabetes Metab Syndr.* (2015) 9:168–76. doi: 10.1016/j.dsx.2015.04.004
101. Lally J, Gallagher A, Bainbridge E, Avalos G, Ahmed M, McDonald C. Increases in triglyceride levels are associated with clinical response to clozapine treatment. *J Psychopharmacol.* (2013) 27:401–3. doi: 10.1177/0269881112472568
102. Procyshyn RM, Honer WG, Barr AM. Do serum lipids predict response to clozapine treatment? *J Psychiatry Neurosci.* (2009) 34:168
103. Krakowski M, Czobor P. Cholesterol and cognition in schizophrenia: a double-blind study of patients randomized to clozapine, olanzapine and haloperidol. *Schizophr Res.* (2011) 130:27–33. doi: 10.1016/j.schres.2011.04.005
104. Carlson MC, Helms MJ, Steffens DC, Burke JR, Potter GG, Plassman BL. Midlife activity predicts risk of dementia in older male twin pairs. *Alzheimers Dement.* (2008) 4:324–31. doi: 10.1016/j.jalz.2008.07.002
105. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. *Arch Neurol.* (2002) 59:1764–7. doi: 10.1001/archneur.59.11.1764
106. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging.* (2000) 21:383–421.
107. De Strooper B, Annaert W. Proteolytic processing and cell biological functions of the amyloid precursor protein. *J Cell Sci.* (2000) 113 (Pt 11):1857–70.
108. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacol Rep.* (2015) 67:195–203. doi: 10.1016/j.pharep.2014.09.004
109. Zheng C, Zhou XW, Wang JZ. The dual roles of cytokines in Alzheimer's disease: update on interleukins, TNF-alpha, TGF-beta and IFN-gamma. *Transl Neurodegener.* (2016) 5:7. doi: 10.1186/s40035-016-0054-4
110. de Chaves EP, Narayanaswami V. Apolipoprotein E and cholesterol in aging and disease in the brain. *Future Lipidol.* (2008) 3:505–30. doi: 10.2217/17460875.3.5.505
111. Gamba P, Testa G, Sottero B, Gargiulo S, Poli G, Leonarduzzi G. The link between altered cholesterol metabolism and Alzheimer's disease. *Ann N Y Acad Sci.* (2012) 1259:54–64. doi: 10.1111/j.1749-6632.2012.06513.x
112. Reed B, Villeneuve S, Mack W, DeCarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA Neurol.* (2014) 71:195–200. doi: 10.1001/jamaneurol.2013.5390
113. Sun MY, Linsenbardt AJ, Emnett CM, Eisenman LN, Izumi Y, Zorumski CF, Mennerick S. 24(S)-hydroxycholesterol as a modulator of neuronal signaling and survival. *Neuroscientist.* (2016) 22:132–44. doi: 10.1177/1073858414568122
114. Dias IHK, Milic I, Lip GYH, Devitt A, Polidori MC, Griffiths HR. Simvastatin reduces circulating oxysterol levels in men with hypercholesterolaemia. *Redox Biol.* (2018) 16:139–45. doi: 10.1016/j.redox.2018.02.014
115. Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. the rotterdam study. *J Neurol Neurosurg Psychiatry.* (2009) 80:13–7. doi: 10.1136/jnnp.2008.150433
116. Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The cache county study. *Arch Gen Psychiatry.* (2005) 62:217–24. doi: 10.1001/archpsyc.62.2.217
117. Sparks DL, Kryscio RJ, Sabbagh MN, Connor DJ, Sparks LM, Liebsack C. Reduced risk of incident AD with elective statin use in a clinical trial cohort. *Curr Alzheimer Res.* (2008) 5:416–21. doi: 10.2174/156720508785132316
118. Li G, Shofer JB, Rhew IC, Kukull WA, Peskind ER, McCormick W, et al. Age-varying association between statin use and incident Alzheimer's disease. *J Am Geriatr Soc.* (2010) 58:1311–7. doi: 10.1111/j.1532-5415.2010.02906.x
119. Zissimopoulos JM, Barthold D, Brinton RD, Joyce G. Sex and race differences in the association between statin use and the incidence of Alzheimer disease. *JAMA Neurol.* (2017) 74:225–32. doi: 10.1001/jamaneurol.2016.3783
120. Zamrini E, McGwin G, Roseman JM. Association between statin use and Alzheimer's disease. *Neuroepidemiology.* (2004) 23:94–8. doi: 10.1159/000073981
121. Simons M, Schwarzler F, Lutjohann D, von Bergmann K, Beyreuther K, Dichgans J, et al. Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: a 26-week randomized, placebo-controlled, double-blind trial. *Ann Neurol.* (2002) 52:346–50. doi: 10.1002/ana.10292
122. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. *Acta Neurol Scand Suppl.* (2006) 185:3–7. doi: 10.1111/j.1600-0404.2006.00690.x
123. Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology.* (2010) 74:956–64. doi: 10.1212/WNL.0b013e3181d6476a
124. Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, van Dyck CH, Aisen PS. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology.* (2011) 77:556–63. doi: 10.1212/WNL.0b013e318228bf11
125. Lin FC, Chuang YS, Hsieh HM, Lee TC, Chiu KF, Liu CK, et al. Early statin use and the progression of Alzheimer disease: a total population-based case-control study. *Medicine.* (2015) 94:e2143. doi: 10.1097/md.0000000000002143
126. Chu CS, Tseng PT, Stubbs B, Chen TY, Tang CH, Li DJ, et al. Use of statins and the risk of dementia and mild cognitive impairment: a systematic review and meta-analysis. *Sci Rep.* (2018) 8:5804. doi: 10.1038/s41598-018-24248-8
127. Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia—systematic review and methodological commentary. *Nat Rev Neurol.* (2015) 11:220–9. doi: 10.1038/nrneurol.2015.35
128. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. *Atherosclerosis.* (2009) 203:325–30. doi: 10.1016/j.atherosclerosis.2008.08.022
129. Taburyanskaya M, Hassig T. Statins and delirium: is there a role? *Curr Atheroscler Rep.* (2015) 17:470. doi: 10.1007/s11883-014-0470-9
130. Vallabhajosyula S, Kanmanthareddy A, Erwin PJ, Esterbrooks DJ, Morrow LE. Role of statins in delirium prevention in critical ill and cardiac surgery patients: A systematic review and meta-analysis. *J Crit Care.* (2017) 37:189–96. doi: 10.1016/j.jcrc.2016.09.025
131. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord.* (2012) 141:1–10. doi: 10.1016/j.jad.2011.12.049
132. Ghanizadeh A, OmraniSigaroodi M, Javadpour A, Dabbaghmanesh MH, Shafiee S. Lovastatin as an adjuvant to lithium for treating manic phase of bipolar disorder: a 4-week, randomized, double-blind, placebo-controlled clinical trial. *Depress Res Treat.* (2014) 2014:730505. doi: 10.1155/2014/730505
133. Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation.* (2004) 109:Iii50–7. doi: 10.1161/01.CIR.0000131519.15067.1f
134. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding statin use in America and Gaps in patient education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol.* (2012) 6:208–15. doi: 10.1016/j.jacl.2012.03.003
135. Cornier MA, Eckel RH. Non-traditional dosing of statins in statin-intolerant patients-is it worth a try? *Curr Atheroscler Rep.* (2015) 17:475. doi: 10.1007/s11883-014-0475-4
136. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. *Cardiovasc Drugs Ther.* (2005) 19:403–14. doi: 10.1007/s10557-005-5686-z
137. Cooper JM, Jones AL. Neuroleptic malignant syndrome or a statin drug reaction? A case report. *Clin Neuropharmacol.* (2009) 32:348–9. doi: 10.1097/WNF.0b013e3181acc92d

138. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the odyssey alternative randomized trial. *J Clin Lipidol.* (2015) 9:758–69. doi: 10.1016/j.jacl.2015.08.006
139. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA.* (2016) 315:1580–90. doi: 10.1001/jama.2016.3608
140. Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis.* (2015) 238:329–35. doi: 10.1016/j.atherosclerosis.2014.12.016
141. Data-Franco J, Berk M. The nocebo effect: a clinicians guide. *Aust N Z J Psychiatry.* (2013) 47:617–23. doi: 10.1177/0004867412464717
142. Dodd S, Dean OM, Vian J, Berk M. A review of the theoretical and biological understanding of the nocebo and placebo phenomena. *Clin Ther.* (2017) 39:469–76. doi: 10.1016/j.clinthera.2017.01.010
143. Saxon DR, Eckel RH. Statin intolerance: a literature review and management strategies. *Prog Cardiovasc Dis.* (2016) 59:153–64. doi: 10.1016/j.pcad.2016.07.009
144. Otruba P, Kanovsky P, Hlustik P. Treatment with statins and peripheral neuropathy: results of 36-months a prospective clinical and neurophysiological follow-up. *Neuro Endocrinol Lett.* (2011) 32:688–90.
145. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet.* (2010) 375:735–42. doi: 10.1016/s0140-6736(09)61965-6
146. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA.* (2011) 305:2556–64. doi: 10.1001/jama.2011.860
147. Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol.* (2011) 57:1535–45. doi: 10.1016/j.jacc.2010.10.047
148. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet.* (2012) 380:565–71. doi: 10.1016/s0140-6736(12)61190-8
149. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J.* (2016) 37:2999–3058. doi: 10.1093/eurheartj/ehw272
150. Kim SH. Drug treatment of dyslipidemia. *J Korean Med Assoc.* (2016) 59:366–73. doi: 10.5124/jkma.2016.59.5.366
151. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* (2014) 63:2889–934. doi: 10.1016/j.jacc.2013.11.002
152. Spence JD, Dresser GK. Overcoming challenges with statin therapy. *J Am Heart Assoc.* (2016) 5:e002497. doi: 10.1161/jaha.115.002497
153. Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. *Nat Rev Cardiol.* (2018) 15:757–69. doi: 10.1038/s41569-018-0098-5
154. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. *J Am Coll Cardiol.* (2016) 67:2395–410. doi: 10.1016/j.jacc.2016.02.071
155. Broncel M, Gorzelak-Pabis P, Sahebkar A, Serejko K, Ursoniu S, Rysz J, et al. Sleep changes following statin therapy: a systematic review and meta-analysis of randomized placebo-controlled polysomnographic trials. *Arch Med Sci.* (2015) 11:915–26. doi: 10.5114/aoms.2015.54841
156. Davison KM, Kaplan BJ. Lipophilic statin use and suicidal ideation in a sample of adults with mood disorders. *Crisis.* (2014) 35:278–82. doi: 10.1027/0227-5910/a000260
157. While A, Keen L. The effects of statins on mood: a review of the literature. *Eur J Cardiovasc Nurs.* (2012) 11:85–96. doi: 10.1016/j.ejcnurse.2010.08.008
158. Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. *Am J Geriatr Pharmacother.* (2012) 10:264–71. doi: 10.1016/j.amjopharm.2012.05.002
159. Muldoon MF, Barger SD, Ryan CM, Flory JD, Lehoczky JP, Matthews KA, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med.* (2000) 108:538–46. doi: 10.1016/S0002-9343(00)00353-3
160. Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med.* (2004) 117:823–9. doi: 10.1016/j.amjmed.2004.07.041
161. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy.* (2003) 23:871–80. doi: 10.1592/phco.23.7.871.32720
162. Bernick C, Katz R, Smith NL, Rapp S, Bhadelia R, Carlson M, et al. Statins and cognitive function in the elderly: the cardiovascular health study. *Neurology.* (2005) 65:1388–94. doi: 10.1212/01.wnl.0000182897.18229.ec
163. Etminan M, Gill S, Samii A. The role of lipid-lowering drugs in cognitive function: a meta-analysis of observational studies. *Pharmacotherapy.* (2003) 23:726–30. doi: 10.1592/phco.23.6.726.32184
164. Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med.* (2015) 30:348–58. doi: 10.1007/s11606-014-3115-3
165. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. *Mayo Clin Proc.* (2013) 88:1213–21. doi: 10.1016/j.mayocp.2013.07.013
166. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* (1981) 30:239–45. doi: 10.1038/clpt.1981.154
167. Asellus P, Nordstrom P, Jokinen J. Cholesterol and CSF 5-HIAA in attempted suicide. *J Affect Disord.* (2010) 125:388–92. doi: 10.1016/j.jad.2010.02.111
168. De Berardis D, Conti CM, Serroni N, Moschetta FS, Carano A, Salerno RM, et al. The role of cholesterol levels in mood disorders and suicide. *J Biol Regul Homeost Agents.* (2009) 23:133–40.
169. Shrivastava S, Pucadyil TJ, Paila YD, Ganguly S, Chattopadhyay A. Chronic cholesterol depletion using statin impairs the function and dynamics of human serotonin(1A) receptors. *Biochemistry.* (2010) 49:5426–35. doi: 10.1021/bi100276b
170. Cham S, Koslik HJ, Golomb BA. Mood, personality, and behavior changes during treatment with statins: a case series. *Drug Saf Case Rep.* (2016) 3:1. doi: 10.1007/s40800-015-0024-2
171. Golomb BA, Kane T, Dimsdale JE. Severe irritability associated with statin cholesterol-lowering drugs. *QJM.* (2004) 97:229–35. doi: 10.1093/qjmed/hch035
172. Roth T, Richardson GR, Sullivan JP, Lee RM, Merlotti L, Roehrs T. Comparative effects of pravastatin and lovastatin on nighttime sleep and daytime performance. *Clin Cardiol.* (1992) 15:426–32. doi: 10.1002/clc.4960150607
173. Takada M, Fujimoto M, Yamazaki K, Takamoto M, Hosomi K. Association of statin use with sleep disturbances: data mining of a spontaneous reporting database and a prescription database. *Drug Saf.* (2014) 37:421–31. doi: 10.1007/s40264-014-0163-x
174. Andrade C. Relative to SSRI users, SSRI-statin users have fewer psychiatric hospital contacts and no increase in suicidal behaviour or all-cause mortality. *Evid Based Ment Health.* (2017) 20:60. doi: 10.1136/eb-2016-102566
175. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev.* (2011) 63:157–81. doi: 10.1124/pr.110.002857
176. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions. *Expert Opin Drug Saf.* (2012) 11:933–46. doi: 10.1517/14740338.2012.712959
177. Paoletti R, Corsini A, Bellosta S. Pharmacological interactions of statins. *Atheroscler Suppl.* (2002) 3:35–40. doi: 10.1016/S1567-5688(02)00002-8
178. Karnik NS, Maldonado JR. Antidepressant and statin interactions: a review and case report of simvastatin and nefazodone-induced

rhabdomyolysis and transaminitis. *Psychosomatics.* (2005) 46:565–8. doi: 10.1176/appi.psy.46.6.565

179. Wang E, Casciano CN, Clement RP, Johnson WW. HMG-CoA reductase inhibitors (statins) characterized as direct inhibitors of P-glycoprotein. *Pharm Res.* (2001) 18:800–6. doi: 10.1023/A:1011036428972
180. Shen H, Li R, Yan R, Zhou X, Feng X, Zhao M, Xiao H. Adjunctive therapy with statins in schizophrenia patients: a meta-analysis and implications. *Psychiatry Res.* (2018) 262:84–93. doi: 10.1016/j.psychres.2018.02.018
181. Andersson M, Elmberger PG, Edlund C, Kristensson K, Dallner G. Rates of cholesterol, ubiquinone, dolichol and dolichyl-P biosynthesis in rat brain slices. *FEBS Lett.* (1990) 269:15–8. doi: 10.1016/0014-5793(90)81107-Y

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