



## OPEN ACCESS

EDITED BY  
Geraldine Zimmer-Bensch,  
RWTH Aachen University, Germany

REVIEWED BY  
Mira Jakovcevski,  
Max Planck Institute of Psychiatry  
(MPI), Germany  
Julia Maria Schulze-Hentrich,  
University of Tübingen, Germany  
Olivia Engmann,  
University Hospital Jena, Germany

## \*CORRESPONDENCE

Xingbin Hu  
hxbyqh@163.com  
Qunxing An  
bestar01@163.com

†These authors have contributed  
equally to this work and share first  
authorship

## SPECIALTY SECTION

This article was submitted to  
Cellular Neuropathology,  
a section of the journal  
Frontiers in Cellular Neuroscience

RECEIVED 16 September 2022

ACCEPTED 17 October 2022

PUBLISHED 02 November 2022

## CITATION

Wang Y, Meng W, Liu Z, An Q and  
Hu X (2022) Cognitive impairment  
in psychiatric diseases: Biomarkers  
of diagnosis, treatment,  
and prevention.  
*Front. Cell. Neurosci.* 16:1046692.  
doi: 10.3389/fncel.2022.1046692

## COPYRIGHT

© 2022 Wang, Meng, Liu, An and Hu.  
This is an open-access article  
distributed under the terms of the  
[Creative Commons Attribution License  
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or  
reproduction in other forums is  
permitted, provided the original  
author(s) and the copyright owner(s)  
are credited and that the original  
publication in this journal is cited, in  
accordance with accepted academic  
practice. No use, distribution or  
reproduction is permitted which does  
not comply with these terms.

# Cognitive impairment in psychiatric diseases: Biomarkers of diagnosis, treatment, and prevention

Yafen Wang<sup>†</sup>, Weicheng Meng<sup>†</sup>, Zhixin Liu<sup>†</sup>, Qunxing An\* and  
Xingbin Hu\*

Department of Blood Transfusion, Xijing Hospital, Fourth Military Medical University, Xi'an, China

Psychiatric diseases, such as schizophrenia, bipolar disorder, autism spectrum disorder, and major depressive disorder, place a huge health burden on society. Cognitive impairment is one of the core characteristics of psychiatric disorders and a vital determinant of social function and disease recurrence in patients. This review thus aims to explore the underlying molecular mechanisms of cognitive impairment in major psychiatric disorders and identify valuable biomarkers for diagnosis, treatment and prevention of patients.

## KEYWORDS

cognitive impairment, psychiatric diseases, schizophrenia, bipolar disorder, autism spectrum disorder, major depressive disorder, biomarkers

## Introduction

Psychiatric diseases are the most enigmatic maladies in medicine, with various causes and limited effective treatment so far. Up to 20% of the population suffers from a common psychiatric disorder each year, especially adolescents aged 10–24 years (Jorm et al., 2017; GBD 2019 Diseases and Injuries Collaborators, 2020). Common psychiatric disorders include schizophrenia (SCZ), bipolar disorder (BD), autism spectrum disorder (ASD), and major depressive disorder (MDD), which together contribute significantly to the global burden of disability and disease (GBD 2019 Diseases and Injuries Collaborators, 2020). They are characterized by persistent, universal, and pathological patterns of abnormal moods, perceptions, behaviors, or higher levels of cognition (Sullivan and Geschwind, 2019; First et al., 2021). Of particular noteworthy, cognitive impairment is a pivotal common characteristic of major psychiatric disorders, which can not only lead to dysfunction, disability and even death of patients, but also impose substantial psychological, economic, and medical burdens on families and society (Lai et al., 2014; Grande et al., 2016; Sharma et al., 2018; Vieta et al., 2018; Jauhar et al., 2022). There is, thus, a growing awareness of the importance of cognitive impairment.

The seven cognitive domains of cognitive impairment identified by MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) typically include notable deficits in the speed of processing, working memory, attention/vigilance, verbal learning, visual learning, reasoning and problem-solving, and social cognition (Nuechterlein et al., 2008; Van Rheenen and Rossell, 2014; Lynham et al., 2022). An epidemiologic study of first-admission psychosis revealed that the prevalence of cognitive impairment in schizophrenia, bipolar disorder, and major depressive disorder was as high as 45, 64, and 77%, respectively (Reichenberg et al., 2009). Currently available therapeutic approaches and researches for cognitive impairment in psychiatric diseases rely on cognitive-enhancing agents and neuroplasticity-based cognitive training primarily (Guercio et al., 2019; Haas et al., 2021; Veselinović and Neuner, 2022). However, there are no objective molecular markers available to early diagnose, guide therapy and evaluate prognosis in existing clinical practice. Therefore, the development of novel and effective objective molecular markers became an urgent need to address limitations in the current.

It is now known that manifold mechanisms contribute to understanding cognitive impairment in psychiatric diseases including genetics, epigenetics, neurotransmitter deficits, proinflammatory cytokines and neurotrophins, metabolism and microbiome-gut-brain axis, and stem cell therapies. An overview of this review is shown in **Figure 1**. The aim of the present review is, therefore, to systematically summarize and evaluate the pathogenesis of cognitive impairment in psychiatric diseases and to identify effective objective molecular markers for diagnosis and potential targets for future therapeutic approaches.

## Genetics

As psychiatric genomics continues to thrive, so do the unprecedented insights of cognitive impairment into psychiatric diseases. Genome-wide association studies (GWAS) has been used extensively in recent years to identify novel genetic loci associated with cognitive phenotype of multiple psychiatric conditions, especially in patients with SCZ (Lencz et al., 2014; Ohi et al., 2015; Smeland et al., 2017; Greenwood et al., 2019). It can identify sequence variation in the human genome and screen for single nucleotide polymorphisms (SNPs) associated with human disease phenotypes, thereby mining genomic regions associated with trait variation (Rees and Owen, 2020). Lencz et al. (2014) identified nominally significant cognitive associations for four SNPs that have previously been robustly associated with SCZ susceptibility and discovered polygenic risk scores for SCZ were associated with lower general cognitive ability. One year later, Ohi et al. revealed that 191 SNPs were related to the cognitive phenotype of SCZ, of

which 115 SNPs (60.2%) have genes located within 10 kb of the SNPs. These genetic variants are moderately related to cognitive trait impairment and are primarily involved in the *N*-methyl-D-aspartate-glutamate (NMDA) network (Ohi et al., 2015). In recent years, Greenwood et al. used a conditional false discovery rate statistical approach, taking advantage of several large GWAS on SCZ and cognitive traits in more than 250,000 participants, 21 genomic regions were found to be shared between SCZ and cognitive traits (Smeland et al., 2017). Another GWAS on 11 SCZ-related neurophysiological and neurocognitive endophenotypes reported that a total of seven regions (3p21, 5p15, 5p12, etc.) exceeding conventional genome-wide significance thresholds were associated with various endophenotype defects, and genes such as neuregulin 3 (NRG3) and hyperpolarization activated cyclic nucleotide gated potassium channel 1 (HCN1) within these regions are primarily implicated in glutamate and axonal dysfunctions (Greenwood et al., 2019). In addition to SCZ, a GWAS of MDD and cognitive function found that there were 48, 116, and 32 SNPs significantly associated with executive function domains, processing speed, and global cognition, respectively. Some of these SNPs are located in genes expressed in brain with important roles in neuronal development (REST), oligodendrocyte maturation (TNFRSF21) and myelination (ARFGEF1) (Thalamuthu et al., 2022). A large GWAS combining data on SCZ ( $n = 82,315$ ), BD ( $n = 51,710$ ), and general intelligence ( $n = 269,867$ ) identified 75 distinct genomic loci associated with SCZ and intelligence, and 12 loci associated with BD and intelligence. Most SCZ risk alleles (61 of 75, 81%) were associated with poor cognitive performance, whereas most BD risk alleles (9 of 12, 75%) were associated with better cognitive performance, revealing a broad genetic overlap between SCZ, BD, and intelligence, albeit in different ways (Smeland et al., 2020).

According to the above mentioned studies, GWAS is being increasingly used in the study of cognitive impairment in mental disorders due to its advantages of effective identification of genetic variation and public usability of data. These massive amount of genomics data provide novel information at an unprecedented scale, but how to use genetic data to develop neurobiological insights and new therapeutic targets is a question that needs to be considered. Candidate genes are typically identified based on their location (i.e., their proximity to loci associated with cognitive impairment in psychiatric disorders) or by integrating findings of GWAS with functional information and gene expression data (Mould et al., 2021). Shortlisting such genes could provide potential drug targets for improving cognitive impairment in patients with psychiatric disorders. For example, the genes involved in the GWAS study of SCZ are targets of drugs with approved indications, such as voltage-gated calcium channels (e.g., CACNA1C and CACNB2) (Lencz and Malhotra, 2015; Hidalgo et al., 2021). However, due to the complexity of the brain, the polygenic nature of cognitive impairment, and the uncertainty of pathogenic mechanisms, no

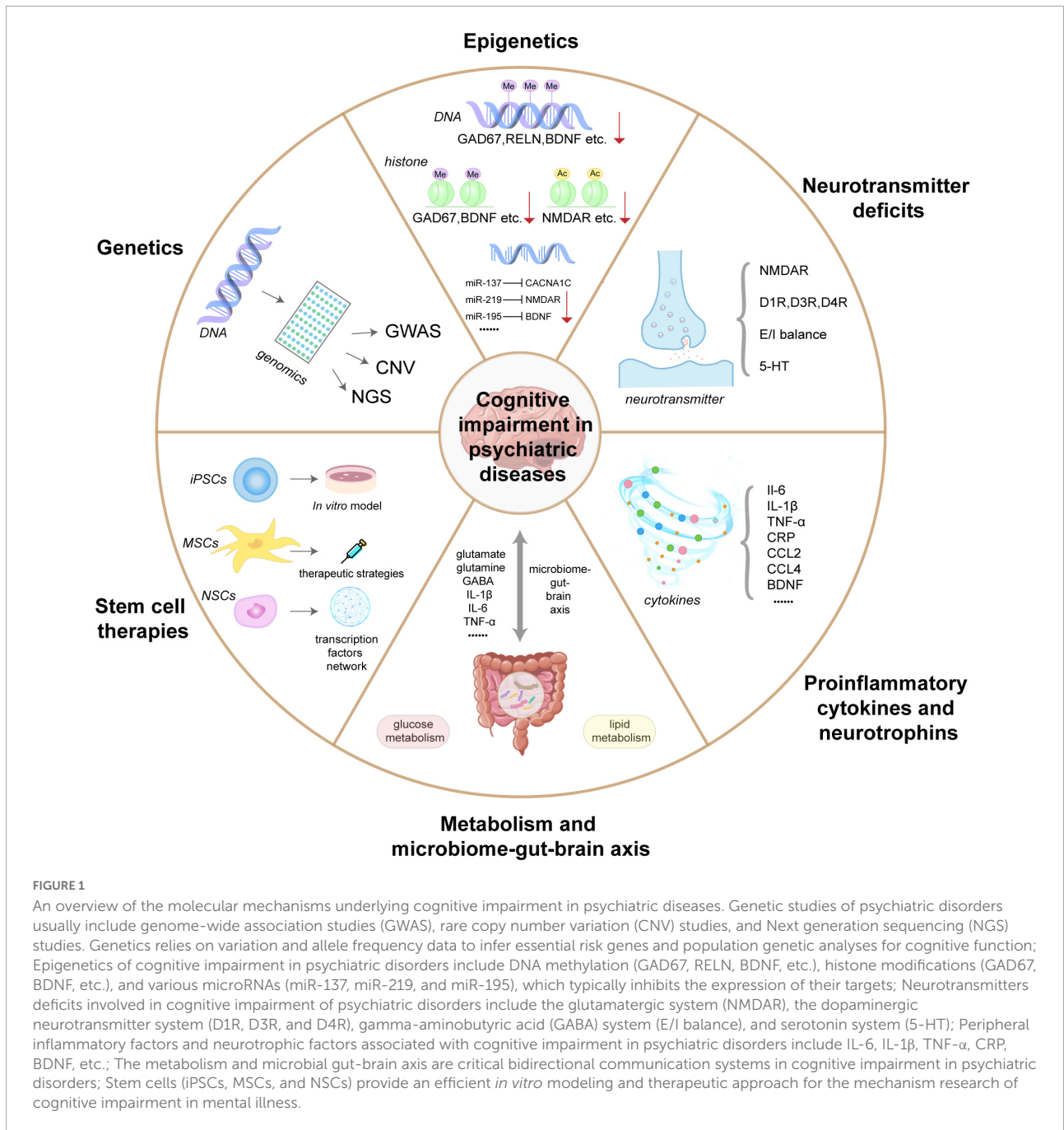


FIGURE 1

An overview of the molecular mechanisms underlying cognitive impairment in psychiatric diseases. Genetic studies of psychiatric disorders usually include genome-wide association studies (GWAS), rare copy number variation (CNV) studies, and Next generation sequencing (NGS) studies. Genetics relies on variation and allele frequency data to infer essential risk genes and population genetic analyses for cognitive function; Epigenetics of cognitive impairment in psychiatric disorders include DNA methylation (GAD67, RELN, BDNF, etc.), histone modifications (GAD67, BDNF, etc.), and various microRNAs (miR-137, miR-219, and miR-195), which typically inhibits the expression of their targets; Neurotransmitter deficits involved in cognitive impairment of psychiatric disorders include the glutamatergic system (NMDAR), the dopaminergic neurotransmitter system (D1R, D3R, and D4R), gamma-aminobutyric acid (GABA) system (E/I balance), and serotonin system (5-HT); Peripheral inflammatory factors and neurotrophic factors associated with cognitive impairment in psychiatric disorders include IL-6, IL-1 $\beta$ , TNF- $\alpha$ , CRP, BDNF, etc.; The metabolism and microbial gut-brain axis are critical bidirectional communication systems in cognitive impairment in psychiatric disorders; Stem cells (iPSCs, MSCs, and NSCs) provide an efficient *in vitro* modeling and therapeutic approach for the mechanism research of cognitive impairment in mental illness.

single therapeutic target or strategy is likely to be effective in all or even most patients. Second, the functions of the individual genes involved in GWAS can be explored in animal models, but it is difficult to see how many human risk alleles can be modeled with current or emerging technologies (Lencz and Malhotra, 2015; Rees and Owen, 2020). As a result, the genetic mechanism of cognitive impairment in mental illness remains challenges.

In addition to GWAS, rare copy number variant (CNV) is another significant genomic study that identifies deletions or duplications of DNA base pairs associated with traits or

diseases (Rees and Owen, 2020). Large (> 100 kb), rare (<1% in the population) CNVs have been shown to confer risk of cognitive impairment in SCZ and ASD (Stefansson et al., 2014; Rees and Kirov, 2021). A CNV analysis of SCZ identified 34 *de Novo* CNVs, and gene-set enrichment analysis suggested that these CNVs may contribute to defects in N-methyl-D-aspartate receptor (NMDAR) postsynaptic signaling and neuronal activity-regulated cytoskeleton-associated protein (known to be important in synaptic plasticity and cognition) (Kirov et al., 2012). CNV carriers predisposed to SCZ and/or autism have

cognitive abnormalities similar to those encountered in SCZ, so these neuropsychiatric CNVs can be used as tools to study the cognitive abnormalities that characterize the disorder (Stefansson et al., 2014). Growing evidence in recent years also clearly implicates rare CNVs hitting genes in SCZ-enriched gene sets were associated with severe cognitive impairment (Kendall et al., 2019a; Hubbard et al., 2021). High-risk CNV is not only related to SCZ and other neurodevelopmental disorders, but is also a factor contributing to impairment in cognitive domains such as memory or perceptual reasoning, and acts as an intermediate risk biomarker of disease (Thygesen et al., 2021). Similarly, autistic probands with multiple pathogenic CNVs and a strong family history presented more severe clinical features and impaired cognition (Sanders et al., 2015; Pizzo et al., 2019). However, from the current research, it appears that the contribution of large CNVs to BD and MDD is smaller than that to SCZ and ASD. Large structural variations often seem to predispose to persistent, widespread brain dysfunction, including impacts on the cognitive and personality development (Green et al., 2016; Kendall et al., 2019b).

Next-generation sequencing (NGS) studies can detect other rare variants, such as rare single nucleotide variants and small insertions/deletions. NGS often have focused on sequencing protein-coding regions of the genome, known as exome sequencing, to identify specific genes or genomes rich in rare variants associated with psychiatric disorders (Rees and Owen, 2020; Satterstrom et al., 2020). Recently, the advent of third-generation sequencing (TGS) technology has revolutionized our ability to sequence genomes and transcriptomes, and throw more lights on the complicate gene structure analysis (Sedlazeck et al., 2018). Compared to NGS technologies, TGS can generate longer sequencing reads, enabling the direct detection of DNA and RNA modifications at single-nucleotide resolution and in a single-molecule manner (van Dijk et al., 2018). It holds great potential for many fields, such as identification of variant-disease associations and methylation, and further promotion of disease diagnosis (Liu et al., 2020; Smith et al., 2020). The polygenic nature of psychiatric disorders challenges advances from genetics to biology. Still, by combining different genomics and functional, pharmaceutical, and clinical trial approaches, we will better understand the mechanism of cognitive impairment in mental disorders, explore better treatment methods, and judge the prognosis of patients.

## Epigenetics

Unlike genetics, epigenetics refers to heritable phenotypic changes that not alter the DNA sequence, including DNA methylation, histone modifications, and various microRNAs (Yao et al., 2016). Epigenetic regulation of cognitive impairment in mental illness has also attracted increasing attention. The PsychENCODE project is first the consortium to compare

neuronal and non-neuronal transcriptomes and epigenomes from post-mortem brains of donors with psychiatric phenotypes, which assesses population epigenetic variation in the human brain and functionally characterizes variation associated with mental illness (Akbarian et al., 2015).

DNA methylation is one of the most studied epigenetic modifications in cognitive impairment, mainly refers to the methylation of CpG dinucleotides on cytosine dinucleotide 5-carbon atoms, which is usually associated with gene silencing (Grayson and Guidotti, 2013; Jaffe et al., 2016; Vogel Ciernia and LaSalle, 2016). Methylation studies of cognitive impairment in SCZ have focused on genes involved in the disease. Previous studies have reported that hypermethylation of the promoters of candidate genes expressed in cognitively related gamma-aminobutyric acid (GABA)-ergic neurons in SCZ is associated with transcriptional downregulation of corresponding mRNA, including glutamate decarboxylase 67 (GAD67/GAD1) and reelin (RELN) (Chen et al., 2002; Dong et al., 2005). Other common methylation candidate genes, include Catechol-O-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), dopamine receptor, and serotonin receptor (Viola and Fries, 2019). The COMT gene encodes Catechol-O-methyltransferase, which affects prefrontal dopamine levels and cognitive symptoms in SCZ (Ehllis et al., 2007). It has been suggested that the methylation of BDNF reduces its expression in SCZ patients, and this change affects the protein level of synaptic density and neuronal cell size and thus affects patients' cognition, but there is some controversy (Ehllis et al., 2007; Boulle et al., 2012; Keller et al., 2014). Methylation of the promoter of dopamine receptor genes (DRD2, DRD3, and DRD4) also alters dopamine expression and causes cognitive deficits associated with SCZ (Cheng et al., 2014; Dai et al., 2014; Chen et al., 2020). Hypermethylation of genes (5HTR1A and HTR2A) that regulates serotonin signaling and serotonin transporter, which are involved in cognition and memory, has been found to be associated with SCZ (Carrard et al., 2011; Abdolmaleky et al., 2014; Cheah et al., 2017). In BD, methylation studies of candidate genes associated with cognitive impairment are similar to those in SCZ (Fries et al., 2016). Evidence for aberrant DNA methylation in ASD can be seen at multiple levels, ranging from gene mutations in epigenetic mechanisms to site-specific and genome-wide changes in DNA methylation (Vogel Ciernia and LaSalle, 2016). Targeted gene-specific DNA methylation changes in ASD included hypermethylation of MECP2, UBE3A, OXTR, SNRPN, MAGEL2, RELN, and GAD1. In contrast, hypomethylation of target candidate genes such as RORA, ERMN, USP24, METTL21C, PDE10A, STX16, and DBT was also found in peripheral blood DNA of ASD subjects (Tremblay and Jiang, 2019). Of these, RELN and GAD1 have been clearly associated with cognitive impairment (Labouesse et al., 2015; Lintas et al., 2016).

Histone modifications including methylation and acetylation of histones have recently been implicated in

cognitive impairment in various psychiatric disorders (Peter and Akbarian, 2011; Jakovcevski and Akbarian, 2012; Girdhar et al., 2018). SCZ patients exhibited defective expression of histone H3K4-trimethylation (H3K4me3) and GABAergic promoter subsets of genes (GAD1, GAD2, NPY, and SST) in the prefrontal cortex, all of which are strongly associated with cognitive impairment (Huang et al., 2007; Gupta et al., 2010). Similarly, mature prefrontal neurons in mice are critically dependent on the maintenance of H3K4-specific methyltransferase-regulated H3K4 methylation which play essential roles in cognition and emotion (Jakovcevski et al., 2015; Javidfar et al., 2017). Thus, GAD1-bound H3K4me3 can be viewed as a molecular link that connects three key factors in SCZ neurobiology—GABA neuronal dysfunction, developmental mechanisms, and molecular responses following antipsychotics (Mitchell et al., 2015). Postmortem brain studies have confirmed that the expression of histone deacetylase 1 (HDAC1) is increased in the prefrontal cortex of SCZ subjects, and the mRNA level of its candidate gene GAD1 is decreased (Sharma et al., 2008). Further studies of mouse models have shown that overexpression of HDAC1 in the prefrontal cortex leads to cognitive impairments such as severe impairment of working memory, increased repetitive behaviors, and abnormal motor response profiles in novel environments (Jakovcevski et al., 2013). Unlike HDAC1, PET neuroimaging and other postmortem studies have confirmed that the expression of HDAC2 is decreased in the dorsolateral prefrontal cortex of SCZ patients, which may be associated with cognitive impairment (Schroeder et al., 2017; Gilbert et al., 2019). However, in contrast to the human studies, overexpression of HDAC2 in mice reduced dendritic spine density, synaptic number, synaptic plasticity, and memory formation by inhibiting neuronal gene expression, such as NMDAR subunits (Guan et al., 2009). But anyway, it is clear that epigenetic changes in the NMDAR gene contribute to NMDAR dysfunction, which leads to synaptic dysfunction and cognitive deficits in SCZ (Bharadwaj et al., 2014; Snyder and Gao, 2020). It has been suggested that treatment with HDAC inhibitors may provide new therapeutic avenues for cognitive deficits in SCZ, either alone or in combination with existing drug therapies (Day and Sweatt, 2012; Hasan et al., 2013). In the studies of BD, investigators used HDAC-specific radioactive tracers to measure HDAC expression in BD patients. They suggested that reduced expression of HDAC may contribute to the impairment of emotional or cognitive processes in BD patients by altering neuroplasticity (Tseng et al., 2020). In ASD, loss-of-function mutations in JARID1C, an X-linked gene encoding H3K4 demethylase, may also be associated with cognitive impairment, as it regulates autism and cognitive dysfunction genes such as SCN2A, CACNA1H, BDNF, and SLC18A1 (Adegbola et al., 2008; Shen et al., 2014). In addition, social deficits in a mouse model of SHANK3-deficient autism are rescued by HDAC inhibitors and knockdown of HDAC2 in the prefrontal cortex (Qin et al., 2018). In fact, there are

numerous cognition-related histone modifications studies of SCZ and ASD, but there are still few histone studies focusing on cognitive impairment in BD and MDD, and studies of the expression of HDAC2 have been inconsistent between human and mice (Peter and Akbarian, 2011; Day and Sweatt, 2012). Reviewing the literature revealed that a decrease in the activity of HDAC2 during early synaptic development leads to a strong facilitation of excitatory synaptic maturation and a modest increase in synaptic number, in contrast, targeting deletion of HDAC2 in mature neurons impairs the maturation of newborn neurons and basal excitatory neurotransmission in the adult brain (Akhtar et al., 2009). Consequently, it is possible that either too much or too little HDAC2 expression may impair cognitive function. The potential of HDAC2 as a therapeutic target may be limited to specific types of diseases and may even be detrimental to other diseases, such as affective disorders, where the promotion of neurogenesis is indicated (Fischer et al., 2010). However, it is important to stress that, the role of target genes that modified by histone in cognitive impairment of psychiatric disorders is clearly established. Therefore, more attention needs to be paid to the expression of histone-modified target genes in the phenotype of mental cognitive impairment.

As an essential epigenetic regulator, it is gradually understood how non-coding RNA (ncRNA) promotes epigenetic processes and how this phenomenon affects cognitive function in psychiatric disorders. The therapeutic potential of non-coding RNA is that they can affect cognition by targeting a large number of genes and signaling pathways simultaneously, such as multiple pathways within a single neuron (Kocerha et al., 2015). In SCZ, researchers measured the expression of multiple miRNAs in patient serum and postmortem brain (Srivastava et al., 2021). SCZ patients with miR-137 risk alleles show more severe negative symptoms and cognitive impairment. Functional validation and prediction targets for miR-137 include multiple risk genes for cognitive impairment in SCZ, such as CACNA1C, GABRA1, GRIN2A, and HTR2C (Green et al., 2013; Wright et al., 2013). In addition, miR-219 and miR-132 regulate NMDAR signaling, which contributes to some of the neurobehavioral and cognitive impairments seen in SCZ (Kocerha et al., 2009; Miller et al., 2012; Balu et al., 2013). MiR-195 is also increased in the brains of SCZ patients and regulates several cognition-related genes, including BDNF and HTR2A (Pan et al., 2021). In the plasma from BD patients treated with lithium or valproate, which significantly modulate levels of BDNF, a key regulator of neuronal homeostasis, miR-134 is altered and manic symptoms are reduced (Rong et al., 2011). MiR-146a-5p is the strongest candidate for ASD pathology. It is not only the unique miRNA significantly upregulated in the ASD patient cohort and four different cell types, but also its target genes, such as NOTCH1, GRIA3, SYT1, NLGN1, etc., are critical for brains development and function (Mor et al., 2015; Fregeac et al., 2016; Nguyen et al., 2016). In the study of depression, some

scholars have demonstrated that the up-regulated expression level of miR-192-5p inhibits the activation of TGF- $\beta$ 1 signaling pathway by binding to Fbln2, thereby improving cognitive impairment and strengthening neurological function in the mouse model of depression (Tang et al., 2019). Overall, the role of miRNAs in cognitive impairment in psychiatric disorders is still under exploration, and similar to methylation and histone modifications, their target molecules are the focus of research. Most of the miRNA changes are directly derived from the postmortem brain and peripheral tissues of patients, reflecting the real situation in the patient's body, and it also has pleiotropic therapeutic potential. Therefore, it is promising to use miRNA as an objective diagnostic biomarker and a new therapeutic tool for cognitive impairment. However, it is precisely because miRNA has multiple targets that its diagnostic specificity in psychiatric disorders, especially cognitive disorders, remains to be determined. In addition, as a part of an epigenetic network, miRNAs may also be coordinated and regulated by other factors. In the future, we should focus far more on the understanding of ncRNA-mediated epigenetic regulation on well-defined cognitive functions, in order to improve the specificity of its diagnosis and treatment.

## Neurotransmitter deficits

The neurotransmitter system, the basis of cognitive control in humans, has been shown to be associated with a variety of psychiatric disorders. Neurotransmitters involved in cognitive impairment in psychiatric disorders include the glutamatergic system, the dopaminergic neurotransmitter system, gamma-aminobutyric acid (GABA) system, and serotonin system (Wang et al., 2019; Cieřlik et al., 2021).

Glutamate synapses transmit most of the fast excitatory neurotransmission and are one of the most critical signals controlling cognitive impairment in psychiatric disorders. Normally glutamate exerts its physiological effects through glutamate-gated ion channels (ionotropic glutamate receptors, iGluRs) and glutamate-activated G protein-coupled receptors (metabotropic glutamate receptors, mGluRs) (Volk et al., 2015). Among them, the ongoing hypofunction of glutamatergic NMDAR is considered to be a key factor of cognitive impairment (Javitt et al., 2018). In SCZ, multiple lines of evidence in pharmacological, genetic, neuroimaging, and postmortem studies support that NMDAR hypofunction may underlie the symptoms of cognitive impairment (Corlett et al., 2011; Moghaddam and Javitt, 2012; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Kort et al., 2017). Abnormalities of NMDAR-mediated neurotransmission have been implicated in behavioral, social and cognitive deficits of ASD associated with a variety of risk alleles (Liu et al., 2017; Wang et al., 2018; Deutsch et al., 2022). Positive allosteric modulators (PAMs) of NMDAR are also used

to treat cognitive deficits in SCZ and some forms of autism (Paul et al., 2013; Burnell et al., 2019). But in studies related to depression, the NMDAR antagonist Memantine improved symptoms of anhedonia and anxiety, as well as cognitive deficits associated with depression (Li et al., 2020).

The dopaminergic system, a key neurotransmitter system, are broadly implicated in psychiatric illnesses (Grace, 2016). Dopamine receptors in the brain are mainly divided into two categories with opposite roles: excitatory D1-like receptors (D1R, include D1R and D5R) and inhibitory D2-like receptors (D2R, including D2R, D3R, and D4R) (Wei et al., 2018). The traditional view of psychiatric disorders claims that positive symptoms are associated with hyperdopaminergic activity and mediated by D2R, while deficits in D1R-mediated dopamine activity are responsible for negative symptoms and cognitive impairment (Lindenmayer et al., 2013; Locke et al., 2018). Therefore, D1R agonists are used to improving cognitive impairment, such as the development of agonists for functionally selective D1 ligands and positive allosteric modulators of D1R (Arnsten et al., 2017; Desai et al., 2021; Abi-Dargham et al., 2022). D2R have also received considerable attention in recent years as regulators of cognitive impairment. Dopamine D3R plays a functional role in performing new object recognition tasks through GSK3 $\beta$  signaling in medial prefrontal cortex. Therefore, D3 R antagonist therapy may be a reasonable method to improve cognitive impairment or episodic memory deficit in BD patients (Chang et al., 2020). In the treatment of SCZ, a highly potent preferential D3 antagonist, F17464, is also being developed, which can significantly improve cognitive function (Bitter et al., 2019). Moreover, recent studies prove that stress exposure in dopamine D4R knockout mice induced significant deficits in SCZ-like behaviors, such as sensorimotor gating, cognitive processes, social engagement, and exploratory behavior, by disrupting GABAergic transmission (Tan et al., 2019).

GABA is a major inhibitory neurotransmitter in the mammalian brain. Dysregulated GABA interneuron activity disrupts the excitatory/inhibitory (E/I) balance in the cortex, which may represent the core pathophysiology of cognitive dysfunction in SCZ, mainly includes the following three aspects (Xu and Wong, 2018). First, reduced expression of parvalbumin (PV) and GAD67 has been found to be associated with altered GABA transmission in SCZ (Lewis et al., 2012; Lewis, 2014; Kim et al., 2016). Second, deficits in GABA inhibitory circuits lead to impaired neural oscillations in SCZ (Lewis et al., 2008; Uhlhaas and Singer, 2010; Chen et al., 2014). Third, alterations in other GABA genes related to GABA neurotransmission, such as GABA transporter type 1 (GAT-1) and NMDA receptor subunits (e.g., NR2A and NR3A) (Scheggia et al., 2018; Xu and Wong, 2018). Similarly, evidence from anatomy, as well as from human and rodent genetics, physiology, and behavior demonstrate that altered balance in E/I is often referred to as a possible ultimate common pathway

in autism (Selimbeyoglu et al., 2017). Decreased number of PV neurons, decreased expression of mRNA encoding receptors for the inhibitory neurotransmitter GABA, and decreased ratio of GABA to glutamate have also been observed in autism patients and in mouse models (Chao et al., 2010; Fatemi et al., 2010; Alabdali et al., 2014; Hashemi et al., 2017). Moreover, changes in GABAergic neuropathology, such as RELN and GAD67, have been detected in the hippocampus and cortex in the brains of patients with BD (Fatemi et al., 2000; Guidotti et al., 2000; Veldic et al., 2007). Decreased GABA levels in the prefrontal cortex, anterior cingulate cortex, cerebrospinal fluid, and plasma have also been demonstrated in studies of major depression (Klempner et al., 2009; Levinson et al., 2010; Northoff and Sibille, 2014; Fee et al., 2017). In conclusion, given the importance of the GABA system in cognitive impairment in psychiatric disorders, it has emerged as a potential target for new pharmacological interventions. Currently,  $\alpha 5/\alpha 3/\alpha 2$  GABA<sub>A</sub> and GABA<sub>B</sub>-mediated pharmacologically modulated receptors have been shown to restore E/I imbalance and cognitive deficits in SCZ patients, and other antagonists, positive and negative allosteric modulators (including dual allosteric modulators), GAT-1 inhibitors, etc., have shown promise in animal preclinical studies (Rudolph and Möhler, 2014; Xu and Wong, 2018; Zafar and Jabeen, 2018). Recent ideas suggest that dual allosteric modulators can reduce the dose required to achieve optimal therapeutic effect, reduce side effects caused by individual drugs, and enhance pro-cognitive effects (Xu and Wong, 2018). Therefore, intentional targeting of multiple receptors may be a promising strategy for improving pharmacological treatment of cognitive impairment in schizophrenia and other neuropsychiatric disorders.

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter that regulates central and peripheral functions and is involved in emotional and appetite regulation, cognition and memory (Meneses, 1999). Increased 5-HT signaling is thought to be associated with SCZ and ASD (Sumiyoshi et al., 1996; Selvaraj et al., 2014; Chen et al., 2017), while decreased 5-HT signaling is thought to be associated with MDD and BD (Lemondé et al., 2003; Albert and Lemondé, 2004). Partial antipsychotic agonists and antagonists targeting the 5-HT 2A receptor and the 5-HT<sub>6</sub> receptor have shown some beneficial antipsychotic and pro-cognitive effects in SCZ and ASD (Meltzer et al., 2003; Amodeo et al., 2014; de Bruin and Kruse, 2015; Fung et al., 2016; Keefe et al., 2018; Yamazaki et al., 2018). Selective serotonin reuptake inhibitors (SSRIs) are novel types of antidepressants, which can inhibit the reuptake of serotonin at synapses, thereby increasing the content of serotonin in the brain and improving cognitive function in patients with MDD, especially vortioxetine, which also modulates 5-HT receptors (Frampton, 2016; Liu L. et al., 2021). In addition to these systems, the cholinergic system is also used to find and develop treatments for cognitive impairment in SCZ. Still, the precise nature of the cholinergic disorder

in patients and its impact on cognitive functions, including attention, is poorly understood to date (Sarter et al., 2012; Santos et al., 2018; Recio-Barbero et al., 2021).

The above studies and summaries show that different neurotransmitter systems play different roles in cognitive impairment. Detailed neurotransmitter systems associated with cognitive impairment in psychiatric disorders was summarized in **Supplementary Table 1**. Currently, the main specific use of the glutamate system in SCZ-related cognitive impairment is represented by the Glycine transporter-1 (GlyT1) inhibitor BI 425809, which enhances NMDAR function through GlyT1 inhibitor and has been granted breakthrough therapy designation by the US Food and Drug Administration (Fleischhacker et al., 2021; Veselinović and Neuner, 2022). In addition, Vortioxetine, the 5-HT system drug, is an FDA-approved multimodal antidepressant that uniquely improves cognitive impairment associated with major depression (Liu L. et al., 2021). Cognitive impairment compounds targeting other systems are still in preclinical animal studies or late development, requiring large samples and long-term individualized studies to obtain effective strategies.

## Proinflammatory cytokines and neurotrophins

Peripheral blood derived biomarkers, which are combined with easy and minimally invasive accessibility, provide a more acceptable and inexpensive option for the diagnosis, monitoring and prognosis of cognitive impairment in mental diseases in recent years. As the representative molecules of inflammation, interleukin-6 (IL-6), IL-1 $\beta$ , tumor necrosis factor alpha (TNF- $\alpha$ ), and C-reactive protein (CRP) in peripheral blood of patients with SCZ, BD, ASD, and MDD have received considerable attention.

IL-6 and TNF- $\alpha$  in SCZ are reported to be positively correlated with poor cognitive performance in most studies, and are often used to evaluate the efficacy of pro-cognitive compounds (Frydecka et al., 2015; Kogan et al., 2018; Zhang et al., 2019; Zhu et al., 2019; King et al., 2021; Adamowicz et al., 2022). The neurocognitive role of IL-6 in SCZ may be due to its ability to alter the survival and transmission of catecholaminergic, serotonergic, and dopaminergic neurons in the hippocampus and prefrontal cortex (Zalcman et al., 1994; Frydecka et al., 2015). There is also evidence that IL-6 increases choroid plexus volume, thinning gray matter and shrinking amygdala, changes that may ultimately lead to cognitive decline (Lizano et al., 2019). Similar studies have shown that high levels of IL-6 in BD, MDD, and ASD exhibit symptoms of neurocognitive deficits, such as impaired sustained attention and orientation and short-term memory (Wei et al., 2011; Barbosa et al., 2018; Jin et al., 2020; Nie et al., 2021).

TNF- $\alpha$  plays a vital role in brain development as it regulates synaptic pruning and plasticity in preadolescence, adolescence, and early adulthood, mediating neuronal homeostasis and dysfunctional signaling (Stellwagen and Malenka, 2006; Park and Bowers, 2010). Studies have shown that levels of soluble tumor necrosis factor receptor 2 (sTNFR2) in plasma are associated with hippocampal volume and cognitive performance in SCZ (Kudo et al., 2018). Other studies have reported TNF variables during the neural progression of BD, suggesting that circulating levels of TNF molecules partially mediate the relationship between prior severe mood episodes and executive functioning in BD, and may serve as novel cognitive interventions (Millett et al., 2020; Zazula et al., 2022). Circadian dysregulation in ASD is strongly associated with elevated TNF levels and immune-inflammatory activity, leading to sleep disturbances and cognitive and behavioral changes (da Silveira Cruz-Machado et al., 2021). TNF- $\alpha$  antagonism has provided encouraging findings in improving depressive symptoms in chronic inflammatory diseases, but direct studies of TNF- $\alpha$  in cognitive impairment in MDD are lacking (Bortolato et al., 2015). Therefore, we still need to tap into the cognitive potential targets in people with primary depression.

The researches of IL-1 $\beta$  and CRP of cognitive impairment in psychiatric disorders is still controversial. Studies have shown that IL-1 $\beta$  may also be a state marker of acute exacerbation in SCZ (Miller et al., 2011). In addition, peripheral IL-1 $\beta$  mRNA levels were found to be negatively correlated with verbal fluency and Broca's area volume in patients with SCZ, and this study linked inflammatory blood biomarkers to cognitive deficits and reduced brain volume in SCZ patients (Fillman et al., 2016). However, other studies have suggested that peripheral IL-1 $\beta$  has no effect on neurocognitive and daily functioning in patients with SCZ (Kogan et al., 2018). In studies of patients hospitalized for bipolar depressive episodes, higher levels of IL-1 $\beta$  were associated with decreased cognitive performance (Poletti et al., 2021). The negative correlation between IL-1 $\beta$  level and overall cognitive function was also observed in MDD patients (Jin et al., 2020).

C-reactive protein is an extensively studied inflammatory biomarker. Some studies suggest that the level of serum high sensitivity C-reactive protein (hs-CRP) is positively correlated with cognitive impairment in patients with SCZ, such as executive function and processing speed, and may represent an objective biological indicator for rapid assessment of cognitive impairment in patients with SCZ (Misiak et al., 2018; Bora, 2019; Zhu et al., 2019; Adamowicz et al., 2022). However, contrary views suggest that hs-CRP is not associated with cognitive impairment, and that higher hs-CRP levels in SCZ may be associated with female and more severe negative symptoms (Joseph et al., 2015). In studies of BD, elevated levels of CRP inflammation may be associated with a broad range of cognitive deficits in patients, and researches have also identified CRP

as a significant positive predictor of proxy cognitive decline (Dickerson et al., 2013; Millett et al., 2021).

Neurotrophins, particularly BDNF and nerve growth factor (NGF), are another type of cytokines associated with cognitive impairment in psychiatric disorders. BDNF and NGF regulate neuronal survival and growth, and affects synaptic efficiency and plasticity (Sofroniew et al., 2001; Park and Poo, 2013). Although several studies have confirmed that BDNF and NGF are expressed at lower levels in peripheral blood of patients with SCZ, MDD, and BD, their association with cognitive impairment remains controversial (Green et al., 2011; Qin et al., 2017; Rao et al., 2017). Some suggest that reduced BDNF levels do not play a major role in the cognitive dysfunction of most SCZ and BD patients (Dias et al., 2009; Bora, 2019). However, recent studies have shown that low serum BDNF levels are associated with cognitive impairment in patients with first-episode and chronic SCZ and non-medicated patients with current depressive episodes of BD II and MDD (Yang et al., 2019; Teng et al., 2021).

Other reported inflammatory biomarker complexes most associated with SCZ cognition include intercellular adhesion molecule-1 and serum amyloid protein (Adamowicz et al., 2022). Inflammatory chemokines associated with cognitive deficits in BD patients include CCL2, CCL4, CCL5, CXCL10, and basic fibroblast growth factor (bFGF) (Poletti et al., 2021).

We note that a recent systematic review and meta-analysis of immune markers in surface blood showed only weak associations with perceptions of mood and psychiatric disorders (SCZ, BD, and MDD), the investigators consider that the observed significant publication and reporting bias is likely to underlie such association inflation in individual studies (Morrens et al., 2022). However, we cannot completely deny the role of peripheral cytokine markers. **Table 1** summarizes the key proinflammatory cytokines and neurotrophins associated with cognitive impairment in psychiatric disorders. The number of inflammatory cytokines is indeed associated with an increased risk of psychosis, most notably IL-1 $\beta$ , IL-6, TNF- $\alpha$ , CRP, and BDNF, although the current literature remains inconsistent (Kogan et al., 2020). More detailed assessments and advanced detection methods are still needed to exploit the value of peripheral biomarkers in future clinical applications.

## Metabolism and microbiome-gut-brain axis

Of note, a growing body of evidence in recent years has indicated that metabolic mechanisms have been linked to learning and memory, mental and emotional health, and neuropsychiatric disorders (Sánchez-Ortí et al., 2022). Several common aspects have been implicated, including glucose metabolism, lipid metabolism, and microbiome-gut-brain axis.



TABLE 1 Peripheral inflammatory factors and neurotrophic factors associated with cognitive impairment in psychiatric disorders.

Cytokines	Description	Disease	References
IL-6	The neurocognitive role of IL-6 in SCZ may be due to its ability to alter the survival and transmission of catecholaminergic, serotonergic, and dopaminergic neurons in the hippocampus and prefrontal cortex	BD, MDD, and ASD	Zalcman et al., 1994; Wei et al., 2011; Frydecka et al., 2015; Barbosa et al., 2018; Jin et al., 2020; Nie et al., 2021
TNF- $\alpha$	Levels of sTNFR2 in plasma are associated with hippocampal volume and cognitive performance	SCZ, BD, and ASD	Kudo et al., 2018; Millett et al., 2020; da Silveira Cruz-Machado et al., 2021; Zazula et al., 2022
IL-1 $\beta$	Peripheral IL-1 $\beta$ mRNA levels were found to be negatively correlated with verbal fluency and Broca's area volume	SCZ and BD	Fillman et al., 2016; Poletti et al., 2021
CRP	The level of serum hs-CRP is positively correlated with cognitive impairment such as executive function and processing speed	SCZ and BD	Misiak et al., 2018; Bora, 2019; Zhu et al., 2019; Adamowicz et al., 2022
BDNF and NGF	BDNF and NGF regulate neuronal survival and growth, and affects synaptic efficiency and plasticity	SCZ, BD, and MDD	Sofroniew et al., 2001; Park and Poo, 2013; Yang et al., 2019; Teng et al., 2021
Intercellular adhesion molecule-1 and serum amyloid protein	They are best correlated with scores on cognitive testing	SCZ	Adamowicz et al., 2022
IL-1 $\beta$ , IL-6, CCL2, CCL4, CCL5, CXCL-10, and bFGF	Higher levels of IL-1 $\beta$ , IL-6, CCL2, CCL4, CCL5, CXCL10, and bFGF are associated with the likelihood of having a poor cognitive performance	BD	Poletti et al., 2021

A study of glucose disorders, cognitive deficits, and white matter abnormalities in first-episode drug-free SCZ has raised strong concerns, suggesting that the interaction between abnormal glucose metabolism and white matter disconnectivity may contribute to cognitive impairment (Zhang X. et al., 2020). In the same year, the role of glycosylation in SCZ was revealed by GWAS (Mealer et al., 2020). Other researchers have also highlighted that proteins involved in excitatory and inhibitory neurotransmission show altered glycan effects in disease states, including  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) and kainate receptor subunits, glutamate transporters excitatory amino acid transporters 1 and 2, and  $\gamma$ -aminobutyric acid A (GABAA) receptors, etc. (Williams et al., 2020). Indeed, two meta-analysis have shown evidence of a significant relationship between cognitive impairment in SCZ and each component of the metabolic syndrome, including hypertension, dyslipidemia, abdominal obesity, and diabetes (Bora et al., 2017; Hagi et al., 2021). Cognitive dysfunction in SCZ may also be associated with central insulin deficits, which involve the regulation of dopamine, glucose metabolism and feeding, and exercise or pharmacological interventions to improve insulin sensitivity may be one way to address cognitive deficits in SCZ (Li et al., 2014; Agarwal et al., 2020). Impaired frontolimbic circuits are associated with significantly reduced glucose uptake, which may account for reduced executive function in BD-I patients during remission (Li et al., 2012). In addition, insulin resistance was significantly associated with verbal memory performance in remitting BD participants without diabetes, even after controlling for other relevant metabolic or therapeutic variables (Salvi et al., 2020). Recent studies also suggest that elevated levels of fasting blood glucose and triglyceride

may be associated with cognitive dysfunction in BD patients. Improving glucose and lipid metabolism in BD patients may help improve some specific areas of cognitive function (Qiu et al., 2022). In ASD subjects, the rate of glucose metabolism in parietal, prefrontal motor and eye areas and amygdala was decreased, which may be related to cognitive tasks (Mitelman et al., 2018). A study of the relationship between insulin resistance and cognition in patients with depression found that higher steady-state plasma glucose was associated with poorer cognitive flexibility in young adults (Wroolie et al., 2015).

Many studies have attempted to clarify the association between cognitive impairment and lipid metabolism in psychiatric disorders. An interesting study found that specific erythrocyte membrane lipid clusters are associated with clinical and cognitive manifestations of dopamine dysfunction in SCZ and hypothesized that this membrane lipid abnormality affects presynaptic dopamine signaling (Tessier et al., 2016). Polyunsaturated fatty acids (PUFA), especially  $\omega$ -3PUFAs, have also been described as important modulators that affect brain resilience and thus central nervous system function (Wysoczański et al., 2016).  $\omega$ -3PUFAs can ameliorate cognitive impairment by upregulating BDNF in SCZ to repair neuronal damage (Guo et al., 2020; Tang et al., 2020). In patients with BD and SCZ, alterations of apolipoprotein C, which affects lipid metabolism and utilization, result in a decline in cognitive performance and hippocampal volume (Knöchel et al., 2017). Studies of BD have also shown that reduced high-density lipoprotein and elevated triglycerides (TG) levels are associated with cognitive deficits, especially in the immediate memory, language domains and executive functioning in BD patients (Hui et al., 2019; Van Rheenen et al., 2021). Consistently, high

serum TG levels showed poor cognitive function in MDD, especially in memory delay (Shao et al., 2017; Guan et al., 2021).

The gut microbiome is a complex microbial ecosystem that has been clearly shown to influence host psychological, emotional, and cognitive functions through various neurophysiological aspects of synaptic plasticity, and may be a key regulator of neural development of the microbiome-gut-brain axis (Rogers et al., 2016; Glinert et al., 2022). Fecal transfer of gut microbiota from SCZ patients has been reported to induce SCZ-related behaviors in germ-free recipient mice, accompanied by alterations in levels of glutamate, glutamine and GABA in the hippocampus (Zheng et al., 2019). Further studies of the metagenome-wide association of gut microbiome features for SCZ identified 27 gut-brain modules, whose bacterial functional potentials include differences in short-chain fatty acid synthesis, tryptophan metabolism, and neurotransmitter synthesis/degradation. In addition, transplanting SCZ-enriched bacterium, *Streptococcus vestibularis*, appears to lead to social behavioral deficits and alter neurotransmitter levels in peripheral tissues in the recipient mice (Zhu et al., 2020). It has also been found that BD-related microbiota, such as *Citrobacter* spp. and *Phascolarctobacterium* spp., can synthesize corresponding neuroactive metabolites, which are potential markers associated with hallmarks of functional connectivity in brain networks, and imply abnormal cognitive function, emotion regulation, and interoception (Li et al., 2022). In studies of ASD, when gut microbiota from human donors with ASD were transplanted into germ-free mice, their brains showed alternative splicing of ASD-related genes that induced signature autistic behaviors. The researchers also treated a mouse model of ASD with candidate microbial metabolites and found that the behavioral abnormalities were improved and neuronal excitability were modulated in the mice (Sharon et al., 2019). Interestingly, a new research suggests that autism-related dietary preferences mediate the autism-gut microbiome association, rather than the microbiome driving ASD (Yap et al., 2021). Studies on MDD have shown that the increase of some proinflammatory bacteria and the decrease of some anti-inflammatory bacteria in patients are related to inflammatory factors (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) and cognitive function, and intestinal microbiota may be responsible for cognitive impairment in patients with MDD (Liu P. et al., 2021).

On the whole, the importance of metabolic syndrome, including obesity, overweight, hypertension, dyslipidemia and insulin resistance, and the microbiome-gut brain-axis in cognitive impairment is gradually being recognized. Researchers have proposed four main therapeutic strategies based on these: wild-type and transgenic probiotics, fecal microbiota transplantation, physical exercise, and a high-fiber diet, and link these therapies to inflammation reduction. These strategies

have the potential to be one of the most important areas in the treatment prospects of cognitive impairment in mental illness (Sun et al., 2020).

## Stem cell therapies

As a therapeutic tool for regenerative medicine, stem cells provide new insights into the treatment of neuropsychiatric disorders and cognitive deficits. Common sources include induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs), which are considered suitable types for transplantation into various animal models with neuropsychopathology and cognitive disorders (Zhang Y. et al., 2020).

Reprogrammed iPSCs from patient-derived somatic cells contribute significantly to recapitulating the development of neuronal cells with disease-specific genetic backgrounds (Soliman et al., 2017). Modeling techniques for inducing disease in iPSCs, including directed differentiation of neuronal subtypes, glial cells, and 3D brain organoid models, are handy for modeling how complex genetic variation leads to disease pathogenesis (Wang et al., 2020; Whiteley et al., 2022). The researchers directly reprogrammed human induced pluripotent stem cells iPSCs from SCZ patients, and then differentiated these disease-specific iPSCs into neurons. SCZ iPSCs neurons showed decreased neuronal connectivity, which was associated with decreased neurite number, PSD95 protein level, and glutamate receptor expression. They also evaluated several antipsychotics on neuronal cultures derived from iPSCs from SCZ patients to assess their ability to rescue neuronal connectivity deficits and other phenotypes found in SCZ neurons (Brennan et al., 2011). In studies of iPSCs-derived brain organoids in SCZ, brain organoids from SCZ patients showed aberrant gene expression in pathways involved in synaptic biology, neurological development, immune responses, and mitochondrial function, as well as specific defects in mitochondrial physiology and diminished responses to stimulation and depolarization (Kathuria et al., 2020a). Similar studies in brain organoids from BD patients have shown abnormalities in the regulation of genes involved in cell adhesion, immune signaling, and ER biology, as well as evidence of defects in neurotransmission (Kathuria et al., 2020b). iPSCs-derived neurons from patients with Rett syndrome (a genetic model of ASD) also exhibit morphological abnormalities, such as fewer synapses, reduced spine density, smaller somatic cell size, altered calcium signaling, and electrophysiological defects, which may be related to GABA dysfunction (Marchetto et al., 2010). Serotonin neurons are dysregulated in depression and are commonly targeted by antidepressants. What is more exciting, two independent research groups have now greatly advanced iPSC research by generating serotonergic neurons that can be studied *in vitro*, thus potentially bringing them into cognitive

impairment studies of depression (O'Shea and McInnis, 2016; Vadodaria et al., 2016; Xu et al., 2016).

Mesenchymal stem cells are one of the most promising stem cell types in therapeutic strategies due to their potent immunomodulatory activity and paracrine regeneration mechanism making them relevant to various diseases related to inflammation and tissue damage (Liu et al., 2019). Intranasal administration of MSC-derived exosomes improved the disruption of social interaction and prepulse inhibition in phencyclidine treated mice by maintaining the viability of GABA-producing neurons, thus significantly attenuating SCZ-like behavior (Tsivion-Visbord et al., 2020). Human umbilical cord MSCs can induce the regulation and production of T peripheral anti-inflammatory cytokine IL-10 and attenuate SCZ related social deficit behaviors in amphetamine-sensitized mice (You et al., 2020). In addition, intraventricular transplantation of bone marrow MSCs also enhanced hippocampal neurogenesis in a mouse model of ketamine-induced neurodevelopment of SCZ, thereby improving social novelty preference (Gobshtis et al., 2021). MSCs have also demonstrated therapeutic potential for immune dysfunction in the pathogenesis of ASD (Liu et al., 2019). In mouse studies with ASD, MSCs transplantation reduced stereotypic behavior, cognitive rigidity, and improved social behavior by increasing hippocampal BDNF protein levels and neurogenesis (Segal-Gavish et al., 2016; Perets et al., 2017). ASD mice treated with intranasal administration of the medicinal MSCs-exosome showed significant improvements in social domains, ultrasonic communication, and repetitive behaviors (Perets et al., 2018). Multiple clinical trials have reported favorable safety and efficacy of MSCs transplantation in children with ASD, including improvements in social relationships and reciprocity, emotional reactivity, speech, language, communication, behavioral patterns, sensory aspects, and cognition (Lv et al., 2013; Sharma et al., 2013). Moreover, the combination of cord blood-MSCs and cord blood monocytes also significantly improved the symptom severity of ASD (Lv et al., 2013). Studies have also shown that adipose-derived MSCs protect mice from chronic mild stress-induced depression-like behaviors by modulating Nrf2/HO-1 and TLR4/NF- $\kappa$ B signaling pathways, therefore, the role of MSCs in the treatment of cognitive impairment in MDD is also anticipated (Huang et al., 2020).

Neural stem cells are known to be essential for brain development and postnatal maintenance of neurogenesis in specific brain regions (Bertolini et al., 2019). Studies from NSCs in the biological chemical purification the transcriptional regulatory factors observed that transcription regulatory factors associated with ASD or SCZ are part of the neural stem cell transcriptional network. The network of transcription factor protein mutations is associated with mental disorders, including low IQ, suggesting that shared transcription network damage level is associated with cognitive dysfunction (Moen et al., 2017).

These studies demonstrate that these three types of stem cells have broad clinical application prospects. iPSCs technology offers new opportunities to mimic disease-related nerve cells from patients (Wang et al., 2020). MSCs and their exosomes, including miRNA, nutrient factors, enzymes and immune regulation derived from them, have shown advantages in the treatment of cognitive disorders (Harrell et al., 2021). The severity of mutations in NSCs-associated transcription factors network proteins highlights a close correlation with the level of cognitive dysfunction (Moen et al., 2017). However, paradoxically, the effectiveness and safety of stem cells almost simultaneously exist, which is a dilemma we must face. These concerns make the clinical application of stem cells limited by safety and ethical issues. Even more exciting for us, with innovations in stem cell disease modeling methods, and precise disease-specific therapeutic doses, regimens, and pathways, new technologies pave the way for future personalized medicine research on stem cells and more effective drug discovery processes in cognitive disorders (Whiteley et al., 2022).

## Conclusion

In this review, we discuss in detail the mechanisms of cognitive impairment in psychiatric disorders including SCZ, BD, ASD, and MDD. An overview of this review is shown in **Figure 1**. (i) Genetics relies on variation and allele frequency data to infer essential risk genes and population genetic analyses for cognitive function; (ii) Epigenetics complements the mechanistic link between environmental exposures and the expression profiles of genes in cognitive impairment; (iii) Defects and imbalances in neurotransmitter systems underlie cognitive impairment in most psychiatric disorders; (iv) Peripheral inflammatory factors and neurotrophic factors are key biomarkers of cognitive impairment in psychiatric disorders; (v) The metabolism and microbial gut-brain axis are critical bidirectional communication systems in cognitive impairment in psychiatric disorders; and (vi) Stem cells provide an efficient *in vitro* modeling and therapeutic approach for the mechanism research of cognitive impairment in mental illness.

Although we have discussed the molecular mechanisms of cognitive impairment in several different ways, they are not completely separate. In fact, the different signals may interact with each other, which contributes to the cognitive impairment of mental illness. Defects in various neurotransmitters and abnormal expression of cytokines constitute the effector molecules and basis of cognitive phenotype. Significant neurotransmitters include NMDAR, dopamine receptors, GABA, and 5-HT (Wang et al., 2019; Cieřlik et al., 2021). Common cytokines include IL-1 $\beta$ , IL-6, TNF- $\alpha$ , CRP, BDNF, and NGF (Park and Poo, 2013; Kogan et al., 2020). Genetics have identified certain susceptibility loci, including neurotransmitter (e.g., NMDA and NMDAR)

and cytokine-related genes (e.g., NRG3), to be significantly associated with cognitive impairment (Ohi et al., 2015; Greenwood et al., 2019). Epigenetics and genetics cooperate to control genome activity in cognitive disorders. Both the target genes of DNA methylation, histone modification, and non-coding RNAs are also various neurotransmitters and cytokines. The genes of cognitive impairment modified by DNA methylation include GAD1, BDNF, DRD3, DRD4, and 5HTR1A (Dong et al., 2005; Carrard et al., 2011; Chen et al., 2014; Dai et al., 2014). The genes of cognitive impairment modified by histone include GAD1, GAD2, NMDAR, CACNA1H, and BDNF (Huang et al., 2007; Adegbola et al., 2008; Snyder and Gao, 2020). The genes of cognitive impairment regulated by non-coding RNAs include GRIN2A, BDNF, HTR2A, and NMDAR (Balu et al., 2013; Wright et al., 2013; Pan et al., 2021). Moreover, metabolism and microbiome-gut-brain axis link gut and brain activities, and they function through various neurotransmitters and cytokines as well, such as GABA, IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (Zheng et al., 2019; Liu P. et al., 2021). Stem cells provided a valuable tool for modeling techniques and potential therapeutic applications (Zhang Y. et al., 2020). They can ameliorate cognitive impairment through paracrine or immunomodulatory effects, and their effector molecules are also neurotransmitters and cytokines, such as GABA, IL-10, and BDNF (Perets et al., 2017; Tsivion-Visbord et al., 2020; You et al., 2020). These mechanisms involve multiple processes of gene expression and regulation, from gene level, transcriptional level, post-transcriptional level to actual expression *in vivo*. In summary, our review provides some kind of complete and dynamic approach to the analysis of the cognitive impairment phenotype of psychiatric disorders.

The specific strengths and weaknesses of each mechanism for diagnosing, treating, and preventing cognitive impairment in mental illness are also reviewed in each section. Based on the current review, we conclude that genetics, epigenetics, and neurotransmitter systems, inflammatory factors, and neurotrophic factors seem to be the more reliable diagnostic basis for cognitive impairment in psychiatric disorders. Moreover, the neurotransmitter system, metabolic and microbial gut-brain axis, and stem cells may be effective targets and tools for the treatment and prevention of cognitive impairment in psychiatric disorders.

## References

- Abdolmaleky, H. M., Nohesara, S., Ghadirivasfi, M., Lambert, A. W., Ahmadkhaniha, H., Ozturk, S., et al. (2014). DNA hypermethylation of serotonin transporter gene promoter in drug naïve patients with schizophrenia. *Schizophr. Res.* 152, 373–380. doi: 10.1016/j.schres.2013.12.007
- Abi-Dargham, A., Javitch, J. A., Slifstein, M., Anticevic, A., Calkins, M. E., Cho, Y. T., et al. (2022). Dopamine D1R receptor stimulation as a mechanistic

pro-cognitive target for schizophrenia. *Schizophr. Bull.* 48, 199–210. doi: 10.1093/schbul/sbab095

Adamowicz, D. H., Shilling, P. D., Palmer, B. W., Nguyen, T. T., Wang, E., Liu, C., et al. (2022). Associations between inflammatory marker profiles and neurocognitive functioning in people with schizophrenia and non-psychiatric comparison subjects. *J. Psychiatr. Res.* 149, 106–113. doi: 10.1016/j.jpsychires.2022.02.029

Finally, the shortcomings mentioned above in the diagnosis, treatment, and prevention mechanisms remain challenges and opportunities that we will continue to face in the future. With rapid advancements in genomics, molecular biology, materials science, innovative technologies, and research methods, biomarkers for various cognitive impairment mechanisms in psychiatric disorders will have great potential for accuracy, sensitivity, and specificity for future diagnosis and treatment.

## Author contributions

YW and WM wrote the first draft of the manuscript. ZL searched the references and revised the manuscript. QA and XH designed the outline and approved the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fncel.2022.1046692/full#supplementary-material>

- Adegbola, A., Gao, H., Sommer, S., and Browning, M. (2008). A novel mutation in JARID1C/SMCX in a patient with autism spectrum disorder (ASD). *Am. J. Med. Genet. A* 146A, 505–511. doi: 10.1002/ajmg.a.32142
- Agarwal, S. M., Caravaggio, F., Costa-Dookhan, K. A., Castellani, L., Kowalchuk, C., Asgariroozbehani, R., et al. (2020). Brain insulin action in schizophrenia: Something borrowed and something new. *Neuropharmacology* 163:107633. doi: 10.1016/j.neuropharm.2019.05.010
- Akbarian, S., Liu, C., Knowles, J. A., Vaccarino, F. M., Farnham, P. J., Crawford, G. E., et al. (2015). The PsychENCODE project. *Nat. Neurosci.* 18, 1707–1712. doi: 10.1038/nn.4156
- Akhtar, M. W., Raingo, J., Nelson, E. D., Montgomery, R. L., Olson, E. N., Kavalali, E. T., et al. (2009). Histone deacetylases 1 and 2 form a developmental switch that controls excitatory synapse maturation and function. *J. Neurosci.* 29, 8288–8297. doi: 10.1523/jneurosci.0097-09.2009
- Alabdali, A., Al-Ayadhi, L., and El-Ansary, A. (2014). Association of social and cognitive impairment and biomarkers in autism spectrum disorders. *J. Neuroinflammation* 11:4. doi: 10.1186/1742-2094-11-4
- Albert, P. R., and Lemonde, S. (2004). 5-HT1A receptors, gene repression, and depression: Guilt by association. *Neuroscientist* 10, 575–593. doi: 10.1177/107385404267382
- Amodeo, D. A., Jones, J. H., Sweeney, J. A., and Ragozzino, M. E. (2014). Risperidone and the 5-HT2A receptor antagonist M100907 improve probabilistic reversal learning in BTBR T + tf/J mice. *Autism Res.* 7, 555–567. doi: 10.1002/aur.1395
- Arnstén, A. F., Girgis, R. R., Gray, D. L., and Mailman, R. B. (2017). Novel dopamine therapeutics for cognitive deficits in schizophrenia. *Biol. Psychiatry* 81, 67–77. doi: 10.1016/j.biopsych.2015.12.028
- Balu, D. T., Li, Y., Puhl, M. D., Benneyworth, M. A., Basu, A. C., Takagi, S., et al. (2013). Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction. *Proc. Natl. Acad. Sci. U.S.A.* 110:E2400–E2409. doi: 10.1073/pnas.1304308110
- Barbosa, I. G., Ferreira, R. A., Rocha, N. P., Mol, G. C., da Mata Chiacchio Leite, F., Bauer, I. E., et al. (2018). Predictors of cognitive performance in bipolar disorder: The role of educational degree and inflammatory markers. *J. Psychiatr. Res.* 106, 31–37. doi: 10.1016/j.jpsychires.2018.09.003
- Bertolini, J. A., Favaro, R., Zhu, Y., Pagin, M., Ngan, C. Y., Wong, C. H., et al. (2019). Mapping the global chromatin connectivity network for sox2 function in neural stem cell maintenance. *Cell Stem Cell* 24, 462–476.e6. doi: 10.1016/j.stem.2019.02.004
- Bharadwaj, R., Peter, C. J., Jiang, Y., Roussos, P., Vogel-Ciernia, A., Shen, E. Y., et al. (2014). Conserved higher-order chromatin regulates NMDA receptor gene expression and cognition. *Neuron* 84, 997–1008. doi: 10.1016/j.neuron.2014.10.032
- Bitter, I., Lieberman, J. A., Gaudoux, F., Sokoloff, P., Groc, M., Chavda, R., et al. (2019). Randomized, double-blind, placebo-controlled study of F17464, a preferential D(3) antagonist, in the treatment of acute exacerbation of schizophrenia. *Neuropsychopharmacology* 44, 1917–1924. doi: 10.1038/s41386-019-0355-2
- Bora, E. (2019). Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: A meta-analysis. *Psychol. Med.* 49, 1971–1979. doi: 10.1017/S0033291719001685
- Bora, E., Akdede, B. B., and Alptekin, K. (2017). The relationship between cognitive impairment in schizophrenia and metabolic syndrome: A systematic review and meta-analysis. *Psychol. Med.* 47, 1030–1040. doi: 10.1017/S0033291716003366
- Bortolato, B., Carvalho, A. F., Soczynska, J. K., Perini, G. I., and McIntyre, R. S. (2015). The involvement of TNF- $\alpha$  in cognitive dysfunction associated with major depressive disorder: An opportunity for domain specific treatments. *Curr. Neuropharmacol.* 13, 558–576. doi: 10.2174/1570159x13666150630171433
- Bouille, F., Van Den Hove, D. L., Jakob, S. B., Rutten, B. P., Hamon, M., Van Os, J., et al. (2012). Epigenetic regulation of the BDNF gene: Implications for psychiatric disorders. *Mol. Psychiatry* 17, 584–596. doi: 10.1038/mp.2011.107
- Brennan, K. J., Simone, A., Jou, J., Gelboin-Burkhart, C., Tran, N., Sangar, S., et al. (2011). Modelling schizophrenia using human induced pluripotent stem cells. *Nature* 473, 221–225. doi: 10.1038/nature09915
- Burnell, E. S., Irvine, M., Fang, G., Sapkota, K., Jane, D. E., and Monaghan, D. T. (2019). Positive and Negative Allosteric Modulators of N-Methyl-d-aspartate (n.d.) Receptors: Structure-Activity Relationships and Mechanisms of Action. *J. Med. Chem.* 62, 3–23. doi: 10.1021/acs.jmedchem.7b01640
- Carrard, A., Salzmann, A., Malafosse, A., and Karege, F. (2011). Increased DNA methylation status of the serotonin receptor 5HT1A gene promoter in schizophrenia and bipolar disorder. *J. Affect. Disord.* 132, 450–453. doi: 10.1016/j.jad.2011.03.018
- Chang, P.-K., Chu, J., Tsai, Y.-T., Lai, Y.-H., and Chen, J.-C. (2020). Dopamine D3 receptor and GSK3 $\beta$  signaling mediate deficits in novel object recognition memory within dopamine transporter knockdown mice. *J. Biomed. Sci.* 27:16. doi: 10.1186/s12929-019-0613-y
- Chao, H. T., Chen, H., Samaco, R. C., Xue, M., Chahrour, M., Yoo, J., et al. (2010). Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature* 468, 263–269. doi: 10.1038/nature09582
- Cheah, S. Y., Lawford, B. R., Young, R. M., Morris, C. P., and Voisey, J. (2017). mRNA Expression and DNA Methylation Analysis of Serotonin Receptor 2A (HTR2A) in the Human Schizophrenic Brain. *Genes* 8:14. doi: 10.3390/genes8010014
- Chen, C. M., Stanford, A. D., Mao, X., Abi-Dargham, A., Shungu, D. C., Lisanby, S. H., et al. (2014). GABA level, gamma oscillation, and working memory performance in schizophrenia. *Neuroimage Clin.* 4, 531–539. doi: 10.1016/j.nicl.2014.03.007
- Chen, J., Zang, Z., Braun, U., Schwarz, K., Harneit, A., Kremer, T., et al. (2020). Association of a reproducible epigenetic risk profile for schizophrenia with brain methylation and function. *JAMA Psychiatry* 77, 628–636. doi: 10.1001/jamapsychiatry.2019.4792
- Chen, R., Davis, L. K., Guter, S., Wei, Q., Jacob, S., Potter, M. H., et al. (2017). Leveraging blood serotonin as an endophenotype to identify de novo and rare variants involved in autism. *Mol. Autism* 8:14. doi: 10.1186/s13229-017-0130-3
- Chen, Y., Sharma, R. P., Costa, R. H., Costa, E., and Grayson, D. R. (2002). On the epigenetic regulation of the human reelin promoter. *Nucleic Acids Res.* 30, 2930–2939. doi: 10.1093/nar/gkf401
- Cheng, J., Wang, Y., Zhou, K., Wang, L., Li, J., Zhuang, Q., et al. (2014). Male-specific association between dopamine receptor D4 gene methylation and schizophrenia. *PLoS One* 9:e89128. doi: 10.1371/journal.pone.0089128
- Cieslik, P., Radulska, A., Burnat, G., Kalinowski, L., and Wierońska, J. M. (2021). Serotonergic-muscarinic interaction within the prefrontal cortex as a novel target to reverse schizophrenia-related cognitive symptoms. *Int. J. Mol. Sci.* 22:8612. doi: 10.3390/ijms22168612
- GBD 2019 Diseases and Injuries Collaborators (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. *Lancet* 396, 1204–1222. doi: 10.1016/s0140-6736(20)30925-9
- Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427. doi: 10.1038/nature13595
- Corlett, P. R., Honey, G. D., Krystal, J. H., and Fletcher, P. C. (2011). Glutamatergic model psychoses: Prediction error, learning, and inference. *Neuropsychopharmacology* 36, 294–315. doi: 10.1038/npp.2010.163
- da Silveira Cruz-Machado, S., Guissoni Campos, L. M., Fadini, C. C., Anderson, G., Markus, R. P., Pinato, L., et al. (2021). Disrupted nocturnal melatonin in autism: Association with tumor necrosis factor and sleep disturbances. *J. Pineal Res.* 70:e12715. doi: 10.1111/jpi.12715
- Dai, D., Cheng, J., Zhou, K., Lv, Y., Zhuang, Q., Zheng, R., et al. (2014). Significant association between DRD3 gene body methylation and schizophrenia. *Psychiatry Res.* 220, 772–777. doi: 10.1016/j.psychres.2014.08.032
- Day, J. J., and Sweatt, J. D. (2012). Epigenetic treatments for cognitive impairments. *Neuropsychopharmacology* 37, 247–260. doi: 10.1038/npp.2011.85
- de Bruin, N. M., and Kruse, C. G. (2015). 5-HT6 receptor antagonists: Potential efficacy for the treatment of cognitive impairment in schizophrenia. *Curr. Pharm. Des.* 21, 3739–3759. doi: 10.2174/1381612821666150605112105
- Desai, A., Benner, L., Wu, R., Gertsik, L., Maruff, P., Light, G. A., et al. (2021). Phase 1 randomized study on the safety, tolerability, and pharmacodynamic cognitive and electrophysiological effects of a dopamine D(1) receptor positive allosteric modulator in patients with schizophrenia. *Neuropsychopharmacology* 46, 1145–1151. doi: 10.1038/s41386-020-00908-0
- Deutsch, S. I., Luyo, Z. N. M., and Burket, J. A. (2022). Targeted NMDA Receptor Interventions for Autism: Developmentally Determined Expression of GluN2B and GluN2A-Containing Receptors and Balanced Allosteric Modulatory Approaches. *Biomolecules* 12:181. doi: 10.3390/biom12020181
- Dias, V. V., Brissos, S., Frey, B. N., Andreazza, A. C., Cardoso, C., and Kapczinski, F. (2009). Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. *Bipolar Disord.* 11, 663–671. doi: 10.1111/j.1399-5618.2009.00733.x
- Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., and Yolken, R. (2013). Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. *J. Affect. Disord.* 150, 456–459. doi: 10.1016/j.jad.2013.04.039
- Dong, E., Agis-Balboa, R. C., Simonini, M. V., Grayson, D. R., Costa, E., and Guidotti, A. (2005). Reelin and glutamic acid decarboxylase67 promoter

- remodeling in an epigenetic methionine-induced mouse model of schizophrenia. *Proc. Natl. Acad. Sci. U.S.A.* 102, 12578–12583. doi: 10.1073/pnas.0505394102
- Ehlig, A. C., Reif, A., Herrmann, M. J., Lesch, K. P., and Fallgatter, A. J. (2007). Impact of catechol-O-methyltransferase on prefrontal brain functioning in schizophrenia spectrum disorders. *Neuropsychopharmacology* 32, 162–170. doi: 10.1038/sj.npp.1301151
- Fatemi, S. H., Earle, J. A., and Mcmenomy, T. (2000). Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. *Mol. Psychiatry* 5:571. doi: 10.1038/sj.mp.4000783
- Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Rooney, R. J., Patel, D. H., and Thuras, P. D. (2010). mRNA and protein levels for GABA $\alpha$ 4, alpha5, beta1 and GABABR1 receptors are altered in brains from subjects with autism. *J. Autism Dev. Disord.* 40, 743–750. doi: 10.1007/s10803-009-0924-z
- Fee, C., Banasr, M., and Sibille, E. (2017). Somatostatin-positive gamma-aminobutyric acid interneuron deficits in subjects with schizophrenia and therapeutic perspectives. *Biol. Psychiatry* 82, 549–559. doi: 10.1016/j.biopsych.2017.05.024
- Fillman, S. G., Weickert, T. W., Lenroot, R. K., Catts, S. V., Bruggemann, J. M., Catts, V. S., et al. (2016). Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca's area volume. *Mol. Psychiatry* 21, 1090–1098. doi: 10.1038/mp.2015.90
- First, M. B., Gaebel, W., Maj, M., Stein, D. J., Kogan, C. S., Saunders, J. B., et al. (2021). An organization- and category-level comparison of diagnostic requirements for mental disorders in ICD-11 and DSM-5. *World Psychiatry* 20, 34–51. doi: 10.1002/wps.20825
- Fischer, A., Sananbenesi, F., Mungenast, A., and Tsai, L. H. (2010). Targeting the correct HDAC(s) to treat cognitive disorders. *Trends Pharmacol. Sci.* 31, 605–617. doi: 10.1016/j.tips.2010.09.003
- Fleischhacker, W. W., Podhorna, J., Gröschl, M., Hake, S., Zhao, Y., Huang, S., et al. (2021). Efficacy and safety of the novel glycine transporter inhibitor BI 425809 once daily in patients with schizophrenia: A double-blind, randomised, placebo-controlled phase 2 study. *Lancet Psychiatry* 8, 191–201. doi: 10.1016/s2215-0366(20)30513-7
- Frampton, J. E. (2016). Vortioxetine: A Review in Cognitive Dysfunction in Depression. *Drugs* 76, 1675–1682. doi: 10.1007/s40265-016-0655-3
- Fregeac, J., Colleaux, L., and Nguyen, L. S. (2016). The emerging roles of MicroRNAs in autism spectrum disorders. *Neurosci. Biobehav. Rev.* 71, 729–738. doi: 10.1016/j.neubiorev.2016.10.018
- Fries, G. R., Li, Q., Mcalpin, B., Rein, T., Walss-Bass, C., Soares, J. C., et al. (2016). The role of DNA methylation in the pathophysiology and treatment of bipolar disorder. *Neurosci. Biobehav. Rev.* 68, 474–488. doi: 10.1016/j.neubiorev.2016.06.010
- Frydecka, D., Misiak, B., Pawlak-Adamska, E., Karabon, L., Tomkiewicz, A., Sedlacek, P., et al. (2015). Interleukin-6: The missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. *Eur. Arch. Psychiatry Clin. Neurosci.* 265, 449–459. doi: 10.1007/s00406-014-0533-5
- Fung, L. K., Mahajan, R., Nozzolillo, A., Bernal, P., Krasner, A., Jo, B., et al. (2016). Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. *Pediatrics* 137:S124–S135. doi: 10.1542/peds.2015-2851K
- Gilbert, T. M., Zürcher, N. R., Wu, C. J., Bhanot, A., Hightower, B. G., Kim, M., et al. (2019). PET neuroimaging reveals histone deacetylase dysregulation in schizophrenia. *J. Clin. Invest.* 129, 364–372. doi: 10.1172/jci123743
- Girdhar, K., Hoffman, G. E., Jiang, Y., Brown, L., Kundakovic, M., Hauberg, M. E., et al. (2018). Cell-specific histone modification maps in the human frontal lobe link schizophrenia risk to the neuronal epigenome. *Nat. Neurosci.* 21, 1126–1136. doi: 10.1038/s41593-018-0187-0
- Glinert, A., Turjeman, S., Elliott, E., and Koren, O. (2022). Microbes, metabolites and (synaptic) malleability, oh my! the effect of the microbiome on synaptic plasticity. *Biol. Rev. Camb. Philos. Soc.* 97, 582–599. doi: 10.1111/brv.12812
- Gobshits, N., Tfilin, M., Fraifeld, V. E., and Turgeman, G. (2021). Transplantation of mesenchymal stem cells causes long-term alleviation of schizophrenia-like behaviour coupled with increased neurogenesis. *Mol. Psychiatry* 26, 4448–4463. doi: 10.1038/s41380-019-0623-x
- Grace, A. A. (2016). Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat. Rev. Neurosci.* 17, 524–532. doi: 10.1038/nrn.2016.57
- Grande, I., Berk, M., Birmaher, B., and Vieta, E. (2016). Bipolar disorder. *Lancet* 387, 1561–1572. doi: 10.1016/s0140-6736(15)00241-x
- Grayson, D. R., and Guidotti, A. (2013). The dynamics of DNA methylation in schizophrenia and related psychiatric disorders. *Neuropsychopharmacology* 38, 138–166. doi: 10.1038/npp.2012.125
- Green, E. K., Rees, E., Walters, J. T., Smith, K. G., Forty, L., Grozeva, D., et al. (2016). Copy number variation in bipolar disorder. *Mol. Psychiatry* 21, 89–93. doi: 10.1038/mp.2014.174
- Green, M. J., Cairns, M. J., Wu, J., Dragovic, M., Jablensky, A., Tooney, P. A., et al. (2013). Genome-wide supported variant MIR137 and severe negative symptoms predict membership of an impaired cognitive subtype of schizophrenia. *Mol. Psychiatry* 18, 774–780. doi: 10.1038/mp.2012.84
- Green, M. J., Matheson, S. L., Shepherd, A., Weickert, C. S., and Carr, V. J. (2011). Brain-derived neurotrophic factor levels in schizophrenia: A systematic review with meta-analysis. *Mol. Psychiatry* 16, 960–972. doi: 10.1038/mp.2010.88
- Greenwood, T. A., Lazzaroni, L. C., Maihofer, A. X., Swerdlow, N. R., Calkins, M. E., Freedman, R., et al. (2019). Genome-wide association of endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) study. *JAMA Psychiatry* 76, 1274–1284. doi: 10.1001/jamapsychiatry.2019.2850
- Guan, J. S., Haggarty, S. J., Giacometti, E., Dannenberg, J. H., Joseph, N., Gao, J., et al. (2009). HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature* 459, 55–60. doi: 10.1038/nature07925
- Guan, L. Y., Hou, W. L., Zhu, Z. H., Cao, J. Q., Tang, Z., Yin, X. Y., et al. (2021). Associations among gonadal hormone, triglycerides and cognitive decline in female patients with major depressive disorders. *J. Psychiatr. Res.* 143, 580–586. doi: 10.1016/j.jpsychires.2020.11.022
- Guercio, G. D., Thomas, M. E., Cisneros-Franco, J. M., Voss, P., Panizzutti, R., and De Villers-Sidani, E. (2019). Improving cognitive training for schizophrenia using neuroplasticity enhancers: Lessons from decades of basic and clinical research. *Schizophr. Res.* 207, 80–92. doi: 10.1016/j.schres.2018.04.028
- Guidotti, A., Auta, J., Davis, J. M., Di-Giorgi-Gerevini, V., Dwivedi, Y., Grayson, D. R., et al. (2000). Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: A postmortem brain study. *Arch. Gen. Psychiatry* 57, 1061–1069. doi: 10.1001/archpsyc.57.11.1061
- Guo, C., Liu, Y., Fang, M.-S., Li, Y., Li, W., Mahaman, Y. A. R., et al. (2020).  $\omega$ -3PUFAs improve cognitive impairments through ser133 phosphorylation of CREB upregulating BDNF/TrkB signal in schizophrenia. *Neurotherapeutics* 17, 1271–1286. doi: 10.1007/s13311-020-00859-w
- Gupta, S., Kim, S. Y., Artis, S., Molfese, D. L., Schumacher, A., Sweatt, J. D., et al. (2010). Histone methylation regulates memory formation. *J. Neurosci.* 30, 3589–3599. doi: 10.1523/jneurosci.3732-09.2010
- Haas, S. S., Antonucci, L. A., Wenzel, J., Ruef, A., Biagiatti, B., Paolini, M., et al. (2021). A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis. *Neuropsychopharmacology* 46, 828–835. doi: 10.1038/s41386-020-00877-4
- Hagi, K., Nosaka, T., Dickinson, D., Lindenmayer, J. P., Lee, J., Friedman, J., et al. (2021). Association between cardiovascular risk factors and cognitive impairment in people with schizophrenia: A systematic review and meta-analysis. *JAMA psychiatry* 78, 510–518. doi: 10.1001/jamapsychiatry.2021.0015
- Harrell, C. R., Volarevic, A., Djonov, V., and Volarevic, V. (2021). Mesenchymal stem cell-derived exosomes as new remedy for the treatment of neurocognitive disorders. *Int. J. Mol. Sci.* 22:1433. doi: 10.3390/ijms22031433
- Hasan, A., Mitchell, A., Schneider, A., Halene, T., and Akbarian, S. (2013). Epigenetic dysregulation in schizophrenia: Molecular and clinical aspects of histone deacetylase inhibitors. *Eur. Arch. Psychiatry Clin. Neurosci.* 263, 273–284. doi: 10.1007/s00406-013-0395-2
- Hashemi, E., Ariza, J., Rogers, H., Noctor, S. C., and Martinez-Cerdeño, V. (2017). The number of parvalbumin-expressing interneurons is decreased in the prefrontal cortex in autism. *Cereb. Cortex* 27, 1931–1943. doi: 10.1093/cercor/bhw021
- Hidalgo, S., Campusano, J., and Hodge, J. (2021). The drosophila ortholog of the schizophrenia-associated CACNA1A and CACNA1B voltage-gated calcium channels regulate memory, sleep and circadian rhythms. *Neurobiol. Dis.* 155:105394. doi: 10.1016/j.nbd.2021.105394
- Huang, H. S., Matevosian, A., Whittle, C., Kim, S. Y., Schumacher, A., Baker, S. P., et al. (2007). Prefrontal dysfunction in schizophrenia involves mixed-lineage leukemia 1-regulated histone methylation at GABAergic gene promoters. *J. Neurosci.* 27, 11254–11262. doi: 10.1523/jneurosci.3272-07.2007
- Huang, X., Fei, G. Q., Liu, W. J., Ding, J., Wang, Y., Wang, H., et al. (2020). Adipose-derived mesenchymal stem cells protect against CMS-induced depression-like behaviors in mice via regulating the Nrf2/HO-1 and TLR4/NF- $\kappa$ B signaling pathways. *Acta Pharmacol. Sin.* 41, 612–619. doi: 10.1038/s41401-019-0317-6
- Hubbard, L., Rees, E., Morris, D. W., Lynham, A. J., Richards, A. L., Pardiñas, A. F., et al. (2021). Rare Copy Number Variants Are Associated With Poorer

- Cognition in Schizophrenia. *Biol. Psychiatry* 90, 28–34. doi: 10.1016/j.biopsych.2020.11.025
- Hui, L., Yin, X. L., Chen, J., Yin, X. Y., Zhu, H. L., Li, J., et al. (2019). Association between decreased HDL levels and cognitive deficits in patients with bipolar disorder: A pilot study. *Int. J. Bipolar Disord.* 7:25. doi: 10.1186/s40345-019-0159-7
- Jaffe, A. E., Gao, Y., Deep-Soboslay, A., Tao, R., Hyde, T. M., Weinberger, D. R., et al. (2016). Mapping DNA methylation across development, genotype and schizophrenia in the human frontal cortex. *Nat. Neurosci.* 19, 40–47. doi: 10.1038/nn.4181
- Jakovcevski, M., and Akbarian, S. (2012). Epigenetic mechanisms in neurological disease. *Nat. Med.* 18, 1194–1204. doi: 10.1038/nm.2828
- Jakovcevski, M., Bharadwaj, R., Straubhaar, J., Gao, G., Gavin, D. P., Jakovcevski, L., et al. (2013). Prefrontal cortical dysfunction after overexpression of histone deacetylase 1. *Biol. Psychiatry* 74, 696–705. doi: 10.1016/j.biopsych.2013.03.020
- Jakovcevski, M., Ruan, H., Shen, E. Y., Dincer, A., Javidfar, B., Ma, Q., et al. (2015). Neuronal Kmt2a/Mll1 histone methyltransferase is essential for prefrontal synaptic plasticity and working memory. *J. Neurosci.* 35, 5097–5108. doi: 10.1523/JNEUROSCI.3004-14.2015
- Jauhar, S., Johnstone, M., and McKenna, P. (2022). Schizophrenia. *Lancet* 399, 473–486. doi: 10.1016/s0140-6736(21)01730-x
- Javidfar, B., Park, R., Kassim, B. S., Bicks, L. K., and Akbarian, S. (2017). The epigenomics of schizophrenia, in the mouse. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 174, 631–640. doi: 10.1002/ajmg.b.32566
- Javitt, D. C., Carter, C. S., Krystal, J. H., Kantrowitz, J. T., Girgis, R. R., Kegeles, L. S., et al. (2018). Utility of Imaging-Based Biomarkers for Glutamate-Targeted Drug Development in Psychotic Disorders: A Randomized Clinical Trial. *JAMA Psychiatry* 75, 11–19. doi: 10.1001/jamapsychiatry.2017.3572
- Jin, K., Lu, J., Yu, Z., Shen, Z., Li, H., Mou, T., et al. (2020). Linking peripheral IL-6, IL-1 $\beta$  and hypocretin-1 with cognitive impairment from major depression. *J. Affect. Disord.* 277, 204–211. doi: 10.1016/j.jad.2020.08.024
- Jorm, A. F., Patten, S. B., Brugha, T. S., and Mojtabai, R. (2017). Has increased provision of treatment reduced the prevalence of common mental disorders? Review of the evidence from four countries. *World Psychiatry* 16, 90–99. doi: 10.1002/wps.20388
- Joseph, J., Depp, C., Martin, A. S., Daly, R. E., Glorioso, D. K., Palmer, B. W., et al. (2015). Associations of high sensitivity C-reactive protein levels in schizophrenia and comparison groups. *Schizophr. Res.* 168, 456–460. doi: 10.1016/j.schres.2015.08.019
- Kathuria, A., Lopez-Lengowski, K., Jagtap, S. S., Mcphie, D., Perlis, R. H., Cohen, B. M., et al. (2020a). Transcriptomic landscape and functional characterization of induced pluripotent stem cell-derived cerebral organoids in schizophrenia. *JAMA Psychiatry* 77, 745–754. doi: 10.1001/jamapsychiatry.2020.0196
- Kathuria, A., Lopez-Lengowski, K., Vater, M., Mcphie, D., Cohen, B. M., and Karmacharya, R. (2020b). Transcriptome analysis and functional characterization of cerebral organoids in bipolar disorder. *Genome Med.* 12:34. doi: 10.1186/s13023-020-00733-6
- Keefe, R. S. E., Harvey, P. D., Khan, A., Saoud, J. B., Staner, C., Davidson, M., et al. (2018). Cognitive Effects of MIN-101 in Patients With Schizophrenia and Negative Symptoms: Results From a Randomized Controlled Trial. *J. Clin. Psychiatry* 79:17m11753. doi: 10.4088/JCP.17m11753
- Keller, S., Errico, F., Zarrilli, F., Florio, E., Punzo, D., Mansueto, S., et al. (2014). DNA methylation state of BDNF gene is not altered in prefrontal cortex and striatum of schizophrenia subjects. *Psychiatry Res.* 220, 1147–1150. doi: 10.1016/j.psychres.2014.08.022
- Kendall, K. M., Bracher-Smith, M., Fitzpatrick, H., Lynham, A., Rees, E., Escott-Price, V., et al. (2019a). Cognitive performance and functional outcomes of carriers of pathogenic copy number variants: Analysis of the UK biobank. *Br. J. Psychiatry* 214, 297–304. doi: 10.1192/bjp.2018.301
- Kendall, K. M., Rees, E., Bracher-Smith, M., Legge, S., Riglin, L., Zammit, S., et al. (2019b). Association of rare copy number variants with risk of depression. *JAMA Psychiatry* 76, 818–825. doi: 10.1001/jamapsychiatry.2019.0566
- Kim, H., Ährlund-Richter, S., Wang, X., Deisseroth, K., and Carlén, M. (2016). Prefrontal parvalbumin neurons in control of attention. *Cell* 164, 208–218. doi: 10.1016/j.cell.2015.11.038
- King, S., Holleran, L., Mothersill, D., Patlola, S., Rokita, K., Mcmanus, R., et al. (2021). Early life adversity, functional connectivity and cognitive performance in schizophrenia: The mediating role of IL-6. *Brain Behav. Immun.* 98, 388–396. doi: 10.1016/j.bbi.2021.06.016
- Kirov, G., Pocklington, A. J., Holmans, P., Ivanov, D., Ikeda, M., Ruderfer, D., et al. (2012). De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol. Psychiatry* 17, 142–153. doi: 10.1038/mp.2011.154
- Klempman, T. A., Sequeira, A., Canetti, L., Lalovic, A., Ernst, C., Ffrench-Mullen, J., et al. (2009). Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. *Mol. Psychiatry* 14, 175–189. doi: 10.1038/sj.mp.4002110
- Knöchel, C., Kniep, J., Cooper, J. D., Stäblein, M., Wenzler, S., Sarlon, J., et al. (2017). Altered apolipoprotein C expression in association with cognition impairments and hippocampus volume in schizophrenia and bipolar disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* 267, 199–212. doi: 10.1007/s00406-016-0724-3
- Kocerha, J., Dwivedi, Y., and Brennand, K. J. (2015). Noncoding RNAs and neurobehavioral mechanisms in psychiatric disease. *Mol. Psychiatry* 20, 677–684. doi: 10.1038/mp.2015.30
- Kocerha, J., Faghihi, M. A., Lopez-Toledano, M. A., Huang, J., Ramsey, A. J., Caron, M. G., et al. (2009). MicroRNA-219 modulates NMDA receptor-mediated neurobehavioral dysfunction. *Proc. Natl. Acad. Sci. U.S.A.* 106, 3507–3512. doi: 10.1073/pnas.0805854106
- Kogan, S., Ospina, L. H., and Kimhy, D. (2018). Inflammation in individuals with schizophrenia - implications for neurocognition and daily function. *Brain Behav. Immun.* 74, 296–299. doi: 10.1016/j.bbi.2018.09.016
- Kogan, S., Ospina, L. H., Mittal, V. A., and Kimhy, D. (2020). The impact of inflammation on neurocognition and risk for psychosis: A critical review. *Eur. Arch. Psychiatry Clin. Neurosci.* 270, 793–802. doi: 10.1007/s00406-019-01073-2
- Kort, N. S., Ford, J. M., Roach, B. J., Gunduz-Bruce, H., Krystal, J. H., Jaeger, J., et al. (2017). Role of N-methyl-D-aspartate receptors in action-based predictive coding deficits in schizophrenia. *Biol. Psychiatry* 81, 514–524. doi: 10.1016/j.biopsych.2016.06.019
- Kudo, N., Yamamori, H., Ishima, T., Nemoto, K., Yasuda, Y., Fujimoto, M., et al. (2018). Plasma levels of soluble tumor necrosis factor receptor 2 (sTNFR2) are associated with hippocampal volume and cognitive performance in patients with schizophrenia. *Int. J. Neuropsychopharmacol.* 21, 631–639. doi: 10.1093/ijnp/pyy013
- Labouesse, M. A., Dong, E., Grayson, D. R., Guidotti, A., and Meyer, U. (2015). Maternal immune activation induces GAD1 and GAD2 promoter remodeling in the offspring prefrontal cortex. *Epigenetics* 10, 1143–1155. doi: 10.1080/15592294.2015.1114202
- Lai, M., Lombardo, M., and Baron-Cohen, S. (2014). Autism. *Lancet* 383, 896–910. doi: 10.1016/s0140-6736(13)61539-1
- Lemone, S., Turecki, G., Bakish, D., Du, L., Hrdina, P. D., Bown, C. D., et al. (2003). Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J. Neurosci.* 23, 8788–8799. doi: 10.1523/jneurosci.23-25-08788.2003
- Lenz, T., Knowles, E., Davies, G., Guha, S., Liewald, D. C., Starr, J. M., et al. (2014). Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: A report from the cognitive genomics consortium (COGENT). *Mol. Psychiatry* 19, 168–174. doi: 10.1038/mp.2013.166
- Lenz, T., and Malhotra, A. K. (2015). Targeting the schizophrenia genome: A fast track strategy from GWAS to clinic. *Mol. Psychiatry* 20, 820–826. doi: 10.1038/mp.2015.28
- Levinson, A. J., Fitzgerald, P. B., Favalli, G., Blumberger, D. M., Daigle, M., and Daskalakis, Z. J. (2010). Evidence of cortical inhibitory deficits in major depressive disorder. *Biol. Psychiatry* 67, 458–464. doi: 10.1016/j.biopsych.2009.09.025
- Lewis, D. A. (2014). Inhibitory neurons in human cortical circuits: Substrate for cognitive dysfunction in schizophrenia. *Curr. Opin. Neurobiol.* 26, 22–26. doi: 10.1016/j.conb.2013.11.003
- Lewis, D. A., Cho, R. Y., Carter, C. S., Eklund, K., Forster, S., Kelly, M. A., et al. (2008). Subunit-selective modulation of GABA type A receptor neurotransmission and cognition in schizophrenia. *Am. J. Psychiatry* 165, 1585–1593. doi: 10.1176/appi.ajp.2008.08030395
- Lewis, D. A., Curley, A. A., Glausier, J. R., and Volk, D. W. (2012). Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* 35, 57–67. doi: 10.1016/j.tins.2011.10.004
- Li, C. T., Hsieh, J. C., Wang, S. J., Yang, B. H., Bai, Y. M., Lin, W. C., et al. (2012). Differential relations between fronto-limbic metabolism and executive function in patients with remitted bipolar I and bipolar II disorder. *Bipolar Disord.* 14, 831–842. doi: 10.1111/bdi.12017
- Li, Y. K., Hui, C. L., Lee, E. H., Chang, W. C., Chan, S. K., Leung, C. M., et al. (2014). Coupling physical exercise with dietary glucose supplement for treating cognitive impairment in schizophrenia: A theoretical model and future directions. *Early Interv. Psychiatry* 8, 209–220. doi: 10.1111/eip.12109

- Li, Z., Lai, J., Zhang, P., Ding, J., Jiang, J., Liu, C., et al. (2022). Multi-omics analyses of serum metabolome, gut microbiome and brain function reveal dysregulated microbiota-gut-brain axis in bipolar depression. *Mol. Psychiatry* [Epub ahead of print]. doi: 10.1038/s41380-022-01569-9
- Li, Z., Wang, G., Zhong, S., Liao, X., Lai, S., Shan, Y., et al. (2020). Alleviation of cognitive deficits and high copper levels by an NMDA receptor antagonist in a rat depression model. *Compr. Psychiatry* 102:152200. doi: 10.1016/j.comppsy.2020.152200
- Lindenmayer, J. P., Nasrallah, H., Pucci, M., James, S., and Citrome, L. (2013). A systematic review of psychostimulant treatment of negative symptoms of schizophrenia: Challenges and therapeutic opportunities. *Schizophr. Res.* 147, 241–252. doi: 10.1016/j.schres.2013.03.019
- Lintas, C., Sacco, R., and Persico, A. M. (2016). Differential methylation at the RELN gene promoter in temporal cortex from autistic and typically developing post-puberal subjects. *J. Neurodev. Disord.* 8:18. doi: 10.1186/s11689-016-9151-z
- Liu, J., Wang, J., Xiao, X., Lai, X., Dai, D., Zhang, X., et al. (2020). A hybrid correcting method considering heterozygous variations by a comprehensive probabilistic model. *BMC Genom.* 21:753. doi: 10.1186/s12864-020-07008-9
- Liu, L., Lv, X., Zhou, S., Liu, Q., Wang, J., Tian, H., et al. (2021). The effect of selective serotonin reuptake inhibitors on cognitive impairment in patients with depression: A prospective, multicenter, observational study. *J. Psychiatr. Res.* 141, 26–33. doi: 10.1016/j.jpsychires.2021.06.020
- Liu, P., Gao, M., Liu, Z., Zhang, Y., Tu, H., Lei, L., et al. (2021). Gut microbiome composition linked to inflammatory factors and cognitive functions in first-episode, drug-naïve major depressive disorder patients. *Front. Neurosci.* 15:800764. doi: 10.3389/fnins.2021.800764
- Liu, Q., Chen, M. X., Sun, L., Wallis, C. U., Zhou, J. S., Ao, L. J., et al. (2019). Rational use of mesenchymal stem cells in the treatment of autism spectrum disorders. *World J. Stem Cells* 11, 55–72. doi: 10.4252/wjsc.v11.i2.55
- Liu, S., Zhou, L., Yuan, H., Vieira, M., Sanz-Clemente, A., Badger, J. D. II, et al. (2017). A rare variant identified within the GluN2B C-terminus in a patient with autism affects NMDA receptor surface expression and spine density. *J. Neurosci.* 37, 4093–4102. doi: 10.1523/jneurosci.0827-16.2017
- Lizano, P., Lutz, O., Ling, G., Lee, A. M., Eum, S., Bishop, J. R., et al. (2019). Association of choroid plexus enlargement with cognitive, inflammatory, and structural phenotypes across the psychosis spectrum. *Am. J. Psychiatry* 176, 564–572. doi: 10.1176/appi.ajp.2019.18070825
- Locke, T. M., Soden, M. E., Miller, S. M., Hunker, A., Knakal, C., Licholai, J. A., et al. (2018). Dopamine D(1) receptor-positive neurons in the lateral nucleus of the cerebellum contribute to cognitive behavior. *Biol. Psychiatry* 84, 401–412. doi: 10.1016/j.biopsych.2018.01.019
- Lv, Y. T., Zhang, Y., Liu, M., Qiuwaxi, J. N., Ashwood, P., Cho, S. C., et al. (2013). Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. *J. Transl. Med.* 11:196. doi: 10.1186/1479-5876-11-196
- Lynham, A. J., Jones, I. R., and Walters, J. T. R. (2022). Web-based cognitive testing in psychiatric research: Validation and usability study. *J. Med. Internet Res.* 24:e28233. doi: 10.2196/28233
- Marchetto, M. C., Carroumeu, C., Acab, A., Yu, D., Yeo, G. W., Mu, Y., et al. (2010). A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell* 143, 527–539. doi: 10.1016/j.cell.2010.10.016
- Mealer, R. G., Williams, S. E., Daly, M. J., Scolnick, E. M., Cummings, R. D., and Smoller, J. W. (2020). Glycobiology and schizophrenia: A biological hypothesis emerging from genomic research. *Mol. Psychiatry* 25, 3129–3139. doi: 10.1038/s41380-020-0753-1
- Meltzer, H. Y., Li, Z., Kaneda, Y., and Ichikawa, J. (2003). Serotonin receptors: Their key role in drugs to treat schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 27, 1159–1172. doi: 10.1016/j.pnpbp.2003.09.010
- Meneses, A. (1999). 5-HT system and cognition. *Neurosci. Biobehav. Rev.* 23, 1111–1125. doi: 10.1016/s0149-7634(99)00067-6
- Miller, B. H., Zeier, Z., Xi, L., Lanz, T. A., Deng, S., Strathmann, J., et al. (2012). MicroRNA-132 dysregulation in schizophrenia has implications for both neurodevelopment and adult brain function. *Proc. Natl. Acad. Sci. U.S.A.* 109, 3125–3130. doi: 10.1073/pnas.1113793109
- Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., and Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biol. Psychiatry* 70, 663–671. doi: 10.1016/j.biopsych.2011.04.013
- Millett, C. E., Harder, J., Locascio, J. J., Shanahan, M., Santone, G., Fichorova, R. N., et al. (2020). TNF- $\alpha$  and its soluble receptors mediate the relationship between prior severe mood episodes and cognitive dysfunction in euthymic bipolar disorder. *Brain Behav. Immun.* 88, 403–410. doi: 10.1016/j.bbi.2020.04.003
- Millett, C. E., Perez-Rodriguez, M., Shanahan, M., Larsen, E., Yamamoto, H. S., Bukowski, C., et al. (2021). C-reactive protein is associated with cognitive performance in a large cohort of euthymic patients with bipolar disorder. *Mol. Psychiatry* 26, 4096–4105. doi: 10.1038/s41380-019-0591-1
- Misiak, B., Stańczykiewicz, B., Kotowicz, K., Rybakowski, J. K., Samochowiec, J., and Frydecka, D. (2018). Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. *Schizophr. Res.* 192, 16–29. doi: 10.1016/j.schres.2017.04.015
- Mitchell, A. C., Jiang, Y., Peter, C., and Akbarian, S. (2015). Transcriptional regulation of GAD1 GABA synthesis gene in the prefrontal cortex of subjects with schizophrenia. *Schizophr. Res.* 167, 28–34. doi: 10.1016/j.schres.2014.10.020
- Mitelman, S. A., Bralet, M. C., Mehmet Haznedar, M., Hollander, E., Shihabuddin, L., Hazlett, E. A., et al. (2018). Positron emission tomography assessment of cerebral glucose metabolic rates in autism spectrum disorder and schizophrenia. *Brain Imaging Behav.* 12, 532–546. doi: 10.1007/s11682-017-9721-z
- Moen, M. J., Adams, H. H., Brandsma, J. H., Dekkers, D. H., Akinci, U., Karkampouna, S., et al. (2017). An interaction network of mental disorder proteins in neural stem cells. *Transl. Psychiatry* 7:e1082. doi: 10.1038/tp.2017.52
- Moghaddam, B., and Javitt, D. (2012). From revolution to evolution: The glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 37, 4–15. doi: 10.1038/npp.2011.181
- Mor, M., Nardone, S., Sams, D. S., and Elliott, E. (2015). Hypomethylation of miR-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. *Mol. Autism* 6:46. doi: 10.1186/s13229-015-0040-1
- Morrens, M., Overloop, C., Coppens, V., Loots, E., Van Den Noortgate, M., Vandenameele, S., et al. (2022). The relationship between immune and cognitive dysfunction in mood and psychotic disorder: A systematic review and a meta-analysis. *Mol. Psychiatry* [Epub ahead of print]. doi: 10.1038/s41380-022-01582-y
- Mould, A., Hall, N., Milosevic, I., and Tunbridge, E. (2021). Targeting synaptic plasticity in schizophrenia: Insights from genomic studies. *Trends Mol. Med.* 27, 1022–1032. doi: 10.1016/j.molmed.2021.07.014
- Nguyen, L. S., Lepleux, M., Makhoul, M., Martin, C., Fregeac, J., Siquier-Pernet, K., et al. (2016). Profiling olfactory stem cells from living patients identifies miRNAs relevant for autism pathophysiology. *Mol. Autism* 7:1. doi: 10.1186/s13229-015-0064-6
- Nie, J., Fang, Y., Chen, Y., Aidina, A., Qiu, Q., Zhao, L., et al. (2021). Characteristics of dysregulated proinflammatory cytokines and cognitive dysfunction in late-life depression and amnesic mild cognitive impairment. *Front. Immunol.* 12:803633. doi: 10.3389/fimmu.2021.803633
- Northoff, G., and Sibille, E. (2014). Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings. *Mol. Psychiatry* 19, 966–977. doi: 10.1038/mp.2014.68
- Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., et al. (2008). The MATRICS consensus cognitive battery, part I: Test selection, reliability, and validity. *Am. J. Psychiatry* 165, 203–213. doi: 10.1176/appi.ajp.2007.07010042
- Ohi, K., Hashimoto, R., Ikeda, M., Yamamori, H., Yasuda, Y., Fujimoto, M., et al. (2015). Glutamate networks implicate cognitive impairments in schizophrenia: Genome-wide association studies of 52 cognitive phenotypes. *Schizophr. Bull.* 41, 909–918. doi: 10.1093/schbul/sbu171
- O'Shea, K. S., and McInnis, M. G. (2016). Neurodevelopmental origins of bipolar disorder: iPSC models. *Mol. Cell. Neurosci.* 73, 63–83. doi: 10.1016/j.mcn.2015.11.006
- Pan, S., Feng, W., Li, Y., Huang, J., Chen, S., Cui, Y., et al. (2021). The microRNA-195 - BDNF pathway and cognitive deficits in schizophrenia patients with minimal antipsychotic medication exposure. *Transl. Psychiatry* 11:117. doi: 10.1038/s41398-021-01240-x
- Park, H., and Poo, M. M. (2013). Neurotrophin regulation of neural circuit development and function. *Nat. Rev. Neurosci.* 14, 7–23. doi: 10.1038/nrn3379
- Park, K. M., and Bowers, W. J. (2010). Tumor necrosis factor- $\alpha$  mediated signaling in neuronal homeostasis and dysfunction. *Cell. Signal.* 22, 977–983. doi: 10.1016/j.cellsig.2010.01.010
- Paul, S. M., Doherty, J. J., Robichaud, A. J., Belfort, G. M., Chow, B. Y., Hammond, R. S., et al. (2013). The major brain cholesterol metabolite 24(S)-hydroxycholesterol is a potent allosteric modulator of N-methyl-D-aspartate receptors. *J. Neurosci.* 33, 17290–17300. doi: 10.1523/jneurosci.2619-13.2013
- Perets, N., Hertz, S., London, M., and Offen, D. (2018). Intranasal administration of exosomes derived from mesenchymal stem cells ameliorates autistic-like behaviors of BTBR mice. *Mol. Autism* 9:57. doi: 10.1186/s13229-018-0240-6



- Perets, N., Segal-Gavish, H., Gothelf, Y., Barzilay, R., Barhum, Y., Abramov, N., et al. (2017). Long term beneficial effect of neurotrophic factors-secreting mesenchymal stem cells transplantation in the BTBR mouse model of autism. *Behav. Brain Res.* 331, 254–260. doi: 10.1016/j.bbr.2017.03.047
- Peter, C. J., and Akbarian, S. (2011). Balancing histone methylation activities in psychiatric disorders. *Trends Mol. Med.* 17, 372–379. doi: 10.1016/j.molmed.2011.02.003
- Pizzo, L., Jensen, M., Polyak, A., Rosenfeld, J. A., Mannik, K., Krishnan, A., et al. (2019). Rare variants in the genetic background modulate cognitive and developmental phenotypes in individuals carrying disease-associated variants. *Genet. Med.* 21, 816–825. doi: 10.1038/s41436-018-0266-3
- Poletti, S., Mazza, M. G., Calesella, F., Vai, B., Lorenzi, C., Manfredi, E., et al. (2021). Circulating inflammatory markers impact cognitive functions in bipolar depression. *J. Psychiatr. Res.* 140, 110–116. doi: 10.1016/j.jpsychires.2021.05.071
- Qin, L., Ma, K., Wang, Z. J., Hu, Z., Matas, E., Wei, J., et al. (2018). Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition. *Nat. Neurosci.* 21, 564–575. doi: 10.1038/s41593-018-0110-8
- Qin, X. Y., Wu, H. T., Cao, C., Loh, Y. P., and Cheng, Y. (2017). A meta-analysis of peripheral blood nerve growth factor levels in patients with schizophrenia. *Mol. Psychiatry* 22, 1306–1312. doi: 10.1038/mp.2016.235
- Qiu, Y., Li, S., Teng, Z., Tan, Y., Xu, X., Yang, M., et al. (2022). Association between abnormal glycolipid level and cognitive dysfunction in drug-naïve patients with bipolar disorder. *J. Affect. Disord.* 297, 477–485. doi: 10.1016/j.jad.2021.10.100
- Rao, S., Martínez-Cengotitabengoa, M., Yao, Y., Guo, Z., Xu, Q., Li, S., et al. (2017). Peripheral blood nerve growth factor levels in major psychiatric disorders. *J. Psychiatr. Res.* 86, 39–45. doi: 10.1016/j.jpsychires.2016.11.012
- Recio-Barbero, M., Segarra, R., Zabala, A., González-Fraile, E., González-Pinto, A., and Ballesteros, J. (2021). Cognitive Enhancers in Schizophrenia: A Systematic Review and Meta-Analysis of Alpha-7 Nicotinic Acetylcholine Receptor Agonists for Cognitive Deficits and Negative Symptoms. *Front. Psychiatry* 12:631589. doi: 10.3389/fpsy.2021.631589
- Rees, E., and Kirov, G. (2021). Copy number variation and neuropsychiatric illness. *Curr. Opin. Genet. Dev.* 68, 57–63. doi: 10.1016/j.gde.2021.02.014
- Rees, E., and Owen, M. J. (2020). Translating insights from neuropsychiatric genetics and genomics for precision psychiatry. *Genome Med.* 12:43. doi: 10.1186/s13073-020-00734-5
- Reichenberg, A., Harvey, P. D., Bowie, C. R., Mojtabai, R., Rabinowitz, J., Heaton, R. K., et al. (2009). Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophr. Bull.* 35, 1022–1029. doi: 10.1093/schbul/sbn044
- Rogers, G. B., Keating, D. J., Young, R. L., Wong, M. L., Licinio, J., and Wesselingh, S. (2016). From gut dysbiosis to altered brain function and mental illness: Mechanisms and pathways. *Mol. Psychiatry* 21, 738–748. doi: 10.1038/mp.2016.50
- Rong, H., Liu, T. B., Yang, K. J., Yang, H. C., Wu, D. H., Liao, C. P., et al. (2011). MicroRNA-134 plasma levels before and after treatment for bipolar mania. *J. Psychiatr. Res.* 45, 92–95. doi: 10.1016/j.jpsychires.2010.04.028
- Rudolph, U., and Möhler, H. (2014). GABA receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. *Annu. Rev. Pharmacol. Toxicol.* 54, 483–507. doi: 10.1146/annurev-pharmtox-011613-135947
- Salvi, V., Di Salvo, G., Korčáková, J., Torriero, S., Aragno, E., Kolenič, M., et al. (2020). Insulin resistance is associated with verbal memory impairment in bipolar disorders. *J. Affect. Disord.* 266, 610–614. doi: 10.1016/j.jad.2020.01.145
- Sánchez-Ortí, J. V., Balanzá-Martínez, V., Correa-Ghisays, P., Selva-Vera, G., Vila-Francés, J., Magdalena-Benedito, R., et al. (2022). Specific metabolic syndrome components predict cognition and social functioning in people with type 2 diabetes mellitus and severe mental disorders. *Acta Psychiatr. Scand.* 146, 215–226. doi: 10.1111/acts.13433
- Sanders, S. J., He, X., Willsey, A. J., Ercan-Sencicek, A. G., Samocha, K. E., Ciccek, A. E., et al. (2015). Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron* 87, 1215–1233. doi: 10.1016/j.neuron.2015.09.016
- Santos, B., González-Fraile, E., Zabala, A., Guillén, V., Rueda, J. R., and Ballesteros, J. (2018). Cognitive improvement of acetylcholinesterase inhibitors in schizophrenia. *J. Psychopharmacol.* 32, 1155–1166. doi: 10.1177/0269881118805496
- Sarter, M., Lustig, C., and Taylor, S. F. (2012). Cholinergic contributions to the cognitive symptoms of schizophrenia and the viability of cholinergic treatments. *Neuropharmacology* 62, 1544–1553. doi: 10.1016/j.neuropharm.2010.12.001
- Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J.-Y., et al. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell* 180, 568–584.e23. doi: 10.1016/j.cell.2019.12.036
- Scheggia, D., Mastrogiacomo, R., Mereu, M., Sannino, S., Straub, R. E., Armando, M., et al. (2018). Publisher correction: Variations in dysbindin-1 are associated with cognitive response to antipsychotic drug treatment. *Nat. Commun.* 9:3560. doi: 10.1038/s41467-018-06062-y
- Schroeder, F. A., Gilbert, T. M., Feng, N., Taillon, B. D., Volkow, N. D., Innis, R. B., et al. (2017). Expression of HDAC2 but not HDAC1 transcript is reduced in dorsolateral prefrontal cortex of patients with schizophrenia. *ACS Chem. Neurosci.* 8, 662–668. doi: 10.1021/acscchemneuro.6b00372
- Sedlazeck, F. J., Rescheneder, P., Smolka, M., Fang, H., Nattestad, M., Von Haeseler, A., et al. (2018). Accurate detection of complex structural variations using single-molecule sequencing. *Nat. Methods* 15, 461–468. doi: 10.1038/s41592-018-0001-7
- Segal-Gavish, H., Karvat, G., Barak, N., Barzilay, R., Ganz, J., Edry, L., et al. (2016). Mesenchymal stem cell transplantation promotes neurogenesis and ameliorates autism related behaviors in BTBR mice. *Autism Res.* 9, 17–32. doi: 10.1002/aur.1530
- Selimbeyoglu, A., Kim, C. K., Inoue, M., Lee, S. Y., Hong, A. S. O., Kauvar, I., et al. (2017). Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice. *Sci. Transl. Med.* 9:eaah6733. doi: 10.1126/scitranslmed.aah6733
- Selvaraj, S., Arnone, D., Cappai, A., and Howes, O. (2014). Alterations in the serotonin system in schizophrenia: A systematic review and meta-analysis of postmortem and molecular imaging studies. *Neurosci. Biobehav. Rev.* 45, 233–245. doi: 10.1016/j.neubiorev.2014.06.005
- Shao, T. N., Yin, G. Z., Yin, X. L., Wu, J. Q., Du, X. D., Zhu, H. L., et al. (2017). Elevated triglyceride levels are associated with cognitive impairments among patients with major depressive disorder. *Compr. Psychiatry* 75, 103–109. doi: 10.1016/j.comppsy.2017.03.007
- Sharma, A., Gokulchandran, N., Sane, H., Nagrajan, A., Paranjape, A., Kulkarni, P., et al. (2013). Autologous bone marrow mononuclear cell therapy for autism: An open label proof of concept study. *Stem Cells Int.* 2013:623875. doi: 10.1155/2013/623875
- Sharma, R. P., Grayson, D. R., and Gavin, D. P. (2008). Histone deacetylase 1 expression is increased in the prefrontal cortex of schizophrenia subjects: Analysis of the national brain databank microarray collection. *Schizophr. Res.* 98, 111–117. doi: 10.1016/j.schres.2007.09.020
- Sharma, S., Gonda, X., and Tarazi, F. (2018). Autism spectrum disorder: Classification, diagnosis and therapy. *Pharmacol. Ther.* 190, 91–104. doi: 10.1016/j.pharmthera.2018.05.007
- Sharon, G., Cruz, N. J., Kang, D. W., Gandal, M. J., Wang, B., Kim, Y. M., et al. (2019). Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell* 177, 1600–1618.e17. doi: 10.1016/j.cell.2019.05.004
- Shen, E., Shulha, H., Weng, Z., and Akbarian, S. (2014). Regulation of histone H3K4 methylation in brain development and disease. *Philos. Trans. R. Soc. Lond. Series B Biol. Sci.* 369:20130514. doi: 10.1098/rstb.2013.0514
- Smeland, O., Bahrami, S., Frei, O., Shadrin, A., O'Connell, K., Savage, J., et al. (2020). Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Mol. Psychiatry* 25, 844–853. doi: 10.1038/s41380-018-0332-x
- Smeland, O. B., Frei, O., Kauppi, K., Hill, W. D., Li, W., Wang, Y., et al. (2017). Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numerical reasoning, reaction time, and general cognitive function. *JAMA Psychiatry* 74, 1065–1075. doi: 10.1001/jamapsychiatry.2017.1986
- Smith, M. A., Ersavas, T., Ferguson, J. M., Liu, H., Lucas, M. C., Begik, O., et al. (2020). Molecular barcoding of native RNAs using nanopore sequencing and deep learning. *Genome Res.* 30, 1345–1353. doi: 10.1101/gr.260836.120
- Snyder, M. A., and Gao, W. J. (2020). NMDA receptor hypofunction for schizophrenia revisited: Perspectives from epigenetic mechanisms. *Schizophr. Res.* 217, 60–70. doi: 10.1016/j.schres.2019.03.010
- Sofroniew, M. V., Howe, C. L., and Mobley, W. C. (2001). Nerve growth factor signaling, neuroprotection, and neural repair. *Annu. Rev. Neurosci.* 24, 1217–1281. doi: 10.1146/annurev.neuro.24.1.1217
- Soliman, M. A., Aboharb, F., Zeltner, N., and Studer, L. (2017). Pluripotent stem cells in neuropsychiatric disorders. *Mol. Psychiatry* 22, 1241–1249. doi: 10.1038/mp.2017.40
- Srivastava, A., Dada, O., Qian, J., Al-Chalabi, N., Fatemi, A. B., Gerretsen, P., et al. (2021). Epigenetics of schizophrenia. *Psychiatry Res.* 305:114218. doi: 10.1016/j.psychres.2021.114218

- Stefansson, H., Meyer-Lindenberg, A., Steinberg, S., Magnusdottir, B., Morgen, K., Arnarsdottir, S., et al. (2014). CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature* 505, 361–366. doi: 10.1038/nature12818
- Stellwagen, D., and Malenka, R. C. (2006). Synaptic scaling mediated by glial TNF- $\alpha$ . *Nature* 440, 1054–1059. doi: 10.1038/nature04671
- Sullivan, P. F., and Geschwind, D. H. (2019). Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. *Cell* 177, 162–183. doi: 10.1016/j.cell.2019.01.015
- Sumiyoshi, T., Stockmeier, C. A., Overholser, J. C., Dilley, G. E., and Meltzer, H. Y. (1996). Serotonin1A receptors are increased in postmortem prefrontal cortex in schizophrenia. *Brain Res.* 708, 209–214. doi: 10.1016/0006-8993(95)01361-x
- Sun, Y., Baptista, L. C., Roberts, L. M., Jumbo-Lucioni, P., McMahon, L. L., Buford, T. W., et al. (2020). The gut microbiome as a therapeutic target for cognitive impairment. *J. Gerontol. A Biol. Sci. Med. Sci.* 75, 1242–1250. doi: 10.1093/gerona/glz281
- Tan, T., Wang, W., Williams, J., Ma, K., Cao, Q., and Yan, Z. (2019). Stress exposure in dopamine D4 receptor knockout mice induces schizophrenia-like behaviors via disruption of GABAergic transmission. *Schizophr. Bull.* 45, 1012–1023. doi: 10.1093/schbul/sby163
- Tang, C. Z., Yang, J. T., Liu, Q. H., Wang, Y. R., and Wang, W. S. (2019). Up-regulated miR-192-5p expression rescues cognitive impairment and restores neural function in mice with depression via the Fbln2-mediated TGF- $\beta$ 1 signaling pathway. *FASEB J.* 33, 606–618. doi: 10.1096/fj.201800210RR
- Tang, W., Wang, Y., Xu, F., Fan, W., Zhang, Y., Fan, K., et al. (2020). Omega-3 fatty acids ameliorate cognitive dysfunction in schizophrenia patients with metabolic syndrome. *Brain Behav. Immun.* 88, 529–534. doi: 10.1016/j.bbi.2020.04.034
- Teng, Z., Wang, L., Li, S., Tan, Y., Qiu, Y., Wu, C., et al. (2021). Low BDNF levels in serum are associated with cognitive impairments in medication-naïve patients with current depressive episode in BD II and MDD. *J. Affect. Disord.* 293, 90–96. doi: 10.1016/j.jad.2021.06.018
- Tessier, C., Sweers, K., Frajerman, A., Bergaoui, H., Ferreri, F., Delva, C., et al. (2016). Membrane lipidomics in schizophrenia patients: A correlational study with clinical and cognitive manifestations. *Transl. Psychiatry* 6:e906. doi: 10.1038/tp.2016.142
- Thalamuthu, A., Mills, N., Berger, K., Minnerup, H., Grotegerd, D., Dannlowski, U., et al. (2022). Genome-wide interaction study with major depression identifies novel variants associated with cognitive function. *Mol. Psychiatry* 27, 1111–1119. doi: 10.1038/s41380-021-01379-5
- Thygesen, J. H., Presman, A., Harju-Seppänen, J., Irizar, H., Jones, R., Kuchenbaecker, K., et al. (2021). Genetic copy number variants, cognition and psychosis: A meta-analysis and a family study. *Mol. Psychiatry* 26, 5307–5319. doi: 10.1038/s41380-020-0820-7
- Tremblay, M. W., and Jiang, Y. H. (2019). DNA methylation and susceptibility to autism spectrum disorder. *Annu. Rev. Med.* 70, 151–166. doi: 10.1146/annurev-med-120417-091431
- Tseng, C. J., Gilbert, T. M., Catanese, M. C., Hightower, B. G., Peters, A. T., Parmar, A. J., et al. (2020). *In vivo* human brain expression of histone deacetylases in bipolar disorder. *Transl. Psychiatry* 10:224. doi: 10.1038/s41398-020-00911-5
- Tsivion-Visbord, H., Perets, N., Sofer, T., Bikovski, L., Goldshmit, Y., Ruban, A., et al. (2020). Mesenchymal stem cells derived extracellular vesicles improve behavioral and biochemical deficits in a phencyclidine model of schizophrenia. *Transl. Psychiatry* 10:305. doi: 10.1038/s41398-020-00988-y
- Uhlhaas, P. J., and Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* 11, 100–113. doi: 10.1038/nrn2774
- Vadodaria, K. C., Mertens, J., Paquola, A., Bardy, C., Li, X., Jappelli, R., et al. (2016). Generation of functional human serotonergic neurons from fibroblasts. *Mol. Psychiatry* 21, 49–61. doi: 10.1038/mp.2015.161
- van Dijk, E. L., Jaszczyszyn, Y., Naquin, D., and Therms, C. (2018). The third revolution in sequencing technology. *Trends Genet.* 34, 666–681. doi: 10.1016/j.tig.2018.05.008
- Van Rheeën, T. E., McIntyre, R. S., Balanzá-Martínez, V., Berk, M., and Rossell, S. L. (2021). Cumulative cardiovascular disease risk and triglycerides differentially relate to subdomains of executive function in bipolar disorder: preliminary findings. *J. Affect. Disord.* 278, 556–562. doi: 10.1016/j.jad.2020.09.104
- Van Rheeën, T. E., and Rossell, S. L. (2014). An empirical evaluation of the MATRICS consensus cognitive battery in bipolar disorder. *Bipolar Disord.* 16, 318–325. doi: 10.1111/bdi.12134
- Veldic, M., Kadriu, B., Maloku, E., Agis-Balboa, R. C., Guidotti, A., Davis, J. M., et al. (2007). Epigenetic mechanisms expressed in basal ganglia GABAergic neurons differentiate schizophrenia from bipolar disorder. *Schizophr. Res.* 91, 51–61. doi: 10.1016/j.schres.2006.11.029
- Veselinović, T., and Neuner, I. (2022). Progress and pitfalls in developing agents to treat neurocognitive deficits associated with schizophrenia. *CNS Drugs* 36, 819–858. doi: 10.1007/s40263-022-00935-z
- Vieta, E., Berk, M., Schulze, T., Carvalho, A., Suppes, T., Calabrese, J., et al. (2018). Bipolar disorders. *Nat. Rev. Dis. Primers* 4:18008. doi: 10.1038/nrdp.2018.8
- Viola, T. W., and Fries, G. R. (2019). A promising era for epigenetic research: Revealing the molecular signature of neuropsychiatric disorders. *Braz. J. Psychiatry* 41, 469–470. doi: 10.1590/1516-4446-2019-0638
- Vogel Ciernia, A., and LaSalle, J. (2016). The landscape of DNA methylation amid a perfect storm of autism aetiologies. *Nat. Rev. Neurosci.* 17, 411–423. doi: 10.1038/nrn.2016.41
- Volk, L., Chiu, S. L., Sharma, K., and Haganir, R. L. (2015). Glutamate synapses in human cognitive disorders. *Annu. Rev. Neurosci.* 38, 127–149. doi: 10.1146/annurev-neuro-071714-033821
- Wang, A. M., Pradhan, S., Coughlin, J. M., Trivedi, A., Dubois, S. L., Crawford, J. L., et al. (2019). Assessing brain metabolism with 7-T proton magnetic resonance spectroscopy in patients with first-episode psychosis. *JAMA Psychiatry* 76, 314–323. doi: 10.1001/jamapsychiatry.2018.3637
- Wang, M., Zhang, L., and Gage, F. H. (2020). Modeling neuropsychiatric disorders using human induced pluripotent stem cells. *Protein Cell* 11, 45–59. doi: 10.1007/s13238-019-0638-8
- Wang, W., Rein, B., Zhang, F., Tan, T., Zhong, P., Qin, L., et al. (2018). Chemogenetic activation of prefrontal cortex rescues synaptic and behavioral deficits in a mouse model of 16p11.2 deletion syndrome. *J. Neurosci.* 38, 5939–5948. doi: 10.1523/jneurosci.0149-18.2018
- Wei, H., Zou, H., Sheikh, A. M., Malik, M., Dobkin, C., Brown, W. T., et al. (2011). IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation. *J. Neuroinflamm.* 8:52. doi: 10.1186/1742-2094-8-52
- Wei, X., Ma, T., Cheng, Y., Huang, C. C. Y., Wang, X., Lu, J., et al. (2018). Dopamine D1 or D2 receptor-expressing neurons in the central nervous system. *Addict. Biol.* 23, 569–584. doi: 10.1111/adb.12512
- Whitley, J. T., Fernandes, S., Sharma, A., Mendes, A. P. D., Racha, V., Benassi, S. K., et al. (2022). Reaching into the toolbox: Stem cell models to study neuropsychiatric disorders. *Stem Cell Rep.* 17, 187–210. doi: 10.1016/j.stemcr.2021.12.015
- Williams, S. E., Mealer, R. G., Scolnick, E. M., Smoller, J. W., and Cummings, R. D. (2020). Aberrant glycosylation in schizophrenia: A review of 25 years of post-mortem brain studies. *Mol. Psychiatry* 25, 3198–3207. doi: 10.1038/s41380-020-0761-1
- Wright, C., Turner, J. A., Calhoun, V. D., and Perrone-Bizzozero, N. (2013). Potential impact of miR-137 and its targets in schizophrenia. *Front. Genet.* 4:58. doi: 10.3389/fgenet.2013.00058
- Wroolie, T. E., Kenna, H. A., Singh, M. K., and Rasgon, N. L. (2015). Association between insulin resistance and cognition in patients with depressive disorders: Exploratory analyses into age-specific effects. *J. Psychiatr. Res.* 60, 65–72. doi: 10.1016/j.jpsychires.2014.10.001
- Wysoczański, T., Sokoła-Wysoczańska, E., Pękala, J., Lochyński, S., Czyż, K., Bodkowski, R., et al. (2016). Omega-3 fatty acids and their role in central nervous system - a review. *Curr. Med. Chem.* 23, 816–831. doi: 10.2174/0929867323666160122114439
- Xu, M. Y., and Wong, A. H. C. (2018). GABAergic inhibitory neurons as therapeutic targets for cognitive impairment in schizophrenia. *Acta Pharmacol. Sin.* 39, 733–753. doi: 10.1038/aps.2017.172
- Xu, Z., Jiang, H., Zhong, P., Yan, Z., Chen, S., and Feng, J. (2016). Direct conversion of human fibroblasts to induced serotonergic neurons. *Mol. Psychiatry* 21, 62–70. doi: 10.1038/mp.2015.101
- Yamazaki, M., Yamamoto, N., Yarimizu, J., Okabe, M., Moriyama, A., Furutani, M., et al. (2018). Functional mechanism of ASP5736, a selective serotonin 5-HT5A receptor antagonist with potential utility for the treatment of cognitive dysfunction in schizophrenia. *Eur. Neuropsychopharmacol.* 28, 620–629. doi: 10.1016/j.euroneuro.2018.03.003
- Yang, Y., Liu, Y., Wang, G., Hei, G., Wang, X., Li, R., et al. (2019). Brain-derived neurotrophic factor is associated with cognitive impairments in first-episode and chronic schizophrenia. *Psychiatry Res.* 273, 528–536. doi: 10.1016/j.psychres.2019.01.051
- Yao, B., Christian, K. M., He, C., Jin, P., Ming, G. L., and Song, H. (2016). Epigenetic mechanisms in neurogenesis. *Nat. Rev. Neurosci.* 17, 537–549. doi: 10.1038/nrn.2016.70

- Yap, C. X., Henders, A. K., Alvares, G. A., Wood, D. L. A., Krause, L., Tyson, G. W., et al. (2021). Autism-related dietary preferences mediate autism-gut microbiome associations. *Cell* 184, 5916–5931.e17. doi: 10.1016/j.cell.2021.10.015
- You, M. J., Bang, M., Park, H. S., Yang, B., Jang, K. B., Yoo, J., et al. (2020). Human umbilical cord-derived mesenchymal stem cells alleviate schizophrenia-relevant behaviors in amphetamine-sensitized mice by inhibiting neuroinflammation. *Transl. Psychiatry* 10:123. doi: 10.1038/s41398-020-0802-1
- Zafar, S., and Jabeen, I. (2018). Structure, function, and modulation of  $\gamma$ -aminobutyric acid transporter 1 (GAT1) in neurological disorders: A pharmacoinformatic prospective. *Front. Chem.* 6:397. doi: 10.3389/fchem.2018.00397
- Zalcman, S., Green-Johnson, J. M., Murray, L., Nance, D. M., Dyck, D., Anisman, H., et al. (1994). Cytokine-specific central monoamine alterations induced by interleukin-1, -2 and -6. *Brain Res.* 643, 40–49. doi: 10.1016/0006-8993(94)90006-x
- Zazula, R., Dodd, S., Dean, O. M., Berk, M., Bortolasci, C. C., Verri, W. A. Jr., et al. (2022). Cognition-immune interactions between executive function and working memory, tumour necrosis factor-alpha (TNF-alpha) and soluble TNF receptors (sTNFR1 and sTNFR2) in bipolar disorder. *World J. Biol. Psychiatry* 23, 67–77. doi: 10.1080/15622975.2021.1925152
- Zhang, L., Zheng, H., Wu, R., Kosten, T. R., Zhang, X.-Y., and Zhao, J. (2019). The effect of minocycline on amelioration of cognitive deficits and pro-inflammatory cytokines levels in patients with schizophrenia. *Schizophr. Res.* 212, 92–98. doi: 10.1016/j.schres.2019.08.005
- Zhang, X., Yang, M., Du, X., Liao, W., Chen, D., Fan, F., et al. (2020). Glucose disturbances, cognitive deficits and white matter abnormalities in first-episode drug-naive schizophrenia. *Mol. Psychiatry* 25, 3220–3230. doi: 10.1038/s41380-019-0478-1
- Zhang, Y., Zhao, Y., Song, X., Luo, H., Sun, J., Han, C., et al. (2020). Modulation of stem cells as therapeutics for severe mental disorders and cognitive impairments. *Front. Psychiatry* 11:80. doi: 10.3389/fpsy.2020.00080
- Zheng, P., Zeng, B., Liu, M., Chen, J., Pan, J., Han, Y., et al. (2019). The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. *Sci. Adv.* 5:eaa8317. doi: 10.1126/sciadv.aau8317
- Zhu, F., Ju, Y., Wang, W., Wang, Q., Guo, R., Ma, Q., et al. (2020). Metagenome-wide association of gut microbiome features for schizophrenia. *Nat. Commun.* 11:1612. doi: 10.1038/s41467-020-15457-9
- Zhu, J., Hu, W., Zhou, Y., Qiao, J., Chang, X., and Tong, Z. (2019). Serum high-sensitivity C-reactive protein levels are positively associated with cognitive impairments in patients with first-episode schizophrenia. *Compr. Psychiatry* 94:152118. doi: 10.1016/j.comppsy.2019.152118