Different Neural Mechanisms Underlie Deficits in Mental Flexibility in Post-Traumatic Stress Disorder Compared to Mild Traumatic Brain Injury

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Mental flexibility is a core executive function that underlies the ability to adapt to changing situations and respond to new information. Individuals with post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) complain of a number of executive function difficulties, one of which is mental *in*flexibility or an inability to switch between concepts. While the behavioral presentation of mental inflexibility is similar in those with PTSD or mTBI, we hypothesized that the differences in their etiology would manifest as differences in their underlying brain processing. The neural substrates of mental flexibility have been examined with a number of neuroimaging modalities. Functional magnetic resonance imaging has elucidated the brain regions involved, whereas electroencephalography has been applied to understand the timing of the brain activations. Magnetoencephalography, with its high temporal and spatial resolution, has more recently been used to delineate the spatiotemporal progression of brain processes involved in mental flexibility and has been applied to the study of clinical populations. In a number of separate studies, our group has compared the source localization and brain connectivity during a mental flexibility set-shifting task in a group of soldiers with PTSD and civilians with an acute mTBI. In this article, we review the results from these studies and integrate the data between groups to compare and contrast differences in behavioral, neural, and connectivity findings. We show that the different etiologies of PTSD and mTBI are expressed as distinct neural profiles for mental flexibility that differentiate the groups despite their similar clinical presentations.

Keywords: mental flexibility, executive function, set-shifting, post-traumatic stress disorder, traumatic brain injury, concussion, magnetoencephalography, functional connectivity

INTRODUCTION

Understanding the nature of cognitive dysfunction in different clinical conditions is essential for prescribing appropriate therapies and for developing new targeted interventions. Both post-traumatic stress disorder (PTSD) and a mild traumatic brain injury (mTBI) are considered acquired brain injuries, and although they can occur on their own, they often co-exist or present

with similar symptoms (1). This overlap is particularly prevalent among military populations (2, 3) and presents a challenge for differential diagnosis. Despite good advances in our understanding of PTSD and mTBI, there remains a great need to continue to identify specific neural mechanisms impacted by either condition, and to explore how dysfunction within these neural mechanisms contribute to, and/or exacerbate, clinical symptomology. This focus, while narrow, is one way to probe deeper into the brain mechanisms that are injured to gain an understanding of how the injury may manifest itself in PTSD or mTBI.

Over the years, our laboratory has used magnetoencephalography (MEG) brain recordings to examine cognitive function in a number of different clinical disorders [for reviews, see Ref. (4, 5)]. Our choice of this modality is based on the advantage that MEG offers both high temporal resolution (in the milliseconds) and very good spatial resolution (in the millimeters). As such, MEG is the ideal choice for examining fast-paced cognitive processes [for a review, see Ref. (6)]. Recently, our group has applied our MEG methods to the study of PTSD and mTBI, exploring the neural underpinnings of various cognitive deficits and, in this article, the results from a subset of these studies that investigated mental flexibility using a set-shifting task are discussed.

Dolan et al. (7) presented a review that compared neuroimaging studies in PTSD and mTBI. They summarized differences and similarities in the presentation of neuropsychological deficits between these two groups. Some items on their list clearly differentiated between PTSD and mTBI (for example, attention, inhibition, and working memory), whereas other items showed mild deficits for both groups (for example, set-shifting). From this summary, one would presume that the brain processes underlying the domains that clearly differentiate the groups would be different while the brain processes underlying domains that have similar presentations would be more similar. To our surprise, our investigation into the neural correlates of set-shifting in PTSD and mTBI showed striking differences in brain function, despite similar behavioral performances. In this perspective article, we collate our MEG data on mental flexibility in individuals with PTSD and mTBI, and reconcile the MEG findings with what is known about the mechanisms of injury. In describing this focused body of work, we hope to demonstrate the power of high spatiotemporal resolution neuroimaging in detecting brain differences despite phenotypically similar presentations. This kind of neuroimaging holds potential for developing new methods for differential diagnosis and offers new avenues for designing individually tailored rehabilitation.

COGNITIVE EXECUTIVE FUNCTIONS

Cognitive executive functions refer to those abilities required to achieve independent goal-oriented behavior (8). Cognitive dysfunction encompasses a broad domain and the nature of the cognitive sequelae can result from a number of different factors. Although not exclusively limited to the frontal lobes, the frontal lobes are thought to carry out the majority of processes involved in cognitive executive functions (9).

In a commonly accepted model of the neural substrates of cognitive executive function, the frontal lobes are divided into anatomically discrete categories that subserve distinct functions. These divisions are as follows: the dorsomedial cortex is required for activation and initiation; the lateral frontal cortex for organizing, planning, reasoning, set-shifting, and monitoring; the ventral–medial/orbital cortex for emotional and behavioral regulation, including inhibition, impulsivity, etc.; and the frontopolar cortex for integration and meta-cognitive functions (10). Thus, using this model, one could postulate that if one knew the mechanism of injury and brain site of injury then one could predict which cognitive deficit would ensue.

Executive Dysfunction in PTSD

The DSM-V (11) criteria for diagnosing PTSD include a history of exposure to a traumatic event with the resultant response involving memory intrusions, trigger avoidance, negative changes in cognition and mood, and alterations in arousal and reactivity. Although the clinical presentation varies, cognitive symptoms are commonly reported, and include impaired concentration, affect, and increased impulsivity. This combination of cognitive-emotional and cognitive-behavioral difficulties results in significant distress as well as impairments in functioning [for review, see Ref. (12)].

Much of the neuropsychological research on PTSD has focused on learning and memory; however, there is increasing evidence suggesting that executive dysfunction plays an important role. A recent review systematically explored this topic and collated studies that directly measured executive functioning in PTSD. The results showed that, in general, the PTSD group did more poorly on both memory and cognitive flexibility, although the precise nature of the deficit was heterogeneous (13). Taking this one step further, another review (14) collated factors that may contribute to PTSD susceptibility or provide disease resilience. The authors proposed that difficulties with executive functions in PTSD are not separate symptoms, but these difficulties underlie and sustain the clinical symptoms of hyperarousal, hypervigilance, and intrusive memories.

It has been proposed (15) that the mechanism of action of PTSD stems from inadequate modulation of the limbic systems by medial prefrontal cortices, suggesting deficits in both limbic systems and medial prefrontal cortex. Referring back to the model of the neural substrates of cognitive executive functions (10) described above (see Cognitive Executive Functions), deficits in the medial prefrontal cortex function would impact task activation and initiation. This impact would fit well with the commonly seen PTSD symptoms of depression, anxiety, and lethargy but would not support an impact on executive dysfunction and mental inflexibility. However, our MEG data (described in the Section "MEG Studies of Mental Flexibility in PTSD") raise the possibility of a hybrid model, whereby the limbic systems are inadequately modulated, not because the medial prefrontal cortices are deficit, but because the limbic response is so overwhelming that they interfere with the normal neural processing sequence. This will be further explored in the Section "MEG Studies of Mental Flexibility in PTSD" below.

Executive Dysfunction in mTBI

A mild traumatic brain injury is defined as an insult to the brain from an external force but can occur *without* direct impact to the head. The mechanism of injury results from biomechanical forces that undergo rapid acceleration and deceleration in both a linear and rotational direction. Linear forces likely cause contusions in the frontal and temporal regions, whereas rotational forces likely cause diffuse axonal injury to the brain's white matter tracts (16). While the impact of these translational and rotational forces cannot be seen on traditional structural MRI imaging in mild TBI (17, 18), new diffusion tensor imaging methods have shown correlations between executive dysfunction and mTBI-related axonal injury in the dorsolateral prefrontal cortices (19), as well as frontal and temporal white matter damage that is related to the degree of cognitive dysfunction (20).

There are numerous reviews describing the impact of mTBI on cognitive dysfunctions, but a recent "review of the reviews" (21) reported that, overall, cognitive dysfunctions exist; however, the magnitude of the effect size for each cognitive domain was variable. Furthermore, there is evidence demonstrating that while all individuals who suffer a concussion demonstrate measurable neurocognitive abnormalities at 15 min post-injury, these symptoms resolve within 48 h for the majority of sufferers (22). However, a percentage, as high as 15% (23), of individuals with a mild TBI go on to have persistent symptoms and these symptoms often involve a number of cognitive complaints and dysfunctions (16).

Referring again to the neural substrates model of cognitive executive functions (10), a traumatic brain injury, with its known frontal/temporal damage, should demonstrate deficits in functions subsumed in lateral cortices (24). These functions include planning, organizing, reasoning, set-shifting, and monitoring. Thus, this model would predict that a traumatic brain injury would have direct impact on set-shifting ability.

ASSESSMENT OF MENTAL FLEXIBILITY

Mental flexibility is a core executive function that allows individuals to update their cognitive strategies in the face of changing goals or environments and is essential to adaptive behavior and learning. The neuropsychological evidence for a specific role of mental *in*flexibility in the pathophysiology of both PTSD and mTBI has been equivocal, and it has been suggested that while both groups show mild deficits, there are no differentiable effects in this domain (7). On the other hand, the neural model of executive functions (24), described above, would postulate that the two groups present differently on this task. To explore these opposing views, a neuroimaging modality with high temporal and spatial resolution, such as MEG, may offer insight. Before we present the neuroimaging literature, we will first present the standard assessments used to measure mental flexibility.

In standardized neuropsychological assessments, mental flexibility is assessed with the Stroop test (25), the trail making test (26, 27), and the Wisconsin card sorting task (WCST) (28). An alternative to the WCST that places fewer cognitive demands on participants is the attentional set-shifting, intra-extra dimensional set shift (IED) test (29), from the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition). We have operationalized the IED set-shifting test for use with MEG neuroimaging. We applied this to individuals with PTSD and mTBI, and we will describe our findings in Sections "MEG Studies of Mental Flexibility in PTSD" and "MEG Studies of Mental Flexibility in mTBI" below.

NEUROIMAGING STUDIES OF MENTAL FLEXIBILITY

Functional magnetic resonance imaging (fMRI) studies, using the Wisconsin card sorting test, have identified neural areas involved in mental flexibility processing, which include a distributed network involving prefrontal and frontal cortical regions [e.g., Ref. (30–33)], as well as associated posterior cortical regions [e.g., Ref. (34–36)]. While fMRI and PET studies have been invaluable in localizing brain regions involved in set-shifting, these modalities cannot capture the millisecond timing, and the fine temporal characteristics, of this fast-paced neurocognitive process. Thus, this is an opportunity where MEG recordings may shed light.

MEG Studies of Mental Flexibility

Magnetoencephalography has been used to examine the spatiotemporal dynamics of mental flexibility processes in typical adults. Using both traditional (37) and modified (38, 39) versions of the WCST paradigm, shifting processes were identified in dorsolateral prefrontal cortex (dlPFC; Brodmann area 9) (37) including the superior frontal gyrus (38), as well as the inferior frontal gyrus (BA 45, 47/12), the anterior cingulate, and supramarginal gyrus (BA 40) (38). These findings fit well the neural model of frontal lobe executive functions (10).

Using the simple intra-extra dimensional set-shift paradigm, our group (40) found that easy shifts activated right inferior frontal gyrus (BA 47) and bilateral dorsolateral prefrontal cortices (right BA 9, left BA 10/11), while more difficult shifts, in addition to those listed above, also recruited right superior frontal gyrus (BA 8/10) and left inferior frontal gyrus (BA 44). Furthermore, bilateral parietal areas were activated in both easy and hard conditions. Together, these MEG studies established that a widespread network of frontal and parietal regions is involved in set-shifting in control adults, and these results serve as a baseline for comparison with clinical groups.

NEUROIMAGING STUDIES OF MENTAL FLEXIBILITY IN PTSD

Early behavioral studies examining PTSD and mental flexibility did not find group differences in performance (41, 42). However, there have been three neuroimaging studies (two fMRI and one MEG) looking at mental flexibility in PTSD, and these show differences suggesting that group differences may be subtle. An fMRI study reported that individuals with PTSD failed to activate the right insula when performing an affective set-shifting task (43) while elite military warriors without PTSD showed increased

right anterior insula activation, perhaps reflecting their ability to perform well in highly stressed military situations (44).

MEG Studies of Mental Flexibility in PTSD

We conducted an MEG study where soldiers with and without PTSD were compared on a battery of executive functions task, including a set-shifting task (45, 46). We (46) found that the control soldiers showed a sequence of activations that looked comparable to adult non-military controls (40), involving dorsolateral frontal cortex, insula, and posterior parietal cortices. On the other hand, the soldiers with PTSD showed these same activations; however, these activations were interrupted by activations in paralimbic regions, specifically the posterior cingulate, parahippocampal gyri, and regions in the temporal lobes.

These findings bring to mind the models of PTSD that suggest that the dysfunctional neurocircuitry seen in PTSD is driven by hyper-reactive limbic areas that are not appropriately modulated by prefrontal cortical control regions (15, 47). Specifically, we also found a dissociation of the response in the paralimbic structures – that is, we found increased activation in the cingulate and parahippocampal cortex in the group with PTSD, while the medial prefrontal cortex and the insula were significantly less active. These findings fit with the model of PTSD and suggest that while cortical regions are active and function normally, it is the hyperactive limbic system which interrupts and disrupts their function, with the result being a less efficient pathway of neural activation, and ultimately, a negative impact on function.

Furthermore, our results corroborate the fMRI studies by Simmons and colleagues (43, 44), which showed that individuals with PTSD failed to adequately activate the right insula when performing a set-shifting task, and the authors proposed that the right insula was a key region for resilience against PTSD and maintenance of performance during stressful situations. We specifically tested this hypothesis by re-constructing time courses of activation in the right insula, and we saw a significant difference with a greater and earlier activation in the right insula in the control soldiers compared to the soldiers with PTSD. This would suggest that the control soldiers specifically recruited the insula, and there is not simply widespread, greater activation in the controls. This may be one mechanism that impedes performance on a set-shifting task in PTSD, possibly contributing to difficulties with mental flexibility, which may underlie deficits in other cognitive executive functions.

Finally, we submitted our data to MEG connectivity analyses and found that over all, there were significant large-scale increases in connectivity in the theta frequency band in the PTSD group compared to controls. This hyperconnectivity was concentrated in networks in the right parietal cortex, and the strength of this hyperconnectivity correlated with increased scores on measures of attention, depression, and anxiety, as well as decreases in performance on the mental flexibility task. Taken together, these data suggest that brain network hyperconnectivity may underlie the mental flexibility difficulties seen in PTSD, and this hyperconnectivity may also play a more general role in the other cognitive sequelae seen in PTSD (45).

Recalling Stuss' model (10) of the neural substrates underlying frontal lobe executive functions, these MEG data suggest that the

mild deficits in mental flexibility seen in PTSD are not due to frontal dysfunction of set-shifting systems, but due to excessive limbic activation that blocks the normal sequence of activations and dissipates processing power via hyperconnectivity in key processing nodes.

NEUROIMAGING STUDIES OF MENTAL FLEXIBILITY IN mTBI

A review of the fMRI literature in mTBI (48) found that in the decade between 1999 and 2009, there were fewer than 20 articles investigating cognitive functioning after an mTBI; these focused on executive functions, including working memory and attention and resting state functional connectivity. The authors concluded that while the studies thus far have enhanced our understanding of the impact of an mTBI on executive functions, working memory, attention, and resting state functional connectivity results have not been definitive, and there is a need for continued investigations of task-related activations within specific brain networks [review by McDonald et al. (48)].

MEG Studies of Mental Flexibility in mTBI

There are even fewer MEG studies in mTBI, and these have focused on exploring brain dynamics with resting state functional connectivity analyses. These studies show that MEG functional connectivity can identify sites of brain injury (49, 50), differentiate individuals with mTBI from controls (51), and correlate cognitive recovery (52) and neuropsychological assessments (53) with decreases in functional connectivity.

To the best of our knowledge, there has only been one MEG study examining the impact of an mTBI on mental flexibility. In parallel with the PTSD study described above in the Section "MEG Studies of Mental Flexibility in PTSD," we acquired MEG data in adult men with a mild TBI recruited from the emergency room at a local trauma unit and compared their brain activations, during a mental flexibility set-shifting task, to a group of adult controls. While accuracy was similar between groups, reaction time was significantly slower in the mTBI group, and their sequence of brain activations was disorganized and recruited additional regions not typically involved in set-shifting. We took this as evidence that individuals with mTBI experience slower and more effortful processing, requiring additional compensatory regions to come on-line to accomplish the task (54). Submission of this dataset to connectivity analyses would be an interesting next step, which may offer additional insight as to which brain regions become less connected and how compensatory mechanisms are working.

Referring again to the neural model of executive functions (10), a traumatic brain injury, with its known frontal/temporal damage, should demonstrate deficits in functions subsumed in lateral cortices (24). Our finding of specific neural differences on a set-shifting task supports this model. It should be noted, however, that the participants in our MEG study (54) were recruited and tested within 2 months of their injury although on measures of health status, symptom severity, and symptom count, the mTBI group reported to be significantly more affected than controls. Since the literature (22) shows that the majority of

symptoms resolve within days to weeks, it is likely that our study tapped early manifestations of the chronic aspects of the cognitive deficits seen in post-concussive syndrome, although this requires further empirical testing.

GENERAL DISCUSSION

The neural model of frontal lobe executive functions (10) would predict that, given the different mechanisms of injury involved in PTSD and mTBI, these conditions would perform differently on tasks of mental flexibility. In our studies, while the behavioral and neuropsychological assessments of mental flexibility looked very similar between these groups, our MEG data showed stark differences that clearly differentiate the two groups. The PTSD group showed abnormal activations in paralimbic systems that acted as an obstruction to normal cognitive processing, while the mTBI group showed reduced cognitive processing ability as evidenced by disorganized and delayed brain activations. These findings not only fit known neuroanatomical models of frontal lobe cognitive functions but also indicate that approaches to rehabilitation and therapy need to consider that different neural mechanisms are at play in these disorders. This would suggest that interventions tailored toward addressing the specific dysfunctional mechanism would offer a more effective treatment and long-term outcome. The impact of these studies and their implications for addressing these disorders underline the value of the high temporal and spatial resolution of MEG and its potential utility to change the way we diagnose and treat PTSD and mTBI.

ACKNOWLEDGMENTS

REFERENCES

1. Bryant R. Post-traumatic stress disorder vs traumatic brain injury. *Dialogues Clin Neurosci* (2011) 13(3):251–62.
2. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol* (2008) 167(12):1446–52. doi:10.1093/aje/kwn068
3. Vasterling JJ, Verfaellie M, Sullivan KD. Mild traumatic brain injury and posttraumatic stress disorder in returning veterans: perspectives from cognitive neuroscience. *Clin Psychol Rev* (2009) 29(8):674–84. doi:10.1016/j.cpr.2009.08.004
4. Taylor MJ, Donner EJ, Pang EW. fMRI and MEG in the study of typical and atypical cognitive development. *Neurophysiol Clin* (2012) 42(1–2):19–25. doi:10.1016/j.neucli.2011.08.002
5. Taylor MJ, Doesburg SM, Pang EW. Neuromagnetic vistas into typical and atypical development of frontal lobe functions. *Front Hum Neurosci* (2014) 8:453. doi:10.3389/fnhum.2014.00453
6. Hari R, Salmelin R. Magnetoencephalography: from SQUIDs to neuroscience. Neuroimage 20th anniversary special edition. *Neuroimage* (2012) 61(2):386–96. doi:10.1016/j.neuroimage.2011.11.074
7. Dolan S, Martindale S, Robinson J, Kimbrel NA, Meyer EC, Kruse MI, et al. Neuropsychological sequelae of PTSD and TBI following war deployment among OEF/OIF veterans. *Neuropsychol Rev* (2012) 22(1):21–34. doi:10.1007/s11065-012-9190-5
8. Posner MI, Petersen SE. The attention system of the human brain. *Annu Rev Neurosci* (1990) 13:25–42. doi:10.1146/annurev.ne.13.030190.000325
9. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev* (2006) 16(1):17–42. doi:10.1007/s11065-006-9002-x
10. Stuss DT. Functions of the frontal lobes: relation to executive functions. *J Int Neuropsychol Soc* (2011) 17(5):759–65. doi:10.1017/S1355617711000695
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association (2013).
12. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. *Nat Rev Neurosci* (2012) 13(11):769–87. doi:10.1038/nrn3339
13. Polak AR, Witteveen AB, Reitsma JB, Olff M. The role of executive function in posttraumatic stress disorder: a systematic review. *J Affect Disord* (2012) 141(1):11–21. doi:10.1016/j.jad.2012.01.001
14. Aupperle RL, Melrose AJ, Stein MB, Paulus MP. Executive function and PTSD: disengaging from trauma. *Neuropharmacology* (2012) 62(2):686–94. doi:10.1016/j.neuropharm.2011.02.008
15. Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. *Expert Rev Neurother* (2011) 11(2):275–85. doi:10.1586/ern.10.198
16. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am* (2014) 37(1):1–11. doi:10.1016/j.psc.2013.11.004
17. McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvorak J, Echemendia RJ, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Br J Sports Med* (2013) 47(5):250–8. doi:10.1136/bjsports-2013-092313
18. Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. *Int Rev Psychiatry* (2003) 15(4):341–9. doi:10.1080/09540260310001606728
19. Lipton ML, Gulko E, Zimmerman ME, Friedman BW, Kim M, Gellella E, et al. Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology* (2009) 252(3):816–24. doi:10.1148/radiol.2523081584
20. Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. *J Head Trauma Rehabil* (2010) 25(4):241–55. doi:10.1097/HTR.0b013e3181e52c2a
21. Karr JE, Areshenkoff CN, Garcia-Barrera MA. The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology* (2014) 28(3):321–36. doi:10.1037/neu0000037
22. McCrea M, Kelly JP, Randolph C, Cisler R, Berger L. Immediate neurocognitive effects of concussion. *Neurosurgery* (2002) 50(5):1032–40. doi:10.1227/00006123-200205000-00017
23. McCrea M, Iverson GL, McAllister TW, Hammeke TA, Powell MR, Barr WB, et al. An integrated review of recovery after mild traumatic brain injury (MTBI): implications for clinical management. *Clin Neuropsychol* (2009) 23(8):1368–90. doi:10.1080/13854040903074652
24. Stuss DT. Traumatic brain injury: relation to executive dysfunction and the frontal lobes. *Curr Opin Neurol* (2011) 24(6):584–9. doi:10.1097/WCO.0b013e32834c7eb9
25. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* (1935) 18(6):643–62. doi:10.1037/h0054651
26. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Motor Skills* (1958) 8:271–6. doi:10.2466/pms.1958.8.3.271

27. Tombaugh TN. Trail making test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* (2004) **19**(2):203–14. doi:10.1016/S0887-6177(03)00039-8

28. Milner B. Effects of different brain lesions on card sorting: the role of the frontal lobes. *Arch Neurol* (1963) **9**:100–10. doi:10.1001/archneur.1963.00460070100010

29. Luciana M, Nelson CA. The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia* (1998) **36**(3):273–93. doi:10.1016/S0028-3932(97)00109-7

30. Konishi S, Kawazu M, Uchida I, Kikyo H, Asakura I, Miyashita Y. Contribution of working memory to transient activation in human inferior prefrontal cortex during performance of the Wisconsin card sorting test. *Cereb Cortex* (1999) **9**(7):745–53. doi:10.1093/cercor/9.7.745

31. Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin card sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J Neurosci* (2001) **21**(19):7733–41.

32. Nagahama Y, Sadato N, Yamauchi H, Katsumi Y, Hayashi T, Fukuyama H, et al. Neural activity during attention shifts between object features. *Neuroreport* (1998) **9**(11):2633–8. doi:10.1097/00001756-199808030-00038

33. Rogers RD, Andrews TC, Grasby PM, Brooks DJ, Robbins TW. Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. *J Cogn Neurosci* (2000) **12**(1):142–62. doi:10.1162/089892900561931

34. Konishi S, Hayashi T, Uchida I, Kikyo H, Takahashi E, Miyashita Y. Hemispheric asymmetry in human lateral prefrontal cortex during cognitive set shifting. *Proc Natl Acad Sci U S A* (2002) **99**(11):7803–8. doi:10.1073/pnas.122644899

35. Lie CH, Specht K, Marshall JC, Fink GR. Using fMRI to decompose the neural processes underlying the Wisconsin card sorting test. *Neuroimage* (2006) **30**(3):1038–49. doi:10.1016/j.neuroimage.2005.10.031

36. Nagahama Y, Okada T, Katsumi Y, Hayashi T, Yamauchi H, Oyanagi C, et al. Dissociable mechanisms of attentional control within the human prefrontal cortex. *Cereb Cortex* (2001) **11**(1):85–92. doi:10.1093/cercor/11.1.85

37. Wang L, Kakigi R, Hoshiyama M. Neural activities during Wisconsin card sorting test – MEG observation. *Brain Res Cogn Brain Res* (2001) **12**(1):19–31. doi:10.1016/S0926-6410(01)00022-2

38. Henaff MA, Bayle D, Krolak-Salmon P, Fonlupt P. Cortical dynamics of a self driven choice: a MEG study during a card sorting task. *Clin Neurophysiol* (2010) **121**(4):508–15. doi:10.1016/j.clinph.2009.11.082

39. Perianez JA, Maestu F, Barcelo F, Fernandez A, Amo C, Ortiz Alonso T. Spatiotemporal brain dynamics during preparatory set shifting: MEG evidence. *Neuroimage* (2004) **21**(2):687–95. doi:10.1016/j.neuroimage.2003.10.008

40. Oh A, Vidal J, Taylor MJ, Pang EW. Neuromagnetic correlates of intra- and extra-dimensional set-shifting. *Brain Cogn* (2014) **86**:90–7. doi:10.1016/j.bandc.2014.02.006

41. Gurvits TV, Lasko NB, Schachter SC, Kuhne AA, Orr SP, Pitman RK. Neurological status of Vietnam veterans with chronic posttraumatic stress disorder. *J Neuropsychiatry Clin Neurosci* (1993) **5**(2):183–8. doi:10.1176/jnp.5.2.183

42. Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN Jr, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology* (2002) **16**(1):5–14. doi:10.1037/0894-4105.16.1.5

43. Simmons A, Strigo IA, Matthews SC, Paulus MP, Stein MB. Initial evidence of a failure to activate right anterior insula during affective set shifting in posttraumatic stress disorder. *Psychosom Med* (2009) **71**(4):373–7. doi:10.1097/PSY.0b013e3181a56ed8

44. Simmons AN, Fitzpatrick S, Strigo IA, Potterat EG, Johnson DC, Matthews SC, et al. Altered insula activation in anticipation of changing emotional states: neural mechanisms underlying cognitive flexibility in special operations forces personnel. *Neuroreport* (2012) **23**(4):234–9. doi:10.1097/WNR.0b013e3283503275

45. Dunkley BT, Sedge PA, Doesburg SM, Grodecki RJ, Jetly R, Shek PN, et al. Theta, mental flexibility, and post-traumatic stress disorder: connecting in the parietal cortex. *PLoS One* (2015) **10**(4):e0123541. doi:10.1371/journal.pone.0123541

46. Pang EW, Sedge P, Grodecki R, Robertson A, MacDonald MJ, Jetly R, et al. Colour or shape: examination of neural processes underlying mental flexibility in posttraumatic stress disorder. *Transl Psychiatry* (2014) **4**:e421. doi:10.1038/tp.2014.63

47. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. *Biol Psychiatry* (2006) **60**(4):376–82. doi:10.1016/j.biopsych.2006.06.004

48. McDonald BC, Saykin AJ, McAllister TW. Functional MRI of mild traumatic brain injury (mTBI): progress and perspectives from the first decade of studies. *Brain Imaging Behav* (2012) **6**(2):193–207. doi:10.1007/s11682-012-9173-4

49. Huang MX, Theilmann RJ, Robb A, Angeles A, Nichols S, Drake A, et al. Integrated imaging approach with MEG and DTI to detect mild traumatic brain injury in military and civilian patients. *J Neurotrauma* (2009) **26**(8):1213–26. doi:10.1089/neu.2008.0672

50. Huang MX, Nichols S, Robb A, Angeles A, Drake A, Holland M, et al. An automatic MEG low-frequency source imaging approach for detecting injuries in mild and moderate TBI patients with blast and non-blast causes. *Neuroimage* (2012) **61**(4):1067–82. doi:10.1016/j.neuroimage.2012.04.029

51. Lewine JD, Davis JT, Bigler ED, Thoma R, Hill D, Funke M, et al. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. *J Head Trauma Rehabil* (2007) **22**(3):141–55. doi:10.1097/01.HTR.0000271115.29954.27

52. Tarapore PE, Findlay AM, Lahue SC, Lee H, Honma SM, Mizuiri D, et al. Resting state magnetoencephalography functional connectivity in traumatic brain injury. *J Neurosurg* (2013) **118**(6):1306–16. doi:10.3171/2013.3.JNS12398

53. Castellanos NP, Paul N, Ordonez VE, Demuynck O, Bajo R, Campo P, et al. Reorganization of functional connectivity as a correlate of cognitive recovery in acquired brain injury. *Brain* (2010) **133**(Pt 8):2365–81. doi:10.1093/brain/awq174

54. da Costa L, Robertson A, Bethune A, MacDonald MJ, Shek PN, Taylor MJ, et al. Delayed and disorganised brain activation detected with magnetoencephalography after mild traumatic brain injury. *J Neurol Neurosurg Psychiatry* (2015) **86**(9):1008–15. doi:10.1136/jnnp-2014-308571