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Brain Networks Subserving Emotion Regulation and Adaptation after Mild Traumatic Brain Injury

Harm J. van der Horn,¹ Edith J. Liemburg,² André Aleman,² Jacoba M. Spikman,³ and Joukje van der Naalt¹

Abstract

The majority of patients with traumatic brain injury (TBI) sustain a mild injury (mTBI). One out of 4 patients experiences persistent complaints, despite their often normal neuropsychological test results and the absence of structural brain damage on conventional neuroimaging. Susceptibility to develop persistent complaints is thought to be affected by interindividual differences in adaptation, which can also be influenced by preinjury psychological factors. Coping is a key construct of adaptation and refers to strategies to deal with new situations and serious life events. An important element of coping is the ability to regulate emotions and stress. The prefrontal cortex is a crucial area in this regulation process, given that it exerts a top-down influence on the amygdala and other subcortical structures involved in emotion processing. However, little is known about the role of the prefrontal cortex and associated brain networks in emotion regulation and adaptation post-mTBI. Especially, the influence of prefrontal dysfunction on development of persistent postconcussive complaints is poorly understood. In this article, we aim to integrate findings from functional and structural MRI studies on this topic. Alterations within the default mode, executive and salience network have been found in relation to complaints post-mTBI. Dysfunction of the medial prefrontal cortex may impair network dynamics for emotion regulation and adaptation post-mTBI, resulting in persistent post-concussive complaints.

Key words: adaptation; brain networks; emotion regulation; mild traumatic brain injury; postconcussive complaints

Introduction

TRAUMATIC BRAIN INJURY (TBI) constitutes a major health burden, reaching far beyond the acute care provided directly after injury.^{1,2} Sequelae of TBI include physical, cognitive, and emotional disturbances, which interfere with daily activities.³ The majority of patients with TBI (85–90%) sustain a mild injury (mTBI).⁴ Although most patients recover within weeks postinjury, approximately 15–25% of patients with mTBI experience postconcussive complaints that may persist for months to even years.^{4,5}

In patients with more-severe TBI, conventional neuroimaging (i.e., computed tomography [CT] and magnetic resonance imaging [MRI]) frequently shows lesions or diffuse abnormalities that may correspond with behavioral and cognitive changes postinjury. Prefrontal lesions, in particular, have a serious impact on outcome after moderate-to-severe TBI.⁶ However, conventional imaging modalities often do not detect any structural brain damage in patients with mTBI,^{7,8} despite the fact that these patients report postconcussive complaints. These negative imaging findings contribute to the ongoing debate as to whether postconcussive complaints in this patient group are the direct result of cerebral damage or emanate from maladaptive behavior.⁹

Studies using more-advanced imaging techniques have provided increased knowledge of the underlying pathophysiology of mTBI. Perfusion CT studies in patients with a normal admission CT have shown frontal lobe abnormalities in the acute phase post-mTBI that correlate with unfavorable outcome.¹⁰ Functional MRI (fMRI) and diffusion tensor imaging (DTI) studies have demonstrated abnormalities in several brain networks in the subacute and chronic phase post-mTBI.^{11–16} However, these imaging studies mainly focused on the role of brain network function in relation to cognitive problems post-mTBI, whereas few studies have investigated the role of networks regarding emotion processing and development of postconcussive complaints. Yet, anxiety and depression are common post-mTBI^{17,18} and are associated with cognitive complaints¹⁹ and vocational outcome.¹⁸

In individual patients, persistent postconcussive complaints are rather unpredictable, despite comparable injury mechanisms. Therefore, an important question in mTBI research concerns which patients are at risk to develop persistent complaints. The vulnerability of patients to develop persistent complaints is likely to be determined by interindividual differences in *adaptation*, which refers to the capacity of an individual to adequately deal with new situations and life events. In mTBI, adaptation defines the interplay

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between acutely arisen impairments postinjury, complaints, stress, and cognitive and emotional processing. The ability to regulate (negative) emotions and stress is an important aspect of adaptation and is reflected by the use of certain coping styles. Active and problem-directed coping styles are considered to be beneficial, in contrast to passive coping styles with a bias toward negative emotions, of which worrying is a typical feature.²⁰ We assume that if patients are not able to cope sufficiently with a changed situation or impairments postinjury, by regulating their emotional state in such a way that they adapt adequately, this may result in the persistence of postconcussive complaints. A study conducted more than two decades ago already demonstrated that asymptomatic patients with mTBI used more-active coping styles than those with persistent complaints.²¹ Improvement of adaptive coping styles, by appropriate (early) psychological interventions, may prevent the development of persistent postconcussive complaints.²⁰

Given that the prefrontal cortex and associated brain networks are crucial for adaptation,^{22,23} prefrontal dysfunction may play a role in development of persistent postconcussive complaints. The aim of this overview was to synthesize findings from available fMRI and DTI literature on (prefrontal) brain network function post-mTBI, in an attempt to explain the role of adaptation, and particularly emotional regulation, in the development of persistent complaints in this patient group. First, the relationship between brain networks and adaptation in patients without TBI and healthy control subjects is described. Second, a comprehensive review of studies on mTBI is provided, and findings are integrated with those of people without TBI, in order to find possible explanations for the development of persistent complaints post-mTBI. Third, our ideas and interpretations are further discussed, and possible limitations, current knowledge gaps, and possible directions for future research are addressed.

Adaptation in People without Traumatic Brain Injury

Cognitive and emotional processes involved in adaptation are intricately intertwined, and that also applies to the corresponding brain networks. In this section, we will provide an overview of the brain networks that are involved in the different aspects of adaptation in people without TBI. Further, we aim to explain how problems with adaptation may arise from disturbed network dynamics and can lead to psychopathology.

Brain networks and adaptation

In everyday life, an individual needs to adapt his or her behavior to a continuously changing environment. In order to do this, adequate shifting between internally and externally directed mental states is imperative. The internally directed mental state of an individual encompasses the attendance to internally generated stimuli, for example, thoughts about one's present self, about past experiences or about upcoming events. The default mode network (DMN) is an important brain network regarding this internally directed mental state.²⁴ This network is highly active when a person is awake, but at rest. Core areas of the DMN are the medial prefrontal cortex (MPFC) and rostral anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the precuneus, and the medial temporal lobes.²⁵ Research has shown that parts of the DMN become active with several internally focused mental tasks, such as self-referential processing and introspection.^{24,26} In general, the DMN is subdivided into two subsystems: a medial frontal subsystem, which is especially important for self-relevant mental exploration, and a medial temporal subsystem, which serves mnemonic processes involving autobiographical memory.²⁶

Regarding the externally directed mental state, several networks are involved, such as the central executive network, the cognitive and executive control networks, and the ventral and dorsal attention networks.^{27–31} We will refer to these networks as the executive networks. Regardless of distinctions between these networks, a common region is the lateral prefrontal cortex. This area is important for several aspects of executive behavior, such as working memory, attention, response inhibition, decision making, and planning.³² The ACC is a crucial area for controlling executive behavior and therefore an important area in the prefrontal cortex.³³

Given that attentional resources are limited, and internally and externally directed networks are involved in different functions, simultaneous activation of the DMN and the executive networks may be ineffective.²⁶ Hence, optimal dynamics between these networks are a prerequisite to adequately adjust mental states to the changing situations in everyday life.^{22,23} This process is directed by the salience network (SN), which consists of the anterior insula/inferior frontal gyrus, the dorsal ACC, and part of the amygdala.²⁷ This network coordinates responses to novel, salient and unpredictable situations, and integrates novel information with previous knowledge and past experiences.³⁴ Importantly, the SN facilitates activation of the executive networks and deactivation of the DMN during cognitive task performance, when processing of external stimuli is required.^{27,28,35} If this mechanism does not work properly, it will result in insufficient suppression of DMN activity, which leads to attention lapses and poor cognitive performance.³⁶ This phenomenon has been described as default mode interference.³⁷

Figure 1 shows spatial maps of the DMN, executive network(s), and salience network. In addition to the MPFC, the PCC seems to play an important role in switching between networks and mental states.³⁸ Although the PCC is most frequently associated with the DMN, it has been shown that during increased cognitive task difficulty, the dorsal PCC more strongly connects to one of the executive networks.³⁹ This finding suggests that this area probably contributes to cognitive control by modulating internally and externally focused attention.

Networks in emotion and stress regulation

Intact network dynamics are crucial for the regulation of emotions and stress.^{22,23} Emotion regulation can be considered a core element of coping, which refers to the ability of an individual to react adequately in emotionally salient, stressful, and often unpredictable situations. Stress is defined as a physical and emotional response to a threatening or challenging internal or external stimulus and is considered beneficial on the short term.⁴⁰ Chronic stress, however, can lead to a variety of physical and mental diseases, including feelings of anxiety and depression.⁴¹

The amygdala, also as a part of the SN, serves to signal emotionally salient external stimuli and contributes to the emotional awareness of an individual.^{27,42,43} Acute (short-term) stress has been found to be related to increased functional connectivity of areas within the SN⁴⁴ and enhanced coupling between the amygdala and the DMN.⁴⁵ How subjects subsequently react and adapt to a stressful situation depends on their ability to actively regulate their emotional state. It has been theorized that a proper balance between internally and externally directed networks is pivotal for adequate emotion regulation and mental health.^{22,23} The prefrontal areas that are associated with both the DMN and the executive networks regulate amygdala activity in response to emotionally salient information, such as a stressful stimulus.^{46–49} This prefrontal-amygdala connectivity is associated with the ability to attenuate negative emotions.⁴⁶ Long-term stress is accompanied by disruptions in these emotion

FIG. 1. Spatial maps representing the main brain networks associated with cognitive and emotional processes underlying adaptation. The default mode network (blue) and executive network(s) (yellow) are involved in internally and externally focused mental processes, respectively. The salience network (red) coordinates switching between these networks and corresponding mental states. Brain sections are displayed in neurological convention. Data were derived from two ongoing studies at our department. Color image is available online at www.liebertpub.com/neu

regulation circuits. For example, patients with a burnout syndrome show reduced functional connectivity between the prefrontal cortex (ACC and dorsolateral prefrontal cortex) and the amygdala.⁵⁰

Networks in mood and anxiety disorders

Disturbances in emotion and stress regulation circuits are a hallmark of several psychiatric diseases, such as depression and anxiety disorders.^{51,52} In general, emotion regulation impairments in these disorders are characterized by altered function of the prefrontal cortex and ACC in association with overactivity of limbic structures, especially the amygdala.^{53–55} However, there are major differences between patients with depression and those with anxiety disorders regarding emotion and stress regulation.

In patients with a major depressive disorder, increased activity and connectivity within the DMN are often found in comparison with healthy subjects, which is thought to be associated with rumination^{52,56} and/or with an increased effort to regulate (negative) emotions.⁵¹ This increase in DMN function appears to be related to increased functional connectivity between the SN and the DMN.⁵⁷

In contrast, self-reflective processes that are considered adaptive in these patients, were found to be associated with increased coupling between the SN and the executive networks.^{56,57}

Patients with anxiety disorders frequently show increased activity and functional connectivity within the SN, which is thought to be reflective of a hypervigilant state.^{51,58} Problems with regulation of SN reactivity may be related to impairment of emotional control in these patients.⁵¹ However, functional connectivity alterations in emotion regulation circuits may vary between anxiety disorder subtypes. For example, social anxiety disorder has been associated with diminished resting-state functional connectivity between the DMN and the amygdala.⁵⁹ In panic disorder and post-traumatic stress disorder (PTSD), heightened functional connectivity has been found between areas of the DMN and the amygdala and the SN.^{58,60}

Summary of findings in people without traumatic brain injury

Adaptation can be hypothesized to depend on the appropriate adjustment of default mode and executive network activity in

response to changing situations. The SN acts as a moderator, by regulating the balance between these networks. For effective emotion regulation, the prefrontal areas are particularly important, because of the influence on the amygdala and SN (reactivity). In general, depression is characterized by increased DMN function, and anxiety disorders are associated with increased SN function. Although the results vary between studies and disease subtypes, in both anxiety and depression disorders, a disturbed interplay is found between brain networks involved in emotion regulation.

Adaptation in Mild Traumatic Brain Injury

In patients with mTBI, an explanation for the persistence of postconcussive complaints is mostly not found with conventional imaging or neuropsychological tests. Although the exact nature of these complaints remains elusive, fMRI and DTI studies have shown the involvement of functional brain regions and networks that are necessary for adaptation and suggest that prefrontal dysfunction may play a pivotal role in the development of complaints post-mTBI. Table 1 provides a summary of the relevant studies on network function and adaptation post-mTBI.

Network dynamics and postconcussive complaints

Patients with mTBI often report cognitive complaints, despite neuropsychological test results that fall within the normal range.¹⁹ Mental fatigue is one of the most frequently reported complaints.⁶¹ fMRI studies have shown increases in activation suggestive of increased mental effort during cognitive task performance.⁶² During highly demanding cognitive tasks, executive networks are frequently found to be hyperactivated (especially the right prefrontal cortex), possibly reflecting the need of engaging additional neural resources to maintain cognitive performance at a sufficient level.⁶² It could thus be hypothesized that this increased mental effort might cause mental fatigue. Alterations within the brain's resting state, expressed as functional connectivity changes within resting-state networks,²⁵ may support this hypothesis. For example, Shumskaya and colleagues demonstrated increased functional connectivity within a right lateralized executive network in patients with mTBI.⁶³ The researchers attributed this finding to a putatively increased awareness to the external world, and they proposed this as an explanation for mental fatigue. In addition, a study in patients with mild-to-severe TBI showed that increased DMN activity was related to attention problems,¹² which is consistent with the default mode interference hypothesis.³⁷ Further, increased functional connectivity between internally and externally directed functional brain networks is associated with cognitive complaints in patients with mTBI.^{64,65} The augmented connectivity of the executive networks with the DMN may facilitate suppression of DMN activity, which reflects an increased effort to prevent default mode interference.

These aforementioned causative mechanisms behind postconcussive complaints are still rather speculative, especially given that in most studies patients have been scanned at one single time point postinjury. Some imaging studies have also measured changes in network connectivity over time.^{66–68} It has been shown that deficits in functional network connectivity become more pronounced over time in patients with complaints, while possible compensatory connectivity changes also seem to arise.^{66,67} For example, increases in temporal connectivity are thought to compensate for frontal connectivity deficits in patients with complaints.⁶⁶ Longitudinal changes in network function may already occur within the first month postinjury.^{67,68} Interestingly, decreased DMN functional connectivity was observed in patients

without postconcussive complaints at 1 week postinjury, which is consistent with previous research.⁶⁹ This reduction in connectivity was found to be (partly) normalized at 1 month postinjury. More longitudinal research is needed to elucidate the causative relationships between mTBI, network changes, and postconcussive complaints.

Emotion regulation and postconcussive complaints

In patients with mTBI, postconcussive complaints are often present together with feelings of anxiety and depression.^{18,70} Cognitive complaints post-mTBI have been shown to be strongly related to emotional distress and premorbid personality traits, whereas only a minor association with cognitive impairment was found.¹⁹ Moreover, it is often difficult to disentangle postconcussive complaints from symptoms that are characteristic for PTSD, which further illustrates that disturbances in emotion and stress regulation are considerably intertwined with the presence of complaints post-mTBI.⁷¹

Few fMRI studies have investigated brain function with regard to anxiety and depression post-mTBI. Recently, Nathan and colleagues have reported that increased functional connectivity of the DMN was associated with anxiety, depression, and attention problems.⁷² In a study on working memory performance in patients with mTBI, depression was associated with increased activity of areas within the DMN and decreased activity of areas associated with executive functioning.⁷³ These findings are in correspondence with studies of patients with a major depressive disorder.⁵² Further, a recent electroencephalography study reported that patients with mTBI and depression are more sensitive to emotional stimuli during cognitive task performance.⁷⁴ The researchers suggested that cognitive performance in these patients puts a demand on those executive areas that are also required for emotional control, resulting in less availability of these resources for emotion regulation purposes. These findings are in line with the point of view that the executive networks are of the utmost importance for emotion regulation and mental health.^{22,23} Based on several other studies, we assume that the extra effort necessary for dealing with external tasks leads to mental fatigue in patients with mTBI, which, in turn, affects the ability to regulate emotions, because of exhaustion of the executive networks.^{62–65}

Emotion regulation thus depends on adequate network functioning and on interaction between the prefrontal cortex and limbic areas and, in particular, the amygdala.^{46–49} Resting-state fMRI studies have demonstrated that decreased medial prefrontal functional connectivity within the DMN is related to a higher number and more-severe postconcussive complaints, including feelings of anxiety and depression, in patients with mTBI.^{75,76} Further, especially, a decreased functional connectivity of the ACC within the DMN and executive networks was associated with a greater number of complaints.⁷⁶ In adolescents with moderate-to-severe TBI, reduced resting-state functional connectivity has been observed between the rostral ACC and the amygdala.⁷⁷ However, this study contained a small number of patients, and the researchers did not report any correlations between functional connectivity and anxiety or depression. To our knowledge, no further information on the function of frontolimbic circuits in emotion regulation post-TBI is available.

It should be noted that the current evidence on network function and emotion regulation post-mTBI is not without contradictions, especially regarding the DMN. For example, some studies reported a relationship between decreased DMN connectivity and disturbed

TABLE 1. SUMMARY OF RELEVANT STUDIES ON BRAIN NETWORK FUNCTION SUBSERVING ADAPTATION IN PATIENTS WITH MTBI

Study	No. of patients	% male	Age, mean, y (SD), range	Time postinjury, wks	Methods	Main results
<i>fMRI studies</i>						
Chen, 2008	40	100	≈28 ^a	22–30	WMT, GLM	↑ activity DMN and ↓ activity EN related to ↑ depression
Johnson, 2012	14 ^b	36	20.6 (1.2), 19–22	1–2	RS, seed-voxel, and ROI-to-ROI	↑ and ↓ FC DMN
Shumskaya, 2012	35	63	Median = 39, 18–60	0–4	RS, ICA	↑ FC right EN
Zhou, 2012	23	74	37.8 (12.9), NR	0–8	RS, seed-voxel, ICA, and hybrid ICA	↑ FC ant. DMN related to ↓ PCC, anxiety, and depression
Messé, 2013	55	67	34.9 (11.5), NR	1–3 and 26	RS, GT	↑ FC temporal lobes in subacute phase, ↓ FC frontal lobes related to ↑ PCC in chronic phase
Sours, 2013	23	48	39.5 (16.4), NR	4–8	RS, Seed-voxel, and ROI-to-ROI	↑ FC of DMN-EN, DMN-SN, and EN-SN related to ↑ PCC
Sours, 2014	41	73	43.7 (17), NR	1 and 4–6	RS, seed-voxel	↓ FC DMN related to ↓ PCC at 1 week postinjury, ↓ FC EN related to ↑ PCC at 5 weeks postinjury
Nathan, 2015	15	100	25.6 (4.4), NR	9–43	RS, ICA, and GOF	↑ FC DMN with ↓ emotional functioning
<i>DTI studies</i>						
Chu, 2010	10	40	15.7 (1.18), 14–17	0–1	Voxel- and ROI-based	↓ MD and ↑ ↓ FA related to ↑ PCC and emotional distress
Rao, 2012	14	71	≈36 ^a	0–4	ROI-based	↓ FA and ↑ ↓ MD related to ↑ depression over time
Strain, 2013	26	100	57.8 (11.3), 41–79	Chronic	TBSS	↓ FA (esp. forceps minor) related to ↑ depression and PCC
Maller, 2014	26	62	≈41 ^a	6–520	TBSS	Altered diffusivity (↓ axial and ↑ radial; i.e. of prefrontal regions) related to major depression post-mTBI
Lange, 2015	72	76	≈34 ^a	6–8	TBSS	No differences between patients with and without PCC
Waljas, 2015	126 ^c	44	37.8 (13.5), 16–64	2–9	ROI-based	No differences between patients with and without PCC
<i>fMRI+DTI studies</i>						
Mayer, 2011	27	44	27.2 (7.4), NR	1–2 and 14–17	FMRI: RS, seed-voxel; DTI: ROI-based	↓ FC DMN and ↑ FC of DMN-EN, relationship with ↑ PCC; ↑ FA of EC and ACR in patients; ↓ FA CB related to ↑ FC DMN only in healthy controls
Stevens, 2012	30	67	31.7 (13.9), 18–55	2–20	FMRI: RS, ICA; DTI: CCA+JICA	↓ FC of ACC in DMN and EN related to ↑ PCC; No changed relationship between FC and FA in DMN, EN, and SN
Zhu, 2015	8	100	20 (1.3), NR	Day 1, day 7, and day 30	FMRI: RS, seed-voxel, and ROI-to-ROI; DTI: tractography and TBSS	↓ FC DMN at day 7, partial recovery at day 30; No changes in structural DMN connectivity

^aMean age for the total mTBI population was estimated using mean ages provided for patient subgroups.^bAn additional group of patients was included to investigate multiple concussions.^cDTI was performed in a subset of 71 patients.

ACR, anterior corona radiata; ant., anterior; CB, cingulum bundle; CCA, canonical correlation analysis; DMN, default mode network; DTI, diffusion tensor imaging; EC, external capsule; EN, executive network(s); esp., especially; FA, fractional anisotropy; FC, functional connectivity; fMRI, functional magnetic resonance imaging; GLM, general linear model; GOF, goodness of fit; GT, graph theory; i.a., inter alia; ICA, independent component analysis; JICA, joint independent component analysis; MD, mean diffusivity; NR, not reported; No., number; PCC, postconcussive complaints; ROI, region of interest; RS, resting-state; SD, standard deviation; SN, salience network; TBSS, tract-based spatial statistics; wks, weeks; WMT, working memory task; y, years.

emotion regulation and increased complaints,^{75,76} whereas others reported the opposite.^{14,72} Moreover, contradictory results have been reported even within a single study.⁷⁶ There are several factors that may explain these varying results, including differences in injury severity (e.g., uncomplicated vs. complicated mTBI), injury mechanism (e.g., civilian mTBI vs. blast-related mTBI), number of sustained concussions (especially relevant for sports-related concussion), time postinjury, sample size, and methods that are used to analyze imaging data. It is also important to realize that network dysfunction is useful to explain neurological mechanisms behind sequelae post-mTBI, but that it does not imply that the cause is mTBI.⁷⁸ For example, preinjury variables, such as differences in personality and vulnerability for psychiatric symptoms, may also significantly affect the functioning of brain circuitry necessary for postinjury adaptation.

Emotion regulation and microstructural injury

Changes in brain networks can be related to functional disturbances and/or underlying microstructural damage of the white matter connections. A recent meta-analysis of DTI studies underlines the vulnerability of the frontal brain areas in patients with mTBI.⁷⁹ DTI studies on emotion regulation post-mTBI have reported a direct link between frontal abnormalities and anxiety and/or depression.^{80–83} However, recent studies have shown that the presence or absence of postconcussive complaints is not related to the presence or absence of microstructural injury.^{78,84} These findings indicate that emotion regulation disturbances and concomitant network dysfunction post-mTBI may be more associated with non-injury-related factors, such as coping styles, than with actual injury.²⁰ The relationship between microstructural injury and functional brain network alterations (measured with fMRI), however, has only been investigated for cognitive performance in patients with mild-to-severe TBI.^{11,14,64,85–87} Regarding emotion regulation and postconcussive complaints post-mTBI, this relationship is still unexposed and requires further attention.

Summary of mild traumatic brain injury findings

Based on recent findings, altered network dynamics involved in switching between internally and externally focused mental states can be hypothesized to be related to persistent postconcussive complaints post-mTBI. Main changes comprise a hyperactive DMN and concomitant increases in activity of both the executive and salience networks to overcome default mode interference, which might result in mental fatigue. Excessive DMN function can also be regarded as a reflection of rumination, similar to that in patients with a major depressive disorder. Further, this increased DMN activity may impede activation of executive networks, which are important for effective emotion regulation. In particular, connectivity within the MPFC may be important for emotion regulation in patients with mTBI, given that the DMN, executive networks, and SN converge in this area. Decreased medial prefrontal connectivity is actually related to more postconcussive complaints. Therefore, the assumption that dysfunction of the MPFC might impair network dynamics for emotion regulation and adaptation, resulting in persistent postconcussive complaints post-mTBI, merits further attention.

Discussion

The development of persistent postconcussive complaints in mTBI is still an intriguing puzzle, which most likely involves

multiple factors in addition to the fact that TBI itself is a heterogeneous condition. Neuroscientists have only just begun to unravel the neural substrates of these complaints. Based on the available imaging literature, we suggest that disturbances in the dynamics of brain networks subserving cognitive and emotional functioning may be involved in adaptive deficits leading to persistent postconcussive complaints. In this article, we have attempted to integrate results from studies on mTBI with those from psychiatric disorders and healthy controls. However, findings cannot simply be extrapolated, given that many differences between patients with and without TBI are present. Network function may also vary between individuals with the same disorder and between healthy controls, which is often unnoticed with the group-directed approach used in neuroimaging analyses. In addition, different areas within a network exert various functions and one cannot attribute one function to one particular brain network. All of these factors impede a straightforward integration of results into one explanatory concept of postconcussive complaints.

We acknowledge that our interpretations need further substantiation owing to the preliminary, and even partly contradictory, nature of the developing data. Nevertheless, research has yielded interesting results, leading to new questions and research goals. It is evident that the function of the prefrontal cortex (and associated networks) needs further assessment, given that this region plays a key role in several aspects of adaptive behavior. The medial prefrontal cortex, and the ACC in particular, serves as an important relay station between the major brain networks involved in cognition and emotion regulation. Owing to the fact that the frontal regions are most vulnerable in mTBI, it seems likely that decreased medial prefrontal function post-mTBI leads to impaired switching between these networks. This may result in default mode interference and emotion regulation deficits, which, in turn, could cause problems with adaptation and subsequent persistent postconcussive complaints. Further, interference of the SN and amygdala with function of the prefrontal cortex might play an important role regarding stress responses and thus in adaptation post-mTBI.

Studying the association between neuroimaging and adaptation strategies, such as preferred coping styles, will certainly increase knowledge on the role of the prefrontal cortex in adaptation post-mTBI. Coping styles are thought to be relatively stable over time.⁸⁸ Hence, susceptibility to develop persistent complaints might be related to individual premorbid brain network organization involved in adaptation. This assumption underlines the difficulty to disentangle preinjury network characteristics from those caused by the injury itself or occurring compensatory in response to the injury. Indeed, recent studies have provided strong evidence that pre-existing psychiatric disorders may be responsible for persistent postconcussive complaints at 1, 3, and 6 months postinjury.^{84,89,90} In most neuroimaging studies on mTBI, psychiatric comorbidity is an exclusion criterion; however, mild pre-existing psychological problems and undiagnosed psychiatric conditions may still be related to network dysfunction post-mTBI. For future research, it might be interesting to investigate the differences in network function between mTBI patients with and without pre-existing mental conditions.

Few studies are available that investigated changes in connectivity over time in patients with mTBI. More knowledge about the longitudinal changes in neural processes underlying adaptive deficits post-mTBI may facilitate the development of more-appropriate interventions. It would be challenging to investigate whether recovery, in terms of reduction of complaints, could result from newly acquired adaptive skills and is reflected in the

restoration of disturbed network dynamics and emotion regulation circuits.

The causal relationships between mTBI, network dysfunction, and postconcussive complaints remain unclear. With DTI studies, possible microstructural changes underlying disturbed functional connectivity patterns post-mTBI can be determined. Combined with fMRI, it offers the opportunity to investigate whether functional changes in emotion regulation circuits are related to specific patterns of axonal injury, or compensatory mechanisms associated with interindividual differences in adaptation and complaints in patients with mTBI. Recent studies are inconclusive on this topic, given that most did not integrate findings from fMRI and DTI data.

To conclude, more research is required to apprehend the role of brain networks in adaptation post-mTBI. We suggest focusing on the prefrontal cortex and the relationship with anxiety, depression, and coping. It is of the utmost importance that future studies include homogenous patient samples and take into account the longitudinal aspects of network alterations and symptomatology post-mTBI.

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