Adaptation after mild traumatic brain injury

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2. Brain Networks Subserving Emotion Regulation and Adaptation After Mild Traumatic Brain Injury

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Abstract

The majority of patients with traumatic brain injury sustain a mild injury (mTBI). One out of four patients experiences persistent complaints, despite their often normal neuropsychological test results and the absence of structural brain damage on conventional neuroimaging. The susceptibility to develop persistent complaints is thought to be affected by inter-individual differences in adaptation, which can also be influenced by pre-injury 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, as 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 after mTBI. Especially, the influence of prefrontal dysfunction on the development of persistent post-concussive complaints is poorly understood. In this paper 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.

Introduction

Traumatic brain injury (TBI) constitutes a major health burden, reaching far beyond the acute care provided directly after injury (Corrigan et al. 2010; Tagliaferri et al. 2006). The sequelae of TBI include physical, cognitive and emotional disturbances, which interfere with daily activities (Benedictus et al. 2010). The majority of patients with TBI (85-90%) sustain a mild injury (mTBI) (Bazarian et al. 2005). Although most patients recover within weeks after injury, approximately 15-25% of the patients with mTBI experiences post-concussive complaints that may persist for months to even years (Bazarian et al. 2005; Willer & Leddy 2006).

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 behavioural and cognitive changes after injury. Prefrontal lesions in particular, have a serious impact on outcome after moderate to severe TBI (Spikman et al. 2012). However, conventional imaging modalities often do not detect any structural brain damage in patients with mTBI (Bazarian et al. 2006; Iverson et al. 2000), despite the fact that these patients report post-concussive complaints. These negative imaging findings contribute to the ongoing debate as to whether post-concussive complaints in this patient-group are the direct result of cerebral damage or emanate from maladaptive behaviour (Wood 2004).

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 after mTBI that correlate with unfavourable outcome (Metting et al. 2009). Functional MRI (fMRI) and diffusion tensor imaging (DTI) studies have demonstrated abnormalities in several brain networks in the subacute and chronic phase after mTBI (Bonnelle et al. 2011; Bonnelle et al. 2012; Jilka et al. 2014; Sharp et al. 2014; Sharp et al. 2011; Mayer et al. 2015). However, these imaging studies mainly focused on the role of brain network function in relation to cognitive problems after mTBI, while few studies have investigated the role of networks regarding emotion processing and the development of post-concussive complaints. Yet, anxiety and depression are common after mTBI (van der Horn et al. 2013; Smith 2006), and are associated with cognitive complaints (Stulemeijer et al. 2007) and vocational outcome (van der Horn et al. 2013).

In individual patients, persistent post-concussive 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 inter-individual 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 between acutely arisen impairments after injury, 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 towards negative emotions, of which worrying is a typical feature (Anson & Ponsford 2006). We assume that if patients are not able to cope sufficiently with a changed situation or impairments after injury, by regulating their emotional state in such a way that they adapt adequately, this may result in the persistence of post-concussive 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 (Bohnen et al. 1992). Improvement of adaptive coping styles, by appropriate (early) psychological interventions, may prevent the development of persistent post-concussive complaints (Anson & Ponsford 2006).

Since the prefrontal cortex and associated brain networks are crucial for adaptation (Cole et al. 2014; Tops et al. 2014), prefrontal dysfunction may play a role in the development of persistent post-concussive complaints. The aim of this overview was to synthesize findings from available fMRI and DTI literature on (prefrontal) brain network function after 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 after 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 TBI

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. Furthermore, 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 behaviour 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 (Andrews-Hanna et al. 2014). 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 (Raichle et al. 2001). Research has shown that parts of the DMN become active with several internally focused mental tasks, such as self-referential processing and introspection (Buckner et al. 2008; Andrews-Hanna et al. 2014). 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 (Buckner et al. 2008).

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 (Seeley et al. 2007; Sridharan et al. 2008; Spreng et al. 2010; Vossel et al. 2014; Cole & Schneider 2007). 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 behaviour, such as working memory, attention, response inhibition, decision making and planning (Tanji & Hoshi 2008). The ACC is a crucial area for controlling executive behaviour and therefore an important area in the prefrontal cortex (Shenhav et al. 2013).

Since 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 (Buckner et al. 2008). Hence, optimal dynamics between these networks are a prerequisite to adequately adjust mental states to the changing situations in everyday life (Cole et al. 2014; Tops et al. 2014). 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 (Seeley et al. 2007). This network coordinates responses to novel, salient and unpredictable situations, and integrates novel information with previous knowledge and past experiences (Uddin 2014). 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 (Seeley et al. 2007; Sridharan et al. 2008; Dosenbach et al. 2006). 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 (Weissman et al. 2006). This phenomenon has been

described as *default mode interference* (Sonuga-Barke & Castellanos 2007).

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 (Leech & Sharp 2014). 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 (Leech et al. 2011). This finding suggests that this area probably contributes to cognitive control by modulating internally and externally focused attention.

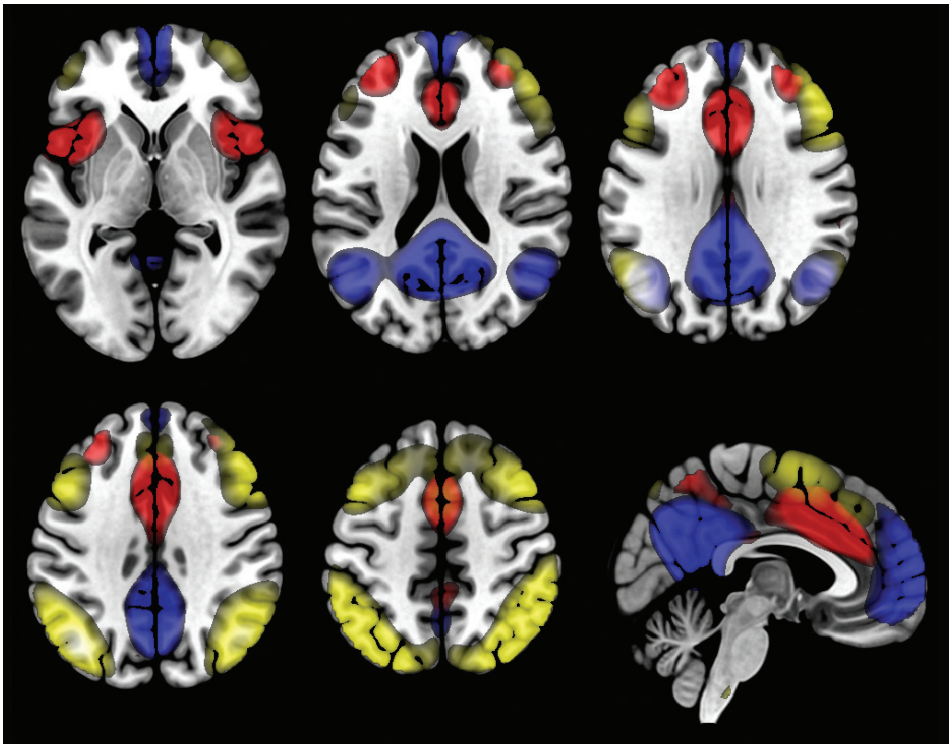

Figure 1: *Spatial maps representing the main brain networks associated with cognitive and emotional processes underlying adaptation. The default mode network (blue) and executive network(s) (yellow) are involved in internally and externally focused mental processes, respectively. The salience network (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.*

Networks in emotion and stress regulation

Intact network dynamics are crucial for the regulation of emotions and stress (Cole et al. 2014; Tops et al. 2014). 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 (de Kloet et al. 2005). Chronic stress, however, can lead to a variety of physical and mental diseases, including feelings of anxiety and depression (Lucassen et al. 2014).

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 (Seeley et al. 2007; Craig 2009; Liberzon et al. 2003). Acute (short-term) stress has been found to be related to increased functional connectivity of areas within the SN (Hermans et al. 2011), and enhanced coupling between the amygdala and the DMN (Veer et al. 2011). 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 (Cole et al. 2014; Tops et al. 2014). 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 (Banks et al. 2007; Herwig et al. 2010; Herwig et al. 2007; Frank et al. 2014). This prefrontal-amygdala connectivity is associated with the ability to attenuate negative emotions (Banks et al. 2007). Long-term stress is accompanied by disruptions in these emotion regulation circuits. For example, patients with a burnout syndrome show reduced functional connectivity between the prefrontal cortex (ACC and DLPFC) and the amygdala (Golkar et al. 2014).

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 (Sylvester et al. 2012; Whitfield-Gabrieli & Ford 2012). In general, emotion regulation impairments in these disorders are characterized by altered function of the prefrontal cortex and ACC in association with over-activity of limbic structures, especially the amygdala (Beauregard et al. 2006; Mochcovitch et al. 2014; Zhong et al. 2011). 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 (Whitfield-Gabrieli & Ford 2012;

Hamilton et al. 2011) and/or with an increased effort to regulate (negative) emotions (Sylvester et al. 2012). This increase in DMN function appears to be related to increased functional connectivity between the SN and the DMN (Manoliu et al. 2014). 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 (Hamilton et al. 2011; Manoliu et al. 2014).

Patients with anxiety disorders frequently show increased activity and functional connectivity within the SN, which is thought to be reflective of a hyper-vigilant state (Sylvester et al. 2012; Sripada et al. 2012). Problems with regulation of SN reactivity may be related to impairment of emotional control in these patients (Sylvester et al. 2012). 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 (Hahn et al. 2011). 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 (Sripada et al. 2012; Pannekoek et al. 2013).

Summary of findings in people without TBI

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 mTBI

In patients with mTBI, an explanation for the persistence of post-concussive 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 after mTBI. Table 1 provides a summary of the relevant studies on network function and adaptation after mTBI.

Network dynamics and post-concussive complaints

Patients with mTBI often report cognitive complaints, despite neuropsychological test results that fall within the normal range (Stulemeijer et al. 2007). Mental fatigue is one of the most frequently reported complaints (Mollayeva et al. 2014). FMRI studies have shown increases in activation suggestive of increased mental effort during cognitive task performance (Bryer et al. 2013). During highly demanding cognitive tasks, executive networks are frequently found to be hyper-activated (especially the right prefrontal cortex), possibly reflecting the need of engaging additional neural resources to maintain cognitive performance at a sufficient level (Bryer et al. 2013). 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 (Raichle et al. 2001), may support this hypothesis. For example, Shumskaya and colleagues demonstrated increased functional connectivity within a right lateralized executive network in patients with mTBI (Shumskaya et al. 2012). The authors 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 (Bonnelle et al. 2011), which is consistent with the default mode interference hypothesis (Sonuga-Barke & Castellanos 2007). Furthermore, increased functional connectivity between internally and externally directed functional brain networks is associated with cognitive complaints in patients with mTBI (Mayer et al. 2011; Sours et al. 2013). 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 post-concussive complaints are still rather speculative, especially since in most studies patients have been scanned at one single time-point post-injury. Some imaging studies have also measured changes in network connectivity over time (Messe et al. 2013; Sours et al. 2014; Zhu et al. 2015). 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 (Messe et al. 2013; Sours et al. 2014). For example, increases in temporal connectivity are thought to compensate for frontal connectivity deficits in patients with complaints (Messe et al. 2013). Longitudinal changes in network function may already occur within the first month after injury (Sours et al. 2014; Zhu et al. 2015). Interestingly, decreased DMN functional connectivity was observed in patients without post-concussive complaints at one week after injury (Zhu et al. 2015), which is consistent with previous research (Johnson et al. 2012). This reduction in connectivity was found to be (partly) normalized at 1 month post-injury. More longitudinal research is

needed to elucidate the causative relationships between mTBI, network changes, and post-concussive complaints.

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
FMRI Studies						
Chen, 2008	40	100	≈ 28*	22-30	WMT, GLM	↑activity DMN & ↓activity EN related to ↑ depression
Johnson, 2012	14 †	36	20.6 (1.2), 19-22	1-2	RS, Seed-voxel & ROI-to-ROI	↑&↓ 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 & hybrid ICA	↑FC ant. DMN related to ↑PCC, anxiety & depression
Messé, 2013	55	67	34.9 (11.5), NR	1-3 & 26	RS, GT	↑FC temporal lobes in sub-acute phase, ↓FC frontal lobes related to ↑PCC in chronic phase
Sours, 2013	23	48	39.5 (16.4), NR	4-8	RS, Seed-voxel- & ROI-to-ROI	↑FC of DMN-EN, DMN-SN & EN-SN related to ↑PCC
Sours, 2014	23	73	43.7 (17), NR	1& 4-6	RS, seed-voxel	↓FC DMN related to ↓PCC at 1 week post-injury, ↓FC EN related to ↑PCC at 5 week post-injury
Nathan, 2015	15	100	26.6 (4.4), NR	9-43	RS, ICA & GOF	↑FC DMN with ↓emotional functioning
DTI studies						
Chu, 2010	10	40	15.7 (1.18), 14-17	0-1	Voxel- & ROI-based	↓MD & ↑↓FA related to ↑ PCC & emotional distress
Rao, 2012	14	71	≈ 36*	0-4	ROI-based	↓FA & ↑↓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 & PCC

Maller, 2014	26	62	≈ 41*	6-520	TBSS	Altered diffusivity (↓axial & ↑radial; i.a. of prefrontal regions) related to major depression after mBTI
Lange, 2015	72	76	≈ 34*	6-8	TBSS	No differences between patients with and without PCC
Waljas, 2015	126 ‡	44	37.8 (13.5), 16-64	2-9	ROI-based	No differences between patients with and without PCC
FMRI + DTI studies						
Mayer, 2011	27	44	27.2 (7.4), NR	1-2 & 14-17	FMRI: RS, seed-vocel; DTI: ROI-based	↓FC DMN & ↑FC of DMN-EN, relationship with ↑PCC; ↑FA of EC & ACR in patients; ↓FA CB related to ↑FC DMN only in healthy controls
Stevens, 2012	30	67	31.7 (31.9), 18-55	2-20	FMRI: RS, ICA; DTI: CCA + jICA	↓FC of ACC in DMN & EN related to ↓PCC; No changed relationship between FC & FA in DMN, EN & SN
Zhu, 2015	8	100	20 (1.3), NR	Day 1, day 7 & day 30	FMRI: RS, seed-voxel & ROI-to-ROI; DTI: tractography & TBSS	↓FC DMN at day 7, partial recovery at day 30; No changes in structural DMN connectivity

**Mean age for the total mTBI population was estimated using mean ages provided for patient subgroups; †An additional group of patients was included to investigate multiple concussions; ‡DTI 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 = post-concussive 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 post-concussive complaints

In patients with mTBI, post-concussive complaints are often present together with feelings of anxiety and depression (van der Horn et al. 2013; Rapoport et al. 2003). Cognitive complaints after mTBI have been shown to be strongly related to emotional distress and pre-morbid personality traits, whereas only a minor association with cognitive impairment was found (Stulemeijer et al. 2007). Moreover, it is often difficult to disentangle post-concussive 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 after mTBI (Lagarde et al. 2014).

Few fMRI studies have investigated brain function with regard to anxiety and depression after mTBI. Recently, Nathan *et al.* have reported that increased functional connectivity of the DMN was associated with anxiety, depression and attention problems (Nathan et al. 2015). 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 (Chen et al. 2008). These findings are in correspondence with studies of patients with a major depressive disorder (Whitfield-Gabrieli & Ford 2012). Furthermore, a recent EEG study reported that patients with mTBI and depression are more sensitive to emotional stimuli during cognitive task performance (Mäki-Marttunen et al. 2014). The authors 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 (Cole et al. 2014; Tops et al. 2014). 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 (Bryer et al. 2013; Shumskaya et al. 2012; Mayer et al. 2011; Sours et al. 2013).

Emotion regulation thus depends on adequate network functioning and on the interaction between the prefrontal cortex and limbic areas, and in particular the amygdala (Banks et al. 2007; Herwig et al. 2007; Herwig et al. 2010; Frank et al. 2014). Resting-state fMRI studies have demonstrated that decreased medial prefrontal functional connectivity within the DMN is related to a higher number and more severe post-concussive complaints, including feelings of anxiety and depression, in patients with mTBI (Zhou et al. 2012; Stevens et al. 2012). Furthermore, especially a decreased functional connectivity of the ACC within the DMN and executive networks was associated with a greater number of complaints (Stevens et al. 2012). In adolescents with moderate to severe TBI, reduced resting-state functional

connectivity has been observed between the rostral ACC and the amygdala (Newsome et al. 2013). 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 the fronto-limbic circuits in emotion regulation after TBI is available.

It should be noted that the current evidence on network function and emotion regulation after mTBI is not without contradictions, especially regarding the DMN. For example, some studies reported a relationship between decreased DMN connectivity and disturbed emotion regulation and increased complaints (Zhou et al. 2012; Stevens et al. 2012), whereas others reported the opposite (Sharp et al. 2011; Nathan et al. 2015). Moreover, contradictory results have been reported even within a single study (Stevens et al. 2012). 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-post injury, 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 following mTBI, but that it does not imply that the cause is mTBI (Lange et al. 2015). For example, pre-injury variables, such as differences in personality and vulnerability for psychiatric symptoms, may also significantly affect the functioning of brain circuitry necessary for post-injury adaptation.

Emotion regulation and microstructural injury

Changes in brain networks can be related to functional disturbances and/or to 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 (Eierud et al. 2014). DTI studies on emotion regulation after mTBI, have reported a direct link between frontal abnormalities and anxiety and/or depression (Chu et al. 2010; Maller et al. 2014; Rao et al. 2012). However, recent studies have shown that the presence or absence of post-concussive complaints is not related to the presence or absence of microstructural injury (Lange et al. 2015; Wäljas et al. 2014). These findings indicate that emotion regulation disturbances and concomitant network dysfunction after mTBI may be more associated with non-injury related factors, such as coping styles, than with actual injury (Anson & Ponsford 2006). 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 (Bonnelle et al. 2011; Sharp et al. 2011; Mayer et al. 2011; Palacios et al. 2012; Palacios et al. 2013; Pandit et al. 2013). Regarding emotion regulation and post-concussive

complaints after mTBI, this relationship is still unexposed and requires further attention.

Summary of mTBI 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 post-concussive complaints after 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. Furthermore, this increased DMN activity may impede the 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, as the DMN, the executive networks and the SN converge in this area. Decreased medial prefrontal connectivity is actually related to more post-concussive complaints. Therefore, the assumption that dysfunction of the MPFC might impair network dynamics for emotion regulation and adaptation, resulting in persistent post-concussive complaints after mTBI, merits further attention.

Discussion

The development of persistent post-concussive 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 post-concussive complaints. In this paper, we have attempted to integrate results from studies on mTBI, with those from psychiatric disorders and healthy controls. However, findings cannot simply be extrapolated, as 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 post-concussive complaints.

We acknowledge that our interpretations need further substantiation due 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, as this region plays a key role in several aspects of adaptive behaviour. 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. As the frontal regions are most vulnerable in mTBI, it seems likely that decreased medial prefrontal function after 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 post-concussive complaints. Furthermore, the interference of the SN and the amygdala with function of the prefrontal cortex, might play an important role regarding stress responses and thus in adaptation after 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 after mTBI. Coping styles are thought to be relatively stable over time (Nielsen & Knardahl 2014). Hence, the susceptibility to develop persistent complaints might be related to individual pre-morbid brain network organisation involved in adaptation. This assumption underlines the difficulty to disentangle pre-injury 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 post-concussive complaints at one, three and six months after injury (Wäljas et al. 2014; Lingsma et al. 2015; Ponsford et al. 2012). In most neuroimaging studies on mTBI, psychiatric co-morbidity is an exclusion criterion; however, mild pre-existing psychological problems and undiagnosed psychiatric conditions may still be related to network dysfunction after 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 after 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 post-concussive complaints remain unclear. With DTI studies, possible microstructural changes underlying disturbed functional connectivity patterns after 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 inter-individual differences in adaptation and complaints in patients with mTBI. Recent studies are inconclusive on this topic, as 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 after 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 after mTBI.