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The Default Mode Network as a Biomarker of Persistent Complaints after Mild Traumatic Brain Injury: A Longitudinal Functional Magnetic Resonance Imaging Study

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Abstract

The objective of this study was to examine longitudinal functional connectivity of resting-state networks in patients with and without complaints after uncomplicated mild traumatic brain injury (mTBI). Second, we aimed to determine the value of network connectivity in predicting persistent complaints, anxiety, depression and long-term outcome. Thirty mTBI patients with three or more post-traumatic complaints at 2 weeks post-injury, 19 without complaints, and 20 matched healthy controls were selected for this study. Resting-state functional MRI (fMRI) was performed in patients at 1 month and 3 months post-injury, and once in healthy controls. Independent component analysis (ICA) was used to investigate the default mode, executive and salience networks. Persistent post-traumatic complaints, anxiety, and depression were measured at 3 months post-injury, and outcome was determined at 1 year post-injury. Within the group with complaints, higher functional connectivity between the anterior and posterior components of the default mode network at 1 month post-injury was associated with a greater number of complaints at 3 months post-injury ($\rho=0.59$, $p=0.001$). Minor longitudinal changes in functional connectivity were found for patients with and without complaints after mTBI, which were limited to connectivity within the precuneus component of the default mode network. No significant results were found for the executive and salience networks. Current results suggest that the default mode network may serve as a biomarker of persistent complaints in patients with uncomplicated mTBI.

Keywords: brain networks; fMRI; functional connectivity; mTBI; persistent complaints

Introduction

THE VAST MAJORITY of the traumatic brain injury (TBI) population comprises patients at the milder end of the injury severity spectrum.^{1,2} Patients with a mild TBI (mTBI) often report post-traumatic complaints in the acute phase post-injury.² These acute complaints evolve into persistent complaints in a quarter of the patients, with complaints in the cognitive and affective domain being most persistent.^{2–7} Despite these lasting complaints, neuropsychological performance usually returns to normal levels 1–3 months after injury,^{8–10} and routine MRI scans often shows no intra- or extra-axial pathology.^{11–13}

There is abundant evidence that (pre-injury) psychological factors have a strong influence on whether or not (sub)acute complaints convert into chronic complaints. An important factor is coping, by which is meant one's capacity to adapt to psychological stressors. In general, an active coping style, including positive thinking, is considered beneficial, whereas passive coping with

worrying is viewed as maladaptive.^{14,15} A key aspect of coping is the ability to regulate negative emotions. The importance of emotion regulation is underlined by the close relationship among post-traumatic complaints, anxiety, and depression after mTBI.^{16–18} Negative illness perception (e.g., the belief that symptoms will have long-lasting negative consequences) further contributes to the persistence of post-traumatic complaints.^{18,19} It seems likely that the interaction between maladaptive coping and negative illness perception increases attention to perceived symptoms and causes anxiety and depression in patients with mTBI, resulting in long-lasting complaints and disability.

In order to understand the neural substrate underlying the persistence of complaints after mTBI, more knowledge is needed regarding longitudinal changes in functional networks after mTBI.^{20–22} Several longitudinal functional MRI (fMRI) studies have been conducted on functional networks in mTBI.^{23–27} These studies have shown increases as well as longitudinal decreases in functional connectivity (FC) of brain networks in patients with mTBI,

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which are thought to reflect delayed injury effects or compensatory mechanisms. In particular, disruptions in FC have been found within and between the default mode network (DMN), executive networks (EN), and salience network (SN), which appear to be related to the presence and scores of post-traumatic complaints and mood disturbances.^{21,24,27–29} Whereas the DMN is primarily involved in internally focused, self-relevant mental processes, the EN are mainly switched on during external goal-directed mental processes; for example, when performing a cognitive task.³⁰ The SN facilitates shifting between these networks and associated mental states.³¹ Most importantly, balanced functional networks are crucial for maintaining a mental equilibrium.^{32,33} For example, although the DMN is needed for planning future events and reviewing past experiences, excessive DMN function is associated with mood disturbances and schizophrenia.³³ In mTBI, it is plausible that ongoing internally directed mental processes underlying maladaptive behavior are related to excessive DMN connectivity, possibly mediated via disturbed connections with the EN and SN.²² Persistent perturbations in these network dynamics may be associated with long-lasting complaints and poor outcome.

To investigate this topic, we conducted a longitudinal resting-state fMRI study in the subacute and early chronic phase after uncomplicated mTBI, and included a group of patients with and without complaints early after injury. We used independent component analysis (ICA) to examine longitudinal changes in FC within and between components of the DMN, EN, and SN. In addition, we assessed whether functional network connectivity at 1 month post-injury was associated with persistent complaints at 3 months post-injury, and with outcome at 1 year post-injury.

Methods

Study participants

This fMRI study was part of a multi-center cohort study (UPFRONT study) on outcome after mTBI conducted between January 2013 and January 2016 in three level 1 trauma centers in the Netherlands (University Medical Center Groningen [UMCG], St. Elisabeth Hospital Tilburg, and the Medical Spectrum Twente).³⁴ Two patient groups were included in the current fMRI study: a group of patients with post-traumatic complaints at 2 weeks post-injury (PTC-present) and a group of patients without post-traumatic complaints at 2 weeks post-injury (PTC-absent). Exclusion criteria for the MRI study were: age <18 and >65 years, abnormalities on admission CT scan (i.e., uncomplicated mTBI), major neurological or psychiatric comorbidity, admission for prior TBI, drug or alcohol abuse, mental retardation, and contraindications for MRI (implanted ferromagnetic devices or objects, pregnancy, or claustrophobia). In addition, a group of 20 healthy controls (HC) was recruited, which was matched to the total mTBI group with respect to age, sex, education level, and handedness. This group consisted of 70% male and 85% right handed subjects, with a median age of 30 years (range: 18–61) and a median education level of 6 years (range: 2–7) according to the Verhage classification system.³⁵

The PTC-present group was part of a larger group of patients with complaints who were asked to participate in a randomized controlled trial on the effects of an early psychological intervention on recovery after mTBI (trial number: ISRCTN86191894).³⁶ Patients were randomized for either cognitive behavioral therapy (CBT) or telephonic counseling (TC). The results of this intervention study are the subject of another article.³⁷ Demographics and injury characteristics of the PTC-present group were comparable with those of the total intervention study sample. To control for possible influences of treatment condition on the current fMRI results, additional comparisons were made between the CBT and TC groups.

The current study was approved by the local Medical Ethics Committee of the UMCG; written informed consent was obtained from all participants. All procedures were performed according to the declaration of Helsinki.

Clinical measures

Self-reported complaints were measured with a 19 item Head Injury Symptoms Checklist (HISC) administered 2 weeks and 3 months post-injury.^{7,38} Patients had to rate presence of current and pre-injury complaints on a three point Likert scale ranging from 0 to 2 (0=never, 1=sometimes, 2=often). Total number of complaints and severity of complaints (summation of all [current–pre-injury] scores) were calculated. Having post-traumatic complaints was defined as reporting three or more complaints (regardless of severity) at 2 weeks post-injury, with at least one complaint within the cognitive (including forgetfulness, poor concentration, slowness, fatigue, and increased need for sleep) and/or affective domain (including irritability, reduced tolerance for noise, and anxiety). Having no complaints was defined as reporting fewer than three complaints.

Feelings of anxiety and depression were measured at 2 weeks and 3 months post-injury using the Hospital Anxiety and Depression Scale (HADS) consisting of seven anxiety (HADS-A) and seven depression (HADS-D) related items (each item with a four point Likert scale ranging from 0 to 3).³⁹ Sum scores of HADS-A and HADS-D scores were used for analyses.

Outcome was determined at 12 months post-injury using the Glasgow Outcome Scale Extended (GOSE).⁴⁰ This structured interview measures outcome on an eight point scale: 8=good recovery, 7=suboptimal recovery, 6=upper moderate disability, 5=lower moderate disability, 4=upper severe disability, 3=lower severe disability, 2=vegetative state, and 1=death. Outcome scores were dichotomized into: favorable (GOSE-score=8) and unfavorable (GOSE <8) outcome.

Behavioral data analyses

The Statistical Product and Service Solutions (SPSS; version 22, Released 2013, IBM Corp., Armonk, NY) was used for data analyses. Normality of data was assessed using Shapiro–Wilk tests. Testing for group differences was done with one way analysis of variance (ANOVA) for normally distributed continuous variables and Kruskal–Wallis and Mann–Whitney *U* tests for non-normally distributed continuous variables. For nominal and ordinal variables, Pearson's χ^2 tests were used. Correlations between age and complaints were assessed using Spearman's rank correlations.

MRI acquisition

Patients underwent scanning at 4 weeks (first visit) and 3 months (follow-up visit) post-injury. For PTC-present patients, scans were made before and after completion of either the CBT or TC sessions. The interval between scans for PTC-absent patients was matched to that of the PTC-present group. Healthy controls underwent scanning once.

A 3.0 T Philips Intera MRI scanner (Phillips Medical Systems, Best, The Netherlands) equipped with a 32 channel SENSE head coil was used for image acquisition. A high resolution transversal T1-weighted sequence image was made for anatomical reference (repetition time [TR] 9 ms; echo time [TE] 3.5 ms; flip angle 8 degrees; field of view [FOV] 256×232×170 mm; reconstructed voxel size 1×1×1 mm). For resting-state imaging, 300 T2*-weighted echo planar imaging volumes were acquired with slices aligned in the anterior commissure (AC)–posterior commissure (PC) plane and recorded in descending order (TR 2000 ms; TE 20 ms; FOV 224×224×136.5 mm; reconstructed voxel size

3.5×3.5×3.5 mm). Participants were instructed to close their eyes and to stay awake (duration: 10 min).

The following sequences were used to examine the presence of micro-hemorrhages: coronal T2-gradient echo (TR 875 ms; TE 16 ms; FOV 230×183×199 mm; reconstructed voxel size 0.45×0.45×4 mm) and transversal susceptibility weighted imaging (TR 35 ms; TE 15 ms; FOV 230×183×150 mm; reconstructed voxel size 0.45×0.45×1 mm). These scans were assessed for traumatic lesions by an experienced neuroradiologist. Twelve patients (24.5%) had one or more micro-hemorrhages. There was no difference in the number of micro-hemorrhagic lesions between PTC-present (median=0, range: 0–37) and PTC-absent (median=0, range: 0–26) patients ($U=284$, $p=0.967$). None of the HC had lesions.

fMRI preprocessing

Statistical Parametric Mapping (SPM12 Wellcome Department, University College London, London, England) implemented in Matlab (version R2014a; MathWorks, Natick, MA) was used for preprocessing, which consisted of slice timing correction, image realignment to the first functional image, co-registration of functional images with individual participants' T1-weighted images, normalization using a diffeomorphic nonlinear registration tool (DARTEL) (isotropic voxels of 3×3×3 mm) to the Montreal Neurological Institute [MNI] template and smoothing (8 mm full-width at half maximum [FWHM] Gaussian kernel).

ICA

Group ICA of fMRI Toolbox (GIFT) version 4.0a, implemented in Matlab, was used for spatial ICA.⁴¹ The mean number of independent components was estimated using minimum description length (MDL) and Akaike's information criterion.⁴² Following subject-specific principal component analysis (PCA) (first step: 44 components, second step: 29 components), group ICA was performed with 29 estimated components and ICASSO was repeated 20 times to establish stability of component decomposition.⁴³ To obtain subject specific components, back-reconstruction was done using spatial temporal regression, and results were scaled to the original data (i.e., % signal change). Identification of neural components was done by H.J.v.d.H. and E.J.L. independently, using previously published literature, spatial regression of network templates provided with GIFT, and by visual inspection using the known characteristics of neural components (peak activations in gray matter; low spatial overlap with known vascular, ventricular, motion, or susceptibility artifacts; dominant low-frequency signal in power spectra). Differences were discussed until consensus was reached. Components corresponding with the DMN, EN, and SN were selected for further analyses.

Within-component FC

Within-component FC was analyzed using the Statistical non-Parametric Mapping (SnPM13) toolbox^{44,45} in SPM12. A between-group ANOVA was used to test for FC differences among HC, PTC-present, and PTC-absent groups during visits one and two. Longitudinal effects were examined for the PTC-present and PTC-absent groups using the paired t test function. Differences in longitudinal effects were tested between the PTC-present and PTC-absent, and between the CBT and TC groups. To this end, spatial maps from scans obtained during the initial visit were subtracted from those obtained during the second visit using the *imCalc* function in SPM12. Subsequently, the resulting images (reflecting the slope of within-component FC) were entered into a two sample t test. All analyses in SnPM were conducted using 10,000 random permutations, and results were deemed significant when surviving voxel-level familywise error (FWE) correction was at $\alpha=0.05$. To facilitate future meta-analyses, unthresholded SnPM output files are available on request.

Between-component FC

Between-component FC was computed using the MANCOVAN toolbox in GIFT.⁴⁶ Prior to calculation of FC, component time courses were de-trended and de-spiked using 3dDespike,⁴⁷ and filtered using a fifth-order Butterworth low-pass filter (<0.15 Hz). FC values were extracted from the *mancovan_results_fnc.mat* output, and further analyzed using in-house developed permutation scripts in Matlab. First, network connectivity during visits one and two was tested among HC, PTC-present, and PTC-absent groups. Second, longitudinal FC effects were examined for the PTC-present and PTC-absent groups using tests for paired samples. Third, to investigate group differences in longitudinal effects of between-component FC, slopes of FC (i.e., FC at follow-up visit minus FC at first visit) were tested between the PTC-present and PTC-absent groups, and between CBT and TC groups. All permutation tests were conducted using 10,000 random permutations. α was set at 0.05, and type I errors were controlled using the Simple Interactive Statistical Analysis (SISA) Bonferroni approach, similar to that described by Li and coworkers.⁴⁸ Contrary to traditional Bonferroni ($\alpha/\text{number of tests or dependent variables}$), this method accounts for the covariance between dependent variables (i.e., component pairs), which was defined as the mean of absolute values in one triangular part of the component pair matrix. Effect sizes were calculated in Matlab using the common language effect size statistic (CL).⁴⁹ Tables containing uncorrected results were added as Tables S1–S3 (see online supplementary material at <http://www.liebertpub.com>).

FC related to clinical measures

For PTC-present patients, associations between within-component FC during the first visit and complaint (number and severity), and HADS-A and HADS-D scores at 3 months post-injury were examined using simple regression in SnPM. In cases with significant results, age was added as a covariate of no interest to check for the confounding effects of age. Also within the PTC-present group, differences in within-component FC during the first visit between patients with a favorable and those with an unfavorable outcome (based on GOSE) at 12 months post-injury were assessed using a two sample t test in SnPM. Post-hoc analyses with age were conducted in cases with significant results. Unthresholded SnPM output files are available on request.

Regarding between-component FC, Spearman's rank correlations were calculated between FC values during visit one and complaint, and HADS-A and HADS-D scores at 3 months post-injury using Matlab ($\alpha=0.05$ with SISA Bonferroni adjustments). Partial Spearman's rank correlations with inclusion of age were run in cases with significant findings. Confidence intervals (CI) were calculated using Fisher's z -transformation ($95\% \text{ CI} = \tanh(\text{arctanh}(r) \pm \frac{1.96}{\sqrt{n-3}})$).⁵⁰ Differences in between-component FC during the first visit between patients with a favorable and those with an unfavorable outcome were examined using permutation tests in Matlab. Post-hoc analyses regarding patients' ages were conducted in cases with significant results. Uncorrected results are added in Tables S1–S3.

Results

Patient characteristics

Thirty-four PTC-present patients were included, of whom four were lost to follow-up. One of the 20 PTC-absent patients did not return for follow-up. Characteristics of the remaining patient sample are listed in Table 1. In addition to the fact that the PTC-absent group contained more male subjects, there were no differences between patient subgroups. This also applies to the comparison between the PTC-present and PTC-absent groups. For the PTC-present group, age was not significantly related to the

TABLE 1. PATIENT CHARACTERISTICS

	PTC-present (n=30)		(3) PTC-absent (n=19)	Diff. 1-2-3	
	(1) CBT (n=13)	(2) TC (n=17)		Statistic (df)	p
Age, median (range), years	27 (19–54)	36 (21–61)	30 (20–62)	$K=0.87$ (2)	0.647
Sex, % male	54	53	90	$\chi^2=6.912$ (2)	0.032
Education level, median (range) ^a	5 (4–7)	6 (5–7)	6 (2–7)	$\chi^2=9.882$ (8)	0.273
Handedness, % right	100	77	79	$\chi^2=3.034$ (2)	0.219
Interval injury to 1st MRI, median (range), days	34 (24–62)	32 (22–52)	32 (22–69)	$K=1.204$ (2)	0.548
Interval injury to 2nd MRI, median (range), days	89 (76–207)	94 (61–114)	94 (77–126)	$K=0.136$ (2)	0.934
GCS-score, median (range)	15 (13–15)	14 (13–15)	15 (13–15)	$K=1.952$ (2)	0.377
Injury mechanism:					
Traffic, % of group	39	59	47	$\chi^2=1.254$ (2)	0.534
Falls, %	61	23	48	$\chi^2=5.548$ (2)	0.062
Sports, %	0	6	0	$\chi^2=1.922$ (2)	0.383
Assault, %	0	6	0	$\chi^2=1.922$ (2)	0.383
Other, %	0	6	5	$\chi^2=0.762$ (2)	0.683

^aEducation level was based on a Dutch classification system (Verhage 1964),³⁵ ranging from 1 (lowest) to 7 (highest).

CBT, cognitive behavioral therapy; Diff., difference; TC, telephone counseling; GCS, Glasgow Coma Scale; PTC, post-traumatic complaints.

number of complaints at 2 weeks ($\rho=0.1$, $p=0.59$) or at 3 months ($\rho=-0.02$, $p=0.94$) post-injury.

Independent components

Twenty-nine components were extracted with ICA. Ten artifact components were discarded. Of the remaining 19 neural components, 8 were selected for further analysis (Fig. 1). Three of these components corresponded with parts of the DMN (DMN1 [posterior cingulate cortex, and precuneus], DMN2 [medial prefrontal

cortex, posterior cingulate cortex, and inferior parietal cortex] and DMN3 [precuneus]); four components corresponded with the EN (left and right frontoparietal network [FPN], dorsal attention network [DAN], and bilateral frontal network); and one component reflected the SN.

Within-component functional network connectivity

A nonparametric between-group ANOVA showed that during visits one and two, FC of none of the components was significantly

FIG. 1. Components of networks of interest.

different among HC, PTC-present, and PTC-absent groups after multiple comparison corrections.

Nonparametric paired *t* tests showed small, but significant longitudinal changes in FC within the DMN for the PTC-present (DMN3), PTC-absent (DMN3) and CBT group (DMN2; Table 2). Further, minor differences in longitudinal connectivity were found between PTC-present and PTC-absent groups (DMN3), and between the CBT and TC groups (DMN2; nonparametric two sample *t* tests). There were no significant results with respect to the EN and SN.

Between-component FC

Permutation tests showed that during the first and second visits, FC of none of the component pairs was significantly different between HC, PTC-present and PTC-absent groups after correction for multiple comparisons. A trend toward significance was observed for FC between the bilateral frontal network and DAN, which was higher in PTC-absent patients than in HC ($p_{\text{uncorr}}=0.008$; $CL=0.74$) during visit one and visit two ($p_{\text{uncorr}}=0.005$; $CL=0.75$). Lastly, no significant changes in longitudinal between-component FC were found for either the PTC-present or PTC-absent group (paired permutation tests), and no differences were present between the PTC-present and PTC-absent groups, or between the CBT and TC groups.

FC related to clinical measures

For PTC-present patients, within-component FC during the first visit was not significantly related to number and severity of complaints and HADS scores at 3 months post-injury (nonparametric regression analyses). Also, no significant differences in within-component FC were found between PTC-present patients with unfavorable and those with favorable outcome at 12 months post-injury (nonparametric two sample *t* tests).

Regarding between-component FC, a significant positive Spearman correlation (at a SISA Bonferroni corrected $\alpha=0.004$) was found between FC of the DMN1–DMN2 pair during the first visit and number of complaints at 3 months post-injury in the PTC-present group (Fig. 2). FC of this component pair was also significantly correlated with severity of complaints at 3 months post-injury ($\rho=0.55$; $p_{\text{uncorr}}=0.003$; 95% $CI=0.21-0.78$). These results remained significant after correction for age. For none of the component-pairs, significant correlations were found between FC during the initial visit and HADS scores at 3 months post-injury. However, a negative correlation that approached significance was found between FC of the bilateral frontal network – SN pair during the first visit and HADS-A scores at 3 months post-injury ($\rho=-0.51$; $p_{\text{uncorr}}=0.009$; 95% $CI=[-0.14] - [-0.75]$).

Between-component FC during the initial visit was not significantly different between PTC-present patients with favorable ($n=17$) and those with unfavorable ($n=13$) outcomes at 12 months post-injury (permutation tests).

Discussion

The most clinically relevant finding of our study was that in the PTC-present group, higher FC between the anterior and posterior part of the DMN during the initial scan was related to a greater number of post-traumatic complaints at 3 months post-injury. This could indicate that the DMN is involved in mechanisms underlying the persistence of complaints. Areas of the DMN are strongly linked to spontaneous thought processes, such as mind wandering

TABLE 2. SIGNIFICANT WITHIN-COMPONENT FUNCTIONAL CONNECTIVITY RESULTS ($p_{\text{FWE}} < 0.05$)

Component	Contrast	Area	Cluster-level		Voxel-level			Peak coordinates			
			k	p _{FWE-corr}	p _{FDR-corr}	T	p _{uncorr}	x	y	z	
Longitudinal effects within groups											
PTC-present group	Pre > post	Left hippocampus	1	0.0109	0.2529	5.71	0.0001		-12	-33	9
PTC-absent group	Pre > post	Right middle frontal gyrus	1	0.0353	0.2428	6.02	0.0001		39	48	3
CBT group	Pre < post	Left middle temporal gyrus	3	0.0171	0.0484	7.55	0.0001		-45	-69	15
Longitudinal differences between groups											
DMN3	PTC-absent > PTC-present	Right middle frontal gyrus	1	0.0246	0.2428	5.11	0.0001		39	48	6
DMN2	TC > CBT	Right middle temporal gyrus	2	0.0231	0.2970	5.64	0.0001		48	-69	12

One voxel = 27 mm³.

CBT, cognitive behavioral therapy; DMN, default mode network; PTC, post-traumatic complaints; TC, telephonic counseling.

FIG. 2. Default mode network (DMN1-DMN2 pair) functional connectivity during the first visit was associated with post-traumatic complaints at follow-up 3 months post-injury.

and envisioning past or future events.^{51,52} Based on our results, it could be speculated that relatively higher DMN FC in patients with complaints is associated with ongoing thoughts about present complaints, sustained injury, or its future consequences, and that this increased state of internally focused mental activity may impede recovery and/or possible treatment effects. In previous research, it has been shown that reduced volume and higher activation of DMN areas are associated with neuroticism, which is one of the Big Five personality traits.^{53,54} Therefore, it would be interesting for future studies on mTBI to investigate if DMN connectivity is associated with maladaptive pre-injury personality characteristics; for example, using questionnaires that measure worrying and rumination.

Regarding within-component FC, we found significant longitudinal decreases in the DMN in patients with mTBI. Although T values were fairly high, clusters were strikingly small, which may question the robustness of these findings. Previous studies have demonstrated longitudinal connectivity changes in areas of the DMN in patients with mTBI and sports-related concussion.^{23,26} As has already been suggested by Meier and colleagues, the DMN may be vulnerable to traumatic injury, because of the high level of functional connections in this network, and the susceptibility of the midline areas to shear strain injury.^{26,55,56} In theory, longitudinal decreases in DMN FC could be interpreted as delayed injury effects, as fading injury effects, or as fading compensatory increases in connectivity that might have occurred in the first days to weeks after injury. However, we did not find any significant differences in within-component FC between the patient groups and HC, either at early measurement or at late measurement between 1 and 3 months after injury. Therefore, we have to conclude that the decreases in FC are not related to effects of injury.

With regard to between-component connectivity, no significant longitudinal results were found for any of the patient groups. These findings match those of other studies, which have failed to demonstrate longitudinal changes in FC among the DMN, EN, and SN.^{21,27} In addition to the possibility that there are no significant longitudinal changes in network connectivity, our null findings may indicate that changes in network function could already have taken

place and reached a plateau during the time frame (i.e., 1st month post-injury) before the first scan. Other studies have demonstrated that longitudinal variations in resting-state FC are prominent within the 1st month,^{24,26,27} and may not occur between 3 weeks and 5 months post-injury.^{21,27} Alternatively, functional network changes in our study groups may have been too subtle to be detected with current methods.

It has been consistently reported that the DMN plays a pivotal role in psychopathology, such as anxiety disorders and major depressive disorder.^{57–59} In the current study, we did not find any significant correlations between DMN connectivity and anxiety or depression after mTBI. However, we did find a borderline significant negative correlation between FC of the bilateral frontal network –SN pair at 1 month and anxiety scores at 3 months post-injury, which fits with the proposed role of the EN and SN in anxiety disorders.⁵⁹

It was not the aim of the current study to investigate psychological treatments, and comparisons were only made to check for confounding effects of treatment conditions within the PTC-present group. A minor difference in connectivity within the DMN was found between the CBT and TC groups. This finding is of questionable relevance because cluster size was small ($k=2$ voxels), and paired tests revealed no longitudinal changes in the FC of this particular cluster for either of the groups. Further, the CBT group is too small to draw any conclusions. Interestingly, regarding the total intervention study, post-traumatic complaints have been shown to decrease significantly from 2 weeks to 3 months post-injury in the TC group, but not in the CBT group.³⁷ It is tempting to speculate that treatment effects are somehow mediated by the DMN. Future fMRI studies are required to investigate the effects of psychological interventions on network connectivity in mTBI.

Despite the interesting results of our study, a major limitation is the lack of a group of patients with post-traumatic complaints who did not receive any treatment. Therefore, it was not possible to determine with certainty the natural course of network function in patients with complaints after mTBI. The group with complaints may be considered a homogenous group, because only a minor difference in network connectivity was found between the CBT and TC groups. However, confounding effects of the intervention conditions on our results cannot be excluded, and, therefore, future studies, including a group of patients with complaints who did not receive treatment, will have to confirm our findings. Also, HC were only scanned once, which is a limitation. Remarkably, most of the significant clusters that emerged in our within-component connectivity analyses contained only one voxel, and the maximum cluster size was three voxels. We performed permutation tests, which have been demonstrated to be superior to parametric methods with respect to the proportion of false positives,⁴⁵ and applied FWE corrections for multiple comparisons. However, it is still possible that our within-component results are caused by type I errors, considering that we did not correct for testing multiple components and clinical measures. Lastly, it also has to be realized that there is a possibility that longitudinal within-component connectivity changes reflect epiphenomena associated with non-injury-related factors or test-retest manifestations without clinical significance.^{60,61}

To summarize, results from this resting state fMRI study suggest that the DMN may serve as a biomarker for selecting patients who are prone to develop persistent complaints. This finding, although preliminary, may hold implications for future development of tailored psychological interventions for patients with mTBI.

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Author Disclosure Statement

No competing financial interests exist.

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