BRAIN CONNECTIVITY
Volume 5, Number 7, 2015

DOI: 10.1089/brain.2014.0293

Functional Connectivity Density and Balance in Young Patients with Traumatic Axonal Injury

Karen Caeyenberghs,[1,2] Roma Siugzdaite,[3] David Drijkoningen,[4] Daniele Marinazzo,[3] and Stephan P. Swinnen[4]

Abstract

Our previous study provided some evidence for the relationship between abnormal structural connectivity and poor balance performance in young traumatic axonal injury (TAI) patients. An enhanced understanding of the functional connectivity following TAI may allow targeted treatments geared toward improving brain function and postural control. Twelve patients with TAI and 28 normally developing children (aged 9–19 years) performed the sensory organization test (SOT) protocol of the EquiTest (Neurocom). All participants were scanned using resting-state functional magnetic resonance imaging series along with anatomical scans. We applied ''functional connectivity density mapping'' (FCDM), a voxel-wise data-driven method that calculates individual functional connectivity maps to obtain both short-range and long-range FCD. Findings revealed that the TAI group scored generally lower than the control group on the SOT, especially when proprioceptive feedback was compromised. Between-group maps noted significantly decreased long-range FCD in the TAI group in frontal and subcortical regions and significantly increased short-range FCD in frontal regions, left inferior parietal, and cerebellar lobules. Moreover, lower balance levels in TAI patients were associated with a lower long-range FCD in left putamen and cerebellar vermis. These findings suggest that long-range connections may be more vulnerable to TAI than short-range connections. Moreover, higher values of short-range FCD may suggest adaptive mechanisms in the TAI group. Finally, this study supports the view that FCDM is a valuable tool for selectively predicting functional motor deficits in TAI patients.

Key words: brain injury; functional connectivity density; fMRI; hubs; network; postural control; resting-state

Introduction

Maintaining balance is a sensorimotor task that requires the generation of a context-dependent motor output based on integration of information from three sensory systems, that is, somatosensory, visual and vestibular system (Gagnon et al., 2004; Shumway-Cook and Horak, 1986). This complex sensorimotor integration requires the efficient functioning of distributed brain networks, which consist of spatially separated brain regions connected by white matter tracts. Our previous diffusion magnetic resonance imaging (MRI) work (Caeyenberghs et al., 2010) in young traumatic axonal injury (TAI) patients demonstrated that lower performance on a postural control task is associated with lower white matter anisotropy in specific sensorimotor pathways/regions, including the internal capsule, the medial lemniscus, the cerebellum and its peduncles. Using a graph theoretical approach, a decreased connectivity degree in the cerebellum and parietal gyrus was found to be significantly correlated with poorer balance performance in TAI patients (Caeyenberghs et al., 2012). Postural control indices have also been reported to be associated with diffusion MRI measures in other disorders. For example, Chan and coworkers (2014) found that the degree of corpus callosum body abnormality correlated with the Tinetti score (a measure of risk of falls) in patients with Parkinson's disease. Another study by Prosperini and associates (2013) in patients with multiple sclerosis, reported that balance impairment was correlated with worse diffusion MRI parameters along the cerebellar connections and supratentorial associative white matter bundles. However, these findings were restricted to structural connectivity. An enhanced understanding of the functional

Departments of [1]Physical Therapy and Motor Rehabilitation and [2]Movement and Sport Sciences, Faculty of Medicine and Health Sciences, University of Ghent, Ghent, Belgium.
[3]Department of Data Analysis, Faculty of Psychological and Pedagogical Sciences, University of Ghent, Ghent, Belgium.
[4]Movement Control and Neuroplasticity Research Group, Group Biomedical Sciences, KU Leuven, Belgium.

connectivity following brain injury may allow for targeted treatments geared toward improving brain function and postural control.

During the last decade, numerous studies have already evaluated functional networks in brain-injured patients by using seed-based functional connectivity (Palacios et al., 2013; Tang et al., 2011) or independent component analysis (ICA) (Sharp et al., 2011; Shumskaya et al., 2012) in resting-state functional MRI (rs-fMRI). Nevertheless, such studies are limited by a restricted choice of a priori regions-of-interest (seed regions), which can underestimate the complexity of relationships assessed across the whole brain. The second group of studies used ICA to identify a consistent set of intrinsic connectivity networks linked to critical sensory, motor, and cognitive brain functions. One such intrinsic network, the default mode network (DMN), including the precuneus/posterior cingulate cortex, medial prefrontal cortex, lateral parietal cortex, and medial temporal lobes, is considered to be involved in the integration of introspective thought, daydreaming or retrieval of memories (Raichle and Snyder, 2007). For example, Sharp and associates (2011) reported overall increased DMN connectivity in patients with moderate/severe brain injury. Another ICA study found a decrease in functional connectivity within the motor-striatal network in acute mild TBI patients (Shumskaya et al., 2012). However, even though they are highly valuable, such ICA/data reduction approaches provide only global rather than local measures of brain connectivity.

In this study, we applied functional connectivity density mapping (FCDM) (Tomasi and Volkow, 2010), an alternative voxel-wise data-driven method that allows ultrafast calculation of individual functional connectivity maps to obtain both short-range and long-range FCD with unprecedented spatial resolution. Our aim was to investigate the effect of TAIs on short- (implicated in functional specialization) and long-range FCD hubs (implicated in functional integration). Statistical parametric mapping was used to identify brain regions exhibiting group effects on short- and long-range FCD. Given prior evidence of a decrease in structural connectivity in the white matter networks in young TAI patients (Caeyenberghs et al., 2012), we expected a decrease of density in the functional hubs, more prominently for long-range connections in TAI patients. Moreover, we wanted to investigate which regions in the cortico-subcortical circuitry could serve as a predictive marker for postural control in TAI patients.

Materials and Methods

Subjects

Forty children and adolescents were included in the analyses, including 12 subjects with TAI (mean age 14.4 years, SD 3.1 years, 5 boys) and 28 control subjects (mean age 15 years, SD 2.3 years, 12 boys). Patients were in the chronic stage, that is, at least 3 months after the injury, where neurological recovery was stabilized. Children with focal lesions (i.e., with volume $>0.5\,cm^3$) were excluded, because the inclusion of such patients introduces a different neuropathology. All patients were recruited from several rehabilitation centers in Belgium. Demographic and clinical characteristics of the TAI group can be found in Table 1. The mean age at the moment of injury was 10 years 6 months (SD 2 years 9 months) and the interval between the injury and the test session was on average 3 years (SD 2 years 9 months). According to the Mayo classification system for injury severity, our TAI group consisted of moderate to severe patients. This system grades patients according to duration of loss of consciousness (three patients had a coma duration $>24\,h$), lowest recorded Glasgow Coma Scale in the first 24 h (only available for one patient), and initial computed tomography (CT) or MRI images (Malec et al., 2007). The local ethics committee for biomedical research of the KU Leuven approved the study. Written informed consent was obtained from each participant or from the patient's first-degree relatives, according to the Declaration of Helsinki.

Postural control

Postural control was assessed using the sensory organization test (SOT) of the EquiTest System (NeuroCom International, Inc.). Subjects stand on the forceplate with the medial malleoli of their ankles aligned to the forceplate's center of rotation under four different sensory conditions. In condition A, when the participant stood on a fixed platform with the eyes open, all three sensory systems (vision, vestibular, and somatosensory) were operational and a baseline measure of stability was obtained. Condition B was the same as condition A but with eyes closed. In condition C, the participant stood with the eyes open and the platform moved in response to his/her sway, resulting in less reliable proprioceptive input. Condition D was identical to condition C except that the eyes were now closed, such that only the vestibular system provided reliable sensory information. The test protocol consisted of three repetitions of each condition, resulting in 12 trials. The testing conditions were randomized and subjects were instructed to stand on the platform as quiet as possible with the arms relaxed along the body. A harness was used for the patient's safety in case (s)he would fall. For each condition the mean of the ellipse area scores from the different trials was used in the analysis. Trials with a fall or trials with an adjustment of the feet to prevent falling, were excluded when calculating the mean. One trial (0.69%) of condition C (eyes open, sway-referenced platform) and one trial (0.69%) of condition D (where both proprioceptive and visual feedback were compromised) were excluded from the TAI group from subsequent analyses. For more details and in-depth discussion of these metrics, the interested reader is referred to Supplementary Material section (Supplementary Data are available online at www.liebertpub.com/brain).

MRI data acquisition

The scanning was performed on a Siemens 3T Magnetom Trio MRI scanner (Siemens) with a 12-channel matrix head coil in the University hospital (Gasthuisberg).

For anatomical details, a 3D magnetization prepared rapid acquisition gradient echo high resolution T1-weighted image (repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, voxel size = $1\times1\times1.1\,mm^3$, slice thickness = 1.1 mm, field of view [FOV] = $256\times240\,mm^2$, 160 contiguous sagittal slices covering the whole brain and brainstem) was acquired.

rs-fMRI series consisted of 200 whole-brain gradient-echo echoplanar images (TR/TE = 3000/30 ms; FOV = $230\times230\,mm^2$; voxel size = $2.5\times2.5\times3.1\,mm^3$, 80×80 matrix;

Table 1. Summary of Demographic and Injury Characteristics for the Traumatic Axonal Injury Group

TAI patient #/age (y)/ gender	*Cause of injury*	*Age at injury (y)*	*Time since injury (y)*	*GCS/coma duration*	*Acute MRI scan within 24 h after injury lesion location/pathology*	*MRI scan at test session lesion location/pathology*
TAI01/ 8.6/M	Traffic accident	7.9	0.7	Coma = 5 days	Subdural hematoma R FL/PL/TL; cortical contusion R FL/PL; DAI in R FL	Microbleeding R centrum semiovale and CC
TAI02/ 18.1/F	Traffic accident	15.6	2.5	Coma = 5 days	Subdural hematoma/hemorrhagic contusion TL/FL; injuries R FL, thalamus, R cerebral peduncle, L mesencephalon; cortical and subcortical hemorrhagic areas in PL/TL	Injuries surrounding drain trajectory in RH (superior frontal gyrus, head nucleus caudatus, crus anterius of internal capsule, thalamus, and pons)
TAI03/ 13.8/F	Impact of object on the head	13.0	0.8	NA	Hemorrhagic contusion L FL, atrophy L FL	Contusion L anterior part of medial and superior frontal gyrus
TAI04/ 16.5/F	Traffic accident	7.2	9.3	NA	Epidural hematoma R FL/TL; shift midline	Injuries in R medial frontal gyrus
TAI05/ 14.2/F[a]	NA	7.7	6.5	NA	NA	Atrophy of the cerebellum; injuries at the level of L FL, premotor cortex, medial frontal gyrus, cingulum, orbitofrontal cortex (L > R); contusion anterior temporal pole (R > L); hemosiderin deposits in CC, L thalamus, striatum (R > L)
TAI06/ 13.4/M	Trafic accident	12.5	0.8	NA	Hemorrhagic contusion L TL; brain edema	Hemosiderosis; DAI PL (superior and inferior), R cerebellum, L superior frontal gyrus
TAI07/ 19.0/F	Fall	12.5	6.5	NA	Subdural hematoma L FL/TL/PL	Hemosiderin deposits R cerebellar vermis
TAI08/ 15.6/F	Traffic accident	12.5	3.2	Coma = 10 days	DAI R TL, internal capsule, supra-orbital R FL, L FL WM (anterior corona radiata), L middle cerebellar peduncle	Atrophy cerebellum; Contusion R FL WM
TAI09/ 13.9/M	Impact of object on the head	13.5	0.3	GCS = 3	DAI FL, TL, L OL (hemorrhagic injury), R TL, cerebellum, CC, external capsule, R globus pallidus, L thalamus, R cerebral peduncle, R mesencephalon	DAI L FL, periventricular WM, body and genu CC, L thalamus, R external capsule, anterior TL (L > R), cerebellum; Limited atrophy cerebellum
TAI10/ 8.5/F[a]	Traffic accident	7.7	0.8	NA	NA	Enlarged fourth ventricle, atrophy of cerebellar vermis, contusion R cerebellar vermis, hypotrophy of middle cerebellar peduncle and L pons; contusion L TL; hemosiderin deposits R FL, L TL, CC; ventricle drain
TAI11/ 11.4/M	Sport injury (equestrian)	9.8	1.5	NA	Contusion L FL/TL; enlarged, asymmetric ventricle (temporal horn)	DAI splenium CC; ventricular drain
TAI12/ 13.3/M	Traffic accident	12.1	1.2	NA	DAI in genu and splenium CC, L FL	Hemosiderin deposits L FL, genu CC

[a]Excluded due to subject motion.

Anatomy codes: WM, white matter; GM, gray matter; RH, right hemisphere; LH, left hemisphere; FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; CC, corpus callosum; R, right; L, left. Other codes: DAI, diffuse axonal injury; y, years; GCS, Glasgow Coma Scale score; MRI, magnetic resonance imaging; M, male; F, female; NA, information not available; TAI, traumatic axonal injury.

slice thickness = 2.8 mm; 50 sagittal slices; scanning order: interleaved descending).

The fMRI series were passed through several preprocessing steps using SPM8 (Welcome Trust Center for Neuroimaging) and REST toolbox (Song et al., 2011). Then, we performed FCDM to obtain the strength of the short-range and long-range functional connectivity density (Tomasi and Volkow, 2010). In the Supplementary Material section, we provide the detailed workflow of the preprocessing and the FCDM.

Statistical analysis

The ellipse areas were subjected to analysis of variance for repeated measurements with between-subjects factor ''group'' (two levels: TAI and control) and the within-subjects factors ''proprioceptive feedback'' (two levels: normal or sway-referenced) and ''visual feedback'' (two levels: normal or absent).

Group differences for short-range and long-range FCD were examined using one-way ANOVA with three covariates of no interest (age, gender, and subject motion as mean framewise displacement measure) in SPM8. To protect against false-positives, we used a double-threshold approach, that is, combining a voxel-based threshold with a minimum cluster size. This nonarbitrary voxel cluster size was determined by using the program AlphaSim (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf) (Ward, 2000). Using REST software (Song et al., 2011) we iterated 100 times the process of random image generation with Gaussian filter FWHM 4 mm and cluster connection radius 5 mm. We specified individual voxel probability threshold ($p_{th} = 0.05$), and by using the whole brain mask (i.e., a default mask in REST made from the apriori template in SPM) only voxels inside the brain were considered. This allowed the cluster size threshold to be reduced while maintaining $\alpha < 0.05$.

Furthermore, the behavioral parameters, that is, ellipse areas of the posturography SOT conditions, were also used to assess relationships between FCD measures and balance using nonparametric Spearman correlations across the total group on one hand and within each of the groups on the other hand.

Finally, time since injury (Table 1) was also used to assess relationships with long- and short-range FCD in the regions in which there were significant between-group differences in FCD. To this end, we applied the Spearman's rank correlation within the TAI group. An exploratory threshold of $p < 0.05$ was used.

Results

Group differences in postural control

Repeated measures analysis of variance showed a significant main effect of proprioceptive feedback [$F(1,36) = 81.78$, $p < 0.001$], and visual feedback [$F(1,36) = 77.58$, $p < 0.001$]. Moreover, a significant main effect of group was found, [$F(1,36) = 6.16$, $p < 0.05$]. The TAI group scored significantly poorer than the control group on all posturography SOT conditions (higher ellipse areas). Furthermore, there was a significant interaction effect between proprioceptive feedback and visual feedback, $F(1,36) = 62.78$, $p < 0.001$ (Fig. 1). *Post hoc* (Tukey) testing revealed that all participants showed more sway when proprioceptive feedback was compromised, and that sway additionally increased when vision was absent (all p's < 0.001). Finally, the interaction between proprioceptive feedback and group was also significant, $F(1,36) = 5.54$, $p < 0.05$. *Post hoc* (Tukey) testing showed that the TAI group performed significantly worse than the controls on both conditions with compromised proprioceptive feedback [C ($p < 0.01$) and D ($p < 0.05$)].

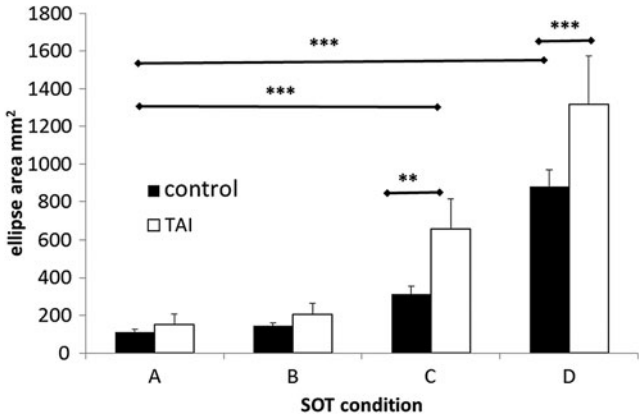

FIG. 1. Behavioral task performance. The traumatic axonal injury (TAI) group performed significantly worse than the controls on the sensory organisation test (SOT; as shown by the higher ellipse areas). TAI, white bars; control, black bars, $^{**}p < 0.01$, $^{***}p < 0.001$.

Functional connectivity density

Figure 2A and B shows the average distribution of short-range and long-range FCD in healthy controls and patients with TAI respectively. Regions with high FCD (shown in red) indicate that they might play important roles in brain networks, namely hubs. Both TAI patients and healthy controls showed similar distributions of their short-range FCD hub regions, including the left precuneus, cuneus, occipital cortex (such as the left fusiform gyrus), parietal cortex (such as the posterior cingulate gyrus), and orbital part of the frontal lobe. The high long-range FCD was mainly distributed in the temporal cortex, parietal cortex (such as the superior parietal gyrus), prefrontal cortex, occipital cortex, and cerebellar lobules. The FCD hubs found in the present study are consistent with previous studies in healthy children and adolescents, and young patient groups (Tomasi and Volkow, 2012a; Wang et al., 2014).

We performed an ANOVA that included Group (TAI, controls) as a between-subjects variable and age, gender, and subject motion as covariates. A threshold of $p < 0.05$ was determined by AlphaSim and used in the statistical analyses. The SPM ANOVA revealed significant differences between groups for both short-range and long-range FCD, as indicated in Table 2.

Between-group maps (as shown in Fig. 3A) noted significantly decreased long-range FCD in the TAI patients in frontal regions, including the left superior and middle frontal gyri and the left middle cingulate gyrus, subcortical regions (including right cerebellum lobule III, cerebellar vermis, left putamen), and the left inferior temporal gyrus. As compared with the controls, the TAI patients showed significantly higher long-

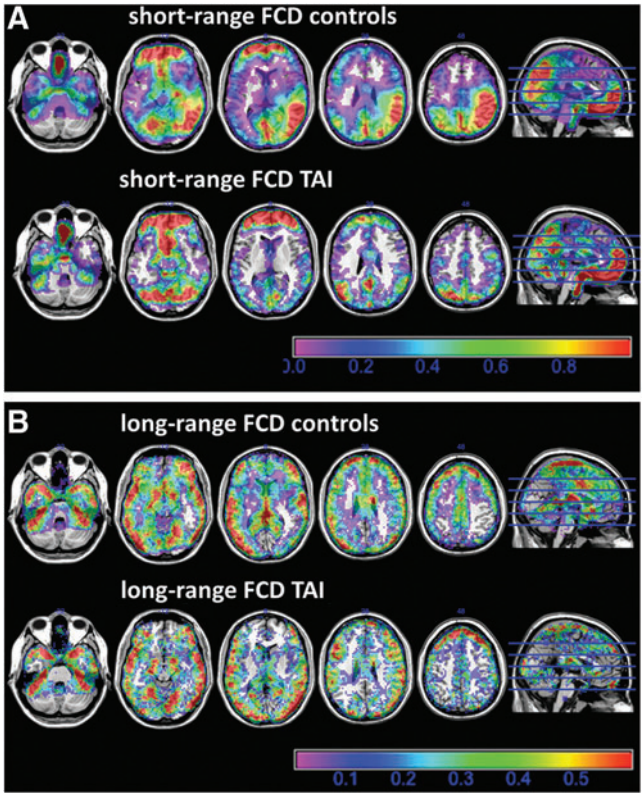

FIG. 2. Distribution of short-range **(A)** and long-range **(B)** functional connectivity density (FCD) in the human brain for 10 TAI patients and 28 typically developing children.

TABLE 2. CLUSTER LOCATIONS (*x*, *y*, AND *z*) IN THE MONTREAL NEUROLOGICAL INSTITUTE STEREOTACTIC SPACE AND STATISTICAL SIGNIFICANCE FOR GROUP EFFECTS ON SHORT-RANGE AND LONG-RANGE FUNCTIONAL CONNECTIVITY DENSITY

Region	*x*	*y*	*z*	*T*
Short range				
TAI > controls				
Frontal mid R	27	45	3	3.95
Parietal inf L	−57	−24	45	3.12
Cerebellum III R	12	−33	−24	2.77
Cerebellum Crus1 L	−33	−63	−30	2.37
Long range				
Controls > TAI				
Frontal sup L	−18	3	69	3.48
Frontal mid L	−30	3	60	3.27
Cerebellum III R	15	−33	−21	3.02
Vermis1_2	3	−36	−15	3.25
Putamen L	−15	9	−9	3.17
Temporal inf L	−51	−6	−33	3.06
Frontal Sup medial L	0	30	12	3.02
Cingulum Mid L	0	−39	33	2.56
Long range				
TAI > controls				
Cerebellum IX L	−6	−51	−33	3.81
Paracentral lobule R	12	−24	66	3.78
Occipital mid L	−30	−78	9	2.80

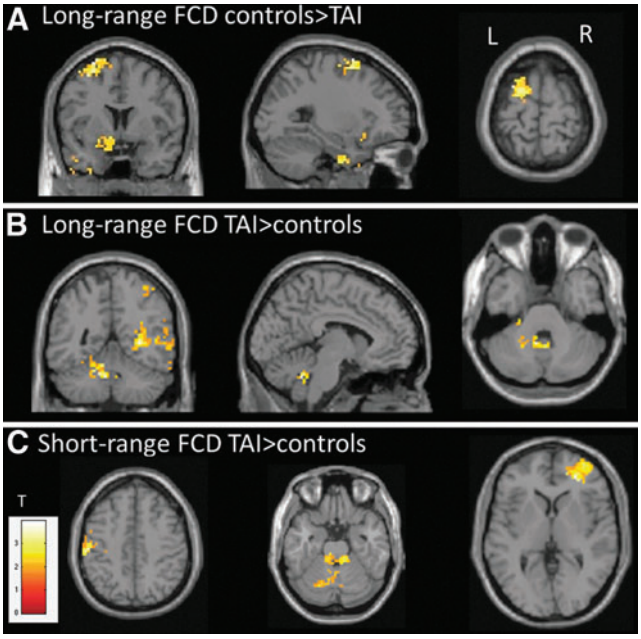

FIG. 3. Between-group maps in FCD.

range FCD in the right paracentral lobule, left middle occipital gyrus, and left cerebellar lobule (IX; Fig. 3B).

Group comparisons showed that short-range FCD was significantly increased in the TAI patients in frontal regions, including the right anterior prefrontal cortex (BA 10), left inferior parietal lobule, and cerebellar regions (left lobule Crus I, right lobule III; Fig. 3C). No regions were found showing higher short-range FCD in controls relative to TAI participants. Although, there were no regions with significantly decreased short-range FCD in TAI, the data support consistently lower short-range FCD in the TAI versus control group as shown in Figure 4.

Relationship between postural control and FCD

Correlation analyses between balance performance and short- and long-range FCD in the brain regions showing significant group differences revealed that only long-range FCD was significantly correlated with ellipse area. No significant correlations were obtained between regions with between-group differences in short-range FCD and postural control. Bonferroni corrections for multiple comparisons were made,

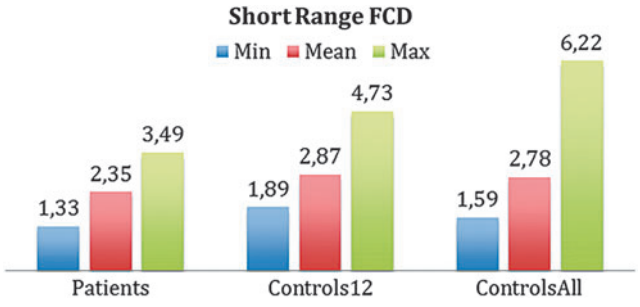

FIG. 4. The average and the range of short-range FCD among TAI patients and controls (total control group and the balanced dataset with 12 controls).

hence $p_{corr} < 0.01$ was considered significant following correction for the two sensory conditions of the SOT (which showed a significant interaction effect) and the two network metrics (short-range and long-range FCD).

Total group correlations. In the total group, Spearman correlation analyses revealed that long-range FCD in the left putamen was negatively correlated with ellipse area of condition A ($r = -0.60$, $p_{corr} < 0.01$), C ($r = -0.61$, $p_{corr} < 0.01$), and D ($r = -0.57$, $p_{corr} < 0.01$). In other words, decrease in long-range FCD of the left putamen within the total group was associated with lower balance performance (i.e., smaller ellipse areas). Also, we found that the ellipse area in condition C with sway-referenced platform within the total group was significantly negatively correlated with long-range FCD of the cerebellar regions, including right cerebellum lobule III ($r = -0.43$, $p_{corr} < 0.01$) and cerebellar vermis I-II ($r = -0.49$, $p_{corr} < 0.01$).

Within-group correlations. The long-range FCD of the left putamen in the TAI group showed a strong negative correlation with ellipse area of condition C ($r = -0.76$, $p_{corr} < 0.01$, Fig. 5). In other words, decrease in long-range FCD within the TAI group was associated with lower balance performance (i.e., smaller ellipse areas) for the condition in which proprioceptive feedback was compromised. Moreover, we found that the long-range FCD of the cerebellar vermis I-II within the TAI group was significantly negatively correlated with ellipse area in the condition where both proprioceptive and visual feedback were compromised ($r = -0.82$, $p_{corr} < 0.01$, Fig. 5). The long-range FCD of the left putamen in the control group showed a negative correlation with ellipse area of condition C (eyes open, sway-referenced platform, $r = -0.53$, $p_{corr} < 0.01$) and condition D (eyes closed, sway-referenced platform, $r = -0.52$, $p_{corr} < 0.01$).

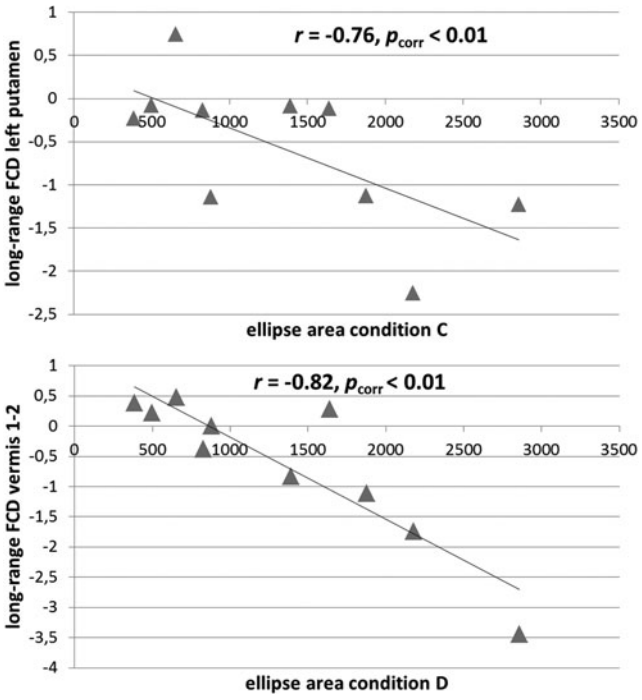

FIG. 5. Plots indicating the relationships between the balance scores (ellipse area in mm^2) and long-range FCD within the TAI group.

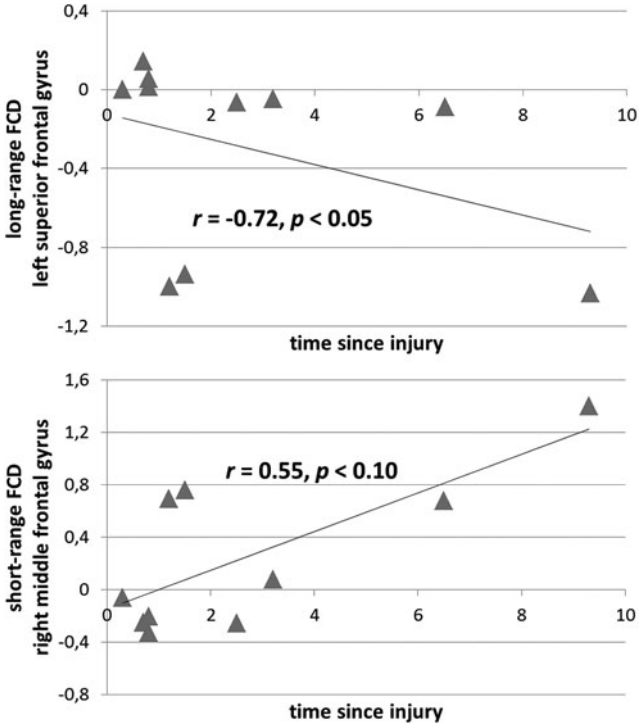

FIG. 6. Plots indicating the relationship between time since injury (in years) and FCD within the TAI group.

Relationship between time since injury and FCD in TAI patients

Regarding time since injury within our TAI group, we observed a significant negative correlation between time since injury and long-range FCD of the left superior frontal gyrus ($r = -0.72$, $p < 0.05$, Fig. 6). Thus, the patients with longer time since injury showed a lower long-range FCD of the left superior frontal gyrus. Moreover, we found a marginal significant positive correlation between time since injury and short-range FCD of the right middle frontal gyrus ($r = 0.55$, $p < 0.10$), revealing that increases in short-range FCD in the TAI patients was associated with longer time since injury.

Discussion

In this study, we determined relations between functional connectivity during resting state and postural control in a young TAI and control group. First, we applied FCDM to assess differences in short-range and long-range FCD between both groups. Second, the functional relevance of these alterations in connectivity was underscored by statistically significant correlations between balance performance and FCD in the TAI group and controls.

Group differences in postural control

Postural control deficits in brain-injured children are not always prominent in standard clinical/neurological examinations or in normal standing conditions (Basford et al., 2003;

Gagnon et al., 2004, Geurts et al., 1996, Kaufman et al., 2006). We have therefore experimentally manipulated reliability of sensory input using the SOT test protocol, representing daily life situations, in which the environment is more challenging (e.g., walking in crowded streets or standing in a bus or train). Our results suggest that TAI patients showed deficits in selecting the accurate and suppressing the compromised sensory inputs, as shown by the larger ellipse areas in conditions with compromised proprioceptive feedback (condition C and D).

Balance deficits have previously been reported in TBI children, primarily by means of clinical tests (Gagnon et al., 1998, 2001, 2004; Geurts et al., 1996, 1999; Ingersoll and Armstrong, 1992; Lehmann et al., 1990; Rubin et al., 1995). Here, use was made of instrumented posturographic measures, which provide a more precise and observer-independent assessment of balance control. Our results are in line with our previous study, demonstrating that the brain-injured group performed significantly worse than the controls on the SOT (Caeyenberghs et al., 2010). In the present study, we did however use a more direct measure of postural sway based on the surface of the COP trajectory, that is, ellipse area. Our results on the SOT replicates previous findings in mild TBI adults, which showed increased instability as measured by the SOT composite score (Guskiewicz et al., 1997, Kaufman et al., 2006; Riemann and Guskiewicz, 2000).

Alterations in long-range connectivity in TAI

Left superior and middle frontal gyri, composed of the premotor cortex and the supplementary motor area/BA6, and cingulate motor regions, demonstrated lower strength of long-range connectivity in TAI patients as compared to controls. These regions are typically associated with motor control actions (Picard and Strick, 2001). The weaker FCD of the motor regions in TAI is consistent with a recent report of reduced task-related activity in motor regions in young patients with mild TBI (Keightley et al., 2014). Although, there were differences in the conditions of the study (resting-state versus working memory task) and the severity of the patient group (moderate/severe versus mild).

Interestingly, the weaker long-range FCD of the left superior frontal gyrus was related with longer time since injury. In other words, the long-range FCD decreases in this motor region appeared to take more time after injury to develop. The most likely mechanism for this longitudinal change is Wallerian degeneration. Deafferentation of white matter fiber tracts following injury results in downstream degeneration of the tract. Furthermore, axons that are damaged but not immediately disconnected continue to undergo subtle changes that include impaired axoplasmic transport, axonal swelling, and ultimate disconnection (Povlishock, 1992). This process of degeneration can last for several months or even years post-injury in humans (Povlishock and Katz, 2005). Our result is consistent with pathologic studies (George and Griffin, 1994) and diffusion MRI studies of TAI [for an excellent review study, see Hulkower et al. (2013)], identifying this slow, progressive degradation and phagocytosis of myelin sheaths, which damages brain structural connectivity and affects neuropsychological functioning. Temporal changes in quantitative resting-state patterns should be further investigated in future studies, which may help to assess recovery from head injury and the long-term impact associated with behavioral impairments caused by brain injury.

Furthermore, we documented lower long-range connectivity density in the left inferior temporal gyrus that can be related to difficulties with perceptual tasks in TAI (Neistadt, 1994; Warren, 1993). The left inferior temporal cortex has been shown to be important in the high-level processing of object-related information (Ungerleider et al., 1998). Our young TAI group also showed decreased long-range connectivity in subcortical regions, including the right cerebellar lobule III, cerebellar vermis, and left putamen, and there was a negative correlation between postural control performance and long-range connectivity in some of these regions.

Relying on our previous study on network functionality in young brain-injured patients (Caeyenberghs et al., 2012), we expected a decrease in functional connectivity. We suggested that a decrease in structural connectivity (i.e., a poorer neurobiological substrate and structural disconnection between neural network nodes) may be directly related to a decrease in functional connectivity. The observed decreased long-range FCD of the young TAI group appears consistent with previous structural network studies (Caeyenberghs et al., 2012, 2014; Pandit et al., 2013; Sharp et al., 2014) and prior studies reporting alterations in diffusion MRI metrics after brain injury (Hulkower et al., 2013). In contrast, several brain regions related to cognitive monitoring and somatosensory function showed increased functional connectivity, indicating a putative compensation mechanism in TAI, as discussed next.

Increased short-range connectivity in TAI

Parietal regions (including the left inferior parietal lobule), cerebellar regions (including left lobule Crus I and right lobule III), and the anterior (rostral) prefrontal cortex demonstrated higher short-range density for the young TAI patients. The anterior (rostral) prefrontal cortex (approximating BA 10) is a large brain region in humans and it is thought to support functions that are central to cognition. A specific role for this region is attending, to a novel degree, either to environmental stimuli, or by contrast, to self-generated or maintained representations (Burgess et al., 2007). Increase in short-range FCD of this region was marginally associated with longer time since injury, suggesting a long-term compensatory finding.

The inferior parietal lobule corresponds to the primary somatosensory area (SI), which is involved in the integration of somatosensory information to guide motor actions (Rizzolatti et al., 1998). Following the nomenclature of Schmahmann (Stoodley and Schmahmann, 2009) and the division of O'Reilly and colleagues (2010), the cerebellar lobule III is part the anterior/''primary sensorimotor'' zone, having strong functional connectivity with (pre)motor cortex and somatosensory cortex, and it is responsible for mediating unconscious proprioception. The cerebellar lobule Crus I, part of the posterior/''supramodal'' zone, has modest input from the prefrontal cortex and contributes to a cognitive involvement in action control (Ramnani, 2012). The results suggest that TAI not only affects the brain's short-range functional connectivity in anterior prefrontal cortex, parietal and cerebellar regions, which is important for cognitive control and somatosensory processing, but also affects long-

range functional connectivity among the left middle occipital gyrus (which comprises the extrastriate cortex, Weiner and Grill-Spector, 2011), the right paracentral lobule (corresponding to S1, see above), and the left cerebellar lobule IX (posterior/''supramodal'' zone, see above) that subserve attentional and multimodal integrating functions (Weiner and Grill-Spector, 2011). This higher proportion of FCD in regions involved with cognitive monitoring and somatosensory processing in TAI children is consistent with our previous task-related fMRI study showing higher activity in TAI patients during the performance of coordination tasks (Caeyenberghs et al., 2009).

Although the TAI group showed evidence of consistently having a lower short-range FCD than the control group (as shown in Fig. 2, upper panel), we did not observe a significant decrease in short-range FCD in the patients with TAI as compared to the controls. We suggest that this is probably due to the wide variation in lesion locations across the patients (as can be seen in Table 1). Contrary, consistency could be observed in the areas with decreased long-range FCD and increased FCD for both short-range and long-range. These results appear to suggest that common long-range connections might be affected by TAI. In other words, despite different lesion locations, same changes in long-range connections could be observed across TAI patients. Similarly, there are common pathways for compensation across TAI patients, which may result from the common long-range disruptions due to the variety of lesion locations. Further studies are needed to confirm these suggestions.

Behavioral relevance of FCD alterations in TAI

Our ultimate goal was to investigate whether alterations in functional connectivity density in the TAI group was associated with impairments in balance, as assessed by the SOT protocol of the EquiTest. Lower balance levels (larger ellipse areas) in TAI were associated with a lower long-range functional connectivity density in subcortical structures, including the left putamen and cerebellar vermis. The putamen (along with the substantia nigra and caudate) is an integral part of the nigrostriatal system and thought to be involved in initiation of movements (Graybiel, 1990). Interestingly, this result is largely consistent with a previous study of Goble and associates (2012) supporting a link between a measure of neural activation in the putamen and performance on a test of proprioceptive sensibility. Since the vermis of the cerebellum contributes to the regulation of whole-body posture and locomotion (Coffman et al., 2011), a decrease in FC density of this region could explain abnormally increased sway in TAI patients. This result is in agreement with our previous diffusion MRI study (Caeyenberghs et al., 2010), showing associations between the SOT balance scores and fractional anisotropy in the cerebellum. These results suggest that evaluation of subcortical structures such as the putamen using rs-fMRI combined with a FCDM approach could be helpful in developing imaging biomarkers for diagnostics/prognosis and may also be useful for evaluating response to interventions in patients with balance deficits following TAI.

Limitations

The most obvious limitation of this study pertains to the rather small group size of the TAI patients. It remains to be seen whether larger groups, allowing more powerful statistical analyses, will provide further confirmation/extension of the obtained results. However, our group was relatively homogeneous in terms of injury mechanism (traffic accidents and falls) and neuropathology (TAI). Related to this issue, balanced datasets should be used in further studies. In this study, similar results were obtained using the balanced group (i.e., selecting 12 controls, age and gender matched). Moreover, we wanted to use the entire control group to obtain a better estimate of the FCD of the population (children and adolescents). Only two studies so far, one study in children with attention deficit/hyperactivity disorder (Tomasi and Volkow, 2012a) and another study in children with anisometropic amblyopia (Wang et al., 2014) have conducted comparisons of short- and long-range FCD in the brains of children. Furthermore, longitudinal studies are needed to determine how changes in functional connectivity density are related to recovery and objective measures of postural control. Taking into account these limitations, this is the first time that such strong relationships between functional connectivity and postural control have been established.

Acknowledgments

Support for this study was provided through a grant from the Research Programme of the Research Foundation—Flanders (FWO; Levenslijn G.0482.10 and G.A114.11).

Author Disclosure Statement

Karen Caeyenberghs has no financial disclosure. The remaining authors have no financial relationships relevant to this article to disclose.

References

Basford JR, Chou LS, Kaufman KR, Brey RH, Walker A, Malec JF, et al. 2003. An assessment of gait and balance deficits after traumatic brain injury. Arch Phys Med Rehabil 84:343–349.

Burgess PW, Dumontheil I, Gilbert SJ. 2007. The gateway hypothesis of rostral prefrontal cortex (area 10) function. Trends Cogn Sci 11:290–298.

Caeyenberghs K, Leemans A, De Decker C, Heitger M, Drijkoningen D, Linden CV, et al. 2012. Brain connectivity and postural control in young traumatic brain injury patients: a diffusion MRI based network analysis. Neuroimage Clin 1: 106–115.

Caeyenberghs K, Leemans A, Geurts M, Taymans T, Linden CV, Smits-Engelsman BC, et al. 2010. Brain-behavior relationships in young traumatic brain injury patients: DTI metrics are highly correlated with postural control. Hum Brain Mapp 31:992–1002.

Caeyenberghs K, Leemans A, Leunissen I, Gooijers J, Michiels K, Sunaert S, et al. 2014. Altered structural networks and executive deficits in traumatic brain injury patients. Brain Struct Funct 219:193–209.

Caeyenberghs K, Wenderoth N, Smits-Engelsman BC, Sunaert S, Swinnen SP. 2009. Neural correlates of motor dysfunction in children with traumatic brain injury: exploration of compensatory recruitment patterns. Brain 132:684–694.

Chan LL, Ng KM, Rumpel H, Fook-Chong S, Li HH, Tan EK. 2014. Transcallosal diffusion tensor abnormalities in predominant gait disorder parkinsonism. Parkinsonism Relat Disord 20:53–59.

Coffman KA, Dum RP, Strick PL. 2011. Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex. Proc Natl Acad Sci U S A 108:16068–16073.

Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. 2001. Frequencies contributing to functional connectivity in the cerebral cortex in ''resting-state'' data. AJNR Am J Neuroradiol 22:1326–1333.

Duarte M, Zatsiorsky VM. 2002. Effects of body lean and visual information on the equilibrium maintenance during stance. Exp Brain Res 146:60–69.

Foerster BU, Tomasi D, Caparelli EC. 2005. Magnetic field shift due to mechanical vibration in functional magnetic resonance imaging. Magn Reson Med 54:1261–1267.

Gagnon I, Forget R, Sullivan SJ, Friedman D. 1998. Motor performance following a mild traumatic brain injury in children: an exploratory study. Brain Injury 12:843–853.

Gagnon I, Friedman D, Swaine B, Forget R. 2001. Balance findings in a child before and after a mild head injury. J Head Trauma Rehabil 16:595–602.

Gagnon I, Swaine B, Friedman D, Forget R. 2004. Children show decreased dynamic balance after mild traumatic brain injury. Arch Phys Med Rehabil 85:444–452.

George R, Griffin JW. 1994. Delayed macrophage responses and myelin clearance during Wallerian degeneration in the central nervous system: the dorsal radiculotomy model. Exp Neurol 129:225–236.

Geurts ACH, Knoop JA, van Limbeek J. 1999. Is postural control associated with mental functioning in the persistent postconcussion syndrome? Arch Phys Med Rehabil 80:144–149.

Geurts ACH, Ribbers GM, Knoop JA, vanLimbeek J. 1996. Identification of static and dynamic postural instability following traumatic brain injury. Arch Phys Med Rehabil 77:639–644.

Goble DJ, Coxon JP, Van Impe A, Geurts M, Van Hecke W, Sunaert S, et al. 2012. The neural basis of central proprioceptive processing in older versus younger adults: an important sensory role for right putamen. Hum Brain Mapp 33:895–908.

Graybiel AM. 1990. The basal ganglia and the initiation of movement. Rev Neurol (Paris) 146:570–574.

Guskiewicz KM, Riemann BL, Perrin DH, Nashner LM. 1997. Alternative approaches to the assessment of mild head injury in athletes. Med Sci Sports Exerc 29:S213–S221.

Hulkower MB, Poliak DB, Rosenbaum SB, Zimmerman ME, Lipton ML. 2013. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. AJNR Am J Neuroradiol 34:2064–2074.

Ingersoll CD, Armstrong CW. 1992. The effects of closed-head injury on postural sway. Med Sci Sports Exerc 24:739–743.

Kaufman KR, Brey RH, Chou LS, Rabatin A, Brown AW, Basford JR. 2006. Comparison of subjective and objective measurements of balance disorders following traumatic brain injury. Med Eng Phys 28:234–239.

Keightley ML, Singh SR, Chen JK, Gagnon I, Leonard G, Petrides M, et al. 2014. A functional magnetic resonance imaging study of working memory in youth after sports-related concussion: is it still working? J Neurotrauma 31:437–451.

Lehmann JF, Boswell S, Price R, Burleigh A, Delateur BJ, Jaffe KM, et al. 1990. Quantitative-evaluation of sway as an indicator of functional balance in posttraumatic brain injury. Arch Phys Med Rehabil 71:955–962.

Malec JF, Brown AW, Leibson CL, Flaada JT, Mandrekar JN, Diehl NN, Perkins PK. 2007. The mayo classification system for traumatic brain injury severity. J Neurotrauma 24:1417–1424.

Neistadt ME. 1994. Perceptual retraining for adults with diffuse brain injury. Am J Occup Ther 48:225–233.

Oliveira LF, Simpson DM, Nadal J. 1996. Calculation of area of stabilometric signals using principal component analysis. Physiol Meas 17:305–312.

O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. 2010. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb Cortex 20:953–965.

Palacios EM, Sala-Llonch R, Junque C, Roig T, Tormos JM, Bargallo N, et al. 2013. Resting-state functional magnetic resonance imaging activity and connectivity and cognitive outcome in traumatic brain injury. JAMA Neurol 70:845–851.

Pandit AS, Expert P, Lambiotte R, Bonnelle V, Leech R, Turkheimer FE, et al. 2013. Traumatic brain injury impairs small-world topology. Neurology 80:1826–1833.

Picard N, Strick PL. 2001. Imaging the premotor areas. Curr Opin Neurobiol 11:663–672.

Povlishock JT. 1992. Traumatically induced axonal injury: pathogenesis and pathobiological implications. Brain Pathol 2:1–12.

Povlishock JT, Katz DI. 2005. Update of neuropathology and neurological recovery after traumatic brain injury. J Head Trauma Rehabil 20:76–94.

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59:2142–2154.

Prosperini L, Sbardella E, Raz E, Cercignani M, Tona F, Bozzali M, Petsas N, Pozzilli C, Pantano P. 2013. Multiple sclerosis: white and gray matter damage associated with balance deficit detected at static posturography. Radiology 268:181–189.

Raichle ME, Snyder AZ. 2007. A default mode of brain function: a brief history of an evolving idea. Neuroimage 37:1083–1090.

Ramnani N. 2012. Frontal lobe and posterior parietal contributions to the cortico-cerebellar system. Cerebellum 11:366–383.

Riemann BL, Guskiewicz KM. 2000. Effects of mild head injury on postural stability as measured through clinical balance testing. J Athl Train 35:19–25.

Rizzolatti G, Luppino G, Matelli M. 1998. The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol 106:283–296.

Rubin AM, Woolley SM, Dailey VM, Goebel JA. 1995. Postural stability following mild head or whiplash injuries. Am J Otol 16:216–221.

Sharp DJ, Beckmann CF, Greenwood R, Kinnunen KM, Bonnelle V, De Boissezon X, et al. 2011. Default mode network functional and structural connectivity after traumatic brain injury. Brain 134:2233–2247.

Sharp DJ, Scott G, Leech R. 2014. Network dysfunction after traumatic brain injury. Nat Rev Neurol 10:156–166.

Shumskaya E, Andriessen TM, Norris DG, Vos PE. 2012. Abnormal whole-brain functional networks in homogeneous acute mild traumatic brain injury. Neurology 79:175–182.

Shumway-Cook A, Horak FB. 1986. Assessing the influence of sensory interaction of balance. Suggestion from the field. Phys Ther 66:1548–1550.

Song XW, Dong ZY, Long XY, Li SF, Zuo XN, Zhu CZ, et al. 2011. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6:e25031.

Stoodley CJ, Schmahmann JD. 2009. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44:489–501.

Tang L, Ge Y, Sodickson DK, Miles L, Zhou Y, Reaume J, et al. 2011. Thalamic resting-state functional networks: disruption in patients with mild traumatic brain injury. Radiology 260:831–840.

Tomasi D, Volkow ND. 2010. Functional connectivity density mapping. Proc Natl Acad Sci U S A 107:9885–9890.

Tomasi D, Volkow ND. 2011. Functional connectivity hubs in the human brain. Neuroimage 57:908–917.

Tomasi D, Volkow ND. 2012a. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 71:443–450.

Tomasi D, Volkow ND. 2012b. Aging and functional brain networks. Mol Psychiatry 17:471, 549–558.

Tomasi D, Volkow ND. 2012c. Gender differences in brain functional connectivity density. Hum Brain Mapp 33:849–860.

Ungerleider LG, Courtney SM, Haxby JV. 1998. A neural system for human visual working memory. Proc Natl Acad Sci U S A 95:883–890.

Van Impe A, Coxon JP, Goble DJ, Doumas M, Swinnen SP. 2012. White matter fractional anisotropy predicts balance performance in older adults. Neurobiol Aging 33:1900–1912.

Wang T, Li Q, Guo M, Peng Y, Li Q, Qin W, Yu C. 2014. Abnormal functional connectivity density in children with anisometropic amblyopia at resting-state. Brain Res 1563: 41–51.

Ward BD. 2000. Simultaneous inference for FMRI data.

Warren M. 1993. A hierarchical model for evaluation and treatment of visual perceptual dysfunction in adult acquired brain injury, Part 2. Am J Occup Ther 47:55–66.

Weiner KS, Grill-Spector K. 2011. Not one extrastriate body area: using anatomical landmarks, hMT+, and visual field maps to parcellate limb-selective activations in human lateral occipitotemporal cortex. Neuroimage 56:2183–2199.

Address correspondence to:
Karen Caeyenberghs
Department of Physical Therapy and Motor Rehabilitation
Campus Heymans (UZ) 2B3, De Pintelaan 185
Ghent 9000
Belgium

E-mail: karen.caeyenberghs@ugent.be