Altered functional connectivity in the motor network after traumatic brain injury

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ABSTRACT

Background: A large proportion of survivors of traumatic brain injury (TBI) have persistent cognitive impairments, the profile of which does not always correspond to the size and location of injuries. One possible explanation could be that TBI-induced damage extends beyond obvious lesion sites to affect remote brain networks. We explored this hypothesis in the context of a simple and well-characterized network, the motor network. The aim of this cross-sectional study was to establish the residual integrity of the motor network as an important proof of principle of abnormal connectivity in TBI.

Methods: fMRI data were obtained from 12 right-handed patients and 9 healthy controls while they performed the finger-thumb opposition task with the right hand. We used both conventional and psychophysiologic interaction (PPI) analyses to examine the integrity of functional connections from brain regions we found to be activated in the paradigm we used.

Results: As expected, the analysis showed significant activations of the left primary motor cortex (M1), right cerebellum (Ce), and bilateral supplementary motor area (SMA) in controls. However, only the activation of M1 survived robust statistical thresholding in patients. In controls, the PPI analysis revealed that left M1, SMA, and right Ce positively interacted with the left frontal cortex and negatively interacted with the right supramarginal gyrus. In patients, we observed no negative interaction and reduced interhemispheric interactions from these seed regions.

Conclusions: These observations suggest that patients display compromised activation and connectivity patterns during the finger-thumb opposition task, which may imply functional reorganization of motor networks following TBI. *Neurology*® 2010;75:168-176

GLOSSARY

Ce = cerebellum; **GCS** = Glasgow Coma Scale; **IFG** = inferior frontal gyrus; **M1** = primary motor cortex; **MMSE** = Mini-Mental State Examination; **MOB** = medial frontal gyrus, orbital part; **NART** = National Adult Reading Test; **PPI** = psychophysiologic interaction; **SMA** = supplementary motor area; **SMFG** = superior medial frontal gyrus; **SMG** = supramarginal gyrus; **SOb** = superior frontal gyrus orbital part; **TBI** = traumatic brain injury.

Traumatic brain injury (TBI) survivors frequently have persistent cognitive impairments, the profile of which does not always correlate with the location of focal lesions. One explanation for this discordance may be that cognitive changes arise from damage to integrated neural networks, instead of focal injury sites.¹ This may result in impaired interaction (functional connectivity) between regions constituting networks that mediate specific functions.

Critical deficits in TBI involve attention, memory, and impulse control,² cognitive processes subserved by complex neural networks.³ While establishing connectivity patterns in these networks is important, a proof-of-principle study that addresses abnormal neural connectivity in TBI may be best initiated in a better-defined neural system, such as the motor network.

The motor network consists of a number of structures, including the primary motor cortex (M1), supplementary motor area (SMA), cerebellum (Ce), and frontoparietal cortices.^{4,5} The

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spatially remote nature of these structures⁶ may make this network particularly vulnerable to white matter injury.^{7–9} While gross motor function often recovers,¹⁰ more subtle abnormalities (e.g., motor preparation) persist and are associated with abnormal activation patterns.^{11,12} However, interactions between these areas that are involved in motor tasks have not been studied following TBI.

In the present study, we used psychophysiologic interaction (PPI) analysis¹³ with fMRI data to establish the nature of interactions between areas that mediate simple unimanual finger movement, and thus we attempted to establish a comprehensive picture of motor network reorganization following TBI.

METHODS **Setting.** We acquired fMRI data while the participants performed a self-paced index finger–thumb opposition task with their right hand in Wolfson Brain Imaging Centre (Cambridge, UK). Each participant performed this task in the same fMRI session with 3 other tasks in a randomized order. The other 3 tasks were working memory, face-place-object-emotional visual recognition, and word-encoding tasks.

Participants. Patient participants were recruited over a 10-month period from a cohort of patients who sustained TBI and were treated at Addenbrooke’s Hospital (Cambridge, UK). All

patients were at least 6 months post-TBI. Exclusion criteria included National Adult Reading Test (NART <70), Mini-Mental State Examination (MMSE <23), left-handedness, history of psychiatric or neurologic disorders, history of drug/alcohol abuse, contraindications for MRI scanning, medication that may affect cognitive performance, and a physical handicap that may prevent completion of testing. We aimed to recruit 12–15 subjects (a generally accepted sample size for a group random-effects fMRI analysis); however, we recruited 14 patients and 11 age-matched healthy controls. Data from 2 patients and 2 controls were excluded due to severe motion artifacts in fMRI data. Data from 9 right-handed healthy controls (3 men and 6 women; 19–53 years of age, mean age = 31.78) and 12 right-handed patients (8 men and 4 women; 20–62 years of age, mean age = 42.75) were analyzed and are reported. Demographic and clinical characteristics of patient participants are shown in table 1. Two patients had mild TBI, scoring 13 points or above on the Glasgow Coma Scale (GCS)¹⁴ at the time of admission to the hospital; 2 had moderate TBI (GCS score 9–12) and 8 had severe TBI (GCS score 8 or below). We identified the site of injury from medical records from the time of the injury and clinical follow-ups and additionally by visually inspecting T1-weighted images that were acquired at the same time as fMRI data. We found that 2 patients had lesions extending to the left SMA. No patients had lesions in the M1.

Standard protocol approvals, registrations, and patient consents. The Cambridgeshire Research Ethics Committee approved the study and all subjects gave informed written consent before participation.

Index finger-thumb opposition task. The self-paced index finger-thumb opposition task consisted of 8 blocks (40-s duration/block) of alternating move or rest condition. At the start of

Table 1 Lesion information for patient participants in this study ^a						
Patient with TBI	Sex	Time since injury, mo	GCS	GOSe	Lesion in motor network	Location of injury
1	F	18	4	7	SMA L	Frontal sup L, ventricular enlargement L
2	M	17	8	8	—	NA
3	M	22	13	5	—	Temporal mid L, temporal sup L, temporal inf R
4	F	61	3	3	—	Temporal pole L, temporal sup L, frontal orb L
5	M	48	3	6	SMA L	Frontal sup L
6	M	49	10	7	—	Temporal inf L, temporal mid L, temporal sup L
7	M	17	5	5	—	Temporal inf R
8	F	14	15	8	—	Temporal pole L, rectus L, frontal orb L, temporal mid R
9	M	35	3	5	—	NA
10	F	6	5	6	—	Corpus callosum, temporal R
11	M	9	11	4	—	Temporal sup L, Frontal mid L, Temporal pole L
12	M	11	4	4	—	Temporal mid L

Abbreviations: ant = anterior; cingulate = cingulate gyrus; frontal = frontal cortex; frontal orb = orbitofrontal gyrus; GCS = Glasgow Coma Scale; GOSe = Glasgow Outcome Scale extended; inf = inferior; med = medial; mid = middle; NA = no lesion observable from the scan; SMA = supplementary motor area; sup = superior; TBI = traumatic brain injury; temporal = temporal gyrus.

^a Lower scores on GCS indicate greater severity of TBI at acute stage¹⁴ and lower scores on GOSe indicate worse outcome.³⁷

each block, the instruction, move or rest, appeared on the screen for 1 second. In response to the instruction to move, the participants tapped the index finger against the thumb at a constant pace. During the rest block, the participants were instructed to relax. Subjects visually fixated on a crosshair in the center of the screen during each block.

fMRI image acquisition and preprocessing. The fMRI data were acquired on a Bruker MedSpec Avance S300 3-Tesla magnetic resonance system (Ettlingen, Germany), by using a gradient-echo echoplanar imaging sequence (repetition time = 1,100 msec, echo time = 30 msec, time of acquisition = 1,600 msec, flip angle 65°, matrix size 64 × 64, field of view 24 × 24 cm, in-plane resolution 3.75 mm × 3.75 mm, 21 oblique slices angled away from the eyes and covered all of the brain, 4 mm

thick, 1-mm gap between slices). Spoiled gradient recalled T1-weighted scans with $0.703 \times 0.859 \times 1 \text{ mm}^3$ voxel size were acquired for anatomic localization.

The fMRI data were preprocessed and analyzed using statistical parametric mapping (SPM5) (Wellcome Department of Cognitive Neurology, London, UK). The preprocessing of the fMRI data included slice-timing correction, within-subject realignment to the first image (12 dummy scans excluded to allow T2 equilibrium), spatial normalization of the functional images to a standard echoplanar imaging template based on the Montreal Neurological Institute reference brain using a 12-parameter linear affine transformation to account for movement artifacts, and a linear combination of 3-dimensional discrete cosine transform basis functions to account for nonlinear deformations. Fi-

Table 2 Group subtractive analysis in move – rest contrast

HC/TBI	Cluster level		Voxel level		Coordinates			Location (BA)	Region
	P _{corrected}	Extent	P _{corrected}	Voxel T	x	y	z		
HC	0.000 ^a	475	0.827	8.69	–40	–14	64	4, 3, 6	Left primary motor cortex, left premotor/supplementary motor area, left primary somatosensory cortex
			0.987	7.04	–46	–12	50		
			0.988	7.00	–38	–16	50		
	0.000 ^a	385	0.989	6.97	20	–54	–30	NA	Right (anterior) cerebellum (6), vermis (4, 5, 8)
			1.000	5.81	2	–60	–14		
			1.000	5.55	2	–62	–30		
	0.008 ^a	157	1.000	5.69	–2	–14	52	6	Left and right supplementary motor area
TBI				5.36	0	–6	62		
				5.08	8	–12	62		
	0.156	75	0.997	6.59	–10	–20	2	NA	Left thalamus
	0.967	18	1.000	5.97	–40	–54	36	40	Left supramarginal gyrus
	0.998	10	1.000	4.81	–28	–4	–8	10	Left putamen
	0.001 ^a	150	0.997	5.66	–32	–16	56	4, 6	Left primary motor cortex, left premotor/supplementary motor area
			1.000	4.94	–44	–6	58		
			1.000	4.73	–30	–16	66		
	0.963	15	0.989	5.89	–42	–18	30	48, 3	Left primary somatosensory cortex
			1.000	5.04	–46	–12	24		
	0.989	12	1.000	5.31	–4	62	0	10	Left frontal gyrus, medial orbital area
	0.996	10	1.000	5.29	–32	0	18	48	Left insula
	0.999	8	1.000	5.04	–2	–68	–18	NA	Vermis (6)
	1.000	4	1.000	4.98	–38	–28	38	3	Left inferior parietal gyrus/primary somatosensory cortex
	1.000	8	1.000	4.82	0	–54	–22	NA	Vermis (6)
	1.000	3	1.000	4.79	18	–12	24	NA	Right caudate
	0.993	11	1.000	4.43	–52	–20	38	3	Left inferior parietal gyrus/primary somatosensory cortex
	1.000	3	1.000	4.37	–48	–8	36	4	Left primary motor cortex
	1.000	3	1.000	4.18	–54	–12	44	4	Left primary motor cortex

Abbreviations: BA = Brodmann area; HC = healthy controls; TBI = traumatic brain injury.

^a Brain regions that survived statistics at cluster level, corrected for the whole brain ($p < 0.05$).

Table 3 PPI analyses

Seed region with MNI coordinates	HC/TBI	+/- PPI	Cluster level		Voxel level		Coordinates			Location (BA)	Region				
			P _{corrected}	Extent	P _{corrected}	Voxel T	x	y	z						
M1 (−40, −14, 64)	HC	+	0.007 ^a	181	0.064	13.87	−10	42	−12	10, 11	MOB (left), anterior cingulum (left)				
					0.528	10.19	−10	42	2						
					1.000	5.65	0	34	−10						
			+	0.999	8	1.000	6.16	−18	54	2	11	SMFG (left)			
		−				0.000 ^a	313	0.805	8.57	−6	6		62	6	SMA (left), middle cingulum (left)
								0.838	8.36	−12	−6		54		
			0.999	5.92	−10			4	44						
			−	0.008 ^a	173	0.901	7.92	48	−52	30	39, 40	SMG (right), angular (right)			
		0.989				6.76	60	−44	38						
		−				0.013 ^a	159	0.999	6.15	52	30		−10	38, 48	IFG (right), IOB (right), insula (right)
			0.999	6.07	44			26	−12						
			1.000	5.07	36			16	−4						
			−	0.059	111	0.999	6.08	28	42	30	46	Middle frontal gyrus (right)			
		1.000				5.49	36	36	28						
M1 (−36, −14, 56)	TBI	+	0.989	12	1.000	4.32	−4	62	4	10	SMFG (left)				
		+	1.000	1	1.000	4.15	−16	52	−12	11	SOB (left)				
SMA (−2, −14, 52)	HC	+	0.082	104	0.560	9.91	−10	42	−12	11	MOB (left)				
		−	0.939	22	1.000	5.54	−60	−28	28	48	SMG (left)				
		−	1.000	4	1.000	5.16	−36	−14	58	6	Premotor cortex (left)				
		−	1.000	5	1.000	4.62	10	−8	66	6	SMA (right)				
		−	1.000	2	1.000	5.00	56	−30	24	48	SMG (right)				
SMA (−12, −4, 54)	TBI														
Ce (20, −54, −30)	HC	+	0.913	24	0.760	8.85	4	38	−6	11	MOB (right), anterior cingulate (right)				
		+	0.990	14	1.000	5.74	−8	42	−12	11	MOB (left)				
		−	0.035 ^a	126	0.747	8.93	52	−52	30	39, 40	SMG (right), angular (right)				
		−	0.000 ^a	955	0.925	7.72	6	−6	60	6, 32	SMA (right), SMA (left), middle cingulum (right)				
					0.954	7.41	0	2	60						
					0.981	6.97	14	16	38						
			−	0.005 ^a	186	0.940	7.57	−60	−22	28	48, 2, 22	SMG (left)			
		0.999				6.16	−58	−28	36						
		1.000				5.16	−66	−20	18						
			−	0.450	52	0.999	6.15	−38	−10	64	6	Premotor area (left)			
		1.000				5.66	−32	−14	58						
		−				0.393	56	1.000	5.73	−38	10		−2	48	Insula (left)
			1.000	5.13	−48			12	−6						
			−	0.299	64			1.000	5.43	34	14	4	48	Insula (right)	
		Ce (18, −54, −22)	TBI	+	0.002 ^a	241	0.953	5.64	2	−58	2	30	Vermis (4, 5), precuneus (right)		
					0.957	5.61	−2	−50	12						
					0.991	5.20	8	−50	16						
+	0.395			58	0.961	5.58	−2	−74	38	7	Precuneus (left)				
+	0.997			9	0.999	4.80	46	−24	48	3	Primary somatosensory area (right)				
+	0.998			8	1.000	4.73	44	−28	42	2	Primary somatosensory area (right)				
+	0.819			30	1.000	4.49	8	−48	36	23	Middle cingulum (right), precuneus (right)				
+	0.739			35	1.000	4.41	−6	−54	42		Precuneus (left)				
					1.000	4.39	−8	−46	42						
+	1.000			1	1.000	4.04	−10	48	16	32	SMFG (left)				

Abbreviations: BA = Brodmann area; Ce = cerebellum; HC = healthy controls; IFG = inferior frontal gyrus; IOB = inferior frontal gyrus, orbital part; M1 = primary motor cortex; MNI = Montreal Neurological Institute; MOB = medial frontal gyrus, orbital part; PPI = psychophysiological interaction; SMA = supplementary motor area; SMFG = superior medial frontal gyrus; SMG = supramarginal gyrus; SOB = superior frontal gyrus, orbital part; TBI = traumatic brain injury; ver = vermis.

^a Brain regions that survived statistics at cluster level, corrected for the whole brain ($p < 0.05$).

Figure 1 Brain activations during finger movements observed by fMRI subtractive analysis (move – rest)

Activations that survived statistics at cluster level corrected for the whole brain are superimposed on a 3-dimensional reconstruction of T1-weighted template image as found in MRIcron. TBI = traumatic brain injury.

nally, the images were smoothed using an isotropic 8 mm³ full width at half maximum Gaussian kernel.

fMRI analysis. The fMRI data were analyzed with the general linear model as implemented in SPM5. Contrast images (e.g., move vs rest) from each subject were combined into a group random-effects analysis. We report results that survived $p < 0.05$ at cluster level, corrected for multiple comparisons across the entire brain ($p < 0.001$ uncorrected for voxels). These results are highlighted in tables 2 and 3. We also report results that survived $p < 0.001$ uncorrected at voxel level only, if the region is an established part of the motor network.

We also performed a PPI analysis. PPI is a form of regression analysis which tests whether coactivations in remote brain areas depend on psychological context.¹³ Therefore, PPI analyses examine connectivity between seed regions and the rest of the brain in the context of a specific task. The seed regions in our PPI analyses comprised spheres (radius = 5 mm) centered on the peak voxels of regions that are significantly more activated during move blocks than during the rest blocks in healthy controls. We report PPI group results at the same thresholds specified for group subtractive contrast analysis.

We used the cluster labeling function of the anatomic automatic labeling (aal)¹⁵ toolbox for SPM5 as well as aal and Brodmann templates of MRIcron software (<http://www.sph.sc.edu/comd/rorden/mricron/>) to label anatomic areas.

RESULTS There was no reported difficulty in performing this simple motor task from study subjects or supervising researchers. This is consistent with published data.¹⁶

Comparison of movement artifacts. In order to establish whether movement affected fMRI data differentially, we carried out a 1-way analysis of variance on each individual's average movement components (x, y, z, roll, pitch, and yaw) of the fMRI images. It did not show any significant differences between controls and patients in any of the 6 components (x: $F_{1,20} = 0.14$, $p = 0.71$; y: $F_{1,20} = 1.23$, $p = 0.28$; z: $F_{1,20} =$

0.03 , $p = 0.86$; roll: $F_{1,20} = 0.04$, $p = 0.84$; pitch: $F_{1,20} = 1.01$, $p = 0.33$; yaw: $F_{1,20} = 0.04$, $p = 0.85$).

Contrast analysis. The subtractive analysis (move – rest) in controls revealed significant activations in the contralateral M1, SMA, and ipsilateral right anterior part of the Ce with some additional movement-related activation that did not survive cluster correction (table 2 and figure 1, left). In patients, the contralateral activation of the left M1 was the most significant activation with some additional movement-related activations (table 2 and figure 1, right). Group comparison of the move – rest contrast showed increased activation of the right insula and left superior medial frontal gyrus (SMFG) in patients compared with controls.

In controls, the inverse contrast (rest – move) revealed deactivations in ipsilateral (right) M1, left inferior frontal gyrus (IFG), left SMFG, and right insula. In contrast, we did not detect deactivations in the brains of patients even at the uncorrected voxel threshold.

PPI analysis. Subject-specific time series from seed regions in the M1, SMA, and Ce were used for PPI analyses. In controls, the Montreal Neurological Institute coordinates of seed regions were as follows: M1 (–40, –14, 64), SMA (–2, –14, 52), and Ce (20, –54, –30) (figure 2). In patients, the coordinate for the M1 seed is (–36, –14, 56). SMA and Ce activations in patients did not survive whole brain cluster-based correction. As such, we lowered the voxel threshold until we found regions close to the ones activated by controls ($p < 0.05$). These were at SMA (–12, –4, 54) and Ce (18, –54, –22).

Connectivity from the primary motor cortex. Connectivity from the primary motor cortex is described in

The results are superimposed on a 3-dimensional reconstruction of T1-weighted image. Ce = cerebellum; IFG = inferior frontal gyrus; INS = insula; IOb = inferior frontal gyrus, orbital part; M1 = primary motor cortex; MCg = middle cingulum; MFG = middle frontal gyrus; MOb = medial frontal gyrus, orbital part; pCu = precuneus; PM = premotor cortex; SMA = supplementary motor area; SMFG = superior medial frontal gyrus; SMG = supra-

figure 2a and table 3. In controls, PPI analyses revealed that functional connectivity between M1 and medial orbital part of left frontal gyrus (MOB) and left SMFG increased during the move block. In addition, M1 negatively interacted with the following regions during the move block: SMA, right supramarginal gyrus (SMG), right IFG, and right middle frontal cortex. In patients, similar positive interactions of M1 occurred with the left superior frontal gyrus orbital part (SOB) and left SMFG, although these did not survive cluster level correction. However, no negative functional interactions were found in TBI.

Connectivity from the SMA. Connectivity from the SMA is described in figure 2b and table 3. In controls, SMA positively interacted with left MOb and negatively with bilateral SMG, SMA, and left premotor cortex. However, no significant interaction from the SMA seed was found in patients.

Connectivity from the cerebellum. Connectivity from the cerebellum is described in figure 2c and table 3. In controls, Ce showed significant negative interactions with bilateral SMG and SMA. Additionally, Ce negatively interacted with the left premotor cortex and bilateral insula, and positively with bilateral MOb in controls. In patients, Ce showed significant positive interaction with the vermis and additionally with left SMFG, right somatosensory area, right middle cingulum, and bilateral precuneus. However, no negative interaction was found in patients.

DISCUSSION In this study, we investigated whether there is 1) TBI-induced alteration in brain activation using subtractive analysis and 2) altered functional interaction between brain regions during performance of the index finger-thumb opposition task using PPI analysis.

As expected, subtractive analysis showed activations of key brain structures in the motor network in controls (figure 1, left). Although there was no detectable or reported difference in task performance between controls and patients, only the activation of M1 (and not SMA or Ce) survived statistical testing in patients (figure 1, right). The smaller sample size for controls ($n = 9$) compared to patients ($n = 12$) and the fact that controls present a larger effect size (z score in M1 = 5.12) than patients (z score in M1 = 3.80) further support the idea that there is a substantial alteration in motor-related brain activations in

marginal gyrus; SMS = somatosensory cortex; SOb = superior frontal gyrus, orbital part; TBI = traumatic brain injury; Ver = vermis. Green lines show positive PPI and red lines negative PPI. Solid line shows significant PPI at cluster level with a $p < 0.05$ corrected for multiple comparisons, whereas dotted line shows significant PPI at voxel level with an uncorrected $p < 0.001$.

patients. The increased activation of the left SMFG and right insula during the move block in patients may reflect compensatory brain activations supporting the performance of this task.

In patients, PPI analyses revealed no significant interactions at the cluster threshold corrected for multiple comparisons from M1, SMA, and Ce seeds, except for the intracerebellar interaction between the Ce seed and the vermis. The overall PPI picture shows that, in contrast to controls, there was no brain region negatively interacting with any of the seed regions in patients. Furthermore, there were fewer interhemispheric interactions compared with controls.

These observations suggest that connectivity between key parts of the motor network may have been compromised by injury. Previous studies have reported white matter tract vulnerability following TBI, especially in the corpus callosum,^{7–9} and it is possible that the observed reduction in the interhemispheric functional interactions is related to corpus callosal damage. Although some compensatory brain activations were found, the observed functional disconnection of the network suggests reduced interhemispheric and perhaps inhibitory control of finger movements in patients.

We considered the possibility that the reduced findings in both subtractive and PPI analyses may have been due to systematic differences in data quality between patients and controls. Participants' head movement during scanning introduces noise to fMRI data. However, when we compared magnitude of movement components, we found no significant differences between controls and patients, suggesting that the quality of the data from controls and patients was comparable and is unlikely to account for our findings. In a sequential finger-thumb tapping experiment in healthy controls, deactivation of M1 ipsilateral to the hand performing the task was found using fMRI.¹⁷ It was suggested that this reflects interhemispheric inhibition of motor cortices via transcallosal fibers.¹⁸ In agreement with this, we found deactivation of the ipsilateral (right) M1 in controls but not in patients.

The role of interhemispheric inhibition of contralateral motor cortex in controlling the output from M1 during execution of simple unimanual finger movement is well-documented^{19–21} and the observed significant negative interaction between M1 in the left hemisphere and right SMG in controls may reflect this interhemispheric inhibition of M1 (figure 2a, red solid lines). In contrast, the lack of negative interaction between M1 and the contralateral brain regions in patients may indicate alteration of such interhemispheric inhibition, as a possible consequence of reduction in transcallosal fiber connec-

tivity.^{22,23} It has been shown that transcranial magnetic stimulation of SMG caused a significant delay in planning goal-oriented actions, without affecting movement execution.²⁴ This observation suggests that the lack of inhibitory interaction between M1 and SMG in this study may reflect delayed planning of self-initiated finger movements in patients. Indeed, slowness of motor function is commonly reported as a long-term symptom following TBI.¹¹

Reduced positive interaction between M1 and intrahemispheric orbitofrontal cortex was found in patients. Lesion to the lateral orbitofrontal area in primates impairs the animal's ability to control its behavior.^{25,26} Therefore, the present result from the PPI analysis may indicate reduced control over finger movement execution in patients.

In subtractive analysis (move – rest), reduced SMA activation was found in patients. This observation is consistent with a previous study on hand movements in patients with TBI.²⁷ SMA is involved in the volitional aspect of motor planning in self-initiated movement.²⁸ Therefore, the lack of significant SMA activation in patients may further suggest impaired planning of finger movement execution. Anatomically, SMA connects to the prefrontal cortex²⁹ and prefrontal lesions lead to reduction in neuronal input to the SMA.³⁰ Five out of 12 patients in this study had prefrontal lesions. Therefore, it is possible that the reduced neuronal input from the prefrontal cortex to the SMA is contributing to the reduced group activation of SMA. A previous report suggests that early preparatory processes are not necessary for movement execution, but are useful in timely anticipation of self-initiated changes in the individual's environment.¹² The same study further suggests that prefrontal cortical lesions induce reorganization of this preparatory motor network. It is possible that such change in the preparatory motor network has occurred in these patients with TBI. SMA in controls maintained a positive interaction with MOB just as in M1 and Ce seeds. Since coactivations of SMA and MOB have been associated with errors in go/no-go task,³¹ the lack of SMA-MOB interaction in patients may reflect reduced error monitoring during the finger-opposition task.

No significant activation of the anterior Ce was found in patients in the subtractive analysis (move – rest). Cerebellar dysfunction following TBI is known to occur frequently.³² Cerebellar Purkinje cells determine the spatiotemporal pattern (e.g., velocity and duration) of movement execution in the cerebellar-thalamic-cortical pathway.⁶ The anterior Ce coordinates movement of the distal portions of the upper and lower limbs that produce refined and highly skilled motor movements.³³ Therefore, the observed

lack of group activation of the anterior Ce in patients may reflect reduced ability to spatially and temporally control self-initiated finger movement. Significant negative interactions of the Ce seed and bilateral SMG and SMA were found in controls. However, no such negative interactions were found in patients. It is known that cerebellar inhibition represents an important measure of cerebellar activity and of the cerebellar-thalamic-cortical pathway integrity.³⁴ Therefore, the lack of negative interaction from the Ce seed further suggests dysfunction of Ce in patients. SMG is an important area for motor representation and motor imagery.³⁵ It may be speculated that the absence of negative interaction from M1, Ce, and SMA to SMG in patients indicates impaired mental representation of finger movements. A robust positive interaction between Ce and the vermis was found in patients. The lack of negative interactions in patients may also represent altered regulation of excitatory and inhibitory neurotransmitters that occur as part of functional change subsequent to focal brain injury.³⁶

Overall, the results from subtractive and PPI analyses suggest that the motor network has adapted and regained gross motor function following TBI, however, it may not have adapted to allow for optimal function (e.g., preparation and control of the movement). More detailed observations of task performance, such as measures of frequency of errors and speed, are required for clarification. The differential evolutionary effect, which emphasizes motor recovery more than cognitive recovery for the survival of organisms, may offer an explanation for the fact that gross motor function recovered quicker than preparatory motor and motor control functions.

Although T1-weighted MRI in these subjects did not show white matter lesions that would explain the disconnectivity we observed in this study, conventional T1-weighted MRI is not a sensitive measure of traumatic axonal injury, which is a likely neuroanatomic substrate for our findings. Tractography using diffusion tensor imaging may be used to clarify this point in the future. Functional connectivity analyses, in combination with structural connectivity analyses, will allow us to investigate the contribution of white matter damage to functional disconnectivity and help clinicians to make more complete diagnosis.

AUTHOR CONTRIBUTIONS

The experimental protocol was developed and optimized by Dr. C.H. Salmond, Prof. D.K. Menon, Prof. B.J. Sahakian, Prof. J.D. Pickard, and Dr. T.A. Carpenter (MR sequence and optimization). The data collection was carried out by Prof. D.K. Menon, Dr. C.H. Salmond, Mrs. J.G. Outtrim, and Dr. J.V. Taylor Tavares. Statistical analysis of imaging data was conducted by Dr. M. Kasahara and Dr. E.A. Stamatakis. The manuscript was prepared by Dr. M. Kasahara, Dr. E.A. Stamatakis, and Prof.

D.K. Menon, and further scientific contributions to the manuscript preparation were provided by Prof. B.J. Sahakian and Prof. J.D. Pickard.

DISCLOSURE

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