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Neural correlates of motor dysfunction in children with traumatic brain injury: exploration of compensatory recruitment patterns

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Traumatic brain injury (TBI) is a common form of disability in children. Persistent deficits in motor control have been documented following TBI but there has been less emphasis on changes in functional cerebral activity. In the present study, children with moderate to severe TBI ($n = 9$) and controls ($n = 17$) were scanned while performing cyclical movements with their dominant and non-dominant hand and foot according to the easy isodirectional (same direction) and more difficult non-isodirectional (opposite direction) mode. Even though the children with TBI were shown to be less successful on various items of a clinical motor test battery than the control group, performance on the coordination task during scanning was similar between groups, allowing a meaningful interpretation of their brain activation differences. fMRI analysis revealed that the TBI children showed enhanced activity in medial and anterior parietal areas as well as posterior cerebellum as compared with the control group. Brain activation generally increased during the non-isodirectional as compared with the isodirectional mode and additional regions were involved, consistent with their differential degree of difficulty. However, this effect did not interact with group. Overall, the findings indicate that motor impairment in TBI children is associated with changes in functional cerebral activity, i.e. they exhibit compensatory activation reflecting increased recruitment of neural resources for attentional deployment and somatosensory processing.

Keywords: Traumatic brain injury; fMRI; motor control; interlimb coordination; children

Abbreviations: DAI = diffuse axonal injury; EPI = echo echoplanar images; FWHM = full width at half maximum; SMA = supplementary motor area; SPM2 = Statistical Parametric Mapping 2; TBI = traumatic brain injury; TE = echo time; SVC = small volume correction; TR = repetition time; VOI = volumes of interest

Introduction

The most frequent cause of disability and death in children and adolescents is traumatic brain injury (TBI) (Sosin *et al*., 1996; Kraus and McArthur, 1996), often due to traffic accidents. TBI children incur deficits in memory, attention, language, problem solving and academic skills. Moreover, motor performance is impaired for years following the insult and specific deficits are often

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reported, such as spasticity, ataxia and bradykinesia (Rossi and Sullivan, 1996).

In the past, persistent deficits in motor control following TBI have been documented by using standardized testing procedures. Chaplin and colleagues (1993), for example, found significant differences between TBI and control children, both on gross-motor subtests (running speed, balance, strength, bilateral coordination) and on fine-motor items such as upper-limb speed and dexterity. Others have found deficits in strength, agility, endurance and coordination (Rossi and Sullivan, 1996). More recent studies have also observed lower performance levels in TBI children in more functional tests such as gait patterns, i.e. significantly reduced velocity, shorter and more variable steps, less step symmetry and impaired balance (Kuhtz-Bushbeck *et al*., 2003*a, b*). In contrast to those behavioural motor tests, medical imaging studies on alterations in cerebral activity in TBI children during motor tasks in general and coordination tasks in particular have not yet been reported.

A question of central importance is which particular brain areas show alterations in TBI children, and whether and how they compensate for the incurred neural insults. Studies in adults following brain damage (such as stroke) have revealed that motor recovery is associated with a cerebral functional reorganization that marks brain 'plasticity'. These mechanisms include both the recruitment of cortical areas in the undamaged hemisphere (Chollet *et al*., 1991; Weiller *et al*., 1992) and activation expansion into cortical areas adjacent to the lesion site (Chollet *et al*., 1991; Nudo *et al*., 1996). The question remains whether such recovery mechanisms can be generalized to other types of brain injuries, such as TBI and to other age groups, such as children.

In addition to the aforementioned compensatory recruitment in cortical areas, there is structural evidence that subcortical structures are vulnerable during TBI insults (Spanos *et al*., 2007). Pathophysiological changes in the cerebellum and the thalamus have been implicated as contributors to motor (coordination) deficits in a number of animal models of TBI (Maxwell *et al*., 2004; Rodriguez-Paez *et al*., 2005; Park *et al*., 2006; Igarashi *et al*., 2007). These insights from animal models await confirmation from functional imaging data in human TBI.

In the present study, we used fMRI to compare brain activation patterns in typically developing children and children with TBI. Because coordination is often affected in children after moderate to severe TBI, we used a complex interlimb coordination task, requiring cyclical flexion–extension movements of the dominant or non-dominant wrist and foot in the same (isodirectional, easy task) and opposite directions (non-isodirectional, difficult task). Previous behavioural studies have revealed that the non-isodirectional coordination pattern is more difficult to perform than the isodirectional pattern in adults and normal children (Carson *et al*., 1995; Swinnen *et al*., 1995; Cavallari *et al*., 2001) as well as in children with Developmental Coordination Disorder (Volman *et al*., 2006). To obtain preliminary insights into differential neural recruitment patterns during motor performance, we compared TBI and control children during isodirectional and non-isodirectional coordination modes, performed with effectors of either the dominant or non-dominant body side. Our primary focus of interest was the study of neural activation differences between both groups with emphasis on mechanisms of compensatory recruitment. This compensatory recruitment was hypothesized to follow two potential paths (Serrien *et al*., 2007): (i) increased activation in regions that support motor- and/or sensory-guided control such as (pre)motor and parietal areas as well as the cerebellum (Bartenstein *et al*., 1997; Rascol *et al*., 1997; Samuel *et al*., 1997) or (ii) intensified activation in frontal lobe areas that reflect augmented cognitive operations (Wu and Hallett, 2005b). This compensatory recruitment was hypothesized to be more pronounced (i) during the difficult (non-isodirectional) as compared with the easy (isodirectional) coordination task and (ii) when controlling the non-dominant as compared with the dominant limb segments. Moreover, based on the aforementioned evidence from animal models of TBI, we explored the activation states of subcortical areas, particularly in cerebellum and thalamus.

Methods

Participants

Twenty-six children participated in the study, including nine children with TBI (mean age 12.8 years, SD 2.7 years, range 9–16 years of age; four boys and five girls) and 17 control children (mean age 12.4 years, SD 2.4 years, range 9–16 years of age; nine boys and eight girls). The demographic and clinical characteristics of the TBI group are shown in Table 1. The children with TBI were recruited from different rehabilitation centres in Belgium. All TBI children were assessed at least 6 months post-injury, when neurological recovery was stabilized. Following their insult, children entered rehabilitation centres and received physiotherapy (2–5 h/week), occupational therapy (2–3 h/week), neuropsychological support and special schooling. At the time of this study, the children no longer participated in formalized motor rehabilitation or retraining programmes. The interval between injury and scanning (age of injury) was on average 3 years, 1 month (SD 2 years, 1 month). Their age at injury was on average 9 years, 10 months (SD 3 years, 11 months). Initial MRI or CT revealed neuropathological consequences in all patients, typical of moderate-to-severe TBI (Table 1). At the time of scanning, most TBI children showed signs of diffuse axonal injury (DAI), as assessed by a neuroradiologist. Children with focal lesions (i.e. with volume $>0.5\,cm^3$) were excluded, because the inclusion of such patients introduces a different neuropathology. Moreover, signal dropout due to focal lesions may significantly bias results. Children were also excluded if they had pre-existing developmental or intellectual disabilities, a progressive disease, or were taking medication. Control children were recruited from regional primary and secondary schools in Belgium. In view of the small group of TBI subjects, 'proportional matching' was conducted, i.e. each TBI subject was matched to two control children on the basis of gender, age and hand preference. All control subjects were screened to ensure that they had no history of neurological damage. Data of one control child was excluded because of pre-existing learning disabilities.

The Edinburgh Handedness Inventory (Oldfield, 1971) was used to determine hand preference. There were three left-handed children in the TBI group and six left-handed children in the control group (mean −79.3, SD 18.9 for the TBI group; mean −75.3, SD 14.2, for the controls). Important to note, the left-handed children in the TBI group were also left-handed before their injury. The average

Table 1 Summary of demographic and injury characteristics for the TBI group

TBI patient No. Age/gender/ handedness	Age at injury	Cause of injury	M-ABC percentil	Acute scan within 24 h after injury Lesion location/pathology	MRI scan at examination Lesion location/pathology
TBI 1: 9/M/LH	5	Traffic accident	50	Subarachnoid haemorrhage, Hemosiderin deposits foramen magnum and clivus	None
TBI 2: 17/F/RH	15	Traffic accident	1	(L) PL/OL contusion, subdural hematoma	Left ventricle enlarged Shearing injuries
TBI 3: 12/F/RH	5	Traffic accident	0	Contusion (location not specified in available records) Brainstem and ventricle haemorrhage	None
TBI 4: 11/M/RH	8	Traffic accident	19	(L) FL/TL contusion	Shearing injuries
TBI 5: 16/M/LH	16	Traffic accident	2	Multifocal haemorrhagic shearing injuries	Shearing injuries
TBI 6: 13/F/RH	11	Fall	4	Lesion and location not specified in available records	Shearing injuries Basal ganglia injuries
TBI 7: 15/F/RH	12	Traffic accident	12	Contusion (location not specified in available records)	None
TBI 8: 9/M/LH	8	Fall	61	(L) FL/PL contusion	Hemosiderin deposits
TBI 9: 13/F/RH	8	Traffic accident	35	(R) FL Subdural hematoma	Shearing injuries

Anatomy codes: FL = frontal lobe; TL = temporal lobe; PL = parietal lobe; OL = occipital lobe; R = right; L = left. Other codes: RH = right-handed; LH = left-handed; M = male; F = female.

Oldfield score of the right-handed children was 80.5 for the TBI group (SD 11.6) and 83.1 (SD 13.4) for the controls.

General motor performance was assessed using the Movement Assessment Battery for Children (M-ABC), including measures of manual dexterity, ball skills and static and dynamic balance (Henderson and Sugden, 1992; Smits-Engelsman, 1998). The TBI group scored on average worse than the control group on the total score of the M-ABC, $t(22) = 2.11$, $P < 0.05$ (Mean TBI = 12.67, Mean control = 5.50), confirming the former's lower mean motor performance levels.

The parents of all participants gave written informed consent. The consent forms and study protocol were approved by the local Ethics Committee of Biomedical Research at Katholieke Universiteit Leuven.

Task

Three conditions enabled the assessment of brain activity across different degrees of coordinative complexity: (i) isodirectional coupling (low coordination complexity) in which the participants combined hand extension with foot dorsal flexion and hand flexion with foot plantar flexion in a cyclical manner (ISODIR), (ii) non-isodirectional coupling (high coordination complexity) in which the two segments were moved in opposite directions (NON-ISODIR), i.e. associating hand extension to foot plantar flexion and hand flexion to foot dorsal flexion and (iii) a rest condition (REST) in which no movements were performed. These tasks were executed with the dominant and non-dominant body side. The children performed all movement tasks at their preferred speed and with comfortable movement amplitudes.

The hands and feet were positioned in a non-ferromagnetic wrist–hand and ankle–foot orthosis, respectively, to restrict movements to the sagittal plane. The frictionless axis of the orthosis was aligned with the anatomical axis of the joint such that movements were not hindered. Angular displacements of the joints were registered by means of high-precision shaft encoders (HP; 4096 pulses per revolution; sampled at 200 Hz) fixed to the rotation axis of the orthosis. This non-ferromagnetic kinematic registration device enabled us to register movements on-line during brain scanning without signal interference.

Participants lay supine in the scanner. The lower legs were supported by a cushion to ensure free ankle rotation. The arms were extended along the trunk and the forearms were supported to enable free movements of the wrists (positioned in pronation). A bite-bar was used to minimize head motion. Additionally, foam pillow packs were applied to the sides of the child's head. Visual templates, announcing the task to be performed, were projected by a Barco 6400i liquid crystal display projector (Kortrijk, Belgium, 1024×768 pixels, 60 Hz) and displayed via a mirror (eye–mirror distance was ~30 cm). Additionally, participants were instructed to look at the fixation cross, displayed in front of them at all times.

Scanning procedure

Special precautions were taken to ensure the children's comfort in the scanner environment. MR images were acquired with a 3-T Intera MR scanner (Philips, Best, The Netherlands), using an eight-element SENSE head coil (MRI Devices, Waukesha, WI, USA). Functional time series consisted of 126 whole-brain gradient-echo echoplanar images (EPIs) [repetition time (TR)/echo time (TE) 3000/33 ms; field of view 230 mm; matrix, 112×112; slice thickness 4.0 mm; interslice gap 0.4 mm; 34 sagittal slices; SENSE factor 2]. Each time series contained three repetitions of the three conditions (REST, ISODIR and NON-ISODIR), presented in random order. Each condition lasted 21 s (corresponding to seven whole-brain images) and was triggered by the presentation of a visual template displaying the task to be performed. Participants performed six scanning runs, three on the dominant body side and three on the non-dominant body side, resulting in a 30-min functional scan session. A bite-bar was used to minimize head motion during scanning.

A three-dimensional SENSE high-resolution T_1-weighted image (TR/TE 9.68/4.6 ms; inversion time 1100 ms; field of view 250 mm; matrix 256×256; slice thickness 1.2 mm; 182 slices; SENSE factor 2) was acquired from each participant for anatomical details. All structural MRI scans were investigated by a neuro-radiologist to

indicate location and type of pathology (e.g. gliosis, shearing, haemorrhage) (Table 1).

Data analyses

Kinematic analysis

The quality of coordination between the limb segments was assessed by means of a continuous relative phase measure, i.e. the subtraction of the phase angles of each limb according to the following formula: $\Phi = \theta_w - \theta_f - \tan^{-1}[(dX_w/dt)/X_w] - \tan^{-1}[(dX_f/dt)/X_f]$ whereby w and f denotes wrist and foot, respectively; θ_w refers to the phase of the wrist movement at each sample, X_w to the position of the wrist after rescaling to the interval –1, 1 for each cycle of oscillation and dX_w/dt to the normalized instantaneous velocity (Kelso, 1984). Absolute deviations from the target relative phase (i.e. 0° and 180° for ISODIR and NON-ISODIR coordination, respectively) were calculated to obtain a measure of relative phase accuracy (AEΦ, phase error). Previous work has shown AEΦ to be a valid measure of overall coordination accuracy (Lee *et al*., 1995). In addition to this relative phase measure, amplitude and frequency of the limb movements were quantified. The spatial measure consisted of the absolute peak-to-peak amplitude for wrist and foot across each individual cycle, averaged across the trial. Frequency was calculated as the average frequency across individual cycles within a trial.

For the statistical analysis, all parameters were determined for each condition and body side and subsequently averaged across repetitions and runs. All statistical analyses consisted of repeated-measures analyses of variance (ANOVA) with the between-factor Group (TBI, Control) and the within-factors Coordination Mode (ISODIR, NON-ISODIR), Body side (DOMINANT, NON-DOMINANT) and/or Limb (hand, foot) (depending on the dependent variable). The level of significance was set to $\alpha = 0.05$.

Imaging analysis

Imaging data were analysed with Statistical Parametric Mapping 2 (SPM2) (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MatLab 6.5 (The MathWorks Inc.). For each subject, all EPI volumes were realigned to the first volume of the first time series, and a mean image of the realigned volumes was created. This mean image was smoothed with a Gaussian kernel of 6 mm full width at half maximum (FWHM). Additionally, the anatomical image was coregistered with the EPI. The mean functional images were normalized to the standard EPI template, as previous studies showed good results for statistical group comparisons when this adult brain template was used for normalizing children's MR images (Thomas *et al*., 2004; Ciesielski *et al*., 2006). Taking into account the age of our subjects (9–16 years old) and image voxel size used (Burgund *et al*., 2002; Kang *et al*., 2003), we considered this procedure to be preferable. Normalization was performed using affine and non-linear transformations. The normalization parameters were subsampled to a voxel size of $2 \times 2 \times 2$ mm and smoothed with a Gaussian kernel of 8 mm FWHM. The images of the left-handed children (runs on the left side) were flipped (right to left, mirrored) such that that the left hemisphere is the motor-dominant hemisphere for all children. The images of the scanning runs performed on the non-dominant side were also flipped to obtain a consistent distribution of activation that was contralateral and ipsilateral to the moving limbs.

All statistical analyses were performed in the context of the General Linear Model (Friston *et al*., 1995a, *b*). First, a general linear model was defined for each subject and each condition was modelled using a boxcar function convolved with the SPM2 haemodynamic response function. An appropriate high-pass filter (cut-off period at 128 s) was applied to remove low frequency drifts. Additionally, six movement parameters derived from realignment were added as covariates of no interest to correct for confounding effects induced by head movement. Motions were only tolerated as long as none of the frames showed motion exceeding 1 voxel size (2 mm). For each subject and body side, the following contrasts of interest were estimated: ISODIR versus REST and NON-ISODIR versus REST.

The principal question was whether TBI children show more elaborate cortical/subcortical recruitment than control children to compensate for their deficits and whether this compensatory recruitment is more pronounced during the difficult as compared to more easy coordination task or non-dominant versus dominant body side. These questions were addressed in a second-level analysis, for which the contrast images of the four conditions for controls and TBI children were entered into a three-way analysis of variance (full factorial ANOVA in SPM5). An appropriate non-sphericity correction was applied in order to account for heteroscedasticity between groups and for covarying observations within subjects. This analysis allowed for the examination of any main effect or interaction between group, coordination pattern and body side. Significantly activated voxels are only reported when they were part of a cluster exceeding 20 voxels (chosen arbitrarily). All results are reported in MNI coordinates.

To control for multiple comparisons, but also consider activations in smaller regions of the brain, two statistical criteria were used in reporting activations. The first criterion, which was appropriate for identifying the largest activation clusters, used a whole-brain multiple comparison correction at $P < 0.05$ (false discovery rate). The second criterion, which was less stringent, initially thresholded images at $P < 0.001$ uncorrected, followed by a correction for multiple testing using the false discovery rate method ($P < 0.05$), applying a small volume correction (SVC). Based on a review on compensatory recruitment in motor disorders (Serrien *et al*., 2007), it was hypothesized that the TBI children would exhibit additional activation in higher-level sensorimotor areas reflecting increased reliance on sensory information processing, and/or in areas reflecting increased cognitive monitoring of motor performance. For this purpose, the SVC option in SPM was used. Suitable regions were selected by creating mask images based on lobar anatomy, cortical and subcortical anatomy and Brodmann areas, derived from the 'Pickatlas' SPM tool (Maldijan *et al*., 2003), i.e. parietal lobe, sensorimotor cortex, premotor cortex, cerebellum and prefrontal cortex.

Specifically, we defined volumes of interest (VOI's) for regions that support motor performance and/or sensory-guided control, such the as the sensorimotor cortex (defined as the pre- and postcentral gyrus), premotor cortex (Brodmann area 6), parietal lobe and cerebellum (according to lobar anatomy). Compensatory activation in these regions as a result of aging or stroke has been reported in previous functional imaging studies (Ward and Frackowiak, 2003; Heuninckx *et al*., 2005; Ward, 2006*a, b*). We defined also VOI's in areas that reflect augmented cognitive operations, such as the dorsolateral prefrontal cortex (corresponding to the middle frontal gyrus) and the precuneus (superior parietal lobule). Overactivity in these regions has been documented in previous motor studies on aging (Heuninckx *et al*., 2005, 2008) and Parkinson's disease (Bartenstein *et al*., 1997; Samuel *et al*., 1997). This approach partially compensated for the reduced power of the whole-brain analysis. The effects were only considered significant if they survived Bonferroni correction resulting in an alpha level of 0.01.

Table 2 Kinematic results

	TBI children				Control children			
	Isodir		Non-isodir		Isodir		Non-isodir	
	Dominant	Non-dominant	Dominant	Non-dominant	Dominant	Non-dominant	Dominant	Non-dominant
Relative phase measures								
AE Φ	31.0° (3.8°)	48.0° (6.5°)	37.1° (4.6°)	43.2° (6.6°)	30.2° (2.4°)	41.7° (4.1°)	35.4 (2.9°)	38.1° (4.2°)
Spatiotemporal measures								
Hand Amplitude (°)	42.2° (5.7°)	43.6° (6.8°)	44.6° (6.1°)	44.6° (6.8°)	27.5° (3.6°)	30.9° (4.3°)	27.9° (3.9°)	31.1° (4.3°)
Foot Amplitude (°)	26.7° (4.3°)	34.2° (4.5°)	28.0° (4.0°)	35.2° (4.3°)	25.6° (2.7°)	27.2° (2.8°)	24.9° (2.5°)	27.8° (2.7°)
Frequency (Hz)	1.01 (0.006)	1.02 (0.008)	0.99 (0.020)	0.99 (0.023)	1.00 (0.003)	1.00 (0.005)	0.98 (0.011)	1.00 (0.013)

Mean values (SDs in parentheses) of movement accuracy, amplitude and frequency for both groups, coordination modes, and body sides. AE, Absolute error.

Results

Kinematic results

The kinematic data of nine TBI and 16 control children were successfully recorded at 200 Hz during the fMRI scanning sessions. Kinematic data of one control child was not recorded due to failure of the computer. Mean values of movement accuracy, amplitude and frequency are shown for both groups, coordination modes and body sides in Table 2.

Relative phase measure

Separate Group (TBI, Control) × Coordination Mode (ISODIR, NON-ISODIR) × Body Side (Dominant, Non-dominant) ANOVAs with repeated measures on the last two factors were conducted on coordination accuracy (phase error, AEΦ). This revealed that coordination performance was reasonably matched between the TBI and Control children, [$F(1,23) = 0.55$, $P > 0.05$], allowing a meaningful interpretation of their brain activation differences. Moreover, no significant main effect of coordination mode was found [$F(1,23) = 0.18$, $P > 0.05$]. The NON-ISODIR coordination mode was performed with similar accuracy as the ISODIR mode. However, AE scores were significantly higher for the non-dominant side as compared to the dominant side, $F(1,23) = 7.25$, $P < 0.01$. The interaction between coordination pattern and body side failed to reach significance [$F(1,23) = 4.30$, $P > 0.05$]. Overall, coordination accuracy was not different between groups.

Spatiotemporal measures

Analysis of mean amplitude was assessed by a $2 \times 2 \times 2 \times 2$ (Group × Limb × Coordination Mode × Body side) ANOVA with repeated measures on the last three factors. Significant differences between groups were determined, $F(1,23) = 4.40$, $P < 0.05$. The TBI children moved with higher amplitude ($M = 37.4°$ for TBI and $M = 27.9°$ for controls). The difference between both limbs [$F(1,23) = 4.25$, $P > 0.05$; hand amplitude, 36.6°; foot amplitude, 28.7°] and body sides [$F(1,23) = 3.59$, $P > 0.05$, dominant amplitude, 30.9°, non-dominant amplitude, 34.3°] failed to reach significance. There was no significant main effect of coordination pattern, [$F(1,23) = 2.17$, $P > 0.05$)]. To assess the potential impact of the amplitude difference between groups on brain activation, amplitude was entered as a covariate in the main ANOVA in SPM5. This did not affect the results, underscoring that amplitude did not confound interpretation of potential brain activation differences.

Analysis of frequency revealed that both groups performed the coordination patterns at a movement frequency of ~1 Hz and no significant differences were found across mode, $F(1,23) = 1.74$, $P > 0.05$, group, $F(1,23) = 0.20$, $P > 0.05$ or body side, $F(1,23) = 1.17$, $P > 0.05$. Accordingly, these basic spatiotemporal measures did not constitute a potential confound in the comparison of brain activation patterns between both groups.

fMRI results

Between-group comparisons

We performed an ANOVA that included Group (TBI, control children) as a between-subjects variable and Coordination Pattern (ISODIR, NON-ISODIR) and Body side (DOMINANT, NON-DOMINANT) as repeated measures. The SPM ANOVA revealed significant differences between groups, with TBI children exhibiting higher activation than control children for the contralateral precuneus. No regions were found more active in control relative to TBI children. The subsequent SVC analysis further characterized the group effect across all task conditions for regions of a priori interest. The contralateral postcentral gyrus, contralateral inferior parietal lobule and ipsilateral posterior cerebellum (lobule VIII, Crus 1) were significantly higher activated in the TBI children and survived significance following Bonferroni correction for number of regions. The obtained regions are shown in Table 3 and the bar plots (Fig. 1) demonstrate the BOLD responses in regions that were increased in the TBI group as compared to the control group. Peaks of activation that were significant at $P < 0.001$ uncorrected but did not survive correction for multiple comparisons in the SVC analysis (including the ipsilateral precuneus and the contralateral middle cingulate cortex) are reported for descriptive/exploratory purposes only (Table 3).

Between-task comparisons

When contrasting the NON-ISODIR with ISODIR movements, the ANOVA demonstrated an increased recruitment of a widespread coordination network (Table 3 and Fig. 2). As compared with the ISODIR task, the more difficult NON-ISODIR coordination task showed significantly higher activation of the superior temporal gyrus, supramarginal gyrus, inferior parietal lobule, ipsilateral superior parietal lobule, ipsilateral middle temporal

Table 3 ***T*-values and localizations (MNI-coordinates) of activation peaks showing significant activations resulting from the 2 × 2 × 2 full factorial ANOVA**

Area activated	Side	*x*	*y*	*Z*	*t*-value	SVC p
Main effect of group: TBI children > controls						
Middle cingulate cortex	Contralateral	−10	−14	42	3.19	0.040*
Postcentral gyrus (somatosensory cortex—hand area)	Contralateral	−48	−24	46	3.90	0.002
	Contralateral	−42	−20	40	3.73	0.004
Inferior parietal lobule (somatosensory cortex)	Contralateral	−38	−42	54	3.56	0.007
Precuneus	Contralateral	−12	−54	64	4.55	
	Ipsilateral	12	−46	62	3.21	0.020*
Cerebellum (Crus 1)	Ipsilateral	26	−72	−36	3.64	0.005
Cerebellum (VIII)	Ipsilateral	30	−64	−42	3.50	0.005
	Ipsilateral	28	−58	−46	3.35	0.007
Main effect of body side: dominant > non-dominant						
Paracentral lobule	Ipsilateral	4	−34	68	5.06	
Supplementary motor area (SMA)	Ipsilateral	6	−22	68	4.92	
	Ipsilateral	6	−12	62	4.80	
Cerebellum (Crus 2)	Contralateral	−30	−72	−44	3.65	
	Contralateral	−22	−70	−40	3.27	
Main effect of coordination pattern: NON-ISODIR > ISODIR						
Supplementary motor area (SMA)	Ipsilateral	6	−12	60	5.40	
	Ipsilateral	6	−2	46	5.09	
Postcentral gyrus (somatosensory cortex)	Contralateral	−36	−42	58	3.65	
Supramarginal gyrus	Contralateral	−46	−28	32	3.43	
	Contralateral	−54	−32	30	3.38	
	Ipsilateral	56	−28	42	2.58	
Inferior parietal lobule	Contralateral	−30	−46	50	3.43	
	Ipsilateral	48	−34	50	2.41	
Superior parietal lobule	Ipsilateral	20	−54	66	5.04	
Precuneus	Contralateral	−14	−56	66	3.80	
Superior temporal gyrus	Ipsilateral	58	−26	16	4.08	
	Contralateral	−56	−30	20	3.92	
Middle temporal gyrus	Ipsilateral	46	−60	−2	3.38	
	Ipsilateral	42	−64	8	2.33	
Thalamus	Contralateral	−14	−26	10	4.18	
	Contralateral	−8	−22	0	4.04	
Pallidum	Contralateral	−20	−4	4	3.05	
Putamen	Contralateral	−32	6	−4	2.48	
Cerebellum (VIII)	Ipsilateral	20	−64	−54	5.04	
	Ipsilateral	26	−56	−44	4.06	
Cerebellum (VI)	Contralateral	−32	−54	−32	2.93	
Cerebellum (IV–V)	Contralateral	−12	−40	−22	2.41	

Two statistical criteria were used in reporting activations: The first criterion used a whole-brain multiple comparison correction at $P < 0.05$ (false discovery rate). This resulted in a significant difference between both groups for precuneus activation. A second criterion was used to identify brain structures with prior expectation of compensatory activation, by using an uncorrected *P*-value of 0.001 and subsequent SVC at $P < 0.01$ (See Methods section for further details). *indicate areas not surviving Bonferroni correction for multiple SVC's.

gyrus, ipsilateral supplementary motor area (SMA), contralateral postcentral gyrus, contralateral precuneus, contralateral thalamus, contralateral pallidum, contralateral putamen and posterior cerebellum (lobules IV–V, VI, VIII).The alternative comparison (ISODIR versus NON-ISODIR) did not reveal any significant activations.

Body side comparisons

The three-way ANOVA revealed also a significant main effect of Body side (Table 3). The tasks executed with the dominant side showed increased activation in the ipsilateral paracentral lobule, ipsilateral SMA and the contralateral posterior cerebellum (Crus 2). The opposite comparison [non-dominant (flipped) > dominant] did not reveal any significant effects. Finally, all interactions between the factors failed to reach significance, even at the threshold of $P < 0.001$ uncorrected.

Discussion

To our knowledge, this study compared for the first time the neural activations between TBI and normal children by means

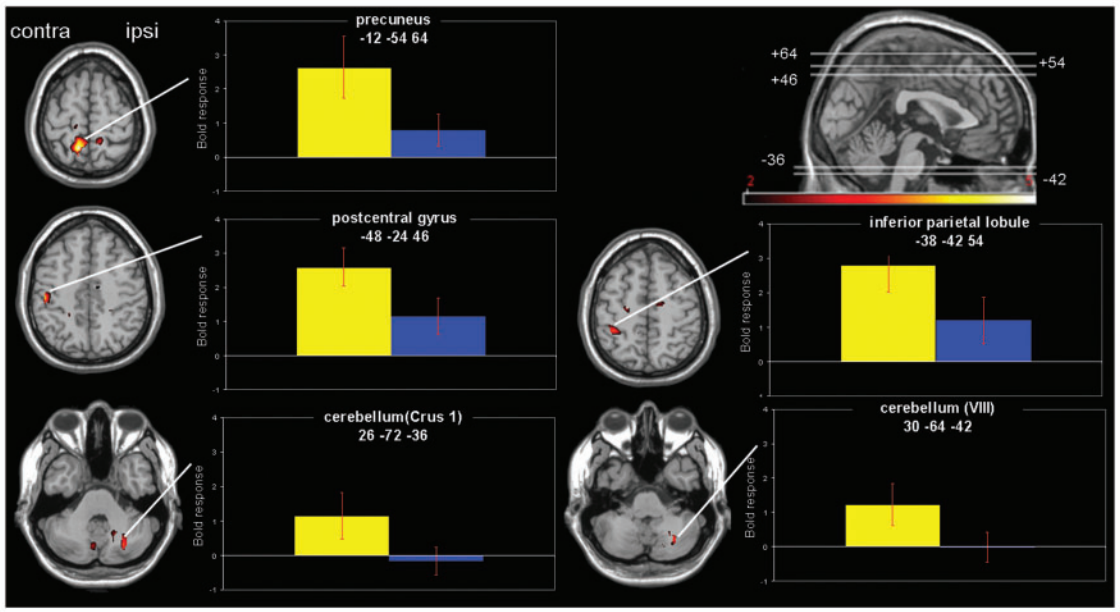

Figure 1 Brain regions showing significantly higher activation in the TBI as compared to the control group (main effect of group). Bar plots show the estimated BOLD responses in arbitrary units for both groups (blue for the control group, yellow for the TBI group). Contra = activation contralateral to the moving limbs; Ipsi = activation ipsilateral to the moving limbs.

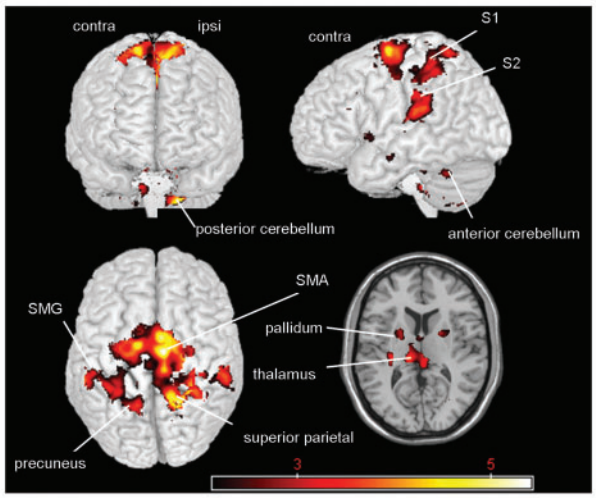

Figure 2 The brain regions overlaid on standard MNI renders, representing significantly higher activation during the NON-ISODIR as compared with the ISODIR movements (main effect of Coordination Pattern). Significant voxels are indicated in the red spectrum ($P < 0.05$, corrected for multiple comparisons), and the height threshold is $t = 2.15$. Contra = activation contralateral to the moving limbs; Ipsi = activation ipsilateral to the moving limbs; S1, primary sensory cortex; S2, secondary somatosensory cortex; SMG, supramarginal gyrus.

of fMRI during interlimb coordination tasks. The principal goal was to determine the compensatory changes in brain activation in TBI children as a result of their insult. Additionally, interactions between group, coordinative complexity and body side were also explored, as discussed next.

Brain activation differences between children with TBI and control children

Across both coordination patterns and body sides, TBI children were found to exhibit higher activation than the control children, suggesting that motor impairment in TBI children is associated with distinct alterations in functional cerebral activity. The observed group differences in brain activation cannot be attributed to mere motor output differences, because overall task parameters, such as coordination accuracy and frequency—which have previously been reported to modulate brain activation (Blinkenberg *et al*., 1996; Rao *et al*., 1996; Debaere *et al*., 2004)—were reasonably matched between the TBI and Control children.

Brain activation changes following *adult TBI* have been reported in previous functional imaging studies using simple motor tasks. For example, Prigatano *et al*. (2004) reported smaller bilateral frontal activation (SMA) in adult TBI patients as compared with controls during right index finger tapping at maximal intrinsic speed (Halstead Finger Tapping Test), even when the behavioural output of the TBI patients was grossly normal. Lotze and colleagues (2006) also showed diminished fMRI signal change in the motor cortical network (contralateral primary sensorimotor cortex, contralateral dorsal premotor cortex and SMAs) in patients with TBI performing unilateral fist clenching motions. Using complex coordination tasks, our results showed more pronounced differences in cortico-subcortical activation between TBI and control children, as described below.

Cortical activation

The use of compensatory (increased) cortical activation to bypass impairments has previously been supported by functional imaging

studies in stroke patients (Ward, 2006*a*), in elderly (Ward and Frackowiak, 2003; Heuninckx *et al*., 2005; Ward, 2006*b*) and in adults with head injuries (Ricker *et al*., 2001; Levine *et al*., 2002). In our study, areas with enhanced activation in the TBI children were predominantly located in the parietal cortex. The TBI children showed a predominantly contralateral (to the moving body side) enhancement of activation in parietal areas covering the postcentral gyrus, inferior parietal lobule and the precuneus.

The parietal lobe is divided into two major regions, the somatosensory cortex and the posterior parietal cortex. As compared with controls, TBI children showed higher activation in the postcentral gyrus and inferior parietal lobule, corresponding to the primary somatosensory area (SI). SI is involved in the integration of somatosensory information to guide motor actions (Rizzolatti *et al*., 1998) and damage to or removal of SI in man and animals has shown various (and sometimes pronounced) somatosensory incapacities (Norssell, 1980). Our findings point to an increased focus on somatosensory processing in TBI children to perform these cyclical coordination patterns. Using the Movement Assessment Battery for Children, we confirmed the lower motor performance levels in children with TBI (see also Rossi & Sullivan, 1996; Kuhtz-Bushbeck *et al*., 2003*a, b*). Apparently, recovery of motor abilities in TBI children was associated with enhanced activity in somatosensory regions. Recently, several neurorehabilitation techniques have been proposed for treating chronic motor deficits in stroke patients. Among other things, these are focussed on the somatosensory system by means of passive movement training or peripheral nerve stimulation (Kaelin-Lang, 2008).

TBI children also activated the precuneus during coordination to a significantly greater degree than controls. The precuneus is part of the posterior parietal cortex which belongs to a widespread network of higher association structures (Cavanna and Trimble, 2006), indicating its central role across a broad spectrum of highly integrative tasks. One such task is attention orientation, whereby the input is filtered and a subset of information is selected for preferential processing (Simon *et al*., 2002). Recent data have supported that the precuneus and superior parietal lobule are involved in top-down or goal-directed attention under the performer's control (Behrmann *et al*., 2004). In our study, the dorso-anterior part of the precuneus (*y* close to –60 mm) showed significant activation, consistent with previous studies (Heuninckx *et al*., 2005; Wenderoth *et al*., 2005; Rocca *et al*., 2007;). In this context, the precuneus was hypothesized to mediate increased attention to and spatial monitoring of the hand and foot trajectories during coordination. It is conceivable that the precuneus may have received input from the somatosensory cortices and/or (posterior) cerebellar regions (discussed later) to orchestrate this function.

Activation in the precuneus has also been documented in previous motor performance studies in the elderly (Zemke *et al*., 2003; Heuninckx *et al*., 2005; Wu and Hallett, 2005*a*) as well as in patients suffering from motor-related disorders (Wu and Hallett, 2005*b*). Accordingly, it appears to be a candidate area for compensatory recruitment in suboptimal central nervous systems (Serrien *et al*., 2007). Overall, the observed differential brain activations between both groups in our study suggest that TBI children exhibited increased attentional deployment to meet the complex spatiotemporal requirements of the hand–foot coordination patterns as well as enhanced somatosensory processing to integrate the afferent information from both limb segments.

Subcortical activation

To our knowledge, alterations in cerebellar activation during motor tasks have not been reported in TBI children so far. Here, the TBI group showed significantly higher activation in the posterior cerebellum. The cerebellum is specifically involved in ipsilateral coordination of different effectors (Ehrsson *et al*., 2000; Debaere *et al*., 2001, 2004; Heuninckx *et al*., 2005). Motor sequencing studies have suggested that the posterior part of the cerebellum is related to the correction of timing errors (Hikosaka *et al*., 1999; Sakai *et al*., 2000). Deficits in time monitoring and reproduction have also been observed in cerebellar patients (Ivry and Keele, 1989). In other words, the posterior cerebellum may contribute to timing adjustment processes. The observed relative increase of posterior cerebellar recruitment in TBI children, which is hypothesized to reflect enhanced error monitoring of interlimb timing, may complement their aforementioned compensatory cortical recruitment patterns for increased attentional deployment and sensory processing. Overall, the increased deployment of neural resources suggests less automatic task performance.

It is also conceivable that neurochemical abnormalities in the cerebellum of the TBI children may account for their altered activation patterns. Several recent studies using animal models of TBI have demonstrated cerebellar Purkinje neuron loss after TBI (Fukuda *et al*., 1996; Mautes *et al*., 1996; Park *et al*., 2006, 2007; Igarashi *et al*., 2007). Furthermore, reduced cerebellar grey matter volume has been shown in children with TBI (Spanos *et al*., 2007). Thus, the present study complements clinical and experimental studies on TBI and emphasizes the vulnerability of the cerebellum to TBI. The increased recruitment of the parietal cortex and the cerebellum complements other studies on patients with motor disorders, such as Parkinson's (Rascol *et al*., 1997; Samuel *et al*., 1997) and Huntington's disease (Bartenstein *et al*., 1997). However, the mechanisms underlying altered recruitment and their exact physiological role remain uncertain.

A common feature across our TBI patients was DAI, the primary neuropathology and cause of coma in TBI, with the greatest implications for long-term outcome at the chronic phase (Levin, 2003). Most TBI children showed signs of DAI in their structural MRI (T1, T2 and FLAIR) as a consequence of sudden head acceleration and deceleration, resulting in shearing and stretching of the axons and, presumably, reduced signal transmission and connectivity. DAI may have contributed to the observed alterations in the brain activation patterns of the TBI group, characterized by both (i) compensatory neural recruitment in parietal areas to increase somatosensory processing and mental effort/attention and (ii) functional changes in the cerebellum.

Scanning children with TBI introduces a number of methodological hurdles that affect interpretation of the results: TBI is a heterogeneous disease with multiple deficits that evolve over time. However, our group was relatively homogeneous in terms of injury mechanism (traffic accidents and falls) and neuropathology (DAI). Moreover, each control was carefully selected to match the patient's demographics (gender and age) and hand preference. The most obvious limitation of the present study is the rather small group size. It remains to be seen whether larger groups allowing more powerful statistical analyses, will provide further confirmation/extension of the obtained results.

Effect of coordination mode and body side

Even though previous research has shown more accurate and consistent coordination performance during the ISODIR than NON-ISODIR mode (Carson *et al*., 1995; Swinnen *et al*., 1995, 1997; Cavallari *et al*., 2001), the present study showed no significant differences between both modes at the behavioural level. However, NON-ISODIR coordination was associated with activation of a more widespread network than ISODIR coordination, involving SMA, temporal areas (superior and middle temporal gyrus), several areas in parietal cortex (postcentral gyrus, inferior parietal lobule, precuneus, supramarginal gyrus) and subcortical areas (cerebellum, thalamus, pallidum, putamen). The increased activations are consistent with the performer's perceived higher difficulty of the NON-ISODIR mode. The observed network extends previous findings (with a less powerful data set and metronome paced movement conditions) in which primarily SMA activation differed between both coordination modes (Debaere *et al*., 2001). Higher activity of the SMA was also reported in other studies on the coordination of non-homologous limbs (Ehrsson *et al*., 2002; Rocca *et al*., 2007).

The observed considerable increase of activity in several subareas of the parietal cortex during the NON-ISODIR as compared to ISODIR coordination pattern is not surprising. The parietal cortex is typically involved in the spatial aspects of movement planning (Rizzolatti *et al*., 1997). Spatial integration is a critical feature of successful NON-ISODIR performance because the limb segments need to be coordinated according to less preferred directional relationships in extrinsic space. Indeed, isodirectionality is a more salient predisposition in perception and action control than non-isodirectionality (Swinnen, 2002; Swinnen and Wenderoth, 2004). Sensory signals from wrist and foot have to be monitored and integrated continuously to preserve coordination. Additionally, performers often experience a tendency to spontaneously regress to the ISODIR mode when performing the NON-ISODIR mode, while the converse transition is much less salient. Preventing this phase shift requires increased attentional deployment and higher alertness of error monitoring mechanisms.

All together, the aforementioned processes refer to increased cognitive involvement in action control in association with enhanced sensory processing for spatiotemporal monitoring of limb segments. We hypothesize that the increased parietal as well as superior temporal (secondary somatosensory cortex, SII) activation, in connection with other cortico-subcortical nodes, accounts for these processes. SII was previously reported to be involved in monitoring whether the sensory signals from the different limb segments match the temporal requirements (Wenderoth *et al*., 2004). Elderly people have also shown SII activation during ipsilateral coordination (Heuninckx *et al*., 2005). The observed parietal (particularly precuneus) and SII activation is also consistent with related work on ipsilateral coordination (Rocca *et al*., 2007).

Interestingly, NON-ISODIR coordination was also associated with increased recruitment of the middle temporal gyrus (area hOc5, V5 complex). This was rather unexpected because no moving visual stimuli were presented during coordination. Although speculative, we assume that this may be associated with vivid mental imagery of motion of the limb segments in opposite directions to assist performance of the NON-ISODIR coordination mode. Rocca *et al*. (2007) also observed activation in this area during performance of the ipsilateral task with the wrist positioned behind versus in front of the trunk in an adolescent group.

In addition to increased cortical recruitment, NON-ISODIR coordination was also associated with activation of thalamus, basal ganglia (putamen and pallidum) and cerebellum (lobes IV–V, VI, VIII). With the present experimental conditions, it is impossible to infer the specific contribution of these areas to NON-ISODIR performance. The potential role of the cerebellum in error monitoring has been discussed in the previous section. The increased activation of the putamen and pallidum is perhaps related to optimization of motor commands and suppression of unwanted ones in the face of the recurring tendency to regress to the easier ISODIR coordination mode but further research is warranted to support this speculation. In summary, the increased recruitment of tempero–parieto–frontal areas in parallel with the principal motor subcortical areas during NON-ISODIR as compared with ISODIR coordination complies with the children's perception of a higher difficulty level and mental effort being associated with the former task. However, the main effect of coordination mode did not interact with group.

As compared with the non-dominant body side, movements of the dominant body side were associated with additional activation in the ipsilateral paracentral lobule and SMA and in the contralateral posterior cerebellum across both groups. No significant Group × Body Side interactions were obtained. The present results are inconsistent with previous work in which movement of the non-dominant limb has usually been shown to result in increased activation of brain areas ipsilateral to the moving limbs, consistent with left hemisphere dominance for motor control (Dassonville *et al*., 1998; Serrien *et al*., 2003; Johnson-Frey *et al*., 2005; Verstynen *et al*., 2005; Gut *et al*., 2007; Wu *et al*., 2008). This deviant finding is possibly due to the different age groups tested as well as the tasks used. More specifically, the majority of the previous studies examined asymmetrical activation patterns for left and right hands/fingers in adults whereas we examined hand/foot coordination.

Conclusion

The TBI children differed from controls in increased activation of cortico-subcortical areas during motor coordination. No evidence was obtained for decreased activation relative to controls. More specifically, TBI children showed higher activation in the precuneus which was hypothesized to reflect increased attentional deployment for task performance. Furthermore, additional activation was shown in somatosensory areas, pointing to integration of somatosensory information for on-line guidance and monitoring of the different effectors. The increased posterior cerebellar activation is consistent with this view. We consider the altered recruitment patterns as an expression of increased cognitive monitoring or less automatic motor performance in children with TBI. It is hypothesized that these modified recruitment patterns compensate for diffuse axonal injury and disruption of white matter connections. From a clinical perspective, these results perhaps suggest that specialist brain injury rehabilitation services should offer extended rehabilitation programmes to promote compensatory neural recruitment in TBI children.

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