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CASE STUDY

Functional MRI of working memory in paediatric head injury

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Abstract
A case study examining the recovery of a 9 year old boy who sustained a severe head injury is reported. The subject sustained damage to the left parietal-occipital and right frontal-parietal regions. Structural and functional imaging and cognitive data were collected at the time of injury and 1 year post-injury. Cognitive assessment revealed improvement over time. Functional imaging at the time of injury revealed minimal activation in the right posterior temporal region. Imaging 1 year post-injury revealed increased activation in the right pre-frontal cortex, bilateral pre-motor cortex and bilateral posterior parietal cortex. This activation pattern is consistent with the performance of unaffected individuals on working memory tasks. These findings differ from those in the adult literature and suggest an alternative pattern of recovery of function in children.

Keywords: *fMRI, paediatric head injury, working memory*

Objectives

Traumatic brain injury (TBI) in children and adolescents is a significant public health concern and accounts for a major proportion of morbidity and mortality in the paediatric population. Advances in neuroimaging, along with neuropsychological testing, have opened the door for a better understanding of the recovery process from TBI. Functional magnetic resonance imaging (fMRI) has been studied to a limited degree in adults with TBI, but no studies have utilized this technology in the paediatric TBI population [1–3].

The current paper utilizes fMRI to explore activation patterns of working memory (WM) in a case of paediatric TBI within the context of a longitudinal assessment. While studies in the adult population have identified patterns of WM following TBI, it is premature to assume that similar results will be observed in the paediatric population due to the complex processes underlying human neurodevelopment and plasticity [4].

Case report

A 9-year-old boy presented to the Emergency Department after sustaining multiple injuries in a pedestrian vs. motor vehicle accident. He was struck by a vehicle travelling 15–20 miles per hour while crossing the street. He sustained a transient loss of consciousness and presented with a Glascow Coma Scale (GCS) of 8 (eye 1, motor 5, verbal 1) and a left frontal skull deformity. He was intubated and followed in the Paediatric Intensive Care Unit. An intra-cranial pressure bolt was placed. No changes in oedema or pressure were noted throughout the 13-day course of hospitalization. He was sedated by phenobarbitol-induced coma through hospital day 7 when he was tapered off this medication. Computerized tomography at admission and 5 days post-injury revealed a left parietal-occipital subdural haematoma and right frontal-parietal contusion. At discharge, he was transferred to a Rehabilitation Unit for 16 days.

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Methods

Subject

The subject is a left handed male who was 8 years, 4 months at the first assessment, *Time* 1, and 9 years, 7 months at the second assessment, *Time* 2. He had no previous history of difficulties with cognitive functioning, attention or school performance. His cognitive, developmental and medical history prior to the accident was unremarkable.

Procedures

Consent was obtained from the parents and assent from the child at the beginning of the study, consistent with the approved human subjects protocol. The subject was assessed at *Time* 1, 30 days post-accident, and again at *Time* 2, 1 year and 3 months later.

Scans were conducted using a 3T GE Signa magnet. The pulse sequence consists of a high resolution T1 weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence with the following parameters: TR 35 ms, TE 6 ms, 45° flip angle, 1.5 mm thick, 0 mm gap, 1 NEX, a 24 cm field of view and a 256×192 matrix size (scan time: 14 minutes). A repeat fast spin echo/double echo sequence was acquired for more precise lesion localization and for comparison to the acute phase clinical scan. A T2* sensitive gradient echo spiral sequence was used for functional imaging [5]. The following parameters were used for fMRI acquisition: 28 axial slices (4 mm thick, 0.5 mm skip) parallel to the anterior and posterior commissure covering the whole brain (TR = 2000 ms, TE = 30 ms, flip angle = 80° and 1 interleave). The field of view was 20 mm and the effective in-plane spatial resolution was 3.125 mm.

Assessment measures

The psychological evaluation consisted of the following measures: Wechsler Intelligence Scales for Children, Third Edition (WISC-III), Woodcock-Johnson Test of Achievement, Revised (WJ-R) at *Time* 1 and the Third Edition (WJ-III) at *Time* 2 and the Child Behavioural Checklist [6–9].

fMRI tasks

Visuospatial WM tasks were employed during functional imaging. The 1-back and 2-back tasks consisted of rest, experimental (E) and control (C) epochs in the following order: Rest-E-C-E-C-E-C-Rest-E-C-E-C-E-C-Rest. Each rest epoch was 30-seconds long, during which the subject passively viewed a blank screen. Experimental epochs began with a 4-second display of the instructions 'Push for 1-Back' or 'Push for 2-Back'. Control epochs began with a 4-second display of the instructions 'Push for Centre'. Each control and experimental epoch consisted of 16 stimuli presented for 500 ms each, with a 1500 ms inter-stimulus interval. The stimulus was the letter 'O' presented in one of nine distinct visuospatial locations in a 3×3 matrix. The subject was instructed to respond if the stimulus was in the same location as in the previous trial for the 1-back task or two previous trials back for the 2-back task. In the control task, the subject was instructed to respond if the stimulus was in the centre position.

Image pre-processing

Images were reconstructed, by inverse Fourier transform, for each of the 261 time points into $64 \times 64 \times 18$ image matrices (voxel size: $3.75 \times 3.75 \times 7$ mm). Functional MRI data were pre-processed using Statistical Parametric Mapping 99 (SPM; Wellcome Department of Cognitive Neurology, London, UK). Images were corrected for movement using least square minimization without higher-order corrections for spin history and normalized to stereotaxic Talairach co-ordinates. Images were then re-sampled every 2 mm using sinc interpolation and smoothed with a 4 mm Gaussian kernel to decrease spatial noise.

Statistical analysis

Statistical analysis was performed using the general linear model and the theory of Gaussian random fields as implemented in SPM99. Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. Low frequency noise was removed with a high pass filter (0.5 cycles per minute) applied to the fMRI time series at each voxel. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 seconds) was applied to the fMRI time series to reduce spatial noise. The effects of interest for each dataset were defined with the relevant contrasts of the parameter estimates. For each of these contrasts, a corresponding contrast image was also generated. Finally, in order to determine the presence of significant clusters of activation, the joint expected probability distribution of height and extent of Z-scores, with height ($Z = 2.33$; $p < 0.01$) and extent ($p < 0.05$) thresholds, with corrections for multiple comparisons at the cluster-level.

Results

Cognitive functioning

Results of cognitive assessments are presented in Table I. Difficulties in behavioural functioning were identified at *Time* 1 and persisted at *Time* 2. Deficits in intellectual functioning which were present at *Time* 1 for non-verbal tasks (Performance IQ) resolved at *Time* 2. Academic functioning, while consistent at *Time* 1, was more variable at *Time* 2 indicating some decrease in expected achievement.

Imaging findings

As seen in Figure 1, anatomic scan at *Time* 1 confirmed lesions in the left parietal-occipital region. Atrophy in this region as well as in the right parietal region was evident at *Time* 2. Activation maps corresponding to the simple (1-back) WM task at *Time* 1 revealed overall diffuse activation of the frontal and occipital cortex and the superior temporal region. *Time* 2 activation showed less diffuse activation concentrated in several regions including frontal and parietal cortices. In particular, activation

Table I. Behavioural, psychological and academic functioning at 1-month and 1-year post-injury.

	1 Month post-injury			1 Year post-injury		
	T-score	S.S.	Range	*T*-score	S.S.	Range
CBCL scores ($M = 50$, SD = 10)						
Activities	44			45		
Social	52			41		
School	43			48		
Total competence	46			42		
Withdrawn	58			58		
Somatic complaints	77*			72*		
Anxious/depressed	58			59		
Social problems	50			51		
Thought problems	57			64		
Attention problems	60			59		
Delinquent behaviour	67**			57		
Aggressive behaviour	51			67**		
Internalizing	69*			67*		
Externalizing	55			65**		
Total problems	63**			64*		
Intellectual functioning ($M = 100$, SD = 15)						
Composite						
VIQ		104	Average		108	Average
PIQ		72	Borderline		90	Average
FSIQ		87	Low Average		99	Average
VC		106	Average		103	Average
PO		79	Borderline		91	Average
FD		93	Average		115	Above average
PS		67	Impaired		96	Average
Sub-tests						
Information		10			10	
Similarities		12			11	
Arithmetic		9			16	
Vocabulary		10			12	
Comprehension		12			9	
Digit Span		8			9	
Picture comp.		10			9	
Coding		2			8	
Picture arr.		5			9	
Block design		8			9	
Object ass.		2			7	
Symbol search		6			10	
Academic functioning ($M = 100$, SD = 15)						
Sub-test						
Letter-word identification		103	Average		97	Average
Calculations		104	Average		111	Above average
Passage comprehension		103	Average		87	Low average
Applied problems		108	Average		98	Average
Writing sample		99	Average		101	Average

*clinical range; **borderline range.

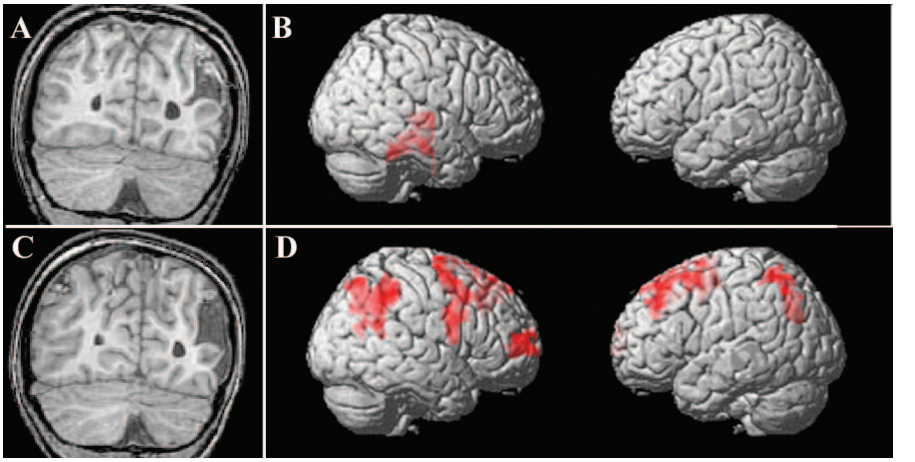

Figure 1. Structural images and 2-back WM activation patterns at 1-month and 1-year post-injury. (*a*) Structural image at *Time* 1 of left parietal-occipital lesion. (*b*) Activation at *Time* 1 of frontal, occipital and superior temporal regions. (*c*) Structural image at *Time* 2 of left parietal-occipital and right parietal lesions. (*d*) Activation at *Time* 2 of pre-frontal, temporal, anterior and posterior occipital regions and pre-motor cortex.

was evident in the pre-frontal region, pre-motor cortex, temporal region, anterior parietal and posterior occipital areas.

Functional imaging of the more challenging (2-back) WM task at *Time* 1 revealed minimal activation confined to the right posterior temporal region (Figure 1(*b*)). However, at *Time* 2, increased activation was present (Figure 1(*d*)). The right pre-frontal cortex, bilateral pre-motor cortex and bilateral posterior parietal cortex showed increased activation indicating a pattern consistent with that of unaffected individuals [10].

The changing pattern of activation from *Time* 1 to *Time* 2 correlates with changes in functional behavioural performance. For the 1-back WM task, the subject evidenced a considerable increase in percentage of correct responses (78–92%) and a substantial decrease in percentage of false alarms responses (16–6%) from *Time* 1 to *Time* 2. Behavioural results were similar for the 2-back WM task in which his percentage of correct responses increased (64–79%) and his percentage of false alarm responses decreased (25–8%).

Conclusions

The subject's overall cognitive performance was consistent with or better than the expected recovery pattern as cited in the paediatric TBI literature providing a solid framework for the evaluation of functional imaging data [11, 12].

Activation patterns at the time of the injury reveal a pattern similar to that described by McAllister et al. [3] and Christdoulou et al. [1] in which activation decreased significantly from the simple to the more challenging WM task with limited activation noted in the right posterior temporal region for the complex task. At 1-year post-injury, activation patterns for the 2-back WM task more closely resembled that of typical individuals. This would seem to support a reorganization of WM function similar to baseline which is unlikely to be due to typical development over the course of the recovery year or lack of insult to the pre-frontal cortex [12–14].

The subject's improved performance differs from reports of persistent deficits identified in adult patients [1–3]. These findings raise questions regarding the differences in recovery of WM function between the developed and developing brain. While it is premature to conclude that neuroplasticity is more robust in the paediatric population in the context of WM, these findings suggest a different trajectory of recovery of function in children. The report presented here is only one case, but provides an initial road-map to exploring the benefits of fMRI in the paediatric TBI population. Further study evaluating longitudinal changes in paediatric TBI using fMRI has the potential to further strengthen one's understanding of the recovery process and provide a means to predict, follow and optimize recovery.

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