Research report

Long-term declarative memory deficits in diffuse TBI: Correlations with cortical thickness, white matter integrity and hippocampal volume

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\textbf{A B S T R A C T}

We investigated structural brain damage in subjects who had suffered severe and diffuse traumatic brain injury (TBI), and examined its relationship with declarative memory impairment. Cortical thickness, diffusion tensor imaging (DTI), and volumetric and shape data of the hippocampus were assessed in a group of 26 adults with severe TBI in the chronic stage and 22 healthy matched controls. Declarative memory was evaluated by Rey’s Auditory Verbal Learning Test (RAVLT). TBI patients performed significantly worse than controls on all RAVLT measures. The group comparison for cortical thickness and DTI revealed a pattern of widespread atrophy in TBI patients. In the TBI group DTI measures correlated with cortical thickness in the prefrontal and parietal regions, including the precuneus. Declarative memory correlated with both cortical thickness and DTI measures. However, although hippocampal volume was significantly decreased in TBI patients, no correlations were found. Multiple regression analysis of all the structural measures revealed that decreases in Fractional anisotropy (FA) and thinning of the left parietal region were the best predictors of memory impairment. In conclusion, cortical thickness reductions in the left hemisphere and a lack of white matter integrity are the main contributors to long-term impairment in declarative memory among patients suffering from severe and diffuse TBI. In this study the hippocampus did not make a significant contribution to memory dysfunctions, suggesting that damage to this structure is compensated for by other regions, with the definitive sequelae being mainly explained by alterations in cortico-subcortical connectivity.

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1. **Introduction**

Traumatic axonal injury (TAI) is considered a progressive event that involves widespread damage to axons throughout the white matter, and it is strongly associated with worse outcomes in severe cases (Adams et al., 2011). Axons first undergo primary injury caused by intense shear and strain forces resulting from rapid acceleration, deceleration, and rotation mechanisms. This is followed by secondary injury, including cytoskeletal disorganization and protein accumulation, leading to delayed axonal disconnection (Povlishock and Katz, 2005). However, not only white matter is affected after TAI. Magnetic resonance imaging (MRI) studies have also shown decreased grey matter volumes (Ding et al., 2008), while a neuropathological study conducted by Maxwell et al. (2010) demonstrated that after TAI there was a greater loss of pyramidal neurons in several cortical regions, producing changes in cortical thickness.

Cortical thickness is the distance from the outer cortical surface to the inner cortical white matter/grey matter boundary, and it can provide an indirect measure of the changes undergone by cortical architecture after cellular events (Fischl and Dale, 2000). In MRI studies of traumatic brain injury (TBI), grey matter atrophy has mainly been investigated by means of voxel-based morphometry (VBM). However, grey matter atrophy measured by VBM includes the local cortical surface and cortical folding, and depends on the overall brain size (Hutton et al., 2009). A better alternative for measuring grey matter atrophy is to use the Freesurfer® software (http://surfer.nmr.mgh.harvard.edu), which provides a more accurate estimate of cortical thickness. Cortical thinning has been reported in paediatric samples after TBI. Merkley et al. (2008) described a diffuse pattern of cortical atrophy involving cortical regions in all lobes, while the pattern found by McCauley et al. (2010) showed frontal predominance. These studies do not exclude focal lesions, thus the effects of TAI cannot be isolated from those of regional grey matter loss due to contusions. Furthermore, studies based on children are influenced by neurodevelopmental brain changes that cannot be extrapolated to the TBI adult population (Shaw et al., 2008).

White matter integrity can be assessed using diffusion tensor imaging (DTI). Fractional anisotropy (FA) is a DTI measure of the degree of directionality of water diffusion and reflects white matter integrity (Mori and Zhang, 2006). In subacute and chronic TBI, FA is decreased (Kraus et al., 2007) and is related with functional outcome (Sidaras et al., 2008; Newcombe et al., 2011). Using a region-of-interest approach, Kraus et al. (2007) found that declarative memory correlated with FA reductions in several fasciculi, while a previous study by our group obtained a significant correlation for the corpus callosum and fornix (Palacios et al., 2011). With a more precise technique of analysis [Tract-Based Spatial Statistics (TBSS)], Kinnunen et al. (2011) identified the fornix as the region most strongly related with memory deficits. A longitudinal study by Wang et al. (2011) found that damage in networks involving several fasciculi in the acute stage could predict memory and learning deficits in the chronic stage. It has also been reported that inter-hemispheric functional connectivity correlates with delayed recall (DR) (Marquez de la Plata et al., 2011).

The aim of the present study was to assess structural brain damage in subjects with diffuse and chronic severe TBI, and to examine its relationship with declarative memory impairment. To this end we used a multimodal approach including measures of cortical thickness, DTI and volumetric and shape data for the hippocampus. To date, no studies have focused on the assessment of declarative memory when taking into account these three measures of structural damage after TAI as the main mechanism of injury in a group of patients without significant focal lesions. We hypothesized that (1) patients will show cortical thickness atrophy, altered white matter integrity and hippocampal reductions compared to controls; (2) cortical thinning will depend in part on white matter alterations; and (3) memory impairment will be explained by damage to the hippocampus and cortical grey matter regions, as well as to their structural connections.

2. **Methods**

2.1. **Subjects**

We applied the following inclusion criteria to a database \( n = 170 \) of chronic stage TBI patients from the Head Injury Unit of the Institut de Neurorehabilitació Güttnan: severe closed-head injury and severe TBI defined as Glasgow Coma Scale (GCS) score \( \leq 8 \); adults aged \( \geq 40 \) years; chronic stage of recovery \( \geq 2 \) years since the TBI; possible diffuse pathology reported in the MRI scans in the sub-acute stage without macroscopic lesions. The exclusion criteria were as follows: injury requiring craniectomy or craniotomy; previous history of TBI, drug intake, and neurological or psychiatric disorders. This left us with 48 candidates, who were scanned. Since we were interested in studying the consequences of TAI after TBI, the neuroradiologist (NB) described the chronic brain lesions seen in the MRI. Patients with large lesions were excluded, together with those whose images presented motion artifacts. The final sample included 26 patients with a mean of age of 27.40 ± 5.15 (see Table 1). They were investigated at a mean time of evolution of 4.20 ± 1.14 years and with a mean degree of severity measured by the GCS of 5.19 ± 1.70. All the patients showed alterations such as microbleeds as a sign diffuse pathology in the T2* and flair sequences. Supplementary Table 1 shows clinical and neuroradiological characteristics for each patient. The etiology of TBI was traffic accident in all cases.

The control group comprised 22 healthy volunteers matched by age, sex, handedness, and education (Table 1). None had a previous history of neurological or psychiatric diseases.

The study was approved by the research ethics committees of the Güttnan Institute for Neurorehabilitation and the University of Barcelona. All participants gave written informed consent.

2.2. **Neuropsychological assessment**

Declarative memory was assessed using a version of the Rey Auditory Verbal Learning Test (RAVLT). In this word
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