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ORIGINAL ARTICLE

Deafferentation in thalamic and pontine areas in severe traumatic brain injury

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Pons

Summary
Purpose: Severe traumatic brain injury (TBI) is characterized mainly by diffuse axonal injuries (DAI). The cortico-subcortical disconnections induced by such fiber disruption play a central role in consciousness recovery. We hypothesized that these cortico-subcortical deafferentations inferred from diffusion MRI data could differentiate between TBI patients with favorable or unfavorable (death, vegetative state, or minimally conscious state) outcome one year after injury.
Methods: Cortico-subcortical fiber density maps were derived by using probabilistic tractography from diffusion tensor imaging data acquired in 24 severe TBI patients and 9 healthy controls. These maps were compared between patients and controls as well as between patients with favorable (FO) and unfavorable (UFO) 1-year outcome to identify the thalamo-cortical and ponto-thalamo-cortical pathways involved in the maintenance of consciousness.
Results: Thalamo-cortical and ponto-thalamo-cortical fiber density was significantly lower in TBI patients than in healthy controls. Comparing FO and UFO TBI patients showed

Abbreviations: DAI, diffuse axonal injuries; DRS, Disability Rating Scale; DTI, Diffusion Tensor Imaging; FO, favorable outcome; GCS, Glasgow Coma Scale; GLM, General Linear Model; GOS, Glasgow Outcome Scale; GOSE, Extended GOS; MRS, Modified Rankin Score; TBI, traumatic brain injury; UFO, unfavorable outcome.

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thalamo-cortical deafferentation associated with unfavorable outcome for projections from ventral posterior and intermediate thalamic nuclei to the associative frontal, sensorimotor and associative temporal cortices. Specific ponto-thalamic deafferentation in projections from the upper dorsal pons (including the reticular formation) was also associated with unfavorable outcome.
Conclusion: Fiber density of cortico-subcortical pathways as measured from diffusion MRI tractography is a relevant candidate biomarker for early prediction of one-year favorable outcome in severe TBI.

Introduction

Severe traumatic brain injury (TBI) is the most common cause of death and disability in young people [1]. It is characterized by the presence of diffuse axonal injuries (DAI) mainly located within deep and axial white matter bundles [2]. These lesions are usually not easily detectable with CT or MRI but may be evidenced from diffusion tensor imaging (DTI) [3], which is a unique technique for probing the white mater fibrous structure [4,5] even in the pathological brain [6]. Studies using DTI [3,7] showed that lesions in specific brain areas were associated with severe disorders of consciousness and that diffusion metrics such as fractional anisotropy (FA) were predictive of the duration of the coma [8]. More importantly, these metrics evaluated at the subacute stage were associated with long-term recovery of consciousness [9—11]. However, these works did not address the question of the alterations of specific white matter tracts in brain networks related to the maintenance of consciousness.

Indeed, long-lasting loss of consciousness characterizing severe TBI has been shown to be associated with the breakdown of integration in large-scale brain networks [12]. Considerable effort has been put forth to show the pivotal role of the thalamus in information exchanges between such networks [13] and particularly in maintenance of consciousness [14—17]. In addition to these thalamo-cortical projections, ascending projections from the pons to the thalamus and the cerebral cortex are involved in arousal, which is of paramount importance in consciousness regulation [18,19]. Thus, quantifying the alterations in thalamo-cortical, ponto-cortical and ponto-thalamic circuits could be of great importance for the patient's consciousness recovery.

In the present paper, we propose to study the alterations of cortico-subcortical (thalamic and pontine) pathways in severe TBI leading to deafferentation of subcortical regions by combining gray matter segmentation from T_1-weighted imaging and fiber tracking from DTI acquisitions that showed its ability to assess alterations in fiber integrity in traumatic lesions [20]. Particular attention was given to the quality control of gray matter segmentation, for which we combined automatic segmentation and visual inspection. We hypothezised that:

- the fiber density of thalamo-cortical, ponto-cortical and ponto-thalamic pathways would be reduced in TBI patients compared with controls;
- TBI patients who did not recover consciousness one year after injury (UFO) would present reduced fiber density in thalamo-frontal white matter tracts compared with TBI patients who recovered consciousness (FO). To test these hypotheses, voxel-wise fiber density was estimated for each individual by using probabilistic tractography and compared between subjects through nonparametric permutation statistical tests.

Patients and methods

Patients

The study was approved by the local scientific ethic committee and all participants (or a close family member for comatose patients) gave their informed consent.

Twenty-seven severe TBI patients were recruited in the Surgical Neuro-Intensive Care Unit of the Pitié-Salpêtrière Hospital, Paris, France. Three patients were excluded due to data analysis failure, so twenty-four patients were finally included (four females, mean age 34.58 years, standard deviation 14.08 years). Patients were included if they met the following criteria:

- adult patient between 18 and 75 years of age;
- inability to follow simple commands, determined at least 7 days and not more than 30 days after TBI, which could not be explained by sedation.

Exclusion criteria were:

- moribund patients (expected survival less than 24 hours);
- physiological instability (e.g., due to hemodynamic instability, increased intracranial pressure, and/or rapidly deteriorating respiratory function) that would preclude MRI scanning;
- contraindication to MRI;
- penetrating head injury;
- a central nervous system condition such as stroke, brain tumour, or a neurodegenerative disease preceding TBI. MRI acquisitions were performed in these 24 patients and also in 9 healthy controls (mean age 32.50 years, standard deviation 8.53 years). No significant age difference was found between controls and FO patients (Wilcoxon rank test, $P = 0.55$), between controls and UFO patients (Wilcoxon rank test, $P = 0.94$) and between UFO and FO patients (Wilcoxon rank test, $P = 0.78$).