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Neuroanatomical basis of paroxysmal sympathetic hyperactivity: A diffusion tensor imaging analysis

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Abstract

Primary objective—Paroxysmal sympathetic hyperactivity (PSH) is observed in a sub-set of patients with moderate-to-severe traumatic brain injury (TBI). The neuroanatomical basis of PSH is poorly understood. It is hypothesized that PSH is linked to changes in connectivity within the central autonomic network.

Research design—Retrospective analysis in a sub-set of patients from a multi-centre, prospective cohort study

Methods and procedures—Adult patients who were <3 weeks after severe TBI were enrolled and screened for PSH using a standard definition. Patients underwent multimodal MRI, which included quantitative diffusion tensor imaging.

Main outcomes and results—Principal component analysis (PCA) was used to resolve the set of tracts into components. Ability to predict PSH was evaluated via area under the receiver operating characteristic (AUROC) and tree-based classification analyses. Among 102 enrolled patients, 16 met criteria for PSH. The first principle component was significantly associated ($p =$

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Declaration of interest

The authors report no conflicts of interest.

0.024, AUROC = 0.867) with PSH status even after controlling for age and admission GCS. In a classification tree analysis, age, GCS and decreased FA in the splenium of the corpus callosum and in the right posterior limb of the internal capsule discriminated PSH vs no PSH with an AUROC of 0.933.

Conclusions—Disconnection involving the posterior corpus callosum and of the posterior limb of the internal capsule may play a role in the pathogenesis or expression of PSH.

Keywords

Diffusion tensor imaging; paroxysmal sympathetic hyperactivity; traumatic brain injury

Introduction

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome observed in a sub-set of patients following severe neurological insults such as trauma, anoxia or stroke. PSH is characterized by periodic, unprovoked episodes of tachypnea, tachycardia, diaphoresis and hypertension typically associated with posturing or dystonic movements [1]. The abrupt onset of these signs can represent a significant therapeutic challenge [2] and the syndrome is associated with variable clinical outcomes [3–6]; however, its mechanisms and neuroanatomical basis remain poorly understood. Previous work utilizing CT and MRI suggested a relationship between PSH and parenchymal injury [7] or damage in subcortical white matter [8], yet a more detailed neuroanatomical characterization is lacking.

The generation of primary autonomic responses within the central nervous system has been localized to discrete sites in the spinal cord, brainstem and hypothalamus. Stimulation, lesion and tracer studies in animals reveal that autonomic outputs are modulated by activity in specific cortical structures including the amygdala, hippocampus, insular cortex, cingulate cortex, dorsolateral prefrontal cortex and middle temporal cortices [9–11]. These observations are corroborated by lesion analysis and functional neuroimaging studies in humans [12–20]. It is postulated that these diverse structures are connected within a ‘central autonomic network’ which integrates visceral perception and efferent autonomic responses with emotion and behaviour [21–23]. Additional research suggests that autonomic responses might be hemispherically lateralized, particularly within the insular cortex, with differentiated cardio-circulatory responses and clinical outcomes observed depending on whether the right or left insula is involved [12, 24–26].

Disruption involving components of the central autonomic network could account for many of the observed clinical findings in PSH. In previous studies of patients with severe traumatic brain injury (TBI), it was found that PSH is prevalent [6] and that damage to selected white matter tracts is prognostically significant [27]. Here, the relationship between traumatic white matter injury and PSH was explored. It was hypothesized that PSH would be associated with damage to tracts connecting the right insular cortex to other components of the autonomic network. A better understanding of the structural underpinnings of PSH could lead to new preventive or therapeutic interventions and improved clinical outcome.

Methods

Subject selection

This study was conducted in a sub-set of patients from the NeuroImaging for Coma Emergence and Recovery (NICER) study, a multi-centre, prospective cohort of adult patients with TBI who underwent clinical assessment, multimodal magnetic resonance imaging and long-term outcome assessment [27–29]. Patients were included in the study if they were identified as comatose (Glasgow Coma Scale [GCS] <8 in the absence of any sedative drug) 7–30 days following TBI and were mechanically ventilated. The time window (7–30 days) was chosen to select acutely injured, persistently comatose patients with TBI that were clinically stable for the imaging protocol. All patients were screened for PSH, which was defined using the modified Blackman criteria [30] as episodic, self-limiting occurrences with at least three of the following features: (1) temperature >38.5 °C, (2) heart rate >130 beats min⁻¹, (3) tachypnea >20 respirations min⁻¹, (4) agitation and (5) rigidity or decerebrate posturing, with clinical signs not better explained by an underlying condition such as sepsis or alcohol withdrawal. Subjects with PSH must have had at least one episode per day for a minimum of 3 days. Patients not demonstrating PSH according to this definition were considered as comparison subjects. The study was conducted with approval from institutional review boards at each participating institution and consent was obtained from patient surrogates.

Magnetic resonance imaging acquisition and analysis

All study patients were screened to ensure that there was no contraindication to MRI scanning. MRI was cancelled or postponed if the patients had an intracranial pressure >20mmHg when lying flat in the supine position, haemodynamic instability defined as the need for vasopressor and/or inotropic support or hypoxemia requiring a FiO₂ >60% and a PEEP >10 cm H₂O. Throughout transport to and from the scanner, patients were continuously monitored with electrocardiogram, oxygen saturation, end-tidal CO₂ and noninvasive arterial pressure. Patients received sedation and neuromuscular blockade during the scanning procedure.

MRI acquisition was performed on a 1.5 T clinical MRI scanner and is detailed elsewhere [27]. In brief, subjects underwent multimodal MRI, which included quantitative diffusion tensor imaging (fractional anisotropy [FA]) acquired in 20 pre-selected white matter tracts. White matter tracts included the middle cerebellar peduncle (MCP); anterior brainstem (ANTBS); posterior brain stem (POSTBS); right and left cerebral peduncle (CP); genu, body and splenium of the corpus callosum (GCC; BCC; SCC); right and left anterior and posterior limb of the internal capsule (ALIC; PLIC); right and left sagittal striatum (SS); right and left superior longitudinal fasciculus (SLF); right and left external capsule (EC); and right and left corona radiata (CR) (Tables I and II). Data are reported as median [Interquartile Range] unless otherwise indicated, with 'R' signifying right side and 'L' signifying left side. All region-specific FA values were normalized to controls at each centre.

Outcomes

Outcomes were evaluated at hospital discharge and 6 and 12 months after injury. Discharge outcome was measured with the Glasgow outcome score (GOS). Six- and 12-month outcomes were assessed using three measures: Extended Glasgow outcome scale (GOSE), modified Rankin score (mRS) and disability rating scale (DRS). The principal endpoint was the dichotomized GOSE at 12 months, with a GOSE 5–8 designating a favourable outcome and a GOSE 1–4 an unfavourable outcome.

Statistical analysis

Descriptive statistics (median and intra-quartile range for continuous variables; frequencies and percentages for categorical variables) were used to describe clinical data by group assignment. Group comparisons for categorical variables were performed using Fisher's exact tests and ordinal comparisons were made with the Wilcoxon-Mann-Whitney test, using Stata software (StataCorp, College Station, TX). Significance was set at $p < 0.05$. Logistic regression was used to separately explore the association between PSH and FA readings in each of the 20 separate white matter tracts, both individually and after controlling for age and initial GCS (i.e. 20 distinct models, each with three predictors). The resulting p -values were used to estimate the number of genuinely true 'null' hypotheses and the overall significance level of 0.05 was adjusted accordingly to control for multiple tests having been performed. Receiver operating characteristic curves were generated and areas under the curve (AUROC) were computed to express the ability of the model to predict PSH. In many cases, logistic regression models using several tracts together were unstable due to correlation among FA readings, making it difficult to produce a unique parsimonious model. Principal component analysis (PCA) was, therefore, used to resolve the set of tracts into a smaller number of (uncorrelated) components derived as a weighted combination of the 20 different FA readings. A tree-based model was also developed to identify a sub-set of FA tracts and their unique cut-points that best predict PSH status.

Results

Patient population

Characteristics of the study population are in Table III. A total of 102 patients were enrolled, among whom 16 met criteria for PSH. Patients who had PSH were significantly younger and had a lower admission GCS. On admission, more patients in the PSH group had unreactive pupils and absent corneal reflexes than the control group. The Marshall scores calculated from the admission head CTs were similar between groups; as was midline shift. The delay from injury to brain MRI was longer in the PSH group, although this difference was not statistically significant. At the time of MRI, the PSH group had significantly worse motor GCS scores than the controls; more patients in the PSH group had unreactive pupils and lacked evidence of visual pursuit, but this difference did not reach statistical significance.

Outcomes

Clinical outcomes are shown in Table III. No significant differences in hospital outcomes were noted between groups. Disability Rating Scales at 6 and 12 months and modified Rankin Scale at 12 months were significantly higher (worse) in the PSH group.

Diffusion tensor imaging analysis

Unadjusted FA values were significantly lower in the PSH group in 14 of the 20 analysed regions of interest. Logistic regression models, both with and without adjustment for age and GCS, revealed several tracts in which reduced FA values were associated with PSH (Table I). Plots of the p -values suggested 12 of the 20 tracts had a genuinely non-significant effect (i.e. 12.3 ‘true null hypotheses’ for unadjusted effects and 12.7 for the adjusted effects). Only one tract (splenium of the corpus callosum) was significantly associated with PSH in the unadjusted model, but the association was not significant if adjusted for age and GCS. Thus, none of the regions were individually significant when adjusted for age and GCS (Table I).

Principal component analysis produced three components that together accounted for 71.7% of the overall variance in FA readings (Table II). The components were rotated (varimax rotation with Kaiser Normalization) to equalize variance across the components and improve interpretability by preventing any given tract from loading on multiple components simultaneously. Table II presents the coefficients (weights) associated with each tract for each of the three principal components; tracts with coefficients less than 0.25 in absolute value are suppressed from viewing as they represent a negligible contribution to the overall component score (relative to those tracts having greater weight). The first principal component, which is comprised of the weighted average of seven regions of interest, represents midline tracts (brainstem, cerebral peduncles, splenium of the corpus callosum) in addition to the posterior limb of the right internal capsule (PLIC_R). The second principal component, a weighted average of six regions of interest, corresponds to right-sided sub-cortical white matter tracts including the internal capsule. The third component, a weighted average of five regions of interest, corresponds to left-sided sub-cortical white matter tracts including the internal capsule. When used in a logistic regression model to predict PSH, the first principal component remained associated ($p = 0.024$) with PSH status even after controlling for age and GCS (Table IV).

Tree-based analysis

FA readings from all 20 tracts together with age and GCS were supplied as (potential) predictors of PSH status in a classification tree (Figure 1). The misclassification rate, as shown by non-PSH/PSH underneath is shown at each termination point. For example, only one subject older than 33.5 years old had PSH, demonstrated as ‘46/1’ under the Age >33.5 termination point. It was found that age, GCS and reduced FA in *SCC* and *PLIC_R* were sufficient to produce a tree with six terminal branches having a misclassification rate of only 7.8% and final AUROC of 0.933 (Table IV). The tree reveals that that the ‘best’ decisions are made based on specific cut-points of FA values and the interaction among those variables. FA in two structures added accuracy to the model in addition to previously cited

parameters of age and initial GCS, specifically injury to the splenium corpus callosum (SCC) and the posterior limb of the internal capsule on the right (PLIC_R).

Discussion

The results, obtained in a prospective multi-centre cohort of patients with severe TBI, suggest an association between PSH, clinical severity and multifocal white matter damage. After adjustment in multivariable and principal component analysis, PSH was linked to lesions in the right-sided posterior limb of the internal capsule and in the splenium or the corpus callosum. It was chosen to employ principal component analysis, as the white matter tracts themselves are highly correlated with one another, producing instability in traditional modelling techniques. This data reduction technique provides insight into the tracts that are more strongly associated with PSH via recursive partitioning. In prior work, it was found that damage to the corpus callosum was a marker of injury severity and prognosis [27]. However, the association between PSH and injury to the posterior limb of the internal capsule on the right may provide evidence of a disconnection between right-sided cortical and subcortical components of the central autonomic network. This work is preliminary and must be verified with additional data-sets.

The findings of multi-focal lesions in patients with PSH extend previous observations. Fernandez-Ortega et al. [7] reported that patients with PSH were more likely to have focal, parenchymal lesions on CT when compared to patients without PSH. In a study of 101 patients who underwent brain MRI less than 30 days following injury, Lv et al. [8] found univariate association between PSH and injury in the periventricular white matter, corpus callosum, basal ganglia and brainstem. However, this study did not include a multivariate model nor did it indicate whether lesions were right- or left-sided and, hence, was unable to evaluate the possibility of lesion lateralization in the development PSH.

It seems plausible that PSH and other hyperadrenergic syndromes arise from disruption within central autonomic systems rather than from focal damage involving a single structure. The excitatory:inhibitory ratio model (EIR), developed by Baguley [31], proposes that the loss of descending inhibition results in exaggerated spinal reactivity, such that sympathetic efflux can be triggered by non-nociceptive peripheral stimuli. Modulation of this circuit likely occurs at several levels including the hypothalamus, which has dense bidirectional connections to cortical structures such as the insula. Direct evidence of insular disconnection was not available since this analysis was centred on anatomical changes in white matter, which have been found previously to be a fundamental feature in severe TBI [27]. More injury was observed to the brain stem in this cohort (Table III), but it is not believed that injury to the brainstem alone produces PSH. In prior investigations, lesions in the brainstem on MRI were not universally present in PSH patients (56%) [8]. Overall, the findings build on the EIR model and indicate that traumatic disconnection of the right insular cortex could play a role in the development PSH after a severe, acute neurologic injury. This observation should be tested prospectively.

The outcomes observed in this cohort are consistent with other studies describing an association between PSH and unfavourable post-TBI functional status [3, 6, 7]. The outcome

scale in which differences between groups were greatest was the DRS. The DRS is a multi-dimensional instrument, which incorporates level of consciousness, assessments of cognition and level of functioning and, hence, may be more sensitive to subtle impairments than the GOS. It is possible that the higher DRS seen in patients with PSH is a reflection of greater cognitive impairment itself driven by more severe white matter injury noted in that group.

This study has several innovations. Quantitative DTI was implemented to evaluate the neuroanatomical basis of PSH in a population of patients with severe TBI. Additionally, PCA was employed to reduce the computational burden of exploring multiple anatomical tracts separately, albeit imposing a much stricter level of statistical significance; the use of PCA had the added benefit of revealing functionally meaningful groupings among the white matter tracts. The use of tree-based classification analysis helps to resolve interactions between predictive variables and to define the optimal place at which to split a collection of FA values; this interaction is not something that can be known in advance and is not easily incorporated into standard logistic regression models without increasing their complexity.

Some limitations should be noted. These results were based on the secondary analysis of a data-set optimized for examining prognosis after TBI and were not optimized for examining the central autonomic network in detail. These associations must be validated in a prospective fashion. Additionally, the analysis was limited to an evaluation of white matter structures; future studies will need to also analyse specific contributions of specific cortical (e.g. insula and its subcomponents) and subcortical (e.g. hypothalamic nuclei) grey matter and link grey and white matter changes. PSH is uncommon (16% of this cohort), resulting in a small sample size. Due to the small sample size, conventional logistic regression was not possible due to instability of the model; this fact motivated the choice to pursue principal components to analyse anatomical associations with PSH. The predictions made by this model will need to be validated with a separate data-set that was not used in the generation of the model.

Conclusion

In patients with PSH, injury to white matter tracts is diffuse and severe, but disruption within the central autonomic network likely plays a role in its pathogenesis or expression. One such disrupted pathway may be the fibres of the right insula via damage to the posterior limb of the ipsilateral internal capsule. Insights gained from this analysis could inform models of central autonomic integration and, it is hoped, suggest strategies for prevention or treatment in patients at risk for PSH.

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Figure 1.

Final decision tree predicting PSH status. Each branch terminates with a decision regarding PSH status and the actual number of subjects at that terminal branch without and with PSH (shown as the ratio of patients with and without PSH).

Table I

Significance of the association between PSH and decreased fractional anisotropy in 20 white matter tracts. Significance of individual FA tracts, with and without adjustment for age and initial GCS, sorted according to unadjusted *p*-value. Area under the receiver operating characteristic curve (AUROC) summarizes predictive ability of model, with values >0.70 regarded as discriminative.

Tract	Unadjusted model		Adjusted model	
	<i>p</i> -value	AUROC	<i>p</i> -value	AUROC*
SCC	0.004	0.71	0.056	0.86
EC_L	0.01	0.713	0.035	0.871
PLIC_L	0.012	0.74	0.021	0.869
SLF_L	0.012	0.692	0.036	0.87
POSTBS	0.016	0.69	0.072	0.856
PLIC_R	0.018	0.696	0.02	0.856
BCC	0.019	0.657	0.255	0.843
ANTBS	0.031	0.67	0.1	0.855
CP_R	0.039	0.692	0.073	0.857
CR_R	0.039	0.653	0.102	0.855
CP_L	0.042	0.679	0.222	0.844
CR_L	0.046	0.656	0.192	0.849
SS_L	0.093	0.64	0.038	0.872
EC_R	0.107	0.669	0.041	0.869
GCC	0.144	0.619	0.086	0.863
SLF_R	0.167	0.608	0.16	0.851
MCP	0.276	0.603	0.208	0.847
ALIC_L	0.326	0.582	0.625	0.839
ALIC_R	0.372	0.609	0.245	0.847
SS_R	0.382	0.581	0.107	0.854

MCP, middle cerebellar peduncle; ANTBS, anterior brainstem; POSTBS, posterior brain stem; CP, cerebral peduncle; GCC, genu of the corpus callosum; BCC, body of the corpus callosum; SCC, splenium of the corpus callosum; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; SS, sagittal striatum; SLF, superior longitudinal fasciculus; EC, external capsule; CR, corona radiata.

Table II

Coefficients (weights) associated with fractional anisotropy values in each tract for each of the three principal components. PCA results giving loadings (coefficients) used to produce a weighted average of FA imaging results. These three principal components (PC) capture 71.7% of the overall variance observed in the 20 distinct tracts. Loadings less than 0.25 in absolute value are not shown.

Tract	PC1	PC2	PC3
CP_R	0.43		
ANTBS	0.41		
POSTBS	0.374		
MCP	0.366		
PLIC_R	0.345		
SCC	0.283		
CP_L	0.255		
EC_R		0.45	
ALIC_R		0.428	
SS_R		0.426	
SLF_R		0.35	
GCC		0.343	
CR_R		0.298	
ALIC_L			0.529
EC_L			0.448
CR_L			0.414
SLF_L			0.338
PLIC_L			0.258
SS_L			
BCC			
% Variance	0.284	0.227	0.206
Cumulative % variance	0.284	0.511	0.717

MCP, middle cerebellar peduncle; ANTBS, anterior brainstem; POSTBS, posterior brain stem; CP, cerebral peduncle; GCC, genu of the corpus callosum; BCC, body of the corpus callosum; SCC, splenium of the corpus callosum; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; SS, sagittal striatum; SLF, superior longitudinal fasciculus; EC, external capsule; CR, corona radiata.

Table III

Patient population and outcomes. Clinical, physiologic and head CT variables in patients with and without PSH. The table also relates clinical neurologic features recorded on the day of brain MRI scanning. Clinical outcomes recorded during hospitalization and over 1 year of follow-up.

	With PSH (<i>n</i> = 16)	Without PSH (<i>n</i> = 86)	<i>p</i> -value
Age (mean ± SD)	26 ± 7	38 ± 16	<0.01
Male gender (% patients)	69%	86%	0.09
GCS on admission (mean ± SD)	4 ± 2	7 ± 4	<0.01
Unreactive pupils on admission (% patients)	50%	20%	0.01
Absent corneal response on admission (% patients)	58%	10%	<0.01
Admission anemia ^a (% patients)	13%	12%	1
Admission hypoxia ^b (% patients)	19%	7%	0.15
Admission hypotension ^c (% patients)	0%	7%	0.59
Marshall CT score ^d (mean ± SD)	3 ± 1	2 ± 1	0.25
CT midline shift (mm)	0.56 ± 1.2	0.83 ± 1.3	0.35
CT basal cistern compression (% patients)	63%	39%	0.08
Number of days TBI to MRI (mean ± SD)	24 ± 9.3	20 ± 9.5	0.08
Unreactive pupils at time of MRI (% patients)	25%	9%	0.1
Visual pursuit at time of MRI (% patients)	6%	30%	0.06
Hospital outcomes			
Days in ICU (mean ± SD)	55 ± 42	40 ± 19	0.45
Death in ICU (% patients)	13%	13%	1
GOS at ICU discharge (mean ± SD)	3 ± 1	3 ± 1	0.14
GOS 1–3 at discharge (% patients)	86%	68%	0.22
Post-discharge outcomes			
6 month GOSE (mean ± SD)	4 ± 2	5 ± 2	0.08
6 month mRS (mean ± SD)	4 ± 2	5 ± 2	0.08
6 month DRS (mean ± SD)	16 ± 9	9 ± 8	<0.01
GOSE 1–5 at 6 months (% patients)	64%	56%	0.58
12 month GOSE (mean ± SD)	4 ± 2	5 ± 2	0.09
12 month mRS (mean ± SD)	4 ± 2	3 ± 2	0.03
12 month DRS (mean ± SD)	12 ± 8	7 ± 7	0.01
GOSE 1–5 at 12 months (% patients)	69%	45%	0.13

^a Serum haemoglobin <10 g dL⁻¹;

^b SaO₂ <95%;

^c SBP <90 mmHg;

^d Marshall et al. [32].

Table IV

Prediction of PSH with principal components and with tree-based classification model. The first principal component (PC1) includes CP_R, ANTBS, POSTBS, MCP, PLIC_R, SCC and CP_L. The second principal component (PC2) includes EC_R, ALIC_R, SS_R, SLF_R, GCC and CR_R. The third principal component (PC3) includes ALIC_L, EC_L, CR_L, SLF_L, PLIC_L, SS_L and BCC.

Tract	Unadjusted model		Adjusted model	
	<i>p</i> -value	AUROC	<i>p</i> -value	AUROC*
PC1	0.011	0.722	0.024	0.867
PC2	0.089	0.646	0.049	0.859
PC3	0.017	0.691	0.079	0.86
Six-node tree				0.933

MCP, middle cerebellar peduncle; ANTBS, anterior brainstem; POSTBS, posterior brain stem; CP, cerebral peduncle; GCC, genu of the corpus callosum; BCC, body of the corpus callosum; SCC, splenium of the corpus callosum; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; SS, sagittal striatum; SLF, superior longitudinal fasciculus; EC, external capsule; CR, corona radiata.