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Anterior Hippocampal Grey Matter Predicts Mental Health Outcome in Functional Neurological Disorders: An Exploratory Pilot Study

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Introduction

Advancements in the management of FND emphasize a “rule-in” diagnosis and roles for cognitive behavioral therapy (CBT)[1] and physical therapy (PT)[2]. Neuroimaging studies have also started delineating the neuropathophysiology of FND[3]. In the same cohort as this present study, we previously identified that impaired mental health and trait anxiety correlated with individual differences in amygdalar volume in patients with FND, while diminished physical functioning was associated with reduced anterior insular volume[4]. In FND, the magnitude of adverse life event burden also correlated with decreased insular and hippocampal volumes[5].

This pilot voxel-based morphometry (VBM) study used a within-group design to investigate the relationship between baseline volumetric profiles and prospectively collected 6-month outcome data in 22 patients with FND. Stratified comparative analyses with 27 controls were performed to contextualize statistically significant within-group findings. Based on the outcome literature[6] and previously described corticolimbic associations with health status and adverse life events[4 5], we hypothesized that baseline amygdalar-hippocampal and cingulo-insular volumes would predict outcome in FND.

Methods

Methods were adapted from Perez et al, 2017[4].

Participants

Twenty-two subjects with FND (19 women, 3 men; age=41.7±11.0; illness duration=3.9±4.6 years) were recruited from the Massachusetts General Hospital (MGH) FND Clinic with baseline (MRI + psychometric data) and follow-up (psychometric only) data collected at 6.4±1.1 months; 4 of 26 initial patients were lost to follow-up. 27 healthy controls (22 women, 5 men; age=40.5±10.8) were also recruited through local advertisements.

Patients met criteria for clinically-established functional movement disorders (n=12), documented (n=8) or clinically-established (n=1) psychogenic nonepileptic seizures and/or exhibited signs of functional weakness (n=9). Eight had mixed symptoms. Inclusion/exclusion criteria were as previously described[4]. Psychiatric comorbidities were assessed through the Structured Clinical Interview for DSM-IV-TR. 19 patients were on psychotropic medications at baseline(Supplemental Table 1).

Prior to enrollment, patients were diagnosed with FND. The term “Functional Neurological Disorder” was communicated, as well as the pertinent motor-subtype. FND was presented as common, real and treatable. Patients were introduced to the www.neurosymptoms.org website and given printed educational materials. Treatments were individualized, emphasizing CBT and PT. Fifteen individuals were in psychotherapy at baseline and 8 were newly referred (including one who remained in supportive psychotherapy while also starting CBT). In CBT, patients were encouraged to explore the relationships between functional symptoms, thoughts, behaviors, emotions and psychosocial factors[1]. Nine were in PT at baseline, and 7 were newly referred. Physical therapists were recommended to use the

Nielsen et al guidelines[2]. Six were started on selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors. Patients did not exclusively receive care at MGH which limited compliance information. Subjects signed informed consent, and the Partners Human Research Committee approved this study.

Patients completed the Short Form Health Survey-36 (SF-36) at baseline and follow-up. A mental health composite score (the average of four mental health related subscores) and a physical health composite score (the average of four physical health related subscores) were calculated per subject so that higher post-treatment vs. baseline scores reflected greater improvement. Baseline Spielberger Trait Anxiety Inventory (STAI-T), Beck Depression Inventory-II, Childhood Trauma Questionnaire and the Life Events Checklist-5 (LEC) “happened to me” scores were also available(See Supplemental Tables 2–3).

MRI acquisition

MRI acquisition and statistical parametric mapping preprocessing using VBM8 were performed as previously described[4].

VBM analyses

Within-group regression analyses adjusting for age and gender were performed in FND subjects to examine relationships between mental or physical health outcome and baseline volumes. For small volume corrections (SVC), bilateral regions-of-interest included the insula, anterior cingulate cortex (ACC), amygdala and hippocampus based on the WFU Pickatlas. A family-wise-error rate of $p < 0.05$ was used for SVCs at the peak-voxel level.

To contextualize statistically significant within-group findings, age and gender adjusted secondary analyses using the general linear model compared FND patients in the top (or bottom) 50 percentile of those who improved in their mental health ($N=11$) to 27 controls.

Results

Psychometrics

Significant associations were observed between mental health outcomes and baseline trait anxiety ($p=0.046$, spearman coefficient=0.43) and lifetime adverse event burden ($p=0.024$, spearman coefficient=-0.48). There were no other significant associations across psychometrics(Supplemental Fig. 1).

VBM

Across patients, mental health improvement positively correlated with baseline left anterior hippocampal grey matter volumes($p_{\text{svc}}=0.027$)(Fig. 1, Supplemental Table 4). The anterior hippocampus label is based on a y-axis between -10 and -21[7]. In separate post-hoc analyses, associations between mental health and hippocampal volume did not remain significant controlling for baseline STAI-T or LEC “happened to me” scores.

Compared to controls, FND patients with the least mental health improvement showed decreased baseline right anterior hippocampal grey matter volume($p_{\text{svc}}=0.011$) and a trend

towards reduced left anterior hippocampal grey matter volume ($p_{\text{uncorrected}} < 0.001$) (Supplemental Table 5).

Discussion

In this pilot, a relationship was observed between relative increases in baseline anterior hippocampal grey matter and 6-month mental health outcome in FND. In secondary between-group analyses, patients with FND with the least mental health improvement showed reduced anterior hippocampal volume compared to controls. These findings suggest that hippocampal volume, predictive of outcome in mood disorders[6], may represent a biomarker of prognosis across several psychopathologies. While the hippocampus has been linked to learning and memory, the anterior hippocampus also plays important roles in anxiety-related processes[7]. The anterior hippocampus is structurally connected to limbic and subcortical structures mediating hypothalamic-pituitary-adrenal axis function; resting-state connectivity profiles in healthy subjects also show that the anterior hippocampus is functionally coupled to the amygdala, ACC, and premotor areas[7]. We speculate that modulation of amygdalar function is a mechanism through which hippocampal volume predicts mental health outcomes[3].

Adjusting for baseline trait anxiety or lifetime adverse event burden, the relationship between hippocampal volume and outcome did not remain significant. This suggests that more research with larger sample sizes is needed to investigate interactions between baseline neuropsychiatric factors, regional brain volumes and outcome. Limitations include a modest sample size, patient heterogeneity, medication use, reliance on self-report measures, and that management was not restricted to one institution. A possible type I error cannot be excluded in this pilot study. While more research is needed, we provide preliminary evidence that anterior hippocampal volume may predict mental health outcomes in FND.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1. Baseline Anterior Hippocampal Grey Matter Volume Predicts Mental Health Outcome in Functional Neurological Disorders

(A) In within-group voxel-based morphometry analyses, improvements in mental health outcome positively correlated with individual-differences in left anterior hippocampal grey matter volumes (z -score=3.76; $p_{\text{sfc}}=0.027$). (B) In secondary between-group analyses, patients with functional neurological disorders (FND) reporting the least improvement in their mental health at 6-month follow-up ($N=11$) exhibited decreased baseline right anterior hippocampal grey matter volume compared to 27 healthy controls (z -score=-3.97; $p_{\text{sfc}}=0.011$). As also displayed, subthreshold group-effects were appreciated in the left anterior hippocampus ($p_{\text{uncorrected}} < 0.001$). Images are thresholded at an uncorrected p -value of 0.005. To display in the scatter plots a measure of grey matter volumes for visualization purposes only, the MarsBar toolbox (<http://marsbar.sourceforge.net/>) was used to extract mean grey matter volumes for each subject at a 5mm sphere centered at the peak voxel of statistically significant findings. R indicates right; L, left; SF-36, Short Form Health Survey-36.