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Brief Communication

Cortical thickness in default mode network hubs correlates with clinical features of dissociative seizures

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ABSTRACT

Background: Dissociative seizures (DS) are a common subtype of functional neurological disorder (FND) with an incompletely understood pathophysiology. Here, gray matter variations and their relationship to clinical features were investigated.
Methods: Forty-eight patients with DS without neurological comorbidities and 43 matched clinical control patients with syncope with structural brain MRIs were identified retrospectively. FreeSurfer-based cortical thickness and FSL FIRST-based subcortical volumes were used for quantitative analyses, and all findings were age and sex adjusted, and corrected for multiple comparisons.
Results: Groups were not statistically different in cortical thickness or subcortical volumes. For patients with DS, illness duration was inversely correlated with cortical thickness of left-sided anterior and posterior cortical midline structures (perigenual/dorsal anterior cingulate cortex, superior parietal cortex, precuneus), and clusters at the left temporoparietal junction (supramarginal gyrus, postcentral gyrus, superior temporal gyrus), left postcentral gyrus, and right pericalcarine cortex. Dissociative seizure duration was inversely correlated with cortical thickness in the left perigenual anterior cingulate cortex, superior/middle frontal gyri, precentral gyrus and lateral occipital cortex, along with the right isthmus-cingulate and posterior-cingulate, middle temporal gyrus, and precuneus. Seizure frequency did not show any significant correlations.
Conclusions: In patients with DS, illness duration inversely correlated with cortical thickness of left-sided default mode network cortical hubs, while seizure duration correlated with left frontopolar and right posteromedial areas, among others. Etiological factors contributing to neuroanatomical variations in areas related to self-referential processing in patients with DS require more research inquiry.

1. Introduction

Dissociative seizures (DS), also known as functional or psychogenic nonepileptic seizures, are paroxysmal episodes of altered awareness and motor control that can superficially resemble epilepsy or syncope, and are frequently misdiagnosed as such [1]. A common form of functional neurological disorder (FND), DS are considered a neuropsychiatric condition that comprises complex autonomic and behavioral responses to perceived threat or dysregulated affect [2]. Impairments in cognitive control are thought to be a key determinant in disinhibiting such seizure-like prepotent behavioral patterns [2,3], and structural white matter analyses have revealed associated variations in fronto-limbic tracts related to inhibition in emotional contexts [4]. A network perspective of pathophysiology suggests that DS are driven by functional and structural alterations across several brain networks including the default mode, salience, central executive, and sensorimotor networks. To identify such alterations as disease biomarkers in this

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population, a recently published research agenda for neuroimaging in FND highlighted the investigation of individual differences regarding clinical features as an important approach and introduced the need for patient controls [5].

The characterization of cortical and subcortical gray matter using morphometric analysis of magnetic resonance imaging (MRI) offers valuable tools to investigate brain properties that might underlie DS. To date, five studies have investigated cortical thickness exclusively in patients with DS [6–10]. Results have been somewhat inconclusive and sample sizes have been limited by single-center prospective recruitment. Furthermore, healthy controls commonly recruited within these series lack background morbidity and chronic stress burden of a paroxysmal disease, which potentially reduces inferences about the specificity of findings. In addition, most studies did not analyze subcortical volumes, but used surface-based measures only. To address these gaps in the literature, we gathered routine imaging data from retrospectively identified patients with DS, using neurologically healthy patients evaluated for syncope as clinical controls, as this diagnosis suggests paroxysmal symptoms without underlying brain pathology. We used volumetric analyses to characterize cortical thickness and subcortical gray matter volume between groups and their relationship to illness duration, seizure frequency, and seizure duration in patients with DS.

2. Methods

2.1. Participants

Patients with DS who received a T1-weighted MRI from the Ruhr Epileptology (a tertiary epilepsy center at the University Hospital Bochum, Germany) between 2010 and 2020 were retrospectively identified. Exclusion criteria included suspected or established comorbid epilepsy and any radiologically reported brain pathology. Information on illness duration, typical seizure duration, seizure frequency, as well as psychiatric comorbidities and medication was extracted from case files. As the typical seizure duration and frequency were primarily documented as estimated ranges, we grouped them into five categories of typical seizure duration ($\leq$1 min; 1–5 min; 5–10 min; 10–30 min; >30 min) and six categories of seizure frequency (several per day; several per week; several per month; several per year; less than one per year; first seizure). Supplementary Fig. S1 depicts the search strategy. The final DS sample consisted of 48 patients (35 females, mean age 34.9, SD 12.9 years, range 18–65; 30 with ictal video-EEG documented diagnosis, 18 based on expert clinical consensus including nine patients fulfilling criteria for probable and nine for possible following published criteria [11]). As a control group, patients diagnosed with syncope who received a T1-weighted MRI were identified from the same database. Functional neurological disorder symptoms or indication of any medical/neurological condition known to be associated with brain pathology led to exclusion of control participants. The control group consisted of 43 syncope patients (30 females, mean age 37.4, SD 13.1 years, range 19–65). The study was approved by the local ethics committee (Reg.-Nr. 20-6897-BR) and conforms with the Declaration of Helsinki.

2.2. MRI data parameters and processing

T1-weighted MRI scans were acquired on two scanners: a 3T Siemens Prisma (85% of patients with DS, 79% of control patients) and a 1.5T Siemens Avanto (15% of patients with DS, 21% of control patients). Given that differences in pulse sequence parameters were inevitable due to the retrospective nature of the study, we used the ComBat technique to harmonize cortical thickness maps prior to statistical analyses to minimize effects of scanner type and sequence parameters [12]. Quality of MRIs were checked visually as well as using MRIQC [13].

For cortical analyses, the FreeSurfer 6.0 recon-all pipeline was used. Results were visually inspected for quality and accuracy, and manually corrected if needed. Prior to statistical analyses, smoothening with a 10-mm full-width at half-maximum Gaussian Kernel was applied to cortical thickness maps. Volumetric analysis of subcortical structures (left and right accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus) was performed using FSL's FIRST. Additional information regarding neuroimaging methods is detailed in the Supplementary Material.

2.3. Statistical analyses

Between-group differences in cortical thickness were analyzed using a two-class GLM. For patients with DS, within-group relationships of clinical features and cortical thickness were analyzed using single-class GLM analyses. All analyses were two-tailed, controlled for age and sex, and corrected for multiple comparison using a Monte Carlo simulation with a cluster-wise forming threshold of $p < .05$.

For subcortical volumes, similar analyses were conducted in SPSS. MANCOVAs and follow-up *t*-tests tested for group differences. Within-group associations between subcortical volume and clinical features were established using partial correlation. All analyses were corrected for age, sex, scanner type, and total intracranial volume (to account for unspecific effects of head size). Bonferroni–Holm was used to correct for multiple comparisons.

3. Results

3.1. Demographic and clinical information

No significant between-group differences were found regarding age and sex (see Supplementary Fig. S2). Mean illness duration of patients with DS was 6.3 years (median 2.5 years, interquartile range 9.5, SD 8.2, range 1 day – 38 years). Information on typical seizure duration was available in 32 patients with DS. Of those, 21% were $\leq$1 min, 40% 1–5 min, 9% 5–10 min, 9% 10–30 min, and >30 min in 21%. Psychiatric diagnoses were noted for 20 patients with DS and are detailed in the Supplementary Results. Documentation of psychiatric comorbidities and medication was not of sufficient quality to be included as a covariate of non-interest in the neuroimaging analyses.

3.2. Between-group analyses

No significant between-group differences in cortical thickness or subcortical volumes were observed.

3.3. Within-group correlations with clinical features

In patients with DS, illness duration negatively correlated with cortical thickness of clusters primarily involving left superior parietal cortex, precuneus, postcentral gyrus, right pericalcarine cortex, and perigenual/dorsal anterior cingulate cortex (all $p < .000001$, all effect sizes between $r = -0.76$ and $r = -0.82$; Fig. 1; Supplementary Fig. S3 for inflated cortex view, Supplementary Table S1 for cluster details). An additional analysis of log-transformed illness duration was performed to account for the non-normal distribution. All clusters except for the left perigenual/dorsal anterior cingulate cortex cluster remained significant (Supplementary Fig. S5).

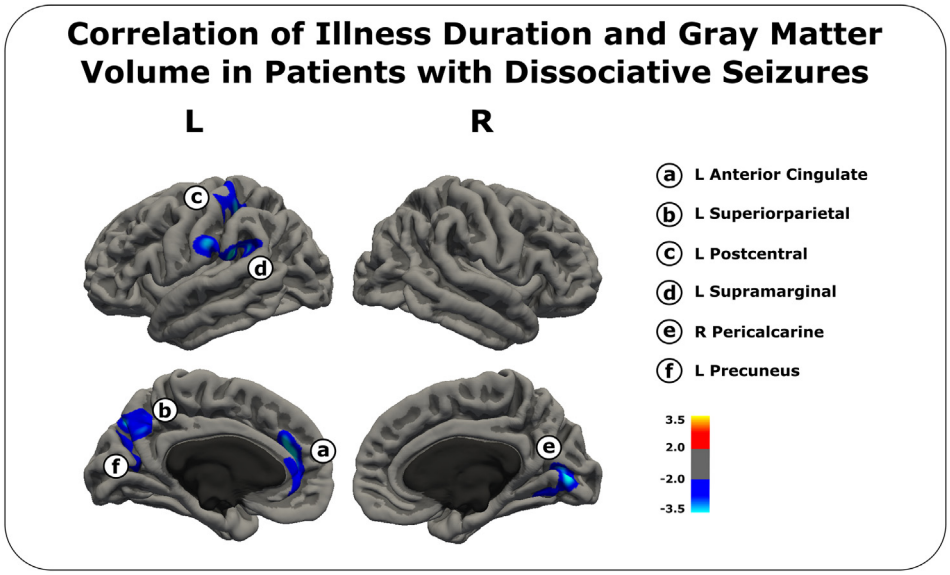

Fig. 1. Correlation between illness duration and cortical thickness in patients with dissociative seizures ($n = 48$). All analyses are corrected for age and sex. Only brain regions containing the largest area of overlap with the clusters along with their correlation coefficients are presented in this figure while an overview of all relevant brain regions can be found in Supplementary Table S1. The color-coding represents z-values.

Typical seizure duration negatively correlated with cortical thickness of clusters containing left rostral anterior cingulate, middle and superior frontal gyrus, precentral gyrus and lateral occipital cortex; and right isthmus-cingulate and posterior-cingulate, middle temporal gyrus, and precuneus (all p between 0.000078 and <0.000001, all effect sizes between $r = -0.54$ and $r = -0.66$; Fig. 2; Supplementary Fig. S4 for inflated cortex view, Supplementary Table S2 for cluster details). An additional analysis of log-transformed typical seizure duration was performed to account for irregular categorization into five brackets of seizure duration. All clusters remained significant, and additional frontal, and caudal anterior and posterior cingulate gyrus clusters were significant (Supplementary Fig. S6).

Seizure frequency and cortical thickness did not show any significant associations. For subcortical structures, no significant correlations with clinical features were found.

4. Discussion

Using surface-based morphometry and subcortical volumetric analysis in 48 patients with DS and 43 control patients with syncope, no between-group differences in cortical thickness or subcortical gray matter volume were evident. This is in contrast with previous results from studies comparing patients with DS to healthy controls [6–10] but consistent with the notion that DS is a mechanistically and neurobiologically heterogeneous condition [5,14].

Longer illness duration was related to reduced cortical thickness of left-sided anterior and posterior cortical midline structures (perigenual/dorsal anterior cingulate cortex, superior parietal cortex, precuneus) and a cluster at the left temporoparietal junction (supramarginal gyrus, postcentral gyrus, superior temporal gyrus). These are functional nodes of the default mode network, which is involved in self-referential processing and previously implicated in FND pathophysiology [5]. A particularly noteworthy observation is the finding that prolonged illness duration correlated with reduced perigenual anterior cingulate cortex cortical thickness, potentially a structural marker of impaired top–down frontal regulation of medial temporal structures [15]. This cluster was not significant in the log-transformed analysis of illness duration. Additionally, epileptic activity in posteromedial default mode network regions have recently been found to be associated with feelings of self-dissociation [16,17], introducing a potential pathomechanistic hypothesis for dissociative symptoms in DS.

Correlations with seizure duration were more widely distributed and of lower strength (see Supplementary Results), providing a less conclusive picture. Patients with longer typical seizures showed reduced cortical thickness in frontopolar prefrontal areas among others. In line with recent modeling of hierarchical frontal lobe function, this result might be related to patients' impaired inhibitory control of stereotyped responses or behavioral patterns towards affective cues [2]. The current finding further partially overlaps with the previously reported association of symptom severity and alterations in medial orbitofrontal cortex [10]. The finding of precentral cortical thickness alterations adds to comparable results reported across DS and FND in general [14].

Limitations of this study include the merging of retrospective data sets from two scanners over a 10-year period, which induces potentially noisy data and inconsistencies in clinical documentation. Therefore, adjusting the analyses for potentially confounding factors of other psychiatric diagnoses, TBI, and effects of childhood maltreatment (which is common in patients with DS [19]) was not possible. Furthermore, the effects of long-term intake of antiepileptic medication on the observed neurobiological findings cannot be determined conclusively. Although our clinical control population had no neurological comorbidity or gross brain pathology on MRI, subtle abnormalities related to cardiovascular conditions associated with syncope cannot be ruled out. Also, it is conceivable that patients with misdiagnosed dissociative syncope-like attacks were among the control group [18]. In a third of patients with DS, the diagnosis was based on expert clinical consensus (without confirmatory ictal video-EEG), which carries a small risk of misdiagnosis [11]. Finally, as in previous retrospective studies (e.g., [20]), varying availability of MRI potentially induces a sampling bias for patients with more severe or more epilepsy-like symptoms. Prospective, longitudinal, multicenter neuroimaging studies including healthy and psychiatric control groups could overcome these limitations [5].

In conclusion, the distribution of cortical thickness variations related to illness duration of DS suggests a role for potential neu-

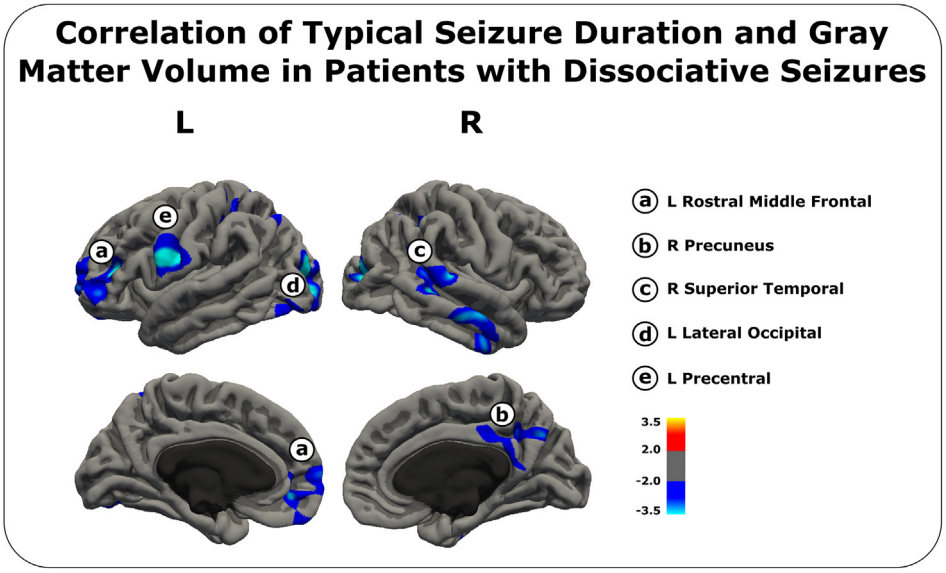

Fig. 2. Correlation between seizure duration and cortical thickness in patients with dissociative seizures (n = 32). All analyses are corrected for age and sex. Only brain regions containing the largest area of overlap with the clusters along with their correlation coefficients are presented in this figure while an overview of all relevant brain regions can be found in Supplementary Table S2. The color-coding represents z-values.

rodevelopmental and neuroplastic changes within the default mode network that require more research inquiry. In light of the incongruence with previous imaging studies, mega-analyses of pooled imaging data will likely assist in further elucidating DS pathophysiology.

Data availability

Anonymized data and analysis scripts will be shared with qualified researchers, contingent on approval by the local ethics committee.

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Conflicts of interest statement

SP receives royalties from Springer for a book on functional neurological disorders. The other authors declare no relevant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108605.

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