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Microstructural integrity of affective neurocircuitry in patients with dissociative seizures is associated with emotional task performance, illness severity and trauma history

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ABSTRACT

Purpose: To identify variations in white matter tract integrity related to behavioural control in response to emotional stimuli in patients with dissociative seizures (DS) and healthy controls (HC), and examine associations with illness characteristics and psychological trauma history.
Methods: Twenty DS patients and 20 HC completed an emotional go/no-go task and questionnaires, and then underwent diffusion tensor imaging (DTI).
Results: Patients had higher false alarm rates in response to negative emotional stimuli than HC. Task performance was correlated with self-reported difficulties in emotional awareness and regulation in everyday life. White matter analysis using tract-based spatial statistics revealed no between-group differences. In patients, fractional anisotropy (FA) in the right uncinate fasciculus, right and left fornix/stria terminalis, and corpus callosum were correlated with task performance. Similar results were found for radial diffusivity (RD), but not mean (MD) or axial diffusivity (AD). In HC, task performance was associated with AD and RD of fewer and smaller clusters in the corpus callosum and right fornix/stria terminalis, and none for FA or MD. Probabilistic tractography of thus identified tracts revealed that mean FA values were correlated with illness parameters (right fornix/stria terminalis with age at onset; posterior corpus callosum with seizure frequency), and psychological trauma history (traumatic experiences during adolescence with anterior corpus callosum).
Conclusions: Patients with DS show impaired behavioural control in response to emotional stimuli. Microstructural variations in task-related neurocircuitry show associations with illness parameters and psychological trauma history. Future studies using psychiatric controls should examine the specificity of these findings.

1. Introduction

Dissociative seizures (DS), also known as psychogenic nonepileptic seizures, are episodes of impaired awareness and motor control that can superficially resemble epileptic seizures or syncope. They are, however, the result of complex neurocognitive dysfunction that remains to be elucidated [1]. In one of the first large treatise on the topic from 1859 (421 cases of "hysteria", 305 with seizures), Pierre Briquet identified emotional stressors such as domestic violence and child maltreatment as common predisposing factors [2]. Early-life psychological trauma has since been confirmed as a prevalent aetiological factor [3], and its neurodevelopmental and psychological repercussion have been explored experimentally [4,5]. Briquet speculated that stressors might impact the “affective part of the brain” in ways that lead to emotion dysregulation and loss of control over reflexive behaviours, which eventually manifest as “hysterical seizures” [2,6]. Current biopsychosocial models indeed consider DS as a type of maladaptive physiological and behavioural response to affective activation [1,7]. Impaired emotional processing is prevalent amongst patients and is thought to facilitate the disinhibition of behavioural scripts that

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constitute the individual's DS [7–9]. In support of this view, we previously found that patients with DS perform worse than healthy controls (HC) in an emotional go/no-go task, and that this impairment is associated with self-reported difficulties in emotional awareness and emotion regulation [10]. This adds to previous studies in patients with DS and other functional neurological disorders (FND), which report an attentional bias and avoidance of emotions [11–16], related to alterations in functional connectivity of limbic and prefrontal regions [17–23].

Here, we investigated whether these deficits are associated with variations in microstructural white matter integrity. Anatomical predispositions likely contribute to DS [24], though neuroimaging studies have yet to converge on a unifying set of findings [25]. Using diffusion tensor imaging (DTI), some have found widespread reductions in fractional anisotropy (FA), an index of microstructural integrity [26], while others found increases [27]. Research on related neuropsychiatric disorders has shown that brain morphology findings from smaller studies often fail to replicate in very large populations [28,29]. Considering the clinical heterogeneity of patients with DS, it would thus be more likely to identify variations in tract integrity in relation to common (though not universal) neuropsychological deficits, rather than unique disorder-specific alterations. Preliminary evidence suggests that circuits involved in emotion processing might be altered in patients with DS [5,25,30]. A pioneering study using DTI in eight patients with DS found a rightward asymmetry in uncinate fasciculus streamlines, which was associated with a younger age at DS onset [31]. In a larger sample (n = 16), the same group found increased connectivity of the left uncinate fasciculus, as well as several other white matter tracts of the left hemisphere using a bottom-up analysis [27]. These findings were interpreted as potential evidence of neuroanatomical correlates of emotion dysregulation, though some have cautioned against over-interpretation in the absence of a concomitant neuropsychological assessment [25]. A recent DTI study of 32 FND patients, including 14 with DS, found reduced microstructural integrity of several limbic and associate tracts [30].

Using a bottom-up DTI analysis, we tested the hypothesis that impairments in emotion processing are related to microstructural white matter integrity of affective neurocircuitry. Furthermore, we explored whether the microstructural integrity of thus identified tracts is associated with illness parameters to assess their clinical relevance. Since early-life trauma can alter trajectories of brain development to affect circuits involved in emotional regulation [5,32], we also tested whether the microstructural integrity of identified tracts was related to self-reported psychological trauma history.

2. Methods

2.1. Subjects

Twenty adults (gender ratio 15f:5 m, mean age 34.9 ± 11.2 years, school education 11.1 ± 1.8 years) with DS were prospectively recruited from our epilepsy centre over 16 months. Exclusion criteria included major neurological comorbidity, pathological brain MRI, suspected comorbid epilepsy, inconclusive video-EEG evaluation, epileptiform discharges on EEG, participation in our previous study [10]. Twenty HC (gender ratio 15f:5 m, mean age 36.6 ± 12.2 years, school education 11.6 ± 1.4 years) were recruited via advertisements, and received 20€ of compensation. HC were excluded if they presented with a history of neurological or current psychiatric disorders (except specific phobias). Groups did not differ regarding age ($t(38) = -.448$, $p = .657$), gender (both groups f:m = 15:5), and years of school education ($t(38) = -1.185$, $p = .244$).

Consistent with usual clinical practice, diagnosis of DS was confirmed by video-EEG or clinical consensus; diagnostic certainty was classified according to international consensus criteria [33] as "documented" in 13 patients and "clinically established" in seven. Mean age of illness onset was 29.7 ± 11.7 years, and mean illness duration was 5.2 ± 5.3 years. Most patients rated their subjective illness burden as 4 on a five-point Likert scale ranging from 1 ("none") to 5 ("severe"). For clinical characteristics see supplementary Table S2.

In accordance with the declaration of Helsinki, all participants provided written informed consent and the study was approved by the ethics committee of the Medical faculty, Ruhr University Bochum (Reg.-Nr. 17-6019).

Age at illness onset, duration of a typical DS, and DS frequency were collected using patient report. DS frequency was stratified into four categories ("less than 1/month", "monthly", "weekly", "daily"). A structured psychiatric interview (Mini-DIPS Open Access) [34] was used to screen all participants for psychiatric disorders. Participants furthermore completed the Traumatic Experiences Checklist (TEC), a self-report checklist regarding life stressors. The TEC allows for a semi-quantitative evaluation of psychological trauma severity (each stressful experience is rated on a scale from 1 "no impact" to 5 "severe impact", with a rating of >2 considered as a relevant impact [35]). The TEC also evaluates the relationship to the perpetrator (parent/sibling vs. other), as well as the category of the traumatic experience (emotional neglect, emotional abuse, bodily threat, sexual harassment, sexual abuse), and the age of the trauma onset in three intervals (0–6, 7–12, 13–18 years). One patient did not fill out the TEC because she did not want to revisit details of her psychological trauma history. In cases of missing details regarding psychological trauma severity, the experiences were counted conservatively as having had low impact.

All study elements were completed on one or two consecutive days, and no treatment was initiated during the study.

2.2. Emotion processing

A custom go/no-go task with emotional and neutral faces was used to measure emotion processing and behavioural control [10]. Subjects were instructed to quickly press a key after each "go" stimulus (a pre-defined emotional expression) and withhold their reaction following a "no-go" stimulus (Fig. 1). Stimuli were presented in random order with a 3:1 ratio of go:no-go trials to provoke a response bias. The task consisted of seven blocks à 40 trials: one training (sad = go vs. neutral = no-go) and six experimental blocks (afraid or angry or happy = go vs. neutral = no-go and vice versa, in randomized order). See supplementary material and [10] for details. In line with prior research [36,37] and our previous study using the same paradigm [10], three parameters of task performance were used to measure emotion recognition and behavioural inhibition towards emotional stimuli: d', accuracy, and false alarm rate. Each performance parameter is reported separately for trials where any emotional face was the go-stimulus (requires emotion recognition), for trials where the no-go-stimulus was "angry" or "afraid" (requires behavioural inhibition upon negative affective stimulus), and for trials where the no-go-stimulus was "happy" (as a valence control to the previous condition). The task was performed outside the scanner in a dedicated examination room.

Emotional awareness and regulation were assessed using the Toronto Alexithymia Scale (TAS-20) [38], the four-item version of the Levels of Emotional Awareness Scale (LEAS) [39,40], and the Emotion Regulation Questionnaire (ERQ) [41,42]. See supplementary materials for psychometric details.

2.3. Neuroimaging

Structural and diffusion weighted data were acquired on a Siemens Magnetom Prisma 3 T Scanner using a 64-channel phased-array head coil. The scanning protocol lasted ~17 min. Head motion was restricted using either sound-isolating headphones or foam pads. Diffusion-weighted images were acquired using pulsed gradient-spin-echo echo-planar-imaging with the following parameters: 2 mm isotropic voxels, 60 axial slices, 64 direction diffusion-weighted (b-value = 1000s/mm^2) and 8 baseline images (b-value = 0 s/mm^2), slice thickness = 2 mm.

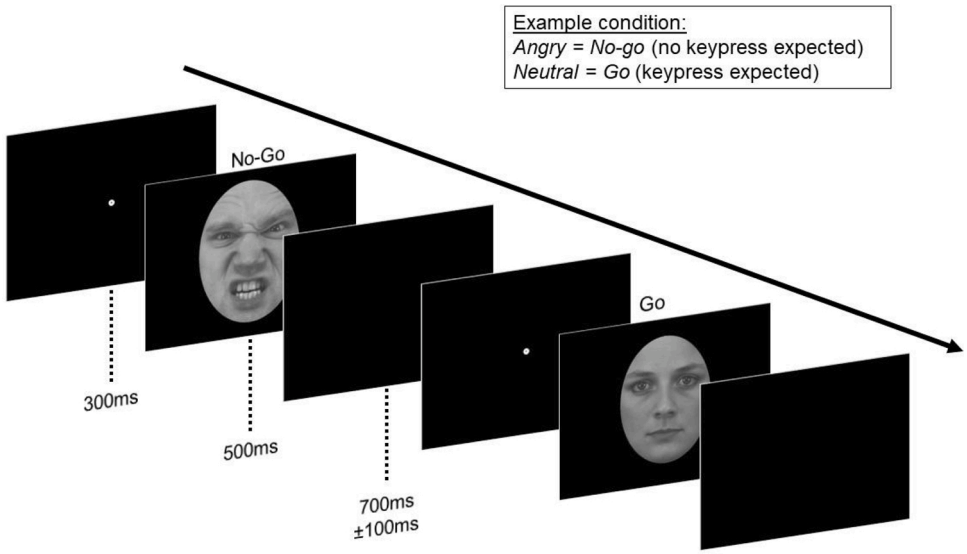

Fig. 1. Visualization of the emotional go/no-go task. Each trial consists of a preparation phase (fixation dot, 300 ms), the stimulus presentation (500 ms) and the inter-trial phase (black screen, 700 ± 100 ms jitter). Responses are registered during stimulus presentation and in the first 500 ms of the inter-trials phase.

High resolution 3D T1-weighted images were acquired using a magnetization prepared rapid gradient-echo sequence with .85 mm isotropic voxels, 208 sagittal slices, slice thickness = .85 mm. See supplementary material for further details.

Voxel-wise statistical analysis of the FA data was carried out using FSL's (Functional Magnetic Resonance Imaging of the Brain Software Library) tract-based spatial statistics (TBSS) to compare whole-brain differences between groups as well as correlations with emotional task performance [43]. For the latter, the TBSS models separately included d', accuracy, or false alarm rate. We repeated these analyses using other DTI measures (mean diffusivity, MD; axial diffusivity, AD; and radial diffusivity, RD). Head motion was adjusted for following previously published procedures [44]. All TBSS analyses were furthermore adjusted for age and gender. Voxelwise statistics used the non-parametric FSL randomise tool [45], running 10,000 Conditional Monte Carlo permutations. Reported results are based on the threshold-free cluster enhancement option, using a corrected statistical threshold of $p < .05$. The anatomical location of significant clusters was determined using the FSL atlasquery tool in conjunction with the Johns Hopkins University ICBM-DTI-81 White-Matter Atlas [46] and the Juelich Histolocial Atlas [47] combined with visual inspection in reference to published white matter atlases [48]. To further analyse the role of specific white matter tracts, tractography analysis was performed using probtrackx2_gpu [49] for tracts of interest based on results from TBSS: fornix/stria terminalis, uncinate fasciculus, and the corpus callosum. A set of curated masks from the FSL xtract tool [50] were used as input for probabilistic tractography. See supplementary materials for further technical details. Mean FA values were extracted using a binarized mask of the reconstructed tracts after applying a threshold to remove voxels containing fibres with a probability of less than .5%.

In a post-hoc analysis we additionally sought to replicate the findings of Hernando et al. [31] by computing asymmetry indices between the right and the left uncinate fasciculus (AI = (R-L)/(R + L)x100) for mean FA and number of reconstructed streamlines (from probtrackx2 waytotal output).

2.4. Statistics

Group comparisons in demographic, psychometric, and behavioural data were performed using t-tests, MANOVAs/MANCOVAs with follow-up t-tests (Student's or Welch's, depending on whether the homogeneity of variances was given or not), or non-parametric Mann-Whitney-U-tests (if normality could not be assumed). Dependent variable selection for MANOVAs/MANCOVAs was based on a priori hypotheses (e.g., all variables that are considered to measure emotion processing were included in one overarching MANOVA/MANCOVA) and formal eligibility (compliance with statistical assumptions). Relationships between tractography results and measures of illness manifestation and traumatic experiences were assessed using partial correlations, while controlling for age, gender, and head motion. Bonferroni-Holm procedure was used to correct for multiple comparisons within each family of tests. Significance level was $p < .05$.

3. Results

3.1. Emotion processing and emotional awareness

To evaluate emotion processing abilities, the results of the emotional go/no-go task (d', accuracy, and false alarm rates) and respective questionnaires (TAS-20, LEAS, ERQ) were analysed. Patients had significantly impaired emotion processing abilities both in behavioural measures and in questionnaires compared to HC: a MANOVA (with group as independent variable; and TAS-20 score, LEAS, ERQ scores, d', accuracy, and false alarm rates as dependent variables) found a significant between-group effect ($V = .436$, $F(7,28) = 5.180$, $p = .001$, effect size: partial $\eta^2 = .564$). To allow a more nuanced view on emotion processing difficulties, we performed a second MANOVA which included the respective subscores of these measures (group as independent variable; and TAS-20 subscores "difficulties identifying feelings", "difficulties describing feelings", "externally oriented thinking", as well as d', accuracy, and false alarm rates each for "negative = no-go" and "positive = no-go" conditions as dependent variables). Again, a significant main effect for group was found ($V = .294$, $F(9,26) = 6.925$, $p < .001$, effect size: partial $\eta^2 = .706$). Bonferroni-Holm-corrected follow-up t-tests for both MANOVAs revealed significantly worse emotion processing abilities in DS patients in both behavioural measures and questionnaires (Table 1). The differences in emotional go/no-go task performance were particularly pronounced and statistically significant across trials in which a negative emotion was the no-go stimulus (but not for positive emotional conditions), revealing an impairment of behavioural inhibition particularly in response to negative emotional stimuli.

Measures of task performance had a significantly higher degree of variance in the patient group (standard deviations for accuracy: DS = .18, HC = .06, Levene's test: $F = 6.318$, $p = .017$; for false alarm rate: DS

Table 1
Values of different measures of emotion processing and emotion regulation.

	DS	HC	p	Type of *t*-test	Effect size (Cohen's d)
Questionnaires					
TAS-20					
Total score	55.4 ± 12.85	38.4 ± 5.94	**<.001***	Student's	1.809
Difficulties identifying feelings	20.85 ± 4.43	11.6 ± 2.76	**<.001***	Student's	2.573
Difficulties describing feelings	14.5 ± 4.51	9.35 ± 2.37	**<.001***	Welch's	1.497
Externally oriented thinking	20.05 ± 5.82	17.45 ± 3.72	.1	Student's	.545
LEAS					
Total score	12.53 ± 3.36	14.6 ± 1.93	.034*	Welch's	.783
ERQ					
Reappraisal	24.95 ± 8.96	29.2 ± 6.95	.102	Student's	.534
Suppression	15.35 ± 6.6	12.15 ± 5.49	.104	Student's	.529
Emotional go/no-go task					
d'					
Emotion = go	1.92 ± 1.04	2.41±.63	.079	Welch's	.585
Negative = no-go	1.44 ± 1.05	2.25±.8	**.01***	Welch's	.87
Positive = no-go	1.75 ± 1.13	2.08±.61	.294	Student's	.377
Accuracy					
Emotion = go	.83 ± .18	.91±.06	.078	Welch's	.524
Negative = no-go	.78 ± .18	.89±.11	**.023***	Welch's	.782
Positive = no-go	.86 ± .13	.92±.07	.058	Welch's	.659
False alarm rate					
Emotion = go	.23 ± .17	.15±.1	.108	Welch's	.574
Negative = no-go	.32 ± .19	.17±.12	**.005***	Student's	.959
Positive = no-go	.24 ± .22	.14±.13	.078	Student's	.59

Mean ± SD as well as p-value and effect size of between-groups comparisons (Student's or Welsh's *t*-test as follow-up to MANOVA). * indicate significant between-group differences (bold = remains significant after Bonferroni-Holm correction for multiple testing). Abbreviations: DS = Dissociative seizures, HC = Healthy controls, TAS-20 = Toronto Alexithymia Scale 20, LEAS = Levels of Emotional Awareness Scale, ERQ = Emotion Regulation Questionnaire.

= .17, HC = .01, Levene's test: F = 2.994, p = .005), which confirms the assumption that impairments in emotion processing is a prevalent, but not universal deficit in patients with DS. To account for this, Wilk's Lambda is reported for MANOVAs and Welch's t-tests are used for follow-up comparisons, as suggested by [51].

We tested for the possible influence of current depressive symptoms or prior adverse experiences on emotion processing abilities by either including "diagnosis of current Major Depression by Mini-DIPS" or the TEC overall score as a covariate in the above-mentioned MANOVA. Both MANCOVAs remained significant after this correction.

To test for group differences in task engagement, effort, or overall psychomotor speed, mean reaction times over all trials and conditions were compared. No significant between-group differences were found (MANOVA: p = .234, follow-up t-tests: all p > .541).

Spearman correlation analyses revealed that behavioural measures of emotion processing (d', false alarm rate each for positive = no-go) were negatively correlated with self-reported "difficulties identifying feelings" and "difficulties describing feelings" as reflected in respective TAS-20 subscores, as well as with the ERQ subscale "reappraisal" (positive correlations) in patients (supplementary Table S3). Similarly, d' and false alarm rate for negative = no-go conditions were significantly correlated with LEAS scores in patients. Such correlations were not found in HC, likely due to the significantly lower within-group variation in both task performance (ceiling effect) and questionnaire scores (floor effects).

3.2. Microstructural integrity of white matter tracts

Whole-brain voxelwise comparison of FA data between groups using TBSS (corrected for age, gender, and head movement) without further covariates revealed no significant differences. The same held true for AD, RD, and MD data.

3.2.1. Association of tract integrity and emotion processing

Significant correlations between microstructural integrity (FA) and emotion processing (d' for emotion = go conditions) were observed in patients, but not in HC. Significant clusters ($p < .05$) were mainly located in bilateral fornix/stria terminalis and right uncinate fasciculus as well as in the corpus callosum (Fig. 2). RD data analysis confirmed these results. No significant correlations were found for AD and MD. In HC, emotion processing correlated with AD and RD in the corpus callosum and the fornix/stria terminalis. See supplementary table S4a and S4b for detailed information on the localization of significant clusters.

3.2.2. Association of tract integrity and clinical features

Based on the TBSS results, a set of tracts was reconstructed using probabilistic tractography: left/right fornix/stria terminalis, right uncinate fasciculus, anterior corpus callosum, and posterior corpus callosum. Correlation analyses between mean FA values of the tracts of interest and illness parameters (Table 2) revealed that the microstructural integrity of the right fornix/stria terminalis was correlated with age at illness onset (r = .537, p = .032), meaning that lower FA values were associated with an earlier illness manifestation. DS frequency was strongly inversely correlated with the microstructural integrity of the posterior corpus callosum (r = −.721, p = .002), and moderately with the right uncinate fasciculus (r = −.513, p = .042), although the latter did not survive Bonferroni-Holm correction.

3.2.3. Association of tract integrity and trauma history

Patients indicated a significantly higher total number of psychologically adverse experiences than HC (Table 3). The number of individual stressors also tended to be higher in all sub-scores, with effect sizes .27 - .49. A closer look at psychological trauma descriptors revealed that patients had a significantly higher number of experiences with high subjective long-term impact than HC (DS = 4.47 ± 4.15; HC = 1.85 ± 2.52, U = 112, p = .028, effect size r = .409), as well as significantly more subjectively impactful experience that were perpetrated by a parent or sibling (DS = 2.11 ± 2.13; HC = .65 ± 1.14; U = 106.5; p = .018; effect size r = .462). Regarding clinical manifestations of psychological trauma, 9/20 patients screened positive for PTSD symptoms in the Mini-DIPS. For further statistical correlation analyses, the TEC total scores were used, since indicators of severity were not completed by all participants for all items.

To examine associations between psychological trauma history and the microstructural integrity of neurocircuitry related to affective behaviour we correlated total TEC scores with mean FA values of the reconstructed tracts while controlling for age, gender, and head movement. The score for traumatic experiences in the age of 13–18 years was significantly correlated with the microstructural integrity of the anterior corpus callosum (r = −.594, p = .015). No other significant correlations between traumatic experiences (neither type of adversity, nor age at traumatic experience) and microstructural tract integrity could be found. See supplementary Tables S5 for details.

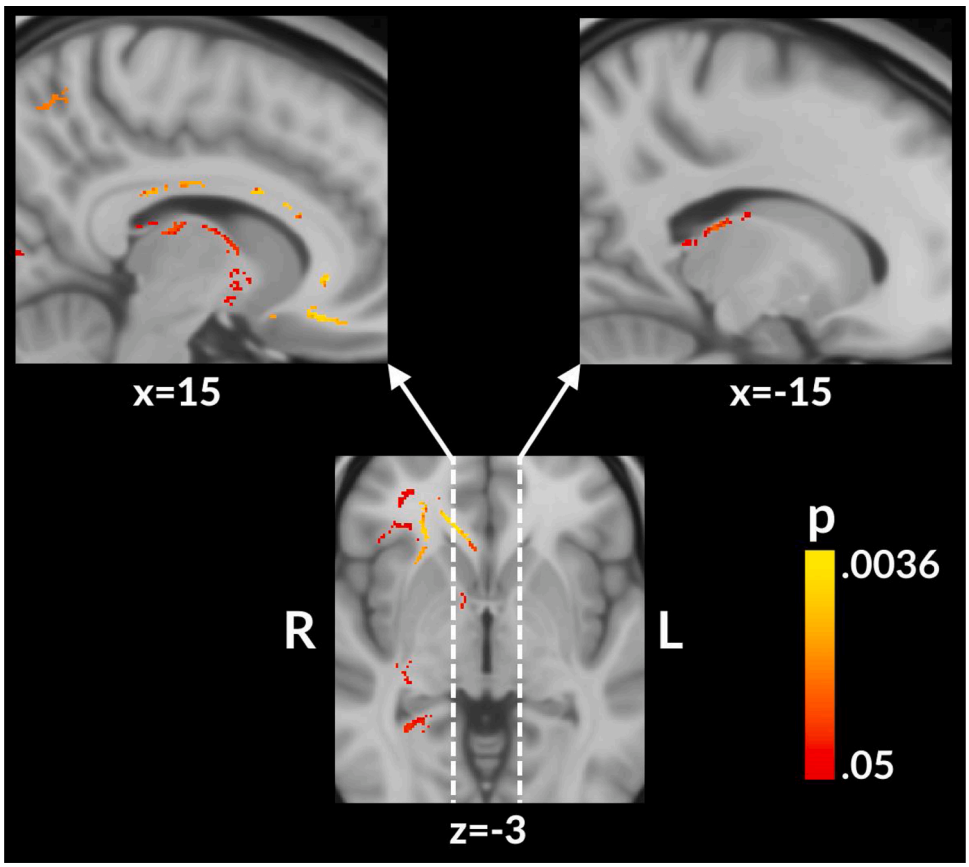

Fig. 2. Representative slices showing TBSS whole-brain voxelwise correlation of microstructural integrity (FA values) with emotion processing abilities (d' for emotion = go conditions), corrected for head motion, age, and gender, in patients with dissociative seizures. X and Z coordinates in MNI-152 space of the slices presented are given.

Table 2
Correlations between the microstructural integrity of tracts of interest and illness parameters.

	Dissociative seizure frequency	Dissociative seizure duration	Age at dissociative seizure onset	Subjective burden of illness
Uncinate fasciculus, right	−.513*	.046	−.422	−.266
Fornix/Stria terminalis, right	−.181	−.403	**.537***	−.475
Fornix/Stria terminalis, left	−.291	.169	.167	−.199
Corpus callosum, anterior	−.399	.036	−.334	−.172
Corpus callosum, posterior	**−.721***	.001	−.038	−.446

Partial correlations between microstructural integrity (mean FA) of tracts of interest and illness parameters, corrected for age, gender, and head motion. * indicate significant correlations (bold = remains significant following Bonferroni-Holm correction for multiple testing).

3.2.4. *Asymmetry of uncinate fasciculus*

In the post-hoc analysis of uncinate fasciculus asymmetry that sought to replicate the main finding from Hernando et al. [31], we did not find significant within-group asymmetries of reconstructed streamlines or FA. The between-group comparison revealed a significantly lower AI of streamlines in patients (DS = −28.83 ± 39.56; HC = −2.06 ± 50.53, p = .045). This indicates a higher leftward asymmetry, which is opposite of what Hernando et al. report. No between-group differences in FA asymmetry were found. Still, the FA asymmetry index was negatively correlated with the age at illness onset (r = −.535, p = .027) when corrected for age, gender, and head movement.

4. Discussion

In this study we first replicated our recent finding that patients show potentially clinically relevant deficits in emotion processing (specifically behavioural inhibition in response to emotional stimuli) [10]. Without imposing a priori restrictions on whole-brain voxelwise analyses we then found that these deficits are associated primarily with reduced microstructural integrity of the right uncinate fasciculus, right and left fornix/stria terminalis, and the corpus callosum – white matter tracts known to be involved in behavioural regulation towards emotional cues [52,53]. Tractographic reconstructions of these connections then revealed that reductions in microstructural integrity correlated with an earlier age of onset for the right fornix/stria terminals, and higher DS frequency for the right uncinate fasciculus and the posterior corpus callosum. Self-reported traumatic experiences in adolescence (13–18 years) were inversely correlated with the anterior corpus callosum microstructural integrity.

In the emotional go/no-go task, mean reaction times showed no between-group differences, indicating normal levels of engagement of patients with DS and emphasizing the performance validity of this behavioural paradigm. Accuracy measures, however, revealed that patients performed worse at the task, especially when a prepared reaction had to be inhibited in response to a negative stimulus (i.e. a face showing anger or fear). The impairment in emotion processing was correlated

Table 3
Traumatic experiences as measured by the TEC.

	DS	HC	p	effect size
TEC				
Total score	6.84 ± 5.22	3.5 ± 3.5	.028*	r = .4
Sub-scores				
Emotional neglect	2.68 ± 3.27	1.15 ± 1.81	.127	r = .304
Emotional abuse	1.53 ± 1.71	.75 ± 1.02	.175	r = .27
Bodily threat	2.26 ± 2.84	1.05 ± 1.28	.149	r = .277
Sexual harassment	1 ± 1.76	.35±.75	.428	r = .194
Sexual abuse	.95 ± 1.75	–	−.095	r = .49
Subjective impact				
Min. 1 experience with high subjective impact	15/19	11/20	.113$^{\chi}$	φ = .245
No. of experience with high subjective impact	4.47 ± 4.15	1.85 ± 2.52	.028*	r = .409
Min. 1 experience with high subjective impact perpetrated by family members	13/19	6/20	.016*$^{\chi}$	φ = .284
No. of experience with high subjective impact perpetrated by family members	2.11 ± 2.13	.65 ± 1.14	.018*	r = .462

Mean ± SD as well as p-value and effect size of between-groups comparisons (Mann-Whitney-U-Test or χ^2-test, as applicable; χ indicates χ^2-test). * indicate significant between-group differences (bold = remains significant after Bonferroni-Holm correction for multiple testing). Abbreviations: DS = Dissociative seizures, HC = Healthy controls, TEC = Traumatic Experiences Checklist.

significantly with scores of self-reported alexithymia and emotion regulation. This finding, as previously noted [10], suggests that difficulties with emotion processing related to external and internal cues are correlated, and that objective measures of emotion processing impairment overlap with real-world difficulties of patients. While the effects were significant only for negative emotions, a trend towards lower accuracy and more false alarms was also observed for positive emotions, which were furthermore significantly correlated with TAS-20 subscores. This suggests general emotion processing difficulties, which appear to be more pronounced for negative emotions. Our findings complement previous neuropsychological studies using emotional facial cues that showed impaired emotion recognition [54] as well as attentional interference effects in behavioural tasks [11,13–16]. Another study found longer response latencies in an emotional face task [17], which is in line with reduced accuracy in timed behavioural tasks such as Stroop or go/no-go tasks. Our results are not contradictory to previously reported findings of emotion avoidance in patients with DS and other FND [13,14,55]: Increased preconscious attention, which interferes with successful inhibition, may lead to a higher false-alarm rate as well as to avoidance of further processing the negative emotion. Together, these observations support the idea that impairments in emotional processing, and specifically its interaction with attentional and behavioural control, may constitute a key deficit related to the precipitation of DS [8,9].

Next, we investigated whether neuroanatomical variations were linked to these impairments. Previous studies found contradicting results regarding group-level differences in microstructural white matter integrity between patients and HC [26,27]. We found no such differences on a group level, in line with the wide heterogeneity in clinical presentation and aetiology observed in patients with DS [1], which makes a disorder-specific universal pathology unlikely. Our post-hoc analysis did not replicate the main findings of rightward uncinate fasciculus asymmetry from Hernando et al. [31]. However, a reproducible variation in neuroanatomy related to variations in phenotype (i.e. illness-relevant neuropsychological deficits) is likely. Indeed, the bottom-up TBSS analysis revealed that emotional task performance was significantly correlated with measures of microstructural integrity of voxel clusters in the following tracts: right uncinate fasciculus, right and left fornix/stria terminalis and the corpus callosum.

Both the fornix and the stria terminalis belong to a neurocircuitry involved in affective behavioural control [53]. The uncinate fasciculus, a major frontolimbic connection, is involved in social and emotional processing and behaviour [52]. Its microstructural integrity after brain injury can predict problems with emotional and behavioural regulation [56], which might partly explain the high prevalence of preceding head injury reported by patients with DS [57].

To explore the potential clinical relevance of the microstructural integrity variation of these tracts, we performed a correlation analysis regarding the respective mean FA values and clinical parameters. We found that DS frequency was inversely correlated with the microstructural integrity of the posterior corpus callosum. Similar correlations have been previously observed in patients with post-traumatic stress disorder [29,58], a condition with significant clinical and pathophysiological overlap with DS [1,59]. We further found that a reduced microstructural integrity of the right fornix/stria terminalis is associated with a younger age at illness onset. A recent study on patients with FND (14/32 with DS), also found a significant correlation between the microstructural integrity of fornix/stria terminalis and illness duration (which reflects age at onset since data was corrected for current age) [30]. A relationship between an earlier age of illness onset and the asymmetry in microstructural integrity between the left and right uncinate fasciculus has been reported earlier [31], which we could replicate.

Patients with DS generally report higher rates of early-life psychological trauma than the general population, especially regarding emotional neglect [3], which was also found in our sample using the TEC questionnaire. Interestingly, patients with dissociative seizures and a history of sexual abuse are 46 % more likely to report emotional triggers than those without such traumatization [60]. Examining the association between neurodevelopmental predisposition and neuropsychological dysfunction (and correcting for current age to account for white matter tract maturation), we found that especially psychological trauma occurring in adolescence (13–18 years) was inversely correlated with microstructural integrity measures of the anterior corpus callosum. This poses the question whether trauma-related deviations of neurodevelopmental trajectories of frontal interhemispheric connections might predispose to abnormal emotion processing and behavioural control, and with that, to DS later in life.

A major limitation of our study design is that it cannot establish whether the observed effects are related to DS specifically, or whether they are attributable to psychopathology such as anxiety, impulsivity or emotional instability. Having screened our HC for current or prior psychiatric illness amplifies this problem by eliminating "background" psychopathology from the control sample. Thus, our claim that we are examining DS pathophysiology, and not just unrelated impairments in a psychiatrically ill sample, hinges on the assumption that behavioural disinhibition during emotional engagement is a mechanistically relevant process in DS. This assumption is derived from clinical observations and theoretical models [1;7], but has not been substantiated experimentally. By demonstrating correlations with illness features (DS frequency and age of onset), and by controlling task performance analyses for current depressive symptoms and prior adverse experiences, we aimed to establish a plausible degree of specificity. However, studies using psychiatric control groups are necessary to clarify this issue.

Limitations of methodology also must be considered. Neutral faces can be perceived as negatively valenced, thus reducing the emotional contrast of stimuli [61,62]. For DTI acquisition, a b-value of 1000 was used. In hindsight, more sophisticated protocols such as multi-shell measurements would have been more appropriate. Our study sample was relatively small, and included seven patients whose DS diagnosis was established on clinical grounds by the epileptology team, rather

than being documented through ictal video-EEG recording. This introduces the risk of misdiagnosis.

5. Conclusion

In conclusion, our investigation confirmed that patients with DS have problems with inhibiting prepared behavioural responses towards negative emotional stimuli. It further revealed that emotional task performance is associated with variations in the microstructural integrity of frontolimbic and interhemispheric white matter tracts. The integrity of several components of this affective neurocircuitry correlate with illness parameters (age at onset and DS frequency) as well as with the number of traumatic experiences during adolescence. Considering the above-mentioned limitations of our methodology and study design, our findings tentatively suggest that the aetiopathogenesis of DS might be partially reflected in structural alterations in brain connectivity.

Declaration of Competing Interest

The authors report no declarations of interest.

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Deidentified data as well as preprocessing and analysis scripts are available upon reasonable request.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2020.11.021.

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