Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Structural alterations of amygdala and hypothalamus contribute to catatonia

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ARTICLE INFO

Keywords:
Catatonia
MRI
Amygdala
Hypothalamus
Freesurfer

ABSTRACT

At present, current diagnostic criteria and systems neglect affective symptom expression in catatonia. This potentially serious omission could explain why putative contributions of limbic system structures, such as amygdala, hippocampus or hypothalamus, to catatonia in schizophrenia spectrum disorders (SSD) have been scarcely investigated so far. To determine whether topographical alterations of the amygdala, hippocampus and hypothalamus contribute to catatonia in SSD patients, we conducted structural magnetic resonance imaging (MRI) of SSD patients with (SSD-Cat, n = 30) and without (SSD-nonCat, n = 28) catatonia as defined by a Northoff Catatonia Rating Scale (NCRS) total score of ≥3 and =0, respectively, in comparison with healthy controls (n = 20). FreeSurfer v7.2 was used for automated segmentation of the amygdala and its 9 nuclei, hippocampus and its 21 subfields and hypothalamus and its associated 5 subunits. SSD-Cat had significantly smaller anterior inferior hypothalamus, cortical nucleus of amygdala, and hippocampal fimbria volumes when compared to SSD-nonCat. SSD-Cat had significantly smaller amygdala, hippocampus and hypothalamus whole and subunit volumes when compared to healthy controls. In SSD-Cat according to DSM-IV-TR (n = 44), we identified positive correlations between Brief Psychiatric Rating Scale (BPRS) item #2 (reflecting anxiety) and respective amygdala nuclei as well as negative correlation between NCRS behavioral score and hippocampus subiculum head. The lower volumes of respective limbic structures involved in affect regulation may point towards central affective pathomechanisms in catatonia.

1. Introduction

Catatonia is one of the most devastating psychomotor disorders in psychiatry, characterized by a specific constellation of hypo- and hyperkinetic motor phenomena, affective symptoms, and disorders of behavior with all three symptom domains being closely intertwined in often clinically heterogeneous presentations (Northoff et al., 1999). For about a decade, scientific research on catatonic symptoms is experiencing a renaissance (for overview of the literature see (Haroche et al., 2020; Hirjak et al., 2020a; Walther et al., 2019)). The recognition of the sensorimotor domain by the Research Domain Criteria (RDoC) initiative and the introduction of catatonia as an independent diagnosis in the ICD-11 classification system have been identified among the most important drivers of this development (Haroche et al., 2020; Hirjak et al., 2020a; Walther et al., 2019). From a neurobiological perspective, recent research has associated catatonia with disrupted structural and functional interactions of cerebellar, prefrontal/cortical motor regions and frontoparietal areas (Hirjak et al., 2020a; Hirjak et al., 2020b; Sambataro et al., 2021). Yet, while these current pathophysiological models could well explain sensorimotor and behavioral disturbances in catatonia, their explanatory power for the affective domain is limited. It is very likely that other brain regions could play a crucial role in the

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https://doi.org/10.1016/j.schres.2022.05.003
Received 29 March 2022; Received in revised form 3 May 2022; Accepted 4 May 2022

expression of affective catatonic symptoms, particularly brain areas that are critically involved in anxiety/fear modulation, i.e. subcortical limbic system structures such as amygdala, hippocampus or hypothalamus.

However, the vast majority of neuroimaging studies published so far did not identify clear associations between catatonic symptoms and dysfunctions of the subcortical limbic system structures. This may be related to modest signal-to-noise ratio in standard structural imaging, as much as it could be related to the lack of specific amygdala, hippocampus and hypothalamus segmentation tools, which could allow a differentiated examination of these structures. To address these gaps in evidence and support the view that limbic system structures play an important role in the pathogenesis of catatonia, the present study investigated the relationship between morphological variations of the amygdala-hippocampus complex and hypothalamus and catatonic symptoms assessed with the Northoff Catatonia Rating Scale (NCRS) in schizophrenia spectrum disorders (SSD) patients. First, using a categorical approach, we sought to investigate whether there is a difference in specific substructures of the amygdala-hippocampus complex and hypothalamus as assessed by newly developed segmentation tools implemented in Freesurfer vers. 7.2 between SSD patients with (NCRS total score ≥ 3; at least 1 point in the three different symptom categories; i.e., motor, behavioral, and affective) and without (NCRS = 0) catatonia. We hypothesized that SSD patients with catatonia will have lower volumes of amygdala, hippocampus and hypothalamus when compared to patients without catatonia. Second, using a dimensional approach (low and high severity of catatonia according to DSM-IV-TR) and in accordance with the model of GABA-driven subcortical-cortical psychomotor circuits, we hypothesized that amygdala, hippocampus and hypothalamus volumes are significantly associated with NCRS affective score in contrast to motor or behavioral disturbances. In addition, we explored specific associations between regional morphology and anxiety, as indicated by Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) item #2.

2. Methods

2.1. Study participants

We examined a total of 111 right-handed (Oldfield, 1971) subjects fulfilling the DSM-IV-TR (Sass et al., 2003) criteria for schizophrenia (n = 104) or schizoaffective disorder (n = 7) ((Hirjak et al., 2019a; Hirjak et al., 2019b)). Diagnoses were made by staff psychiatrists and confirmed using the German versions of the Structured Clinical Interview for DSM-IV-TR axis I and II disorders (SCID) and examination of the case notes (DH and SF). Patients were excluded if: (i) they were aged <18 or >65 years; (ii) they had a history of brain trauma or neurological disease (especially movement disorders); (iii) they had shown alcohol/substance use disorder within 12 months prior to participation; or (iv) they had MRI contraindications. Medical conditions potentially affecting central nervous system function, as well as cardiovascular or metabolic diseases in SSD patients were excluded by physical examination, laboratory control, ECG, EEG and MRI. Further, no complication of catatonia, such as dehydration or electrolyte disorders, as indicated by laboratory findings were detected in any of the patients on the day of MRI investigation.

Twenty right-handed healthy controls (HC) were also studied. Exclusion criteria included MRI contraindications, a history of psychiatric, neurological, cardiovascular or metabolic illness, prior head trauma, and current alcohol or drug abuse. None of the control subjects had a first-degree relative with a psychiatric disorder or was receiving psychopharmacological treatment.

The local Ethics Committees (Medical Faculties Heidelberg and Mannheim at Heidelberg University, Germany) approved the study. We obtained written informed consent from all study participants after all aims and procedures of the study had been fully explained.

2.2. Clinical assessment

All SSD participants were examined during inpatient treatment within one week after partial remission of acute psychopathological symptoms. All relevant study procedures (e.g. psychometric testing, motor assessment and MRI examination) were completed within 3 days. None of the SSD patients was treated with benzodiazepines or anticholinergic agents at the time of the psychometric testing, motor assessment and MRI examination. All but five patients (5/111 = 4.5% antipsychotic-free) were on a stable daily dose of antipsychotic medication for at least 14 days. For a better comparability among studies, the daily doses of antipsychotic medication were converted to olanzapine equivalents (OLZ) (Leucht et al., 2015). For the examination of the catatonic syndrome we used the German version of the NCRS (Hirjak et al., 2016). The scale measures the presence and severity of motor (13 items), affective (12 items), and behavioral (15 items) catatonic symptoms. In the first step, we used a clear cut-off to identify SSD patients with (NCRS total score ≥ 3; at least 1 point in the three different dimensions; i.e., motor, behavioral, and affective) and without (NCRS = 0) catatonia. In the second step, we assumed a neurobiological continuum between SSD patients with low and high severity of catatonia. Therefore, we used the DSM-IV-TR criteria for catatonia [1 motor and at least 1 other symptom (behavioral or affective)] to examine the morphological alterations of amygdala, hippocampus and hypothalamus in SSD patients underlying the catatonic syndrome (Sass et al., 2003). With this approach, we sought to cover a broader spectrum of the catatonic symptoms truly reflecting the dimensional view on catatonia (low and high expression of symptoms). Finally, the severity of anxiety was determined using the corresponding BPRS item #2 (Overall and Gorham, 1962). All clinical and sensorimotor rating scales were performed by two raters (SF and DH), who reached an intraclass correlation coefficient > 0.85.

2.3. Structural MRI data acquisition

MRI scans were acquired at the Central Institute of Mental Health, Mannheim, Germany, using a 3.0 Tesla Siemens Trio whole-body imaging system and a T1-weigthed magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: repetition time (ms): 2530; echo time (ms): 3.8; inversion time (ms): 1100; flip angle: 7°; number of averages: 1; slice thickness (mm): 1; image columns: 256; image rows: 256; phase encoding direction: ROW; voxel size *x* (mm): 1; voxel size *y* (mm): 1; number of volumes: 1; number of slices: 176; number of files: 176.

2.4. Image processing

FreeSurfer v7.2 (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999) was used for segmentation of nine amygdala nuclei, 21 hippocampal subfields and nine hypothalamus subunits (for further details on these methods see http://surfer.nmr.mgh.harvard.edu/). In particular, nine amygdala nuclei and 21 hippocampal subfields volume estimates were obtained using a joint hippocampal subfields and amygdala nuclei segmentation algorithm (Iglesias et al., 2015; Iglesias et al., 2016; Saygin et al., 2017). This tool was developed based on the hippocampal module released with FreeSurfer 6.0. The tool uses a probabilistic atlas built with ultra-high resolution ex vivo MRI data (~0.1 mm isotropic) to produce an automated segmentation of the 21 hippocampal substructures (incl. molecular subregion added to nearest neighbor) and the amygdala (which is subdivided into lateral, basal, accessory basal, central, medial, cortical and paralaminar nuclei; and cortico-amygdaloid transition and anterior amygdala areas; see (Saygin et al., 2017) for details). The main advantage of this method is that joint segmentation of hippocampus and amygdala ensures that structures do not overlap or leave gaps in between. Second, we also used a novel tool released in Freesurfer vers. 7.2 and developed by Billot et al. (2020) for

an automated segmentation of the hypothalamus and associated subunits (anterior-inferior, anterior-superior, posterior, Inferior tubular, and superior tubular). This tool enables automated segmentation of the hypothalamus and its associated 5 subunits in 3D T1-weighted scans of approximately 1 mm isotropic resolution.

Finally, the estimated total intracranial volume (eTIV) was calculated with FreeSurfer as recommended. FreeSurfer makes use of the relationship between the intracranial volume (ICV) and the linear transform to MNI305 space (talairach.xfm) as described in Buckner et al. (Buckner et al., 2004). SF and DH checked segmentation results and found no relevant artifacts in the included subjects.

2.5. Statistical analyses

We used *R* version 4.0.4 and *RStudio* version 1.3.1093. Initially, a descriptive analysis for demographic, clinical and volumetric data in catatonic and non-catatonic SSD patients (Table 1) was performed. Then, homogeneity of variances and normality of all amygdala, hippocampus and hypothalamus regions in all three study groups was asserted using Levene's test and Shapiro-Wilk test, respectively.

2.5.1. Group differences

In a first step, we used ANCOVA with study group as the independent variable and with age, sex, education and eTIV as covariates to identify significant volumetric differences between SSD-Cat, SSD-nonCAT and HC. Substructures with significant ANCOVA results (p-value <0.05) were considered for post-hoc Duncan test. In a second step, for completeness, and to rule out potential effects of the overall symptom load, we employed ANCOVA based on General Linear Model as implemented in *R* with PANSS total score as a covariate to determine the morphological differences between patient groups (SSD-Cat vs. SSD-nonCat). Finally, to exclude that the results in SSD patients were unduly driven by duration of illness, we rerun the analyses using both PANSS total score and duration of illness as covariates. To account for false positive findings within the group differences, p-values were corrected using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

2.5.2. Structure-symptom associations

In the third step, associations between amygdala, hippocampus and hypothalamus substructures and NCRS as well as Brief Psychiatric Rating Scale (Overall et al., 1967) (BPRS) item #2 scores (reflecting anxiety) in patients with catatonia according to DSM-IV-TR [1 motor and at least 1 other symptom (behavioral or affective), n = 44] were explored using partial correlations by treating age, gender, education, medication, PANSS total score, SAS total score and eTIV as covariates. A nominal significance threshold of $p \leq 0.05$ was defined. To account for false positive findings within the structure/symptom-associations, p-values were corrected using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

3. Results

3.1. Clinical and demographic characteristics

Demographic and clinical characteristics of the three study groups (SSD-Cat, SSD-nonCAT and HC) are shown in Table 1. Thirty out of 111 SSD patients (27%) were defined as having catatonia according to NCRS. The control group which comprised twenty-eight SSD patients operationally defined as not having catatonia according to NCRS (NCRS total score = 0) was well balanced (propensity matched) for age, gender, education and OLZ equivalents. 30 SSD patients with and 28 SSD patients without catatonia according to NCRS were considered for between-group analyses. The HC group (n = 20) was well balanced (propensity matched) for age, gender and education.

For completeness, forty-four out of 111 SSD patients (39,6%) were identified as having catatonia according to DSM-IV-TR (Sass et al., 2003) and considered for correlation analysis. 39 SSD patients (39/111 = 35.1%) did not satisfy NCRS or DSM-IV-TR criteria for catatonia and were excluded from further analyses. Finally, since the NCRS criteria for catatonia are similar to those according to DSM-5-TR (at least 3 catatonic symptoms), it can be said that a total of 30 SSD patients met the DSM-5-TR criteria for catatonia.

3.2. Group differences

Volumetric characteristics of the three study groups in amygdala, hippocampus and hypothalamus are shown in Table 2. Step-wise increasing nominal volumes from SSD-Cat to SSD-nonCAT and to HC are visible in the majority of analyzed substructures. However, only the

Table 1
Clinical and demographic variables in schizophrenia spectrum disorder (SSD) patients with catatonia (SSD-Cat) and without catatonia (SSD-nonCat) and healthy controls (HC).

Variable	SSD-Cat (n = 30)	SSD-nonCat (n = 28)	HC (n = 20)	$F/X^2/t$	*Df*	Sig. (two-tailed)
Age[a]	39.4 ± 10.49	38.71 ± 10.77	40.7 ± 13.55	0.177	2	0.838
Gender (m/f)[b]	16/14	13/15	10/10	6	4	0.191
Education (years)[a]	13.77 ± 2.42	13.25 ± 3.16	13.45 ± 1.76	0.296	2	0.744
Olanzapine equivalents[c]	18.0 ± 9.65	18.8 ± 12.55	–	−0.268	51	0.790
Duration of illness (years) [c]	12.27 ± 11.53	7.57 ± 8.92	–	1.741	54	0.087
GAF score	57.97 ± 14.97	75.00 ± 15.99	–	−4.181	55	**<0.001**
PANSS total score[c]	80.27 ± 20.73	56.39 ± 19.70	–	4.497	56	**<0.001**
PANSS positive score[c]	18.93 ± 8.18	13.21 ± 6.24	–	3.004	54	**0.004**
PANSS negative score[c]	21.17 ± 8.63	13.36 ± 6.38	–	3.935	53	**<0.001**
PANSS general score[c]	40.40 ± 11.85	29.93 ± 9.82	–	3.672	55	**<0.001**
BPRS total	43.17 ± 13.93	31.86 ± 11.97	–	3.322	56	**0.002**
BPRS item # 2[c]	3.37 ± 1.65	2.50 ± 1.55	–	2.062	55	**0.043**
NCRS affective score[c]	2.8 ± 1.67	0.0 ± 0.0	–	9.188	29	**<0.001**
NCRS motor score[c]	1.87 ± 1.33	0.0 ± 0.0	–	7.675	29	**<0.001**
NCRS behavior score[c]	2.27 ± 1.20	0.0 ± 0.0	–	10.333	29	**<0.001**
NCRS total score[c]	6.9 ± 2.60	0.0 ± 0.0	–	14.511	29	**<0.001**
SAS total score[c]	3.27 ± 2.24	2.14 ± 2.17	–	1.938	55.92	0.058

Data are mean ± standard deviation.
Abbreviations: *PANSS* Positive and Negative Symptoms Scale, *BPRS* Brief Psychiatric Rating Scale, *BPRS item #2* Anxiety, *GAF* Global Assessment of Functioning, *NCRS* Northoff Catatonia Rating Scale, *SAS* Simpson Angus Scale.
[a] F, Df, and p values were obtained using ANOVA.
[b] χ^2, Df and p values were obtained using the Chi-squared test.
[c] t, Df and p values were obtained using independent sample t-tests (two-tailed).

Table 2
Morphological variables in schizophrenia spectrum disorder (SSD) patients with catatonia (SSD-Cat) and without catatonia (SSD-nonCat) and healthy controls (HC).

Amygdala volume (mm^3)	SSD-Cat (n = 30)	SSD-nonCat (n = 28)	HC (n = 20)	*F*	*Df*	Sig.	Duncan test (5%)
Total volume	1696.82 ± 190.55	1766.63 ± 150.44	1839.26 ± 184.73	4.572	2	0.013	HC > SSD-nonCAT > SSD-Cat
Lateral nucleus	633.06 ± 69.60	658.24 ± 51.48	681.99 ± 72.39	3.687	2	0.030	HC > SSD-nonCAT > SSD-Cat
Basal nucleus	430.14 ± 52.14	446.37 ± 42.49	469.26 ± 50.86	4.394	2	0.016	HC > SSD-nonCAT > SSD-Cat
Accessory basal nucleus	260.32 ± 31.72	272.39 ± 29.04	283.74 ± 36.44	3.568	2	0.033	HC > SSD-nonCAT > SSD-Cat
Anterior amygdaloid area	51.94 ± 7.92	55.50 ± 5.51	59.68 ± 7.59	7.603	2	**0.001**	HC > SSD-nonCAT, SSD-Cat
Central nucleus	48.49 ± 7.48	49.19 ± 6.54	50.93 ± 6.92	0.326	2	0.723	–
Medial nucleus	24.42 ± 5.56	25.94 ± 5.28	27.61 ± 6.04	1.885	2	0.159	–
Cortical nucleus	26.63 ± 3.70	28.63 ± 3.14	28.79 ± 3.32	3.967	2	0.023	HC, SSD-nonCAT > SSD-Cat
Corticoamygdaloid trans.	173.32 ± 21.79	181.11 ± 19.15	186.41 ± 22.88	2.453	2	0.093	–
Paralaminar nucleus	48.50 ± 5.41	49.26 ± 5.12	50.86 ± 5.60	1.025	2	0.364	–

Hippocampus volume (mm^3)	SSD-Cat (n = 30)	SSD-nonCat (n = 28)	HC (n = 20)	*F*	*Df*	Sig.	Duncan test (5%)
Total volume	3293 ± 352.39	3416.50 ± 272.15	3520.05 ± 342.30	3.353	2	0.041	HC > SSD-nonCAT > SSD-Cat
Hippocampal tail	545.23 ± 72.41	564.02 ± 55.49	583.72 ± 77.07	3.353	2	0.041	HC > SSD-nonCAT > SSD-Cat
Subiculum body	235.08 ± 27.04	238.94 ± 23.62	241.56 ± 30.63	0.299	2	0.742	–
CA1 body	120.43 ± 20.22	121.80 ± 14.24	129.71 ± 21.71	1.219	2	0.302	–
Subiculum head	181.61 ± 28.94	190.36 ± 19.32	194.56 ± 22.21	1.957	2	0.149	–
Hippocampal fissure	151.02 ± 23.92	147.53 ± 22.14	150.11 ± 24.10	0.353	2	0.704	–
Presubiculum head	134.67 ± 17.10	141.91 ± 10.85	144.55 ± 13.97	3.233	2	0.045	HC > SSD-nonCAT > SSD-Cat
CA1 head	494.85 ± 70.03	509.18 ± 50.43	534.68 ± 62.85	2.344	2	0.103	–
Presubiculum body	159.99 ± 21.03	170.98 ± 23.25	172.52 ± 16.88	2.962	2	0.058	–
Parasubiculum	63.35 ± 10.25	66.30 ± 8.93	65.41 ± 8.19	0.786	2	0.460	–
Molecular layer head	311.42 ± 38.51	325.19 ± 28.24	336.84 ± 35.88	3.605	2	0.032	HC > SSD-nonCAT > SSD-Cat
Molecular layer body	214.34 ± 24.39	223.00 ± 19.16	229.23 ± 25.90	2.484	2	0.091	–
GC.ML.DG. head	143.64 ± 18.24	148.50 ± 16.07	154.23 ± 17.40	2.189	2	0.120	–
GC.ML.DG. body	124.80 ± 14.72	129.04 ± 14.74	130.16 ± 14.94	0.747	2	0.477	–
CA4 head	119.41 ± 13.89	123.79 ± 13.70	128.09 ± 13.31	2.521	2	0.088	–
CA4 body	110.55 ± 13.55	113.48 ± 13.25	114.67 ± 12.46	0.445	2	0.643	–
Fimbria	72.88 ± 14.79	85.62 ± 13.89	83.98 ± 15.31	6.662	2	**0.002**	HC, SSD-nonCAT > SSD-Cat
CA3 head	117.76 ± 17.42	119.16 ± 15.48	124.62 ± 13.64	0.811	2	0.449	–
CA3 body	84.24 ± 12.82	85.08 ± 12.43	87.94 ± 14.47	0.193	2	0.825	–
HATA	58.93 ± 9.56	60.16 ± 8.37	63.57 ± 9.54	1.160	2	0.319	–
Hippocampal body	1122.31 ± 114.99	1167.95 ± 96.30	1189.76 ± 115.91	2.794	2	0.068	–
Hippocampal head	1625.64 ± 198.09	1684.53 ± 149.74	1746.57 ± 172.71	3.058	2	0.053	–

Hypothalamus volume (mm^3)	SSD-Cat (n = 30)	SSD-nonCat (n = 28)	HC (n = 20)	*F*	*Df*	Sig.	Duncan test (5%)
Total volume	406.39 ± 27.08	421.98 ± 28.11	426.33 ± 34.96	4.504	2	0.014	HC > SSD-nonCAT > SSD-Cat
Anterior inferior	16.03 ± 2.67	18.74 ± 3.09	18.40 ± 3.04	8.401	2	**0.003**	SSD-nonCAT, HC > SSD-Cat
Anterior superior	22.96 ± 2.36	24.05 ± 3.63	24.46 ± 3.39	1.318	2	0.274	–
Posterior	119.05 ± 9.98	121.48 ± 11.12	122.98 ± 12.67	0.590	2	0.557	–
Inferior tubular	133.44 ± 10.88	138.43 ± 11.01	141.99 ± 14.04	4.032	2	0.021	HC > SSD-nonCAT > SSD-Cat
Superior tubular	114.91 ± 10.09	119.28 ± 12.73	118.48 ± 10.98	1.921	2	0.154	–
eTIV[a]	$1.53 \times 10^6 \pm 1.22 \times 10^5$	$1.52 \times 10^6 \pm 1.45 \times 10^5$	$1.57 \times 10^6 \pm 1.46 \times 10^5$	0.690	2	0.505	–

Data are mean ± standard deviation.
Abbreviations: *Corticoamygdaloid trans.* = corticoamygdaloid transition area, *eTIV* = estimated total intracranial volume.
F, Df, and *p*-values were obtained using ANCOVA with age, eTIV, sex and education as covariates. *p*-Values that survived Benjamini-Hochberg correction for multiple testing are highlighted in bold.
[a] eTIV was obtained using ANOVA.

anterior amygdaloid area ($p = 0.001$), fimbria ($p = 0.002$) and anterior inferior hypothalamus ($p = 0.003$) survived the Benjamini-Hochberg correction for multiple testing.

First, ANCOVA revealed significant volumetric differences in several amygdala, hippocampus and hypothalamus substructures between the three study groups (for details see Table 2), most notably in total amygdala volume ($p = 0.01$), basal nucleus of amygdala ($p = 0.01$), anterior amygdaloid area ($p = 0.001$), hippocampus fimbria ($p = 0.002$) and anterior inferior hypothalamus ($p = 0.003$) (Fig. 1). Only anterior amygdaloid area ($p = 0.001$), hippocampus fimbria ($p = 0.002$) and anterior inferior hypothalamus ($p = 0.003$) survived Benjamini-Hochberg correction for multiple testing.

Second, according to ANCOVA (for details see Table 2), SSD-Cat (NCRS total score ≥ 3; n = 30) had significantly smaller hippocampal fimbria ($p = 0.02$) and anterior inferior hypothalamus ($p = 0.002$) volumes when compared to non-catatonic patients (NCRS total score = 0; n = 28) after adjusting for PANSS total (Table 3). Only anterior inferior hypothalamus ($p = 0.002$) survived Benjamini-Hochberg correction for multiple testing (Table 3). After using both PANSS total score and duration of illness as covariates, SSD-Cat had significantly smaller anterior inferior hypothalamus ($p = 0.003$) volumes when compared to non-catatonic patients (see Supplementary material for results).

3.3. Structure-symptom associations

In the third step, following a dimensional approach to define catatonic patients according to DSM-IV-TR (n = 44), partial correlations (using age, gender, education, medication, eTIV, PANSS total and SAS total as covariates) between amygdala nuclei, hippocampal subfields and hypothalamus subunits and NCRS (sub-)scores revealed a significant relationship between hippocampus subiculum head volume ($p = 0.04$) and NCRS behavioral score (s. Table 4). Finally, for completeness, a relationship between amygdala total ($p = 0.03$) as well as lateral

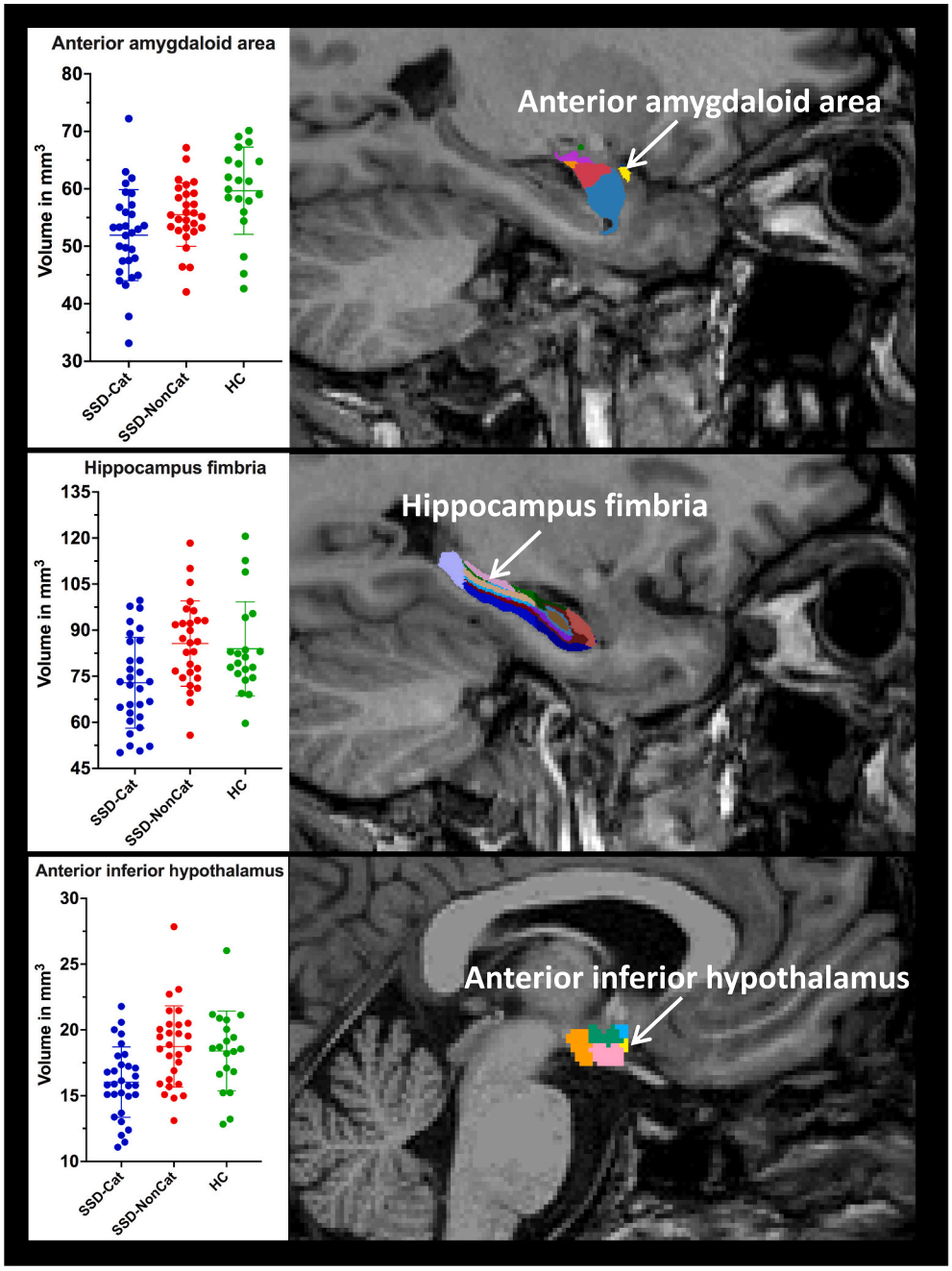

Fig. 1. Scatter plots showing anterior amygdaloid area, hippocampus fimbria and anterior inferior hypothalamus volumes in SSD patients with (SSD-Cat, n = 30) and without (SSD-nonCat, n = 28) catatonia and healthy controls (HC, n = 20).

nucleus volume ($p = 0.02$) and BPRS item #2 (Table 4) was identified. None of these structure-function associations survived Benjamini-Hochberg correction for multiple testing.

4. Discussion

This study explored alterations of specific amygdala-hippocampus complex and hypothalamus subregions underlying catatonic syndrome in SSD. Three main findings emerged: (1) SSD patients with catatonia had significantly smaller volumes of anterior inferior hypothalamus when compared to non-catatonic SSD patients. (2) SSD patients with catatonia had significantly smaller amygdala, hippocampus and hypothalamus volumes when compared to HC, with these differences not only affecting total volumes, but also specific subunits. (3) According to our dimensional approach, we detected associations between amygdala nuclei volumes and NCRS affective scores and BPRS item #2 (reflecting anxiety). However, these correlations did not survive correction for multiple comparisons and showed only trend level associations.

The first two findings implicate limbic structures in the pathogenesis of catatonia and are important for a number of reasons: First, catatonia has previously been associated with structural lesions in limbic regions (Ahuja, 2000). Second, autoimmune damage of limbic and extralimbic brain areas might also lead to schizophreniform and catatonic symptoms (Herken and Prüss, 2017). For instance, 70% of anti-NMDA receptor encephalitides show catatonic symptoms (Rogers et al., 2019). Third, a number of case reports have shown that there is a relationship between anxiety/fear and motor symptoms (Moskowitz, 2004). In particular, catatonic patients with severe anxiety tend to hardly move (e.g.

Table 3
Volumetric differences in schizophrenia spectrum disorder (SSD) patients with catatonia (SSD-Cat) and without catatonia (SSD-nonCat) revealed by Analysis of Covariance (ANCOVA) with PANSS total as covariate.

Amygdala volume	*p* value	
	PANSS	SSD-Cat vs. SSD-nonCAT
Total volume	0.727	0.263
Lateral nucleus	0.686	0.269
Basal nucleus	0.815	0.332
Accessory basal nucleus	0.887	0.232
Anterior amygdaloid area	0.313	0.248
Central nucleus	–	–
Medial nucleus	–	–
Cortical nucleus	0.688	0.101
Corticoamygdaloid trans.	–	–
Paralaminar nucleus	–	–

Hippocampus volume	*p* value	
	PANSS	SSD-Cat vs. SSD-nonCAT
Total volume	0.478	0.372
Hippocampal tail	0.322	0.668
Subiculum body	–	–
CA1 body	–	–
Subiculum head	–	–
Hippocampal fissure	–	–
Presubiculum head	0.838	0.135
CA1 head	–	–
Presubiculum body	–	–
Parasubiculum	–	–
Molecular layer head	0.717	0.265
Molecular layer body	–	–
GC.ML.DG. head	–	–
GC.ML.DG. body	–	–
CA4 head	–	–
CA4 body	–	–
Fimbria	0.327	0.020
CA3 head	–	–
CA3 body	–	–
HATA	–	–
Hippocampal body	–	–
Hippocampal head	–	–

Hypothalamus volume	*p* value	
	PANSS	SSD-Cat vs. SSD- nonCAT
Total volume	0.260	0.212
Anterior inferior	0.610	**0.002**
Anterior superior	–	–
Posterior	–	–
Inferior tubular	0.735	0.199
Superior tubular	–	–

Data are ANCOVA *p*-values.
Abbreviations: *Corticoamygdaloid trans.* corticoamygdaloid transition area. *PANSS* Positive and Negative Syndrome Scale.
p-Values were obtained using PANSS total score as covariate in ANCOVA. *p*-Values that survived Benjamini-Hochberg correction for multiple testing are highlighted in bold.

akinesia) or to stiffen completely (e.g. rigidity and flexibilitas cerea). In line with this, recent evidence showed that aberrant higher-order frontoparietal networks which, biochemically, are insufficiently modulated by gamma-aminobutyric acid (GABA)-ergic and glutamatergic transmission might lead to catatonic symptoms (Hirjak et al., 2020a; Northoff, 2000, 2002a, 2002b). Further, disturbances of frontoparietal networks may affect the subcortical structures (e.g., limbic structures and striatum), biochemically modulated by dopamine and lead to severe motor symptoms. Fourth, the fact that catatonic patients experience severe affective symptoms can be explained by failure to correctly interpret negative stimuli. It has been shown that patients with catatonia

Table 4
Structure-symptom association in schizophrenia spectrum disorder (SSD) patients with catatonia (dimensional approach, n = 44).

Amygdala volume	*p* values[a]				
	BPRS #2	NCRS affective	NCRS motor	NCRS behavior	NCRS total
Total volume	0.033[b]	n.s.	n.s.	n.s.	n.s.
Lateral nucleus	0.016[c]	n.s.	n.s.	n.s.	n.s.
Basal nucleus	0.034[d]	n.s.	n.s.	n.s.	n.s.
Accessory basal nucleus	0.040[e]	n.s.	n.s.	n.s.	n.s.
Anterior amygdaloid area	n.s.	n.s.	n.s.	n.s.	n.s.
Central nucleus	n.s.	n.s.	n.s.	n.s.	n.s.
Medial nucleus	n.s.	n.s.	n.s.	n.s.	n.s.
Cortical nucleus	n.s.	n.s.	n.s.	n.s.	n.s.
Corticoamygdaloid trans.	n.s.	n.s.	n.s.	n.s.	n.s.
Paralaminar nucleus	n.s.	n.s.	n.s.	n.s.	n.s.

Hippocampus volume	*p* values				
	BPRS #2	NCRS affective	NCRS motor	NCRS behavior	NCRS total
Total volume	n.s.	n.s.	n.s.	n.s.	n.s.
Hippocampal tail	n.s.	n.s.	n.s.	n.s.	n.s.
Subiculum body	n.s.	n.s.	n.s.	n.s.	n.s.
CA1 body	n.s.	n.s.	n.s.	n.s.	n.s.
Subiculum head	n.s.	n.s.	n.s.	**0.041**[f]	n.s.
Hippocampal fissure	n.s.	n.s.	n.s.	n.s.	n.s.
Presubiculum head	n.s.	n.s.	n.s.	n.s.	n.s.
CA1 head	n.s.	n.s.	n.s.	n.s.	n.s.
Presubiculum body	n.s.	n.s.	n.s.	n.s.	n.s.
Parasubiculum	n.s.	n.s.	n.s.	n.s.	n.s.
Molecular layer head	n.s.	n.s.	n.s.	n.s.	n.s.
Molecular layer body	n.s.	n.s.	n.s.	n.s.	n.s.
GC.ML.DG. head	n.s.	n.s.	n.s.	n.s.	n.s.
GC.ML.DG. body	n.s.	n.s.	n.s.	n.s.	n.s.
CA4 head	n.s.	n.s.	n.s.	n.s.	n.s.
CA4 body	n.s.	n.s.	n.s.	n.s.	n.s.
Fimbria	n.s.	n.s.	n.s.	n.s.	n.s.
CA3 head	n.s.	n.s.	n.s.	n.s.	n.s.
CA3 body	n.s.	n.s.	n.s.	n.s.	n.s.
HATA	n.s.	n.s.	n.s.	n.s.	n.s.
Hippocampal body	n.s.	n.s.	n.s.	n.s.	n.s.
Hippocampal head	n.s.	n.s.	n.s.	n.s.	n.s.

Hypothalamus volume	*p* values for ANCOVA				
	BPRS #2	NCRS affective	NCRS motor	NCRS behavior	NCRS total
Total volume	n.s.	n.s.	n.s.	n.s.	n.s.
Anterior inferior	n.s.	n.s.	n.s.	n.s.	n.s.
Anterior superior	n.s.	n.s.	n.s.	n.s.	n.s.
Posterior	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior tubular	n.s.	n.s.	n.s.	n.s.	n.s.
Superior tubular	n.s.	n.s.	n.s.	n.s.	n.s.

Data are multiple regression p-values.
Abbreviations: *Corticoamygdaloid trans.* corticoamygdaloid transition area, eTIV estimated total intracranial volume. n.s. = not significant.
For significant *p*-values, Pearson correlation coefficient (r) and 95% confidence interval of Pearson correlation coefficient r(95% CI) are also reported: [b][$r = 4.1 * 10^{1}$; 95% CI: $3.4 * 10^{0}$–$7.8 * 10^{1}$]; [c][$r = 1.9 * 10^{1}$; 95% CI: $3.8 * 10^{0}$–$3.4 * 10^{1}$]; [d][$r = 1.1 * 10^{1}$; 95% CI: $9.2 * 10^{-1}$–$2.2 * 10^{1}$]; [e][$r = 6.0 * 10^{0}$; 95% CI: $2.8 * 10^{-1}$–$1.2 * 10^{1}$]; [f][$r = -5.8 * 10^{0}$; 95% CI: $-1.1 * 10^{1}$ to $-2.6 * 10^{-1}$].

[a] p values were obtained using multiple correlation with Age, Sex, Education, medication, eTIV, PANSS total and SAS total as covariates.

are more vulnerable to stressful internal and external stimuli (Taylor et al., 2019). In addition, patients with catatonia often show strong negative affect (i.e. emotional fragility, depression, anxiety or sensitivity to stress) (Taylor et al., 2019). The clinical relevance of this is underlined by the fact that benzodiazepines (e.g. lorazepam and diazepam) - which mediate their effect by allosteric GABAergic modulation - are effective standard treatment options in catatonia. The almost immediate effect of benzodiazepines on affective and motor symptoms implicates the crucial role of the GABAergic system in the neurobiology of catatonia (Taylor et al., 2019). Several reasons support this notion: the outstanding and almost immediate effect of GABAergic agents (e.g. lorazepam or diazepam) is well-known, as much as it is known that such agents rapidly relieve affective symptoms (e.g. anxiety, fear) in catatonic patients (Northoff et al., 1995). In this context it is also noteworthy that the antipsychotic clozapine, possibly by its $GABA_B$-modulating properties (Nair et al., 2020), has been reported to improve catatonic symptoms of catatonia (Lander et al., 2018), even in patients with depression (Chattopadhyay et al., 2012), suggesting transdiagnostic anti-catatonic effects. However, the systematic review of Lander et al., 2018 (Lander et al., 2018) examined solely withdrawal catatonia, the majority of which occurred upon discontinuation of benzodiazepines (24 patients) or clozapine (20 patients). Furthermore, massive affective dysregulation manifests itself as a motor or behavioral symptomatology either in the sense that the patients become akinetic or hyperkinetic, and sometimes very impulsive and aggressive (Hirjak et al., 2020a). Intense affects such as fear and anxiety have been listed as triggers of absolute tonic immobility already in the historical literature by Karl Ludwig Kahlbaum (Moskowitz, 2004; Shorter and Fink, 2018). Another line of evidence pointing towards the involvement of limbic structures in the pathogenesis of catatonia is the association between autoimmune encephalitis and catatonic symptoms, to the point that catatonic signs in daily clinical care are considered warning signs of a possible underlying autoimmune etiology in first episode psychosis (Herken and Prüss, 2017; Rogers et al., 2019). Yet, finally, from an evolutionary perspective, it has been suggested that catatonia may represent a primitive response to fear, e.g. prolonged immobility as reaction to threats (Lander et al., 2018; Moskowitz, 2004; Perkins, 1982).

Such findings overlap with results implicating limbic structures in the pathogenesis of SSD: It has been shown that in SSD patients positive as well as neutral stimuli seem to coactivate hedonic and aversive emotions compared to control participants (Cohen and Minor, 2010). Furthermore, genome-wide association studies and analysis of copy number variants have hinted at GABAergic signaling alterations in SSD (Devor et al., 2017; Pocklington et al., 2015) and postmortem studies have shown abnormalities in GABAergic systems in SSD (Lewis et al., 2005), including hippocampus (Knable et al., 2004). The relevance of the limbic system in SSD is also underscored by factor analyses of rating scales such as PANSS, which have repeatedly shown the prevalence of anxiety and depression factors in schizophrenia (Kay and Sevy, 1990; Peralta and Cuesta, 1994) as well as by the fact that anxiety disorders such as social phobia or generalized anxiety disorder co-occur with SSD (Achim et al., 2011; Bermanzohn et al., 2000; Pallanti et al., 2004). Symptoms of anxiety might even be prominent during the prodromal phase or psychotic relapse, possibly representing a treatment target (Birchwood and Spencer, 2001). In addition, research on stress and affect also links schizophrenia to alterations in hypothalamic-pituitary-adrenal (HPA) axis. Baseline cortisol was reported to be increased in unmedicated schizophrenia participants (Girshkin et al., 2014) and cortisol was associated with anxiety and stress-intolerance in at-risk subjects (Karanikas and Garyfallos, 2015). The HPA axis, on the other hand, is modulated by hippocampus and amygdala (Ulrich-Lai and Herman, 2009). In this context it is also noteworthy that amygdala dysfunction has been described in SSD (Anticevic et al., 2012). Finally, the dexamethasone suppression test has been discussed as a diagnostic aid to identify underlying depression in catatonia (Greden and Carroll, 1979), because catatonic patients suffering from fear are often not able to speak about their symptoms.

Eventually, our findings also corroborate an earlier SPECT study by Ebert and colleagues (Ebert et al., 1992) that showed abnormal regional cerebral blood flow (rCBF) in the limbic system and hippocampus of two patients with catatonic syndrome compared to eight healthy and ten psychiatric controls. The authors postulated that temporal hypoperfusion might be caused by the loss of sensory input in catatonia (Ebert et al., 1992). Other whole-brain studies have found no correlations between catatonia and limbic structures, perhaps because they did not use the appropriate analysis tools to examine fine structures of the limbic system.

Our study for the first time implicated anterior inferior hypothalamus in the pathogenesis of catatonia in SSD. From a biological perspective, anterior inferior hypothalamus contains suprachiasmatic nucleus and supraoptic nucleus. Of these two, supraoptic nucleus seems particularly interesting since it produces –together with paraventricular nucleus- oxytocin and vasopressine, which have been implicated in the pathogenesis of SSD. Several lines of evidence point towards a role of these neuropeptides in schizophrenia: they seem to be able to modulate monoaminergic neurotransmitters such as dopamine and to play a role in neurogenesis (Rodríguez et al., 2020). Their role has not only been discussed in SSD but also in stress and anxiety, which represent prevalent features in catatonia (Cid-Jofré et al., 2021). Structural abnormalities of hypothalamus in schizophrenia have been described with conflicting results and an association with HPA axis abnormalities has been proposed (Bernstein et al., 2010). Furthermore, vasopressin mRNA expression in supraoptic nucleus has been reported as reduced, although the result was not statistically significant (Busch et al., 2019). Besides, the expression of the vasopressin- and oxytocin-degrading enzyme insulin-regulated aminopeptidase (IRAP) has been reported as reduced in suprachiasmatic nucleus (Bernstein et al., 2017). These findings have propelled the investigation of neuropeptides as a potential treatment target in schizophrenia.

Our study also contributes to the discussion of distinct amygdala nuclei volume reductions in SSD (Barth et al., 2021; Bell et al., 2022). Both Barth et al. (2021) and Bell et al. (2022) reported reduced volumes of amygdala nuclei in schizophrenia compared to healthy controls (Barth et al., 2021; Bell et al., 2022). Our results are in accordance with this as far as SSD-Cat are concerned, but the nominally reduced amygdala nuclei volumes in our SSD-nonCAT group were not statistically significant after correction for multiple testing. Apart from methodological differences between the studies such as 3 T measurement at one MRI site and application of the most up-to-date FreeSurfer version 7.2 in our study, we believe that our results complement and refine those results by showing different degrees of volume reduction in specific SSD subsets (SSD-Cat vs. SSD-nonCAT).

4.1. Limitations

Despite the strengths such as the inclusion of three groups (SSD-Cat, SSD-nonCAT and HC) and a novel segmentation algorithm provided by Freesurfer v7.2, this structural MRI study also has some potential limitations: First, due to the cross-sectional design, the present work cannot contribute to the ongoing discussion of state vs. trait markers in catatonia. Second, SSD itself have been related to brain atrophy in previous MRI studies of other groups (for review see Hirjak et al., 2020a, 2020b) and this may limit sensitivity of detecting atrophy due to catatonia. Further, we are aware of the substantial difference in the duration of illness between catatonic and non-catatonic patients. Although this difference did not meet statistical significance ($p = 0.087$), such differences can have a large effect in multivariable analyses. It is possible that they merely represent brain shrinkage related to more years of disease progress in the catatonic group. Still, after including duration of illness

as a covariate in the analysis, we found a significant between-group difference in the anterior inferior hypothalamus ($p = 0.003$) suggesting a crucial role of the hypothalamus in the pathogenesis of catatonia. Third, cumulative life-time medication might modulate structural alterations in amygdala, hypothalamus and hippocampus (Mamah et al., 2012; Velakoulis et al., 2006; Yang et al., 2021). Fourth, this study examined solely structural alterations of the amygdala, hippocampus, and hypothalamus and did not included other limbic areas. Since previous structural MRI studies used techniques that examined cortical limbic structures, but were unable to account sufficiently for the convoluted morphological relationships among amygdala, hypothalamus and hippocampus, the main goal of this study was to apply a recently available automatic segmentation method to specifically examine amygdala, hypothalamus, and hippocampus morphology in catatonia. Still, examination of the limbic structures is a methodological challenge because of the small size, unclear boundaries, and considerable anatomical variability of amygdala, hippocampus and hypothalamus subunits (Li et al., 2016). Fifth, numerous results, particularly structure-symptoms associations, did not survive correction for multiple testing, which could be due to insufficient statistical power associated with moderate group sizes, but also the large number of amygdala, hippocampus and hypothalamus subregions under investigation. Therefore, we strongly acknowledge transdiagnostic MRI studies on catatonic symptoms that also include MRI modalities such as T2-weighted images. Finally, although higher level of anxiety (as measured with BPRS item #2) may have led to an inflation of NCRS scores, anxiety is one of the central affective symptoms of catatonia. This is one of the reasons why Edward Shorter and Max Fink called catatonia as “Madness of Fear” (Shorter and Fink, 2018).

5. Conclusion

The data support a neuromechanistic model of catatonia that emphasizes a key role of distinct subcortical limbic structures involved in modulation of fear and anxiety. This study also underscores the potential of dimension- and domain-based characterization of SSD patients, an approach that is urgently needed given the clinical and neurobiological heterogeneity of schizophrenia spectrum syndromes. Such an approach is compatible with the RDoC initiative pioneered by the NIMH, as much as it is in line with the European tradition and Karl Ludwig Kahlbaum's original description of catatonia as psychomotor syndrome.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.05.003.

Role of the funding source

This work was supported by the German Research Foundation (DFG) (grant number DFG HI 1928/5-1 and 1928/6-1 to D.H., WO 1883/17-1 to R.C.W. and EB 187/8-1 to S.F.) and German Federal Ministry of Education and Research (BMBF; grant 01GQ1102 to H.T.). The DFG and BMBF had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

CRediT authorship contribution statement

DH, RCW and KMK: design of the study. DH and SF: data collection. SF, DH and KMK: data analysis. SF and DH: first draft of the manuscript. SF, DH, RCW, GAB, MMS, GN, LSG, HT and AML: interpretation of the results, discussion of the topic, writing and manuscript revision.

Declaration of competing interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgements

We are grateful to all participants and their families for their time and interest in the study.

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