The relationship between recent PTSD secondary to sexual assault, hippocampal volume and resting state functional connectivity in adolescent girls

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ABSTRACT

Objective: Improved understanding of the time course of neural changes associated with adolescent PTSD would elucidate the development of the disorder and could inform approaches to treatment. We compared hippocampal volumes and resting state functional connectivity (RSFC) in adolescent girls with post-traumatic stress disorder (PTSD) secondary to sexual assault, within six months of onset and age- and gender-matched, non-trauma exposed healthy controls (HCs) in São Paulo, Brazil. We also examined the relationship between pre- and post-treatment PTSD symptoms and RSFC.

Method: We collected brain structure, RSFC, and PTSD symptoms in 30 adolescents with PTSD (mean age: 15.7 ± 1.04 years) and 21 HCs (mean age: 16.2 ± 1.21 years) at baseline. We collected repeated measures in 21 participants with PTSD following treatment; 9 participants dropped out. Hippocampal volume and RSFC from hippocampal and default mode network (DMN) seeds were compared between participants with PTSD and HCs. We examined associations between within-subject changes in RSFC and PTSD symptoms following treatment.

Results: No hippocampal volumetric differences between groups were found. Compared to HCs, adolescents with recent PTSD had reduced RSFC between hippocampus and the lateral parietal node of the DMN, encompassing the angular gyrus, peak coordinates: −38, −54, 16; 116 voxels; peak F1,47 = 31.76; FDR corrected p = 0.038. Improvements in PTSD symptoms were associated with increased RSFC between hippocampus and part of the lateral parietal node of the DMN, peak coordinates: −38, −84, 38; 316 voxels; peak F1,47 = 40.28; FDR corrected p < 0.001.

Conclusion: Adolescents with recent PTSD had reduced hippocampal-DMN RSFC, while no group differences in hippocampal volume were found, suggesting that hippocampal function, but not structure, is altered early in the course of PTSD. Following treatment, hippocampal-DMN RSFC increased with symptom improvement and may indicate an important neural mechanism related to successful PTSD treatment.

1. Introduction

Sexual assault and post-traumatic stress disorder (PTSD) are prevalent mental health issues for children and adolescents that can have long-lasting effects. Globally, 18.0–19.7% of girls, and 7.4%–7.6% of boys report sexual abuse according to survey research (Pereda et al., 2009; Stoltenborgh et al., 2011). Prevalence rates of sexual assault among adolescent girls are high in Brazil, making the study of PTSD among adolescent girls important in this country. For example, in May 2020 the Brazilian Ministry of Women, Family and Human Rights estimated that in Brazil, 25–33% of girls would become victims of sexual abuse or exploitation before the age of 18, based on 2018–2019 data (Brazilian Ministry of Women, 2020). Furthermore, the urgency of this issue is increasing: according to the United Nations Children’s Fund

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Across childhood, rates of sexual assault peak during adolescence. For example, in Brazil, sexual assault prevalence rates for girls peak between age 15 and 19 and constitute 93.8% of all cases for girls (Waiselfisz, 2012). Furthermore, a meta-analysis found that rates of PTSD in trauma-exposed children and adolescents are higher for interpersonal trauma, such as assault, than for non-interpersonal trauma, such as natural disaster (Alisic et al., 2014). Consistent with this result, this meta-analysis also found that girls exposed to interpersonal trauma have the highest rates of PTSD among any pediatric group (Alisic et al., 2014). Due to the high prevalence rates of sexual assault and PTSD for adolescent girls in Brazil, and the potential for severe and long-lasting effects, it is vital to learn about the neural correlates of PTSD in this group, as well as treatment-related changes. Furthermore, it is currently unknown how PTSD treatment alters the brain in adolescents. Therefore, improved understanding of the time course of neural changes associated with adolescent PTSD and a mechanistic understanding of how and when current PTSD treatments work may lead to future improvements in intervention protocols.

Trauma exposure and PTSD during childhood/adolescence can lead to brain changes observable during adulthood. For example, meta-analyses have found that childhood maltreatment exposure is associated with reduced hippocampal volume in adults (Paquola et al., 2016; Riem et al., 2015), similar to findings that PTSD is associated with reduced hippocampal volume in adulthood (Nelson and Tumpap, 2017). While an earlier study suggested that smaller hippocampal volume may be related to genetic factors and constitute a risk factor for PTSD (Gilbertson et al., 2002), more recent research aiming to separate genetic and environmental effects on hippocampal volume in PTSD determined that the environment contributes more than genetic factors to smaller hippocampal volume (Bremner et al., 2021).

The hippocampus has been an important region of interest in PTSD research for many years. In addition to evidence pointing to smaller hippocampi in adults with PTSD, the hippocampus plays a key role in memory, a function related to symptoms unique to PTSD, such as re-experiencing (Desmedt et al., 2015; Joshi et al., 2020). For example, the hippocampus has been found to be critically involved in episodic memory (Eichenbaum, 2004), autobiographical memory (Cabeza and St Jacques, 2007), fear learning (Lovett-Barron et al., 2014; Sanders et al., 2003) and fear extinction (Ji and Maren, 2007; Radulovic and Tronson, 2010), functions that have been shown to be impacted by PTSD (Joshi et al., 2020; Kunimatsu et al., 2020; Stevens et al., 2018; Thome et al., 2020; Zuj and Norrholm, 2019).

While the literature examining the association between PTSD and reductions in hippocampal volumes has been fairly consistent in adults, results concerning PTSD-related reductions in hippocampal volume in pediatric samples has been mixed, with some studies finding an association between PTSD and hippocampal size (Carrion et al., 2007; Keding and Herringa, 2016; Morey et al., 2016; Tulper and De Bellis, 2006), and others finding none (Ahmed et al., 2012; Carrion et al., 2001; De Bellis et al., 2002). If hippocampal volume changes related to stress or PTSD take time to develop (Sapolsky et al., 2000), this may explain the mixed findings in the pediatric literature and the resulting discrepancy between the results in adult and pediatric studies. A recent meta-analysis aiming to elucidate the mixed results in the pediatric PTSD literature aimed that children with PTSD had smaller hippocampal volume than peers without PTSD (Kribakaran et al., 2020), suggesting that with enough data, PTSD-related hippocampal volume changes in children can be observed, consistent with results in adults.

These results are corroborated by animal research. Rodent studies examining the impact of stress on neural structure have similarly found that stress leads to hypotrophy of hippocampal dentrites (Henckens et al., 2015; Sousa et al., 2000) and hippocampal volume reduction (Golub et al., 2011; Lee et al., 2009). Stress-induced dendritic hypotrophy could be associated with reductions in hippocampal connectivity, and stress-driven reductions in dendritic complexity in rodents have been suggested as a possible mechanism for the reductions in hippocampal volume observed in participants with PTSD (Fenster et al., 2018). Consistent with rodent studies finding hippocampal dendritic hypotrophy following stress exposure, human studies of hippocampal function, via functional magnetic resonance imaging (fMRI), have found reduced hippocampal resting state functional connectivity (RSFC) in PTSD (Bao et al., 2021; Koch et al., 2016; Miller et al., 2017; Sheynin et al., 2020; Viard et al., 2019).

The DMN is a large-scale network of intrinsically connected brain regions that is altered in a wide range of psychiatric disorders and is associated with self-referential cognitive activity (Frewen et al., 2011; Menon, 2011). RSFC metrics of the DMN have been found to have excellent test-retest reproducibility, making it an ideal target for investigations into the mechanisms underlying PTSD and treatment-based recovery (Mak et al., 2017). Self-referential cognitive processing is altered in women with PTSD such that individuals with PTSD endorse more negative and fewer positive self-descriptive adjectives (Frewen et al., 2011); therefore, it is not surprising that altered DMN connectivity has also been found in PTSD (Viard et al., 2019). More specifically, both adults and adolescents with PTSD have been found to have reduced RSFC between nodes of the DMN in which the hippocampus can be included (Bao et al., 2021; Koch et al., 2016; Miller et al., 2017; Sheynin et al., 2020; Viard et al., 2019). Furthermore, reduced connectivity between hippocampus and DMN nodes has been found to relate to PTSD symptoms: in adolescents with PTSD, increased symptom severity has been associated with reduced RSFC between the hippocampus and the posterior cingulate cortex, another node of the DMN (Sheynin et al., 2020; Viard et al., 2019). Given previous findings in animal models suggesting that PTSD-related dendritic hypotrophy reduces hippocampal connectivity, a reduction in connectivity could reflect underlying dendritic hypotrophy and eventually, hippocampal volume reduction.

Improved understanding of the time course of neural changes associated with adolescent PTSD would elucidate the development of the disorder and could inform approaches to treatment. For example, if differences in neural functional connectivity emerge before structural changes, it may be possible that treatment could be more effective in this earlier time frame before structural changes become observable. This would suggest that increased attention to early treatment is warranted to prevent subsequent neural sequelae of PTSD. Furthermore, a better understanding of the timing of PTSD-related neural changes could suggest new areas of inquiry, such as comparing treatment outcomes within the time frames before and after structural changes emerge, or examining the relative timing of neural changes in different groups, e.g. in adults and older adults compared to adolescents.

To examine if PTSD-related changes in connectivity precede changes in hippocampal volume in adolescents, it is necessary to examine RSFC and hippocampal volume close to the onset of the disorder. Therefore, the present study explores hippocampal volume and seed-based RSFC in 30 adolescent girls with PTSD secondary to sexual assault, within six months of the assault, and 21 healthy age-matched healthy controls (HCs). In addition, participants with PTSD were assessed again for clinical symptoms and RSFC following treatment. Participants with PTSD were either provided individual interpersonal therapy (IPT) (Markowitz et al., 2015), group IPT (Campanini et al., 2010) or Sand Play (Roelers, 2019). Examining neural correlates of treatment across different treatment types should provide results that are more generalizable.

Consistent with the previous literature, we hypothesized that, compared to HCs, participants with PTSD would have reduced within-DMN connectivity, particularly between the hippocampus and other DMN nodes. Since stress-related dendritic hypotrophy in the hippocampus has been theorized to gradually lead to reductions in hippocampal volume, and since the participants with PTSD were assessed within 6 months of sexual assault, we hypothesized that we would not
find differences in total hippocampal volume between participants with PTSD and HCs at baseline. In addition, given that symptom severity has been previously found to relate to reductions in hippocampal connectivity (Viard et al., 2019), and since PTSD treatment has been found to increase DMN connectivity in adults (Zhu et al., 2018), we hypothesized that symptom improvement would be associated with increased hippocampal-DMN connectivity. To our knowledge, this is the first study to examine the effects of treatment on RSFC in adolescent PTSD.

2. Method

2.1. Participants

Thirty adolescent girls who met DSM-5 criteria for PTSD resulting from sexual assault within the previous six months (mean age: 15.7 ± 1.04 years) were recruited from the Perola Byington Hospital. Twenty-one non-trauma exposed, age-matched female HCs (mean age: 16.2 ± 1.21 years) were recruited from the hospital’s adolescent outpatient medical clinic. Demographic variables are in Table 1. Between group differences in demographic variables were assessed via independent samples t-test or chi square tests and p values for these analyses are provided in Table 1. Parents provided informed consent and adolescents provided assent. All procedures were approved by the Institutional Review Board of the Universidade Federal de São Paulo.

Inclusion criteria for the PTSD group were: 1) PTSD due to sexual assault diagnosed within the last six months via Kiddie Schedule for Affective Disorders and Schizophrenia, present and lifetime version (K-SADS-PL); and 2) aged between 14 and 17. The exclusion criteria were: 1) a diagnosis of a psychotic, bipolar, or obsessive-compulsive disorder, prior or subsequent to the sexual assault via the K-SADS-PL; 2) a diagnosis of PTSD due to a trauma-type other than sexual assault via the KSADS and/or CAPS, 3) serious medical condition or IQ < 70 on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011); 4) past six-month substance use disorder, assessed via the KSADS; and 5) pregnancy.

The inclusion criteria for the healthy control subjects were: 1) no current or past psychiatric diagnosis (K-SADS-PL); 2) no trauma exposure, as assessed via responses on the K-SADS-PL, the Childhood Trauma Questionnaire and open ended questions about other traumatic experiences including exposure to violence 3) aged between 14 and 17. MRI contraindication and being male were exclusionary for both groups. All participants were post-menarche to provide relative balance of pubertal development.

2.2. Measures

PTSD symptoms were assessed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS) (Weathers et al., 2018) before and after treatment. Total scores, as well as scores for each of the four symptom clusters (reexperiencing, CAPS-B; avoidance, CAPS-C; negative mood and cognitions, CAPS-D; and arousal and reactivity, CAPS-E) were used as regressors of interest in RSFC analyses. The K-SADS-PL and a demographic questionnaire were collected at baseline to assess diagnosis, and collect demographic data, respectively. Handedness was assessed via the Edinburgh Handedness Inventory (Ransil and Schachter, 1994), and is reported in Table 1.

2.3. Clinical interventions

Participants with PTSD were randomly assigned to interpersonal therapy (IPT; n = 16) (Markowitz et al., 2015) or Sandplay Therapy (SPT; n = 14) (Roesler, 2019). Initially, the study planned to provide group IPT (n = 5) (Campanini et al., 2010), which participants reported preferring. However, due to feasibility issues, including clinician reluctance to keep on patients waiting for groups to form before starting treatment, individual IPT (Markowitz et al., 2015) was subsequently provided (n = 11).

IPT, originally developed to treat depression, has been successfully adapted to PTSD (Markowitz et al., 2015), and current work is testing a group-based adolescent adaptation of IPT for PTSD. IPT for PTSD conceptualizes PTSD as a disorder strongly influenced by interpersonal variables and concentrates on improving symptoms by fostering positive changes in current interpersonal encounters (Markowitz et al., 2015). Treatment emphasizes recognition and expression of emotions, as well as navigating role disputes and role transitions (Markowitz et al., 2015). IPT for PTSD has been found to have greater efficacy for sexually traumatized patients with PTSD than prolonged exposure therapy (PE) or relaxation therapy and may be particularly useful due to its focus on interpersonal relationships (Markowitz et al., 2017). Individual IPT for PTSD treatment in the current study started with a family psycho-educational session, about PTSD and treatment, followed by 12, 60-min sessions, and ended with a second family psychodidactic session. During this 12th session, a summary of the treatment was provided. When providers determined that continued treatment could be helpful, participants with PTSD and their families were offered continued psychiatric treatment provided by a study psychiatrist. When the patient or family sought continued psychotherapy, referrals to free, city-based therapists were provided.

Group treatment for PTSD has been theorized to reduce feelings of isolation and stigma in individuals who have been sexually assaulted and has been shown to be an effective treatment for women with PTSD (Krupnick et al., 2008; Zlotnick et al., 1997). Group IPT for PTSD also started with a family session covering psychodidactic about PTSD and treatment was provided. Group IPT was then provided for 12 weeks, in 90-min sessions (Campanini et al., 2010), following the same principals described above for individual IPT. In addition, 2 individual check-in
sessions were conducted with each patient, half-way through and at the end of treatment. In these sessions, the symptoms of the participants with PTSD were monitored and psychoeducation for the family was provided as necessary.

Sandplay therapy (SPT) is a non-verbal psychotherapeutic technique that consists of the creation of scenarios by participants with PTSD through the use of sand, water and miniature figures and objects in a tray (Roessler, 2019). The scenarios are theorized to assist the patient in the process of understanding their psychic dynamics (Roessler, 2019). The effectiveness of SPT for PTSD has largely been studied outside of the US and Europe, and has been found to reduce PTSD symptoms in children and adults (Hwang, 2017; Jang et al., 2019; Kim, 2017). SPT has been used as an alternative approach to treating PTSD in victims of sexual assault because some individuals with PTSD are reluctant or unable to talk about trauma-related subjects with the therapist, and SPT does not require individuals to talk about trauma-related matters. SPT sessions were preceded by a session of psychoeducation providing information about the disorder and treatment. Similar to the IPT treatment, SPT was provided for 12, 60-min sessions. At the end of treatment, a psychoeducation session was provided for the family. In the case that providers determined that continued treatment could be helpful, during this session, patients with PTSD and their families were offered continued psychiatric treatment, provided by a study psychiatrist. When the patient or family sought continued psychotherapy, referrals to free, city-based therapists were provided. If no additional treatment was indicated, a summary of the treatment was provided.

2.4. MRI data acquisition

A high-resolution anatomical T1-weighted image was acquired from each participant for hippocampal volumetric analyses and to aid with registration of RSFC data. The structural sequence was: 3D T1 scan (repetition time [TR] = 2500 ms, echo time [TE] = 3.1 ms, inversion time = 900 ms, field of view [FOV] = 240 × 240 × 180 mm³, matrix size = 256 × 256 × 150, slice thickness = 1.2 mm, flip angle = 9°).

RSFC data was acquired while participants rested with eyes open while viewing a black fixation point presented on a white background (1 run; 10 m, 6s) with a 3 T Phillips Achieva (isotropic resolution 3 × 3 × 3 mm³, TR = 2.5 s, TE = 30 ms, 300 vol, ascending slice order) in 32 channel head coil. Before the resting state data were acquired the following sequences were acquired: Localizer, Coronal T2, Axial T2, axial FLAIR, DTI, multivoxel spectroscopy.

2.5. Structural preprocessing

Structural MRI data were processed using FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu). Standard preprocessing steps, via ‘recon-all’ were applied to T1 weighted images including head motion correction, skull stripping, Talairach space transformation, segmentation of subcortical while matter regions and deep gray matter nuclei, signal intensity normalization and surface deformation based on intensity gradients. Total hippocampal volume were estimated for each hemisphere. In addition to the automated quality control process embedded within FreeSurfer 6.0. all segmented scans were visually inspected, and participants were excluded if they failed to meet segmentation standards. Hippocampi from one PTSD participant and two HC participants were excluded from analyses due to erroneous hippocampal segmentation.

2.6. fMRI preprocessing

Standard image preprocessing was performed using CONN toolbox version 17 via SPM 12 for functional connectivity analysis (Whitfield-Gabrieli and Nieto-Castanon, 2012). Slice timing correction was applied. Volumes were realigned, then co-registered with a high-resolution anatomical scan, and normalized into Montreal Neurological Institute (MNI) space, resampled at two mm. Images were smoothed with a Gaussian kernel of eight mm full width at half maximum (FWHM). To minimize the influence of non-neural contributors to the fMRI signal, the BOLD time-series was regressed against 1) five orthogonal time series extracted from white matter and cerebrospinal fluid separately using CompCor (component-based noise correction) methods and 2) 12 motion-related regressors (six estimated motion parameters plus their 1st -order derivatives from the rigid realignment preprocessing step in SPM). BOLD signal was also “scrubbed” by identifying and removing volumes (and the adjacent, neighboring volumes) with frame wise displacement (FD) > 0.5 mm or global signal intensity changes >3 SD estimated using the artifact detection tool (ART; www.nitrc.org/projects/artifact_detect). One participant was excluded from Time 1 and Time 2 analyses, since more than 20.0% of volumes were scrubbed from her Time 1 data, leaving a total of 29 participants with PTSD and 21 HCs. In Time 2 analyses, an additional participant was excluded due to more than 20.0% of volumes being scrubbed from her Time 2 data, leaving a total of 19 participants with PTSD analyzed in Time 2 analyses. Other signal processing in the pipeline included temporal band-pass filtering (0.008-0.09 Hz) and linear detrending.

2.7. Structural data analysis

To control for whole hippocampal volumes for total intracranial volume before performing between-group analyses, we divided each individual’s left and right whole hippocampal volume by her total intracranial volume, and used this value in subsequent analysis. To determine if there are hippocampal volume differences between participants with PTSD and HCs within 6 months of trauma exposure, we compared the proportion of the whole hippocampal volume to total intracranial volume between groups via a regression while controlling for IQ, with separate analyses for left and right whole hippocampi.

2.8. fMRI data analysis

RSFC analyses used a total of 7 seeds. Seeds in the bilateral hippocampus (seeds 1 & 2) from the AAL atlas (Tzourio-Mazoyer et al., 2002) and the DMN seeds from CONN’s network atlas (Whitfield-Gabrieli and Nieto-Castanon, 2012): the medial prefrontal cortex (mPFC; seed 3), left and right lateral parietal (seeds 4 & 5) and posterior cingulate cortex (PCC; seeds 6 & 7) regions were used to examine RSFC. Differences in connectivity between the chosen seeds and other brain areas were examined using a whole-brain voxel-wise threshold of p < 0.001, with a cluster-size FDR corrected threshold of p < 0.05, two-sided. Brain regions included in specific clusters were identified using automated anatomical labeling in xjview (http://www.alivelearn.net/xjview/).

At Time 1, differences in RSFC between participants with PTSD and HCs were examined via one-way ANCOVA, using IQ as a covariate, since IQ has been shown to impact functional connectivity (Ezaki, dos Reis, Watanabe, Sakaki and Masuda, 2020; Pezoulas et al., 2017). IQ was measured by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011) (Table 1). Results were considered significant if the cluster size met FDR correction of p < 0.05, two-sided, to correct for multiple comparisons.

Since the research question probed the relationship between symptom change and RSFC, and not the impact of different treatment types, data from across the three treatment groups was combined. In participants with PTSD, within-subject changes in RSFC were examined via a general linear model analysis with the change in clinical symptoms, measured via changes in CAPS-5 (Weathers et al., 2018) scores and sub-scale scores, predicting change in RSFC before and after PTSD treatment. RSFC maps were created using hippocampal and DMN seeds. The relationship between within-subject changes in brain connectivity in participants with PTSD between Time 1 and Time 2 and change in 1) total CAPS-5 score, 2) reexperiencing symptoms cluster score (CAPS-B), 3) avoidance and numbing symptoms cluster score (CAPS-C), 4)
negative mood and cognitions symptoms cluster score (CAPS-D), and 5) hyperarousal symptoms cluster score (CAPS-E) were examined in CONN. Results were considered significant if the cluster size met FDR correction of \( p < 0.05 \), two-sided, to correct for multiple comparisons.

3. Results

3.1. PTSD symptoms

Of the 30 participants with PTSD who participated at Time 1, 21

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### Table 2

PTSD- and symptom change-related alterations in resting state functional connectivity.

| Analysis | Seed | MNI Peak | Cluster Size (Voxels) | Peak Level \( p \) | Connectivity with Other Areas | AAL Regions | Direction of Change |
|----------|------|----------|-----------------------|-----------------|--------------------------------|-------------|---------------------|
| PTSD vs HC at T1 | R. Hippocampus | –38, –54, 16 | 116 | 31.76 | L. Angular Gyrus | Decreased in PTSD |
| | R. Lateral Parietal DMN node | –16, –74, –4 | 2511 | 31.07 | Bilateral Lingual Gyrus, Occipital Fusiform Gyrus, Occipital Pole, Bilateral Intracalcarine Cortex, Cuneal Cortex, R. Supracalcarine Cortex | Increased in PTSD |
| | | –2, 36, 22 | 733 | 22.87 | Bilateral Paracingulate Cortex, Anterior Cingulate Gyrus, Bilateral Frontal Pole, Bilateral Superior Frontal Gyrus | Increased in PTSD |
| | | –32, 22, 16 | 114 | 21.36 | L. Frontal Orbital Cortex | Increased in PTSD |
| | | –6, 20, 62 | 101 | 19.45 | L. Superior Frontal Gyrus | Increased in PTSD |
| | | –16, –92, 18 | 605 | 24.51 | R. Occipital Pole, R. Lateral Occipital Cortex, R. Cuneal Cortex | Increased in PTSD |
| | | –14, –94, 18 | 588 | 29.55 | L. Occipital Pole, L. Lateral Occipital Cortex, L. Cuneal Cortex | Increased in PTSD |
| | | –52, 38, 18 | 210 | 26.74 | L. Inferior Frontal Gyrus, L. Frontal Pole, L. Middle Frontal Gyrus | Increased in PTSD |
| | | –14, –74, –6 | 103 | 17.38 | L. Lingual Gyrus | Increased in PTSD |
| Change in Total CAPS score (T2 vs T1) | R. Hippocampus | –40, –62, 18 | 375 | 41.05 | L. Lateral Occipital Cortex, L. Angular Gyrus | Increased at T2 |
| | | –54, 16, 20 | 154 | 29.39 | L. Inferior Frontal Gyrus | Increased at T2 |
| | | –50, –70, 22 | 108 | 28.63 | R. Lateral Occipital Cortex | Increased at T2 |
| | | –30, –18, –22 | 122 | 55.31 | R. Hippocampus | Increased at T2 |
| | | –52, 4, –20, 18 | 82 | 30.01 | R. Temporal Pole, R. Superior Temporal Gyrus | Increased at T2 |
| | | –32, 26, 18 | 72 | 50.77 | L. Insula | Decreased at T2 |
| Change in Re-experiencing (CAPS-R; T2 vs T1) | L. Hippocampus | –22, 58, 28 | 111 | 30.15 | L. Frontal Pole | Increased at T2 |
| | | –68, –42, –14 | 233 | 64.99 | R. Middle Temporal Gyrus, Inferior Temporal Gyrus | Decreased at T2 |
| | | –22, –22, –18 | 166 | 35.47 | L. Hippocampus, L. Parahippocampal Gyrus | Increased at T2 |
| | | | | | R. Hippocampus | Increased at T2 |
| | | –68, –46, –14 | 123 | 35.99 | R. Middle Temporal Gyrus | Decreased at T2 |
| | | –30, –76, 10 | 110 | 34.14 | L. Lateral Occipital Cortex, L. Occipital Pole | Decreased at T2 |
| Change in Avoidance (CAPS-C; T2 vs T1) | R. Hippocampus | 0, –42, 40 | 168 | 28.78 | Posterior Cingulate Gyrus, Precuneus Cortex | Increased at T2 |
| | | –32, –20, –50 | 102 | 25.46 | L. Precentral Gyrus | Decreased at T2 |
| | | –62, –48, –14 | 108 | 36.63 | R. Inferior Temporal Gyrus, R. Middle Temporal Gyrus | Decreased at T2 |
| | | –66, 48, 82 | 110 | 32.20 | L. Inferior Temporal Gyrus, L. Middle Temporal Gyrus | Decreased at T2 |
| Change in Negative Mood & Cognitions (CAPS-D; T2 vs T1) | R. Hippocampus | –38, –64, 18 | 105 | 40.01 | L. Lateral Occipital Cortex, L. Angular Gyrus | Increased at T2 |
| | | –34, –32, 72 | 98 | 23.43 | R. Postcentral Gyrus | Decreased at T2 |
| | | –50, –70, 20 | 97 | 34.14 | R. Lateral Occipital Cortex | Increased at T2 |
| | | –42, –78, 32 | 82 | 25.51 | L. Lateral Occipital Cortex | Increased at T2 |
| Change in Arousal Reactivity (CAPS-E; T2 vs T1) | R. Hippocampus | –36, –66, –8 | 400 | 60.69 | L. Lateral Occipital Cortex, L. Angular Gyrus | Increased at T2 |
| | | –48, 14, 28 | 135 | 28.81 | L. Inferior Frontal Gyrus, L. Middle Frontal Gyrus, L. Precentral Gyrus | Increased at T2 |
| | | –50, –68, 24 | 111 | 35.54 | R. Lateral Occipital Cortex | Increased at T2 |

Notes: Results were found using a whole-brain voxel-wise threshold of \( p < 0.001 \), controlling for IQ, with a cluster-size FDR corrected threshold at \( p < 0.05 \), 2-sided.  
\( a \) Indicates a hippocampal/DMN node connection.
completed treatment and returned for a Time 2 assessment. Seven subjects dropped out of the study. More specifically, 2 participants stopped attending therapy sessions and did not respond to outreach, 1 participant missed 4 consecutive therapy sessions, 1 participant completed all therapy sessions, but did not come in for her final follow-up study assessment, 1 participant became actively suicidal and no longer met inclusion criteria for the follow up portion of the study, 1 participant’s PTSD symptoms resolved, and she stopped attending therapy subsequently, and 1 stopped participating due to COVID infection. In addition, 2 participants moved away during the course of the study, one due to being stalked by the perpetrator of her assault. Participants with PTSD who completed individual or group IPT no longer met PTSD criteria following treatment. All participants with PTSD who completed SPT also improved clinically, and no longer met criteria for PTSD, except for 1 participant, whose symptoms increased from Time 1 to Time 2. Comparing CAPS change scores for participants who received IPT vs SPT via an independent samples t-test did not reveal a significant difference between groups: \( t(19) = 1.26, p = 0.22 \). Similarly, no between treatment difference on the CAPS subscales was found: CAPS B, \( t(19) = 0.22, p = 0.80 \); CAPS C, \( t(19) = 0.73, p = 0.47 \); CAPS D, \( t(19) = 1.33, p = 0.19 \); CAPS E, \( t(19) = 1.05, p = 0.30 \). A 20-point reduction on the CAPS is considered clinically meaningful (Monson et al., 2008). The average reduction in CAPS score across all participants with PTSD was 32.5 ± 20.8 (Table 1). Excluding the SPT participant whose symptoms worsened over the course of the study, the mean reduction in CAPS score across all participants was 35.8 ± 14.9.

### 3.2. MRI results: hippocampal volume

Three participants, one PTSD, two healthy controls, were excluded from analyses, due to errors in hippocampal segmentation. Linear regression was used to test if group membership (PTSD vs HCs) and IQ predicted hippocampal volume divided by total intracranial volume. At T1, while controlling for IQ, no differences were found between PTSD and HC participants in whole hippocampal volume divided by total intracranial volume via regression analyses. For the left hippocampus, the regression was not significant, \( F(2, 46) = 0.95, p = 0.39 \), and the effect of group was also not significant, \( \beta = -0.10, p = 0.49 \). Similarly, for the right hippocampus, the regression was not significant, \( F(2, 46) = 1.01, p = 0.37 \), and the effect of group was also not significant, \( \beta = 0.04, p = 0.80 \). Due to the lack of significant results no corrections for multiple comparisons were performed.

### 3.3. fMRI results: seed-based connectivity

At T1, compared with HCs and while controlling for IQ via one-way ANCOVA, participants with PTSD had decreased connectivity between the right hippocampus seed and a cluster in the lateral parietal node of

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**Fig. 1.** A) Participants with PTSD has reduced connectivity between the right hippocampus seed and left angular gyrus (a key node of the DMN), compared to controls. B & C) As total PTSD symptoms improved, connectivity between right hippocampus and left angular gyrus increased. C. Symptom-related increases in connectivity from the right hippocampus seed to the left angular gyrus were also found for negative moods and cognitions (Panel D; CAPS D), and arousal and reactivity (Panel E; CAPS E).
the DMN, encompassing the left angular gyrus (peak coordinates: \(-38, -54, 16\); 116 voxels; peak \(F_{1,47} = 31.76; FDR\) corrected \(p < 0.038\); Table 2; Fig. 1). The results reported in this section focus on the hypothesized hippocampus-DMN connectivity. Additional results are reported in Table 2. For example, participants with PTSD had increased connectivity between nodes of the DMN (left lateral parietal and PCC) and occipital and frontal regions.

To ensure that results weren’t influenced by left-handed (\(n = 2\)) or ambidextrous participants (\(n = 2\)), analyses comparing PTSD participants with HC at T1 were all run right-handed participants only. Results were largely consistent with results including all participants, although notably, the increased connectivity for HC between the right hippocampus seed and a cluster in the lateral parietal node of the DMN, encompassing the left angular gyrus, was no longer significant at an FDR corrected \(p < 0.05\). Results are reported in Supplementary Table 1.

Examining the effect of within-subject improvements in PTSD symptoms on RSFC between Time 1 and Time 2 via general linear model analysis, we found that as the total CAPS score decreased, the connectivity between the right hippocampus seed and left angular gyrus increased (peak coordinates: \(-40, -62, 18\); 375 voxels; peak \(F_{1,17} = 41.05; FDR\) corrected \(p < 0.001\); Table 2; Fig. 1). Between Time 1 and Time 2, increased connectivity was also found between the left lateral parietal DMN seed and the right hippocampus (peak coordinates: \(30, -18, -22\); 122 voxels; peak \(F_{1,17} = 55.31; FDR\) corrected \(p = 0.015\)). Consistent with these results, decreases in re-experiencing symptoms (CAPS-B) were associated with increased connectivity between the left lateral parietal DMN seed and the left hippocampus (peak coordinates: \(-22, -22, -18\); 166 voxels; peak \(F_{1,17} = 35.47; FDR\) corrected \(p < 0.001\)). Furthermore, decreases in both negative mood and cognitions (CAPS-D) and arousal and reactivity (CAPS-E) were associated with increased connectivity between the right hippocampus seed and left angular gyrus (peak coordinates: \(-38, -64, 18\); 105 voxels; peak \(F_{1,17} = 40.01; FDR\) corrected \(p = 0.011\); CAPS-E: peak coordinates: \(-36, -66, 28\); 400 voxels; peak \(F_{1,17} = 60.69; FDR\) corrected \(p < 0.001\)). Improvements in avoidance symptoms (CAPS-C) were associated with increased connectivity between the right hippocampus and the posterior cingulate gyrus (peak coordinates: \(0, -42, 40\); 168 voxels; peak \(F_{1,17} = 28.78; FDR\) corrected \(p < 0.024\)). Additional RSFC results are reported in Table 2.

4. Discussion

We collected structural brain and RSFC data in adolescent girls with PTSD secondary to sexual assault occurring within the previous six months, and age- and gender-matched HC participants with no history of trauma. We found no differences in total hippocampal volume when comparing participants with PTSD with age- and gender-matched non-trauma exposed HCs. We found that girls with PTSD had decreased within DMN connectivity, consistent with previous studies examining RSFC in PTSD in adults (Koch et al., 2016; Miller et al., 2017; Sheynin et al., 2020), including a meta-analysis (Bao et al., 2021), and studies examining RSFC in adolescents with and without PTSD (Sheynin et al., 2020; Viard et al., 2019). More specifically, we found PTSD-related decreased connectivity between hippocampus and angular gyrus, a region encompassed by the lateral parietal node of the DMN, compared to HCs (Table 2; Fig. 1). These results are consistent with previous studies of RSFC in PTSD finding reduced hippocampus-lateral parietal connectivity (Chen and Etkin, 2013; Lazarov et al., 2017). Furthermore, previous research has reported decreases in hippocampus-lateral parietal connectivity in females but not in males (Halpern et al., 2021), highlighting the importance of examining PTSD-related differences in RSFC in one gender at a time. Finding differences in hippocampal RSFC, but not hippocampal volume is consistent with results from the preclinical literature showing that stress leads to hypotrophy of hippocampal dendrites (Henckens et al., 2015; Sousa et al., 2000), and suggests that PTSD-related reductions in hippocampal connectivity may precede reductions in hippocampal volume, as has been theorized in the preclinical literature (Fenster et al., 2018).

For participants with PTSD who were scanned a second time following PTSD treatment, symptom improvement on the CAPS-S was associated with increased RSFC between the hippocampus, used as the seed in analysis, and angular gyrus, a part of the lateral parietal node of the DMN and the same connection found to be reduced in girls with PTSD prior to treatment. These results suggest that as PTSD symptoms improve, hippocampal-DMN connectivity begins to normalize (see Table 1 and Fig. 1). Increased connectivity between the hippocampus and the angular gyrus was also found to relate to improvements in certain symptom clusters including negative moods and cognitions (CAPS-D), and arousal and reactivity (CAPS-E). In addition, using the lateral parietal seed of the DMN, which includes the angular gyrus, improvements in re-experiencing symptoms (CAPS-B) were associated with increased connectivity with the hippocampus. Thus, PTSD-related decreased connectivity between the hippocampus and other regions of the DMN, and treatment-related increases in connectivity may be more strongly associated with some symptom clusters than others.

The connection between the hippocampus and the lateral node of the DMN, encompassing the angular gyrus, was weaker in girls with PTSD than in HC, and increased with symptom improvement overall. More specifically, this hippocampus-lateral DMN node connectivity increased as re-experiencing symptoms, negative mood and cognition, and arousal and reactivity symptoms decreased. Both the hippocampus and the angular gyrus are part of a network of regions involved with episodic memory, and with autobiographical memory, i.e., personally relevant memories, remembered from an individual’s own perspective (Squire and Dede, 2015; Thakral et al., 2017; Zlomuzica et al., 2018). Therefore, it is possible that a PTSD diagnosis is characterized by alterations in episodic and autobiographical memory that are associated with a weakening in the connectivity between the hippocampus and angular gyrus, and that the successful treatment of PTSD involves reconsolidation of autobiographical and episodic memory, related to a strengthening of hippocampal – angular gyrus connectivity (Schiller et al., 2010; Wagner et al., 2015).

Previous meta-analyses have found smaller hippocampal volume in adults with PTSD (Nelson and Tumpap, 2017). While findings have been more mixed in the child and adolescent PTSD literature (Ahmed et al., 2012; Carrion et al., 2001, 2007; De Bellis, Hall, Boring, Frustaci and Moritz, 2001; De Bellis et al., 2002; Keding and Herrigna, 2016; Morey et al., 2016; Tupper and De Bellis, 2006), a recent meta-analysis similarly found smaller hippocampal volume in children (Kribakaran et al., 2020). A potential explanation for less consistent findings of smaller hippocampal volume in childhood PTSD may relate to the time it takes for PTSD-related volume changes to become observable (Sapolsky et al., 2000). Preclinical studies in rodents suggest that stress-driven reductions in hippocampal volume may be driven by dendritic hypotrophy (Henckens et al., 2015; Sousa et al., 2000), and some researchers theorize that reductions in dendritic complexity could be a mechanism for reductions in hippocampal volume (Fenster et al., 2018). Therefore, one possibility is that stress-induced dendritic hypotrophy could reduce hippocampal connectivity, and over time this reduction in connectivity could lead to reductions in hippocampal volume. Consistent with this possibility, reductions in hippocampal-DMN RSFC have been found in PTSD in adults (Koch et al., 2016), and decreased hippocampal-DMN RSFC have been found to relate to PTSD symptom severity in adolescents (Sheynin et al., 2020; Viard et al., 2019).

Another possibility is that PTSD-related reductions in hippocampal volume and changes in hippocampal connectivity are the result of different PTSD-related mechanisms of risk and response. Two treatment studies examining hippocampal volume in adults with PTSD before and after treatment have found that hippocampal volume was not altered by treatment (Rubin et al., 2016; van Rooij et al., 2015). In addition, these studies found that treatment responders had larger hippocampi than non-responders, and treatment responders did not differ from healthy...
controls in hippocampal volume, suggesting that smaller hippocampal volumes may constitute a risk factor for non-response to PTSD treatment or for the persistence of PTSD symptoms (Rubin et al., 2016; van Rooij et al., 2015). These studies provide a finer-grained understanding of previous research suggesting that smaller hippocampal volume is associated with greater PTSD risk (Gilbertson et al., 2002). It is possible that we did not find hippocampal volume differences between PTSD patients and controls due to our patient group consisting almost exclusively of adolescents who were treatment responders. In this case, the functional connectivity differences we found that were associated with PTSD symptomatology, both before and after treatment, would be mechanistically unrelated to hippocampal size.

The hippocampus has long been a key region of interest for PTSD research, due to the role it plays in memory, fear learning, and fear extinction, functions that are perturbed by PTSD (Joshi et al., 2020). Furthermore, connectivity within the DMN, including the hippocampus, is associated with autobiographical memory and self-referential thought (Frewen et al., 2011; Menon, 2011), processes that are also altered by PTSD (Frewen et al., 2011; Philippi et al., 2019). Here, we found that improvements in both arousal and reactivity symptoms are associated with increased hippocampal-DMN connectivity in a sample of young women exposed to sexual trauma. These results are consistent with previous research linking PTSD-related alterations in self-referential processing to arousal symptoms in women with PTSD secondary to interpersonal trauma (Philippi et al., 2019). Previous research has found unique neural alterations linked to different types of trauma in childhood (Teicher et al., 2016). Therefore, it is possible that the observed pattern of results, i.e., changes in hippocampal RSFC but not hippocampal volume, could be unique to PTSD secondary to sexual assault in adolescent girls.

Overall, our results suggest that successful treatment of PTSD is associated with increases in hippocampal-DMN connectivity. Future research replicating these results is necessary to determine if improvement in PTSD symptoms is consistently associated with increased/normalized hippocampal-DMN connectivity, if some symptom clusters (e.g. arousal and reactivity or re-experiencing) are more related to hippocampal-DMN connectivity than others, and if results are specific to PTSD secondary to sexual assault.

If PTSD-driven reductions in hippocampal connectivity lead to later hippocampal volume reduction, it is possible that detection and successful treatment of PTSD earlier in the course of the illness could avert long-term neural changes related to PTSD. Future longitudinal studies of PTSD-related changes in brain structure and function are required to confirm these results and to explore the possibility that early detection and treatment of PTSD could prevent long-term negative neural outcomes. Future studies could also examine the relationship between the efficacy of treatment and hippocampal volume. It may also be beneficial for future studies to compare the impact of PTSD treatment on functional connectivity with the impact of CBT on other disorders, e.g., an anxiety disorder, to determine if the effects of treatment on functional connectivity are disorder-specific, or transdiagnostic.

Strengths of this study include collecting measurements of brain structure and RSFC close to the onset of the disorder, allowing us to begin to probe the time course of neural changes related to PTSD. Furthermore, this study collected within-subject repeated measures of RSFC pre- and post-PTSD treatment, allowing us to examine the relationship between symptom improvement and changes in RSFC. While previous studies have found relationships between PTSD symptoms and RSFC in adolescents, no previous studies have examined the impact of PTSD treatment on RSFC in adolescents.

The small sample size in each of three treatment arms, individual IPT, group IPT and SPT limit the ability of current results to comment on the effect of treatment-type on symptom change-related changes in RSFC. Furthermore, given that the severity of depression and anxiety symptoms were not measured separately from PTSD symptoms, we were limited in our ability to control for more general effects of treatment on symptom change and related RSFC. However, we found that connectivity between the hippocampus and the lateral parietal node of the DMN increased along with improvement of symptoms unique to PTSD, e.g., re-experiencing (CAPS-B) and arousal and reactivity (CAPS-E), suggesting that the improvement of PTSD-specific symptoms play a role in our results. In addition, other trauma experiences were not controlled for in analyses, leading to the possibility that our RSFC results could be influenced by exposure to other traumas. However, a diagnosis of PTSD due to another trauma was an exclusion criterion. Therefore, only participants for whom the precipitant to the PTSD diagnosis was sexual assault were included in the study. Our PTSD and HC groups differed in terms of education and IQ. While RSFC analyses accounted for IQ, as IQ has been shown to impact RSFC (Ezaki et al., 2020; Pezoulas et al., 2017), this remains a limitation of the study. RSFC in HCs was collected at one timepoint, limiting our ability to interpret treatment related RSFC changes. Finally, since our analyses were hypothesis-driven, and limited to hippocampal and DMN seeds for RSFC analyses, additional PTSD- and treatment-related brain changes, not reported here, are possible.

This study suggests that recent PTSD due to sexual assault is related to functional, but not structural changes in the brain. Present results also demonstrate a correlation between improvements in PTSD symptoms following treatment and concomitant changes in RSCF. More specifically, these results suggest that PTSD-related RSFC changes may precede previously documented structural changes in the hippocampus. Replication of these results could imply that previous mixed findings in the pediatric literature regarding PTSD-related hippocampal volume reduction may be due to variability in the time between onset of the disorder and when participants took part in research, or that this pattern of results could be related to recent PTSD secondary to sexual assault. Alternatively, these results could support different mechanisms leading to an association between PTSD and neural structure and connectivity, with smaller hippocampal size as a potential a risk for non-response to treatment (Rubin et al., 2016; van Rooij et al., 2015), and changes in neural connectivity related to PTSD symptomatology (Shenyn et al., 2020; Viard et al., 2019).

CRediT authorship contribution statement

Tamara J. Sussman: Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Jonathan Posner: Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Andrea Parolin Jackowski: Supervision, Writing – review & editing. Adriana Correa: Methodology, Writing – original draft. Elis Viviane Hoffmann: Data curation, Writing – review & editing. Fernanda Porto de Oliveira Peruzzi: Data curation, Writing – review & editing. Fernando Rodrigues Grecco: Data curation, Writing – review & editing. Samara Hipolito Nitschke: Methodology, Writing – original draft. Maria Eugenia Mesquita: Conceptualization, Methodology, Supervision, Writing – review & editing. Bernd Uwe Foester: Conceptualization, Writing – original draft, Felipe Benatti di Cillo: Data curation, Writing – review & editing. Marcelo Peijo Mello: Supervision, Writing – review & editing. Ana Carolina Coelho Milan: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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