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Cortical gyrification morphology in PTSD: A neurobiological risk factor for severity?

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a prevalent psychiatric disorder, particularly among military personnel and veterans. Cortical gyrification, as a specific metric derived from structural MRI, is an index of the convoluted folding and patterning of the gyri and sulci, and is thought to facilitate the efficiency of local neuronal wiring. It has the potential to act as a neurobiological risk factor for emergent psychiatric disorders – to date, it has been understudied in PTSD. Here, using a local measure of the degree of gyrification (local Gyrification Index, *l*GI) we investigate cortical gyrification morphology in 48 adult male soldiers with (n = 23) and without (n = 25) a PTSD diagnosis. We also examine the relation between *l*GI and PTSD severity within the PTSD group. General linear models yielded significant between-group differences with greater *l*GI found in PTSD in a cluster located in the medial occipito-parietal lobe on the left hemisphere and reduced *l*GI in a cluster located on the lateral surface of the parietal lobe on the right hemisphere. Brain-behaviour analyses within the PTSD group yielded significant positive associations between *l*GI and PTSD severity in a cluster located in the frontal cortex of the left hemisphere and scattered clusters located within all lobes of the right hemisphere. After accounting for the effects of comorbid psychiatric symptoms common in PTSD, the associations in the right hemisphere reduced to clusters only located in the frontal lobe, while the cluster in the left hemisphere remained significant. Our results suggest that atypical cortical gyrification in parietal and occipital regions may be implicated in the psychopathology of PTSD diagnosis, and properties of prefrontal gyrification associated with the emergent severity of PTSD after trauma. The importance of these regions in PTSD may be attributed to a pre-existing neurobiological risk factor, or neuromorphological changes after trauma precipitating emergent psychiatric illness. Our brain-behaviour relations provide support for the existing literature by highlighting the importance of the frontal lobe in the pathogenesis of PTSD. Future large-scale longitudinal studies including female participants may infer causal implications of atypical gyrification in PTSD and shed light on the potential effect of sex on this brain metric.

1. Introduction

Post-traumatic stress disorder (PTSD) can occur after exposure to a traumatic event and is characterized by re-experiencing symptoms, such as flashbacks, persistent avoidance of trauma-related stimuli, negative thoughts and mood, and arousal and reactivity symptoms such as hypervigilance (American Psychiatric Association, 2013). PTSD is a relatively common disorder, with incident rates of 5–10% (Kessler et al., 2005; Breslau 2009), and higher prevalence rates evident among military veterans (Friedman et al., 1994; Richardson et al., 2010; Creamer et al., 2011; Gates et al., 2012; Boulos and Zamorski 2013; Hines et al., 2014). Certain developmental components are known to increase the

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risk of developing PTSD (e.g. early life mistreatment, socio-economic status and IQ), as well as pre-existing and developmental neurobiological risk factors that predispose individuals to the disorder after trauma (Breslau et al., 1995; Kessler et al., 2017).

With advancements in neuroimaging techniques, subcomponents of cortical volume (surface area and cortical thickness) can be studied, each reflecting different genetic and cellular processes (Rakic 1995; Panizzon et al., 2009). These surface-based morphometry measures have been studied using structural MRI in PTSD literature (Heyn and Herringa., 2019; Rinne-Albers et al., 2020; Wrocklage et al., 2017), however, cortical gyrification, as a specific measure derived from MRI, has received less attention, with only one known study to date (Chu et al., 2017). Cortical gyrification, the characteristics of folds (gyri) and grooves (sulci) of the cortex, begins to take place prior to birth, and intensifies during the third trimester of fetal life (Chi et al., 1977). It peaks during toddlerhood (Raznahan et al., 2011; Li et al., 2014), declines sharply during childhood and adolescence (Cao et al., 2017), and then very slowly decreases from early adulthood onwards into older age (Hogstrom et al., 2013; Klein et al., 2014).

Among the numerous theories proposed regarding the formation of gyrification in brain development, one of the earliest postulates that the folding of the cortex may primarily be driven by external constraints such as the limited space of the skull placed upon the rapidly growing surface area (Le Gros Clark, 1945). Alternatively, (Van Essen, 1997) proposed the tension-based hypothesis of cortical folding, postulating that tension along axons in early development may drive strongly interconnected regions to pull towards one another and form gyri and allow less connected regions to drift apart and form the sulci of the cortex. Thus, cortical convolution and increased gyrification are thought to reflect an optimal organization of the cortex which facilitate increasingly efficient local circuit wiring, as the convoluted folding of the cortical sheet expands the possible surface area relative to a fixed and constrained volume (e.g. the cranium), and thus also allow the presence of numerous underlying axonal connections in a limited space. Gyrification has been found to directly relate to functional and structural macrocircuitry, correlating with measures of functional coupling as well as structural connectivity in neuropsychiatric conditions (Bos et al., 2015). As such, changes in regional GI may reflect micro-, meso- and macroscopic disparities in cortical circuitry that arise during neurodevelopment in the early lifespan.

Although higher cortical gyrification has been widely associated with higher intelligence levels in normative literature (Luders et al., 2008; Gregory et al., 2016), this does not necessarily indicate superiority of higher gyrification findings compared to lower gyrification levels as previous studies have reported higher gyrification in neurodevelopmental disorders (Yang et al., 2016) and other psychiatric disorders (Sasabayashi et al., 2019) compared to typically developing individuals. Given we know that PTSD has been associated with hypersynchronous neural dynamics (Dunkley et al., 2015) and altered connectivity more generally (Jin et al., 2017), these observations would align with those findings of altered and elevated neurocircuitry connectivity.

Cortical gyrification can be measured using different global (i.e. Gyrification Index, GI) and local constructs. In recent years, studies have focused on the computation of local Gyrification Index (*l*GI), an extension the 2D GI measure which quantifies the degree of local gyrification by estimating the amount of cortex hidden within sulci while taking into consideration the 3D nature of the brain (Schaer et al. 2008, 2012). *l*GI has been widely implemented in studying cortical gyrification morphology in neurodevelopmental disorders such as autism spectrum disorder (Kohli et al., 2019) and attention-deficit hyperactivity disorder (Ambrosino et al., 2017), as well as affective disorders like major depressive disorder (Depping et al., 2018) and generalized anxiety disorder (Molent et al., 2018), which are common comorbid conditions to PTSD. *l*GI has been proposed as an existing clinical risk factor for emergent psychiatric diseases preceding the maximal change in neurodevelopmentally-driven gyrification (Harris et al., 2007; Das et al., 2018).

To our knowledge, only one study to date has investigated cortical gyrification in PTSD (Chu et al., 2017), and that was against a group of healthy controls rather than an appropriately matched trauma-exposed control group with similar life experiences – such a robust control group would provide evidence that gyrification abnormalities reflect a predisposition to developing PTSD after trauma, rather than a neurobiological consequence of the stressor and/or trauma, per se. Here, we examined local gyrification indices in adults with military-related PTSD by 1) examining *l*GI differences in PTSD compared to trauma-exposed controls who did not develop PTSD (PN); and 2) exploring the potential functional implications of gyrification by investigating the direct relationship between *l*GI and PTSD severity, accounting for comorbid factors. Given known associations between levels of intelligence and gyrification (Luders et al., 2008; Gregory et al., 2016), and the association of IQ with PTSD outcome (Marx et al., 2020), as well as the strong correlation between *l*GI and surface area (Forde et al., 2017), we control for the effects of these two variables in our data-driven analyses. Given the wealth of existing PTSD literature that reveals a role for hypoactive and cortical morphological changes in prefrontal cortex to be associated with the disorder, we predict a reduction in local prefrontal gyrification that directly scales with PTSD severity.

2. Materials and methods

2.1. Participants

A total of 48 (n = 23 PTSD - "PTSD Group"; n = 25 trauma-exposed, no PTSD – "PN Group") adult male participants were recruited from the Canadian Armed Forces. The PTSD group were recruited through an Operational Trauma Stress Support Centre (OTSSC), and a clinical diagnosis of PTSD was made by a military psychiatrist or psychologist specialising in trauma-related mental health injuries. Soldiers with PTSD were assessed using a semi-structured psychometric interview, with the onset of PTSD traced to an operationally-related traumatic event (Category A1). A PTSD diagnosis was made based on criteria in Diagnostic and Statistical Manual of Mental Disorders IV-TR Edition (DSM IV-TR) (American Psychiatric Association 2000). Participants were currently receiving mental health treatment that had been diagnosed between 1 and 4 years prior to taking part in the study.

Participants in the PN group were combat-exposed, frontline troops in similar deployed roles who were exposed to traumatic events but did not meet the clinical criteria for PTSD. They were matched against participants with PTSD based on their years of military service, experience, and education levels, and were not included in the study if they had any pre-existing neuropsychiatric condition(s). Furthermore, they were specifically screened to exclude a diagnosis of PTSD or childhood trauma. They served in similar front-line combat roles as the PTSD group, and therefore experienced similar operational and environmental stressors, and witnessed similar traumatic events as those who did develop PTSD.

PTSD severity was assessed on the day of the scan in the PTSD group using the PTSD CheckList (PCL; Weathers et al., 1993). For all participants, Intelligence quotient (IQ) scores were obtained through Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999); Anxiety using the Generalized Anxiety Disorder 7 (GAD7) questionnaire (Spitzer et al., 2006); and depression scores assessed using Personal Health Questionnaire 9 (PHQ9; Kroenke et al., 2001).

Any potential participants that were screened for either group were excluded if they had a history of a traumatic brain injury (TBI), through a review of their electronic health record, telephone interview, and administration of the Defence and Veteran's Brain Injury Centre (DVBIC) screening tool. Further exclusions included ferrous metal inside the body or implanted medical devices that might be MRI contraindications, neurological disorders, and certain ongoing medications

(anticonvulsants, and/or benzodiazepines, or other GABA modulators). This was a naturalistic study, and as such withdrawing treatment would be unethical to partake in the study, given the suicidality of those with PTSD – as such, participants undergoing treatment including evidenced-based psychotropic medication(s), such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norephedrine reuptake inhibitors (SNRIs), and Prazosin were allowed to partake in this study.

Exclusion criteria for both groups included standard neuroimaging safety exclusions, uncorrected vision, having any history of premorbid neurological, psychological or psychiatric disorders, a history of traumatic brain injury (mild, moderate, or severe, and including concussion which is considered a subtype of mild TBI), if they were taking anti-convulsant medications, benzodiazepines and GABA modulators, or had significant artifacts in their MRI scan.

2.2. Neuroimaging data acquisition parameters

Structural images were obtained using 3 T (MAGNETOM Tim Trio, Siemens AG, Erlangen, Germany) scanners with a 12-channel head coil. A T_1-weighted 3D sagittal magnetization-prepared rapid gradient echo (MP-RAGE) sequence was utilized, with 1 mm isotropic voxel resolution, a FOV of 192 × 240 × 256mm with a 256 × 256 matrix and 192 slices. Sequence parameters included: TR = 2300 ms, TE = 2.96 ms, TI = 900 ms, and FA = 9°. During image acquisition head stabilization and motion restriction was facilitated using foam padding around the head.

2.3. Image processing

FreeSurfer software version 6.0 (https://surfer.nmr.mgh.harvard.edu) was utilized for image processing and reconstruction, the steps of which have been thoroughly described in previous work (Greve and Fischl 2018). Briefly, T_1-weighted images are registered to MNI305 atlas prior to intensity normalization, skull stripping and white matter segmentation steps. During the tessellation step, a cortical surface mesh is computed for each individual scan. Pial (gray matter-cerebral spinal fluid, CSF, boundary) and white (gray-white matter boundary) surfaces are then differentiated. Following the inflation step, using spherical registration, individual scans are registered to FreeSurfer's template space called fsaverage. Lastly, cortical segmentation based on Desikan/Killany atlas is performed.

2.3.1. Quality control

Quality control on FreeSurfer output was performed based on ENIGMA Cortical Quality Control Protocol 2.9 (April 2017, http://enigma.ini.usc.edu) by visually inspecting the data for accurate gray-white matter segmentation and cortical labelling. Manual trouble-shooting was performed when needed (i.e. to correct for inaccurate gray-white matter or gray matter-CSF boundary segmentation or improper skull stripping). 4 participants (n = 1 PN, n = 3 PTSD) were excluded due to imaging artifacts (n = 1) and inaccurate gray-white matter boundary segmentation (n = 3). The total number of participants included for statistical analyses are 44 adult males (n = 24 PN, n = 20 PTSD), with a range of 26–48 years of age (Table 1). The majority of the sample are right handed (n = 34) with the rest being either left handed (n = 9) or ambidextrous (n = 1).

Table 1
Participant demographics.

	PTSD (n = 20)	PN (n = 24)	p-value
Mean age ± SD [range]	37.8 ± 6.5 [26–48]	32.9 ± 4.5 [27–40]	0.00772
Mean FSIQ ± SD [range]	110.3 ± 13.5 [82–129]	119.2 ± 11.6 [95–137]	0.02639
Mean PCL ± SD [range]	¶ 62.5 ± 7.5 [46–77]	N/A	

PN trauma-exposed, no PTSD group; *PTSD* Post-traumatic stress disorder group; *FSIQ* Full Scale Intelligence Quotient; *SD* Standard deviation; ¶ the PCL score demographic information is for the 18 PTSD participants that have this information available and on whom brain-behaviour analyses were conducted.

2.3.2. Local Gyrification Index (lGI)

*l*GI was computed on FreeSurfer by running a single flag for each participant and computing the degree of gyrification locally at thousands of vertices across each hemisphere (Schaer et al., 2008). *l*GI is a 3D measure of the ratio between the area of an estimated circular region of interest (ROI; 25 mm radius) on the pial surface and the area of the corresponding ROI on the outer surface (a smooth surface constructed by FreeSurfer which covers the cortex and does not follow the protuberances of the cortex). An *l*GI of 5 represents a highly folded cortex (indicating five times more cortex buried within sulci compared to the exposed cortex in a particular region) and an *l*GI of 1 represents a smooth cortex.

2.4. Statistical analyses

To compare *l*GI differences between groups, we undertook a whole-brain approach and conducted General Linear Models (GLMs) on Query, Design, Estimate, Contrast (QDEC) application on FreeSurfer, which utilizes the DODS (different offset, different slope) design matrix. We controlled for the effects of age, surface area and IQ (all variables demeaned). *l*GI was not smoothed as the computation of this construct makes it a relatively smooth measure (Schaer et al., 2012). We corrected for multiple comparisons using Monte-Carlo z-simulations ($p < 0.05$).

Next, we explored potential *l*GI- PTSD severity relations within the PTSD group across the whole-brain using FreeSurfer's QDEC application. We controlled for the effects of age, surface area, IQ, anxiety and depression (all demeaned including PCL scores). We explored associations while controlling for different combinations of these covariates to assess the potential contribution of each. We corrected for multiple comparisons using Monte Carlo z-simulations ($p < 0.05$). Brain-behaviour relations were only conducted within PTSD participants as PCL scores were not available for PN participants.

R software (https://www.r-project.org/) was used to investigate between-group characteristic differences in age and Full-scale IQ (FSIQ).

3. Results

3.1. Participant characteristics

Using independent t-tests, we found PTSD and PN groups to be significantly different in age ($p = 0.008$) with higher mean ages in the PTSD group. As predicted, groups were also significantly different in FSIQ ($p = 0.026$) with higher mean FSIQ scores in the PN group (Table 1).

3.2. PTSD is associated with regional effects of lGI in occipito-parietal cortices

The GLM model yielded significant differences in *l*GI between PTSD and PN groups in the parietal lobes, bilaterally, and the left occipital lobe. Specifically, greater *l*GI was found in PTSD relative to PN in a cluster located in the medial occipito-parietal fissure and inferior part of the precuneus within the left hemisphere (peak localized in precuneus, $p = 0.0001$, Fig. 1a). Conversely, reduced *l*GI was found in PTSD relative to PN in a cluster located on the lateral surface of the parietal lobe on the right hemisphere (peak localized on the inferior parietal gyrus, $p = 0.0001$, Fig. 1b). Result of the main effect of IQ is presented in supplementary materials (Fig. S1). No significant group-by-IQ interactions were observed in either hemisphere.

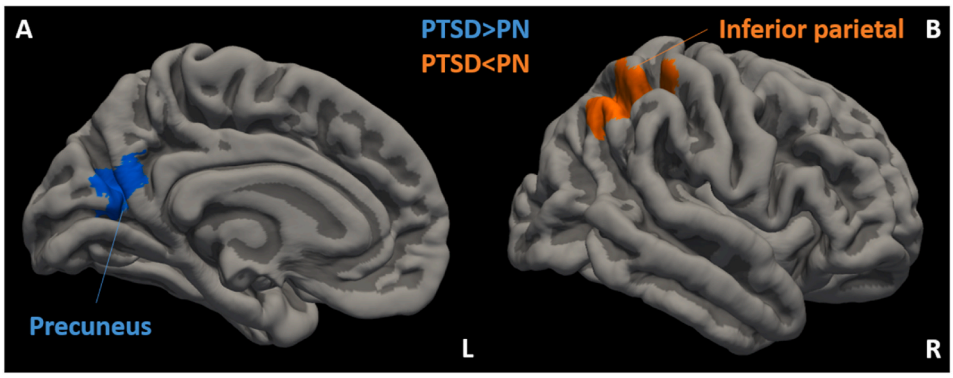

Fig. 1. PTSD shows differential effects in occipito-parietal gyrification indices. Group differences in *l*GI with *A)* greater *l*GI in PTSD relative to PN in a cluster straddling the parieto-occipital fissure and precuneus of the left hemisphere (p = 0.0001) and *B)* reduced *l*GI in PTSD relative to PN in a cluster centred on the inferior parietal lobule of the right hemisphere (p = 0.0001).

3.3. PTSD severity is directly related to cortical lGI

For the brain-behaviour analyses, 2 PTSD participants were excluded due to not having completed the PCL questionnaire. As a result these analyses were conducted on n = 18 PTSD participants. When controlling for the effects of age, surface area and IQ, we found significant positive associations between *l*GI and PTSD severity in a cluster straddling the operculum/pars triangularis in the inferior portion of the frontal cortex and insular region of the left hemisphere. Positive relationships with severity were found in the right hemisphere as well, including superior portions of the dorsolateral prefrontal cortex and lateral orbito-frontal cortex, and inferior regions of the occipital cortex, including the inferior part of the calcarine (Fig. 2).

When we controlled for the effects of age, surface area, and comorbid psychiatric symptoms including anxiety and depression, we found significant positive associations in the same cluster on the left hemisphere, but on the right hemisphere, significant associations were only observed in clusters located in the frontal cortex (Fig. 3).

4. Discussion

The investigation of cortical gyrification morphology in PTSD literature is still in its infancy, with our study, to the best of our knowledge, marking the second study of this disorder. Our findings show increased gyrification in PTSD relative to trauma-exposed control participants in the left medial parietal and occipital lobes, and reduced gyrification in the right parietal lobe. This suggests these areas are involved in the pathogenesis of PTSD, either acting as a pre-existing neurobiological risk factor, or perhaps representing gross neuromorphological changes after traumatic stress and associated with emergent psychiatric illness. With the current data it is impossible to categorically say that either is responsible, as we did not have pre-trauma baseline scans – it may be that these *l*GI effects represent a pre-existing risk factor for PTSD, given the fact that *l*GI only fluctuates very slowly over the age span comprising early and middle adulthood, the age of the participants scanned here. It is also plausible that atypical gyrification found in our study may be a result of exposure to earlier trauma or chronic stress, given that gyrification atypicalities in the left lingual gyrus have also been reported in maltreated versus non-maltreated children (Kelly et al., 2013). However, Kelly et al. (2013) observed reduced lGI in this visual region compared to controls, while we found greater lGI in our PTSD group compared to trauma-exposed controls. This discrepancy in the direction of effect may be due to the older mean age of our sample reflecting a differing adaptation to stress or traumatic exposure in adults compared to children. Alternatively, it may be due to the differences in our comparison groups as our control group consists of individuals who have also been exposed to trauma and thus most probably contain differing structural morphologies compared to a typically developing control group with previous no trauma exposure. Surprisingly, only a small overlapping area in the right parietal lobe was significant in the between-group comparisons and showed data-driven associations with symptom severity; however, when accounting for comorbid psychiatric symptoms (common in PTSD), that association disappeared, leaving a number of bilateral regions that were related to severity of symptoms. Our findings do not replicate results of the only other PTSD study investigating gyrification morphology which reported atypicalities in the frontal lobe (Chu et al., 2017). As stated above, this may also partially be due to methodological differences between our studies, including a distinction between our comparison groups. Whereas study by Chu et al. (2017) included healthy non-traumatized controls as their comparison group, our study includes individuals who have been exposed to traumatic stress in comparable deployed roles, but did not develop PTSD, thus suggesting these differences are directly related to the pathogenesis of PTSD, rather than traumatic stress per se. Other methodological distinctions between our studies exist that may explain the discrepancies in our findings, including rigorous controlling of covariates in our analyses (i.e. age, surface area and IQ).

Gyrification is highly variable even when measured across

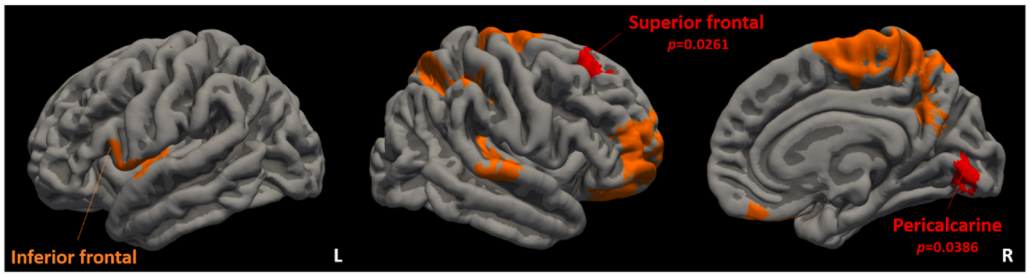

Fig. 2. PTSD severity is associated with gyrification in numerous cortical areas. Positive associations between *l*GI and PTSD severity within PTSD group when controlling for the effects of age, surface area and IQ (all other *ps* = 0.0001).

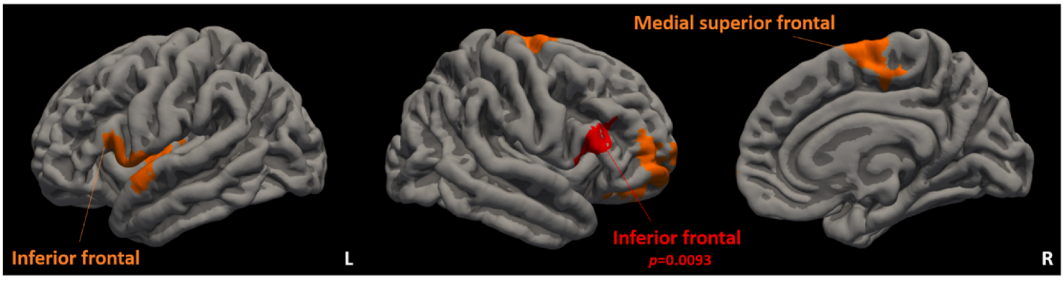

Fig. 3. Cortical gyrification is related to PTSD severity even after accounting for comorbid psychiatric symptoms. Positive associations between *l*GI and PTSD severity within PTSD group when controlling for the effects of age, surface area, anxiety and depression (all other *ps* = 0.0001).

monozygotic twins in healthy typical controls and psychiatric cases, despite high rates of concordance found in other structural indices such as in cortical volume (White et al., 2002; Kates et al., 2009). Such findings highlight the important combined roles of both genetic & non-genetic factors in modifying cortical gyrification, compared to cerebral volume which is almost entirely under genetic control (White et al., 2002; Kremen et al., 2010). This suggests environmental factors during development and in aging play a large role in explaining the natural variation of gyrification itself.

In line with this, the important role of environmental factors has been further implicated through findings of previous studies showing the effect of postnatal experiences, such as training (Zhang et al., 2016) and meditation (Luders et al., 2012), on cortical gyrification plasticity and modulation. Thus, it is possible that altered gyrification found here may be due to early-life developmental effects, and/or neuroplasticity, specifically as the result of chronic operational stress and trauma, as well as other environmental factors that contribute to the emergence of PTSD. However, given the cross-sectional nature of our study, it is challenging to infer causal implications because it is just as plausible that altered gyrification in our PTSD group may have been a pre-existing neurobiological risk factor.

Atypical cortical gyrification found in our study may reflect dysregulated and dysmaturated cortical organization and connectivity in PTSD, as well as numerous sequential underlying prenatal processes involved in the development and expansion of the cerebral cortex including neurogenesis, gliogenesis and migration (Rash et al., 2019). More research is needed to understand these underlying cellular and mechanical processes to elucidate the gyrification anomalies and the underlying neural mechanisms involved in a potential pre-disposition to PTSD. Our finding of atypical gyrification in the precuneus region in individuals with PTSD is in line with atypicalities reported in other psychiatric disorders including major depressive disorder, borderline personality disorder (Depping et al., 2018) and trait anxiety (Miskovich et al., 2016), suggesting that dysregulated gyrification in this region may be implicated in the psychopathology of affective disorders. These disorders are highly comorbid in PTSD, often accompanying the primary diagnoses (Mott et al., 2014). Previous studies highlight the involvement of precuneus in episodic memory (Cavanna and Trimble 2006), a subdivision of explicit memory referring specifically to recalling past personalized events or experiences (Tulving 1972) which in turn has autobiographical references (Tulving 1983). This is directly related to the definition of PTSD diagnosis as it includes characteristics such as flashbacks or reliving the traumatic event. In line with this, a positive correlation between functional activation in precuneus, among other regions, and PTSD symptom severity (Clinician-Administered PTSD Scale, CAPS) has been found in individuals with acute stress disorder during presentations of images related to personalized trauma experienced (Cwik et al., 2017). Further, precuneus is involved in aspects of attention (Cavanna and Trimble 2006) which is related to PTSD given evidence of attentional control difficulties in individuals with this diagnosis (Bardeen and Fergus 2016; Bardeen et al., 2015; Olatunji et al., 2013). Taken together, our findings of dysregulated cortical gyrification in precuneus further supports the involvement of this brain region in PTSD psychopathology. Our finding of hypogyrification in PTSD in the right parietal lobe is in agreement with findings of reduced cortical volume in PTSD in this lobe, along with other regions (Eckart et al., 2011).

We found associations between *l*GI and PTSD severity in a cluster straddling the operculum region and insula in the left hemisphere and in clusters located spanning partial areas of all the lobes on the right hemisphere. However, when we also controlled for the effects of anxiety and depression, two traits that are highly correlated with PTSD, our brain-behaviour associations on the right hemisphere tapered down to clusters located in the frontal lobe, while the cluster on the left hemisphere remained significant. This is interesting because it indicates and supports existing literature which consistently highlight the importance of the frontal lobe in the pathogenesis of PTSD, in line with numerous other structural MRI studies (Chu et al., 2017; Eckart et al., 2011; Woodward et al., 2009). It is worthy to note the exploratory nature of these brain-behaviour analyses, and hence the fact that making any firm conclusions at this point in time is implausible, due to the limited number of participants (n = 18 PTSD) with available PTSD severity scores. Our work marks the first attempt in investigating local gyrification morphology, using *l*GI, in a group of PTSD individuals versus trauma-exposed, rather than typically developing, controls who've shared similar life experiences as the PTSD group. Nevertheless, a limitation of our study is the small sample size (n = 18) in our brain-behaviour analyses which render firm conclusions implausible. However, given the exploratory nature of these analyses they are highly valuable due to being the first attempt to investigate this relation in PTSD diagnosis against a carefully matched trauma-exposed control group. Another limitation is the lack of our ability to infer causal implications of gyrification atypicalities found in our PTSD group given the cross-sectional nature of our study. Lastly, the significant differences in age between our groups is a limitation which we attempted to address by controlling for the effect of this variable in our statistical analyses – however, these data presented here should be interpreted with that caveat.

Future large-scale studies, including female participants are needed to further investigate cortical gyrification morphology in individuals with PTSD and the potential effect of sex on this brain metric. Moreover, longitudinal studies would shed light on causal implications of cortical gyrification atypicalities found in individuals with a PTSD diagnosis and whether gyrification indices are reliable predictor of emergent pathology after trauma. This can be addressed by measures of baseline gyrification prior to frontline deployment, for example. Longitudinal studies would also help determine whether dysregulated cortical gyrification is modulated in line with treatment, and whether gyrification indices would act as an effective predictor of treatment response. Future studies should also examine brain-behaviour relations with larger sample sizes to contribute to our understanding of potential functional implications of gyrification in PTSD.

5. Conclusions

In conclusion, this work supports the existing literature on the importance of the dysregulated structural morphology of the frontal lobe in the pathogenesis and severity of PTSD, and additionally supports an increasing literature base that shows parietal and occipital brain regions are involved in the psychopathology and symptomatology of PTSD.

CRediT authorship contribution statement

Avideh Gharehgazlou: Formal analysis, Methodology, Software, Validation, Visualization, Writing - original draft. **J. Don Richardson:** Writing - review & editing. **Rakesh Jetly:** Conceptualization, Study conception, Recruitment, Writing - review & editing. **Benjamin T. Dunkley:** Data curation, Funding acquisition, Project administration, Investigation, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100299.

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