Cortical thickness abnormalities in patients with post-traumatic stress disorder：A vertex-based meta-analysis

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Abstract

Neuroimaging studies report altered cortical thickness in patients with post-traumatic stress disorder (PTSD), but the results are inconsistent. Using anisotropic effect-size seed-based d mapping (AES-SDM) software with its recently-developed meta-analytic thickness mask, we conducted a meta-analysis of published studies which used whole-brain surface-based morphometry, in order to define consistent cortical thickness alterations in PTSD patients. Eleven studies with 438 patients and 396 controls were included. Compared with all controls, patients with PTSD showed increased cortical thickness in right superior temporal gyrus, and in left and right superior frontal gyrus; the former survived in subgroup analysis of adult patients, and in subgroup comparison with only non-PTSD trauma-exposed controls, the latter in subgroup comparison with only non-trauma-exposed healthy controls. Cortical thickness in right superior frontal gyrus was positively associated with percentage of female patients, and cortical thickness in left superior frontal gyrus was positively associated with symptom severity measured by the clinician-administered PTSD scale. These robust results may help to elucidate the pathophysiology of PTSD.

Keyword: cortical thickness; magnetic resonance imaging; post-traumatic stress disorder; meta-analysis

1 Introduction

Post-traumatic stress disorder (PTSD) is characterized by re-experience, hyperarousal, avoidance, negative thoughts and emotions in response to a triggering traumatic event (Shalev et al., 2017). Lifetime prevalence is 2-5%, varying with sociodemographic factors and country of residence (Atwoli et al., 2015; Koenen et al., 2017), and gender (with females at increased risk) (Koenen et al., 2017; Steven Betts et al., 2013). The World Health Organization World Mental Health Survey found that 70% of people had experienced at least one traumatic life event (Benjet et al., 2016), which poses a potential risk for PTSD. Given its severe effects on life quality and social function, there is an urgent need for better understanding of the underlying pathophysiology, and for neuroanatomical biomarkers to support early diagnosis and timely intervention.

The non-invasive neuroimaging technique of structural magnetic resonance imaging (sMRI) has been widely used to detect brain structural abnormalities in PTSD (Bremner et al., 2003; Bromis et al., 2018; Nardo et al., 2013; Pavić et al., 2007). The most-widely used structural index is grey matter volume, measured either using whole-brain voxel-based morphometry (VBM) or region of interest (ROI) analysis. However, there is increasing interest in surface-based morphometry (SBM) studies investigating cortex thickness, conveniently automated in e.g. FreeSurfer software by delineating the grey/white matter boundary and the pial surface of the cerebral cortex. Cortical thickness, measured as the shortest distance between these two surfaces, is more sensitive than cortical volume to pathology but less susceptible to partial volume effects,

and is a heritable and relatively stable structural brain characteristic that reflects the development of neurons, glial cells and nerve fiber bundles (Winkler et al., 2010). Cortical thickness changes with normal development (Wallace et al., 2015), aging (Fjell et al., 2014) and certain pathologies (Suh et al., 2019; Zarei et al., 2013). There is a relationship between persistent pressure and cortical thickness (Averill et al., 2017; Habets et al., 2011; Ranger et al., 2013), and pressure may change the expected trajectory of cortical development (Merz et al., 2019). All this makes cortical thickness a promising neuroimaging biomarker for exploring the pathophysiology of PTSD.

A number of neuroimaging studies have investigated cortical thickness in PTSD, but the published results are inconsistent. Some studies of PTSD report lower cortical thickness in insula (Ahmed et al., 2012), left frontal gyrus (Bing et al., 2013; Kinzel et al., 2020; Liu et al., 2012), right frontal gyrus (Kinzel et al., 2020; Liu et al., 2012), bilateral parietal lobe (Liu et al., 2012; Qi et al., 2013), anterior cingulated cortex (Bing et al., 2013; Qi et al., 2013), right temporal gyrus (Bing et al., 2013; Kinzel et al., 2020) and left temporal gyrus (Kinzel et al., 2020) relative to healthy controls. Other studies report higher cortical thickness in left calcarine cortex (Qi et al., 2013), right superior temporal gyrus, inferior parietal lobule, left precuneus (Li et al., 2016), right dorsolateral prefrontal cortex, left superior and inferior frontal cortex (Lyoo et al., 2011) compared with controls. Other studies find no significant differences in cortical thickness between PTSD patients and controls (Bruehl et al., 2013; Nicholas D. Fogleman et al., 2017; Hu et al., 2018; Knight et al., 2017; Landré et al., 2010). There are several possible reasons for these inconsistencies. One is differences in control types:

for example cortical thinning is reported in the superior frontal gyrus, hippocampal gyrus, inferior parietal lobes, anterior cingulate cortex and posterior cingulate cortex in PTSD patients compared with non-PTSD trauma-exposed controls, but thickening in the left calcarine cortex in comparison with trauma-exposed non-PTSD controls (Qi et al., 2013). Different trauma types may have different effects on brain structure: PTSD patients exposed to subway disaster had greater cortical thickness in the right dorsolateral prefrontal cortex, left superior frontal cortex and the left inferior frontal cortex (Lyoo et al., 2011); by contrast women with PTSD after sexual abuse showed normal cortical thickness (Landré et al., 2010). Such inconsistencies make this a promising area for meta-analysis to integrate the published data, improving on the power of the individual studies (Hernandez et al., 2020).

Coordinate-based meta-analysis is a widely accepted method for integrating image data at the whole-brain level (Albajes-Eizagirre and Radua, 2018). Published meta-analyses of morphometric studies in PTSD have mainly focused on VBM studies. A meta-analysis comparing PTSD patients with non-PTSD controls (Kühn and Gallinat, 2013) found decreased grey matter volume in anterior cingulate cortex, ventromedial prefrontal cortex, left middle temporal gyrus and left hippocampus. A PTSD study using two different control groups (Li et al. 2014) found grey matter volume alterations in left hippocampus, left middle temporal gyrus and right superior frontal gyrus compared with non-PTSD controls, and in the left occipital cortex compared with non-trauma-exposed controls; there were grey matter volume changes in the prefrontal cortex compared with both control groups. A meta-analysis of PSTD patients with

different trauma types (Meng et al 2016) found grey matter volume changes in bilateral medial prefrontal cortex, anterior cingulate cortex, insula, striatum, left hippocampus and amygdala in PTSD caused by single incident trauma, and grey matter volume changes in left insula, striatum, amygdala and middle temporal gyrus in PTSD caused by prolonged trauma. In a meta-analysis of both ROI and VBM studies (Bromis et al. 2018), the ROI meta-analysis found decreased brain volume, intracranial volume, and volumes of the hippocampus, insula and anterior cingulate in PTSD patients compared with all controls; the VBM meta-analysis found decreases in the medial prefrontal cortex, including the anterior cingulate. Anisotropic effect-size seed-based d mapping (AES-SDM) software is widely used for VBM meta-analyses. AES-SDM combines both peak coordinates and statistical parameter graphs, which greatly enhances the sensitivity of meta-analyses even with small samples (Radua et al., 2014, 2012). It can also support complementary jack-knife, subgroup, meta-regression and covariate analyses, and heterogeneity Q maps. For SBM studies in AES-SDM, a FreeSurfer mask for cortical thickness has recently been developed to improve precision and statistical significance (Li et al., 2020). This makes AES-SDM the ideal tool for this, the first meta-analysis of cortical thickness alterations in patients with PTSD.

Thus, the first aim of this study is to apply AES-SDM with its cortical thickness mask to published whole-brain SBM studies of PTSD to identify the most consistent cortical thickness abnormalities across studies, different control types and trauma types were also considered. Since the disease severity may be associated with the degree of cortical thickness alteration (for example, cortical thickness in the left intraparietal

sulcus and left angular gyrus positively correlates with the severity of symptoms in PTSD patients (Ross et al., 2021)), the second aim is to explore the contribution to cortical thickness differences of disease severity, as well as other demographic, clinical and methodological variables.

2 Methods

2.1 search and study selection

We conducted a systematic search using PubMed, Embase, Web of Science and Ovid to select relevant studies published up to November 2020, with the following search terms: "posttraumatic" or "PTSD" or "trauma"; and "cortical thickness" or "cortical thinning" or “freesurfer”. We manually checked references of retrieved articles for additional relevant studies. We conducted the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

The inclusion criteria were: 1) studies comparing whole-brain cortical thickness between patients with PTSD and controls (either non-PTSD trauma-exposed or non-trauma-exposed healthy subjects); 2) studies reporting Montreal Neurological Institute (MNI) or Talairach coordinates; 3) studies published in English. The exclusion criteria were: 1) reported grey matter volume or cortical area rather than cortical thickness； 2) region of interest (ROI) study rather than whole-brain analysis； 3) coordinates in stereotaxic space unavailable even after contacting the authors； 4) sample overlap with other included studies, in which case the study with largest sample size was included.

The literature search and study selection are summarized in Figure1.

2.2 Meta-analysis of cortical thickness

AES-SDM software version 4.3.1 (www.sdmproject.com) was used for meta-analyses, comparing cortical thickness difference between PTSD and control groups. MRIcron software (www.mricro.com/mricron/) was used to visualize AES-SDM maps.

The AES-SDM methods are briefly introduced here, being described in detail elsewhere (Radua et al., 2014). The peak coordinates of cortical thickness differences and statistical t values were extracted from included studies at the whole-brain level. If t values were not reported, the z or p values was converted into t-statistic values online (www.sdmproject.com/utilities/?show=Statistics). SDM then converts the reported peak coordinates to a standard MNI space and then recreates each study's signed differential map (findings from studies reporting no group difference were recreated with a null effect size). Finally, SDM calculates a mean meta-analytic signed map via voxel-wise calculation of the random-effects mean of the study maps, accounting for both positive and negative effects. We used a threshold of $p = 0.005$ with peak $Z = 1$ and cluster extent = 10 voxel (Radua et al., 2012) .

2.3 Subgroup meta-analysis and jackknife sensitivity analysis

If sufficient datasets were available, we performed sensitivity subgroup analyses to test the robustness of the statistically significant findings by excluding studies with potential confounds one-by-one. We conducted subgroup meta-analysis of adult patients, and of studies using analysis in Freesurfer. We also carried out separate

subgroup meta-analyses of studies using two kinds of control groups: trauma-exposed non-PTSD controls, and non-trauma-exposed healthy controls. We could not obtain sufficient data for direct comparison between the two control groups. We conducted subgroup meta-analyses of single-incident traumatic events and prolonged traumatic events for the trauma specific cortical thickness alterations.

A jackknife sensitivity analysis was used to test the reliability of the results. Briefly, we iteratively repeated the analysis each time excluding 1 dataset. The results are deemed highly replicable if a given region remains significant in all or most combinations of studies (Radua and Mataix-Cols, 2009). We conducted jackknife analysis for the pooled meta-analysis and all subgroup analyses.

2.4 Meta-regression analysis

Linear meta-regression analyses were carried out using the following variables: age; percentage of females; clinical symptom severity measured by clinician-administered PTSD scale (CAPS); mean time since trauma. To minimize the detection of spurious relationships, the probability threshold was set at 0.0005 (Radua et al., 2012, 2014) . Regions other than those detected in the main analyses were discarded, as were fits obviously driven by too few studies (Radua and Mataix-Cols, 2009). We displayed the main output for each variable in a map of the regression slope.

2.5 Analysis of heterogeneity and publication bias

Publication bias was assessed by testing funnel plots using Egger's test in SDM, in which any result with $p < 0.05$ was regarded as having significant publication bias.

If publication bias was found, a trim and fill analysis (Duval and Tweedie, 2000) was used to evaluate the number of missing studies and reassess the funnel plot after their inclusion. We conducted funnel plots for the pooled meta-analysis and subgroup analysis more than 10 studies. Inter-study heterogeneity was estimated using Q statistics. We used a threshold of $p = 0.005$ with peak $Z = 1$ and cluster extent = 10 voxels to estimate cluster's heterogeneity.

3 Results

3.1 Included studies and sample characteristics

Systematic search of the databases yielded 799 articles. Of these, 11 whole-brain SBM studies reported cortical thickness (Ahmed et al., 2012; Bing et al., 2013; Bruehl et al., 2013; Fogleman et al., 2017; Hu et al., 2018; Knight et al., 2017; Landré et al., 2010; Liu et al., 2012; Lyoo et al., 2011; Ross et al., 2021) and met the criteria of our meta-analysis, comprising 13 datasets with 438 PTSD patients (276 females and 162 males), 301 trauma-exposed non-PTSD controls (152 females and 149 males), and 95 non-trauma-exposed healthy controls (67 females and 28 males). One study (Fogleman et al., 2017) compared two subgroups (patients with and without mild traumatic brain injury) with the same non-PTSD control group, and another (Ross et al., 2021) reported independent comparisons in children and adult patients; in each we treated each subgroup comparison as an independent dataset.

Table1 shows demographic and clinical characteristics of subjects in the studies included. Eleven (Bing et al., 2013; Bruehl et al., 2013; Fogleman et al., 2017; Hu et

al., 2018; Knight et al., 2017; Landré et al., 2010; Li et al., 2016; Liu et al., 2012; Lyoo et al., 2011; Ross et al., 2021) of thirteen datasets included 709 adult participants, and the remaining two datasets (Ahmed et al., 2012; Ross et al., 2021) included 125 children and adolescent patients. Two datasets (Knight et al., 2017; Liu et al., 2012) included only 42 male participants and four datasets included only 259 female participants. Seven datasets (Ahmed et al., 2012; Bruehl et al., 2013; Knight et al., 2017; Landré et al., 2010; Lyoo et al., 2011; Ross et al., 2021) included 125 patients with PTSD comorbid with depression. In ten datasets (Bing et al., 2013; Bruehl et al., 2013; Fogleman et al., 2017; Knight et al., 2017; Landré et al., 2010; Li et al., 2016; Lyoo et al., 2011; Ross et al., 2021) which included 378 PTSD patients, the threshold was corrected for multiple comparisons; three datasets (Ahmed et al., 2012; Hu et al., 2018; Liu et al., 2012) which included 60 PTSD patients used an uncorrected threshold. Depending on the traumatic event, the types of trauma are classified as single-incident traumas and prolonged/repetitive traumas (Cody and Beck, 2014; Van Der Kolk et al., 2005). Five datasets (Bing et al., 2013; Hu et al., 2018; Li et al., 2016; Liu et al., 2012; Lyoo et al., 2011) included 156 PTSD patients with single-incident traumatic events, including motor accidents, earthquake, coal mine flood and subway disaster; six datasets (Fogleman et al., 2017; Knight et al., 2017; Landré et al., 2010; Ross et al., 2021) included 247 PTSD patients with prolonged traumatic events, including combat, violence and sexual abuse.

3.2 Pooled meta-analysis of all included studies

The main meta-analysis of 13 datasets revealed, in PTSD patients compared with

all controls, increased cortical thickness in three clusters including the right superior temporal gyrus (Z = 1.545, p < 0.001, BA 22), right superior frontal gyrus (Z = 1.220, p < 0.001, BA 10) and left superior frontal gyrus (Z = 1.238, p < 0.001, BA 9) (Table2 and Figure 2). No region had significantly decreased cortical thickness. The Egger test showed no significant publication bias in in right superior frontal gyrus (bias = -0.27, t = -0.34, p = 0.742) and left superior frontal gyrus (bias = -0.28, t = -0.30, p = 0.766). The Egger test in right superior temporal gyrus showed significant publication bias (bias = -2.46, t = -2.67, p = 0.022) but trim and fill analysis revealed that the funnel plot showed no significant publication bias with the addition of those missing studies (Supplementary Materials, Figure S1). The results showed no significant between-study heterogeneity.

In the jackknife analysis for the main analysis, results of right superior temporal gyrus were preserved throughout 12 datasets, and results of right superior frontal gyrus and left superior frontal gyrus were preserved throughout 11 datasets; thus the results of right superior temporal gyrus, left and right superior frontal gyrus were all highly replicable (Supplementary Materials, Table S1).

3.3 Subgroup meta-analysis

The subgroup meta-analysis of adult studies included 11 datasets that compared 376 adult PTSD patients with 333 controls. The adult patients had increased cortical thickness in right superior temporal gyrus (Z = 1.605, p < 0.001, BA 22) (Supplementary Materials, Table S2). There were too few datasets for subgroup meta-

analysis of children and adolescent patients.

The subgroup meta-analysis of studies using Freesurfer included 12 datasets that compared 428 PTSD patients with 386 controls. The PTSD patients had increased cortical thickness in the right superior temporal gyrus ($Z = 1.565$, $p < 0.001$, BA 22), right superior frontal gyrus ($Z = 1.236$, $p < 0.001$, BA 10) and left superior frontal gyrus ($Z = 1.255$, $p < 0.001$, BA 9), which are the same results as the pooled meta-analysis (Supplementary Materials, Table S3).

The subgroup meta-analysis of studies comparing PTSD patients with trauma-exposed non-PTSD controls included 9 datasets that compared 271 PTSD patients with 301 non-PTSD controls. The PTSD patients had increased cortical thickness in right superior temporal gyrus ($Z = 1.624$, $p < 0.001$, BA 22) (Supplementary Materials, Table S4).

The subgroup meta-analysis of studies comparing PTSD patients with non-trauma-exposed healthy controls included 4 datasets that compared 167 PTSD patients with 95 non-trauma-exposed controls. The PTSD patients had increased cortical thickness in right superior frontal gyrus ($Z = 1.359$, $p < 0.001$, BA 10) (Supplementary Materials, Table S5).

The subgroup meta-analysis of studies using threshold correction included 10 datasets that compared 378 PTSD patients with 313 controls. The PTSD patients had increased cortical thickness in the right superior temporal gyrus ($Z = 1.586$, $p < 0.001$, BA 22), right superior frontal gyrus ($Z = 1.360$, $p < 0.001$, BA 10) and left superior

frontal gyrus (Z = 1.367, p < 0.001, BA 9) (Supplementary Materials, Table S6).

The subgroup meta-analysis of studies of PTSD patients exposed to single-incident traumatic events included 5 datasets that compared 156 PTSD patients with 185 controls; these PTSD patients had increased cortical thickness in right superior temporal gyrus (Z = 1.613, p < 0.001, BA22) (Supplementary Materials, Table S7). The subgroup meta-analysis of studies of PTSD patients exposed to prolonged traumatic events included 6 datasets that compared 247 PTSD patients with 172 controls; these PTSD patients had increased cortical thickness in both left superior frontal gyrus (Z = 1.794, p < 0.001, BA9) and right superior frontal gyrus (Z = 1.593, p < 0.001, BA 10) (Supplementary Materials, Table S8).

The result of jackknife analysis for subgroups were highly replicable (Supplementary Materials, Table S9). The Egger test of funnel plot asymmetry was not statistically significant in the bilateral superior frontal gyrus. Though the Egger test detected publication bias in the right temporal gyrus in three subgroups, trim and fill analysis of the funnel plot asymmetry implied no publication bias in this region.

3.4 Meta-regression analyses

The percentage of female patients was positively associated with increased cortical thickness in right superior frontal gyrus (Z = 1.398, p < 0.0005, BA 10), although this was driven by only three datasets (Figure3). The symptom severity measured by CAPS was positively associated with increased cortical thickness in left superior frontal gyrus (Z = 1.761, p < 0.0005, BA 9), although this was driven by only two datasets (Figure3).

We detected no effect of age, mean time since trauma on cortical thickness alteration.

4 Discussion

To the best of our knowledge this is the first vertex-based meta-analysis of whole-brain SBM studies to investigate cortical thickness changes in patients with PTSD relative to controls. The main findings were that, compared with all control subjects, patients with PTSD show increased cortical thickness in the right superior temporal gyrus, and left and right superior frontal gyrus. The results were robust and remained reproducible in the jackknife sensitivity analyses and in subgroup meta-analysis of studies using Freesurfer software and of studies using threshold correction. The abnormality in right superior temporal gyrus appeared robust in subgroup meta-analysis of adult patients with PTSD and of PTSD patients exposed to single-incident traumatic events.

On the question of different control groups, the result in right superior temporal gyrus remained significant when compared with trauma-exposed non-PTSD controls, and the result in right superior frontal gyrus when compared with non-trauma-exposed healthy controls. There were significant positive associations between the percentage of female patients, symptom severity and the cortical thickness in right superior frontal gyrus and left superior frontal gyrus.

Right superior temporal gyrus in PTSD

Right superior temporal gyrus is an important hub for speech and language in the brain (Yi et al., 2019) and contains several important structures, including the primary

auditory cortex of Heschl's gyrus and the auditory association cortical area (Kasai et al., 2003). The superior temporal gyrus plays a key role in short-term auditory sensory memory (Sabri et al., 2004). Intrusive memory of traumatic events is one of the main features of PTSD. This can present different perceptual patterns, with recurrent auditory memory in addition to visual memory of the traumatic event, or other forms of memory (Cwik et al., 2017; Ehlers et al., 2002). The superior temporal gyrus may mediate mechanisms involved in intrusive auditory memory in PTSD patients. In addition, the superior temporal gyrus is functionally connected to the amygdala, and patients with PTSD show greater positive connectivity between the right amygdala and the right superior temporal gyrus (Roy et al., 2015; Sripada et al., 2012). The amygdala is a subcortical emotional processing area (Gao et al., 2019), and plays a central role in hypervigilance, fear conditioning and expression in PTSD (Koenigs and Grafman, 2009). Superior temporal gyrus is thought to be involved in the regulation of amygdala activity and the higher cognitive processing of fear experiences (Quirk et al., 1997). Cortical thickness is positively correlated with the expression of genes marking CA1 pyramidal cells, astrocytes, and microglia (Shin et al., 2018). Some studies suggest that the anxiety-like behaviours and flashes of fear memory in PTSD can be attributed to the increase of microglia activation and neuro-inflammation (Li et al., 2021).

Our meta-analysis found increased cortical thickness in the right superior temporal gyrus of PTSD patients. Consistently, previous neuroimaging studies in PTSD have reported higher grey matter volume (Bellis et al., 2002; Niedtfeld I et al., 2013), higher ADC (Liu et al. 2016), and higher regional cerebral blood flow in the right superior

temporal gyrus by both MRI arterial spin labeling (Schuff et al., 2011) and single photon emission computed tomography (Bonne et al., 2003); and that higher activation of the right superior temporal gyrus is related to the severity of PTSD, especially for patients with dissociation symptoms (Cwik et al., 2017; Hopper, 2007; Lanius et al., 2002); and a positive correlation between the intensity of dissociation symptoms and the resting-state connectivity of superior temporal gyrus (Bluhm et al., 2009). The Eggers test revealed potential publication bias in the right superior gyrus finding, and although this was corrected by trim and fill, the result should be treated with caution.

Superior frontal gyrus in PTSD

The superior frontal gyrus is part of the prefrontal cortex (PFC), the regulatory center for mood and cognition (Goldberg et al., 2006). Dysfunction of PFC can lead to overactivity of the amygdala, which is related to enhanced fear acquisition and overexpression of fear response (Rauch et al., 2006). Previous neuroimaging studies of PTSD have reported increased CBF (Schuff et al., 2011), enhanced regional homogeneity (ReHo) (Yin et al., 2012), and increased nodal centrality in the superior frontal gyrus (Long et al., 2013). It may be related to altered processing of negative emotions, and may underlie avoidance (Veltmeyer et al., 2006) and over-alertness (Jatzko et al., 2006) in PTSD.

In a previous meta-analysis of structural MRI studies in PTSD, both ROI and VBM studies showed decreased grey matter volume in the superior frontal gyrus

(Bromis et al., 2018). A VBM meta-analysis also reported lower grey matter volume in right superior frontal gyrus in PTSD patients compared with trauma-exposed non-PTSD controls (Li et al. 2014). However, our meta-analysis found higher cortical thickness of the superior frontal gyrus. Grey matter volume is the mathematical product of cortical surface area and cortical thickness (Winkler et al., 2010). The development patterns of cortical thickness and surface area differ from each other, and from the development trajectory of cortical volume (Wierenga et al., 2014). Such dissociations of grey matter volume loss and cortical thinning have been reported for example in patients with chronic schizophrenia (Kong et al., 2015). This warrants further investigation in PTSD.

We found cortical thickness in the left superior frontal gyrus to be positively correlated with CAPS score. Cortical thickness is determined by the number of neurocytes per cortical column (Panizzon et al., 2009). Anti-inflammatory cytokines such as IL-10 can influence this by reducing the damaging effects of inflammatory processes on neurons and synapses (Moore et al., 2001) and promoting neuronal development (Sharma et al., 2011). Clinically, higher circulating IL-6 and IL-10 concentrations are positively associated with the severity of PTSD symptoms (Rodney et al. 2020) . It may be, therefore, that neuroinflammatory changes mediate the causal connection between symptom severity and cortical thickness. Previous functional studies also reported that the clustering coefficient and nodal efficiency of the left superior frontal gyrus are positively correlated with CAPS (Suo et al., 2015), that left superior frontal gyrus has a slightly stronger association with CAPS re-experiencing

lifetime sub-scores (O'Doherty et al., 2017), and that the Checklist-Civilian Version score is positively correlated with the dynamic functional connectivity between the parahippocampal gyrus and the left superior frontal gyrus (Chen et al. 2021).

Gender differences are reported in structural and functional imaging studies in PTSD (De Bellis et al., 2015; McGlade et al., 2020; Shvil et al., 2014). In our meta-analysis, the percentage of female patients with PTSD was positively associated with the cortical thickness in the right superior frontal gyrus. Gender differences are very important in PTSD; the prevalence in women is almost twice that of men (Chapman et al., 2012; Kilpatrick et al., 2013), and female PTSD patients tend to have worse, longer symptoms and more complications (Kilpatrick et al., 2013; Tolin and Foa, 2006). These differences have been attributed to multiple factors such as the type of trauma (Silove et al., 2017), differences in cognitive and behavioral responses to traumatic events (Tolin and Foa, 2006), influences of gender roles, genetic predisposition and hormonal influences (Christiansen and Berke, 2020). Previous studies on PTSD have shown that structural changes in the brain are associated with gender. For example, female PTSD patients showed larger grey matter volumes than males in Rolandic operculum, postcentral gyrus, insular, thalamus and medial prefrontal gyrus (Qi et al. 2020). Our findings also suggest effects of gender on brain structure in PTSD patients, and future studies need to address this directly.

The effects of disease and stress

It is suggested that disease and stress may have distinct effect on brain structures

in PTSD (Li et al., 2014; Merz et al., 2019; Nardo et al., 2013; Tyborowska et al., 2018; Zhang et al., 2016). Consistently, we found different cortical thickness alterations in studies comparing patients against the two different control groups. In principle, comparison with trauma-exposed non-PTSD controls isolates the directly disease-related changes, which might be of two kinds: either reflecting a predisposition to develop PTSD, or a by-product of the PTSD disease process and its consequences. (An example of the former may be suggested by the observation of hippocampal volume alteration in both PTSD patients and their non-exposed monozygotic twins (Gilbertson et al. 2002, 2007)). On this criterion our results in the right temporal gyrus appear to be disease-related. On the other hand, a relation to stress cannot be ruled out. A link to inflammation is suggested in the discussion above, and a recent study (Jeong et al., 2021) found that non-PTSD trauma-exposed individuals have increased medial prefrontal cortical thickness compared to healthy controls. In any case our result needs to be treated with caution, as only 4 datasets comparing PTSD and non-trauma-exposed healthy controls were included.

The effect of trauma types

Trauma can be divided into single-incident traumas and repetitive/prolonged (often interpersonal) traumas. These patients show different symptom profiles, with the latter group's anger being more directed at themselves and former's more directed at others (Hagenaars et al., 2011). In our subgroup of prolonged trauma, PTSD patients

had increased cortical thickness in bilateral superior frontal gyrus. In a study of military veterans, PTSD patients showed increased centrality compared to controls in right superior frontal gyrus (Sun et al., 2018). A recent study of PTSD patients found cortical thickness alterations in the frontal regions in patients with a history of childhood maltreatment compared to those without (Bomyea et al. 2020). In our subgroup of single-incident traumas, PTSD patients showed increased cortical thickness in only the right superior temporal gyrus. A previous functional study (Lei et al., 2015) of PTSD following single-incident trauma (earthquake) found increased nodal centralities in the default-mode network including the superior temporal gyrus.

5 Limitations of this study

First, only a limited number of SBM studies, especially with positive results (7 of 13 datasets), could be included even after trying to contact the authors of suitable studies which did not report the coordinates, and publication bias could not be completely ruled out. Specifically, there were too few studies to support severity of trauma exposure, and duration of time since trauma. Second, analysis of neuroimaging data in children requires in general different methods than adult datasets (Phan et al., 2018). We did not exclude data from older children and adolescents due to limitations in the number of included papers, but future studies will need to focus on adults and children separately. Third, it remains unclear whether the change in the cortical thickness reflects a predisposition to develop PTSD or a consequence of suffering from PTSD. Further longitudinal research would help with this. Fourth, though the result in the right superior temporal gyrus is robust in jackknife sensitivity analysis, we detected

potential publication bias, albeit correctable by trim and fill. Finally, the included studies have several comorbid psychopathologies, such as major depressive disorders. Though this may present a more typical patient group, we cannot confirm the thickness increase is unique to PTSD.

6 Conclusions

In conclusion, this meta-analysis applied AES-SDM with a recently-developed mask to integrate whole-brain surface-based morphometric studies in PTSD. PTSD patients had significantly and robustly increased cortical thickness in right superior temporal gyrus, left and right superior frontal gyrus. These findings provide important new information about brain structural change in PTSD, and may help to throw light on its pathophysiology. Further studies are needed to discuss to what extent alterations are related to the disease as against the stress to which it is a response

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Figure legends

Figure 1 The process of literature search and selection criteria

Figure 2 Differences in cortical thickness identified by meta-analysis of all included studies. Increased cortical thickness was found in the right superior temporal gyrus, right superior frontal gyrus and left superior frontal gyrus for patients with PTSD compared with controls in pooled meta-analysis. Abbreviations: R right; STG superior temporal gyrus; L left; SFG superior frontal gyrus

Figure3 The results of meta-regression analysis. Association between the percentage of female patients with PTSD and cortical thickness differences in left superior frontal gyrus and right superior frontal gyrus. The percentage of female patients with PTSD was positively associated with increased cortical thickness in right superior frontal gyrus ($Z = 1.398$, $P<0.0005$; BA 10). CAPS was positively associated with increased cortical thickness in left superior frontal gyrus ($Z = 1.761$, $P<0.0005$; BA 9). The Effect size for creating those plots were extracted from the peak of maximum slope significance and every dot stands for a study. Abbreviations: R right; STG superior temporal gyrus; L left; SFG superior frontal gyrus; CAPS clinical symptom severity