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ABSTRACT

Randomized controlled trials have shown efficacy of trauma-focused psychotherapies in youth with post-traumatic stress disorder (PTSD), but little is known about the relationship between treatment response and alternations in brain structures associated with PTSD. In this study, we longitudinally examined the association between treatment response and pre-to posttreatment changes in structural magnetic resonance imaging (MRI) scans using a voxel-based morphometry approach. We analyzed MRI scans of 35 patients (ages 8–18 years, 21 female) with PTSD (80%) or partial PTSD (20%) before and after eight weekly sessions of trauma-focused psychotherapy. PTSD severity was assessed longitudinally using the Clinician-Administered PTSD scale for Children and Adolescents to divide participants into responders and non-responders. Group by time interaction analysis showed significant differences in grey-matter volume in the bilateral insula due to volume reductions over time in non-responders compared to responders. Despite the significant group by time interaction, there were no significant group differences at baseline or follow-up. As typical development is associated with insula volume increase, these longitudinal MRI findings suggest that treatment non-response is associated with atypical neurodevelopment of the insula, which may underlie persistence of PTSD in youth. The absence of structural MRI changes in treatment responders, while in need of replication, suggest that successful trauma-focused psychotherapy may not directly normalize brain abnormalities associated with PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a common mental health disorder that develops in approximately 16% of youth exposed to traumatic events, which may include domestic violence, sexual abuse and accidents (Alisic et al., 2014). Youth with PTSD are troubled by frequent re-experiencing of the traumatic event, persistent avoidance, hyperarousal and negative alterations in cognition and mood (American Psychiatric Association, 2013). These symptoms can interfere with social functioning and school performance and have a negative effect on the quality of life of the affected youth and their families (Carrion et al., 2002). Moreover, they are a crucial factor in shaping the vulnerability to depression and suicidality later in life (Molnar et al., 2001; Sunley et al., 2020). Furthermore, youth exposed to traumatic events with clinically

important symptoms of PTSD but with subthreshold criteria for PTSD (partial PTSD) also demonstrate substantial functional impairment and distress which do not differ from youth meeting full PTSD criteria (Carrion et al., 2002). All of the above highlight the vital importance of effective treatment for youth with PTSD and partial PTSD.

Multiple randomized controlled trials (RCTs) have shown efficacy of trauma-focused psychotherapies in youth with PTSD (Morina et al., 2016). However, less is known about the association between treatment response and morphometric brain changes in youth with PTSD (Zantvoord, J.B. et al., 2013a). Examining changes in structural magnetic resonance imaging (MRI) measurements associated with treatment response can provide a better understanding of why some youth recover after trauma-focused psychotherapy, while in some PTSD persists (Zantvoord, J.B. et al., 2013a). This is important because, response

varies considerably among individuals, with up to 30–50% of youth who do not benefit sufficiently from treatment (Bradley et al., 2005; Diehle et al., 2015), leading to persistent PTSD symptoms and longer treatment trajectories.

Meta-analyses of structural neuroimaging studies in adults with PTSD found differences in MRI measurements possibly suggestive of reduced grey-matter volume (GMV) of the hippocampus, ventromedial prefrontal cortex (vmPFC) including the anterior cingulate cortex (ACC) and insula relative to adults exposed to trauma without PTSD (Bromis et al., 2018; Logue et al., 2018). These interconnected structures have a critical role in fear conditioning, extinction learning and emotional processing which are impaired in PTSD (Careaga et al., 2016; Etkin and Wager, 2007). Importantly, these structures undergo substantial maturation throughout childhood and adolescence; with hippocampus volume increase in girls, amygdala volume increase in boys, as well as late maturation of the prefrontal cortex and insula volume increase in both sexes (Dennis et al., 2014; Lenroot and Giedd, 2006; Shaw et al., 2008; Tamnes et al., 2017; Zantvoord, J.B. et al., 2013b).

Interestingly, cross-sectional studies in youth with PTSD did not find reduced hippocampal volume and findings on vmPFC volume have been mixed, with some reporting larger vmPFC volumes, while others reported smaller vmPFC and ACC volumes or no difference relative to healthy controls (Carrion et al., 2009; Keding and Herringa, 2015; Morey et al., 2016). Divergent structural brain findings between youth and adults with PTSD might indicate developmental effects that are not yet apparent until adulthood as well as plastic response to illness over time (Keding and Herringa, 2015; Weems et al., 2019). A recent naturalistic longitudinal study in youth aged 8–18 years with PTSD, indeed suggests that PTSD persistence is characterized by sustained reduced prefronal cortex (PFC) volume, abnormal PFC development and abnormal development of amygdala-hippocampus and amygdala (vm-) PFC connectivity (Heyn et al., 2019).

There remains a debate as to whether successful trauma-focused psychotherapy may reverse structural abnormalities associated with PTSD and might influence development of brain structures associated with PTSD persistence. Results from longitudinal morphometric studies in adult patients with PTSD have been mixed. The majority of these studies have used small samples and focused on the hippocampus, with most (Laugharne et al., 2016; Lindauer et al., 2005; Van Rooij et al., 2015), but not all (Levy-Gigi et al., 2013) suggesting that hippocampal volume does not change with trauma-focused psychotherapy. Few studies have looked beyond hippocampus volume, showing amygdala (Laugharne et al., 2016), parahippocampal gyrus (Bossini et al., 2017) and prefrontal volume increase and ACC volume decrease (Boukezzi et al., 2017; Helpman et al., 2016) from pre-to posttreatment. To the best of our knowledge, no study has been published which examined morphometric changes associated with treatment response in youth with PTSD.

In the present longitudinal study, we investigated longitudinal changes in MRI measurements in youth with PTSD or partial PTSD treated with trauma-focused psychotherapy. We used pre- and post-treatment 3T MRI scans along with voxel-based morphometry (VBM) to compare brain-wide changes in treatment responders relative to non-responders. Overall, we hypothesized that treatment response would be associated with changes in MRI measurement suggestive of volume increases in brain areas associated with PTSD (hippocampus, insula and vmPFC including the ACC), while non-response would be characterized by volume decreases in these areas.

2. Materials and methods

2.1. Participants

Our initial sample consisted of 61 participants (39 female) diagnosed with PTSD or partial PTSD. Participants entered trauma-focused psychotherapy as part of a larger RCT comparing trauma-focused cognitive

behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) (Diehle et al., 2015). Of these participants, 40 (34 right-handed) completed treatment as well as pre- and posttreatment scans (Fig. S1 in Supplementary material). All participants were Dutch speaking, and aged 8–18 years. Participants were recruited between April 2011 and September 2018 at the outpatient child psycho-trauma center of the department of child and adolescent psychiatry, de Bascule in Amsterdam, The Netherlands. Youth were referred by child welfare services, physicians or their general practitioner. For eligibility, diagnoses for PTSD or partial PTSD were established clinically by an experienced child and adolescent psychiatrist or psychologists according to the DSM-IV-TR criteria using both child reports on the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) semi-structured interview (Nader et al., 1996) and caregiver reports from the PTSD scale of the Anxiety Disorders Interview Schedule – Parent Version (ADIS-P) (Verlinden et al., 2014). (Partial) PTSD diagnosis was determined using joint-child and caregiver reports on individual symptoms. A symptom was established as present, if either child or caregiver reported its presence. Partial PTSD was defined as either fulfilling two of the three PTSD symptom clusters or having one symptom present in each of the three symptom clusters (Stein et al., 1997). Furthermore, participants were required to have a CAPS-CA total score indicating at least mild PTSD symptom severity (>20 points). Exclusion criteria were: acute suicidality, IQ < 70, pregnancy, neurological disorders or serious medical illnesses (one patient was excluded due to an incidental finding on the MRI, see Fig. S1) or meeting the criteria of one of the following diagnosis: psychotic disorders, substance use disorder or pervasive developmental disorder. If participants were taking psychotropic or central nervous-active medication, medication was required to be stable for at least three weeks (five weeks for fluoxetine) before and during the trauma-focused psychotherapy. In our sample three participants were taking psychotropic medication (one sertraline and two methylphenidate). In accordance with procedures approved by the Institutional Review Board of the Amsterdam University Medical Center and the declaration of Helsinki, written informed consent was obtained from all parents or legal guardians. Written informed consent from youth aged 12 years and older and assent from youth aged 11 and younger, was also obtained from the youth themselves. All participants received a monetary incentive for participation (€5 for each assessments).

2.2. Treatment

All participants received eight weekly protocolized sessions of either TF-CBT or EMDR. Treatment was delivered by experienced therapists who were all trained in TF-CBT and EMDR before the initiation of the study. Supervision by experts on TF-CBT and EMDR was provided throughout the study. Treatment protocols, training and supervision of therapists, as well as treatment fidelity have been described in detail previously (Deblinger et al., 2011; Shapiro, 2001; Zantvoord et al., 2019).

Trained psychologists administered the CAPS-CA and the PTSD scale of the ADIS-P semi-structured interviews to measure PTSD symptom severity before and after treatment. Caregiver reports on the ADIS-P were used to complement child reports and clinical observation (e.g. when a child is unable to disclose certain symptoms due to avoidance). Participants and their caregivers additionally completed the Dutch Revised Child Anxiety and Depression Scale (RCADS(-P)) questionnaires to assess depressive and anxiety symptoms (Chorpita et al., 2000). Symptom change was calculated by subtracting the baseline from the posttreatment CAPS-CA total score. There is no established definition of a response criterion or a consensus definition of response terms in the child trauma treatment field. Based on the psychometric properties of the CAPS (-CA) and previous treatment outcome studies using the CAPS-CA, we used ≥30% reduction of CAPS-CA total score as response criterion for clinically meaningful improvement, and ≥50% reduction of

Table 1
Subject characteristics.

	Responders (n = 21) ≥ 30% CAPS-CA	Non-responders (n = 14) <30% CAPS-CA	p-value[a]
Sociodemographic characteristics			
Female (%)	52.3	71.4	.260
Age (years; mean, SE)	12.4 (0.68)	13.6 (0.76)	.448
West European Ethnicity (%)	68.4	50.0	.305
Current educational level (%)			
Elementary school	57.1	28.6	.189
Middle/High school lower level	0.0	7.1	
Middle/High school middle level	28.6	35.7	
Middle/High school higher level	14.4	14.3	
Vocational school	0.0	14.3	
Household income (%)			
< €25.000	31.2	37.5	.776
€25.000-35.000	25.0	12.5	
> €35.000	43.8	50.0	
Weight (kg; mean, SE)	50.4 (3.43)	52.1 (2.52)	.144
Current psychotropic medication (%)	9.5	7.1	.805
Smoking (%)	5.5%	10.0%	.662
Alcohol >1 consumption/day (%)	0%	0%	N/A
Trauma characteristics			
Index trauma (%)			
Sexual abuse	28.6	28.6	.358
Domestic violence	23.4	21.4	
Community violence	14.3	35.8	
Accidents/Medical	14.3	14.3	
Other	19.0	0.0	
Multiple-event trauma exposure (%)	61.2	42.3	.268
Age at index trauma (years; mean, SE)	9.5 (0.82)	9.9 (1.27)	.126
Time since index trauma (years; mean, SE)	3.1 (0.58)	3.7 (0.95)	.053
Clinical characteristics			
CAPS-CA study entry (mean, SE)[b]			
Total	51.8 (4.90)	57.7 (7.01)	.231
Re-experiencing	15.1 (1.92)	19.8 (2.82)	.430
Avoidance	21.7 (2.32)	20.6 (3.23)	.912
Hyperarousal	15.4 (2.05)	18.7 (2.67)	.641
Full PTSD diagnosis (%)	76.2	85.7	.490
RCADS study entry (mean, SE)[b]			
MDD	10.5 (1.58)	12.4 (2.05)	.710
GAD	7.8 (1.17)	5.9 (0.97)	.209
OCD	6.2 (1.02)	5.5 (0.71)	.076
PD	8.0 (1.59)	7.9 (1.77)	.541
SAD	6.8 (0.96)	4.6 (1.34)	.883
SP	12.1 (1.89)	11.1 (1.83)	.225

Abbreviations: CAPS-CA, Clinician-Administered PTSD Scale for Children and Adolescents; RCADS, Revised Child Anxiety and Depression Scale; MDD, major depressive disorder; GAD, general anxiety disorder; OCD, obsessive compulsive disorder; PD, panic disorder; SAD, separation anxiety disorder; SP, social phobia; SE, standard error.

[a] Independent samples *t*-test for continuous and x^2 tests for categorical variables.

[b] Ranges: CAPS-CA total, 0–139; RCADS MDD, 0–30; RCADS GAD, 0–18; RCADS OCD, 0–18; RCADS PD, 0–27; RCADS SAD, 0–21; RCADS SP, 0–27.

CAPS-CA total score as response criterion for substantial clinical improvement (Diehle et al., 2013; Weathers et al., 2001).

2.3. Imaging data acquisition and preprocessing

All scans were acquired at the Amsterdam University Medical Center using a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands). Please refer to Supplementary material for technical details of the applied MR sequences.

MRI images were preprocessed with the CAT12 toolbox (r1446, http://www.neuro.uni-jena.de/cat/) and SPM12 (r7487, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB R2017a (The Mathworks, Natick, MA). Preprocessing was performed by running the longitudinal segmentation pipeline of CAT12 with default parameters. Detailed preprocessing procedures are described in the Supplementary material. Each segmentation was checked visually and using the quality measures provided by the CAT12 toolbox. This led to the exclusion of four participants due to poor segmentation quality and one participant due to the presence of an incidental finding. These procedures led to a total sample of 35 participants in the longitudinal analysis.

To facilitate the analyses of the group by time interaction for GMV and white-matter volume (WMV), difference images were computed by subtracting the posttreatment scans of each patient from their corresponding pretreatment scans.

3. Statistical analysis

3.1. Clinical and demographic data

The distribution of baseline clinical, trauma and demographic characteristics across responders and non-responders was examined using X^2-tests for categorical variables, independent sample *t*-tests for normally distributed continuous variables and Mann-Whitney tests for non-normally distributed continuous variables. Paired sample *t*-test were used to examine pre-to posttreatment symptom change. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago IL, USA).

3.2. MRI data

We investigated the group by time interaction of GMV/WMV images using a two-sample test of the within-subject difference images. Familywise error (FWE) correction for whole-brain, two-sided tests as well as the two investigated segmentations of the threshold-free cluster enhanced (TFCE) statistic were performed using synchronized permutations (n = 10000) (Smith and Nichols, 2009; Winkler et al., 2016). Alpha was set to 0.025, additionally Bonferroni-correcting for the two response criteria investigated. To correct for the effect of gender and age on total brain volume, obtain valid localized GMV/WMV estimates, and control for baseline PTSD symptom severity, we included mean-centered total intracranial volume (TIV), age, gender and baseline CAPS-CA total scores as covariates for each patient in all analyses. A detailed justification of the included covariates can be found in the Supplementary material. All statistical tests utilized the PALM toolbox (a115, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM).

In addition, we performed a region-of-interest (ROI) analysis by repeating the analyses described above focusing on specific ROIs associated with PTSD: bilateral hippocampus, amygdala, ACC, vmPFC and insula. Hippocampus, amygdala, ACC and insula masks were extracted from the conservatively thresholded (maxprob 50%) Harvard-Oxford atlas (Desikan et al., 2006). The vmPFC masks was obtained from a previous study by Delgado and colleagues (https://neurovault.org/collections/5631/) (Delgado et al., 2016). These analyses were only performed with the GMV images.

4. Results

4.1. Demographic and clinical characteristics

A summary of participant characteristics is presented in Table 1 and Table S1. Based on joint child (CAPS-CA) and caregiver (ADIS-P) reports, 80% of participants met the full DSM-IV diagnostic criteria for PTSD at baseline, the remaining 20% met criteria for partial PTSD. The average baseline CAPS-CA score was M = 54.14 points, SD = 23.84, which is indicative of moderately severe PTSD. The most common index

trauma was sexual abuse, followed by community violence and domestic violence. 54.3% of participants were exposed to multiple-event trauma and the remaining 45.7% was exposed to single-event trauma. Average age at trauma exposure was M = 9.62 years, SD = 4.09 (range 3–16) and average time since trauma was M = 3.32 years, SD = 3.02 (range 0–11).

4.2. Changes in psychopathology

Treatment completers and non-completers did not differ in baseline sociodemographic, trauma or clinical characteristics. Across the completer sample, we found significant reductions in CAPS-CA total score ($t(34)$ = 7.90, p < .001, Cohen's effect size (d) = 1.35), re-experiencing ($t(34)$ = 7.92, p < .001, d = 1.39), avoidance ($t(34)$ = 5.43, p < .001, d = 0.94) and hyperarousal clusters ($t(34)$ = 3.39, p = .002, d = 0.59).

Applying the 30% response criterion yielded 21 responders and 14 non-responders, applying the 50% response criterion yielded 13 responders and 22 non-responders. See Table 1 and Table S1 for the distribution of baseline sociodemographic, trauma or clinical characteristics between responders and non-responders using the 30% response criterion and 50% response criterion respectively. There were no significant group differences at baseline when using the 30% criterion. When applying the 50% response criterion, responders had a lower

average time since trauma, CAPS-CA total score, CAPS-CA re-experiencing score and female to male ratio at baseline (p < .05).

4.3. Changes in brain morphometry

When applying the 30% response criterion, a significant group by time interaction effect in the GMV was observed (Fig. 1 and Table 2).

Table 2
Significant clusters of the group by time interaction analysis for the GMV.

Region (according to AAL atlas)	MNI-coordinates (peak) [x, y, z]	Peak $-\log_{10}(P_{FWE})$	Number of voxels
Right Rolandic Operculum, Right Insula	48, −6, 7.5	1.762	223
Left Rolandic Operculum, Left Insula	−39, −7.5, 16.5	1.658	29
Left Insula	−40.5, −13.5, 9	1.618	11
Right Superior Temporal Pole, Right insula	49.5, 7.5, −6	1.604	2

GMV: Grey-matter volume; AAL: Automated Anatomical Labeling atlas.

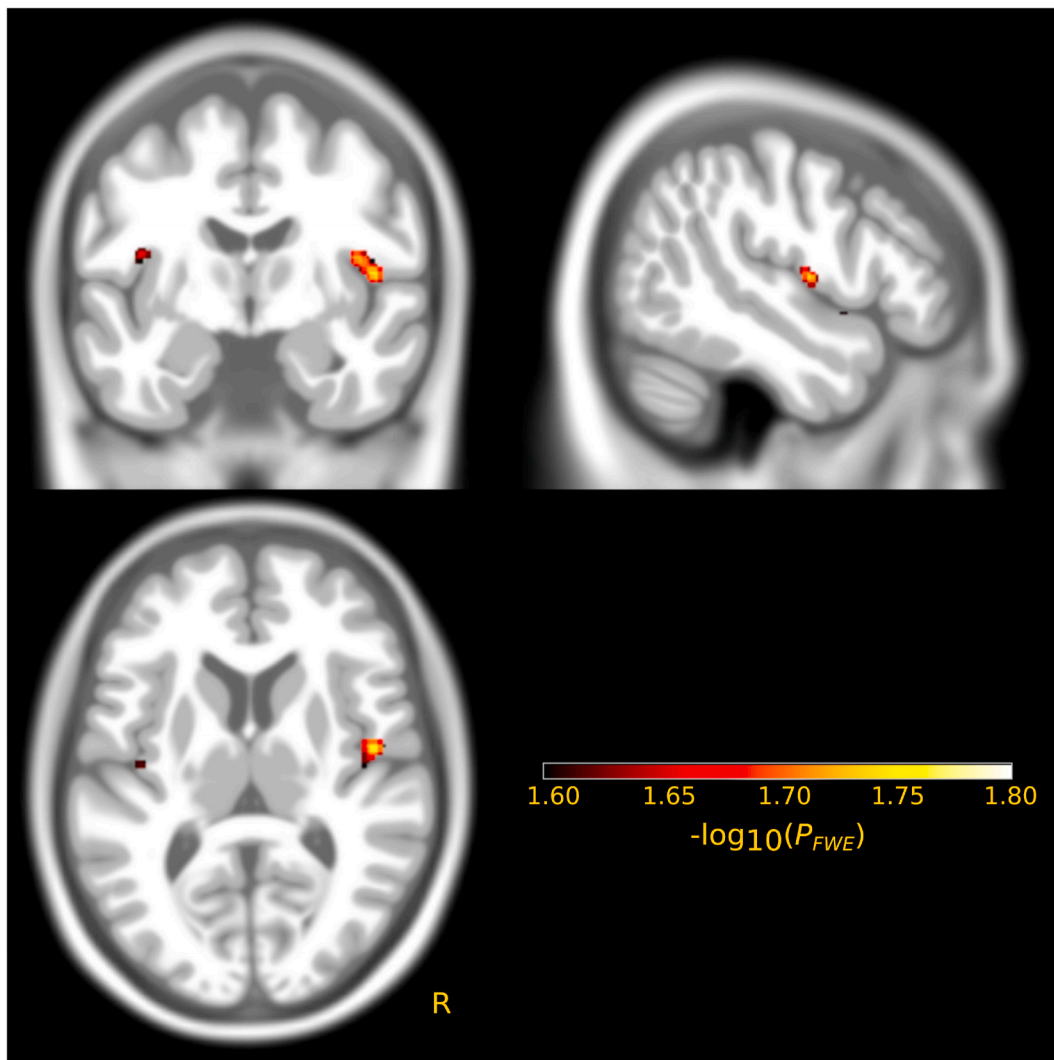**Fig. 1.** Results of the group by time interaction of the GMV data for the 30% response criterion. Figure shows -log10 transformed FWE-corrected p-values thresholded at alpha = 0.025. Significant clusters include the right and left insula. Results are visualized on the average T1 image transformed to MNI-space build on 555 subjects of the IXI data base distributed with the CAT12 toolbox. MNI-coordinates: 49, −7, 9.

Four clusters involving the right posterior insula/rolandic operculum, the left posterior insula/rolandic operculum, the left insula and the right anterior insula/superior temporal pole showed a significant interaction effect after FWE correction for multiple comparisons. These results were related to a decrease of GMV over time in non-responders compared to responders (Fig. 2). Post-hoc tests investigating time-effects per group and difference between groups at each time point showed no significant difference after further correction for the number of post-hoc tests. When applying the 50% criterion, no group by time interaction effects in GMV or WMV were observed. The additional ROI analysis revealed no significant interaction in additional brain regions for both criteria.

4.4. Post-hoc analyses

To facilitate further understanding of the main findings we conducted exploratory post-hoc analyses investigating gender by group, gender by group by time, age by time and age by time by group interactions as well the continuous association between pre-to posttreatment change in total CAPS-CA scores and delta GMV/WMV. As post-hoc tests were exploratory and were not further corrected for the additional number of tests performed, results have to be interpreted cautiously. All post-hoc analyses are fully described in the Supplementary material and are only briefly summarized here. There was no significant effect of the gender by group or gender by group by time interaction. Also, no significant effect was found for the age by time or age by group by time interaction. However, when investigating the age by time interaction within the responders and non-responders groups separately, we found a significant positive effect of age and delta GMV within the left insula for the responders group only ($n_{voxel} = 563$, peak $-\log10(p_{FWE}) = 2.24$, peak MNI coordinates $= -36, 3, 4.5$ [mm], Fig. S2).

Finally, we did not find any significant association between pre-to posttreatment change in total CAPS-CA scores and delta GMV/WMV.

5. Discussion

We investigated trauma-focused psychotherapy-related changes in structural MRI measurements in youth with PTSD. Our results show that treatment non-responders, relative to responders are characterized by a decrease over time of GMV in the bilateral anterior and posterior insula. These differences were only observed when applying a lenient response criterion ($\geq$30% CAPS-CA reduction) and not when applying a stricter

response criterion ($\geq$50% CAPS-CA reduction). Apart from the insula we did not find evidence for differential volume change in other brain areas associated with PTSD.

The insula can be subdivided in distinct regions, each with their own set of functions: the posterior insula is involved in the detection, interoceptive awareness and interpretation of somatosensory and autonomic stimuli. By integration with attentional systems the anterior insula initiates emotional experience and appropriate autonomic and behavioral responses to stimuli that are important to an individual (Menon and Uddin, 2010; Paulus and Stein, 2006; Uddin, 2015). In typically developing youth, developmental change of the anterior insula is characterized by linear volume increase throughout childhood and adolescence, while volume increase of the posterior insula shows a quadratic trajectory, in which volume increase flattens during late adolescence (Shaw et al., 2008; Tamnes et al., 2017). Our results show that in youth with PTSD, non-response to trauma-focused psychotherapy in comparison to treatment response is characterized by longitudinal bilateral volume decrease in both the posterior and anterior insula. Exploratory moderation analyses, indicated that while the responder group showed age-related volume increase over time of the left (but not right) insula, the non-responders group failed to show age-related increase over time (Fig S2.). This suggests that difference in insula volume change over time, reflects an absence of normal developmental volume increase of the insula in non-responders. Surprisingly, differential insula volume change occurred within three months, which is a short period, as developmental change typically progresses gradually over years. In addition, the absence of volume changes in treatment responders, suggests that successful trauma-focused psychotherapy may not directly normalize differences on MRI measurements associated with PTSD, which may take longer than the timespan of the current study. From another neurodevelopmental perspective, successful trauma-focused psychotherapy may cease adverse neurodevelopmental effects, at least for the duration of treatment.

The anterior insula is an integral hub in the 'salience network' and the posterior insula has been identified as a multimodal convergence zone for sensory information and body condition; both the anterior and posterior insula have been implicated in PTSD (Herringa et al., 2012; Menon and Uddin, 2010; Nicholson et al., 2016). Functional neuroimaging studies of the insula as a whole and insula subregions have shown greater activation and increased functional connectivity with the amygdala in response to salient stimuli in adults with PTSD (Etkin and
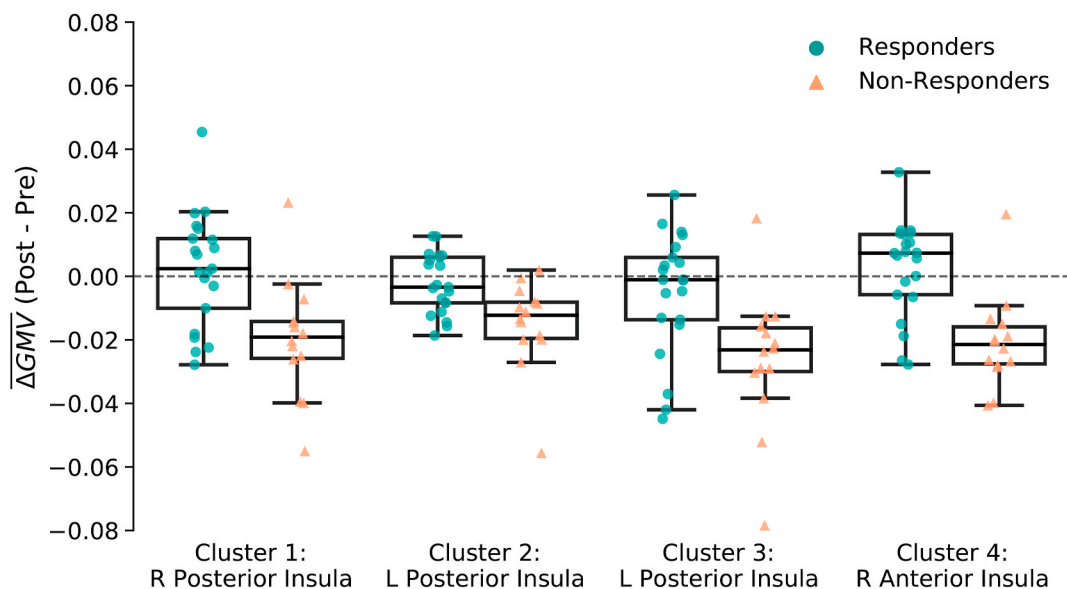

Fig. 2. Average delta GMV values extracted from the four significant clusters of the group by time interaction analysis using the 30% criterion. Boxplots summarize the data of individual responders (circles) and non-responders (triangles).

Wager, 2007). Sustained enhanced insular activation and connectivity in response to salient stimuli might initially represent an adaptive response to prolonged threat, which becomes maladaptive and increases PTSD risk if it persists when threat ceases (Van Wingen et al., 2011). Interestingly, successful trauma-focused psychotherapy has been associated with decrease in (anterior) insula activity and connectivity with the amygdala in both adults and youth with PTSD (Cisler et al., 2016; Thomaes et al., 2012; Van Rooij et al., 2016).

Whereas PTSD patients show increased insula function, some but not all prior structural neuroimaging studies show decreased insula volumes in both adults and adolescents with PTSD (Bromis et al., 2018; Herringa et al., 2012; Klabunde et al., 2017; Kühn and Gallinat, 2013; Meng et al., 2014). These findings suggest decreased insula volume as either a developmental risk factor for PTSD or as a plastic response to illness. The former possibility suggests that heightened insula activation represents a compensation for reduced insula volume in predisposed individuals, while the latter possibility suggests that reduced insula volume is a consequence of heightened insula activation in PTSD patients. Furthermore, previous studies in adults have shown that PTSD related brain abnormalities are more pronounced in patients with chronic PTSD compared to patients with new onset PTSD (Chao et al., 2014). Our study provides supportive evidence for a longitudinal association between PTSD persistence and failure of both anterior and posterior insula volume to increase over time in youth. This poses a potential explanation for the reduced insula volumes found in some cross-sectional studies comparing adult PTSD patients and healthy controls (Bromis et al., 2018; Kühn and Gallinat, 2013; Meng et al., 2014). In our study differential insula volume change occurred over a surprisingly short treatment period of eight weeks. If abnormal insula development would be a continuous process, this would consistently result in distinctively smaller insula volumes in patients in which PTSD persists over a period of years. However, prior cross-sectional studies in patients with persistent PTSD have not found evidence for consistent or pronounced insula volume differences. This further emphasizes that interpretation of the nature of structural MRI changes should be done with caution. Weinberger and Radulescu have for instance pointed out that variations measured with MRI can be associated with variation in water content, tissue perfusion, body weight, cholesterol levels, imperceptible head motion, endogenous steroid levels, time of day, and exercise and mental activities, rather than represent only gain or loss of regional brain tissue (Weinberger and Radulescu, 2020). Longitudinal neuroimaging studies with high resolution (7T) MRI scans, which examine neurodevelopmental trajectories of children with PTSD when they develop into adolescence and adulthood could help to further clarify the underlying mechanisms of structural MRI changes.

Interestingly, we only found evidence for differential longitudinal MRI changes when applying a lenient response criterion (30% CAPS-CA reduction) to divide responders and non-responders. With the 30% response criterion the non-responder group is smaller and more selective, representing true non-response. With the 50% response criterion this group is less selective as it also contains youth who are partial responders (30%–50% improvement). Including partial responders in the non-responder group could thus have obscured group by time differences related to non-response and could be an explanation for the differential findings employing the 30% or 50% criterion.

In contrast to some studies in adults with PTSD, we were unable to identify longitudinal changes in other brain areas, notably in areas which have been implicated in PTSD and undergo considerable developmental change throughout childhood and adolescence, such as the hippocampus and (vm-) PFC (Bromis et al., 2018; Giedd and Rapoport, 2010; Logue et al., 2018). Even with our ROI analysis in these regions, we were unable to detect longitudinal changes, reducing the chance of type II error. A recent naturalistic longitudinal study in youth with PTSD showed persistence of PTSD over a one-year period to be associated with sustained reduced PFC volume, abnormal PFC development and abnormal development of amygdala-hippocampus and amygdala (vm-)

PFC connectivity (Heyn et al., 2019). Also, the few structural neuroimaging studies of trauma-focused psychotherapy in adults that found evidence for pre-to posttreatment changes, found longitudinal volume increase of the hippocampus and PFC (Boukezzi et al., 2017; Helpman et al., 2016; Levy-Gigi et al., 2013). One possible explanation could be that changes in hippocampus and (vm-)PFC are latent and only become apparent after a longer period or later in development (Lindauer et al., 2005). This is supported by the notion that time between scans is considerably shorter in the current study relative to both the naturalistic longitudinal study in youth with PTSD and treatment outcome studies in adults with PTSD. This emphasizes the need for studies with longer follow-up periods to establish if short-term structural MRI changes persist over time and whether there are changes associated with psychotherapy response that do not become apparent directly after treatment but are expressed later on in development.

The present study details novel findings regarding the relationship between longitudinal insula changes and treatment response in youth with PTSD. It is not, however, without limitations. First, because it is considered unethical to withhold or delay a potentially effective treatment in youth with PTSD, we were unable to include a waitlist control group in the current study. The absence of a waitlist control group impedes controlling for non-treatment related factors with potential effects on brain morphometry, for example exposure to ongoing stressful life events such as ongoing third custody cases and out-of-home placement during the course of treatment. Therefore, the question whether there is a causal link between insula volume change and treatment non-response remains inconclusive. Establishing causality would be important because evidence for morphometric change specific to treatment non-response would support the troubling possibility that treatment non-response represents an ongoing environmental stressor, above and beyond PTSD persistence alone, and might in turn accelerate abnormal neurodevelopment (Felmingham et al., 2009; Keding and Herringa, 2015). Furthermore, because we did not have long-term follow-up scans, we could not assess if changes in MRI measurements persist over time or if there are changes which are expressed later in development. Both stress the need for future treatment studies with long-term naturalistic follow-up scans after trauma-focused psychotherapy. Second, although the majority (80%) of included youth had a full PTSD diagnosis, the remaining 20% had a partial PTSD diagnosis. Including youth with partial PTSD increased clinical heterogeneity and might have lowered overall treatment response due to a floor effect, however, by including youth with partial PTSD, our sample better reflects the real-life clinical setting, which adds to the ecological validity of our findings. Furthermore, the distribution between full and partial PTSD patients did not differ between responders and non-responders at baseline (Table 1), rendering it unlikely that the inclusion of partial PTSD patients influenced our main MRI findings. Third, youth were randomized to receive either TF-CBT or EMDR, and both treatment conditions were collapsed for the current analysis. Due to limited power it was not feasible to examine differences between treatment responders and non-responders separately for both treatment conditions. Importantly, efficacy of both treatment conditions has been shown comparable in an RCT with considerable sample overlap with the current study (Diehle et al., 2015). Finally, our study had a substantial drop-out rate, as 34% of randomized patients were lost to follow-up. Although such dropout rates reflect routine clinical practice and treatment completers and non-completers did not differ on baseline demographic, clinical and trauma related variables, there is a possibility that drop-out could have influenced our main findings through attrition bias. Nevertheless, baseline variables were matched in the 30% responder and non-responder groups, suggesting that the MRI results are not related to clinical, demographic or trauma related differences at baseline.

To our knowledge, this is the first report of structural MRI changes related to trauma-focused treatment response in youth with PTSD. Our findings show that treatment non-responders are characterized by failure to show age-related volume increase over time in both the anterior

and posterior insula. This may suggest a relationship between PTSD persistence after treatment and ongoing atypical development within the salience network. On the other hand, the absence of MRI changes in treatment responders suggests that successful trauma-focused psychotherapy might be associated with a (temporary) delay or surcease of abnormal brain development but not with a direct normalization of PTSD related brain abnormalities. Future studies with a long-term follow-up period after treatment should first aim to replicate our findings and determine if changes in MRI measurements persist after treatment, secondly examine if these changes are specific to trauma-focused psychotherapy response or related to the course of PTSD in general, and finally assess potential effects related to treatment response which are expressed later in development.

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Author contributions

Conception and design of the study: JZ, RJL, GvW. Data acquisition: JZ, JE, RodK. Analysis of the data: PZ, JZ, GvW. Interpretation: JZ, PZ, GvW. Drafting the manuscript: JZ, PZ. Critical revision of the manuscript for important intellectual content: all authors. All the authors have approved the final article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.10.037.

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