1. Introduction

Posttraumatic stress disorder (PTSD) is a disabling disorder associated with resting state functional connectivity alterations. However, whether specific brain regions are altered in PTSD or whether the whole brain network organization differs remains unclear. PTSD can be treated with trauma-focused therapy, although only half of the patients recover after treatment. In order to better understand PTSD psychopathology our aim was to study resting state networks in PTSD before and after treatment. Resting state functional magnetic resonance images were obtained from veterans with PTSD (n = 50) and controls (combat and civilian controls; n = 54) to explore which network topology properties (degree and clustering coefficient) of which brain regions are associated with PTSD. Then, PTSD-associated brain regions were investigated before and after treatment. PTSD patients were subdivided in persistent (n = 22) and remitted PTSD patients (n = 17), and compared with combat controls (n = 22), who were also reassessed. Prior to treatment associations with PTSD were found for the degree of orbitofrontal, and temporoparietal brain regions, and for the clustering coefficient of the anterior cingulate cortex. No significant effects were found over the course of treatment. Our results are in line with previous resting state studies, showing resting state connectivity alterations in the salience network and default mode network in PTSD, and also highlight the importance of other brain regions. However, network metrics do not seem to change over the course of treatment. This study contributes to a better understanding of the psychopathology of PTSD.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
2. Materials and methods

2.1. Participants

In total, 53 PTSD patients, 29 veteran controls (combat controls) and 26 civilian controls (healthy controls) were included, who were all male. Patients were recruited from one of four outpatient clinics of the Military Mental Healthcare Organization, The Netherlands. Patients were included after a psychologist or psychiatrist diagnosed PTSD. PTSD diagnosis was confirmed using the Clinician Administered PTSD scale (CAPS ≥ 45; Blake et al., 1995). The Structural Clinical interview for DSM-IV (SCID-I; First et al., 1997) was applied to diagnose comorbid disorders. A trained psychologist or PhD student administered the interviews. Control participants were recruited via advertisements, and the interviews (SCID and CAPS) were also applied to investigate PTSD symptoms and psychiatric disorders. Inclusion criteria for controls were no current psychiatric or neurological disorder, and no presence of current PTSD symptoms (CAPS ≤ 15).

After an interval of six to eight months 39 PTSD patients and 22 combat controls were reassessed with interviews and MRI. In order to match the civilian controls to the veteran groups on age, the civilian controls were recruited after the veterans. However, due to scanner updates during our protocol re-assessment of the civilian controls was not performed. Baseline and follow-up scans of the veteran groups were all performed before the scanner update. During the six to eight months interval patients received trauma-focused therapy, in line with Dutch and international treatment guidelines (Balkom et al., 2013; Bisson et al., 2007; Foa et al., 2000). Trauma-focused therapy included trauma-focused cognitive behavioral therapy (TFCBT) and/or eye-movement desensitization and reprocessing (EMDR), which are both effective therapeutic strategies that have similar efficacy (Bisson et al., 2007). A clinician applied the treatment (treatment as usual), and decided which strategy was applied initially. Based on PTSD diagnosis at the reassessment according to DSM-IV criteria (American Psychiatric Association, 1994) PTSD patients were divided into a remitted group (no PTSD diagnosis at reassessment; n = 17), and a symptom persistent group (PTSD diagnosis at reassessment; n = 22). After receiving a complete written and verbal description of the study all participants gave written informed consent. The Medical Ethical Committee of the UMC Utrecht approved the study, and the study was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.2. Image acquisition and pre-processing

Resting state functional magnetic resonance images were obtained on a 3.0 Tesla scanner (Philips Medical System, Best, the Netherlands: T2*-weighted echo planar interleaved images, repetition time TR = 1600 ms, TE = 23 ms, flip angle = 72.5°, field of view (FOV) 256 × 208 × 120, 30 transverse slices, 64 × 51 matrix, total scan time 8 min and 44.8 s, 0.4 mm gap, acquired voxel size 4 × 4 × 3.60 mm), where participants were asked to focus on a fixation cross, while letting their mind wander and relax. Images were pre-processed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), and the Resting-State fMRI Data Analysis Toolkit (restfmri.net; Song et al., 2011). Pre-processing included slice-time correction, realignment, co-registration with a T1-weighted high resolution scan acquired during the same scan session (TR = 10 ms, TE = 4.6 ms, flip angle 8°, 200 sagittal slices, FOV 240 × 240 × 160, matrix of 304 × 259), normalization, spatial smoothing (8 FWHM), de-trending, and band-pass filtering (0.01–0.08 Hz). Individuals that showed excessive motion (>2 mm in x, y, z direction or >2° in pitch, roll, yaw rotation) were excluded from analyses (three PTSD patients, one healthy control), resulting in baseline data of 50 PTSD patients and 54 controls, and data at reassessment of 39 PTSD patients and 22 combat controls. To correct for physiological noise and motion, nuisance parameters were included as regressors in the analyses (cerebrospinal fluid signal, white matter signal, and
individual realignment parameters). Using the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002), the mean time-series of 90 anatomical structures were extracted and correlated with each other (Pearson’s correlation) to create individual subject correlation matrices. The cerebellar regions were excluded, since the cerebellum was not included in the FOV for all subjects. The correlation matrices were used for calculation of network measures.

2.3. Network metrics

Network metrics were calculated with the brain connectivity toolbox (https://sites.google.com/site/bctnet/Home; Rubinov and Sporns, 2010). The individual correlation matrices were thresholded over a range of initial height thresholds (ranging from 0 to 0.9 in steps of 0.1), where a 0.1 threshold indicates that only correlations higher than 0.1 are preserved in the weighted correlation matrix. The minimum threshold was 0 in order to circumvent interpreting negative correlations, which can be induced due to pre-processing steps (Van Dijk et al., 2010), and up to 0.9 since 1 is the maximum value of a correlation coefficient. Several thresholds were investigated to prevent bias of selecting one threshold. For each of the matrices node-specific degree and clustering coefficient were calculated (undirected). These network metrics were chosen since they are basic graph metrics that have a straightforward neurobiological interpretation (Rubinov and Sporns, 2010). The degree of a node is the number of connections of a node that link the node to the rest of the network, indicating the importance or centrality of a node in the network (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). The clustering coefficient is the number of connections to the nearest neighbors of a node as a fraction of the maximum number of possible connections between the nearest neighbors, which is a measure of functional segregation (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

2.4. Network statistics

To explore which pre-treatment (baseline) network properties were related to PTSD, backward Wald regression was applied (IBM SPSS statistics version 21). Backward Wald regression determines the most optimal fitted model, with a minimum number of variables, which best explains the factor of interest (group: PTSD versus non-PTSD). The veteran (trauma-exposed) and civilian (non-trauma-exposed) controls were not investigated as separate groups, since we were not interested in the effects of trauma exposure in particular, but in PTSD-related characteristics. Therefore we investigated PTSD patients versus all controls combined. Backward regression also provides a data-driven method without a priori specified variables of interest. To circumvent co-linearity the left and right hemisphere were analyzed separately, as well as the degree and clustering coefficient. In a case where the model did not run due to convergence of the variables in the algorithm, one of two variables with the highest correlation was removed from the regression model, and regarded as representing both variables in the final model. Bonferroni correction was applied for the number of backward regression models investigated ($p < 0.05/40 = 0.00125$ is deemed significant). The brain regions that were consistently associated with PTSD in the optimal fitted model over at least four height thresholds were further investigated over the course of treatment. A minimum of four thresholds was chosen to reduce false positives found (e.g. results for a single threshold), and to reduce bias by selecting one representative threshold, but also to retain sensitivity for detecting connectivity variables related to PTSD. Of note, the method of thresholding and reporting results over thresholds remains subject of discussion, and optimal procedures should be developed in order to standardize analysis methods (Drakesmith et al., 2015). To give an indication for the direction of the relation the mean b-value was calculated. For these regions repeated measure ANOVA’s were utilized to assess treatment-related changes over time between remitted and persistent PTSD patients and combat controls (3 groups × 2 time points). Bonferroni correction was applied to correct for the number of brain regions that were investigated. Furthermore, correlational analyses between symptom improvement (ΔCAPS = baseline CAPS – reassessment CAPS) and change in network characteristics for the PTSD associated brain regions were explored within the PTSD group.

3. Results

3.1. Demographics

An overview of the demographical and clinical data can be found in Tables 1 and 2. Age and handedness did not differ between PTSD patients ($n = 50$) and controls ($n = 54$; see Table 1). Educational level as measured with the international standard classification of education (ISCED; Schneider, 2013) was higher in controls than in PTSD patients, but parental education did not differ. Early life trauma was also higher in PTSD patients, which was driven by the civilian controls, who reported the lowest early trauma experiences. PTSD severity as measured with the CAPS was higher in PTSD patients than in controls. At the reassessment, 17 PTSD patients were remitted and 22 still had a PTSD diagnosis, in line with previously response rates of 50% (Bisson et al., 2013). The remitted and persistent PTSD patients and combat controls ($n = 22$) did not differ in age, education, handedness, early life trauma, number of times deployed, time since last deployment, or time between scans (see Table 2). The remitted and persistent PTSD groups showed no difference in number of treatment sessions, and psychotropic medication (see Table 2). About a third of the patients was taking psychotropic medication at baseline, mostly selective serotonin reuptake inhibitors (SSRI) and benzodiazepines. After six to eight months, more persistent PTSD patients were using prescribed medication. Persistent PTSD patients had more comorbid mood disorders at baseline, and more comorbid anxiety disorders at both time points. At baseline persistent PTSD patients showed a trend significant higher symptom severity compared to remitted PTSD patients.

Table 1

Demographical characteristics for PTSD patients and controls at baseline. ISCED = international standard classification of education; CAPS = clinician-administered PTSD scale; SSRI = selective serotonin re-uptake inhibitor; SARI = serotonin antagonist and reuptake inhibitor.

| Category                                      | PTSD (mean ± SD) | Controls (mean ± SD) | Test-value (df) | p-Value |
|-----------------------------------------------|------------------|----------------------|-----------------|---------|
| Number of participants                        | 50               | 54                   |                 |         |
| Veterans/civilian                             | 50/0             | 29/25                |                 |         |
| Age (range 21–57)                             | 36.30 (± 9.64)   | 35.74 (± 6.68)       | $t_{(102)}$ = −0.29 | 0.769   |
| Education (ISCED)                             |                  |                      |                 |         |
| Own                                           | 3.80 (± 1.24)    | 4.35 (± 1.58)        | $t_{(98)}$ = 2.59 | 0.010   |
| Mother                                        | 2.54 (± 1.35)    | 3.02 (± 1.63)        | $t_{(98)}$ = 1.60 | 0.114   |
| Father                                        | 3.50 (± 1.92)    | 3.28 (± 1.82)        | $t_{(97)}$ = −0.58 | 0.566   |
| Edinburgh handedness inventory (left/ambidextrous/right) | (4/4/41)         | (2/4/48)             | $X^2(2) = 0.98$ | 0.614   |
| Early trauma inventory                        | 4.82 (± 4.57)    | 2.58 (± 2.04)        | 3               | 0.005   |
| CAPS total score                              | 70.44 (± 13.42)  | 50.06 (± 4.56)       | $t_{(102)}$ = −32.75 | $p < 0.001$ |
3.2. PTSD versus controls — baseline associations

Results from the backward regression models (p < 0.00125) can be found in the Supplementary information (Supplementary Tables S1–S4). Baseline PTSD was significantly associated with degree and clustering coefficient of a variety of brain regions. Brain areas that were associated with PTSD in the optimal fitted models for at least four thresholds are listed below (see Fig. 1 and Table 3).

A positive mean b-value for predicting PTSD group membership was consistently (≥4 thresholds) found for the bilateral olfactory gyrus, right precuneus and left fusiform gyrus. This might indicate that PTSD had on average higher degree in these brain regions compared to controls. A negative mean b-value for predicting PTSD group membership was consistently (≥4 thresholds) found for the degree of the bilateral rolandic operculum, left orbital inferior frontal gyrus, left orbital superior frontal gyrus, right superior temporal gyrus, right inferior temporal gyrus, left angular gyrus, left superior parietal gyrus, left posterior cingulate gyrus, left middle temporal pole, and left pallidum. This might indicate that PTSD had on average lower degree of these brain areas versus controls. The clustering coefficient from the left anterior cingulate cortex was also negatively associated with PTSD for four thresholds. No significant correlations were found between network metrics and symptom severity (CAPS score) at baseline.

3.3. Treatment effects

There were no significant (Bonferroni corrected) group or group by time interaction effects found with the repeated measures ANOVAs (p < 0.05/16 = 0.003 is deemed significant). Post-hoc analysis of the remitted versus persistent PTSD patients showed a significant group by time interaction effect of the pallidum degree (threshold 0.4 and 0.5, p < 0.003), where remitted PTSD showed an increase in degree or clustering coefficient while persistent PTSD patients did not change over time or showed an increase. No significant correlations were observed between the difference in network metrics and symptom improvement (ΔCAPS).

4. Discussion

In this resting state functional MRI study, baseline PTSD-related functional whole brain network properties were investigated, and followed up after treatment. Prior to treatment, we observed that network topology of orbitofrontal regions, the left cingulate cortex, parietal regions, and temporal regions was associated with PTSD over several thresholds. This indicates that PTSD is associated with aberrant information integration in these brain regions. Longitudinal analyses showed no main effects of group or group by time interaction effects over the course of treatment in these brain regions.
Our results are in line with previous cross-sectional resting state whole brain fMRI network studies, reporting decreased orbitofrontal connectivity (Jin et al., 2014), decreased frontal and temporal degree (Suo et al., 2015), and a trend for increased precuneus degree (Lei et al., 2015). A magnetic encephalography (MEG) study also reported increased connectivity of the precuneus (amongst other regions) in PTSD (Dunkley et al., 2014). In addition, a state specific network comprising the cingulate cortex network can differentiate patients from controls (Li et al., 2014). Seed analyses have also shown reduced resting state functional connectivity of the precuneus/posterior cingulate cortex and temporoparietal regions during rest in PTSD patients versus trauma-exposed and non-trauma-exposed controls, which are regions involved in the DMN (Bluhm et al., 2009; Chen and Etkin, 2013; Sripada et al., 2012b). Our results also indicate that DMN regions have reduced degree in PTSD, but on average an increased degree for the precuneus. This indicates that the DMN regions are less integrated in and of less importance for the whole brain network, except for the precuneus, which is more integrated in the whole brain network. The precuneus is involved in autobiographical memory and is also related to self-referential processing (Kelley et al., 2002; Cavanna and Trimble,

| Lobe    | Brain region                              | Mean b | Min. b | Max. b | Frequency |
|---------|-------------------------------------------|--------|--------|--------|-----------|
| Positive| FrONTAL                                   | 0.240  | 0.030  | 0.810  | 5         |
|         | Right olfactory gyrus                     |        |        |        |           |
|         | Left olfactory gyrus                      | 0.080  | 0.060  | 0.120  | 4         |
|         | PARIETAL                                  | 0.276  | -0.170 | 1.610  | 4         |
|         | Right precune                             |        |        |        |           |
|         | OCCIPITAL                                  | 0.037  | -0.194 | 0.130  | 4         |
|         | Left fusiform gyrus                       |        |        |        |           |
|         | CENTRAL                                   | -0.262 | -1.020 | -0.080 | 6         |
|         | Right rolandic operculum                  | -0.063 | -0.440 | 0.460  | 4         |
|         | Left rolandic operculum                   |        |        |        |           |
|         | FRONTAL                                   | -0.235 | -0.460 | -0.060 | 5         |
|         | Left orbital inferior frontal gyrus        |        |        |        |           |
|         | Left orbital superior frontal gyrus        | -0.137 | -0.178 | -0.090 | 4         |
|         | TEMPORAL                                   | -0.008 | -0.900 | 0.200  | 6         |
|         | Right inferior parietal gyrus             | -0.106 | -0.520 | 0.260  | 5         |
|         | Left angular gyrus                        | -0.090 | -0.160 | -0.040 | 4         |
|         | Left superior parietal gyrus              | -0.160 | -0.290 | -0.070 | 4         |
|         | LIMBIC                                    | -0.763 | -3.040 | 2.450  | 4         |
|         | Left anterior cingulate gyrus (clustering coefficient) | -0.294 | -0.880 | -0.040 | 4         |
|         | Left posterior cingulate gyrus            |        |        |        |           |
|         | Left middle temporal pole                 | -0.078 | -0.110 | -0.050 | 4         |
|         | SUBCORTICAL                                | -0.004 | -0.118 | 0.150  | 5         |

Fig. 1. Brain regions with PTSD-associated clustering coefficient (ACC) and degree (all other regions). Positive associations are presented in warm colors (red, orange), and negative associations in cool (blue) colors. Slices \( y = -8 \) & \( z = 22 \); \( y = 18 \); \( x = -29 \). Abbreviations: ANG = angular gyrus, ACC = anterior cingulate cortex, FUS = fusiform gyrus, ITG = inferior temporal gyrus, Mid TP = middle temporal pole, oIFG = orbital inferior frontal gyrus, OLF = Olfactory gyrus, oSFG = orbital superior frontal gyrus, PAL = pallidum, PCC = posterior cingulate cortex, PREC = precuneus, ROL = rolandic operculum, SPG = superior parietal gyrus, STG = superior temporal gyrus.
Reduced activation of the precuneus has been reported in PTSD patients during encoding of neutral memory (Geuze et al., 2007), while more sensitivity of precuneus to memory formation in an emotional context has also been reported (Whalley et al., 2009). Furthermore, precuneus activity has been related to trauma memory generalization (Hayes et al., 2011), and flashbacks (Whalley et al., 2013). Thus, alterations in the precuneus are associated with PTSD and may potentially be related to altered memory- and self-referential processes, such as memory deficits, intrusions or flashbacks. These findings altogether suggest that the DMN is disturbed in PTSD, and that the number of connections of the precuneus is increased, which warrants further investigation.

Furthermore, we found associations with PTSD in the degree of the pallidum, Rolandic operculum, and middle temporal pole, and in the clustering coefficient of the ACC. These are regions that may be regarded as nodes of the salience network (SN; Lei et al., 2015; Menon, 2011). Previous resting state fMRI studies indicated higher functional connectivity between SN brain regions in PTSD versus both trauma-exposed as non-trauma-exposed controls (Daniels et al., 2010; Lei et al., 2015; Sripada et al., 2012b). A structural graph analysis also indicated higher pallidum centrality in PTSD versus non-trauma-exposed controls (Long et al., 2013). This is in line with our results, showing increased importance of the pallidum in the whole brain network. However, other salience network regions had on average lower degree in PTSD (by showing a negative average b-value). This indicates that these regions are less important in the whole brain network in PTSD. Increased connectivity may therefore only be present between specific regions (such as the pallidum) or with limbic brain regions such as the amygdala and the insula, which were regions of interest in the previous resting state studies. Our results do, however, subscribe the importance of SN regions for PTSD. In addition, the average lower clustering coefficient in PTSD observed here suggests that the ACC neighbors have reduced connectivity with each other. This may indicate that information integration in the ACC network is reduced in PTSD. Reduced ACC resting state functional connectivity with the thalamus, amygdala, PCC/prefrontal regions has been reported in PTSD versus non-trauma-exposed controls (Kennis et al., 2014), trauma-exposed controls (Sripada et al., 2012a; Yin et al., 2011) or both (Sripada et al., 2012b). Thus, our results together with previous findings indicate altered connectivity and potentially information processing of the SN is associated with PTSD.

In addition to the DMN and SN, it has been suggested that the central executive network (CEN) is a third important network that can be related to dysfunction in psychiatric disorders, and this model is described as a triple network model (Menon, 2011). Our results support this model by showing an association between PTSD and the degree of important nodes of the CEN, i.e. the superior parietal gyrus, and the orbital part of the IFG and SFG, are associated with PTSD (Menon, 2011). Future studies should investigate if resting state alterations in PTSD are specific to these three networks compared to other networks.

Furthermore, network metrics in the fusiform gyrus and olfactory cortex were on average higher in PTSD, suggesting that these brain areas are more important in the whole brain network in PTSD patients versus controls. Interestingly, altered olfactory perception has been reported in PTSD, which is strongly related to activity of the olfactory cortex (Vasterling et al., 2000; Vermetten et al., 2007; Zald and Pardo, 2000). Furthermore, increased activation of the fusiform gyrus in PTSD versus both trauma-exposed and non-trauma-exposed controls was reported in a meta-analysis (Patel et al., 2012). In addition, previous studies reported higher activity of occipital brain areas in response to trauma-related pictures in PTSD (Hendler et al., 2001; Hendler et al., 2003), and during dissociative responses (Lanius et al., 2005; Whalley et al., 2013). Thus, we could hypothesize that altered network topology of the fusiform gyrus and the olfactory cortex may be related to altered visual and olfactory perception in PTSD, and potentially to dissociative symptoms. However, future research should establish the importance of these brain regions in PTSD.

Although we expected to find differences over the course of treatment between controls, remitted and persistent PTSD, our results did not show any group or group by time interaction effects in the longitudinal analysis. Only when comparing remitted and persistent PTSD patients a significant interaction effect was observed in the pallidum. This indicates that treatment may alter network topology in relation to remission from PTSD, although caution should be taken when interpreting these results. Interestingly, the regions previously related to remission from PTSD or treatment outcome were not associated with PTSD at baseline in our sample (e.g. amygdala, hippocampus, medial PFC; Roy et al., 2010; Simmons et al., 2013; van Rooij et al., 2015a). Alternative approaches (e.g. using treatment-theory driven a priori specified seeds), potentially focusing on pallidum functional connectivity, may provide more sensitivity to treatment related alterations in neural networks.

A number of limitations have to be taken into account when interpreting the findings of this study. First, dividing the PTSD group into a persistent and remitted group resulted in two small samples. However, analyzing the PTSD patient group as a whole did not reveal any general treatment effects, indicating the group subdivision did not underlie the null findings. In addition, by applying whole brain analyses (and not investigating a selection of a priori regions of interest) strong multiple comparison correction was required. Therefore, to confirm that treatment may not alter PTSD-related network metrics, additional research with larger samples of PTSD patients is needed before and after treatment to investigate (heterogeneity in) remission from PTSD. Patients and controls differed on educational level. However, since we did not find correlations with ISCED level and PTSD-related network metrics and their parental education did not differ, educational level is not likely to influence our results. In addition, adding educational level into backward regression (threshold 0.3) did not change the observed association between network metrics and PTSD; similar brain regions remained included in the most optimal fitted model. Thus, although educational level may be lower in PTSD patients, this does not directly interact with the association between brain topology and PTSD.

Furthermore, the healthy controls were not followed up after treatment, due to scanner updates. Therefore, including them at baseline may influence the results, especially since the healthy controls differed from the patients in early life trauma. However, exploration of backward regression without the healthy controls showed similar brain regions (threshold 0.3), indicating that the effects were not (fully) driven by inclusion of healthy controls (with lower early life trauma) at baseline. Also, only one female participant applied for this study, and therefore we did not include women here. This hampers generalization of our results to women. The remitted and persistent PTSD group differed in comorbidity. However, there were no significant correlations between PTSD-related network metrics and comorbidity. Therefore, it is not expected that including patients with comorbidity majorly affects our results.

Despite the great care taken to minimize the effects of motion by including regressors (realignment parameters, cerebrospinal fluid signal and white matter signal), the BOLD signal measured to calculate resting state functional connectivity can still be confounded by other temporal patterns, such as cardiac and respiratory patterns, and motion (Van Dijk et al., 2010). Furthermore, we selected only positive connections by thresholding, initial parcellation; Drakesmith et al., 2015; Patenaude et al., 2017; Poldrack, 2010). In addition, the methodology to create a neural network representation or connectome is relatively new, is still developing, and has many analytical degrees of freedom (e.g. thresholding, initial parcellation; Drakesmith et al., 2015; Rubinov and Sporns, 2010). Therefore, we presented results of several applied thresholds. Future maturation of the methodology should.
provide more standard approaches in order to better compare results between studies.

5. Conclusion

This study indicates that resting state network measures of orbitofrontal, temporal and parietal brain regions, and the cingulate cortex are associated with PTSD. This is in line with previous studies reporting alteration in resting state functional connectivity in the salience network and default mode network. In addition, some regions (orbitofrontal, superior parietal) of the central executive network were also found to be associated with PTSD. Therefore, our results may be interpreted from the triple network model perspective, indicating that indeed the salience, default mode and central executive network are of importance for PTSD psychopathology. However, these PTSD associated network metrics do not seem to change over the course of treatment. This study contributes to a better understanding of the psychopathology of PTSD, and PTSD treatment.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.12.008.

Financial support

This research was funded by the Dutch Ministry of Defence.

Conflict of interest

None.

Acknowledgments

We thank Dr. Iris Eekhout for her advise on the statistical analysis and Alieke Reijnen MSc for her valuable comments. This study is financially supported by the Dutch Ministry of Defence.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders: DSM IV, fourth ed. American Psychiatric Association, Washington DC.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual for Mental Disorders: DSM 5, fifth ed. American Psychiatric Association, Washington DC.

Aupperle RL, Allard CR, Simmons AN, Flagan T, Thorp SR, Norman SB, Paulus MP, Stein MB, 2013. Neural responses during emotional processing before and after cognitive therapy for battered women. Psychiatry Res. Neuroimaging 214 (1), 55.

Balkom A, Vliet I, Emmelkamp P, Bockting C, Spijker J, Hermens M, Meeuwissen J, 2014. Multidisciplinaire richtlijn angststoornissen (derde revisie). Richtlijn voor de behandeling van angststoornissen. Trimbos-Instituut, Utrecht.

Bisson, J.J., Ehlers, A., Matthews, R., Pilling, S., Bryant, R., 2007. Changes in anterior cingulate and amygdala after cognitive behavioral therapy of post-traumatic stress disorder. Psychol. Sci. 18 (2), 127–129.

Bisson, J.I., Roberts, N.P., Andrew, M., Cooper, R., Lewis, C., 2013. Psychological therapies for chronic post-traumatic stress disorder: systematic review and meta-analysis. Br. J. Psychiatry 199, 97–104.

Bisson, J.J., Roberts, N.F., Andrew, M., Cooper, R., Lewis, C., 2013. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. The Cochrane Database of Systematic Reviews 12, CD003388.

Blake DD, Wetherell FW, Nagy LM, Kaloupek DG, Charney DS, Keane TM, 1995. The development of a clinician-administered PTSD scale. J. Trauma. Stress. 8 (1), 75–90.

Bluhm RL, Williamson PC, Osuch E, Freewen PA, Stevens TK, Boksmans K, Neufeld, R.W.J., Théberge J, Lanius RA, 2009. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. J. Psychiatr. Neurosci. 34 (3), 187–194.

Bradley, R., Greene, J., Russ, E., Dutra, L, Westen, D, 2005. A multidimensional meta-analysis of psychotherapy for PTSD. Ann. J. Psychiatr. 162 (2), 214–227.

Brown VM, Labar KS, Haswell CC, Gold AL, Boll SK, Van Voorhees E, Mac CE, Calhoun PS, Fairbank JA, Green KT, et al., 2014. Altered resting-state functional connectivity of bocalateral and centromedial amygdala complexes in posttraumatic stress disorder. Neuropsychopharmacology 39 (2), 351–359.

Bryant RA, Felmingham K, Whitford TJ, Kemp A, Hughes G, Peduto A, Williams LM, 2008a. Rostral anterior cingulate volume predicts treatment response to cognitive-behavioural therapy for posttraumatic stress disorder. J. Psychiatr. Neurosci. 33 (2), 142–146.

Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L, 2008b. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol. Med. 38 (4), 553–561.

Bullmore, E., Sporns, O., 2000. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 (3), 186–198.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129 (3), 564–583.

Chen, A.C., Etkin, A., 2013. Hippocampal network connectivity and activation differentiate post-traumatic stress disorder from generalized anxiety disorder. Neuropsychopharmacology 38 (10), 1889–1898.

Daniels JK, Mcfarlane AC, Bluhm RL, Moorees R, Richard Clark C, Shaw M, Williamson PC, Denison M, Lanius RA, 2010. Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. J. Psychiatr. Neurosci. 35 (4), 258–266.

Drakesmith M, Caeyenberghs K, Dutt A, Lewis G, David AS, Jones DK, 2015. Overcoming the effects of false positive and threshold bias in graph theoretical analyses of neuroimaging data. NeuroImage 118, 313–333.

Dunleavy, B.T., Doebus, S.M., Sedge, P.A., Grodecki, R.J., Shek, P.N., Pang, E.W., Taylor, M.J., 2014. Resting-state hippocampal connectivity correlates with symptom severity in post-traumatic stress disorder. NeuroImage: Clinical 5, 377–384.

Fani, N., Ashraf, A., Afzal, N., Jawed, F., Kitayama, N., Reed, L., Brenner, J.D., 2011. Increased neural response to trauma scripts in posttraumatic stress disorder following paroxetine treatment: a pilot study. Neurosci. Lett. 491 (3), 196–201.

Felmingham, K, Kemp A, Williams L, Das P, Hughes G, Peduto A, Bryant R, 2007. Amygdala and ventral anterior cingulate activation predicts treatment to cognitive behavioral therapy for post-traumatic stress disorder. Psychol. Med. 38 (4), 553–561.
Reijnen, A., Rademaker, A.R., Vermetten, E., Geuze, E., 2014. Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: a 2-year longitudinal analysis. Eur. Psychol. 30, 341–346.

Rothbaum, B.O., Davis, M., 2003. Applying learning principles to the treatment of post-trauma reactions. Ann. N. Y. Acad. Sci. 1008, 112–121.

Roy, M.J., Francis, J., Friedlander, J., Banks-Williams, L., Lande, R.G., Taylor, P., Blair, J., McEllan, J., Law, W., Tarpley, V., Patt, I., Yu, H., Mallinger, A., Difede, J., Rizzo, A., Rothbaum, B., 2010. Improvement in cerebral function with treatment of posttraumatic stress disorder. Ann. N. Y. Acad. Sci. 1208, 142–149.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. NeuroImage 52 (3), 1059–1069.

Schneider, S.L., 2013. The international standard classification of education 2011. Comparative Social Research 30, 365–379.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., 2011. REST: A framework for functional magnetic resonance imaging data processing. PLoS ONE 6 (9).

Sripada, R.K., King, A.P., Garfinkel, S.N., Wang, X., Sripada, C.S., Welsh, R.C., Liberzon, I., 2012a. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J. Psychiatry Neurosci. 37 (4), 241–249.

Sripada, R.K., King, A.P., Welsh, R.C., Garfinkel, S.N., Wang, X., Sripada, C.S., Liberzon, I., 2012b. Neural dysregulation in posttraumatic stress disorder: Evidence for disrupted equilibrium between salience and default mode brain networks. Psychosom. Med. 74 (9), 904–911.

Suo, X., Lei, D., Li, K., Chen, F., Li, F., Li, L., Huang, X., Liu, S., Li, L., Kemp, G.J., et al., 2015. Disrupted brain network topology in pediatric posttraumatic stress disorder: a resting-state fMRI study. Hum. Brain Mapp. 36 (9), 3677–3686.

Tursich, M., Ros, T., Frewen, P.A., Kluetsch, R.C., Calhoun, V.D., Lanius, R.A., 2015. Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. Acta Psychiatr. Scand. 132 (1), 29–38.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289.

Van den Heuvel, M.P., Hulshoff Pol, H.E., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur. Neuropsychopharmacol. 20 (8), 519–534.

Van Dijk, K.R.A., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103 (1), 297–321.

Van Rooij, S.J., Kennis, M., Vink, M., Geuze, E., 2015a. Predicting treatment outcome in PTSD: a longitudinal functional MRI study on trauma-unrelated emotional processing. Neuropsychopharmacology http://dx.doi.org/10.1038/npp.2015.257.

Van Rooij, S.J., Geuze, E., Kennis, M., Rademaker, A.R., Vink, M., 2015b. Neural correlates of inhibition and contextual cue processing related to treatment response in PTSD. Neuropsychopharmacology 40 (3), 667–675.

Van Rooij, S.J.H., Kennis, M., Sprouseman, R., van den Heuvel, M.P., Kahn, R.S., Geuze, E., 2015c. Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. Psychol. Med. 45 (13), 2737–2746.

Vasterling, J.J., Bradley, K., Sutker, P.B., 2000. Olfactory identification in combat-related posttraumatic stress disorder, J. Trauma. Stress. 13 (2), 241–253.

Vermetten, E., Schmah, C., Southwick, S.M., Bremner, J.D., 2007. Positron tomographic emission study of olfactory induced emotional recall in veterans with and without combat-related posttraumatic stress disorder. Psychopharmacol. Bull. 40 (1), 8–30.

Whalley, M.G., Rugg, M.D., Smith, A.P.R., Dolan, R.J., Brewin, C.R., 2009. Incidental retrieval of emotional contexts in post-traumatic stress disorder and depression: an fMRI study. Brain Cogn. 69 (1), 98–107.

Whalley, M.G., Kroes, M.C.W., Huntley, Z., Rugg, M.D., Davis, S.W., Brewin, C.R., 2013. An fMRI investigation of posttraumatic flashbacks. Brain Cogn. 81 (1), 151–159.

World Medical Association, 2013. Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA — Journal of the American Medical Association 310 (20), 2191–2194.

Yin, Y., Jin, C., Hu, X., Duan, L., Li, Z., Song, M., Chen, H., Feng, B., Jiang, T., Jin, H., et al., 2011. Altered resting-state functional connectivity of thalamus in earthquake-induced posttraumatic stress disorder: a functional magnetic resonance imaging study. Brain Res. 1411, 98–107.

Zald, D.H., Pardo, J.V., 2000. Functional neuroimaging of the olfactory system in humans. Int. J. Psychophysiol. 36 (2), 165–181.