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Resting state Functional Connectivity of the Anterior Cingulate Cortex in Veterans With and Without Post-traumatic Stress Disorder

Mitzy Kennis,[1,2]* Arthur R. Rademaker,[1,2] Sanne J.H. van Rooij,[1,2] René S. Kahn,[2] and Elbert Geuze[1,2]

[1]*Research Centre-Military Mental Healthcare, Ministry of Defence, CX, Utrecht, The Netherlands*
[2]*Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, CX, Utrecht, The Netherlands*

Abstract: Post-traumatic stress disorder (PTSD) is an anxiety disorder that is associated with structural and functional alterations in several brain areas, including the anterior cingulate cortex (ACC). Here, we examine resting state functional connectivity of ACC subdivisions in PTSD, using a seed-based approach. Resting state magnetic resonance images were obtained from male veterans with ($n = 31$) and without ($n = 25$) PTSD, and healthy male civilian controls ($n = 25$). Veterans with and without PTSD (combat controls) had reduced functional connectivity compared to healthy controls between the caudal ACC and the precentral gyrus, and between the perigenual ACC and the superior medial gyrus and middle temporal gyrus. Combat controls had increased connectivity between the rostral ACC and precentral/middle frontal gyrus compared to PTSD patients and healthy civilian controls. The resting state functional connectivity differences in the perigenual ACC network reported here indicate that veterans differ from healthy controls, potentially due to military training, deployment, and/or trauma exposure. In addition, specific alterations in the combat controls may potentially be related to resilience. These results underline the importance of distinguishing trauma-exposed (combat) controls from healthy civilian controls when studying PTSD. *Hum Brain Mapp 36:99–109, 2015.* © 2014 Wiley Periodicals, Inc.

Key words: post-traumatic stress disorder; anterior cingulate cortex; resting state; fMRI; superior medial gyrus; middle temporal gyrus; precentral gyrus; veterans; trauma

INTRODUCTION

Post-traumatic stress disorder (PTSD) is an anxiety disorder that may develop after experiencing a traumatic event [American Psychiatric Association, 1994]. Since many veterans experience traumatic events during deployment, veterans are at increased risk for developing PTSD. The prevalence of PTSD among veterans assessed with questionnaires is 6.2–12.9% in American veterans deployed to Iraq and Afghanistan [Hoge et al., 2004] and 6.7–8.9% in Dutch veterans deployed to Afghanistan [Reijnen et al., 2014], but prevalence rates vary in different studies depending on sampling strategies [Richardson et al., 2010].

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*Correspondence to: Mitzy Kennis, Research Centre-Military Mental Healthcare, Lundlaan 1, 3584 CX Utrecht, The Netherlands. E-mail: M.Kennis@umcutrecht.nl

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TABLE I. Coordinates for the five left and right seeds are given in coordinates defined in Montreal Neurological Institute space

Seed	ACC region	MNI coordinates		
		x	*y*	*z*
Seed 1	Caudal ACC	±5	−10	47
Seed 2	Dorsal ACC	±5	14	42
Seed 3	Rostral ACC	±5	34	28
Seed 4	Perigenual ACC	±5	47	11
Seed 5	Subgenual ACC	±5	25	−10

PTSD is characterized by symptoms of re-experiencing of the event, avoidance of trauma-related stimuli and emotional numbing, and hyperarousal [American Psychiatric Association, 1994]. Neuroimaging techniques have been utilized to investigate the biology of PTSD. These studies have revealed anatomical and functional alterations in brain areas such as the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC, [Pitman et al., 2012; Shin and Liberzon, 2010]).

Alterations in the ACC seem to be more pronounced in PTSD compared to social anxiety or specific phobia [Etkin and Wager, 2007], although other anxiety disorders are also associated with alterations in the ACC, such as obsessive-compulsive disorder [Fitzgerald et al., 2005; Melcher et al., 2008; Ursu et al., 2003]. Studies report hypoactivation of the rostral ACC in PTSD versus controls during symptom provocation using script-driven imagery [Britton et al., 2005; Lanius et al., 2001, 2007], during the presentation of trauma-related stimuli [Hou et al., 2007; Yang et al., 2004], and the presentation of negative stimuli [Kim et al., 2008; Lanius et al., 2003; Shin et al., 2001, 2005; Williams et al., 2006]. Several studies have reported that nonthreatening salient stimuli induce dorsal ACC hyperactivity in PTSD versus controls [Bryant et al., 2005; Felmingham et al., 2009; Milad et al., 2009; Rougemont-Bücking et al., 2011; Shin et al., 2011]. Thus, depending on the tasks investigated in these studies, there seems to be a tendency that the rostral ACC is hypoactive in PTSD, while the dorsal ACC is hyperactive in PTSD. Investigating subdivisions of the ACC is, therefore, of substantial importance when investigating the neurobiology of PTSD.

In functional magnetic resonance imaging (fMRI) studies investigating resting state functional connectivity in PTSD specific subdivisions of the ACC were shown to have reduced connectivity with different brain areas. First, the rostral/perigenual ACC showed reduced connectivity with the PCC/precuneus [Sripada et al., 2012b], and resting state functional connectivity of these regions correlated with symptom severity [Lanius et al., 2010]. Second, the dorsal ACC had reduced connectivity with the thalamus [Yin et al., 2011]. Third, dorsal and rostral ACC showed reduced negative functional connectivity with the amygdala [Sripada et al., 2012a]. However, these studies applied seed-based analysis using the PCC/precuneus (and vmPFC), thalamus, or amygdala as regions of interest, respectively. None of these studies have taken the ACC or subdivisions of the ACC as a region of interest during resting state functional connectivity analysis in PTSD. Therefore, it remains unclear whether more ACC abnormalities in functional connectivity are present in PTSD or whether these abnormalities are restricted to connectivity between the ACC and PCC/precuneus, thalamus, and amygdala. A further comprehensive analysis of resting state functional connectivity of the subdivisions of the ACC is thus required.

Studies investigating cytoarchitecture and function of the ACC have generally distinguished four subdivisions [Etkin et al., 2011; Palomero-Gallagher et al., 2009; Shackman et al., 2011; Vogt et al., 2003]. A systematic examination of subdivisions in the ACC with resting state functional connectivity showed that five distinct networks were separable within the ACC [posterior to anterior: caudal, dorsal, rostral, perigenual, and subgenual; see Table I and Fig. 1 for the seed locations of these subdivisions. Kelly et al., 2009; Margulies et al., 2007]. The existence of five subdivisions of the ACC has also been confirmed with diffusion tensor imaging, investigating structural connectivity [Beckmann et al., 2009]. In addition, the ACC subserves separable functions along its axis, although the relationship is complex and functions overlap amongst regions. The caudal ACC is involved in motor control [Dum and Strick, 1991], the dorsal ACC in cognitive control [Chouinard and Paus, 2006; Paus, 2001], the rostral ACC in conflict monitoring [Botvinick et al., 2004], the perigenual ACC in self-referential and social processing [Amodio and Frith, 2006; Kelley et al., 2002], and the subgenual ACC in emotional regulation [Drevets et al., 1997; Phan et al., 2002].

Here, we investigate resting state functional connectivity of these five functionally diverse ACC subdivisions in

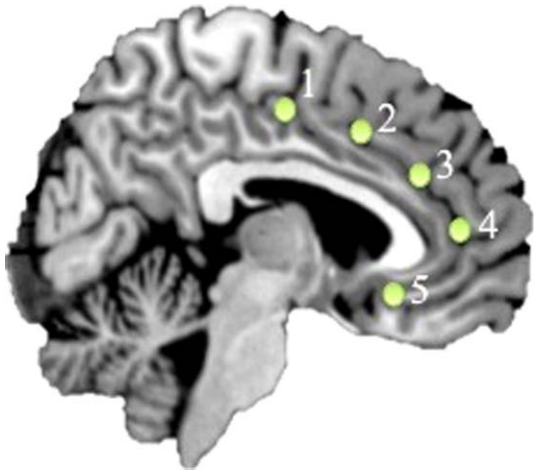

Figure 1.
Location of the ACC seeds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

PTSD to provide a thorough investigation of cingulate dysfunction in PTSD. These five seeds have been selected as they exhibit distinct resting state functional connectivity patterns in healthy subjects [Margulies et al., 2007], and have been related to other psychiatric disorders and human development [Camchong et al., 2011; Davey et al., 2012; Kelly et al., 2009]. We compare PTSD patients with two control groups: a combat control group, consisting of deployed veterans who have experienced similar traumatic events as the PTSD patients, and a healthy civilian control group. By including two control groups, general effects of military training and deployment, which includes trauma exposure, can be investigated. To rule out any effects of medication, only PTSD patients that were medication naive or patients that occasionally used benzodiazepines, but had not taken benzodiazepines at least 48 h prior to scanning were included. Differences found in resting state connectivity with subdivisions of the ACC have shown alterations in the rostral, dorsal, and perigenual subdivisions in PTSD patients [Lanius et al. 2010; Sripada et al. 2012a,b; Yin et al. 2011]. Thus, we hypothesized that resting state functional connectivity of the dorsal, rostral, perigenual, and subgenual networks were reduced in PTSD versus controls. No differences in the caudal ACC network were expected. Furthermore, we expected that PTSD patients deviate the most from healthy controls, while combat controls were expected to have an intermediate phenotype.

METHODS

Participants

In total, 37 male veterans with PTSD, 27 male veterans without PTSD (combat controls), and 26 healthy never deployed male civilian controls (healthy controls) were included in this study. All patients were recruited from one of four outpatient clinics of the Military Mental Health Care Organization in Utrecht, The Netherlands. Patients were included if they met diagnostic criteria for PTSD according to the DSM-IV [American Psychiatric Association, 1994]. PTSD severity was assessed with the clinician administered PTSD scale [CAPS; Blake et al., 1995]. Control participants were recruited via advertisements. The veterans (with or without PTSD) were mostly deployed to Afghanistan (PTSD patients: $n = 18$; combat controls: $n = 17$). Most patients ($n = 33$) were medication naive, and four patients occasionally used benzodiazepines, but had not taken benzodiazepines in the 48 h prior to the scan. After receiving a complete written and verbal description of the study all participants gave informed consent. Participants received financial compensation for their participation. The Medical Ethical Committee of the UMC Utrecht approved the study, and the study was performed in accordance with the Declaration of Helsinki [Seoul, 2008].

Data Acquisition

Functional and structural images were obtained using a 3.0 Tesla magnetic resonance imaging scanner (Philips Medical System, Best, The Netherlands). To allow the participants to adapt to the scanner environment a T1-weighted high resolution image was acquired before the resting state scan (TR = 10 ms TE = 4.6 ms flip angle 8,200 slices sagittal orientation, FOV 240 × 240 × 160, matrix of 304 × 299). This image was utilized for coregistration and segmentation purposes. For the resting state scan participants were asked to relax, to let their mind wander and to focus on the fixation cross. Three hundred and twenty images were collected (T_2^* 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 sec, 0.4 mm gap, acquired voxel size 4 × 4 × 3.60 mm).

Image Analyses

Preprocessing was conducted with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) and comprised slice-timing correction, realignment, coregistration with the anatomical scan, normalization, and spatial smoothing (8 mm FWHM). Scans were resliced to 4 mm^3 isotropic voxel size. Participants were excluded when motion parameters (derived from the realignment step) during the acquisition of the resting state images exceeded 2 mm in any direction (x, y, or z) and 2 degrees rotation (pitch, roll, or yaw). In addition, participants were excluded when small movements (0.5 mm frame displacement) were detected in more than 173 images. Six PTSD patients, two combat controls, and one healthy control were excluded from further analysis due to excessive motion. In addition, mean motion and the number of movements were compared between these groups.

The Data Processing Assistant for Resting-State fMRI (DPARSF) was utilized for further analyses [restfmri.net; Song et al., 2011], which is based on MRIcroN (http://www.mricro.com), SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), and the Resting-State fMRI Data Analysis Toolkit [Song et al., 2011]. Resting state images were band-pass filtered (0.01–0.08 Hz), and detrended. To correct for physiological processes and motion, nine nuisance parameters were included as covariates in the analysis (six motion parameters from the realignment step, mean global signal, white matter signal, and cerebral spinal fluid signal).

Functional Connectivity Analysis

Five bilateral seed points in the ACC were selected, the same as in Kelly et al. [2009]. Thus, 10 spherical seeds (3.5 mm radius) were created around each seed point coordinate [see Table I and Fig. 1; Kelly et al., 2009; Margulies

et al., 2007]. The mean time series for each of those seeds was extracted for each individual and correlated with the time series of every voxel in the brain, to create functional connectivity maps. These correlation maps were normalized using Fishers z-transform. The individual z-maps were used for second-level group analysis (full factorial design, SPM). Since global mean signal was used as nuisance regressor, negative correlations could be induced [Murphy et al., 2009]. Therefore, analyses were restricted to regions with positive functional connectivity. A positive functional connectivity map was created per seed over all participants, which was used as an inclusive mask (caudal left $k = 9701$, right $k = 9343$; dorsal left $k = 10437$, right $k = 10876$; rostral left $k = 9951$, right $k = 9714$; perigenual left $k = 9558$, right $k = 9788$; subgenual left $k = 7445$, right $k = 7194$). For every 10 seeds an F-test was applied to determine whether there were differences between the three groups. Cluster-level multiple comparison correction was applied according to Gaussian Random Field theory [Cox, 1996]. A initial voxel detection height threshold of $P < 0.001$ was applied and a subsequent cluster threshold extent was calculated for each F-test, corresponding to a Bonferroni corrected $P < 0.0001$, based on Monte Carlo simulations as implemented in the REST toolbox [restfmri.net; Song et al., 2011]. A whole brain mask was used for calculating these thresholds (25,622 voxels). The minimum corrected cluster sizes for the right hemisphere networks were $k = 25$ (caudal), $k = 28$ (dorsal), $k = 25$ (rostral), $k = 33$ (perigenual), and $k = 25$ (subgenual). The critical cluster sizes for the left hemisphere networks were $k = 24$ (caudal), $k = 29$ (dorsal), $k = 23$ (rostral), $k = 32$ (perigenual), and $k = 26$ (subgenual). False discovery rate and family wise error were also determined for the peak voxels within clusters of significant difference. Post hoc t-tests were performed ($P < 0.001$, restricted to the clusters of group differences from the F-test) to investigate the direction of group differences.

Post Hoc Analyses

In addition, the effects of the diagnosis of comorbid depression and the effects of educational level, measured with the international standard classification of education [ISCED; Schneider, 2013] on the clusters of significant differences were investigated by including these variables as covariates.

RESULTS

Participants

Patients, healthy controls, and combat controls did not differ in age and handedness. There were also no significant differences between patients and combat controls in the number of times they were deployed and the time since their last deployment. There was no significant difference between patients and combat controls in educational level as measured with the ISCED [Schneider, 2013]. The healthy control group had higher educational level than both veterans with and without PTSD ($F = 5.916$, $P = 0.004$). PTSD patients had significant higher CAPS scores than both combat controls and healthy controls ($F = 630.925$, $P = 0.000$). Twenty PTSD patients met the current diagnostic criteria for the following comorbid disorders, as assessed with the SCID I [First et al., 1997]: major depressive disorder (MDD, $n = 9$), MDD and an anxiety disorder combined ($n = 6$), anxiety disorder ($n = 2$), MDD and a somatoform disorder combined ($n = 2$), and a somatoform disorder ($n = 1$). An overview of demographical and clinical data is presented in Table II.

Functional Connectivity

Spatial connectivity maps

Significant resting state functional connectivity for the seeds located in the right hemisphere is presented in Figure 2 for each group. Similar networks were found with the left hemisphere seeds. The spatial connectivity maps of the ACC subdivision network revealed that PTSD and control groups had overlapping regions that were functionally connected with the ACC seeds. Supporting Information Table S1–S3 lists the locations of the peak functional connectivity of the right ACC seeds for the three groups separately (height threshold $P < 0.001$). There were no significant differences in motion parameters between the groups.

Group differences

Significant differences between the groups were found in the caudal, rostal, and perigenual ACC network (see Fig. 3, Table III, and Fig. 4). Resting state functional connectivity of the bilateral dorsal, and subgenual ACC did not differ significantly between the groups.

Caudal ACC. Group differences were found in resting state functional connectivity between the right caudal ACC seed and the right precentral gyrus (73 voxels; peak value $z = 4.67$; peak MNI coordinates 28, −24, 56), and left caudal ACC with the left precentral gyrus (25 voxels; peak value $z = 4.32$; peak MNI coordinates −28, −24, 64). Post hoc t-test showed that the caudal ACC seeds had reduced functional connectivity with the right precentral gyrus in both veterans with and without PTSD as compared to the healthy control group. The patients and combat controls did not differ in resting state functional connectivity of the right caudal ACC.

Rostral ACC. The left rostral ACC network differed in connectivity with the left precentral gyrus (30 voxels; peak value $z = 4.22$; peak MNI coordinates −40, 0, 44). The cluster was located on the precentral gyrus and extended into the middle frontal gyrus (MFG). Combat controls showed increased connectivity between these regions versus both

TABLE II. Demographical and clinical data

N	PTSD patient (mean ± SD) 31	Combat Control (mean ± SD) 25	Civilian Control (mean ± SD) 25	*F* or *t* or X^2 value	Sig. (two-tailed)
Age (range 21–57)	35.58 (± 9.66)	36.04 (± 10.15)	34.16 (± 9.32)	$F_{(2)} = 0.256$	0.775
Education (ISCED)	3.90 (± 1.47)	4.20 (± 1.50)	5.16 (± 1.18)	$F_{(2)} = 5.916$	0.004
Frequencies ISCED (2/3/4/6/7)	(7/4/13/6/1)	(3/5/10/5/2)	(0/0/12/10/3)		
Handedness (left/right)	(27/4)	(22/3)	(25/0)	$X^2_{(4)} = 3.875$	0.423
Number of times deployed (range 1–15)	2.61 (± 3.68)	2.44(± 1.47)	—	$t = -0.221$	0.826
Number of times deployed (1/2/3/>3)	(16/5/6/4)	(9/6/4/6)	—		
Time since last deployment (years)	8.03 (± 9.22)	5.52 (± 6.38)	—	$t = -1.202$	0.235
Country of last deployment					
Afghanistan	18	17	—		
Former Yugoslavia	6	4	—		
Other	7	4	—		
CAPS total score	67.09 (± 11.01)	5.00 (± 4.42)	4.92 (±4.37)	$F_{(2)} = 630.925$	0.000
Current comorbid disorder (SCID)	20	—	—		
Major depressive disorder	9				
Major depressive & anxiety disorder	6				
Anxiety disorder	2				
Major depressive & somatoform disorder	2				
Somatoform disorder	1				

ISCED: international scale for education; EHI: Edinburgh Handedness Inventory; CAPS: clinician administered PTSD scale; SCID: structured clinical interview for DSM IV Axis II disorders.

PTSD patients and controls. No differences in the right rostral ACC network were found.

Perigenual ACC. Alterations in the right perigenual ACC network were found in the right superior medial gyrus (SMG; 123 voxels; peak value $z = \text{Inf}$; peak MNI coordinates 4, 64, 10). Reduced functional connectivity with the left SMG was found in both veterans with and without PTSD as compared to the healthy controls.

The left perigenual ACC also showed differences between the groups in resting state functional connectivity with the left SMG (109 voxels; peak value $z = 4.43$; peak MNI coordinates −8, 64, 4), and the left middle temporal gyrus (MTG; 55 voxels, peak value $z = 4.14$; peak MNI coordinates −56, 0, −28). Veterans with and without PTSD patients had reduced connectivity between the left perigenual ACC and the left SMG and MTG compared to healthy controls.

Post Hoc Analyses. Educational level and comorbid depression were included as covariates in post hoc analyses. Covarying for educational level did not affect significance of the clusters that were significantly different. Covarying for comorbid depression reduced the clustersize of the left precentral cluster in the left caudal and left rostral ACC network below the minimum cluster size threshold.

DISCUSSION

In this study, resting state functional connectivity of five regions of the ACC were examined to determine differences between PTSD patients, combat controls and healthy controls. The three groups showed similar functional connectivity patterns, comparable with previous studies [Camchong et al., 2011; Davey et al., 2012; Kelly et al., 2009; Margulies et al., 2007], but there were some regional differences found between groups. Differences were found in resting state functional connectivity of the caudal, rostral, and perigenual ACC. Veterans with and without PTSD showed reduced functional connectivity of the caudal ACC with the precentral gyrus and perigenual ACC with the SMG and MTG as compared to the healthy controls. In addition, combat controls showed increased functional connectivity between the rostral ACC and precentral gyrus (extending into the MFG) versus PTSD patients and healthy controls.

Decreased functional connectivity between the caudal ACC and the precentral gyrus in veterans with and without PTSD compared to healthy controls suggests that military training or deployment, including trauma exposure, influence the caudal ACC network. Both the caudal ACC and precentral gyrus are involved in motor control [Chouinard and Paus, 2006; Dum and Strick, 1991; Paus, 2001]. In addition, activity of the (anterior) precentral gyrus has been related to attention and memory in humans [Simon et al., 2002], and to defensive behavior in monkeys [Graziano and Cooke, 2006]. Physical exercise and vigilance and alertness training that are part of military training may thus be related to the reported reduced caudal ACC connectivity with the precentral gyrus in the veteran groups [Jolles et al., 2013; Kelly and Garavan, 2005; Ma et al., 2011]. Conversely, there is some evidence that

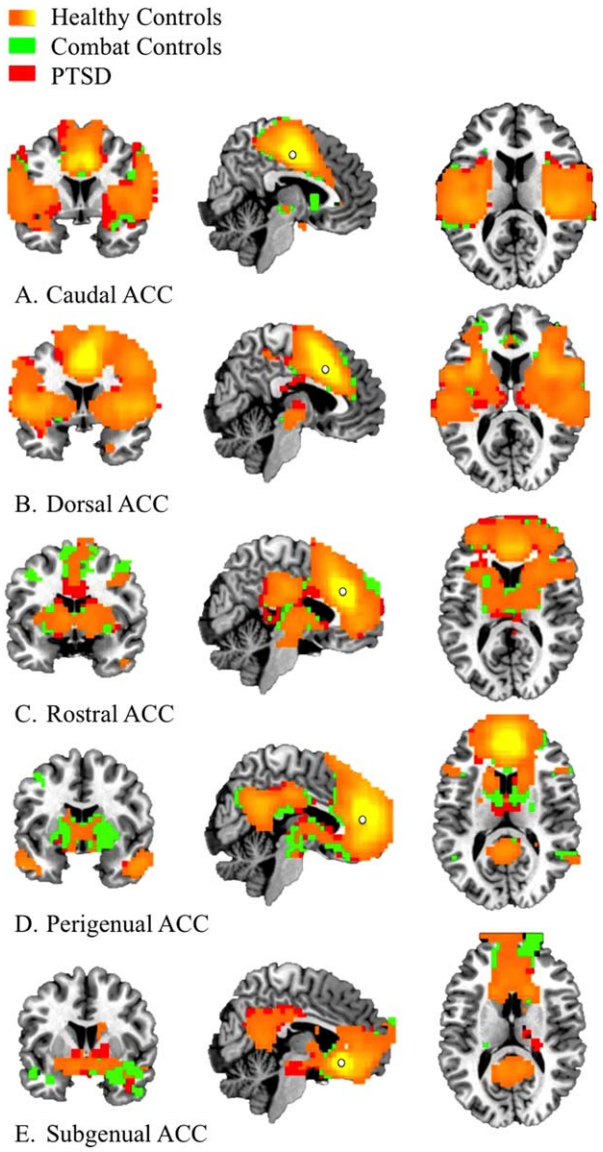

Figure 2.

Positive resting state functional connectivity of the ACC seeds located in the right hemisphere. Orange–yellow = healthy controls, green = combat controls, red = PTSD. The white circle represents the seed location. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

supports the hypothesis that alterations in brain connectivity can occur after deployment in healthy veterans; sustained altered functional connectivity after deployment has been reported, including dorsal ACC coupling with the amygdala [Van Wingen et al., 2011, 2012]. This indicates that differences in functional connectivity can be induced by deployment. Thus, our results in the caudal ACC network may indeed represent military training or deployment effects. However, this interpretation is still speculative, as other factors such as personality, or substance and alcohol use may also influence the results. For example, personality dimensions have also been related to altered resting state functional connectivity [Adelstein et al., 2011; Kennis et al., 2013].

The differences between healthy controls and veterans with PTSD in connectivity of the perigenual ACC with the left MTG and SMG are in line with studies investigating the default mode network. This is a network that is active during rest and deactivated during task performance [Greicius et al., 2003]. Reduced default mode network connectivity in PTSD patients versus healthy controls of these brain areas has been reported [Bluhm et al., 2009; Daniels et al., 2010], as well as reduced default mode network activation during self-referential processing [Bluhm et al., 2012]. Furthermore, the medial prefrontal cortex (mPFC), including the perigenual ACC and SMG, has been reported to show reduced activation in PTSD versus controls during emotional tasks [Pitman et al., 2012; Shin and Liberzon, 2010; Shin et al., 2005]. Reductions of gray

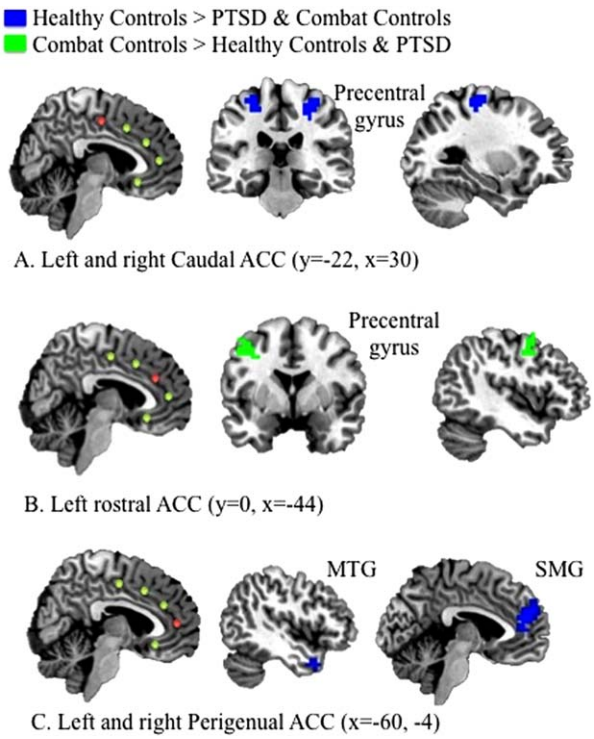

Figure 3.

Clusters of significant differences between the PTSD patients (PTSD), combat controls, and healthy controls (corrected $P < 0.0001$). The left sagittal slice shows the seed locations (in green circles), and the red circle represents the seed of the particular network. **A**: Differences in the right caudal ACC network are found in the precentral gyrus. **B**: Differences in the left rostral ACC network are found in the precentral gyrus, extending into the MFG. **C**: Differences in the perigenual ACC network are found in the left MTG, and SMG. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE III. Location and z-value of the peaks within the clusters of significant different resting state functional connectivity between the PTSD, combat control and civilian control groups per seed (*F*-test)

Seed	Minimum corrected-cluster size (voxels)[a]	Number of voxels	Peak Value (z)	MNI coordinates			BA	Brain area	FDR-corrected *P*-value	FWE-corrected *P*-value
				x	*y*	*z*				
Right										
Caudal ACC	$k = 25$	73	4.67	28	−24	56	6	Right Precentral Gyrus	0.027	0.039
Perigenual ACC	$k = 33$	123	3.71	4	64	0	10	Right Superior Medial Gyrus	0.000	0.000
Left										
Caudal ACC	$k = 24$	25	4.32	−28	−24	64	4	Left Precentral Gyrus	0.087	0.163
Rostral ACC	$k = 23$	30	4.22	−40	0	44	6	Left Precentral Gyrus	0.315	0.230
Perigenual ACC	$k = 32$	109	4.43	−8	64	4	10	Left Superior Medial Gyrus	0.000	0.000
		55	4.14	−56	0	−28	21	Left Middle Temporal Gyrus	0.002	0.047

[a]Initial height thresholded at $P < 0.001$, minimum cluster size (k) corresponding to Bonferroni-corrected $P < 0.0001$, using a whole brain mask (25,622 voxels).
ACC: anterior cingulate cortex; BA: Brodmann area. FDR and FWE-corrected *P*-values are also presented for the peak voxels.

matter of the MTG and medial PFC have also been reported in PTSD patients versus healthy controls [Kühn and Gallinat, 2013]. In line with these studies, our results also suggest alterations in the default mode network in PTSD.

However, whether these results are due to trauma exposure remains unclear, since these described studies investigated either trauma-exposed or healthy controls and not both control groups. Alterations in medial PFC have been reported during negative emotional experience in veterans with and without PTSD versus healthy controls [Phan et al., 2006], although alterations in the medial PFC during exposure to traumatic memories have also been reported specifically for PTSD patients versus combat and healthy controls [Britton et al., 2005]. Differences between trauma-exposed healthy controls and nontrauma exposed controls in structure and connectivity of the default mode network have been reported [Ganzel et al., 2008; Geuze et al., 2008; Philip et al., 2013; Phan et al., 2006]. Similarly, our results showed differences between the combat controls and healthy controls in perigenual ACC connectivity with the SMG. In addition, two resting state studies found a relation between a reduction in functional connectivity measures in the PFC after exposure to traumatic events (measured with reduced synchronisation with magnetoencephalography [James et al., 2013], and with reduced global connectivity and hub-like properties of the ventrolateral PFC and decreased local network connectivity of the dorsal ACC [Cisler et al., 2014]). In line with these studies, we report decreased resting state functional connectivity between prefrontal regions (SMG-perigenual ACC) in combat exposed veterans versus healthy controls. It is, therefore, plausible that this reduction in connectivity during rest is related to trauma exposure. The perigenual ACC network is generally related to social processing and self-referential processing [Amodio and Frith, 2006; Kelley et al., 2002]. These results suggest that experiencing a period of deployment including many stressful situations may alter the network that subserves these processes. Alternatively, military training may alter social processing and self-referential processing as well. For example, being trained to follow orders, which is a social process, may alter the default mode network. In addition, a selection bias, induced by self-selection to join military service, may also be related to these differences in default mode network connectivity.

Specific differences for the combat controls versus the PTSD and healthy control group were found. Combat controls showed reduced left rostral ACC connectivity with the precentral gyrus, extending into the MFG, as compared to the patients and healthy controls. It has been argued that differences found in trauma-exposed controls in particular can provide information on resilience to developing PTSD after experiencing trauma [van der Werff et al., 2013]. Therefore, it is tempting to hypothesise that reduced connectivity of the precentral gyrus/MFG with the rostral ACC that is specific for combat control may be a protective factor for developing PTSD, and may be a measure of resilience. There are some studies providing support for this interpretation. Two fMRI studies have reported increased prefrontal cortex and ACC activation during attentional tasks in trauma-exposed controls specifically

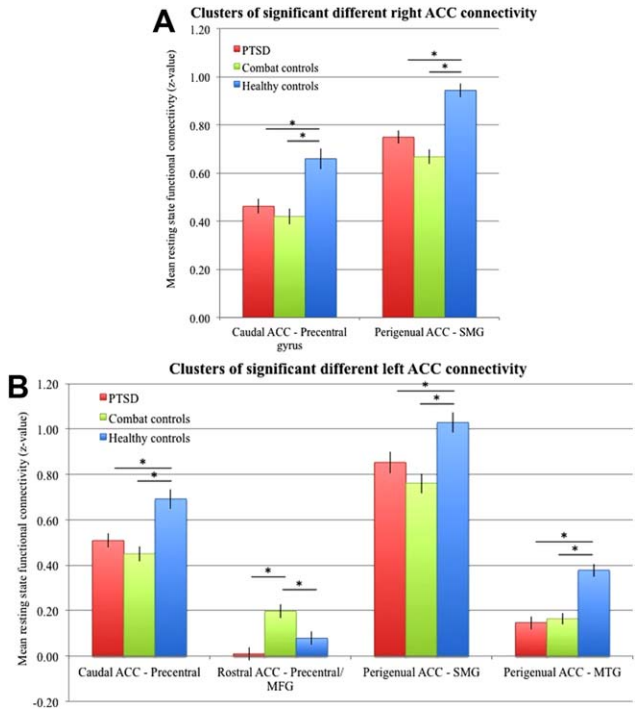

Figure 4.

A: Mean resting state functional connectivity (mean z-value) for the PTSD patients (red), combat controls (green), and healthy controls (blue) for the clusters that differed between the groups for the ACC seeds located in the right hemisphere. **B**: Mean resting state functional connectivity (mean z-value) for the PTSD patients (blue), combat controls (red), and healthy controls (green) for the clusters that differed between the groups for the ACC seeds located in the left hemisphere. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

versus both PTSD patients and healthy nontraumatized controls [Blair et al., 2013; New et al., 2009]. They argue that recruitment of the medial PFC and regions of the ACC during attentional tasks may be an effective strategy to cope with negative emotions, and thus also with traumatic experiences. Furthermore, increased MFG activation during symptom provocation paradigms has been correlated to resilience as measured with a resilience questionnaire [Daniels et al., 2012]. Therefore, we complement these findings by showing reduced connectivity in the precentral gyrus/MFG with the rostral ACC in combat controls specifically. Thus, increased precentral gyrus/MFG – rostral ACC connectivity may be related to successful coping with trauma exposure (resilience). However, this interpretation remains speculative since other confounding factors, such as personality or drug and alcohol use may also influence the findings.

Several limitations need to be addressed. First, the healthy control group differed from the PTSD patients on educational level. However, it is unlikely that this influenced the results, since including ISCED level as covariate did not affect the results. Second, this study only included male veterans with PTSD. Thus, the results may not be generalized to females and to the healthy population. Third, the majority of our PTSD group had comorbid major depressive disorder (as is consistent with most PTSD studies). Differences between PTSD patients with and without major depressive disorder have been reported [Kemp et al., 2007; Kennis et al., 2014; Lanius et al., 2007]. Whether these results are specific to PTSD as compared to other major depressive disorder remains unclear. However, post hoc analysis, in which current diagnosis of depression was included as a covariate, did not change the majority of results. Fourth, we restricted analyses to positive functional connectivity, since global signal regression was applied which can induce spurious negative functional connectivity. Therefore, this study is limited to the regions that show similar activation patterns and does not investigate regions that are anticorrelated to our seeds. Finally, we resliced our scans into 4 mm^3 isovoxels, as this is the closest round number to our original acquired voxel size. However, this is a relatively large voxel size for functional connectivity analyses [e.g., 1 mm^3 in Kelly et al., 2009]. Therefore, our results carry a higher risk for partial volume effects. Although, functional connectivity studies on the default mode network in PTSD apply similar methods [Bluhm et al., 2009; 4 mm^3 isovoxels, Daniels et al., 2010; 5 mm^3 isovoxels).

To gain a complete image of the alterations in the brain network in PTSD and after trauma exposure, whole brain complex network analysis, such as graph theory-based network analysis [Rubinov and Sporns, 2010], should be applied. In contrast with seed-based analysis, where only a limited number of interactions are investigated, whole brain interaction analyses may identify key brain areas that are altered in functional connectivity in patients versus controls. By mapping out alterations of brain networks in patients with PTSD versus trauma-exposed and nontrauma-exposed controls, better treatments for the disorder can be developed in the future. For example, mindfulness and meditation have been shown to alter resting state functional connectivity of the default mode network [Kilpatrick et al., 2011; Taylor et al., 2011, 2013]. In addition, resting state networks can be modulated by brief transcranial magnetic stimulation [TMS; Chen et al., 2013]. Thus, when deviations in resting state networks are mapped (that differ from both trauma-exposed controls as healthy controls), methods to modify these networks can be applied to treat psychiatric disorders such as PTSD. In addition, resting state parameters in fMRI have been shown to be predictive of the (development of) symptom severity in PTSD [Lanius et al., 2010; Zhou et al., 2012], and resting state parameters measured with fMRI or positron emission tomography have been related to treatment outcome in depression [Guo et al., 2013; Mayberg et al., 1997]. Thus, further exploration of resting state characteristics of PTSD versus trauma-exposed controls and healthy

nontrauma-exposed controls may potentially be helpful for diagnostic and predictive purposes.

CONCLUSION

This was the first study that focussed on resting state networks of the ACC in PTSD. The results show that the caudal and perigenual ACC network differed between veterans with and without PTSD and healthy controls. Furthermore, combat controls had increased connectivity in the rostral ACC network compared to PTSD patients and healthy controls. These results indicate that military training, deployment or trauma exposure may alter resting state functional connectivity. The regional ACC connectivity differences we demonstrated underline the importance of distinguishing trauma-exposed combat controls and healthy civilian controls when studying PTSD.

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