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The stressed brain - discovering the neural pathways to risk and resilience

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Chapter 7

Resilience to childhood maltreatment is associated with increased resting-state functional connectivity of the salience network with the lingual gyrus.

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Abstract

Background

The experience of childhood maltreatment is related to an increased risk of developing a variety of psychiatric disorders, as well as a change in the structure of the brain. However, not much is known about the neurobiological basis of resilience to childhood maltreatment. This study aims to identify resting-state functional connectivity (RSFC) patterns specific for resilience to childhood maltreatment, focusing on the default mode and salience network and networks seeded from the amygdala and left dorsomedial prefrontal cortex.

Methods

Resting-state functional MRI scans were obtained in 33 individuals. Seeds in the bilateral amygdala, the dorsal anterior cingulate cortex (dACC), the posterior cingulate cortex and the left dorsomedial prefrontal cortex were defined and used to examine whether resilient individuals differed from vulnerable individuals and healthy controls in RSFC with other brain regions.

Results

Within the salience network, the resilient group was associated with increased RSFC between the left dACC and a region containing the bilateral lingual gyrus and the occipital fusiform gyrus compared to both the vulnerable group and the healthy controls.

Conclusions

In this study, we found RSFC patterns specific for resilient individuals. Regions that are implicated are related on a functional level to declarative memory and the processing of emotional stimuli.

Introduction

With estimates of almost 10% of all children living in the U.S. being subjected to child maltreatment, prevalence of child maltreatment is high (U.S. Department of Health and Human Services, 2009). The most common types of child maltreatment are emotional neglect, emotional abuse, physical abuse and sexual abuse. Exposure to child maltreatment has been related to adverse effects like disturbances of mental health that can persist well into adulthood. Associations have been found between childhood maltreatment and an increased risk of a variety of DSM-IV axis I and axis II mental disorders, including mood, anxiety, substance abuse and impulse control disorders (MacMillan et al., 2001; Afifi et al., 2008; Scott et al., 2010; Afifi et al., 2011). In addition, it has been found that childhood maltreatment has an effect on the morphology of the left medial prefrontal cortex (mPFC; (van Harmelen et al., 2010) and on connectivity in the resting brain (van der Werff et al., 2013a). While the experience of childhood maltreatment increases the chance of developing psychopathology in some individuals, others will not develop symptoms or will return to a stable level of functioning very soon after the adverse life events have ended. These individuals are usually described as being resilient.

Resilience can be understood as ‘a dynamic process encompassing positive adaptation within the context of significant adversity’ (Luthar et al., 2000). Protective psychological factors found to be associated with the facilitation of resilience after childhood maltreatment include highly developed cognitive skills, high self-esteem, internal locus of control, external attribution of blame, ego-control and (extra)familial support (Cicchetti and Rogosch, 1997; Cicchetti, 2010). In contrast to the studies on protective psychological factors, studies on the neurobiological mechanisms involved in resilience are still very scarce. The available data suggests the involvement of neurocircuitry involved in stress reactivity and emotion processing, such as the limbic network. Key brain regions in this circuitry are the amygdala, the hippocampus and parts of the medial prefrontal cortex (Shin and Liberzon, 2010). The amygdala is associated with memory consolidation of emotional experiences and the acquisition of fear responses (LeDoux, 2000). It is reciprocally connected to the hippocampus, which plays an important role in declarative memory (memories that can be consciously recalled such as facts and knowledge; (Bremner, 2007). In this limbic network, the medial prefrontal cortex has a more regulating function and plays a role in the inhibition of fear responses and modulating emotional responsiveness (Veer et al., 2011). In line with a central role for the limbic network are the findings of New et al (2009). In this functional MRI (fMRI) study, the authors

hypothesized that resilient individuals process their emotions differently than non-resilient individuals. Using an explicit emotion regulation task, they indeed found that during deliberate regulation of emotional responses, regions of the prefrontal cortex showed more activation in resilient individuals compared to vulnerable individuals and healthy controls (New et al., 2009).

It has been demonstrated that fMRI during resting-state (i.e. in the absence of externally controlled tasks, stimuli or instructions) can reliably measure coherent low-frequency fluctuations in regional brain activity, allowing the monitoring of activation and functional connectivity in the resting brain (Fox and Raichle, 2007). With resting-state fMRI a number of functional networks have been consistently identified. Three networks that are of interest when studying the neurobiological basis of resilience are the previously discussed limbic network, but also the default mode network (DMN) and the salience network. The DMN contains the precuneus, the posterior cingulate cortex, medial prefrontal cortex, and parts of the parietal cortex (Raichle et al., 2001). The DMN is thought to be associated with the retrieval and manipulation of episodic memories and with semantic knowledge, self-referential processing and prospective memory (Raichle et al., 2001; Buckner et al., 2008; Kim, 2012). Hence, this network may be relevant for a better understanding of the neurobiology of resilience, as intrusive memories of traumatic events and decreases in self-esteem are typically reported in vulnerable individuals after the experience of a traumatic event. In line with this, alterations in DMN functioning have also been related to depressive symptoms and the presence of stress-related psychopathologies (Kluetsch et al., 2012; Marchetti et al., 2012; Schwindt et al., 2012; Whitfield-Gabrieli and Ford, 2012).

The salience network, containing the bilateral anterior insula and bilateral dorsal anterior cingulate cortex (dACC), is important in assessing the relevance of internal and external stimuli in order to guide behavior (Seeley et al., 2007). Experiencing traumatic events like childhood maltreatment has been associated with the development of a cognitive bias toward unpleasant stimuli that indicate potential threat (McNally et al., 2000). Recently, a study indeed revealed differences in resting-state functional connectivity (RSFC) in both the limbic and salience network in a group of adults with a history of childhood emotional maltreatment (van der Werff et al., 2013a). Importantly, RSFC of the limbic, DMN and salience networks in resilient individuals may provide more insight in the neural mechanisms involved in resilience, but this has not been investigated yet.

Therefore, in the present study we aim to study RSFC in individuals resilient to childhood maltreatment, comparing them with matched healthy controls without a history of childhood maltreatment and with individuals with a history of childhood maltreatment and psychopathology. We use a 'seed'-based approach in which an in the literature previously described key anatomical structure of a specific network is used as a starting point for the RSFC, i.e. seed. Using seeds enables us to identify specific resting-state networks in a new sample, in a reliable and reproducible manner.

Given the association of the limbic network with stress responsiveness and emotion processing, and the link between emotion regulation and resilience (New et al., 2009; Shin and Liberzon, 2010), we hypothesize to find differences in RSFC within the limbic network in resilient individuals compared to non-resilient individuals and healthy controls. Furthermore, given the function of the salience network and the involvement of the ACC in a variety of anxiety disorders including posttraumatic stress disorder (PTSD; (Damsa et al., 2009) we hypothesize to find specific alterations in RSFC in resilient individuals. In addition, based on its function and findings in depression and anxiety disorder, we hypothesize alterations in RSFC in the DMN (Greicius, 2008; Veer et al., 2010). Finally, as we previously found an effect of childhood maltreatment on the structure of a region in the left mPFC, we also hypothesize alterations in RSFC in this region (van Harmelen et al., 2010)

Methods

Participants

Subjects were drawn from the large-scale longitudinal Netherlands Study of Depression and Anxiety (NESDA; (Penninx et al., 2008). They were recruited in three manners: (1) From the community through two cohorts available through prior studies, (2) through recruitment from primary care practices, (3) through recruitment from mental health organizations. To determine whether subjects had a psychiatric disorder the Composite International Diagnostic Interview (CIDI) was completed (Robins et al., 1988). Subjects scoring positive for disorders other than major depressive disorder, panic disorder, social anxiety disorder or general anxiety disorder were excluded from the study. All subjects without MRI contraindications were invited to participate in the MRI part of the study, resulting in 301 included subjects. From the 301 subjects with a resting-state fMRI scan we formed three groups. The resilient group consisted of 12 subjects who reported having experienced any type of childhood maltreatment more than once based on responses to the

Nemesis interview and scored negative on the lifetime occurrence of any of the DSM-IV axis-1 disorders. Due to having the eyes opened during the resting-state scan, data from one participant were excluded, resulting in our resilient group consisting of 11 subjects. The two other groups were pairwise matched to the first group on variables: gender, scan location, age and highest level of completed education. The vulnerable group consisted of 11 individuals reported to have experienced childhood maltreatment more than once and scored positive on any of the included DSM-IV axis-1 disorders for the last six months. This resulted in a group that was vulnerable to both depressive and anxiety disorders. The third group consisted of 11 healthy controls. Individuals in this group neither experienced childhood maltreatment (reported 'never' on each of the four categories of childhood maltreatment during the Nemesis trauma interview) nor reported any lifetime psychopathologies on the CIDI. Demographics are reported in Table 1.

To be absolutely sure none of the resilient or healthy controls had suffered from a PTSD we retrospectively administered the PTSD Symptom Scale – Interview Version (PSS-I; (Foa et al., 1993). Participants were asked how often (never, 0; a few times a month, 1; a few times a week, 2; a few times a day or continuously, 3) they had experienced each of the 17 criteria on the three subscales for PTSD as listed in DSM-IV (i.e. five items on Cluster B: re-experiencing; seven on Cluster C: avoidance/numbing and five on Cluster D: arousal) during a period of four weeks when the symptoms were the most severe. Finally, they were asked whether this was also the case during the last month and to indicate in which year of the last five years the symptoms had been the most severe. A symptom was scored as present when experienced at least a few times a week (Brewin et al., 2002).

Childhood maltreatment

Childhood maltreatment was assessed through the use of the Nemesis trauma interview (de Graaf et al., 2002). In this interview, respondents were asked whether they had experienced emotional neglect, emotional abuse, physical abuse and/or sexual abuse before the age of 16, what their relationship to the perpetrator was, and how often the childhood maltreatment had occurred (responses were recorded as: 0 = never, 1 = once, 2 = sometimes, 3 = regularly, 4 = often, or 5 = very often). To compare frequency of experienced maltreatment between the groups, we added the sum scores of how often the childhood maltreatment occurred to Table 1. Emotional neglect was described as: 'people at home didn't listen to you, your problems were ignored, you felt unable to find any attention or support from the people in your house'. Emotional abuse was described as: 'you were cursed at, unjustly punished,

your brothers and sisters were favored – but no bodily harm was done’. Physical abuse was described as: ‘you were kicked, beaten with hands or other objects, or other forms of physical abuse were done to you’. Sexual abuse was described as: ‘were you sexually touched against your will, or forced to touch another sexually’. Our definition of child maltreatment is in line with the definitions of both the department of health & human services of the USA and the Centers for disease control and prevention. This definition states: ‘Child maltreatment involves any act or series of acts of commission or omission by a parent or other caregiver that results in harm, potential for harm or threat of harm to a child (Leeb et al., 2008).

Severity of the experienced childhood maltreatment was assessed retrospectively using the childhood trauma question-naire (CTQ; (Bernstein et al., 1997; Thombs et al., 2009)

Data acquisition

Image acquisition took place at either one of the three participating scanning locations, situated in the University Medical Centers in Leiden, Amsterdam and Groningen, using Philips 3T MR-systems (Best, The Netherlands). These systems were equipped with a SENSE-8 (Leiden University Medical Center and University Medical Center Groningen) or SENSE-6 (Academic Medical Center, Amsterdam) channel head coil, respectively. As part of a fixed imaging protocol (scan sequence: Tower of London, word encoding, T1-weighted scan, word recognition, perception of facial expression, resting-state scan), resting-state functional MRI (RS-fMRI) data were acquired for each subject. Subjects were instructed to lie as still as possible, with their eyes closed and without falling asleep. After completion of the scan all subjects confirmed not having fallen asleep. To obtain RS-fMRI data, T2*-weighted gradient-echo echo-planar imaging was used with the following scan parameters in Amsterdam and Leiden: 200 whole-brain volumes; repetition time (TR) 2300 ms; echo time (TE) 30 ms; flip angle 80°; 35transverse slices; no slice gap; matrix 220 mm × 220 mm; voxel size 2.3 mm × 2.3 mm; slice thickness 3 mm. The total scan duration of the RS-fMRI was 7.51 min. Scan parameters in Groningen were the same except for echo time 28 ms; 39 axial slices; voxel size 3.45 mm × 3.45 mm. For registration purposes as well as gray matter density analysis, anatomical images were acquired using a sagittal 3-dimensional gradient-echo T1-weighted sequence with the following scan parameters: repetition time (TR) 9 ms; echo time (TE) 3.5 ms; flip angle 80°; 170 sagittal slices; no slice gap; matrix 256 ms × 256 ms; voxel size 1 mm isotropic. The total scan duration of the anatomical scan was 4.5 min. A neuroradiologist examined all anatomical images. No abnormalities were found.

Table 1. Demographic and clinical characteristics of the resilient group (1), the vulnerable group (2) and the control group (3)

	(1) Resilient group (<i>n</i> =11)	(2) Vulnerable group (<i>n</i> =11)	(3) Control group (<i>n</i> =11)	Group (1) vs (2) <i>P</i> value	Group (1) and (3) <i>P</i> value
Gender, % M/F	27.3/72.7	27.3/72.7	27.3/72.7	1.000 ^a	1.000 ^a
Handedness, % L/R	0/100	0/100	0/100	1.000 ^a	1.000 ^a
Age, Mean (SD)	40.36 (10.94)	39.73 (9.61)	40.45 (9.47)	.975 ^b	.375 ^b
Highest completed education, Mean (SD)	6.64 (2.29)	6.64 (1.43)	6.55 (1.64)	.634 ^c	.943 ^c
Current CIDI Diagnosis,					
MDD, <i>n</i>	0	3	0	<.0001 ^a	1.000 ^a
ANX, <i>n</i>	0	3	0	<.0001 ^a	1.000 ^a
CDA, <i>n</i>	0	5	0	<.0001 ^a	1.000 ^a
HC, <i>n</i>	11	0	11	<.0001 ^a	1.000 ^a
PSS-I PTSD diagnosis,					
Scan Location Amsterdam, <i>n</i>	0	2	0	<.0001 ^a	1.000 ^a
Scan Location Leiden, <i>n</i>	3	3	3	1.000 ^a	1.000 ^a
Scan Location Groningen, <i>n</i>	6	5	5	.670 ^a	.670 ^a
NEO-FFI neuroticism, Mean (SD)	25.64 (4.68)	43.73 (8.39)	25.09 (4.55)	.611 ^a	.611 ^a
NEO-FFI extraversion, Mean (SD)	42.18 (5.00)	29.81 (10.12)	45.45 (5.34)	<.0001 ^c	.797 ^c
NEO-FFI openness, Mean (SD)	31.73 (6.00)	32.90 (6.24)	30.00 (4.77)	.003 ^b	.153 ^b
NEO-FFI agreeableness, Mean (SD)	42.45 (5.34)	42.64 (6.22)	46.56 (4.5)	.656 ^b	.464 ^b
NEO-FFI conscientiousness, Mean (SD)	41.54 (3.93)	34.00 (5.66)	42.63 (5.2)	.942 ^b	.066 ^b
BAI at baseline, Mean (SD)	2.27 (1.79)	20.64 (10.18)	2.64 (5.89)	.002 ^b	.585 ^b
BAI at scanning, Mean (SD)	3.00 (2.63)	14.45 (9.94)	2.00 (2.76)	<.0001 ^c	.151 ^c
MADRS at scanning, Mean (SD)	1.30 (1.70)	13.55 (6.01)	.82 (1.54)	<.0001 ^c	.282 ^c
IDS at scanning, Mean (SD)	5.50 (3.14)	24.91 (14.21)	3.82 (4.64)	<.0001 ^c	.512 ^c
# of negative life events	5.18 (2.04)	6.36 (2.11)	4.18 (1.89)	<.0001 ^c	.085 ^c
Trauma Type,				.686 ^b	.638 ^b
Emotional Neglect, <i>n</i>	11	11	0		<.0001 ^a
Emotional Abuse, <i>n</i>	5	5	0	1.000 ^a	<.0001 ^a
Physical Abuse, <i>n</i>	3	4	0	1.000 ^a	.647 ^a
Sexual Abuse, <i>n</i>	1	2	0	.534 ^a	<.0001 ^a
Sum score frequency of maltreatment, mean (SD)	6.27 (5.10)	6.27 (3.10)	0	.606 ^c	<.0001 ^c
CTQ, Mean (SD)	46.09 (17.26)	45.40 (8.88)	29.90 (4.38)	.654 ^c	.001 ^c

ANX = anxiety disorder; BAI = Beck Anxiety Inventory; CDA = comorbid major depressive disorder and anxiety disorder; CIDI = Composite International

Diagnostic Interview; CTQ = Childhood trauma questionnaire; IDS = Inventory of depressive symptomatology; MADRS = Montgomery-Åsberg Depression

Rating Scale; PSS-I = Posttraumatic stress disorder Symptom Scale – Interview Version; PTSD = posttraumatic stress disorder

^a = Chi-Square Test.^b = Independent Sample t-test.^c = Mann-Whitney U Test

Data Preprocessing

The RS-fMRI images were preprocessed using FEAT (FMRI Expert Analysis Tool) version 5.90, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl; (Smith et al., 2004). Non-brain tissue removal was applied to the structural images. Motion correction was applied (subject movement >3 mm in any direction, resulted in exclusion of the data from further analysis) to the RS-fMRI data along with non-brain tissue removal, spatial smoothing using 6 mm full-width at half-maximum Gaussian kernel, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, 0.01 Hz cut-off). RS-fMRI data were registered to the high-resolution structural image (T1) and subsequently the T1 image was registered to the 2 mm isotropic MNI-152 (T1 standardbrain average over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) images. The resulting transformation matrices derived from these registration steps were then combined to obtain a native to MNI space transformation matrix and its inverse (MNI to native space).

Statistical analysis

Resting-state data were analyzed using seed-based correlations identifying three networks of interest: the limbic network, the DMN and the salience network. The following seed regions of interest were selected: bilateral amygdala for the limbic network, bilateral dACC for the salience network (Margulies et al., 2007) and posterior cingulate cortex (PCC) for the DMN (Fox et al., 2005). The bilateral amygdala seeds were created in standard space using the Harvard-Oxford Subcortical Structural Probability maps. Timecourses of fMRI signal in these locations are known to correlate strongly with the timecourses of fMRI signal in the other constituents of their network, thus allowing the replicable identification of the network. Post hoc, this was checked by examining the main effects of the seeds. In addition to the seeds, a mask was created for the structural abnormality earlier identified in individuals reporting childhood emotional maltreatment located in the left mPFC (van Harmelen et al., 2010), as well as a white matter mask and a cerebrospinal fluid (CSF) mask. MNI coordinates for each of the seeds are reported in Table 2.

Around every coordinate a 4 mm sphere was created. These spheres were then transformed to native space using the inverse transformation matrices obtained during registration in the preprocessing phase. Spatially averaged time series were extracted for each seed and each subject. A time series was also extracted for the global signal. For each subject and for each network separately, a multiple regression

Table 2. Networks of interest						
Network	Constituents	Function	Seed region	MNI Coordinates		
				x	y	z
Limbic network	Amygdala, insula, hypothalamus, hippocampus, mPFC	Stress reactivity and emotion processing	Left Amygdala	-20	-6	-16
			Right Amygdala	26	-2	-18
Salience Network	Bilateral anterior insula dACC	Assessing the relevance of internal and external stimuli in order to guide behavior	Left dACC	-6	18	28
			Right dACC	6	18	28
Default Mode Network	Precuneus, PCC, mPFC, and medial, lateral and inferior parietal cortex	Retrieval and manipulation of episodic memories and semantic knowledge, self-referential processing and prospective memory	PCC	-2	-36	37
Left mPFC			Left mPFC	-11	23	40
Confound Regressors			Left WM	-24	26	18
			Right WM	24	26	18
			Left CSF	-4	4	14
			Right CSF	4	4	14
This table describes each of the studied networks, the regions involved in the networks, the function of the networks, the chosen seed regions to probe the networks and the MNI coordinates of the chosen seeds. MNI = Montreal Neurological institute; dACC = dorsal anterior cingulate cortex; PCC = posterior cingulate cortex; mPFC = medial prefrontal cortex; CSF = cerebrospinal fluid; WM = white matter.						

analysis was performed using the general linear model (GLM) as implemented in FSL (Smith et al., 2004). The timecourses that were extracted from the voxels in all of our seed regions were entered as a regressor in a GLM for each network separately. Nine nuisance regressors were included in the model: signal from the white matter, CSF signal, and the global signal, as well as six motion parameters (three translations and three rotations). The global signal was included to reduce artifacts associated with physiological signal sources (i.e. cardiac and respiratory; (Raichle et al., 2001; Birn et al., 2006). After reslicing the resulting individual correlation maps and their corresponding within-subject variance maps into 2 mm isotropic MNI space, they were entered into a higher level within and between groups mixed effects analysis (one- and two-sample t-test).

For each subject, gray matter density maps were derived from the anatomical scans. Participants in this study were drawn from the same sample (the NESDA) as the subjects used to investigate the structural abnormalities of childhood emotional maltreatment (van Harmelen et al., 2010). In this study differences were found in adults who experienced childhood emotional maltreatment when compared to adults who did not experience childhood emotional maltreatment. Therefore, in order to control for structural differences possibly confounding differences in functional connectivity and to correct for the effects of possible misregistration (Oakes et al., 2007), information about gray matter density of each subject was included as a voxelwise confound regressor. To achieve this, information about each voxel's gray-matter partial volume was directly fed into the GLM. Groups were compared using the GLM including age and scan location as additional covariates in each comparison. Cluster correction was applied in all group analyses with an initial cluster forming threshold of $Z > 2.3$ and a corrected $p < .05$.

Results

Psychometric data

In line with our expectancies the resilient group displayed significantly less symptoms than the vulnerable group based on the symptoms questionnaires (Beck Anxiety Inventory, Montgomery-Åsberg Depression Rating Scale and Inventory of Depressive Symptomatology). The resilient group did not differ on these questionnaires from the control group. When comparing the scores on the Neuroticism subscale of the Neuroticism Extraversion Openness Five Factor Inventory, the resilient group scored significantly lower on neuroticism compared to the vulnerable group, and higher on the extraversion and conscientiousness subscales. However, the resilient group did

not differ in scores on any of the subscales compared to the healthy control group. Importantly, type, frequency, and severity of childhood maltreatment did not differ between the resilient and vulnerable groups. Psychometric data are reported in Table 1.

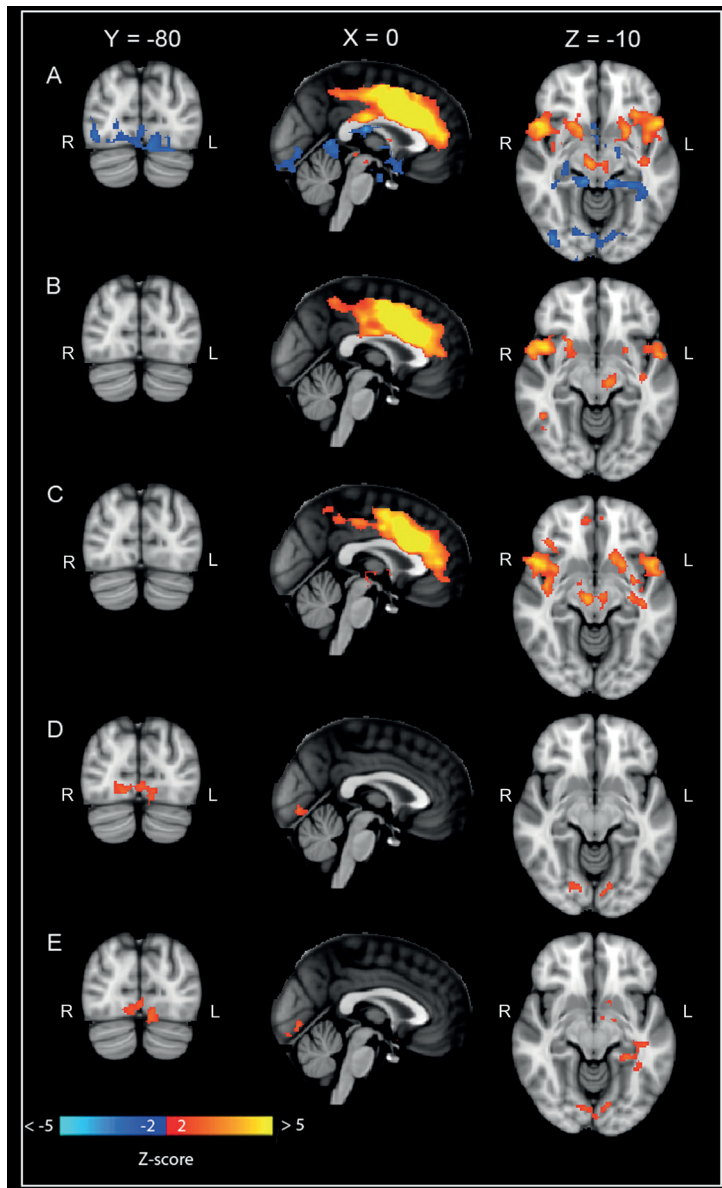
Resting-state functional connectivity

Analysis of the main effects of the seeds in each of the three groups showed connectivity between the seed chosen for the specific networks and other structures known to be constituents of these networks. In other words, our seeds probed the networks in a correct manner. Analysis of the left dACC seed (the seed in the salience network) revealed an increase in negative connectivity with a region including the lingual gyrus and the occipital fusiform gyrus in the resilient group when compared to the healthy controls. A similar increase in negative connectivity was found in these regions in the resilient group when compared to the non-resilient group (Figure 1). This means that, in the resilient group relative to both the vulnerable group and healthy controls, activation of the dACC is more strongly associated with deactivation of the lingual gyrus and the occipital fusiform gyrus and vice versa.

Discussion

The aim of this study was to investigate differences in RSFC associated with resilience to childhood maltreatment. We hypothesized alterations in RSFC associated with resilience from limbic network, salience network and DMN seeds and from a medial prefrontal region previously shown to be morphologically altered in a group of individuals who had been exposed to childhood maltreatment (van Harmelen et al., 2010). Analysis of the connectivity of the salience network seeds (the bilateral dorsal anterior cingulate cortex seeds) showed increased negative connectivity between the left dorsal anterior cingulate cortex seed and the bilateral lingual gyrus and occipital fusiform gyrus in the resilient group when compared to our vulnerable group, as well as when compared to the control.

Task related neuroimaging studies have shown that the lingual gyrus is associated with verbal declarative memory and identification of emotional facial expressions (Bremner et al., 2004; Kitada et al., 2010). In psychiatric studies, the lingual gyrus has been associated with trauma-related psychopathology (i.e. PTSD (Yin et al., 2011). It has also been shown that patients with PTSD display deficits in verbal declarative memory (Bremner et al., 2004). In addition, during exposure to traumatic stimuli, PTSD patients show an increase in activation of areas involved in memory and

Figure 1. Resting-state functional connectivity of the left dorsal anterior cingulate cortex

RSFC of the left dorsal anterior cingulate cortex. (A) The main effect for the resilient group. (B) The main effect for the vulnerable group. (C) The main effect for the control group. (D) The difference between the resilient group and the vulnerable group. (E) The difference between the resilient group and the control group. Images are z-statistics, overlaid on the MNI-152 1 mm standard brain. The left hemisphere of the brain corresponds to the right side of the images. MNI coordinates displayed at the top of the figure correspond with the coordinates of the displayed slices underneath the coordinates.

visuospatial processing, including the lingual gyrus, whereas non-PTSD trauma exposed individuals show a decrease of activation in the same regions (Bremner et al., 1999). However, due to the design of these studies it remains unclear whether these effects are to be attributed to the presence of psychopathology in PTSD patients or to the presence of resiliency factors in non-PTSD trauma exposed individuals. Our finding of increased RSFC between the left dACC and a region of the brain including the bilateral occipital fusiform gyrus and lingual gyrus in both our group comparisons, leads us to believe this might be specific for resilience. The difference in RSFC between the salience network (with its function to identify possibly harmful stimuli) and the bilateral occipital fusiform gyrus and lingual gyrus might reflect an increased ability of resilient individuals to identify and encode harmful experiences in verbal declarative memory. As impairment of this ability has often been related to the development of trauma-related disorders (Bremner et al., 2004; Samuelson, 2011), it could very well be that an increased ability facilitates resilience. This suggestion fits the dual representation theory, which states that in order to successfully process a trauma, the memories must be fully processed by the verbally accessible memory system, a system comparable to verbal declarative memory (Brewin et al., 1996). On a more psychological level, it has already been suggested that declarative memories can promote resilience through the capacity to evoke soothing emotional responses, which is a useful adaptive coping mechanism (Davis, 2001).

An alternative explanation may be based on the role of the lingual gyrus in the identification of emotional facial stimuli (Kitada et al., 2010). The salience network has a function that is closely related: assessing the relevance of internal and external stimuli. The association in RSFC between these brain regions in the resilience group could therefore be well explained on a functional level. As mentioned, our resting-state data were acquired as part of a fixed imaging protocol immediately after a facial expression task (van Tol et al., 2011). In this task a variety of faces with different emotions were presented and participants had to identify the gender. Previously, it was shown that childhood maltreatment is associated with enhanced amygdala reactivity to emotional (van Harmelen et al., 2013). It could be that processing of the stimuli during the facial expression task influenced our measure of RSFC in a different manner in the resilience group, compared to the vulnerable group and the healthy controls.

To the best of our knowledge, no previous study has been conducted that investigated RSFC patterns related to resilience. What is presently known about the neurological

mechanisms of resilience is often derived from studies comparing patients with trauma-related psychopathology with traumatized non-psychopathology individuals (for a review see: (van der Werff et al., 2013b). As these studies typically do not include healthy individuals without trauma exposure as a third group, it is not possible to determine whether group differences between trauma-exposed psychopathology and trauma-exposed non-psychopathology subjects are due to aberrant brain structures or functions in the patient group or to resilient characteristics in the non-psychopathology group. By adding a healthy control group without childhood maltreatment nor psychopathology, our design facilitated investigation of resilient specific RSFC patterns. We managed to match our subjects in a pair-wised manner, in this way controlling for age, gender, scan location and highest finished educational level. Importantly, we found an effect with the same direction and in the same region of the brain in two between-groups comparisons, making a stronger case for a resilient specific effect. Finally, our study facilitates replication and further research as a seed-based region-of-interest approach was used to analyze the data.

A limitation to our study is the small sample size of 11 individuals per group. Due to this group size findings should be considered preliminary. We have used a cross sectional approach for our study, therefore it is not possible to draw cause and effect conclusions from our findings. Another potential limitation is that it is unknown whether between-group differences in heart rate variability and breathing influenced the results, as we did not monitor physiological activity in the current study. However, regressing out global signal changes has shown to at least partly filter out the effects of cardiac and respiratory fluctuations (Raichle et al., 2001; Birn et al., 2006). Childhood maltreatment and severity were measured retrospectively using self-report, therefore the presence of a recall bias cannot be ruled out. Finally, as we discussed in our introduction resilience is a dynamic and multidimensional construct. We are aware that our operationalization of resilience, following previous studies on neurobiological characteristics of resilience (New et al., 2009), might not fully capture this dynamic and multidimensional nature of resilience.

In summary, our preliminary study shows alterations in RSFC in resilient individuals in a network involved in the processing of emotional stimuli and of areas of the brain involved in declarative memory. These alterations may be related to an increased ability of resilient individuals to identify and encode harmful experiences in verbal declarative memory. Future research should replicate our preliminary findings and further explore the specific neurobiological basis of resilience.

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