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Early Life Stress Modulates Amygdala-Prefrontal Functional Connectivity: Implications for Oxytocin Effects

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Abstract: Recent evidence suggests that early life stress (ELS) changes stress reactivity via reduced resting state functional connectivity (rs-FC) between amygdala and the prefrontal cortex. Oxytocin (OXT) modulates amygdala connectivity and attenuates responses to psychosocial stress, but its effect appears to be moderated by ELS. Here we first investigate the effect of ELS on amygdala-prefrontal rs-FC, and examine whether ELS-associated changes of rs-FC in this neural circuit predict its response to psychosocial stress. Secondly, we explore the joint effect of OXT and ELS on the amygdala-prefrontal circuit. Eighteen healthy young males participated in a resting-state fMRI study of OXT effects using a double-blind, randomized, placebo-controlled, within-subject crossover design. We measured the rs-FC to bilateral amygdalae and subsequently assessed changes of state anxiety and prefrontal responses to psychosocial stress. Multiple linear regressions showed that ELS, specifically emotional abuse, predicted reduced rs-FC between the right amygdala and pregenual anterior cingulate cortex (pgACC), which in turn predicted elevated state anxiety after psychosocial stress. In subjects with lower ELS scores, stronger pgACC-amygdala rs-FC predicted stronger pgACC deactivation during the psychosocial stress task, and this rest-task interaction was attenuated by OXT. In subjects with higher ELS scores however, the rest-task interaction was altered and OXT showed no significant effect. These findings highlight that ELS reduces pgACC-amygdala rs-FC and alters how rs-FC of this circuit predicts its stress responsiveness. Such changes in pgACC-amygdala functional dynamics may underlie the altered sensitivity to the effects of OXT after ELS. *Hum Brain Mapp 35:5328–5339, 2014.*

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INTRODUCTION

Substantial evidence shows that experiential factors like early life stress (ELS) can shape individual differences in stress reactivity [Davidson and McEwen, 2012; McEwen, 2012]. Stressful social experience in early life, such as maternal separation of animal pups, or maltreatment of human children, can cause persisting changes in the autonomic, neuroendocrine, and immune system [Carpenter et al., 2007, 2010; for reviews, see Heim and Binder, 2012; Pryce et al., 2005; Sanchez et al., 2001]. These changes in brain and body are associated with anxiety-like behaviors and altered responses to psychosocial stress, and may increase the risk for mental illnesses, especially those associated with dysregulated response to psychosocial stress, in adulthood [Green et al., 2010]. However, the neural mechanisms underlying the impact of ELS on responses to psychosocial stress are still not fully understood.

Recent neuroimaging studies suggest that ELS biases stress reactivity via structural and functional changes within the amygdala-prefrontal circuit, most notably in the pathway between amygdala and medial prefrontal areas including the pregenual anterior cingulate cortex (pgACC). This pathway is an important regulatory circuit that helps to optimize behavioral and physiological reactions towards adversity [Gianaros et al., 2008; Pezawas et al., 2005; Wager et al., 2009]. Activity changes in pgACC during psychosocial stress are crucial for regulating amygdala and downstream endocrine responses [Dedovic et al., 2009a,b; Kern et al., 2008; Pruessner et al., 2008]. An increase in pgACC-amygdala coupling is critical for recovering from acute stress [van Marle et al., 2010; Veer et al., 2011]. Decreased structural and functional connectivity between pgACC and amygdala also predicts trait [Kim and Whalen, 2009; Pezawas et al., 2005], state [Kim et al., 2011a] and pathological anxiety [Etkin et al., 2010; see review in Kim et al., 2011b]. Furthermore, both structure and activity of the pgACC and amygdala are highly susceptible to the influence of early stressful experiences [Davidson and McEwen, 2012; Lederbogen et al., 2011; Tottenham, 2012]. Gee et al. [2013] recently found altered pgACC-amygdala connectivity during perception of fearful faces in children who experienced early life stress. Burghy et al. [2012] used resting state functional connectivity (rs-FC) to examine the functional integrity of the amygdala-prefrontal circuit independent of task demands. They found that ELS-associated elevation in childhood cortisol predicted decreased amygdala-prefrontal rs-FC in adolescence. ELS effects on functional dynamics of the pgACC-amygdala circuit in adulthood remain less characterized. Moreover, accumulating evidence shows that task-based activity and behavior can be predicted from individual rs-FC differences in the corresponding neural circuit [Boly et al., 2007; He, 2013; Mennes et al., 2010, 2011; Northoff et al., 2010; Weissman et al., 2006]. While ELS has been associated with elevated anxiety and dysregulated response to psychosocial stress [Heim and Binder, 2012], it remains unclear whether the ELS-associated changes in pgACC-amygdala rs-FC can predict anxiety state raised by acute psychosocial stress, or predict how this neural circuit reacts to psychosocial stress.

The pgACC-amygdala pathway is also part of a neural network modulated by oxytocin (OXT) [for review, see Meyer-Lindenberg et al., 2011]. This neuropeptide has been shown to alleviate physiological responses to psychosocial stress [de Oliveira et al., 2012; Heinrichs et al., 2003; Quirin et al., 2011]. However, in individuals who experienced ELS, OXT effects on social emotion processing seem to be altered [Bakermans-Kranenburg and van IJzendoorn, 2013; Bakermans-Kranenburg et al., 2012; Meinlschmidt and Heim, 2007; Riem et al., 2013a,b; van Ijzendoorn et al., 2011]. Our recent study showed that subjects who experienced ELS had blunt responses in both pgACC and amygdala during psychosocial stress, and oxytocin yielded opposite effects with increased pgACC and amygdala deactivation in these subjects when compared with the control group [Grimm et al., 2014]. This suggests that pgACC and amygdala play crucial role in the neural mechanisms underlying the OXT x ELS interaction, but less is known about the OXT effects on the circuitry coupling between these two regions. An abundance of evidence has shown that OXT changes amygdala coupling in various social-emotion tasks [Kirsch et al., 2005; Riem et al., 2012; Rilling et al., 2012; Wittfoth-Schardt et al., 2012]. A recent study suggests that OXT may also change amygdala resting state functional connectivity [Sripada et al., 2013]. It has yet to be investigated whether OXT modulates pgACC-amygdala rs-FC independent of task demands, and whether OXT yields differential modulation in this neural circuit in subjects with and without ELS experience.

In this study, we first aim to investigate effects of ELS on rs-FC using bilateral amygdalae as seed regions. According to previous evidence of ELS effects on pgACC and amygdala, we expect that ELS reduces the rs-FC between these two regions. We also hypothesize that the ELS-associated changes in pgACC-amygdala rs-FC predict state anxiety and pgACC responses induced by acute psychosocial stress. Second, we aim to investigate the joint effect of OXT and ELS on amygdala rs-FC. Considering previous findings of altered sensitivity to OXT effects after

ELS, we hypothesize that OXT modulates pgACC-amygdala coupling differently in subjects with and without a history of ELS.

MATERIAL AND METHODS

Assessment of ELS

Early life stress was quantified using the Childhood Trauma Questionnaire [CTQ; Bernstein and Fink, 1998]. The CTQ is a 28-item self-report questionnaire that retrospectively assesses five types of adverse childhood experiences: emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse. Scores range from 5 to 25 for each subscale with high scores indicating strong exposure to the corresponding type of maltreatment.

Subjects

Eighteen healthy young male participants (mean age 27.8 ± 4.4, age range 21–36 years old, three left handed) were recruited from a pre-existing community-dwelling sample. All subjects were free of any neurological or psychiatric condition, as determined by the short version of the Structured Clinical Interview for DSM-IV [SCID; Wittchen et al., 1997]. A verbal intelligence test [Lehrl et al., 1995] showed that IQ levels of all subjects (mean IQ 112.9 ± 16.8) were in or above the range of the norm. Written informed consent was obtained for all assessments, and subjects were reimbursed for participation. The study was conducted in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of the Germany Psychological Society.

Study Design

In a double-blind, placebo-controlled, within-subject design, participants received either OXT (Syntocinon Spray; Novartis, Basel, Switzerland) or a placebo (PLA; sodium chloride solution) intranasally in two separate experimental sessions. The sequence of OXT and PLA sessions was balanced across subjects. It has been shown that intranasally applied neuropeptides (e.g., vasopressin) can cross the blood-brain barrier and increase cerebrospinal fluid (CSF) as well as plasma concentration within 15–30 min [Born et al., 2002]. It therefore allows for studying oxytocin effects on brain functions [Heinrichs and Domes, 2008]. Previous studies also demonstrate increases in OXT plasma concentration 30 - 40 min after intranasal administration of 24 IU [Burri et al., 2008; Gossen et al., 2012]. We therefore administered OXT or PLA 45 min before fMRI scanning in the present study. Following a standardized protocol used in previous studies [Domes et al., 2013; Gamer and Buchel, 2012; Gamer et al., 2010; Hurlemann et al., 2010; Labuschagne et al., 2010], participants self-administered a single intranasal dose of 24 IU OXT/PLA (three puffs per nostril, each puff with 4 IU, or 6.82 mg) under the supervision of the experimenter. Participants abstained from alcohol during the 24 h, and from exercise, caffeine and food for 1 h before the experiment.

In each scanning session, the subjects underwent an 8-min resting-state measure, where they were asked to rest silently, watch a white fixation cross against a black background, and remain "relaxed and awake." After each resting-state measure, psychosocial stress was induced using the Montreal Imaging Stress Task [MIST; Dedovic et al., 2005; Pruessner et al., 2008], where the subjects completed a series of challenging mental arithmetic tasks while being scanned. The task induces psychosocial stress using elements of uncontrollability and social evaluative threat [for full task description, see Supporting Information, as well as Dedovic et al., 2005].

Psychological and Physiological Measures

Before scanning started, the subjects completed the German version of the Spielberger State-Trait Anxiety Inventory [STAI; Spielberger and Sydeman, 1994]. To assess transient anxiety induced by the stress task, subjects completed the State Anxiety Inventory again after each scanning session. This study was part of a larger project probing OXT effects on stress reactivity [Grimm et al., 2014]. Saliva samples were collected with the Salivette sampling device (Sarstedt Inc.) before (i.e. 45 min after OXT or PLA administration) and immediately after the MIST task [for full description, see Grimm et al., 2014]. Like previous findings [Dedovic et al., 2005; Pruessner et al., 2008], Grimm et al. [2014] also found that the MIST task elicits anxiety state and cortisol stress responses. In the current study, 15 out of 18 subjects had valid salivary cortisol data. To validate that stress induction did work in our sample, state anxiety and salivary cortisol levels before and after the MIST were compared by paired-sample T tests.

Structural and Resting-state Functional MRI

MRI acquisition

Structural and functional MRI data were acquired on a Siemens Trio 3T scanner using a 12-channel radio-frequency (RF) head coil. T1-weighted structural images were acquired with the following parameters: 176 sagittal slices covering the whole brain, repetition time (TR) = 1,900 ms, echo time (TE) = 2.52 ms, flip angle = 9°, 256 × 256 matrix, voxel size $1 \times 1 \times 1$ mm^3. For each resting-state measure, 210 volumes of T2*-weighted echo-planar images (EPIs) were acquired with the following parameters: 37 axial slices covering the whole brain, TR = 2,300 ms, TE = 30 ms, flip angle = 70°, 64 × 64 matrix, field of view = 192 × 192 mm^2, voxel size = $3 \times 3 \times 3$ mm^3. For each

psychosocial stress session, 3 runs of 220 volumes of T2*-weighted EPIs were acquired (see Supporting Information).

Rs-fMRI preprocessing and connectivity analysis

Functional images were pre-processed using MATLAB 2012 (The Mathworks, Natick, MA), SPM8 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk) and DPARSF [Data Processing Assistant for Resting-State fMRI; http://www.restfmri.net/forum/DPARSF; Yan and Zang, 2010]. The first 10 volumes were discarded to allow the MR signal to achieve T1 equilibration. The images were first corrected for the acquisition time differences between slices, and then realigned to the first volume to correct for head motion between volumes. Physiological noise was reduced by (1) regressing out signals from the white matter (WM), cerebrospinal fluid (CSF) and the 6 head movement parameters (translation: x, y, z and rotation: pitch, roll, yaw), (2) removing linear tread and filtering the data to the infra-low frequency band (0.01–0.08 Hz). Importantly, global signal removal was not performed to avoid falsely increasing the anticorrelation between time series [Murphy et al., 2009].

We used a seed-based approach to estimate resting state functional connectivity. Two binary ROIs were drawn in the left and right amygdala according to the intersection between an anatomical mask [Automated Anatomical Labeling, AAL; Tzourio-Mazoyer et al., 2002] and the result of a meta-analysis of 163 fMRI studies on emotional processing [Wager et al., 2012]. These ROIs, representing bilateral amygdala based on both anatomical atlas and previous neuroimaging findings on emotion, were then reversed-normalized to each subject's mean functional image using SPM8, generating native-space ROIs for each subject. The time course of average pre-processed BOLD signal within each seed region was then correlated with signals in each voxel in the whole brain. The Pearson correlation coefficients were transformed to Z values (Fisher's Z), resulting in a map representing the voxel-wise strength of functional connectivity to the seed region (zFC map).

For further statistics at the group level, single-subject/session zFC maps were normalized to the MNI space using the normalization parameters estimated by T1 structural image unified segmentation, and smoothed with a Gaussian kernel of 8-mm Full-Width-Half-Maximum (FWHM).

Statistical Analyses

2nd-level whole brain and ROI analysis of rs-FC

For each seed region and each subtype of ELS, we first performed a series of voxel-wise multiple linear regressions on zFC maps from all single-subjects/sessions. Main predictors were scores on this subscale, OXT, and their interaction product term, while controlling for covariates like age, IQ, and experimental sequence. Mean-centered predictors were used to reduce multicollinearity. Results were reported at a threshold of FDR corrected $P < 0.01$, cluster size > 100 voxels.

On the basis of peak voxels reported from this whole-brain analysis, we built spherical (radius = 5 mm) regions of interest (ROIs), and extracted the strength of rs-FC as Z values. To examine whether ELS-associated changes in amygdala rs-FC can predict state anxiety after the induction of psychosocial stress, we performed a second series of multiple linear regression analyses. Rs-FC strength was entered as main predictor, along with age, IQ, oxytocin, and experimental sequence as covariates.

Hierarchical multiple regression analysis of rs-FC strength predicting circuitry response during psychosocial stress

If rs-FC between amygdala and a certain brain region is linearly associated with a certain subtype of ELS, and can predict changes in state anxiety induced by psychosocial stress, it is likely to mediate ELS effects on stress reactivity. We therefore investigated whether the ELS-associated changes of rs-FC could predict the responses in this brain region during psychosocial stress. We calculated BOLD signal percent change (SPC) of this region during the induction of psychosocial stress (see Supporting Information), and tried to predict the SPC with a hierarchical multiple regression model run in three steps. First, age, IQ and experimental sequence were entered as covariates, meanwhile ELS, OXT, and rs-FC strength to amygdala were entered as main predictors. In the second step, we included the interaction product terms of each pair of the three main predictors. In the final step a three way interaction OXT $\times$ ELS $\times$ rs-FC was entered. All predictors were mean-centered. To examine an interaction effect, we tested whether successive regression steps significantly increased the variance explained by the model (ΔR^2). When a statistically significant interaction emerged, it was interpreted according to the guidelines outlined by Aiken and West [1991].

RESULTS

Psychological and Physiological Measures

Scores on the emotional neglect, emotional abuse and physical neglect subscales fell into the high and low categories defined by previous normative data [Scher et al., 2001] (i.e. -1 SD $\leq$ the 50th percentile of the norm; $+1$ SD $\geq$ the 90th percentile of the norm; see Table I). All subjects scored low on the subscales of physical abuse and sexual abuse subscale ($+1$ SD not exceeding the 50^{th} percentile of normative data; see Table I).

There were no significant correlations between any CTQ score with age and IQ. The scores on the subscales of emotional neglect (EN) and physical neglect (PN) correlated

TABLE I. Comparison between CTQ scores and previous normative data

CTQ	Mean (SD)	Range	Norm (Scher et al., 2001) 50th percentile	Norm (Scher et al., 2001) 90th percentile
Total score	37 (11.7)	25–68	29	41
Emotional neglect	10.6 (5.0)	5–23	5	11
Emotional abuse	8.3 (4.2)	5–17	5	9.85
Physical neglect	7.1 (3.0)	5–16	5	9
Physical abuse	5.8 (1.1)	5–8	7	9
Sexual abuse	5.2 (0.4)	5–6	5	5

CTQ, childhood trauma questionnaire.

significantly with trait anxiety (for EN, $r(16) = 0.521$, $P < 0.05$; for PN, $r(16) = 0.531$, $P < 0.05$). We observed higher state anxiety ($t(16) = 3.348$, $P < 0.01$) and salivary cortisol level ($t(13) = 2.514$, $P < 0.05$) after stress induction. Among all CTQ subscales, only scores on emotional abuse (EA) correlated significantly with state anxiety after stress ($r(17) = 0.50$, $P < 0.05$).

Resting State Functional Connectivity (rs-FC)

ELS modulates pgACC-amygdala rs-FC

With the right amygdala as seed region, multiple linear regression showed that as severity of emotional abuse (EA) increases, rs-FC significantly decreases between right amygdala and a series of distributed brain regions (Table II), especially medial prefrontal areas like the pregenual and subgenual anterior cingulate cortex (pgACC/sgACC), as well as the dorsomedial prefrontal cortex (DMPFC) (Table II and Fig. 1A,B). We observed no significant effect of OXT or OXT × EA interaction. No significant effect was found when using other subtypes of ELS as predictors, or when the left amygdala was used as seed region.

Moreover, ROI analysis showed that the rs-FC between left pgACC (MNI coordinate: [−6, 39, 3]) and right amygdala significantly predicted state anxiety after the induction of psychosocial stress (Beta = −0.55, $t(28) = -3.00$, $P < 0.01$) (Fig. 1C). Further analyses revealed that the association between rs-FC strength, EA and state anxiety post stress was not mediated by gray matter volume changes in either pgACC or amygdala (see Supporting Information). Similar linear relations between rs-FC strength and state anxiety after stress were also found in the sgACC (MNI

TABLE II. Brain regions in which rs-FC strength to the right amygdala are negatively associated with emotional abuse

Region	BA	*T* value	MNI coordinates *x*	MNI coordinates *y*	MNI coordinates *z*	Cluster size (#voxels)
Left inferior frontal gyrus, pars triangularis	46	7.30	−45	33	12	2,527
Left dorsomedial prefrontal cortex	9	5.53	−6	39	27	
Left obitofrontal cortex	11	5.03	−15	51	−15	
Left putamen		4.86	−30	0	−9	
Right inferior frontal gyrus, pars triangularis	46	6.42	54	30	27	615
Right middle frontal gyrus	46	5.82	48	45	12	
Right inferior frontal gyrus	47	5.32	45	42	−3	
Left supramarginal gyrus	40	5.86	−54	−30	30	645
Left inferior parietal lobule	40	5.46	−54	−42	51	
Left inferior parietal lobule	40	4.97	−39	−48	42	
Right globus pallidus		5.68	9	−3	0	499
Right putamen		4.92	27	15	−6	
Right anterior insula	13	4.65	36	18	0	
Right orbitofrontal cortex	11	5.49	27	36	−15	113
Right orbitofrontal cortex	11	4.35	27	48	−15	
Right orbitofrontal cortex	11	4.15	12	48	−12	
Left pregenual anterior cingulate cortex	32	5.12	−6	42	0	126
Left subgenual anterior cingulate cortex	24	4.58	0	33	−3	
Left pregenual anterior cingulate cortex	32	4.09	−6	39	3	
Right posterior cerebellum		4.92	9	−87	−30	222
Right posterior cerebellum		4.83	18	−75	−39	
Right posterior cerebellum		4.41	15	−81	−27	
Right precentral gyrus	4	4.81	63	−24	45	362
Right rolandic operculum	42	4.39	63	−18	15	
Right supramarginal gyrus	40	4.22	57	−42	33	

Results were reported with a threshold of FDR corrected $P < 0.01$, cluster size > 100 voxels; BA, Brodmann area; MNI, Montreal Neurological Institute.

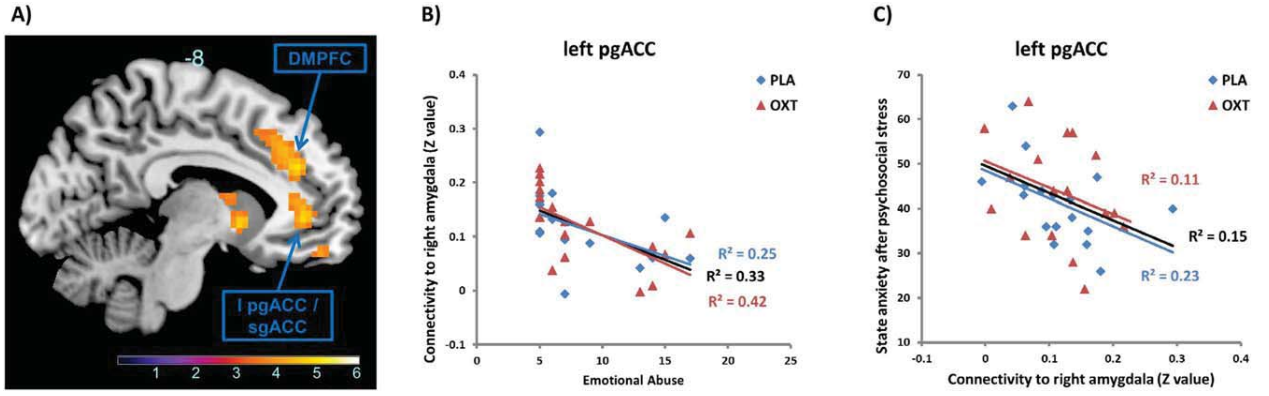

Figure 1.

(**A**) In the pgACC, sgACC and DMPFC, the rs-FC to right amygdala was negatively predicted by emotional abuse (FDR corrected $P < 0.01$, cluster size > 100 voxels). (**B**) Scatter plot illustrating the linear relationship between emotional abuse and decreased rs-FC between left pgACC and right amygdala. (**C**) pgACC-amygdala rs-FC negatively predicted state anxiety after psychosocial stress. PLA, placebo session; OXT, oxytocin session. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

coordinate: [0, 33, −3]; Beta = −0.43, $t(28) = -2.44$, $P < 0.05$) and the left DMPFC (MNI coordinate: [−6, 39, −27]; Beta = −0.39, $t(28) = -2.22$, $P < 0.05$).

ELS and OXT jointly modulate pgACC-amygdala rest-task interaction

To investigate whether pgACC-amygdala rs-FC predicts pgACC responsiveness to psychosocial stress, signal percent change (SPC) of pgACC was calculated during the induction of psychosocial stress. We used a hierarchical multiple regression model to predict the SPC of pgACC. The model with the three-way interaction OXT × ELS × rs-FC was significant ($R^2 = 0.48$, $F(10,25) = 2.31$, $P < 0.05$). Adding the OXT × ELS × rs-FC interaction significantly improved the model on pgACC SPC during psychosocial stress ($\Delta R^2 = 0.23$, F Change$(4,25) = 2.79$, $P < 0.05$).

To decompose this interaction, we conducted follow-up hierarchical multiple regressions separately for placebo and oxytocin sessions. In the placebo session, pgACC-amygdala rest-task interaction was significantly modulated by ELS ($\Delta R^2 = 0.34$, F Change$(1,11) = 8.50$, $P < 0.05$). Specifically, in subjects with low ELS scores, rs-FC negatively predicted pgACC SPC ($r(8) = -0.65$, $P = 0.057$), while in subjects with high ELS scores this correlation was positive ($r(8) = 0.36$, $P > 0.1$; Fischer's $Z = -2.08$, $P < 0.05$) (Fig. 2A). Comparing the oxytocin and placebo sessions, the effect of OXT on pgACC-amygdala rest–task interaction was found to depend on ELS experience: in subjects with low ELS scores, OXT significantly attenuated rest–task interaction (Fischer's $Z = -2.01$, $P < 0.05$) (Fig. 2B); while in subjects with higher ELS scores, there was no difference between OXT and placebo sessions (Fig. 2C).

DISCUSSION

We found that emotional abuse was associated with decreased rs-FC between right amygdala and pregenual anterior cingulate cortex (pgACC). This linear association cannot be accounted for by individual differences in age, IQ, or gray matter volume of corresponding areas. Previous studies have indicated atrophy in amygdala-prefrontal white matter trajectory and reduced rs-FC in the same circuit in children and adolescents who had experienced ELS [Burghy et al., 2012; Eluvathingal et al., 2006]. Consistent with these findings, our study showed that experience of emotional abuse in early life can predict decreased pgACC-amygdala rs-FC in adulthood. It is worth noticing that emotional abuse predicted elevated state anxiety after psychosocial stress, and was the only significant predictor of pgACC-amygdala rs-FC among the subtypes of ELS in our regression analyses. Previous studies have shown that depending on the severity and subtype, ELS may have different effects on the stress regulation system, such as either excessive or dampened neuroendocrine response to acute psychosocial stress [Carpenter et al., 2007; Heim et al., 2001]. It has also been reported that out of the five subtypes of ELS, emotional abuse was the only significant predictor of diminished cortisol response [Carpenter et al., 2009]. Adding to this evidence, our finding suggests that although different subtypes of ELS often occur together, their respective influence needs to be dissociated in further studies.

Heightened anxiety and amygdala activity have been reported in children who experienced stressful caregiving in early life [Tottenham, 2012; Tottenham et al., 2010]. Altered pgACC-amygdala rs-FC has also been associated with trait anxiety [Kim et al., 2011a,b; Veer et al., 2012]. In line with these previous findings, we observed both

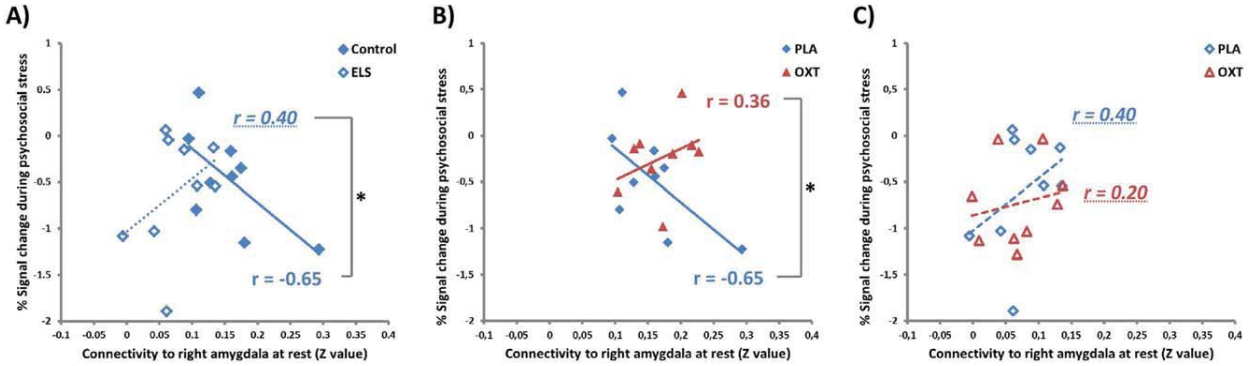

Figure 2.

(**A**) In the placebo session, ELS significantly modulated how pgACC-amygdala rs-FC predicted pgACC SPC during psychosocial stress. In subjects with lower ELS scores, stronger pgACC-amygdala rs-FC predicted stronger pgACC deactivation during stress; whilst in subjects with high ELS scores, increases in pgACC-amygdala rs-FC predicted weaker pgACC deactivation during stress. (**B**) In subjects with lower ELS scores, OXT significantly modulated the rest-task interaction between pgACC-amygdala rs-FC and pgACC deactivation during stress; (**C**) whilst in subjects with high ELS scores, the effect of OXT was not significant. PLA, placebo session; OXT, oxytocin session; $^{*}P < 0.05$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

heightened trait anxiety and elevated state anxiety after psychosocial stress as ELS scores increased. We also found that decreased pgACC-amygdala rs-FC predicted elevated state anxiety and pgACC deactivation during a psychosocial stress task. Moreover, this rest–task interaction within the pgACC-amygdala circuit differed between subjects with high and low ELS scores. In subjects with low ELS scores, stronger pgACC-amygdala rs-FC predicted stronger pgACC deactivation. Previous animal models of stress reactivity suggested a crucial regulatory function of pgACC over amygdala [Herman et al., 2005; Pruessner et al., 2008]. We show for the first time that pgACC-amygdala rs-FC can predict subsequent stress-induced pgACC deactivation and state anxiety, supporting a continuous and dynamic frontolimbic modulation that is crucial in maintaining homeostasis. In subjects with higher ELS scores, we observed not only decreased pgACC-amygdala rs-FC, but also altered interaction between pgACC-amygdala rs-FC and stress-induced pgACC deactivation, i.e., stronger pgACC-amygdala rs-FC predicted weakened pgACC deactivation. In addition to previous findings that ELS is related to reduced amygdala-prefrontal rs-FC [Burghy et al., 2012], our finding reveals the impact of ELS on rest-task interaction in the pgACC-amygdala circuit, highlighting ELS effects on the continuous functional dynamics in this neural circuit both at rest and during stress.

Of importance, the ELS effect was only observed on rs-FC to right but not left amygdala. Previous findings on lateralization of ELS effects were inconsistent [Burghy et al., 2012; Gee et al., 2013; van der Werff et al., 2013b], and the evidence on amygdala lateralization during emotion processing is also somewhat complex. Contrary to the well-known right hemisphere dominance model of emotion processing which derives largely from studies of cortical lesions [Lane and Nadel, 2000], several meta-analyses on human neuroimaging data reported no significant amygdala lateralization. It is emphasized that lateralization might rather be related to age, gender, personality [Wager et al., 2003; Zald, 2003], stimulus type or other methodological variables [Costafreda et al., 2008; Fusar-Poli et al., 2009]. One recent quantitative meta-analysis examined the temporal dynamics of bilateral amygdala and pointed out that the right amygdala is under more rapid modulation and returns to baseline level faster [Sergerie et al., 2008]. The decreased rs-FC strength we found between pgACC and amygdala may reflect alterations in the rapid and dynamic modulation of the right amygdala, which is crucial for emotional regulation. However, it has also been reported that the right amygdala is associated with greater rs-FC in men than in women [Kilpatrick et al., 2006]. A recent developmental study on unattended fear reported activation of left amygdala in young children, which shifted to the activation of right amygdala and ACC in adults [Hung et al., 2012]. The amygdala lateralization we found might therefore also be due to the fact that we only investigated healthy young males. To further verify this finding of lateralization, future studies with female samples and subjects in a wider age range are needed.

Interestingly, not only did subjects with higher ELS scores show reduced pgACC-amygdala rs-FC and weakened rest–task interaction, they were also less sensitive to the

modulation by OXT. We found that OXT moderated the rest–task interaction between pgACC-amygdala rs-FC and stress-induced pgACC deactivation. However, this moderation effect by OXT seemed diminished in subjects with higher ELS scores. Consistent with previous findings on the ELS-dependent effect of OXT [Bakermans-Kranenburg and van IJzendoorn, 2013; Bakermans-Kranenburg et al., 2012; Meinlschmidt and Heim, 2007; Riem et al., 2013a,b; van Ijzendoorn et al., 2011], our result suggests that changes in the pgACC-amygdala circuit in subjects with higher ELS scores may underlie their decreased sensitivity to OXT.

Several previous studies reported OXT effects on amygdala functional connectivity with various brain regions in specific task contexts [Kirsch et al., 2005; Riem et al., 2012; Rilling et al., 2012; Wittfoth-Schardt et al., 2012]. A recent exploratory study reported enhanced rs-FC between amygdala and ventromedial prefrontal cortex (vmPFC) after OXT administration in healthy male subjects [Sripada et al., 2013]. Contrary to this result, we found that the pgACC-amygdala rs-FC itself was not modulated by OXT. Instead of a general OXT effect on functional coupling in this circuit, our finding suggests that OXT modulates the pgACC-amygdala circuit in response to the particular task demand during psychosocial stress. It should be noted that our study sample is younger and within smaller age range compared to that are reported by Sripada et al., 2013. This divergent finding could be due to age-related effect, which has been reported on pgACC-amygdala FC [St Jacques et al., 2010], as well as on central nervous system oxytocin level in animal models [Ebner et al., 2013; Huffmeijer et al., 2013]. Another recent study in healthy female subjects reported no OXT effect on amygdala rs-FC, but an OXT $\times$ ELS interaction on rs-FC between PCC and cerebellum instead [Riem et al., 2013b]. Gender specific OXT effect has been previously reported on stress reactivity and emotional processing [Ditzen et al., 2013; Domes et al., 2010]. The observed OXT effect on rs-FC may therefore also be gender specific. This calls for more human OXT studies with subjects of both gender, and of old age.

Oxytocin has received increasing attention in the treatment of anxiety symptoms in various psychiatric diseases [Epperson et al., 1996; Macdonald and Feifel, 2013; Pitman et al., 1993], such as social phobia [Guastella et al., 2009; Labuschagne et al., 2010]. However, not all observed effects were beneficial [Macdonald et al., 2013; Olff et al., 2013; Pincus et al., 2010]. It has been suggested that the effect of oxytocin might be more closely related to ELS exposure than to psychiatric symptoms [Simeon et al., 2011]. Our finding highlights the need to consider ELS history and pgACC-amygdala functional coupling in future oxytocin studies in healthy and clinical samples.

Our study provides new insights regarding the interplay between ELS, pgACC-amygdala rs-FC, stress reactivity, and the stress-buffering effect of oxytocin. However, one should be cautious with interpretations of causal relations. We considered retrospective self-report of different subtypes of ELS as continuous indices in the regression analyses. These linear associations should be examined in future prospective studies with larger sample sizes. Furthermore, it should be mentioned that our sample consisted of healthy individuals with various degrees of ELS exposure. Although this helps to dissociate ELS effects from psychiatric symptoms and medication effects, it is not known whether the subjects will develop psychiatric diseases later in life. It is critical for future clinical studies to identify individuals who are vulnerable and resilient to the detrimental influence of ELS [Cisler et al., 2013; van der Werff et al., 2013a]. Several previous studies suggest that cortisol stress responses in male subjects are greater, and less sensitive to aging effects as compared to those in females [for reviews, see Kajantie and Phillips, 2006; Kudielka et al., 2009; Otte et al., 2005]. For this reason, we investigated only young male subjects in the current study, in hopes of probing the effect of ELS and OXT in a more homogeneous sample. Because gender and age have been found to modulate amygdala FC [Kilpatrick et al., 2006; St Jacques et al., 2010], ELS effect and OXT effect on stress reactivity [Ditzen et al., 2013; Heim et al., 2010], caution should be taken when generalizing our finding to females and samples of older age.

CONCLUSION

In summary, we found that ELS was associated with decreased rs-FC and reversed rest-task interaction during psychosocial stress in the pgACC-amygdala circuit. OXT attenuated this rest-task interaction in subjects with lower ELS scores, but yielded no effect in subjects with higher ELS scores, suggesting a crucial role of pgACC-amygdala function dynamics in the ELS-dependent effect of OXT. It is therefore critical to consider ELS and functional dynamics in the pgACC-amygdala circuit, when developing therapeutic interventions based on the stress-buffering effect of OXT.

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