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Research paper

Depression is associated with hyperconnectivity of an introspective socio-affective network during the recall of formative relationship episodes

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ABSTRACT

Background: Depression and the experience of early adversity are associated with impairments in interpersonal and social cognitive functioning. The neural mechanisms involved in these impairments remain insufficiently understood.
Methods: In a sample of 48 depressed and 50 healthy participants, we explored seed-to-voxel functional connectivity (FC) during the recall of formative relationship episodes using functional magnetic resonance imaging.
Results: While depressive symptoms were associated with increased FC of brain regions that form an introspective socio-affective network, such as the precuneus, bilateral anterior insula, dorsal anterior cingulate cortex, left amygdala, and medial prefrontal cortex, early adversity linked to decreased FC of brain regions mediating emotion processing such as the bilateral anterior insula and increased FC of the bilateral parahippocampal gyrus.
Limitations: We report both results that are corrected for the number of seeds tested in FC analyses using strict Bonferroni adjustments and unadjusted results as part of an exploratory analysis.
Discussion: Our findings suggest that depression and early adversity are associated with differential FC patterns in the brain during the recall of formative relationship episodes. Hyperconnectivity of an introspective socio-affective network associated with depressive symptoms may link to enhanced self-focus and emotional reactivity. Patterns of neural activation associated with early adversity may underpin numbed affective states or enhanced affective memory regulation. Overall, these findings inform about the neural underpinnings of a reflective ability that is predictive of the adaptation to depression and to early adversity and relevant for psychotherapy outcomes.

INTRODUCTION

Depression is a severe, recurrent, and frequent mental disorder (Bromet et al., 2011). Early adversity, which is the experience of childhood neglect or physical, sexual or emotional abuse, is a potent risk factor for depression, yet not all individuals exposed to early adversity develop a depression (Dube et al., 2003; Heim et al., 2008; Selous et al., 2019). Both, depression and early adversity, are associated with impairments in interpersonal functioning and social cognition (Brüne et al., 2016; Fischer-Kern and Tmej, 2019; Gabbard et al., 2006; Johnson et al., 2002; Zlotnick et al., 2000).

Interpersonal functioning refers to a person's ability to interact with significant others. Social cognition describes the capacity to think about mental and affective states in others and oneself (Keysers and Gazzola, 2006) and is inherently related to interpersonal functioning (De Meulemeester et al., 2017). Both, interpersonal functioning and social cognition, have their foundations in the caregiving context of the early life years (Fonagy et al., 2004). Disturbances in the early caregiving relationships such as forms of unresponsive parenting or experiences of neglect or abuse can engender dysfunctional interpersonal behavior patterns and impairments in social cognition, and later mental health issues (Kobak et al., 2016; Lyons-Ruth and Jacobvitz, 2016; Sroufe et al., 2000; Styron and Janoff-Bulman, 1997).

The individual's capacity to reflect on past formative relationship experiences and how these are associated with current interpersonal behavior patterns links to her or his ability to induce changes in these patterns (Fonagy and Allison, 2014; McCullough, 2003). This reflective capacity links to the umbrella concept of social cognition. Social cognitive abilities are thought to mediate both the adaptation to depression (Cusi et al., 2011; Luyten et al., 2012) and the association of early

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adversity to later psychopathology (Cloitre et al., 2005; Hopfinger et al., 2016; Wright et al., 2009).

Neuroimaging research has provided some insights on the neural mechanisms implicated in deficient social cognition in depressed patients (Cusi et al., 2012). Schilbach et al. (2014) provide an integrative account of this literature: they conducted a meta-analysis on resting state functional magnetic resonance imaging (fMRI) studies and suggested that social cognitive impairments in depression are underpinned by hyperactivity in an introspective socio-affective network. This network is composed of the dorsomedial prefrontal cortex (dmPFC), the subgenual and dorsal anterior cingulate cortex (sgACC and dACC), the left amygdala, and the precuneus.

There is also evidence for altered neural activation underpinning impaired social cognition in the context of early adversity (Heany et al., 2018; Pechtel and Pizzagalli, 2011). Several studies report that the experience of early adversity is accompanied by decreased functional connectivity (FC) in the default mode network (DMN) (Bluhm et al., 2009; Sripada et al., 2014). It has been suggested that experiences of early adversity interfere with the development of the DMN and associated aspects of social cognition such as self-referencing, prospection and autobiographical memory (Daniels et al., 2011).

So far, we lack insight on how depression and early adversity link to neural activation in the context of reflecting interpersonal behavior. We recently developed an fMRI task that specifically explores the neural correlates of recalling emotionally arousing and self-relevant relationship episodes (Wade-Bohleber et al., 2019). In healthy participants, we found that recalling self-relevant relationship episodes modulates neural activation in brain areas commonly associated with memory processes, self-generated thought, and affective processing, such as the parahippocampal gyrus (PHG), the precuneus, the anterior insula (AI) and the pre-supplementary motor area (pre-SMA).

The aim of the current study was to investigate if depression and early adversity are associated with differential patterns of FC during self-relevant relationship episode recall. Specifically, we explored task-based FC in a seed-to-voxel analysis. We chose the seeds corresponding to the reported findings in healthy participants (Wade-Bohleber et al., 2019). First, we investigated group differences in neural activation between depressed and healthy participants. Second, adopting a dimensional approach, we explored if neural activation correlated with severity of depressive symptoms (hereafter depressivity) and with severity of early adversity.

Based on previous evidence that social cognitive impairments in depression are associated with hyperactivation in socio-affective networks (Schilbach et al., 2014), we expected that depression and depressivity would be associated with increased FC of the chosen ROIs with brain areas such as the dmPFC, sgACC, dACC and left amygdala. Moreover, based on previous evidence on altered DMN FC in individuals who have experienced early adversity (Daniels et al., 2011), we hypothesized that early adversity would link to decreased FC of the chosen ROIs to relevant brain areas of the DMN such as the medial prefrontal cortex.

MATERIALS and METHODS

Participants

Depressed and healthy participants were recruited via an university mailing list, local internet platforms, a short newspaper article informing about the study, and the distribution of flyers in a nearby orthopedic hospital, at the university campus, and in medical practices. Additionally, depressed participants were referred by psychiatrists and psychologists affiliated with local psychotherapeutic training institutes.

Exclusion criteria for healthy participants were any type of current psychiatric disorder and a history of a depressive disorder in the past. Inclusion criteria for participants with depression was a primary DSM-IV diagnosis of major depressive disorder (MDD). Exclusion criteria for both groups were antidepressant medication, current or anamnestic substance abuse or dependence, a current or anamnestic psychotic disorder, insufficient German language skills, or any criteria that would interfere with MRI safety regulations (e.g. pregnancy, metal implants, etc.).

All study participants provided written informed consent. The ethics committee of the canton of Zurich approved the study.

Fifty-seven healthy participants were included in a first step. Seven healthy participants had to be excluded from analyses due to a.) an incorrectly conducted preparation task (one participant), b.) technical failure (four), d.) antidepressant medication (one), e.) dropout (one).

Seventy-seven individuals suffering from depressive symptoms interested in participating in the study were included in a first step. Twenty-nine of these participants were excluded because a.) another psychiatric disorder was the primary diagnosis (nine), b.) the depressive symptoms had already remitted since the first contact with the study team or were not sufficiently severe for a MDD diagnosis (four), c.) a history of substance abuse (two), d.) antidepressant medication (nine), e.) drop out (four), f.) metal piercings that could not be removed (one). This resulted in a final sample of 50 healthy and 48 depressed participants. Table 1 describes the sociodemographic characteristics of the final sample. The two groups differed neither in age ($t(96) = 0.77$, $p = .45$), nor years of education ($t(82) = 1.07$, $p = .29$) nor concerning their gender ($X^2(1, 98) = 0.14$, $p = .70$). Depressed participants showed higher scores on the Childhood Trauma Questionnaire (CTQ) than healthy participants ($t(54.30) = -3.04$, $p < 0.05$, $d = 0.64$).

Instruments

Mini-DIPS

The mini-DIPS (Margraf, 1994) is a structured clinical interview based on the diagnostic criteria of DSM IV and ICD 10, allowing to diagnose anxiety, obsessive-compulsive, affective (depressive and bipolar), somatoform, and eating disorders and problematic alcohol and substance use. It also includes a psychosis screening. For each disorder, the mini-DIPS comprises general screening questions as well as more detailed questions exploring specific symptoms. The mini-DIPS is a short form of the DIPS (Diagnostic Interview for Mental Disorders [Diagnostisches Interview für psychische Störungen]) and its reliability and validity have been repeatedly tested (Margraf et al., 2017).

BDI

The Beck Depression Inventory II (BDI II, Beck et al., 1996; Hautzinger et al., 2006) evaluates depressive symptoms during the prior two weeks. The self-report questionnaire comprises 21 items which are answered on a 4-point Likert scale. Internal reliability in our sample was excellent (Cronbach's alpha = 0.97).

Table 1
Sociodemographic characteristics of the sample.

Variables	Healthy (n = 50)	Depressed (n = 48)
Age (n = 98)	M = 33.5 (SD = 9.45)	M = 41.5 (SD = 16.19)
Gender (n = 98)	N	N
Female	38	38
Male	12	10
Years of education (n = 84)	M = 14.14 (SD = 3.11)	M = 13.43 (SD = 2.98)
BDI (n = 94)	M = 3.33 (SD = 4.46)	M = 28.41 (SD = 9.78)
CTQ (n = 85)[1]	M = 31.6 (SD = 5.48)[2]	M = 37.73 (SD = 12.36)

Notes. BDI = Beck Depression Inventory-II, CTQ = Childhood Trauma Questionnaire.[1] Frequencies of different experiences of abuse and neglect are reported in supplementary table S1 (CTQ subscales with cut off values defined according to Häuser et al., 2011) and group differences in supplementary table S2. [2]The CTQ overall score averages M = 31.74 (SD = 10.17) in a community sample (Scher et al., 2001).

Table 2
Definition of region of interest (ROI) templates based on neurosynth.org.

ROI	MNI-coordinates			Diameter (in mm)	Number of studies included in meta-analysis	Term used for search
	x	y	z			
AI *R* +	36	17	0	10	681	Anterior insula
AI L	−36	17	0	10		
PHG *R* +	28	−42	−12	10	602	Parahippocampal
PHG L	−28	−42	−12	10		
Precuneus	0	−60	38	10	1014	Precuneus
Pre-SMA	0	17	50	10	129	Pre supplementary

Notes. AI = anterior insula, *L* = left, PHG = parahippocampus, Pre-SMA = pre-supplementary motor area, *R* = right.

CTQ

The Childhood Trauma Questionnaire (CTQ, Bernstein et al., 2003; Wingenfeld et al., 2010) is a self-report instrument comprising 25 clinical and three validity items. The 25 clinical items explore adverse experiences before the age of 17 years. They are answered on 5-point Likert scales and add up to an overall score. Moreover, items can be allocated to five subscales: emotional, physical, and sexual abuse, and emotional and physical neglect. Internal reliability for the overall score in our sample was good (Cronbach's alpha = 0.89).

Procedures

A psychologist conducted the clinical interview mini-DIPS with the study participants and a preparation task for the fMRI scanning procedure. Both, the preparation and fMRI task, are described in detail elsewhere (Wade-Bohleber et al., 2019). In short, participants developed three narratives about an emotionally arousing and self-relevant relationship episode with a significant other ("self-relevant" condition). Participants also developed three narratives about relationship episodes, which they had observed in others and in which they had not been implicated themselves ("other" condition). The narratives were associated with pictorial cues (Interpersonal Relations Picture System, IRPS, Fuchs et al., 2018, Fig. 1), which then served as stimuli during fMRI scanning. These IRPS stimuli illustrate two or more stick figures interacting with each other. They also comprise control stimuli depicting two or more stick figures in a neutral position with no interaction being illustrated ("control" condition).

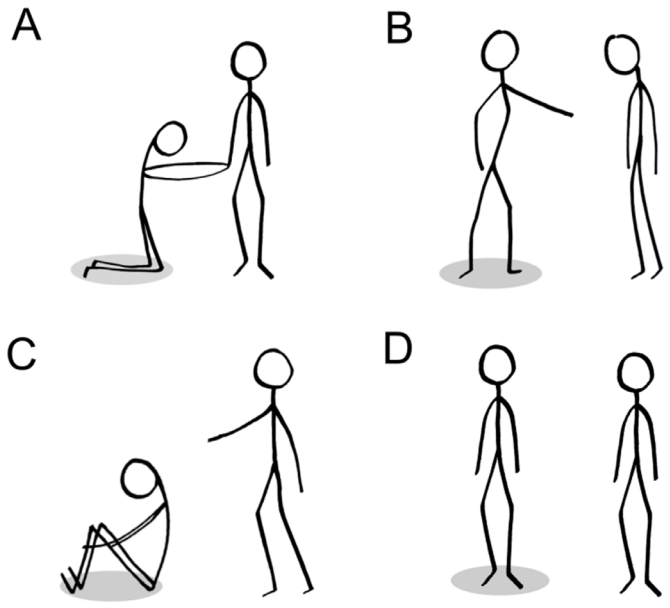

Fig. 1. Examples of IRPS stimuli illustrating interpersonal behavior patterns: A. clinging, B. accusing, C. closing off, D. control stimulus.

FMRI experimental design

Stimuli were arranged in a pseudo-randomized mixed block design. The experimental design is illustrated in Fig. 2. The stimuli were shown for 16 s, followed by two rating scales evaluating subjective arousal and valence, each presented for 8 s. Each block comprised three stimuli with reference to self, three stimuli with reference to others, and three control stimuli respectively. After each block, participants viewed a fixation cross for 20 s. Self-relevant blocks and other blocks were repeated six times, leading to a presentation of 6 × 3 self-relevant stimuli and 6 × 3 stimuli with reference to others. Control blocks were repeated four times, leading to a presentation of 4 × 3 control stimuli. Blocks were arranged in two sessions with the whole experiment taking 32 min in total (not counting a break).

FMRI data acquisition

Data acquisition was performed on a Philips Intera 3T whole-body MR unit equipped with a 32-channel Philips SENSE head coil. Functional time series were acquired with a sensitivity-encoded single-shot echo-planar sequence (SENSE-sshEPI) (Pruessmann et al., 1999). The following acquisition parameters were used in the fMRI protocol: echo time = 35 ms, field of view = 220 mm x 220 mm x 128 mm, acquisition matrix = 80 × 80, voxel size: 2.75 mm x 2.75 mm x 4 mm, SENSE acceleration factor $R = 2.0$. Using a mid-sagittal scout image, 32 contiguous axial slices were placed along the anterior-posterior commissure plane covering the entire brain with a TR of 2000 ms ($\theta = 80°$). The first five acquisitions were discarded to eliminate the influence of T1 saturation effects. An anatomical T1-weighted structural image was also acquired (FOV = 220 × 220 × 135 mm; acquisition matrix = 224 × 187, interpolated to 224 × 224; reconstructed voxel size = 0.98 × 0.98 × 1.5mm^3, 180 slices).

Behavioral data analyses

We used linear mixed models to explore within and between group (healthy and depressed participants) differences of arousal and valence ratings in the different conditions (self-relevant, other, control). Group and condition were modeled as fixed effects and participants as random effects. Moreover, we explored associations of arousal and valence ratings with BDI and CTQ scores using linear mixed models. Condition, BDI, and CTQ were modeled as fixed effects and participants as random effects. We conducted these analyses in IBM SPSS Statistics 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp).

FMRI data analyses

Functional connectivity analyses

FC analyses were performed in Matlab 2018b (The Mathworks, Inc., Natick, Massachusetts) using the toolbox CONN 18b (Whitfield-Gabrieli and Nieto-Castanon, 2012, www.nitrc.org/projects/conn, RRID:SCR_009550). We conducted preprocessing using the CONN-

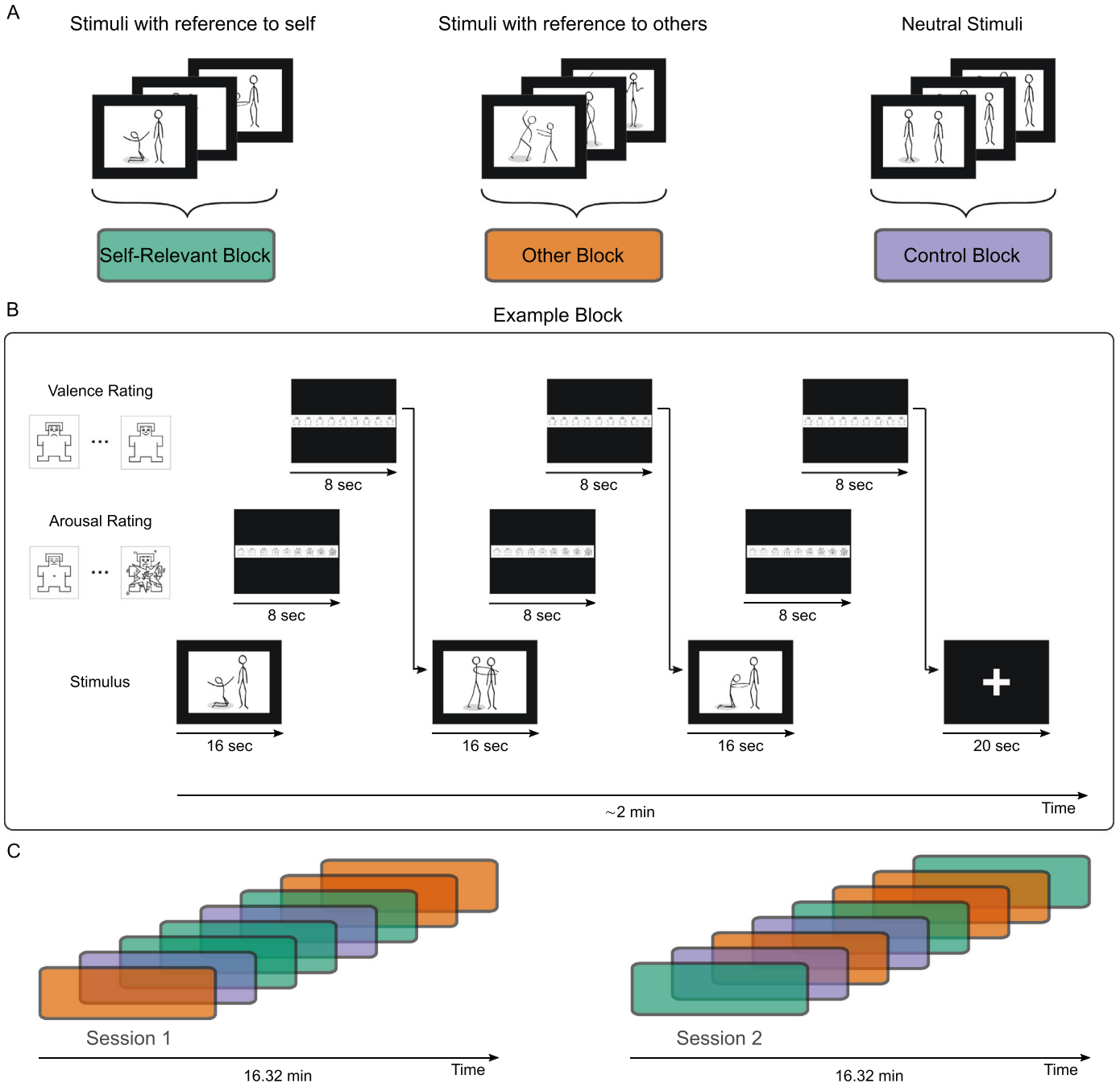

Fig. 2. Illustration of the experimental design of the fMRI task. Adapted from Wade-Bohleber et al., 2019, p. 786. A. Three cues to self-relevant relationship episodes and three cues to relationship episodes observed in others as well as control stimuli were pseudo-randomized in blocks (Self-Relevant Block, Other Block, Control Block). B. A block consisted of three stimuli shown for 16 s followed by rating scales of arousal and valence shown for 8 s each. At the end of one block we showed a fixed cross for 20 s. C. Self-Relevant Blocks, Other Blocks, Control Blocks were pseudo-randomized and arranged in two sessions.

default pipeline for analyses in Montreal Neurological Institute (MNI) - space, which included realignment and unwarping for motion correction, slice-time correction, automatic detection of artifactual scans (Artifact Detection Tool (ART) - based scrubbing), normalization, and spatial smoothing (using a full width at half maximum (FWHM) kernel of 8 mm). Denoising comprised single-subject linear regression analyses in order to remove artifacts due to movement (12 motion covariates: motion parameters plus temporal derivatives), to physiological effects (total of 10 CompCor eigenvariates: 5 each from eroded white matter and cerebrospinal fluid masks), and to artifactual scans. Finally, the resulting bold oxygenated level dependent (BOLD) time series were band-pass filtered (0.01 – 0.1 Hz).

We explored FC during the condition self-relevant compared to the condition other (contrast A) and to the condition control (contrast B). We performed seed-based FC analyses. Based on findings of our previous study employing the same fMRI task with healthy participants (Wade-Bohleber et al., 2019), we chose the PHG, the AI, the precuneus, and the pre-SMA as ROIs. ROI templates were built based on automated term-based meta-analyses performed on neurosynth.org. Search terms and MNI - co-ordinates of the templates' locations are described in Table 2 and illustrated in Fig. 3. SweetView (http://www.sweetneuron.at/wp/sweetview/) served to visualize the templates' locations. We chose bilateral templates for the PHG and the AI and one (centered) template each for the precuneus and pre-SMA. We used the WFU

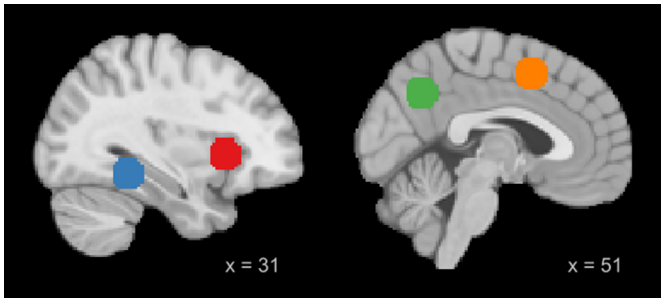

Fig. 3. Region of interest (ROI) templates. Red = anterior insula, blue = parahippocampus, green = precuneus, orange = pre-supplementary motor area.

PickAtlas toolbox (Maldjian et al., 2003) to build the ROI templates (spheres).

Seed-to-voxel correlations were first computed for each subject (1st level analyses): Pearson product-moment correlation coefficients (Pearson's r) were calculated between the BOLD time series in the seed and the time series of all other voxels. These Pearson's r correlation coefficients were converted to normally distributed z-scores using Fisher transformation. At the group level, we used two-sample t-tests to explore group differences between depressed and healthy participants. Moreover, linear regression analyses served to explore associations of BDI and CTQ scores with seed-to-voxel correlations (controlled for age and gender and BDI and CTQ scores respectively). We implemented statistical thresholds of p(uncorr) < 0.001 at the single voxel level and p(FDR-corr) < 0.05 at the cluster level. Additionally, analyses were corrected for multiple comparisons using strict Bonferroni adjustments (3 analysis types x 4 ROIs) leading to an adjusted alpha threshold of $p = 0.004$. However, given their rigidity and risk of type II errors, we also report unadjusted results as part of an exploratory analysis.

In a post-hoc exploratory analysis, we tested if subjective arousal and valence was associated with FC during the condition self-relevant compared to the condition other (contrast A) and compared to the condition control (contrast B). To this end, we calculated differences in the subjective ratings of arousal and valence in between the respective conditions and used linear regression analyses to explore if these were associated with FC in contrast A and B. We report these findings without adjustment for multiple comparisons in the supplements (supplementary analyses A).

Independent of the FC analyses, we also explored BOLD activation in the bilateral AI, bilateral PHG, precuneus, and pre-SMA. The methods and results for this set of analyses are reported in the supplements (supplementary analyses B).

RESULTS

Behavioral ratings

Table 3 and Fig. 4 indicate mean values of arousal and valence ratings per group and condition. Linear mixed models indicated that participants of both groups rated higher arousal for the condition self-relevant ($B = 3.53$, SE $B = 0.24$, $p < 0.001$) and other ($B = 1.77$, SE $B = 0.24$, $p < 0.001$) than for the control condition. Depressed and healthy participants did not differ in arousal ratings per condition. Participants of both groups also rated valence differently in the three conditions: the condition self-relevant ($B = -2.14$, SE $B = 0.19$, $p < 0.001$) and other ($B = -1.27$, SE $B = 0.19$, $p < 0.001$) were rated more negatively in valence than the control condition. Depressed and healthy participants did not differ in valence ratings per condition.

Linear mixed models revealed that BDI scores were not associated with arousal ratings. Higher CTQ scores were associated with lower arousal ratings in the self-relevant condition ($B = -0.07$, SE $B = 0.02$, $p < 0.001$) in comparison to the control condition. Neither BDI nor CTQ scores were associated with valence ratings.

Table 3
Means of subjective arousal and valence ratings of stimuli of the self-relevant condition to stimuli of the other, and control condition per group.

	M(self-relevant)	M(other)	M(control)
Arousal			
Healthy	5.41 (SD = 1.43)	4.23 (SD = 1.46)	2.04 (SD = 1.17)
Depressed	5.75 (SD = 1.52)	4.00 (SD = 1.62)	2.21 (SD = 1.50)
Valence			
Healthy	3.49 (SD = 1.04)	3.78 (SD = 0.92)	5.41 (SD = 1.19)
Depressed	2.99 (SD = 1.16)	3.86 (SD = 0.65)	5.13 (SD = 0.83)

Functional connectivity results

Functional connectivity results for the contrast A) self-relevant > other

Differences in seed-to-voxel FC between healthy and depressed participants for contrast A) (recall of self-relevant relationship episodes compared to recalling relationship episodes involving others) are reported in Table 4. Associations of seed-to-voxel FC with BDI scores for contrast A) are listed in Table 5. Fig. 5 illustrates these associations. FC of the AI with clusters of voxels in the left amygdala and the dACC positively correlated with BDI scores. FC of the pre-SMA with clusters of voxels in the dACC (extending into the vmPFC) and in the dmPFC positively correlated with BDI scores.

Associations of seed-to-voxel FC with CTQ scores for contrast A) are listed in Table 6. Fig. 6 illustrates these associations. FC of the AI with a cluster of voxels in the posterior insula negatively correlated with CTQ scores. FC of the pre-SMA with clusters of voxels in the right ventrolateral prefrontal cortex (vlPFC) and the AI negatively correlated with CTQ scores and with a cluster of voxels in the PHG/fusiform gyrus that positively correlated with CTQ scores. FC of the PHG with a cluster of voxels in the dACC/pre-SMA positively correlated with CTQ scores.

Functional connectivity results for the contrast B) self-relevant > control

Differences in seed-to-voxel FC between healthy and depressed participants for the contrast B) (recall of self-relevant relationship episodes compared to control condition) are reported in Table 7. Associations of seed-to-voxel FC with BDI and CTQ scores are listed in Table 8 and Table 9.

Fig. 7 illustrates some of these associations. FC of the precuneus with the insula was increased in depressed compared to healthy participants. FC of the precuneus with approximately the same cluster of voxels in the insula also positively correlated with BDI scores.

DISCUSSION

This study explored differences in neural activation during the recall of self-relevant relationship episodes in healthy and depressed participants. We also investigated associations of neural activation with the severity of depressive symptoms, i.e. depressivity, and experiences of early adversity.

We compared neural activation during the recall of self-relevant relationship episodes to neural activation during the recall of relationship episodes involving others (contrast A) and neural activation during the recall of self-relevant relationship episodes to neural activation during viewing control stimuli (contrast B).

Our main focus was to explore FC using seed-to-voxel analyses of predefined ROIs. We report both, results that are corrected for multiple comparisons using strict Bonferroni adjustments, and unadjusted results as part of an exploratory analysis given the rigidity of Bonferroni adjustments and risk of Type II errors.

In a group comparison to healthy participants, depressed participants showed increased FC of the AI to the right TPJ (unadjusted) when they recalled self-relevant relationship episodes compared to episodes involving others (contrast A). Moreover, depressivity correlated with

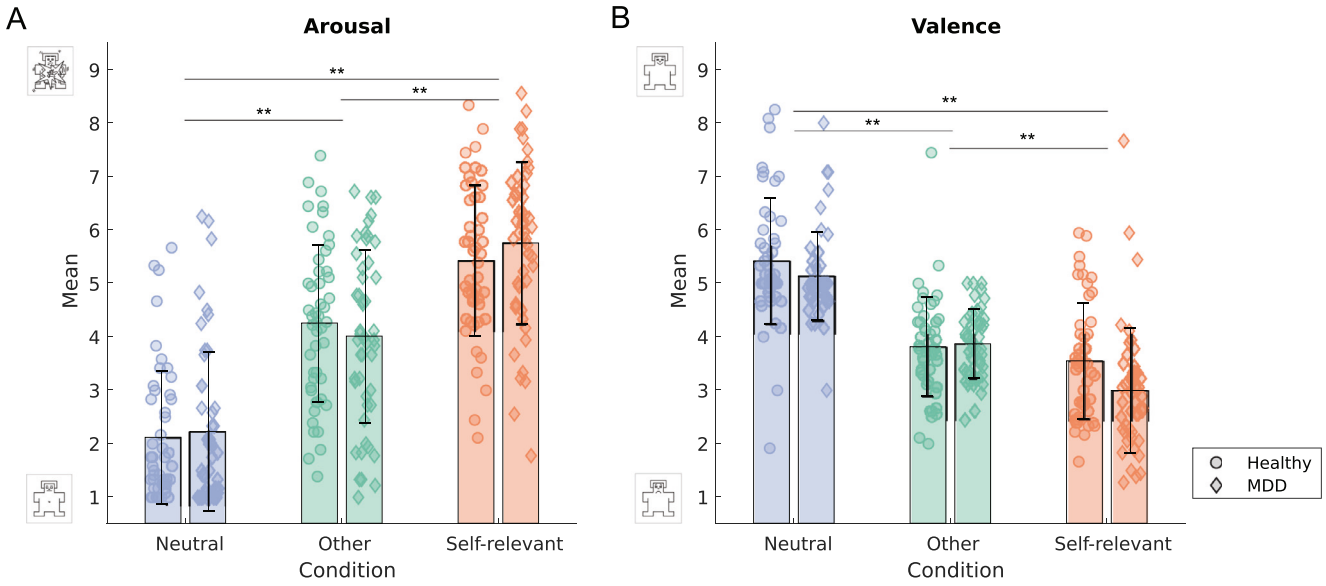

Fig. 4. A. Mean arousal ratings per group and condition. B. Mean valence ratings per group and condition. Lower values indicate negative valence and higher values positive valence.

Table 4
Seed and region showing differences in functional connectivity related to group in the self-relevant compared to the other condition (contrast A).

Seed/ Test	Region	Hemi-sphere	BA	Direction	Coordinates			Cluster Size	Size p-FDR
					x	y	z		
AI (bil)									
Depressed > Healthy	TPJ / Supramarginal Gyrus	R	22	pos	44	−40	18	112	.007

Notes. AI = anterior insula, BA = Brodman area, bil = bilateral, pos = positive, TPJ = temporoparietal junction, *R* = right.

Table 5
Seeds and regions showing functional connectivity changes related to depressive symptomatology in the self-relevant compared to the other condition (contrast A).

Seed/ Predictor	Region	Hemi-sphere	BA	Direc-tion	Coordinates			Cluster Size	Size p-FDR
					x	y	z		
AI (bil)									
BDI	Amygdala	L		pos	−30	−2	−14	95	.01
BDI	dACC	R	32	pos	6	34	22	68	.04
BDI	Fusiform/Cere-bellum	L	18/37	neg	−20	−70	−20	157	.002*
pre-SMA									
BDI	dACC/vmPFC	bil	32	pos	6	32	24	871	<0.001*
BDI	dmPFC	R	8	pos	−14	42	40	80	.02

Notes. AI = anterior insula, BA = Brodman area, BDI = Beck Depression Inventory II, bil = bilateral, dACC = dorsal anterior cingulate cortex, dmPFC = dorsomedial prefrontal cortex, *L* = left, pre-SMA = pre-supplementary motor area, *R* = right. * = significant at $p < .004$ (corrected for multiple comparisons using Bonferroni adjustments).

increased FC of the AI with the left amygdala (unadjusted), the dACC (unadjusted), and decreased FC of the AI with the left fusiform gyrus. Depressivity also correlated with increased FC of the pre-SMA with the dACC and right dmPFC (unadjusted).

In a group comparison to healthy participants, depressed participants displayed increased FC of the precuneus to the insula and several temporal and frontal brain areas when they recalled self-relevant relationship episodes compared to the control condition (contrast B). Moreover, depressivity correlated with increased FC of the precuneus with the insula (unadjusted) and several frontal, parietal, and temporal regions (partly unadjusted).

Early adversity was associated with different patterns of functional connectivity. When participants recalled self-relevant relationship episodes compared to episodes involving others (contast A), early adversity correlated with decreased FC of the AI with the posterior insula and with decreased FC of the pre-SMA with the vlPFC and AI. Moreover, early adversity was associated with increased FC of the PHG with a cluster extending from the dACC into the pre-SMA and several areas in the motor cortices.

In sum, we observed group differences between healthy and depressed participants as well as specific associations of depressivity and early adversity in functional connectivity. We found that depressivity was associated with increased FC of brain regions relevant for introspective and socio-affective processes while early adversity was generally associated with decreased FC in similar brain areas with the exception of the PHG.

Behavioral results

Behavioral ratings indicated that healthy and depressed participants found the recall of formative self-relevant relationship episodes emotionally more arousing and associated with more negative feelings than the recall of relationship episodes involving others and the control condition. This suggests that our experimental procedure allowed for

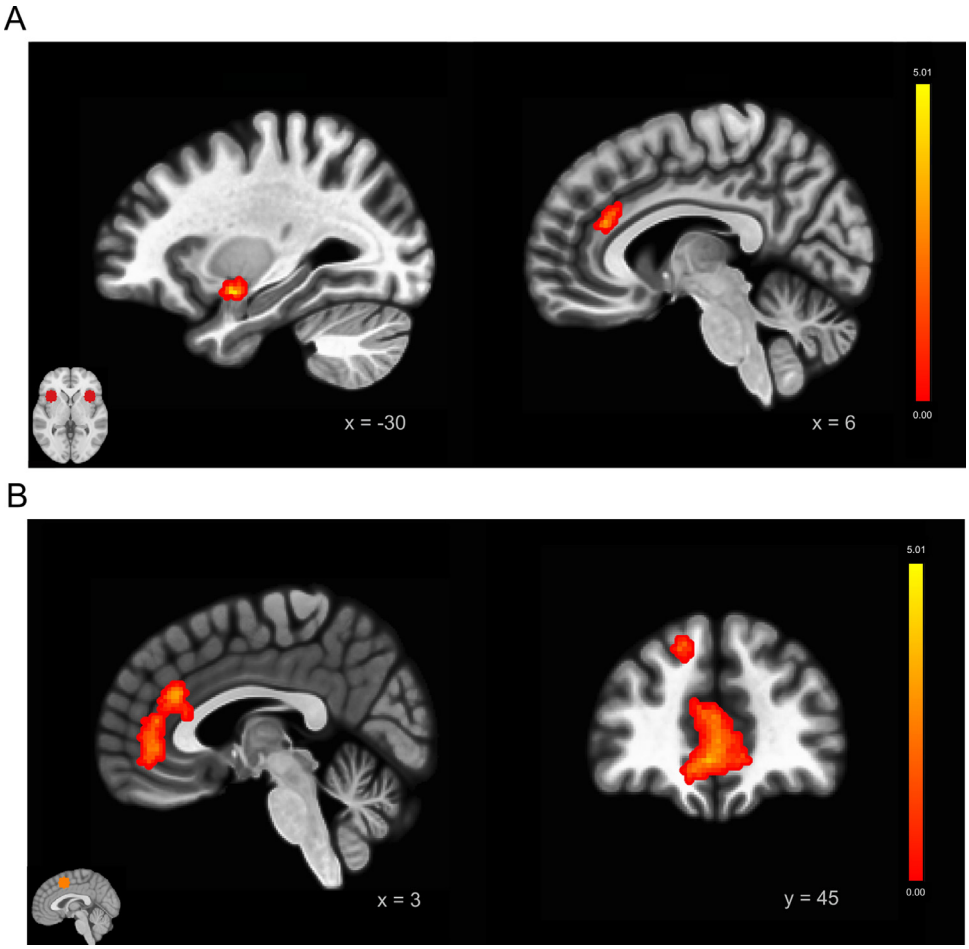

Fig. 5. Associations of seed-to-voxel functional connectivity (FC) with Beck Depression Inventory II scores (BDI) in the self-relevant compared to the other condition (contrast A). A. Seed: anterior insula, illustrated at the bottom left at $z = +1$, FC to clusters of voxels in the left amygdala and dorsal anterior cingulate cortex positively correlated with BDI. B. Seed: pre-supplementary motor area, illustrated at the bottom left at $x = -1$, FC to clusters of voxels in the dorsal anterior cingulate and right dorsomedial prefrontal cortex positively correlated with BDI.

the elaboration of individual, affectively salient stimuli. Surprisingly, we did not find differences in arousal or valence ratings that related to depression or depressivity. Early adversity was associated with lower arousal ratings for the recall of self-relevant relationship episodes. This may indicate a reduced emotional experience during our task associated with early adversity.

Neuroimaging results

Functional connectivity associated with depression

Recalling self-relevant relationship episodes compared to relationship episodes involving others (contrast A). In a group comparison to healthy participants, depressed participants showed increased FC of

Table 6
Seeds and regions showing functional connectivity changes related to early adverse experiences in the self-relevant compared to the other condition (contrast A).

Seed/ Predictor	Region	Hemi-sphere	BA	Direc-tion	Coordinates			Cluster Size	Size p-FDR
					x	y	z		
AI (bil)									
CTQ	Insula (post)	R	13	neg	46	4	−8	196	<0.001*
Precuneus									
CTQ	Premotor cortex	R	6	pos	54	10	46	253	<0.001*
pre-SMA									
CTQ	vlPFC	R	10	neg	44	50	0	182	<0.001*
CTQ	AI	R	13	neg	40	16	−8	106	<0.001*
CTQ	PHG/Fusiform	R	37	pos	26	−46	−12	144	<0.001*
PHG (bil)									
CTQ	dACC/pre-SMA	R/L	6	pos	2	6	48	251	<0.001*
CTQ	Primary motor cortex	L	6	pos	−46	−4	30	354	<0.001*
CTQ	Primary motor cortex	R	6	pos	38	−8	50	322	<0.001*
CTQ	Primary motor cortex	L	6	pos	−36	−8	52	83	.02

Notes. AI = anterior insula, bil = bilateral, CTQ = Childhood Trauma Questionnaire, dACC = dorsal anterior cingulate cortex, *L* = left, neg = negative, PHG = Parahippocampus, pos = positive, pre-SMA = pre-supplementary motor area, vlPFC = ventrolateral prefrontal cortex *R* = right.* = significant at $p < .004$ (corrected for multiple comparisons using Bonferroni adjustments).

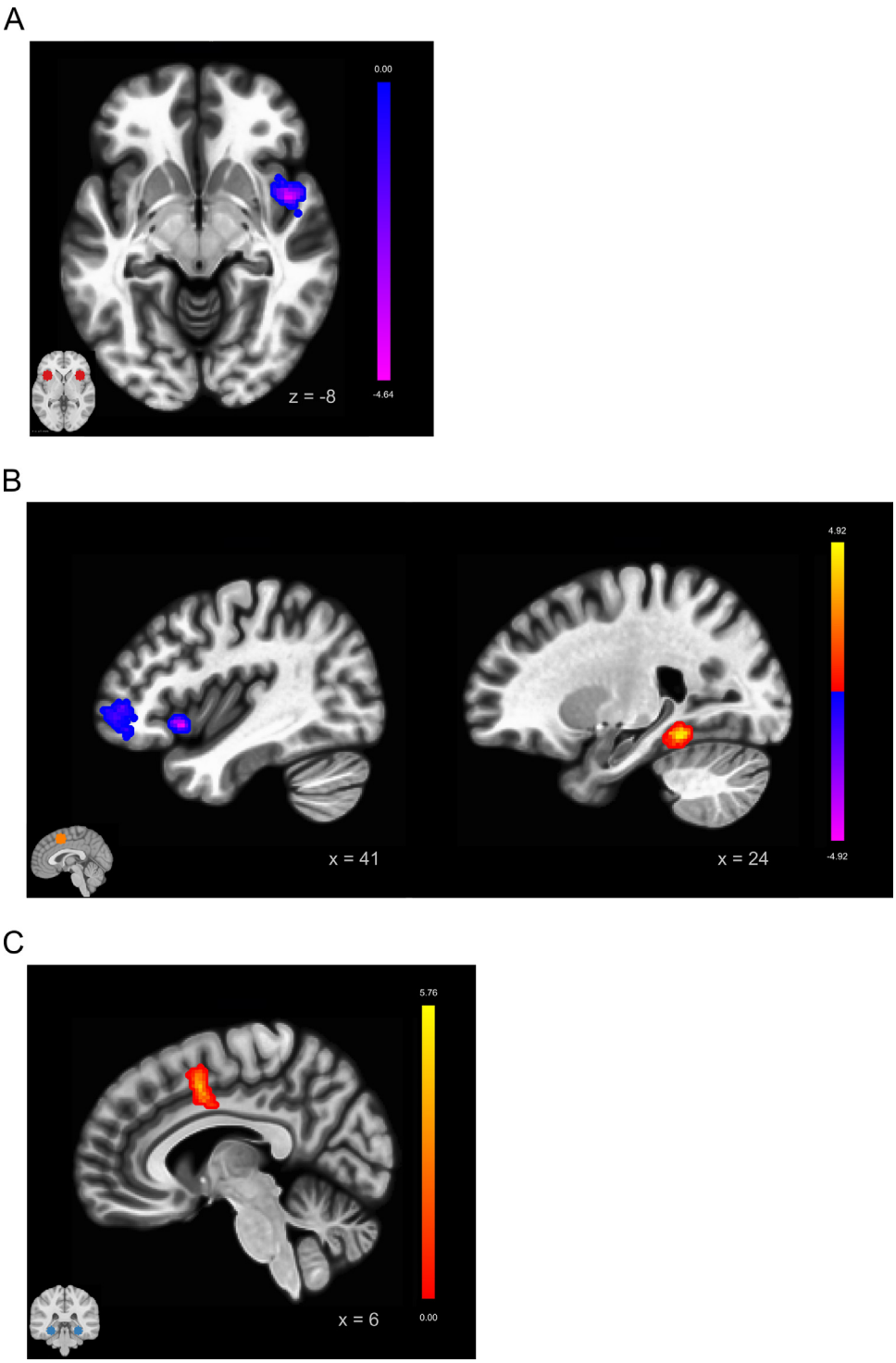

Fig. 6. Associations of seed-to-voxel functional connectivity (FC) with Childhood Trauma Questionnaire (CTQ) scores in the self-relevant compared to the other condition (contrast A). A. Seed: anterior insula (AI), illustrated at the bottom left at $z = +1$, FC to clusters of voxels in the posterior insula negatively correlated with CTQ scores. B. Seed: pre-supplementary motor area (pre-SMA), illustrated at the bottom left at $x = -1$, FC to clusters of voxels in the ventrolateral prefrontal cortex and anterior insula negatively correlated with CTQ scores. FC to a cluster of voxels in the parahippocampus / fusiform gyrus positively correlated with early adversity. C. Seed: parahippocampus (PHG), illustrated at the bottom left at $y = -36$, FC to a cluster of voxels in the dorsal anterior cingulate cortex (dACC) extending into the pre-supplementary motor area (pre-SMA) positively correlated CTQ scores.

Table 7
Seeds and regions showing differences in functional connectivity related to group in the self-relevant compared to the control condition (contrast B).

Seed/Test	Region	Hemi-sphere	BA	Direc-tion	Coordinates			Cluster Size	Size p-FDR
					x	y	z		
Precuneus									
Depressed > Healthy	Insula	R	13	pos	34	−10	14	85	.001*
Depressed > Healthy	Precuneus (surrounding seed)	bil	18	pos	8	−74	24	100	.001*
Depressed > Healthy	Auditory cortex	R	22	pos	60	−14	2	227	.001*
Depressed > Healthy	Pimary motor cortex	L	4	neg	−50	−10	48	133	.001*

Notes. bil = bilateral, *L* = left, pre-SMA = pre-supplementary motor area, *R* = right, vmPFC = ventromedial prefrontal cortex.* = significant at $p < .004$ (corrected for multiple comparisons using Bonferroni adjustments).

Table 8
Seeds and regions showing functional connectivity changes related to depressive symptomatology experiences in the self-relevant compared to the control condition (contrast B).

Seed/ Predictor	Region	Hemi-sphere	BA	Direc-tion	Coordinates			Cluster Size	Size p-FDR
					x	y	z		
Precuneus									
BDI	Primary motor cortex	L	4	pos	−38	−18	44	154	.002*
BDI	Insula	R	13	pos	32	−8	12	69	.04
BDI	Planum temporale	R	22	pos	52	−12	−6	65	.04
BDI	Primary motor cortex	R	4	pos	42	−12	24	60	.04
BDI	Primary somatosensory cortex	R	1	pos	34	−30	64	57	.04

Notes. BDI = Beck Depression Inventory II, *L* = left, pos = positive, *R* = right.* = significant at $p < .004$ (corrected for multiple comparisons using Bonferroni adjustments).

the AI to the right TPJ (unadjusted) when they recalled self-relevant relationship episodes in contrast to relationship episodes involving others (contrast A). The AI is a core node of the salience network that serves to detect individually relevant stimuli (Menon and Uddin, 2010). Additionally, the AI is relevant for interoceptive awareness and emotion processing (Craig, 2009). Both, the AI and the right TPJ coactivate when reorienting attention (Krall et al., 2015) and FC at rest indicates that the TPJ is associated with the salience network (Kucyi et al., 2012). Increased AI – TPJ FC in depression may underpin differences in salience of the self-relevant relationship episodes for depressed compared to healthy participants.

Moreover, depressivity correlated with increased FC of the AI with the left amygdala (unadjusted), the dACC (unadjusted), and decreased FC of the AI with the fusiform gyrus. Additionally, we observed that depressivity was associated with increased FC of the pre-SMA with the dACC and dmPFC (unadjusted). The brain regions in which we observed these patterns of aberrant FC are involved in different aspects of emotion processing and regulation (Etkin et al., 2015; Kohn et al., 2014). Etkin et al. (2015) suggest that amygdala, insula, and dACC are mostly involved with emotional reactivity: The amygdala may serve to detect motivational, i.e. salient, information of a stimulus, the insula provides relevant interoceptive information for its processing, while the dACC presumably integrates other individual motivational demands. Increased FC of these regions may thus be an indicator of enhanced emotional reactivity associated with depression in the context of the recall of self-relevant relationship episodes. In contrast, the pre-SMA and medial and lateral prefrontal areas are thought to mediate explicit emotion regulation (Etkin et al., 2015). Increased FC of these brain areas in the context of our task may also mirror increased attempts of emotion regulation. Schilbach et al. (2014) propose that parts of this emotion regulation network identified by Etkin et al. (2015) form an introspective socio-affective network. This network is thought to mediate important affective and introspective processes as well as interpersonal behavior and expectations. Important nodes of this network are the dACC, the left amygdala, and the dmPFC (together with the subgenual cingulate cortex and precuneus). These thus overlap with regions in which we observed increased FC related to depressivity.

In a post-hoc exploratory analysis, we observed that across all subjects, ratings of subjective arousal were associated with increased FC of the precuneus with several medial and lateral prefrontal brain areas such as the vmPFC, dACC, and dlPFC (cf. supplementary analysis A, table S3 and Fig. S2). These brain regions partly overlap with the DMN and the introspective socio-affective network described by Schilbach and colleagues (2014) suggesting that arousing self-relevant memories particularly mobilize these brain networks

Recalling self-relevant relationship episodes compared to the control condition (contrast B). In a group comparison to healthy participants, depressed participants showed higher FC of the precuneus with the insula (unadjusted) and a temporal and frontal cluster of voxels when they recalled self-relevant relationship episodes in contrast to viewing control stimuli (contrast B). FC of the precuneus to approximately the same set of voxels in the insula also correlated with depressivity (unadjusted). The precuneus is a functional hub of the DMN (Raichle, 2015) and seems to be specifically involved in self-related mental representations (Cavanna and Trimble, 2006). Schilbach et al. (2014) also allocate the precuneus to an introspective socio-affective network. Meta-analytic evidence demonstrates increased FC of the precuneus in depression and it has been suggested that precuneus dysfunction plays a crucial role in the neurobiological pathways of this disorder (Zhong et al., 2016). Increased FC of the precuneus with the insula associated with depressivity may underpin an increased self-focus and more pronounced affective involvement: as already discussed, the insula is an important region for interoception, the subjective experience of feelings and emotion processing (Craig, 2009; Pollatos et al., 2007; Schilbach et al., 2012).

Functional connectivity associated with early adversity

Recalling self-relevant relationship episodes compared to relationship episodes involving others (contrast A). Early adversity was associated with decreased FC of the AI to the posterior insula, and of the pre-SMA to the AI and the vlPFC when participants recalled self-relevant relationship episodes compared to the episodes involving others (contrast A). It has been demonstrated that early adversity links to reduced FC in several networks in the brain, both task-related and at rest (Cisler et al., 2013; Teicher et al., 2016; Wang et al., 2014). For instance, Cisler et al. (2013) explored connectivity between nodes of an emotional regulation network and found that early adversity correlated negatively with the global connectivity within this network. Similarly, Wang et al. (2014) observed reduced FC in what they called a prefrontal-limbic-thalamic-cerebellar circuitry. Our findings suggest that this is also the case for brain regions implicated in emotion processing such as the insular cortex and the pre-SMA in the context of the recall of formative relationship experiences.

In contrast to these findings of reduced FC of the AI and the pre-SMA, we also observed increased FC of the PHG with the dACC/pre-

Table 9
Seed and region showing functional connectivity changes related to early adverse experiences in the self-relevant compared to the control condition (contrast B).

Seed/ Predictor	Region	Hemi-sphere	BA	Direc-tion	Coordinates			Cluster Size	Size p-FDR
					x	y	z		
Precuneus									
CTQ	Primary somatosensory cortex	L	1	neg	−34	−42	62	110	.02

Notes. CTQ = Childhood Trauma Questionnaire, *L* = left, neg = negative.

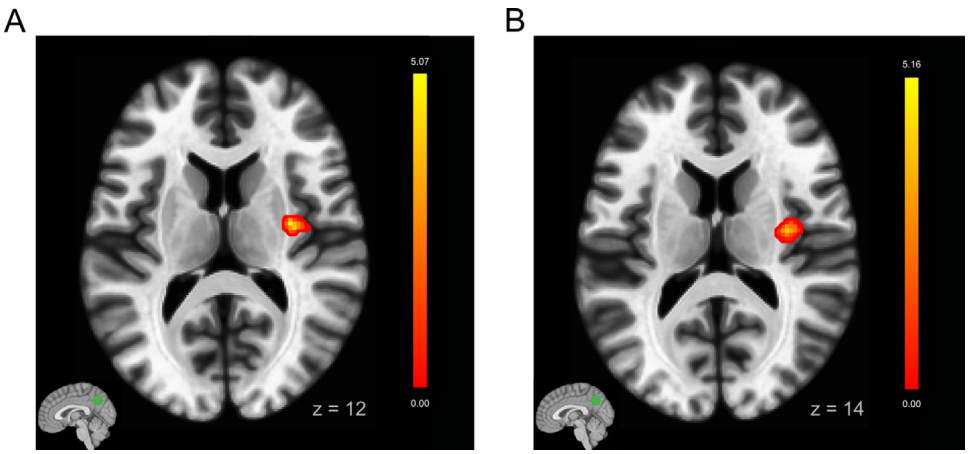

Fig. 7. Associations of depression and depressivity in functional connectivity (FC) in the self-relevant compared to the control condition (contrast B). A. Seed: Precuneus, illustrated at the bottom left at $x = -2$, increased FC to a cluster of voxels in the insula in depressed compared to healthy participants. B. Seed: Precuneus, illustrated at the bottom left at $x = -2$, FC to clusters of voxels in the insula positively correlated with BDI scores.

SMA and several areas of the motor cortices that was associated with early adversity. PHG function can be linked to self-referential memory processing (Martinelli et al., 2013). The PHG connects to the hippocampus and structural alterations in this part of the temporal lobe are among the best replicated findings in neuroimaging research on the effects of early adversity (Teicher et al., 2016). However, these effects appear to be less pronounced in individuals who have experienced early adversity but not developed psychopathology (Calem et al., 2017). Intriguingly, Richter et al. (2019) recently found that increased hippocampal function is associated with resilience in individuals with experiences of early adversity. Here, we find increased FC of the PHG with various other brain areas that is associated with early adversity but not depression. We speculate that this may be a marker of resilient processes. For instance, it is possible that PHG – dACC/pre-SMA FC links to enhanced affective memory regulation in the context of the recall of conflicting self-referential autobiographic memories. The dACC has been, in fact, associated with the recall of remote contextual fear memories in rodents (Frankland et al., 2004) and increased hippocampal-dACC FC with the recall of conditioned fear stimuli in a new context in humans (Hermann et al., 2016). These findings suggest an important regulatory role of the dACC in the recall of emotional memories.

Recalling self-relevant relationship episodes compared to the control condition (contrast B). Independent of FC analyses, we reported analyses of BOLD activation in the defined ROIs in the supplements. We found that more severe early adversity was associated with less pronounced differences in neural activation in the bilateral AI and the pre-SMA when participants recalled self-relevant relationship episodes compared to the control condition (contrast B). Given the implication of both of these regions in interoceptive awareness, the subjective experience of emotions and their regulation (Craig, 2009; Etkin et al., 2015), we speculate that these findings relate to a reduced emotional experience during our task. This would be in line with the behavioral ratings: early adversity was associated with lower arousal in the self-relevant condition. Reduced emotional experiences in the context of our task may either link to a tendency towards overall blunted affective states or to an adaptive enhanced emotion regulation in the context of a recall of salient interpersonal stimuli. In this context, it is interesting to note that traumatized individuals are thought to alternate between states of emotional under- and overarousal, which have also been linked to insular hypo- or hyperactivation (Frewen and Lanius, 2006; Lanius et al., 2010). Moreover, early adversity has also been conceptualized to engender emotional impoverishment (Schimmenti and Caretti, 2016). However, the findings reported here need to be interpreted with care as they were not corrected for multiple comparisons.

Overall discussion of neuroimaging findings

Taken together, we observed different patterns of functional connectivity associated with depression, including depressivity, and early adversity during the recall of self-relevant relationship episodes. Depressivity was linked to increased FC of brain regions that mediate emotion processing and self-referencing and that can be functionally allocated to an introspective socio-affective network (Schilbach et al., 2014). Hyperconnectivity of this network linked to depressivity may mirror a failure to adequately modulate neural activation in the associated brain regions. This possibly underpins an increased self-focus, a form of affective rumination, and inflated emotional reactivity in the context of recalling formative relationship experiences. Schilbach et al. (2014) provided meta-analytic evidence on hyperactivity of this network associated with depression at rest. Our observations are thus in line with these previous findings, yet refer to task-based connectivity patterns. They are also consistent with our initial hypotheses.

In contrast, early adversity was associated with patterns of FC that only partly matched our initial hypotheses. We had expected to observe decreased FC of the ROIs with the DMN. In fact, early adversity was associated with decreased FC of regions implicated in emotion processing, a finding that nonetheless fits well into the existing literature (Teicher et al., 2016). It has been previously suggested that reduced FC of relevant brain regions may underpin both deficient emotion regulation as well as affective blunting (Frewen et al., 2008; Jatzko et al., 2006; Lang et al., 2012). Additionally, we observed increased FC of the PHG, a region connected to the hippocampus, which has consistently been implicated in the effects of early adversity. As a specific finding associated with early adversity but not depressivity, we speculate that hyperconnectivity of the PHG with the dACC may underlie enhanced affective memory regulation in the context of the recall of self-relevant relationship episodes. This may indicate some form of resilient process (cf. Richter et al., 2019). However, these speculations need to be tested in a more defined experimental set-up (e.g. comparing larger groups of healthy and depressed participants with and without history of early adversity).

Limitations

Several limitations of our study need to be addressed. First, not all of our FC findings were corrected for multiple comparisons regarding the number of ROIs employed in the seed-based analyses and therefore need to be interpreted with caution. We chose to do so as Bonferroni adjustments are rigid and increase the risk of Type II errors. Second, our fMRI task has certain methodological limitations that we have already discussed elsewhere (Wade-Bohleber et al., 2019), yet some aspects are noteworthy in light of the findings discussed here. Our aim was to

develop an fMRI task with high ecological validity. We thus tried to capture a mental process, the recall of a specific, self-relevant relationship episode, that is relevant for depression and individuals with experiences of early adversity. However, this also implies that our task involves a multitude of cognitive and affective processes such as autobiographic memory retrieval, mental imagery, self- and other-referencing and emotion regulation. These processes can thus not be distinguished in our task. Future studies employing our fMRI task may consider implementing some adaptations in order to distinguish some of these processes, e.g. by controlling for emotional valence and arousal of autobiographic episodes. Further, it is important to note that we compared our active condition (self-relevant) to two control conditions. One of these conditions (control) only implicated viewing neutral control stimuli, thus not mobilizing any memory retrieval. Third, our fMRI task is cognitively demanding as participants need to remember which visual cue indicates a specific relationship episode. As depression is associated with divers cognitive impairments (Kircanski et al., 2012), participants with depression may have performed more poorly in our task than the healthy participants. Fourth, it is noteworthy that we found several associations of depression and depressivity with patterns of FC, yet we failed to demonstrate such associations with neural activation in the chosen ROIs independent of FC (analyses reported in the supplements). This was a surprising finding. However, evidence on alterations in task based neural activation in specific brain regions remains inconsistent in depression (Müller et al., 2017), while findings on aberrant functional connectivity in depression are more coherent, particularly at rest (Brakowski et al., 2017; Kaiser et al., 2015). In fact, it has been suggested that alterations in brain activation underpinning depression may be best understood in terms of altered network connectivity rather than in terms of aberrant responses of specific brain regions (Li et al., 2018).

Future directions

Here, we presented findings of different neural connectivity patterns associated with depression, depressivity and early adversity in the context of the recall of a self-relevant relationship episode. The ability to reflect on formative relationship experiences is associated with the ability to adapt current perceptions and behaviors in the interpersonal context (Fonagy and Allison, 2014). Such reflective abilities are targeted in specialized psychotherapeutic approaches (Bateman and Fonagy, 2010). They may predict both a better adaptation to early adversity (Cloitre et al., 2005) and depression (Di Schiena et al., 2011; Güleç et al., 2013) and also more positive treatment outcomes in psychotherapy (Ekeblad et al., 2016; Gullestad et al., 2013; Katznelson et al., 2019). It will be of interest to explore if our fMRI task can also serve to elucidate neural mechanisms underlying these reflective abilities in order to predict treatment responses to psychotherapy.

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Institutional boardreview

This study was approved by the ethics committee of the canton of Zurich (reference number: EK: KEK-ZH.Nr. 2011–0298).

CRediT authorship contribution statement

L.M. Wade-Bohleber: Investigation, Formal analysis, Visualization, Writing - review & editing. **H. Boeker:** Supervision. **S. Grimm:** Formal analysis, Writing - review & editing. **M. Gärtner:** Formal analysis. **J. Ernst:** Investigation. **D.A. Recher:** Investigation. **N. Buergi:** Investigation, Visualization. **E. Seifritz:** Resources. **A. Richter:** Supervision, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.110.

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