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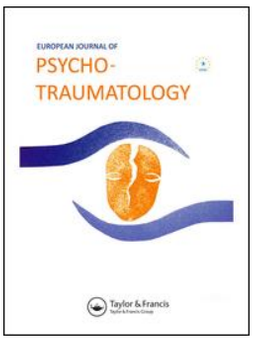

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CLINICAL RESEARCH ARTICLE

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Unresolved–disorganized attachment adjusted for a general psychopathology factor associated with atypical amygdala resting-state functional connectivity

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ABSTRACT

Background: Recent research has identified a general psychopathology factor (GPF), which explains overlap in presentation of psychopathological symptoms. Unresolved–disorganized attachment (Ud) is another transdiagnostic risk factor that may be relevant to explain differences in patient characteristics within diagnostic classifications.

Objective: In the current study, we examined unique relations of resting-state functional connectivity (RSFC) with Ud and GPF.

Method: RSFC data were collected from a mixed group of adolescents (N = 74) with and without psychiatric disorder, as part of the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA) study. Ud was measured using the Adult Attachment Interview (AAI). Associations between Ud, GPF, and RSFC of the amygdala and dorsal anterior cingulate cortex (dACC) and with amygdala–medial frontal connectivity were examined.

Results: Ud was positively associated with greater functional connectivity between the left amygdala and the left lateral occipital cortex, precuneus, and superior parietal lobule. Furthermore, Ud was negatively associated with left amygdala–medial frontal cortex connectivity. GPF was not significantly associated with dACC or amygdala connectivity.

Conclusions: Atypical amygdala connectivity may reflect a vulnerability factor rather than a biomarker of psychopathology. The unique association of Ud and amygdala RSFC, adjusted for a GPF, across participants with and without various classifications of psychopathology illustrates that dimensional approaches based on the AAI may complement psychiatric classifications in clinical research and practice.

Apego no resuelto desorganizado ajustado a un Factor de Psicopatología General asociado con conectividad funcional atípica de la amígdala en estado de reposo

Antecedentes: La investigación reciente ha identificado un factor de psicopatología general (GPF, en su sigla en inglés), que explica la superposición en la presentación de los síntomas psicopatológicos. El apego no resuelto-desorganizado (Ud) es otro factor de riesgo transdiagnóstico que puede ser relevante para explicar las diferencias en las características de los pacientes dentro de las clasificaciones diagnósticas.

Objetivo: En el presente estudio, examinamos las relaciones únicas de conectividad funcional en estado de reposo con el Ud y GPF.

Método: Los datos de conectividad funcional en estado de reposo (RSFC, en su sigla en inglés) se recopilaron de un grupo mixto de adolescentes (N = 74) con y sin trastorno psiquiátrico, parte del Estudio de Imagen de las Vías Emocionales en Adolescentes Clínicos (EPISCA, en su sigla en inglés). El Ud se midió utilizando la Entrevista de Apego Adulto (AAI, en su sigla en inglés). Se examinaron las asociaciones entre el Ud, GPF y RSFC de la amígdala y la corteza cingulada anterior (dACC, en su sigla en inglés) y con la conectividad medial-frontal de la amígdala.

Resultados: El Ud se asoció positivamente con una mayor conectividad funcional entre la amígdala izquierda y la corteza occipital lateral izquierda, precuneus y el lóbulo parietal superior. Además, el Ud se asoció negativamente con la conectividad entre la corteza

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KEYWORDS
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PALABRAS CLAVE
Factor de Psicopatología General; apego no resuelto-desorganizado; amígdala; conectividad funcional en estado de reposo; corteza cingulada dorsal anterior; corteza prefrontal medial; psicopatología; adolescentes

关键词
一般精神病理因素; 未解决的紊乱依恋; 杏仁核; 静息状态功能连接; 背前扣带皮层; 内侧前额叶皮质; 精神病理学; 青少年

HGHLIGHTS

- Unresolved–disorganized attachment adjusted for a general psychopathology factor is positively associated with greater left amygdala resting-state functional connectivity and the left lateral occipital cortex, precuneus, and superior parietal lobule.
- Unresolved–disorganized attachment is negatively associated with left amygdala–medial frontal cortex connectivity.

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Supplementary material for this article can be accessed here.

medial-frontal y la amígdala izquierda. El GPF no se asoció significativamente con la conectividad de la dACC o la amígdala.
Conclusiones: La conectividad atípica de la amígdala puede reflejar un factor de vulnerabilidad en lugar de un biomarcador de psicopatología. La asociación única del Ud y la conectividad RSFC y amígdala, ajustada para un GPF, entre participantes con y sin varias clasificaciones de psicopatología ilustra que los enfoques dimensionales basados en la AAI pueden complementar las clasificaciones psiquiátricas en la investigación y práctica clínica.

• The general psychopathology factor is not significantly associated with dorsal anterior cingulate cortex or amygdala connectivity.

控制一般精神病理因素的紊乱依恋与杏仁核静息态功能连接失常相关

背景：最近的研究发了现一般精神病理学因素（GPF）可以解释精神病理症状表现的重叠。未解决的紊乱依恋（Ud）是另一种跨诊断风险因素，可能与诊断分类中患者特征的差异有关。
目的：在目前的研究中，我们研究了静息态功能连接与Ud和GPF的独特关系。
方法：从患有精神疾病和健康的青少年的混合样本中（N = 74）收集静息态功能连接 （RSFC）数据，这是临床青少年情绪路径影像研究（EPISCA）的一部分。使用成人依恋访谈（AAI）测量Ud，检查了Ud，GPF，杏仁核和前扣带皮层（dACC）的RSFC与杏仁核 - 内侧额叶连接之间的关联。
结果：Ud与左侧杏仁核、左侧枕叶皮质、楔前叶和顶上小叶之间的功能连接性正相关。此外，Ud与左侧杏仁核 - 内侧额叶皮层连接呈负相关。GPF与dACC或杏仁核连接无显著相关性。
结论：失常杏仁核连接可能是易感因素，而不是精神病理学的生物标志物。在有和没有各种精神病理学分类的被试之间， 控制GPF后Ud和杏仁核RSFC连接的独特关联，说明AAI的维度可以补充临床研究和实践中的精神病学分类。

1. Introduction

Psychopathology and unresolved–disorganized attachment (Ud) (Bowlby, 1969, 1980; Hesse & Main, 2000) are different yet interrelated clinical constructs (Lyons-Ruth, Pechtel, Yoon, Anderson, & Teicher, 2016; Patalay et al., 2015; Riem et al., 2019) that can impair adolescent functioning. Ud is characterized by signs of disoriented and/or dissociated, disorganized narratives in cases of loss or abuse, which indicate simultaneous or sequential contradictory strategies to deal with the loss or other trauma, and often display a lack of reflective functioning (Fonagy, Steele, Moran, Steele, & Higgitt, 1991). Ud is thought to be a transdiagnostic risk factor that is relevant across psychopathologies (Lyons-Ruth & Jacobvitz, 2016; Riem et al., 2019) and accounts for patient characteristics not included in diagnostic categories. The general psychopathology factor (GPF), which represents lesser-to-greater severity of psychopathology across disorders, has also been identified as a transdiagnostic factor that represents clinical presentations on a continuum, contrary to diagnostic categorical classifications such as in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which are not optimal for research, partly because of the overlap between diagnostic categories and difficulty classifying individual patients (Caspi et al., 2014; Patalay et al., 2015; Tackett et al., 2013). The Ud and GPF transdiagnostic factors, however, may provide a useful measure for clinical research, particularly for neuroimaging studies of brain function; however, this prospect has not yet been fully explored.

Early life stress and adversity have negative consequences for physical and mental health, attachment, and psychosocial adjustment across the lifespan (Anda et al., 2006; Felitti et al., 1998). As to mental health, experiences of loss and abuse increase the risk for psychopathology, including post-traumatic stress disorder (PTSD), and anxiety and depressive disorders (Cloitre et al., 2009; Fonagy et al., 1991; MacMillan et al., 2003; McLaughlin, Sheridan, & Lambert, 2014; Schmaal et al., 2016). Neuroimaging studies of child and adult psychopathology are increasingly investigating the effects of early life stress on psychopathology; however, they have neglected the role of attachment. Child maltreatment and neglect, particularly from parental perpetrators, may lead to Ud, which can be measured in patients as a disorganized/disoriented, incoherent, state of mind when narrating childhood attachment experiences (Bowlby, 1969, 1980; Hesse & Main, 2000). Current and future attachment relationships and the transition to adult functioning are negatively impacted by Ud (Hesse, 2016). A meta-analysis of over 200 adult attachment studies showed that the prevalence of Ud within a mixed clinical sample was 43%, which was significantly higher than in normative groups (Bakermans-Kranenburg & van IJzendoorn, 2009), evidence that Ud is a transdiagnostic risk factor that may increase vulnerability to various psychiatric disorders. Furthermore, Ud has a higher representation among individuals with a history of abuse, serious other trauma, or loss (Hesse, 2016; Hesse & Main, 2000).

In addition to negative effects on attachment relationships, early life adversity is associated with neurobiological alterations that may interfere with brain development (Rinne-Albers, van der Wee, Lamers-Winkelman, & Vermeiren, 2013). Specifically, child abuse and neglect has been associated with altered resting-state functional connectivity (RSFC) of the

amygdala and dorsal anterior cingulate cortex (dACC), as well as attenuated cognitive control through the medial prefrontal cortex (Wang et al., 2014). The amygdala and dACC are considered crucial brain structures in detecting and responding to threats (Graham & Milad, 2011; Phelps & LeDoux, 2005), and show heightened reactivity to emotionally negative stimuli in individuals with a history of maltreatment (Teicher, Samson, Anderson, & Ohashi, 2016). The dACC amplifies this fear response to threat through excitation of the amygdala, whereas the medial prefrontal cortex inhibits amygdala activation through a negative-feedback cycle (Feng, Feng, Chen, & Lei, 2014; Schuwerk et al., 2014; Teicher et al., 2016), thereby reducing anxiety and the intensity of emotional reactions. However, there is evidence for impaired inhibition of the amygdala by the medial prefrontal cortex in individuals with a history of adversity (Wang et al., 2014). Impaired emotional regulation related to amygdala and dACC hyperactivation may, in turn, increase the risk for the development of psychopathology.

Indeed, heightened activation of the amygdala and dACC has been implied in PTSD (Lyons-Ruth et al., 2016; Shalev, Liberzon, & Marmar, 2017; Vermetten & Lanius, 2012) and several other psychiatric disorders known to be related to childhood adversity, such as depression and anxiety (Grant et al., 2014; Strawn et al., 2012). For example, in anxiety and depressive disorders the dACC was shown to be involved in location-specific fear network function and fear recovery (Lang et al., 2009; Mechias, Etkin, & Kalisch, 2010; Suarez-Jimenez et al., 2018) A meta-analysis observed abnormalities in the fronto-amygdala circuitry in individuals across the internalizing spectrum, possibly reflecting a general emotional disturbance that is shared across diagnostic classifications (Marusak et al., 2016). Thus, disruptions in the fronto-amygdala circuitry seem to play a general role in psychopathology and may underlie high levels of comorbidity. This may therefore be a potential neural substrate underlying GPF. Another possibility is, however, that these resting-state functional abnormalities are not a true biomarker of general psychopathology, but instead are the result of abuse experiences. Multiple studies provide evidence that brain abnormalities in maltreated individuals are not directly linked to psychopathology because they are found in maltreated individuals with psychopathology but also in resilient individuals with a history of maltreatment but without psychopathology (for a review, see Teicher et al., 2016). This raises the question of whether abuse experiences, Ud, and psychopathology have unique patterns of altered RSFC.

In the current study, we will therefore examine whether Ud and GPF show unique amygdala and dACC RSFC. We were specifically interested in amygdala and dACC connectivity as previous research points to altered connectivity in these regions in maltreated individuals as well as in individuals with psychopathology (Teicher et al., 2016). As previous studies indicate that fronto-amygdala circuitry disruptions are shared by psychiatric disorders (Marusak et al., 2016), we investigated unique associations between Ud, GPF, and connectivity with the amygdala and the medial frontal cortex as an a priori connection of interest. Ud was assessed with the 'gold standard' Adult Attachment Interview (AAI) (Cassidy, 2016; Hesse, 2016). It should be noted that Ud represents a *current* state of mind with respect to childhood attachment experiences, and is derived exclusively from the language used in the narrative about potentially traumatic experiences. Despite low levels of reflective functioning that may obscure self-reports on adverse experiences, the incoherence of the narrative may uncover mental distress not immediately accessible to the adolescent. Our study, therefore, adds to previous neuroimaging studies that examined neurobiological effects of abuse using retrospective self-report questionnaires, without taking into account whether the narrative about the trauma was (dis)organized. We hypothesized that Ud and GPF would show unique RSFC of the amygdala and dACC.

2. Methods

2.1. Design and sample

Seventy-four participants from the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA) study (van Hoof, van Lang, Speekenbrink, van IJzendoorn, & Vermeiren, 2015) ($N = 77$) were involved in the current study. They were recruited from mental health centres and local advertisements according to specified inclusion and exclusion criteria (van den Bulk et al., 2013; van Hoof et al., 2015) (see supplemental material) and available coded AAI (Hesse, 2016). Dropout was due to anomalous magnetic resonance imaging (MRI) findings ($n = 2$), technical scanning problems, or poor imaging data quality ($n = 2$). Within this group there were 21 adolescents with childhood sexual abuse (CSA), 28 adolescents with anxiety and/or depressive disorders (DEP), and 25 non-clinical adolescents (CNTR). Unresolved loss or trauma (continuous and categorical) was determined with the AAI coding system (Hesse, 2016). Information about pubertal status was missing for 10 participants. For these participants, pubertal status was imputed using gender and age.

Written informed assent and consent was obtained from all adolescents and their parents. Participants received financial compensation including travel expenses. The medical ethics committee of the Leiden University Medical Centre approved the study (nr. P08.175).

2.2. Procedure

After adolescents and their parents had given assent and consent to participate in the EPISCA study they filled out questionnaires, usually at home, and were tested for intelligence quotient (IQ) and interviewed for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) classification and attachment representation at the clinic in separate appointments. Scanning was usually performed on separate days, depending on the availability of the scanner.

2.3. Adult Attachment Interview

The AAI (Hesse, 2016) (see supplemental material) is a one-hour-long semi-structured interview, validated for adolescents. The AAI asks how the interviewee thinks about the relationship with parents or other primary caregivers in his or her youth, how these experiences have influenced him or her, how the actual relationship with parents or other primary caregivers is, and whether there were any experiences of severe illness, separation, fear, trauma, or loss. The interviewee is asked to give specific examples supporting each evaluation. Not the autobiographical content, but rather the coherence of the narrative matters.

After transcription and coding of the AAI according to the manual (Hesse, 2016) by a certified coder, an attachment representation classification can be given. In organized attachment representations there is one coherent mental strategy with regard to attachment figures, either secure–autonomous or insecure. In Ud representations, different mental strategies with regard to attachment figures are used simultaneously or sequentially, which are often contradictory, as becomes apparent when coding the narrative. A scale score for unresolved loss or trauma of 5.5 or above also renders a classification unresolved–disorganized (Hesse, 2016) (see supplemental material and manual). In the current study, unresolved trauma was examined as a continuous variable to enhance statistical power. A log transformation was applied because the distribution was skewed. Since Ud is hypothesized to be a transdiagnostic factor for psychopathology, like no other (in)secure attachment representation (Cassidy, 2016; Hesse, 2016), we chose to use Ud in our connectivity analyses.

2.4. General psychopathology factor

To estimate the effects of psychopathology separately from Ud, we decided to use a GPF. The GPF represents lesser-to-greater severity of psychopathology that is associated with negative emotionality (Tackett et al., 2013), compromised brain integrity (Caspi et al., 2014), lower IQ, higher negative affectivity, and lower effortful control in 1954 children from a birth cohort, aged 6–8 years (Neumann et al., 2016). The GPF has also been shown a significant single-nucleotide polymorphism heritability of 38% ($SE = 0.16$, $p = .008$) (Neumann et al., 2016). The use of the GPF was also shown to be valid in girls (Lahey et al., 2015) and in young adolescents (Patalay et al., 2015). The GPF was estimated for our sample using parent and self-report measurements for behavioural and emotional problems in children and adolescents: the Youth Self Report (YSR) (Achenbach, 1991a), Child Behavior CheckList (CBCL) (Achenbach, 1991b), Revised Child Anxiety and Depression Scale (RCADS) (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000), Trauma Symptom Checklist for Children (TSCC) (Briere, 1996), Children's Depression Inventory (CDI) (Kovačs, 1992), and Adolescent Dissociative Experiences Scale (A-DES) (Armstrong, Putnam, Carlson, Libero, & Smith, 1997). Principal component analysis was performed using these (sub)scales. The Kaiser–Meyer–Olkin statistic showed sampling adequacy (KMO = .92). There were two components with eigenvalues larger than 1 (eigenvalue component 1 = 9.24, eigenvalue component 2 = 1.40). The scree plot showed an inflection justifying the extraction of one component explaining 61.63% (see Table S2 for an overview of the loadings). Individual factor scores were calculated to estimate the GPF (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). Factor score coefficients were calculated using the regression method. These coefficients were multiplied with the (sub)scale scores to obtain factor scores, which represent individual standardized scores on the GPF, based on their scores on the constituent scales. All calculations were performed in SPSS with principal component analysis. See Table S1 and Figure S1 in the supplemental material for the mean psychopathology scores across the psychopathology groups.

2.5. Image data acquisition

Images were acquired on a Philips 3T MRI system (Philips Healthcare, Best, The Netherlands), equipped with a SENSE-8 head coil. Scanning took place at the Leiden University Medical Center. Before scanning, all participants were introduced to the scanning situation by lying in a dummy scanner and hearing scanner sounds. For each subject, a sagittal three-dimensional gradient-echo T1-weighted image was acquired (repetition time = 9.8 ms; echo time = 4.6 ms; flip angle = 8°; 140 sagittal slices; no slice gap; field of view = 256 × 256 mm; 1.17 × 1.17 × 1.2 mm voxels; duration = 4:56 min) as part of a larger, fixed imaging protocol. Resting-state functional MRI data were acquired, using T2*-weighted gradient-echo echo-planar imaging of 160 whole-brain volumes (repetition time 2200 ms; echo time 30 ms; flip angle 80°; 38 transverse slices; no slice gap; field of view 220 mm; in-plane voxel size 2.75 × 2.75 mm; slice thickness 2.72 mm; total duration of the resting-state run 6 min). Participants were instructed to lie still with their eyes closed and not to fall asleep.

2.6. Statistical analysis

2.6.1. Pre-statistics

The FEAT module of the FSL software (FMRIB's Software Library, http://www.FMRIb.ox.ac.uk/fsl) (Smith et al., 2004) was used to apply the following pre-statistics processing: motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal using BET (Smith, De Stefano, Jenkinson, & Matthews, 2001), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 6.0 mm, and high-pass temporal filtering (high-pass filter cut-off = 100.0 s). Functional scans were registered to the T1-weighted images, which were registered to standard space in order to calculate the transformation matrix for the higher level group analysis (Jenkinson et al., 2002).

2.6.2. Functional connectivity analysis

A seed-based correlation approach was used for the current study (Murphy & Fox, 2017). We created binary masks of the left and right amygdala and left and right dACC. Coordinates of the seed regions were similar to a previous study examining resting-state connectivity in relation to depressive symptoms in partly the same sample (amygdala: $x = \pm 22$, $y = -6$, $z = -16$; dACC: $x = \pm 6$, $y = 18$, $z = 28$) (Pannekoek et al., 2014). Masks were created as spheres (4 mm radius, similar to Pannekoek et al., 2014) centred on these coordinates. After transforming the masks to native space, the mean time series for each participant were extracted from the voxels in the seed regions. The times series of the left and right amygdala were then entered as regressors in a general linear model (GLM) to examine amygdala connectivity, and the left and right dACC time series were entered as regressors in a separate GLM to examine dACC connectivity. In addition, cerebrospinal fluid, white matter, and the global signal were added as regressors to the model to reduce the influence of artefacts caused by physiological signal sources on the results (Fox & Raichle, 2007).

The temporal derivative of each regressor was added to the model, similarly to Pannekoek et al. (2014), resulting in 10 regressors in each model. Motion parameters were also added to the model. Contrasts of interest were the parameter estimates corresponding to the regressor of the left and right amygdala and left and right dACC, which represents functional connectivity with that region. First-level analyses were performed in native space. These first-level contrast images and the corresponding variance images of connectivity with each seed region were transformed to standard space and submitted to second-level mixed-effects group whole-brain analyses using FMRIB's Local Analysis of Mixed Effects (FLAME). In the second-level analysis, the positive and negative correlations between amygdala and dACC connectivity and unresolved loss and trauma score and GPF were assessed. Unresolved status and GPF were included in the same model, as the aim of the current study was to examine unique correlates of Ud and GPF. Composite score age and pubertal status, gender, and IQ were confound regressors in the model. Non-parametric permutation inference was conducting using FSL's randomize with threshold-free cluster enhancement (TFCE) to obtain family-wise error-corrected clusters ($p < .05$) (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Finally, because of the prominence of the medial frontal cortex in previous studies of social–emotional processing (Crone, 2014; Waugh, Lemus, & Gotlib, 2014) and general psychopathology (Marusak et al., 2016), connectivity between the amygdala and a medial frontal cortex region of interest (ROI) was examined. The left and right medial frontal cortex was anatomically defined using the Harvard–Oxford cortical atlas (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and used as an inclusive mask for the analysis of amygdala connectivity.

3. Results

3.1. Clinical sample characteristics

The mean age of the participants was 15.42 years (*SD* 1.67, range 12–20 years), and they had a total mean IQ of 103.28 (*SD* 8.89, range 81–119); 85.1% ($n = 63$) of the participants were female. As to cultural background, 1.4% were Asian (CSA $n = 1$), 93.2% were Caucasian (CSA $n = 20$, DEP $n = 25$, CNTR $n = 24$), 1.4% were Surinamese (DEP $n = 1$), and 2.7% were Latin American (DEP $n = 2$). Four adolescents (5.4%; CSA $n = 2$, DEP $n = 2$) were on stable selective serotonin reuptake inhibitor (SSRI) use (three fluoxetine, one sertraline). Pubertal stage was assessed according to the following categories using the Pubertal Development Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988): prepubertal (CSA $n = 1$), early pubertal (DEP $n = 1$), midpubertal (CNTR $n = 6$, DEP $n = 1$), late pubertal (CSA $n = 10$, DEP $n = 14$, CNTR $n = 13$), and postpubertal (CSA $n = 10$, DEP $n = 12$, CNTR $n = 6$).

Clinical assessment of this sample (as detailed in the supplemental material) revealed that the mean score for post-traumatic symptoms (TSCC) was 34.13 (*SD* 22.72, range 0–98), for depression (CDI) 12.84 (*SD* 9.17, range 0–40), for anxiety (RCADS) 25.88 (*SD* 14.96, range 0–70), for dissociation (A-DES) 1.44 (mean total score; *SD* 1.42, range 0–6.37), for youth self-report problems (YSR) 18.78 (*SD* 11.13, range 0–44), and for reported internalizing problems by parents (CBCL) 13.60 (*SD* 9.68, range 0–42).

3.2. Unresolved loss or trauma score (AAI)

The AAI (Hesse, 2016) mean score for unresolved loss or trauma in this sample was 2.42 (*SD* 1.81, range 1–8). Based on the AAI (Cassidy, 2016; Hesse, 2016), 36.5% of the adolescents were classified as secure (CNTR $n = 13$, DEP $n = 11$, CSA $n = 3$), 41.9% as dismissive (CNTR

$n = 11$, DEP $n = 11$, CSA $n = 9$), and 21.6% as Ud (CNTR $n = 1$, DEP $n = 6$, CSA $n = 9$). No adolescents in this sample were classified as preoccupied (Cassidy, 2016; van Hoof et al., 2015). See Table 1 for the mean GPF, age, IQ, and PDS scores for the Ud and non-Ud groups and see Table S1 for general psychopathology scores for the separate groups (CSA-PTSD, internalizing, control, and Ud versus non-Ud). There was no significant correlation between Ud and GPF (Pearson $r = .203$, $p = .083$, covariance 0.84).

3.2.1. Amygdala connectivity

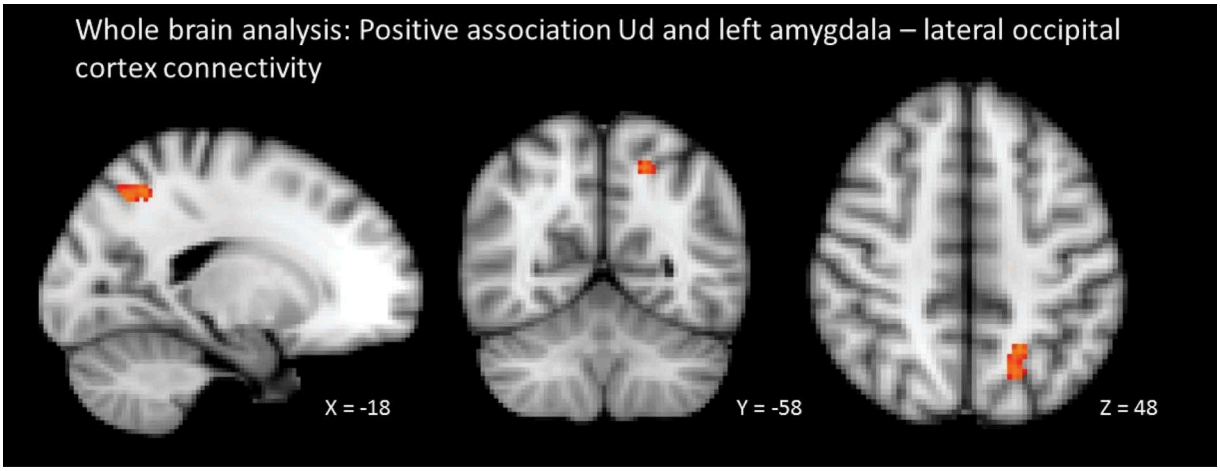
Whole-brain analysis showed a significant positive association between Ud and connectivity of the left amygdala, with left lateral occipital cortex (LOC), precuneus, and superior parietal lobule (Brodmann area 7), after adjusting for GPF, age, pubertal status, IQ, and gender (family-wise error corrected $p < .05$) (Table 2 and Figure 1(a)). The whole-brain analysis did not reveal significant associations between amygdala connectivity and GPF.

Connectivity between the amygdala and the medial frontal ROI was significantly and negatively correlated with Ud, controlling for GPF, age, puberty status, IQ, and gender (family-wise error corrected $p < .05$) (Table 2 and Figure 1(b)), indicating reduced connectivity in individuals showing higher levels of unresolved loss and trauma. No significant association was found between GPF and amygdala–medial frontal cortex connectivity.

3.2.2. dACC connectivity

The whole-brain connectivity analyses with the dACC as seed region did not reveal associations with Ud or GPF (however, see supplemental material).

a.



b.

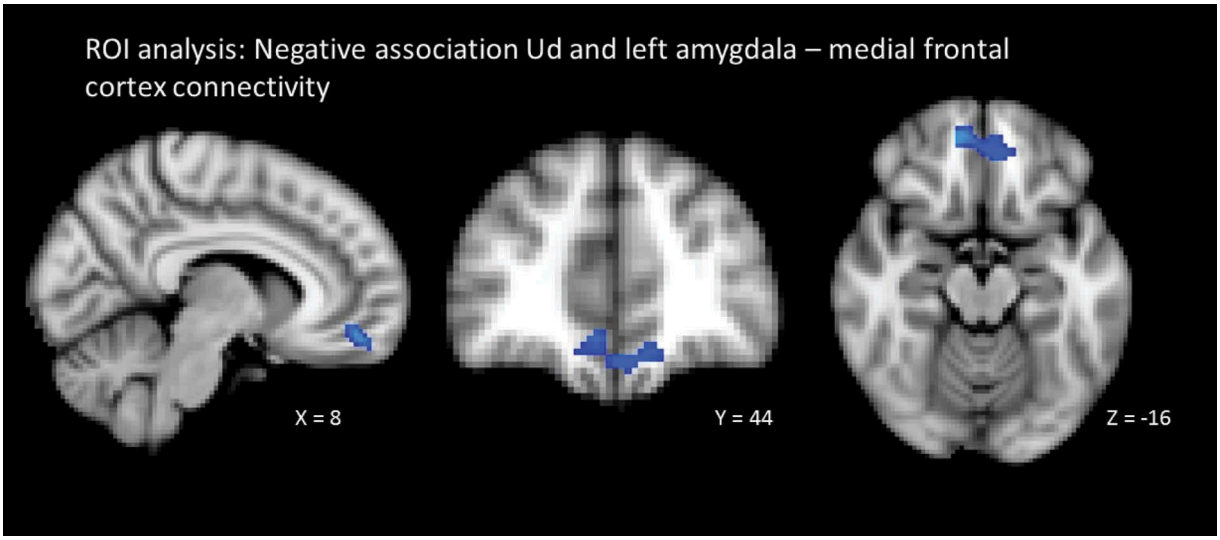


Figure 1. (a) Significant positive association between unresolved loss and trauma and left amygdala–lateral occipital cortex connectivity, resulting from the whole-brain analysis, Threshold Free Cluster Enhancement (TFCE) family-wise corrected, $p < .05$. (b) Significant negative association between unresolved loss and trauma and left amygdala–medial frontal cortex connectivity, resulting from the region of interest (ROI) analysis, TFCE family-wise corrected, $p < .05$. The right side of the brain corresponds to the left hemisphere and vice versa.

Table 1. General psychopathology scores, age, total IQ, and PDS scores for the Ud and non-Ud groups.

	Ud (N = 16)		Non-Ud (N = 58)	
	M	*SD*	*M*	*SD*
GPF	0.38	0.97	−0.11	0.99
Age	15.56	1.63	15.38	1.69
Total IQ	99.38	8.40	104.36	8.89
PDS scores	4.19	0.98	4.22	0.73

M, mean; *SD*, standard deviation; GPF, general psychopathology factor; IQ, intelligence quotient; PDS, Pubertal Development Scale; Ud, unresolved–disorganized attachment.

4. Discussion

The aim of this study was to investigate whether unresolved loss or trauma (Ud) as assessed with the AAI and a GPF were differentially associated with amygdala and dACC functional connectivity in a mixed group of adolescents with CSA-related PTSD, anxiety and depressive disorders and without psychiatric symptoms. After adjusting for GPF, pubertal status, age, gender, and IQ, we found that individuals with higher levels of Ud showed stronger left amygdala connectivity with the lateral occipital cortex, precuneus, and left superior parietal lobule compared to individuals with lower levels of Ud. In addition, Ud was negatively associated with left amygdala–medial frontal cortex connectivity. Our study suggests that across diagnoses, Ud is associated with specific RSFC of the left amygdala. This finding means that individuals' functional connections vary according to attachment status, regardless of specific psychopathology.

The amygdala is part of the limbic network and is involved in fear, fight, flight, and freeze reactions to traumatic experiences controlled by the hypothalamic–pituitary–adrenal axis (Rinne-Albers et al., 2013). The urgency of these conditions, as well as their long-term impact, may hamper specific reflective functioning called mentalization, i.e. reflection about thoughts, emotions, and behaviour of the self and others (Luyten & Fonagy, 2015). A critical element of Ud is that individuals coded high for Ud often lack reflective functioning and awareness of their own psychological states. Our findings on the connectivity of the amygdala may reflect a lack of awareness of fear states, rather than regulatory deficits alone. Because Ud is assessed through coding of language rather than self-reported psychopathology, this indirect method of assessing mental distress may reveal the neural basis of psychopathology better than self-reported mental health.

Our finding that amygdala connectivity with the lateral occipital cortex is enhanced in individuals with Ud shows parallels with our previous study, which showed enhanced LOC–hippocampus connectivity in Ud (van Hoof et al., in press). Altered LOC activity is associated with atypical processing of emotional stimuli and has been implicated in higher level visual processing, including emotional scene perception (Sabatinelli et al., 2011). In addition, we observed enhanced functional connectivity with the precuneus and the left superior parietal lobe in adolescents with Ud. The precuneus is part of the default mode network (resting consciousness) and has been associated with self-consciousness, memory, directing attention in space, both when an individual makes movements and when imaging or preparing them, visuospatial mental operations, and mental imagery/modelling other people's views (Cattaneo & Rizzolatti, 2009; Cavanna, 2007; Cavanna & Trimble, 2006). The left superior parietal lobe is involved in spatial orientation, and visual and sensorimotor input from the hand. Both precuneus and superior parietal lobe involvement have been implicated in PTSD with symptoms of dissociation, depersonalization, and derealization (Nicholson et al., 2015), and in particular the precuneus may be associated with Ud and its relative lack of reflective functioning.

In addition, a negative association between Ud and amygdala connectivity with the medial frontal cortex was found, possibly indicating altered amygdala inhibition by the medial frontal cortex. Such an impaired functional connectivity within the amygdala–medial (pre)frontal circuit increases the propensity for excessive fear as it promotes amygdala hyperactivity and diminished medial prefrontal control. It suggests less rational, cortical control by the medial frontal cortex, such as evaluating choices, handling errors, and cognition of social interaction (Crone, 2014; Waugh et al., 2014), and may explain why emotions and behaviour have dominance over cognitions in cases of Ud. Aghajani et al. (2016) previously suggested that disrupted basolateral amygdala–medial prefrontal connectivity might be a reliable neural marker of PTSD and a prominent feature of paediatric PTSD in part of the same sample (Rinne-Albers et al., 2013; Shin & Liberzon, 2010; Sripada et al., 2012; Wolf & Herringa, 2016). Our findings show that the atypical amygdala–medial (pre)frontal connectivity could additionally be a neural marker of Ud, as the current dysconnectivity was associated with Ud and not with GPF. As previous work demonstrated a rather strong association between PTSD

Table 2. Cluster size, lowest *p*-value, and coordinates of the significant clusters resulting from the analyses with the amygdala as seed region.

Contrast	Region	Voxels	*p*	*x*	*y*	*z*
Unresolved loss and trauma +	Left superior parietal lobule	80	.02	−20	−56	48
	Left superior parietal lobule	25	.04	−24	−52	34
	Left lateral occipital cortex	8	.05	−28	−66	34
Unresolved loss and trauma[a] −	Right medial frontal cortex	189	.02	12	50	−16

[a]Results from the region of interest (ROI) analysis with the medial frontal cortex as a priori defined ROI.

and Ud, longitudinal research should investigate the developmental relationships between these phenomena and their underlying neural structures and functions (Harari et al., 2009).

Whereas the amygdala is part of the limbic network, the dACC is part of the salience network and is involved in selection of stimuli that are deserving of our attention, judgement, and discrimination, social sensitivity, and many autonomic functions (motor and digestive functions, regulation of blood pressure and heart rate) (Seeley et al., 2007). The anterior cingulate cortex contains spindle or von Economo neurons (von Economo & Koskinas, 1925), which allow rapid communications across areas, aiding the frontoparietal mirror neuron system in mentalization. The dACC connects primarily to cognitive brain regions such as the medial prefrontal cortex and is active in concert with the basolateral amygdala during the appraisal and expression of fear (Etkin, Egmer, & Kalisch, 2011; Teicher et al., 2016).

Evidence for the lateralization of amygdala function is accumulating (Baas, Aleman, & Kahn, 2004; Sergerie, Chochol, & Armony, 2008). The dominant notion seems to be that the right amygdala mediates relatively global and transient emotional responses, while the left amygdala seems to serve more specific and sustained forms of emotional responding. In more detail, the right basolateral amygdala is thought to encode precise affective features (e.g. punishment), while the left centromedial amygdala is thought to process general affective valence (e.g. good versus bad) (Styliadis, Ioannides, Bamids, & Papedelis, 2014). In this respect, it is interesting that Ud was found to be associated with the left amygdala, as attachment representation comprises a profound, sustained form of relating to others.

Our findings are consistent with previous studies showing that unresolved loss or abuse is a transdiagnostic risk factor for increased vulnerability to psychopathology in general (Lyons-Ruth et al., 2016; Riem et al., 2019). Moreover, these findings indicate that amygdala alterations previously found in patients with PTSD, depression, or anxiety disorders are not a specific biomarker for individual mental disorders, but instead may be common to several disorders with overlapping psychopathological symptoms. Amygdala atypical resting-state connectivity seems to be related to underlying factors associated with childhood attachment experiences which may be predisposing for vulnerability to fear generation and mental disorders (Admon, Milad, & Hendler, 2013).

4.1. Limitations

Some limitations should be considered. Owing to the fairly small sample size and the restricted ranges of age, IQ, gender, and ethnicity, the results should be replicated in larger samples with a wider array of clinical diagnoses. The GPF was based on self-report of symptoms and not on clinical interview scores. In addition, because of the cross-sectional design of our study, the results should be interpreted with caution to avoid reverse causality and, therefore, definitive conclusions about cause and effects cannot be drawn.

5. Conclusion

We found that Ud is uniquely related to amygdala RSFC across psychopathologies, possibly indicating that disrupted amygdala connectivity reflects a vulnerability factor rather than a biomarker of psychopathology. This study shows that the search for underlying dimensions of attachment and psychopathological symptoms across and beyond conventional diagnostic classifications may uncover commonalities and differences at the neural level explaining the aetiology of common disorders. Ud may be especially helpful in uncovering underlying dimensions of psychopathology, since coding of the AAI is not dependent on the (conscious) content of the narrative about past experiences or on a high level of reflective functioning about loss or trauma. Instead, the AAI is coded for coherence of mind, the (in)coherent use of language in the verbatim transcribed interview, without the participant's awareness.

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References

Achenbach, T. M. (1991a). *Manual for the youth self-report and 1991 profile*. Burlington: University of Vermont, Department of Psychiatry.
Achenbach, T. M. (1991b). *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington: University of Vermont, Department of Psychiatry.
Admon, R., Milad, M. R., & Hendler, T. (2013). A causal model of post-traumatic stress disorder: Disentangling predisposed from acquired neural abnormalities. *Trends in Cognitive Sciences*, *17*(7), 337–347.
Aghajani, M., Veer, I., van Hoof, M. J., Rombouts, S. A. R. B., van der Wee, N. J. A., & Vermeiren, R. R. J. M. (2016). Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. *Human Brain Mapping*, *37*, 1120–1135.
Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., … Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience*, *256*, 174–186.
Armstrong, J. G., Putnam, F. W., Carlson, E. B., Libero, D. Z., & Smith, S. R. (1997). Development and validation of a measure of adolescent dissociation: The adolescent dissociative experiences scale. *The Journal of Nervous and Mental Disease*, *185*(8), 491–497.
Baas, D., Aleman, A., & Kahn, R. S. (2004). Lateralization of amygdala activation: A systematic review of functional neuroimaging studies. *Brain Research. Brain Research Reviews*, *45*(20), 96–103.
Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2009). The first 10,000 adult attachment interviews: Distributions of adult attachment representations in clinical and non-clinical groups. *Attachment & Human Development*, *11*(3), 223–263.
Bowlby, J. (1969). *Attachment and loss, vol. I. Attachment*. London: Hogarth Press.
Bowlby, J. (1980). *Attachment and loss, vol. III. Loss*. New York: Basic Books.
Briere, J. (1996). *Trauma Symptom Checklist for Children (TSCC) professional manual*. Odessa, FL: Psychological Assessment Resources.
Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H. L., Israel, S., … Moffitt, T. E. (2014). The p factor: One general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science*, *2*(2), 119–137.
Cassidy, J. (2016). The nature of the child's ties. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research and clinical applications* (3rd ed., pp. 3–24). New York, London: The Guilford Press.
Cattaneo, L., & Rizzolatti, G. (2009). The mirror neuron system. *Archives of Neurology*, *66*(5), 557–560.
Cavanna, A. E. (2007). The precuneus and consciousness. *CNS Spectrums*, *12*(7), 545–552.
Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*, *129*, 564–583.
Chorpita, B. F., Yim, L., Moffitt, C., Umemoto, L. A., & Francis, S. E. (2000). Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*, *38*(8), 835–855.
Cloitre, M., Stolbach, B. C., Herman, J. L., Van der Kolk, B., Pynoos, R., Wang, J., & Petkova, E. (2009). A developmental approach to complex PTSD: Childhood and adult cumulative trauma as predictors of symptom complexity. *Journal of Traumatic Stress*, *22*(5), 399–408.
Crone, E. A. (2014). The role of the medial frontal cortex in the development of cognitive and social affective performance monitoring. *Psychophysiology*, *51*, 943–950.
Etkin, A., Egmer, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93.
Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., … Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) study. *American Journal of Preventive Medicine*, *14*(4), 245–258.
Feng, P., Feng, T., Chen, Z., & Lei, X. (2014). Memory consolidation of fear conditioning: Bi stable amygdala connectivity with dorsal anterior cingulate and medial prefrontal cortex. *Social Cognitive and Affective Neuroscience*, *9*(11), 1730–1737.
Fonagy, P., Steele, M., Moran, G., Steele, H., & Higgitt, A. (1991). The capacity for understanding mental states: The reflective self in parent and child and its significance for security of attachment. *Infant Mental Health Journal*, *13*, 200–216.
Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Reviews*, *8*, 700–711.
Graham, B. M., & Milad, M. R. (2011). The study of fear extinction: Implications for anxiety disorders. *The American Journal of Psychiatry*, *168*, 1255–1265.
Grant, M. M., White, D., Hadley, J., Hutcheson, N., Shelton, R., Sreenivasan, K., & Deshpande, G. (2014). Early life trauma and directional brain connectivity within major depression. *Human Brain Mapping*, *35*, 4815–4826.
Harari, D., Bakermans-Kranenburg, M. J., de Kloet, C. S., Geuze, E., Vermetten, E., Westenberg, H. G. M., & van IJzendoorn, M. H. (2009). Attachment representations in Dutch veterans with and without deployment-related PTSD. *Attachment & Human Development*, *11*(6), 515–536.
Hesse, E. (2016). The adult attachment interview: Protocol, method of analysis, and selected empirical studies: 1985–2015. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment research and clinical applications* (3rd ed., pp. 553–597). New York, London: The Guilford Press.
Hesse, E., & Main, M. (2000). Disorganized infant, child, and adult attachment: Collapse in behavioral and attentional strategies. *Journal of the American Psychoanalytic Association*, *48*(4), 1097–1127, discussion 1175–1187.
Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*, 825–841.

Kovačs, M. (1992). *Children's Depression Inventory (CDI) manual*. NewYork, NY: Multi-Health Systems.

Lahey, B. B., Krueger, R. F., Rathouz, P. J., Waldman, I. D., & Zald, D. H. (2017). A hierarchical causal taxonomy of psychopathology across the life span. *Psychological Bulletin*, *143*(2), 142–186.

Lahey, B. B., Rathouz, P. J., Keenan, K., Stepp, S. D., Loeber, R., & Hipwell, A. E. (2015). Criterion validity of the general factor of psychopathology in a prospective study of girls. *Journal of Child Psychology and Psychiatry*, *56*(4), 415–422.

Lang, S., Kroll, A., Lipinski, S. J., Wessa, M., Ridder, S., Christmann, C., … Flor, H. (2009). Context conditioning and extinction in humans: Differential contribution of the hippocampus, amygdala and prefrontal cortex. *The European Journal of Neuroscience*, *29*, 823–832.

Luyten, P., & Fonagy, P. (2015). The neurobiology of mentalizing. *Personality Disorders: Theory, Research, and Treatment*, *6*(4), 366–379.

Lyons-Ruth, K., & Jacobvitz, D. (2016). Attachment disorganization from infancy to adulthood: Neurobiological correlates, parenting contexts, and pathways to disorder. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research and clinical applications* (3rd ed., pp. 667–695). New York, London: The Guilford Press.

Lyons-Ruth, K., Pechtel, P., Yoon, S. A., Anderson, C. M., & Teicher, M. H. (2016). Disorganized attachment in infancy predicts greater amygdala volume in adulthood. *Behavioural Brain Research*, *308*, 83–93.

MacMillan, S., Szeszko, P. R., Moore, G. J., Madden, R., Lorch, E., Ivey, J., … Rosenberg, D. R. (2003). Increased amygdala: Hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *Journal of Child and Adolescent Psychopharmacology*, *13*(1), 65–73.

Marusak, H. A., Thomason, M. E., Peters, C., Zundel, C., Elrahal, F., & Rabinak, C. A. (2016). You say 'prefrontal cortex' and I say 'anterior cingulate': Meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomatology. *Translational Psychiatry*, *6*(11), e944.

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47*, 578–591.

Mechias, M.-L., Etkin, A., & Kalisch, R. (2010). A meta-analysis of instructed fear studies: Implications for conscious appraisal of threat. *NeuroImage*, *49*, 1760–1768.

Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *NeuroImage*, *154*, 169–173.

Neumann, A., Pappa, I., Lahey, B. B., Verhulst, F. C., Medina-Gomez, C., Jaddoe, V. W., … Tiemeier, H. (2016). Single nucleotide polymorphism heritability of a general psychopathology factor in children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(12), 1038–1045.

Nicholson, A. A., Densmore, M., Frewen, P. A., Théberge, J., Neufeld, R. W., McKinnon, M. C., & Lanius, R. A. (2015). The dissociative subtype of posttraumatic stress disorder: Unique resting-state functional connectivity of basolateral and centromedial amygdala complexes. *Neuropsychopharmacology*, *40*(10), 2317–2326.

Pannekoek, J. N., van der Werff, S. J. A., Meens, P. H. F., van Den Bulk, B. G., Jolles, D. D., Veer, I. M., … Vermeiren, R. R. J. M. (2014). Aberrant resting-state functional connectivity in limbic and salience networks in treatment-naïve clinically depressed adolescents. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *55*(12), 1317–1327.

Patalay, P., Fonagy, P., Deighton, J., Belsky, J., Vostanis, P., & Wolpert, M. (2015). A general psychopathology factor in early adolescence. *The British Journal of Psychiatry : The Journal of Mental Science*, *207*, 15–22.

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity and initial norms. *Journal of Youth and Adolescence*, *17*(2), 117–133.

Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, *48*, 175–187.

Riem, M. M. E., van Hoof, M. J., Garrett, A. S., van der Wee, N. J. A., van IJzendoorn, M. H., & Vermeiren, R. R. J. M. (2019). General psychopathology factor and unresolved disorganized attachment uniquely correlated to white matter integrity using diffusion tensor imaging. *Behavioural Brain Research*, *359*, 1–8.

Rinne-Albers, M. A. W., van der Wee, N. J. A., Lamers-Winkelman, F., & Vermeiren, R. R. J. M. (2013). Neuroimaging in children, adolescents and young adults with psychological trauma. *European Child & Adolescent Psychiatry*, *22*(12), 745–755.

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., … Jeffries, J. (2011). Emotional perception: Meta-analyses of face and natural scene processing. *NeuroImage*, *54*, 2524–2533.

Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., … Hibar, D. P. for the ENIGMA-Major Depressive Disorder Working Group. (2016). Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group. *Molecular Psychiatry*, *21*(6), 806–812.

Schuwerk, T., Döhnel, K., Sodian, B., Keck, I. R., Rupprecht, R., & Sommer, M. (2014). Functional activity and effective connectivity of the posterior medial prefrontal cortex during processing of incongruent mental states. *Human Brain Mapping*, *35*, 2950–2965.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(9), 2349–2356.

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *32*(4), 811–830.

Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-traumatic stress disorder. *The New England Journal of Medicine*, *376*, 2459–2469.

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, *35*, 169–191.

Smith, S. M., De Stefano, N., Jenkinson, M., & Matthews, P. M. (2001). Normalized accurate measurement of longitudinal brain change. *Journal of Computer Assisted Tomography*, *25*, 466–475.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Supp l1), S208–219.

Sripada, R. K., King, A. P., Welsh, R. C., Garfinkel, S. N., Wang, X., Sripada, C. S., & Liberzon, I. (2012). Neural dysregulation in posttraumatic stress disorder: Evidence for disrupted

equilibrium between salience and default mode brain networks. *Psychosomatic Medicine*, *74*(9), 904–911.

Strawn, J. R., Bitter, S. M., Weber, W. A., Chu, W.-J., Whitsel, R. M., Adler, C., … DelBello, M. P. (2012). Neurocircuitry of generalized anxiety disorder in adolescents: A pilot functional neuroimaging and functional connectivity study. *Depression and Anxiety*, *29*, 939–947.

Styliadis, C., Ioannides, A. A., Bamids, P. D., & Papedelis, C. (2014). Amygdala responses to valence and its interaction by arousal revealed by MEG. *International Journal of Psychophysiology*, *93*, 121–133.

Suarez-Jimenez, B., Bisby, J. A., Horner, A. J., King, J. A., Pine, D. S., & Burgess, N. (2018). Linked networks for learning and expressing location-specific threat. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(5), E1032–E1040.

Tackett, J. L., Lahey, B. B., van Hulle, C., Waldman, I., Krueger, R. F., & Rathouz, P. J. (2013). Common genetic influences on negative emotionality and a general psychopathology factor in childhood and adolescence. *Journal of Abnormal Psychology*, *122*(4), 1142–1153.

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews. Neuroscience*, *17*, 652–666.

van den Bulk, B. G., Koolschijn, P. S., Meens, P. H. F., van Lang, N. D. J., van der Wee, N. J. A., Rombouts, S. A. R. B., … Crone, E. A. (2013). How stable is activation in the amygdala and prefrontal cortex in adolescence? A study of emotional face processing across three measurements. *Developmental Cognitive Neuroscience*, *4*, 65–76.

van Hoof, M. J., Riem, M. M. E., Garrett, A. S., Pannekoek, J. N., van der Wee, N. J. A., van IJzendoorn, M. H., & Vermeiren, R. R. J. M. (in press). *Unresolved-disorganized attachment associated with smaller hippocampus and increased functional connectivity beyond psychopathology*.

van Hoof, M. J., van Lang, N. D. J., Speekenbrink, S., van IJzendoorn, M. H., & Vermeiren, R. R. J. M. (2015). Adult attachment interview differentiates adolescents with childhood sexual abuse from those with clinical depression and controls. *Attachment & Human Development*, *17*(4), 354–375.

Vermetten, E., & Lanius, R. (2012). Biological and clinical framework for post-traumatic stress disorder. In T. E. Schlaepfer & C. B. Nemeroff Eds., *Handbook of clinical neurology, chapter 18 Neurobiology of psychiatric disorders* (Vol. 106 3rd series, pp. 291–342).Elsevier

von Economo, C., & Koskinas, G. N. (1925). *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Berlin: Springer.

Wang, L., Dai, Z., Peng, H., Tan, L., Ding, Y., He, Z., … Li, L. (2014). Overlapping and segregated resting-state functional connectivity in patients with major depressive disorder with and without childhood neglect. *Human Brain Mapping*, *35*, 1154–1166.

Waugh, C. E., Lemus, M. G., & Gotlib, I. H. (2014). The role of the medial frontal cortex in the maintenance of emotional states. *Scan*, *9*, 2001–2009.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397.

Wolf, R. C., & Herringa, R. J. (2016). Prefrontal-amygdala dysregulation to treat in pediatric posttraumatic stress disorder. *Neuropsychopharmacology*, *41*, 822–831.