Unresolved-disorganized attachment, psychopathology, and the adolescent brain

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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 with Ud and GPF.

Method: Resting state functional connectivity (RSFC) data were collected from a mixed group of adolescents (*N* =74) with and without psychiatric disorder, part of the Emotional Pathways' Imaging Study in Clinical Adolescents study. Ud was measured using the Adult Attachment Interview (AAI). Associations between Ud, GPF, and RSFC of the amygdala and 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 connectivity, 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.

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, Van Hoof, et al., 2019) that can impair adolescent functioning. Ud is characterized by signs of disoriented and/or dissociated, disorganized narratives in case of loss or abuse, that 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, Van Hoof, 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 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 posttraumatic stress disorder (PTSD) and depressive disorders (Cloitre et al., 2009; 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 is 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 trans-diagnostic 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 emotion regulation related to amygdala and dACC hyperactivation may in turn increase 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) Interestingly, 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 co-morbidity. It 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 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' 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 might 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.

METHODS

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 centers and local advertisements according to specified in- and exclusion criteria (Van den Bulk et al., 2013; Van Hoof et al., 2015)(see supplemental material) and available coded AAI (Hesse, 2016). Drop-out was due to anomalous 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 sex and age.

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

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 IQ and interviewed for DSM-IV classification and attachment representation at the clinic in separate appointments. Scanning was usually performed on separate days, depending on availability of the scanner.

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 its 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 unresolved-disorganized attachment representations different mental strategies with regard to attachment figures are used simultaneously or sequentially, 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. Ud being hypothesized to be a trans-diagnostic factor for psychopathology like no other (in)secure attachment representation (Cassidy, 2016; Hesse, 2016), we choose to use Ud in our connectivity analyses.

General Psychopathology Factor

To estimate the effects of psychopathology separate from Ud we decided to use a general psychopathology factor. The general psychopathology factor 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 to 8

years (Neumann et al., 2016). The general psychopathology factor has also been shown a significant Single Nucleotide Polymorphism (SNP) heritability of 38% (SE=0.16, p=.008) (Neumann et al., 2016). The use of the general psychopathology factor was also shown to be valid in girls (Lahey et al., 2015) and in young adolescents (Patalay et al., 2015). The general psychopathology factor was estimated for our sample using parent and self-report measurements for behavioral and emotional problems in children and adolescents: 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), 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 in order to estimate the general psychopathology factor (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.

Image data acquisition

Images were acquired on a Philips 3T magnetic resonance imaging system (Philips Healthcare, Best, The Netherlands), equipped with a SENSE-8 head coil. Scanning took place at the Leiden University Medical Centre. Prior to scanning, all participants were introduced to the scanning situation by lying in a dummy scanner and hearing scanner sounds. For each subject, a sagittal 3- 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: 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 2.75x2.75 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.

Statistical analysis

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 (highpass filter cutoff = 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).

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 = ±22; y = -6; z = -16; dACC: x = ±6; y = 18; z = 28)(Pannekoek et al., 2014b). Masks were created as spheres (4 mm radius, similar to Pannekoek et al., 2014b) centered 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 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, CSF, white matter and the global signal were added as regressors to the model in order to reduce the influence of artifacts caused by physiological signal sources on the results (Fox & Raichle, 2007).

The temporal derivative of each regressor was added to the model similar to Pannekoek et al., 2014b, 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 correlation between amygdala and dACC connectivity and Unresolved loss and trauma score and GPF was 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, sex, and IQ were confound regressors in the model. Non-parametric permutation inference was conducting using FSL's randomise 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 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.

RESULTS

Clinical sample characteristics

Mean age of the participants was 15.42 years (SD 1.67, range 12-20), and 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), 2.7% were Latin-American (DEP *N*=2). Four adolescents (5.4%; CSA *N*=2, DEP *N*=2) were on stable SSRI use (three fluoxetine, one sertraline). Puberty 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), postpubertal (CSA *N*=10, DEP *N*=12, CNTR *N*=6).

Clinical assessment of this sample (as detailed in supplemental material) revealed that the mean score found for post-traumatic symptoms was 34.13 (Briere, 1996; TSCC; SD 22.72; range 0-98), for depression 12.84 (Kovačs, 1992; CDI; SD 9.17; range 0-40), for anxiety 25.88 (Chorpita et al., 2009; RCADS; SD 14.96; range 0-70), for dissociation 1.44 (Armstrong et al., 1997; A-DES mean total score; SD 1.42; range 0-6.37), for self-report problems youth 18.78 (Achenbach, 1991b; YSR; SD 11.13; range 0-44) and for reported internalizing problems by parents 13.60 (Achenbach, 1991a; CBCL; SD 9.68; range 0-42).

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), 21.6% as Unresolved-disorganized (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 U versus nonU). There was no significant correlation between Ud and GPF (Pearson $r = .203$, $p = .083$, covariance 0.84).

Table 1. Mean (SD) general psychopathology scores (GPF), age, pubertal status (Pubertal Development Scale (PDS), and total IQ scores for the Ud versus non-Ud group. *$p < .05$

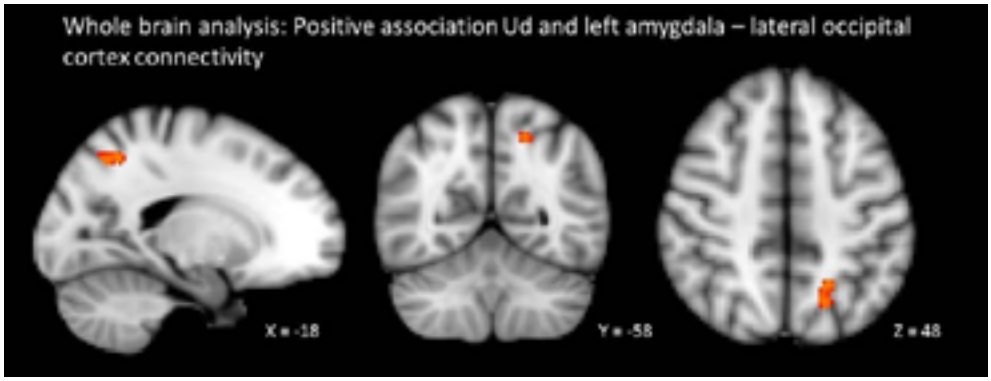
	UD (N=16)		Non-UD (N = 58)		
	M	*SD*	*M*	*SD*	*t*
GPF	0.38	0.97	-0.11	0.99	-1.76
Age	15.56	1.63	15.38	1.69	-0.39
Total IQ	99.38	8.40	104.36	8.89	2.03*
PDS scores	4.19	0.98	4.22	0.73	0.17

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, puberty status, IQ, and sex (family-wise error corrected $p < .05$, see Table 2 and Figure 1A). 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 sex (family-wise error corrected $p < .05$, see Table 2 and Figure 1B), 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.

A)



B)

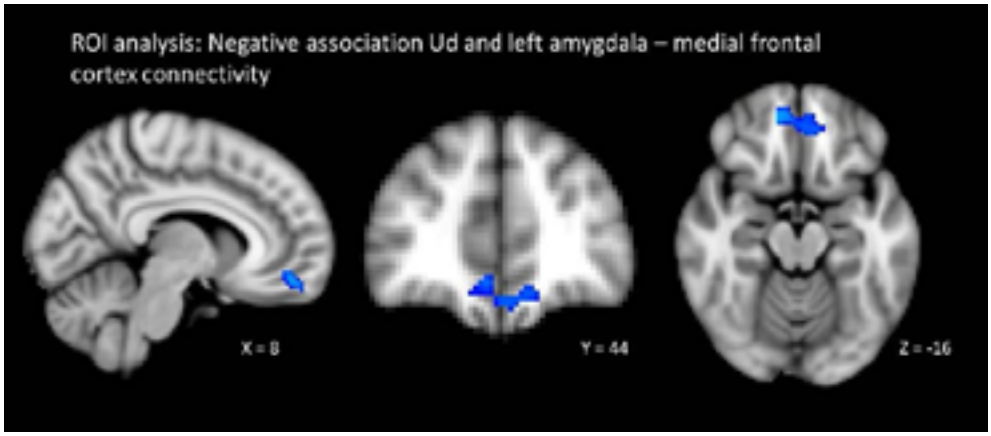


Figure 1. A) Significant positive association between Unresolved loss and trauma and left amygdala – lateral occipital cortex connectivity, resulting from the whole brain analysis, TFCE family-wise corrected, $p < .05$. **B)** Significant negative association between Unresolved loss and trauma and left amygdala – medial frontal cortex connectivity, resulting from the ROI analysis, TFCE family-wise corrected, $p < .05$. The right side of the brain corresponds to the left hemisphere and vice versa.

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 +	L Superior Parietal Lobule	80	0.02	-20	-56	48
	L Superior Parietal Lobule	25	0.04	-24	-52	34
	L Lateral Occipital Cortex	8	0.05	-28	-66	34
Unresolved loss and trauma[a] -	R Medial Frontal Cortex	189	0.02	12	50	-16

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

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).

DISCUSSION

The aim of this study was to investigate whether unresolved loss or trauma (Ud) as assessed with the AAI and a general psychopathology factor (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, puberty status, age, sex, 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 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. The finding means that individuals' functional connections vary according to attachment status, regardless of specific psychopathology.

The amygdala is part of the limbic network and involved in fear, fight, flight and freeze reactions to traumatic experiences controlled by the HPA-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 behavior 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 for 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 that 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/modeling 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 behavior have dominance over cognitions in case 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 pediatric 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 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 involved in selection of stimuli that are deserving of our attention, judgment and discrimination, social sensitivity and many autonomic functions (motor and digestive functions, regulation of blood pressure and heart rate)(Seeley et al., 2007). The ACC contains spindle or so called Von Economo neurons (Von Economo & Koskinas, 1925), which allow rapid communications across areas, which aids 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 appraisal and expression of fear (Etkin, Egmer, & Kalisch, 2011; Teicher et al., 2016).

Evidence for 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. More in 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 vs bad)(Styliadis, Ioannides, Bamids, & Papedelis, 2014). In this respect it is interesting that Ud was found to be associated with left amygdala, as attachment representation comprises a profound, sustained form of relating to others.

Our findings are consistent with our previous studies showing that unresolved loss or abuse is a trans-diagnostic risk factor for increased vulnerability to psychopathology in general (Lyons-Ruth et al., 2016; Riem, Van Hoof, 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 RS 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).

LIMITATIONS

Some limitations should be considered. Due to the fairly small sample size and the restricted ranges of age, IQ, sex, and ethnicity, 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. Also, because of the cross-sectional design of our study, interpretation of results should be done with caution to avoid reverse causality and therefore, definitive conclusions about cause and effects cannot be drawn.

CONCLUSION

In conclusion, we found that Ud is uniquely related to amygdala RSFC connectivity 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 might uncover commonalities and differences at the neural level explaining etiology of common disorders. Ud might 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 nor 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 of the verbatim transcribed interview, without the participants' awareness.

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DISCLOSURE STATEMENT

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SUPPLEMENTAL MATERIAL CHAPTER 6 (as published)

A.1 Supplemental material

A.1.1 Introduction

It should be noted that the combination of PTSD with experiences of interpersonal adversities such as childhood trauma warrants a diagnosis of complex PTSD (Ford, 2015) or according to the American Psychiatric Association 'PTSD with dissociative symptoms' (Choi et al., 2017) and shows a different clinical presentation (e.g. dissociation, behavioral symptoms, emotional dysregulation) than PTSD without childhood trauma.

A.1.2 In- and exclusion criteria EPISCA

The adolescents were part of the Emotional Pathways' Imaging Study in Clinical Adolescents (EPISCA), a longitudinal study in which adolescents were followed over a six-month period. The adolescents with and without clinical symptoms underwent a diagnostic assessment and an MRI scanning protocol at three points in time (at baseline, 3 months, 6 months; Van den Bulk, 2013). AAI (Hesse, 2016) and clinical characteristics of the group and neuroimaging data were reported previously (e.g. Van Hoof et al., 2015; Pannekoek et al., 2014b; Aghajani et al., 2016).

Related to the neuroimaging protocol all participants met the following inclusion criteria: aged between 12 and 20 years, estimated full scale IQ $\geq$ 80 as measured by Dutch versions of the Wechsler Intelligence Scales for Children (WISC-III; Wechsler, 1991) or Adults WAIS-III; Wechsler, 1997), being right-handed, normal or corrected-to-normal vision, sufficient understanding of the Dutch language, no history of neurological impairments and no contraindications for MRI testing (e.g. braces, metal implants, lead tattoos, irremovable piercings, claustrophobia or possible pregnancy). The adolescents with childhood sexual abuse (CSA) were recruited at two psychotraumacenters in the Leiden region of the Netherlands. Inclusion for CSA was having experienced sexual abuse during their life time more than once by one or more perpetrators in- or outside the family, and being referred for treatment at a psychotraumacenter. The inclusion criteria for adolescents with anxiety and/or depressive disorders were: being referred for outpatient treatment, having a clinical diagnosis of DSM-IV depressive and/or anxiety disorders (Silverman, Saavedra, Pina, 2001) and no history of CSA (see Van Hoof et al., 2015). Exclusion criteria for both clinical groups were: 1) a primary DSM-IV diagnosis of Attention Deficit and Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, Pervasive Developmental Disorders, Tourette's syndrome, Obsessive-Compulsive Disorder, bipolar disorder, and psychotic disorders; 2) amphetamine medication on the day of scanning or current use of

psychotropic medication other than stable use of SSRI's; and 3) current substance abuse. The non-clinical adolescents were recruited through local advertisement, with the following inclusion criteria: no clinical scores on validated mood and behavioral questionnaires or past or current DSM-IV classification, no history of traumatic experiences and no current psychotherapeutic intervention of any kind.

To objectify any abuse or neglect as well as risk for functional impairment and morbidity (Karam et al., 2014), we verified police reports, involvement of child welfare, and family custody or other child protection measures as to have an estimate of the severity and impact of problems. Most adolescents with CSA (87%) reported during the AAI serious and/or longstanding physical sexual contact including repeated or group rape, in 63.6% by a person other than an attachment figure. In addition, 36.4% of the CSA group also experienced physical abuse, 22.7% by a person other than an attachment figure, 9.1% by an attachment figure, in one case by both. Sexual abuse was reported to the police in 60.9%, child welfare was involved in 56.5% of the cases, while 17.4% had a child protection measure (family custody). None of the participating non-clinical adolescents and those with anxiety and/or depressive disorders had experienced CSA, but they did mention physical and emotional abuse, bullying, and other incidents. Non-clinical adolescents had not been involved with police, child welfare or child protection, while 23% of the adolescents with anxiety and/or depressive disorders had child welfare involvement.

From the original sample of 82 adolescents, three participants were excluded due to technical problems, i.e. failed voice and video recording (one adolescent with CSA), unintelligible recording (one non-clinical adolescent), incorrect interview technique (one non-clinical adolescent). Two participants (one non-clinical adolescent and one adolescent with anxiety/depressive disorder) were excluded because they refused the AAI because of the interview itself. Of the N=77 in the remaining sample, 86% were girls. All CSA adolescents fulfilled the DSM-IV criteria for PTSD, according to the ADIS (Silverman et al., 2001), however one adolescent missed a point on the interference score to fully qualify for PTSD. SSRI's were used by four of the adolescents with CSA and two of those with anxiety and/or depressive disorder.

A.1.3 Questionnaires and tests

A.1.3.1 YSR: Youth Self-Report (Achenbach, 1991a) and CBCL: Child Behavior Checklist (Achenbach, 1991b), with Dutch translations by Verhulst and colleagues (Verhulst, Van der Ende, Koot, 1991; 1997). The YSR and CBCL are self-report questionnaires using a 3-point scale to assess social-emotional and behavioral problems in adolescents. The CBCL is the questionnaire for parents, the YSR for adolescents 11 years and older. There are 9 subscales and 3 main scales (total score, externalizing problem score and internalizing problem score) In this study we used the internalizing problem scores of the YSR and CBCL.

A.1.3.2 ADIS: The Anxiety Disorders Interview Schedule Child and Parent Versions (ADIS C/P; Silverman et al., 2001) are semi structured interviews designed specifically for DSM-IV classification of anxiety and other related disorders such as depression and PTSD in children and adolescents. Strong test-retest reliability was shown for combined and individual ADIS-C/P diagnoses. Intra-class correlations were excellent. Interrater reliability between child and parent versions of the ADIS was reported to be excellent. In this study, the ADIS was applied to all participants by certified trained clinicians and researchers.

A.1.3.3 TSCC: The Trauma Symptom Checklist for Children (TSCC; Briere, 1996) is a 54-item self-report for children and adolescents aged 8-17, which measures trauma-related symptoms. In the present study, only the TSCC total score was used as subscales overlapped significantly, with a Cronbach's alpha coefficient of .96. 10.3% of the total sample showed scores above the cut-off of 60 suggesting acute and chronic posttraumatic symptomatology (Briere, 1996).

A.1.3.4 A-DES: The Adolescent Dissociative Experiences Scale (Armstrong et al., 1997) is a self-report for adolescents aged 11-18 measuring possible dissociation. The A-DES has good reliability and validity. In this study, the mean total score on the A-DES was used as a measure of dissociation, which had a Cronbach's alpha coefficient of .95. 5.4% of the total sample showed scores above the cut-off of 4 suggesting pathological dissociation (Armstrong et al., 1997).

A.1.3.5 CDI: The Children's Depression Inventory (Kovačs, 1992) is a 27-item, self-rated, depression symptoms-oriented scale suitable for youths aged 7 to 17. The CDI has good psychometric properties of validity and reliability (Cronbach's alpha .71 to .86)(Timbremont, Braet, Dreessen, 2004), though discriminant validity has been subject to discussion. In this study, the total CDI score had a Cronbach's alpha coefficient of .93. 33.8% of the total sample showed scores above the recommended cut-off of 16 (Roelofs et al., 2010).

A.1.3.6 RCADS: The Revised Child Anxiety and Depression Scale (Chorpita et al., 2000; Oldehinkel, 2000) is a self-rated, anxiety and depressive symptoms-oriented 47-item-scale for children aged 6 to 18. Items are scored based on a four-point scale and grouped as depressive disorder, generalized anxiety disorder, social phobia, anxiety disorder NAO and obsessive-compulsive disorder. Chorpita and colleagues (2000) reported evidence for validity and reliability of the RCADS in clinical and healthy control adolescents. In this study, the total score of the RCADS was used as a measure for severity of experienced symptomatology (Cronbach's α = .95). Besides, the depression scale (Cronbach's α = .89) and the cumulative anxiety scales (Cronbach's α = .94) were used.

A.1.3.7 AAI: the Adult Attachment Interview (Main, Kaplan, & Cassidy, 1985) is coded according to the DEFU system (Hesse, 2016): dismissive (Ds), preoccupied (E), secure-autonomous (F), unresolved-disorganized (Ud). Ds, E and F classifications are organized forms of attachment, while Ud represents disorganized forms of attachment. In organized attachment representations, there is one coherent mental strategy with regard to attachment figures, either secure-autonomous (F) or insecure (Ds or E). In disorganized attachment-representation different mental strategies with regard to attachment figures are used simultaneously or sequentially, often contradictory. A high to moderate coherence of the narrative is seen in secure-autonomous (F) attachment interviews in which the interviewee can give ample evidence for general evaluative statements made regarding attachment relationships and attachment experiences whether good or bad. In case of unresolved loss or trauma, the attachment representation is labeled unresolved-disorganized (Ud). This classification can be given in addition to a Ds, E or F classification. A fifth category, cannot classify (CC), is used when the interviewee presents contrasting attachment strategies for attachment figures in the course of the interview resulting in very low coherence of narrative. In most studies U and CC are combined in one category, Unresolved-disorganized. Coherence of mind and unresolved for loss or trauma (Ulosstrauma) are two dimensional scales of the AAI which are assigned scores rated between 1-9. Lowest score for Coherence means there is little or no coherence of mind, highest score for Ulosstrauma means there is high impact of loss or trauma.

The AAI has been administered to more than 10,000 respondents since its development (Bakermans-Kranenburg, & Van IJzendoorn, 2009). The AAI is found to have remarkably good test-retest, discriminant reliability as well as predictive validity. In this study, the AAI was administered by MJvH and CIG, verbatim transcribed according to protocol, and coded by GK (trained by Diane and Dave Pederson), and SdH (trained by Diane and Dave Pederson, and June Sroufe). Both reached intercoder reliability standards in the AAI classification system. Ten cases were also coded by MJBK. Interrater agreement in this sample was 80% for F-nonF, 90% for Ud-nonUd and 70% for four-way classification (DEFU). Kappa's for coding F-nonF (.59) and Ud-nonUd (.62) were both statistically significant and reasonable to satisfactory.

We focused our analyses on the unresolved versus non-unresolved (non-Ud) comparison because the distribution of continuous unresolved scores was skewed and because our previous study revealed structural and functional brain abnormalities in individuals with unresolved versus without unresolved classification (Riem, Van Hoof, et al., 2019; Van Hoof et al., in press).

A.1.3.8 WISC-III-NL and WAIS-III: Short versions of the Wechsler Intelligence Scale for Dutch Children aged 6-16 years, WISC-III-NL (Wechsler, 1991; Kaufman, Kaufman,

Balgopal, & McLean, 1996) and adolescents aged 16 and above and adults, the Wechsler Adult Intelligence Scale, WAIS-III (Wechsler, 1997) were used. They consisted of six subtests: picture completion, similarities, picture arrangement, arithmetic, block design and comprehension. In earlier studies, these subtests were found to give a valid and reliable IQ estimate (reliability coefficient > .90)(Kaufman, et al., 1996).

A.1.3.9 PDS: The Pubertal Development Scale (Petersen et al., 1988) measures the actual level of physical development during puberty. It is a 5-item self-report that measures items like body growth, body hair, skin changes for both sexes. For boys, there are items on beard growth and voice changes. For girls, there are items on breast growth and menstrual bleeding. Items can be answered on a 5-point scale with a total score range of 0-20. Internal consistency is adequate for both sexes, consistent across samples, while the predictive validity of the PDS is satisfactory (Robertson et al., 1992). The following distribution was found for the current sample: Prepubertal (N = 1), early pubertal (N = 1), midpubertal (N = 4), late pubertal (N = 22), postpubertal (N = 25). Information about pubertal status was missing for 10 participants. For these participants, pubertal status was imputed using gender and age.

A.1.4. Statistical analysis

Functional connectivity analysis.

In addition to left and right amygdala, and left and right dACC time series, CSF, white matter and the global signal were added as regressors to the statistical model of a seed based correlation approach. The global signal was added to the model. It should be noted that there is no consensus regarding the global signal for RSFC analyses (Murphy & Fox, 2017). Adding the global signal to resting state analyses has both advantages and disadvantages. We added the global signal in the analyses of the current study in order to increase comparability with a previous resting state study with partly the same sample (Van Hoof et al., in press).

A.1.5 Results

dorsal anterior cingulate cortex (dACC)

As mentioned in the article itself, the whole brain connectivity analyses with the dACC as seed region did not reveal associations with Ud or GPF. However, there was a significant negative association between GPF and left dACC connectivity with the right body of the corpus callosum, right superior fronto-occipital fasciculus, and right corticospinal tract, controlling for Ud, age, puberty status, IQ, and sex (TFCE family-wise error corrected, $p < .05$, see Table A.2 and Figure A.2).

A.1.6 Discussion

Our current findings on GPF revealed a negative association of GPF with the left ACC functional connectivity with the right body of the corpus callosum, superior fronto-occipital fasciculus, and corticospinal tract (Peer, Nitzan, Bick, Levin, & Arzy, 2017). In a Diffusion Tensor Imaging (DTI) study on the same sample Riem, Van Hoof and colleagues (2019) found that GPF was associated with reduced fractional anisotropy in the genu and body of the corpus callosum, which suggests demyelinization in these areas. The findings of the current study indicate that a GPF is also related to functional white matter abnormalities. Although previous studies often discarded white matter signals as noise, recent evidence suggests that white matter tracts are correlated to grey matter resting-state networks (Ding et al., 2018; Peer et al., 2017). Thus, white matter activities and connectivities seem to have a functional role and disturbances in these networks may underlie a general vulnerability to psychopathology.

As we adjusted for white matter noise, we felt that the finding on GPF and dACC could however not be included in the main manuscript itself. However, there is discussion about the existence and meaning of connectivity between RSFC, grey matter and white matter (Ding et al., 2018). We therefore do mention our initial findings in the supplemental material, as our conclusion would have been different had we included the dACC-GPF connectivity finding in the main manuscript, namely that Ud and GPF both represent independent trans-diagnostic predisposing risk factors as follows from the argumentation below.

Since there is common heritability and large co-morbidity among mental disorders, it seems likely that a GPF may account for a general increase in vulnerability (Smith et al., 2001; Lahey, Applegate, Hakes, Zald, Hariri, & Rathouz, 2012; Lahey, Zald, Perkins, Villalta-Gil, Werts, Van Hulle, … & Waldman, 2018; Caspi & Moffitt, 2018). Whether an individual will develop a mental disorder may depend on individual resilience factors such as personality, IQ, (epi)genetic factors, coping strategies, parenting or positive attachment experiences, that may counterbalance risk factors that are present (Schuwerk et al., 2014). In this study, Ud and GPF were found to be related to atypical amygdala respectively dACC functional connectivity networks. Therefore, an alternative hypothesis for Ud being a trans-diagnostic factor (Riem, Van Hoof et al., 2019) may be that both Ud and GPF represent trans-diagnostic predisposing risk factors for developing stress-related and affective mental disorders (Caspi & Moffitt, 2018), though independently from each other as they did not correlate in this study. Caution is, however, required in drawing causal conclusions from this cross-sectional study, as unmeasured third factors or reversed causality may be also possible.

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A.1.8 Tables

Table S1. Mean (SD) general psychopathology scores for the anxiety/depression, CSA-related PTSD, and control group, and Ud versus non-Ud group.

Group	N	M	SD	range
Anxiety/depression	26	0.45	0.86	-0.88 – 2.34
CSA-PTSD	18	0.39	0.87	-0.86 – 1.90
Control	19	-0.95	0.54	-1.66 – 0.12
Ud	12	0.23	1.03	-1.31 – 1.90
Non-Ud	51	-0.04	1.00	-1.66 – 2.34

Table S2. Factor loadings for the Trauma Symptom Checklist for Children (TSCC), Children's Depression Inventory (CDI), Revised Child Anxiety and Depression Scale (RCADS), Adolescent Dissociative Experiences Scale (A-DES),Youth Self Report (YSR), and Child Behavior Check List (CBCL), resulting from the Principal Component Analysis.

Subscale	Loading
RCADS separation anxiety	.79
RCADS social phobia	.80
RCADS panic disorder	.69
RCADS generalized anxiety disorder	.74
RCADS obsessive compulsive disorder	.79
RCADS depressive disorder	.89
CDI	.84
YSR internalizing problems	.88
CBCL internalizing problems	.63
TSCC_depression	.92
TSCC anxiety	.75
TSCC_PTSD	.87
TSCC dissociation	.83
TSCC sexual concerns	.56
ADES	.70

Table A.1. Mean (SD) general psychopathology scores for the anxiety/depression, CSA-related PTSD, and control group, and Ud versus non-Ud group.

Group	N	M	SD	range
Anxiety/depression	26	0.45	0.86	-0.88 – 2.34
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Non-Ud	51	-0.04	1.00	-1.66 – 2.34

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

Contrast	Region	Voxels	*p*	x	y	z
GPF -	R Corticospinal tract	50	0.03	22	-16	30

Legend: GPF = General Psychopathology Factor

A.1.9 Figures

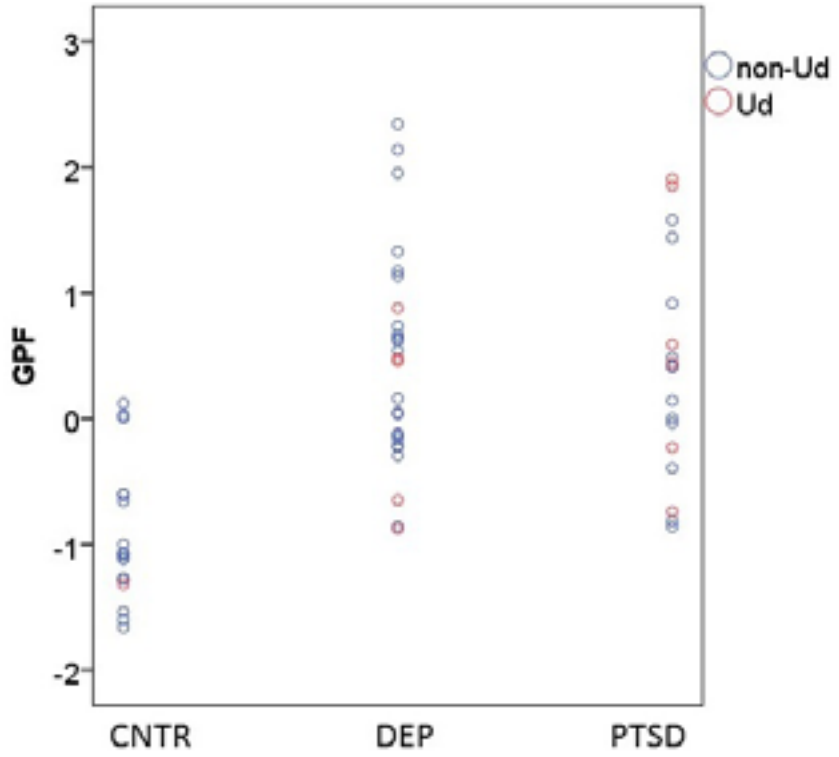

Figure A.1. Scatterplot of general psychopathology scores for the Ud, non-Ud, anxiety/depression (DEP), PTSD, and control group (CNTR)

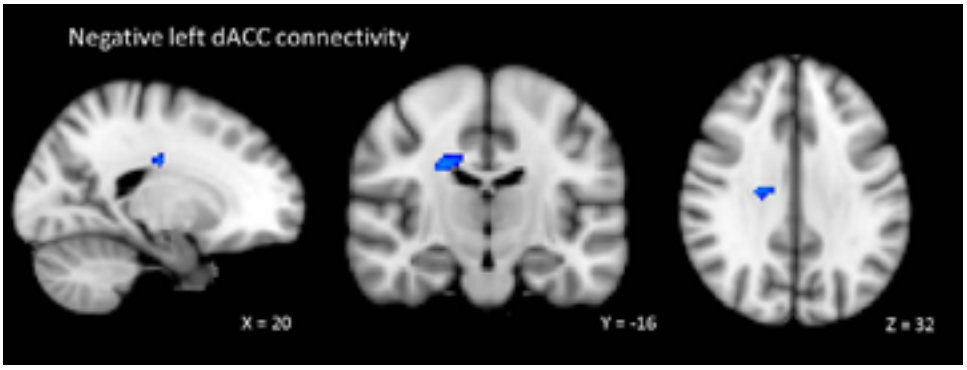

Figure A.2. Significant negative connectivity between GPF and left dACC and the right body of the corpus callosum, superior fronto-occipital fasciculus, and corticospinal tract, TFCE family-wise corrected, $p < .05$. The right side of the brain corresponds to the left hemisphere and vice versa.