Unresolved-disorganized attachment, psychopathology, and the adolescent brain

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General psychopathology factor and unresolved-disorganized attachment uniquely correlated to white matter integrity using diffusion tensor imaging

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ABSTRACT

Background: A dimensional approach of psychopathology focuses on features and risk factors that are shared across diagnoses. In support for this dimensional approach, studies point to a general psychopathology factor (GPF) associated with risk for multiple psychiatric disorders. It is, however, unknown how GPF relates to white matter integrity (WMI). In the current diffusion tensor imaging (DTI) study, we examined how GPF relates to abnormalities in a skeleton representation of white matter tracts, taking into account a trans-diagnostic risk factor: unresolved-disorganized attachment (Ud) resulting from loss or trauma.

Methods: Unique associations between GPF, Ud, and WMI were examined in a combined sample of adolescents ($N = 63$) with childhood sexual abuse-related posttraumatic stress disorder ($N = 18$), anxiety and depressive disorders ($N = 26$) and without psychiatric disorder ($N = 19$). WMI was measured using DTI. Ud was measured using the Adult Attachment Interview. We controlled for puberty stage, gender, age, and IQ.

Results: Controlling for GPF, Ud was associated with reduced fractional anisotropy (FA) in the splenium and inferior fronto-occipital fasciculus (IFOF). Controlling for Ud, GPF was associated with reduced FA in the genu and body of the corpus callosum.

Conclusions: Decreasing WMI in the genu and body with increasing psychopathology across diagnoses suggests demyelinization in these areas and may underlie comorbidity and presence of symptoms that transcend psychopathological diagnoses. In contrast, trauma-related WMI reductions in the splenium and IFOF may account for heterogeneity within diagnostic categories as a function of childhood trauma. These findings support the importance of a dimensional approach in addition to traditional diagnostic classifications in clinical research and practice.

1. INTRODUCTION

Psychiatric disorders have traditionally been viewed as categorical and distinct psychopathological conditions. However, recent research on mental health shows accumulating evidence for a dimensional approach of psychopathology and points to overarching features and trans-diagnostic factors (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Caspi, Houts, Belsky, Goldman-Mellor, Harrington, Israel, et al., 2014; Lahey, Rathouz, Keenan, Stepp, Loeber, & Hipwell, 2015). Given the high rates of comorbidity among mental disorders and the evidence that many disorders exist on a continuum, it has been argued that the underlying structure of psychopathology is reflected by a general psychopathology factor (GPF) that represents lesser-to-greater severity of psychopathology (Caspi et al., 2014). Although there is increasing attention for this novel dimensional approach for psychopathology in mental health research, clinical neuroscience is only beginning to investigate the neural mechanisms underlying mental disorders across traditional diagnostic

classifications of psychopathology (Zald, & Lahey, 2017). Numerous neuroimaging studies in search for biomarkers for psychopathological conditions point to structural and functional brain abnormalities (Hanson, Knodt, Brigidi, & Hariri, 2018; Miller, Hamilton, Sacchet, & Gotlib, 2015), but fail to find neural features with specificity to individual disorders, possibly because of comorbidity and the existence of a GPF (Zald, & Lahey, 2017).

The high comorbidity rates among mental disorders concur with the observation that risk for psychopathology is not disorder specific. For example, a recent study indicates that the GPF shows a significant Single Nucleotide Polymorphism (SNP) heritability of 38% in children (Neumann, Pappa, Lahey, Verhulst, Medina-Gomez, Jaddoe, et al., 2016). Thus, genetic factors may enhance the risk for psychopathology in general rather than or in addition to heritability of specific disorders. Similarly, environmental influences contribute to a general risk for psychopathology. More specifically, childhood trauma has been shown to increase the risk for a range of psychiatric disorders, including depression, anxiety disorders and posttraumatic stress disorder (PTSD)(Green, McLaughlin, Berglund, et al., 2010), possibly because it interacts with genetic risk factors to interfere with brain development (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Consistent with this suggestion, studies on white matter integrity (WMI) in PTSD due to maltreatment show reduced WMI in structures subserving emotional, learning, and memory functions, such as the cingulum, corpus callosum and associated fasciculi. For example, Rinne-Albers and colleagues (Rinne-Albers, Van der Werff, Van Hoof, Van Lang, Lamers-Winkelman, Rombouts, et al., 2016) found abnormalities of WMI in the genu, body and splenium of the corpus callosum in adolescents with PTSD related to childhood sexual abuse (CSA) compared to a control group. Abnormalities of the integrity of the corpus callosum may be the consequence of stress hormones associated with maltreatment earlier in life and may underlie deficits in emotional dysregulation that are often experienced by these individuals (Heim et al., 2008; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002).

Structural brain abnormalities have also been found in healthy individuals with experiences of maltreatment, regardless of psycho-pathology (Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015). This indicates that previous neuroimaging findings with clinical and non-clinical samples are possibly confounded by neurobiological consequences of childhood trauma. Indeed, research shows that the hippocampal volume reductions that are often observed in depressed patients are only found in patients diagnosed with depression and experiences of childhood maltreatment, but not in depressed patients without experiences of maltreatment (Heim et al., 2008). This finding has been interpreted as support for the existence of heterogeneity within psychopathological diagnoses as a function of childhood trauma (Teicher, & Samson, 2013) and is in line with clinical observations that depression with maltreatment is often more severe and predicts an unfavorable treatment outcome (Nanni, Uher, & Danese, 2012). Thus, childhood trauma may explain heterogeneity within diagnoses and may be related to neural substrates that are nonspecifically related to

multiple psychopathological conditions.

Not all maltreated individuals develop a mental disorder. A substantial number of children are resilient and develop well in the context of adversity (Masten, Best, & Garmezy, 1990). Multiple resilience factors, such as IQ, personality, genetic factors, parenting or positive experiences in attachment relationships, may explain individual variability in the pathways from trauma to (mal)adaptation (Masten, Best, & Garmezy, 1990). Good quality relationships with parents, peers, and romantic partners across childhood, adolescence and adulthood appear especially important predictors of a good prognosis after childhood trauma and may help in resolving issues related to childhood trauma (Collishaw, Pickles, Messer, Rutter, Shearer, & Maughan, 2007). Previous neuroimaging studies on the neurobiological effects of maltreatment have not taken into account the role of *current* state of mind with respect to childhood attachment experiences. Childhood trauma is mostly assessed retrospectively in studies examining brain structure in maltreated individuals and it is unknown whether it matters if the trauma has been resolved or not, for example through psychotherapy or resilience factors. From an attachment theory perspective, unresolved loss or trauma is characterized by a disorganized/disoriented attachment representation, that is, a disorganized/disoriented mental state with respect to childhood attachment relationships. It results from loss of or being abused by a trusted caregiver or another very traumatic incident (Hesse, 2016). Individuals with a disorganized state of mind show signs of incoherence, that is disorientation and disorganization, in their speech when they are questioned about traumatic events and/or they may present contradictory approach-avoidance strategies towards parents and other attachment figures (Hesse, 2016). Previous meta-analytic results show a prevalence of unresolved-disorganized attachment of 43% in clinical samples (Bakermans-Kranenburg, & Van IJzendoorn, 2009) and suggest that unresolved-disorganized attachment may be a trans-diagnostic risk factor for increased vulnerability to multiple psychiatric disorders. It is, however, not known whether and how psychopathology and unresolved-disorganized attachment differentially relate to brain structure and functioning.

In the current Diffusion Tensor Imaging (DTI) study, we will examine whether unresolved loss and trauma, and GPF are differentially related to WMI abnormalities in specific tracts. The current study is the first attempt to examine the unique neural correlates of a GPF in a combined clinical sample consisting of adolescents with CSA-related PTSD, anxiety and/or depressive disorders, and healthy controls. To our knowledge, only one previous study examined the association between general psychopathology and structural abnormalities (Romer, Knodt, Houts, Brigidi, Moffitt, Caspi, et al., 2017). Romer and colleagues (Romer et al., 2017) showed that general liability for psychopathology correlated with structural alterations in a cortico-cerebellar circuitry in a sample of adolescents (> 18 years) without psychiatric diagnoses, but it is unclear whether this finding can be generalized to individuals with more severe psychiatric symptoms since the sample consisted of non-

clinical adolescents and psychiatric symptoms were not measured extensively. Moreover, trans-diagnostic risk factors for psychopathology were not examined. In the current study, we use the Adult Attachment Interview (AAI) (Hesse, 2016) to assess trans-diagnostic risk factors. We hypothesize that 1) a GPF and unresolved-disorganized attachment (Ud) are differentially related to white matter abnormalities, and 2) after adjusting for a GPF, Unresolved attachment is associated with a reduction in WMI in regions that have previously been associated with childhood adversity, that is, the cingulum, corpus callosum and the superior longitudinal fasciculus (Daniels, Lamke, Gaebler, Walter, & Scheel, 2013).

2. METHODS AND MATERIALS

2.1. Participants

Sixty-three participants from the EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents; *N* = 77;(Van Hoof, Van Lang, Speekenbrink, Van IJzendoorn, & Vermeiren, 2015) were recruited according to specified in- and exclusion criteria (Van den Bulk, Koolschijn, Meens, Van Lang, Van der Wee, Rombouts, et al., 2013) (see also supplemental material). They were further selected based on availability of an AAI and a DTI scan (*N* = 72). Drop-out occurred due to poor imaging data quality and artifacts on DTI scans (*N* = 9). Within the final group there were 18 adolescents with childhood sexual abuse related posttraumatic stress disorder (CSA-PTSD), 26 adolescents with anxiety and/or depressive disorders (DEP) and 19 non-clinical adolescents (CNTR).

Our study sample consisted of 53 females and 10 males. Mean age was 15.49 years (SD 1.72, range 12–20) and total mean IQ was 103.25 (SD 8.77, range 81–119). As to cultural background, 1.6% was Asian, 92.1% was Caucasian, 4.8% was Surinamese, 1.6% was Latin-American. Four adolescents (CSA-PTSD *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), see supplemental material). Attachment and clinical characteristics of the originally larger total EPISCA sample (*N* = 77) without neuroimaging data were reported separately (Van Hoof, et al., 2015).

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. P 08.175).

2.2. *Adult attachment interview*

The Adult Attachment Interview (AAI; Hesse, 2016); see also supplemental material) is a one hour long administered semi-structured interview, validated for adolescents (Allen, Moore, Kuperminc, & Bell, 1998). The AAI asks how the interviewee thinks about the relationship with parents or other primary caregivers in his or her childhood, how these experiences have influenced him or her, how the actual relationship with parents or other primary caregivers is currently and whether there were any childhood experiences of illness, separation, fear, trauma or loss. The interviewee is asked to give specific examples supporting each evaluation. The coherence of the narrative determines the score, not its autobiographical content (Hesse, 2016).

After verbatim transcription of the AAI a certified coder rates the interview and assigns an attachment representation classification described by Hesse (2016). 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 (Hesse, 2016). Individuals receive a scale score for Unresolved loss or trauma and a score of 5.5 or above leads to a classification of unresolved-disorganized (Hesse, 2016) (see Supplemental material)

2.3. *General psychopathology factor*

The general psychopathology factor represents lesser-to-greater severity of psychopathology that is associated with higher negative affectivity, life impairment and compromised brain integrity (Caspi et al., 2014). The use of the general psychopathology factor was also shown to be valid in previous studies with adolescents [e.g. 3]. A GPF was estimated using parent and self-report measurements for behavioral and emotional problems in children and adolescents: Trauma Symptom Checklist for Children (TSCC; Briere, 1996), Children's Depression Inventory (CDI; Kovačs, 1992), Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000; Oldehinkel, 2000), Adolescent Dissociative Experiences Scale (A-DES; Armstrong, Putnam, Carlson, Libero, & Smith, 1997),Youth Self Report (YSR; Achenbach, 1991b; Verhulst, Van der Ende, & Koot, 1997), and Child Behavior CheckList (CBCL; Achenbach, 1991a; Verhulst, Van der Ende, & Koot, 1996). A Principal Component Analysis was performed using these (sub)scales. The Kaiser-Meyer-Olkin statistic showed sampling adequacy (KMO = 0.92). 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 ex- plaining 61.63% (see Table 1 for an overview of the loadings). Individual factor scores were calculated in order to estimate the general psychopathology factor (Caspi et al., 2014; Franke, 2016; Lahey, Applegate, Hakes, Zald, Hariri, & Rathouz, 2012; Lahey, et al., 2015).

Table 1

Factor loadings and factor score coefficients 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	Factor score coefficients
RCADS separation anxiety	0.79	0.09
RCADS social phobia	0.80	0.09
RCADS panic disorder	0.69	0.07
RCADS generalized anxiety disorder	0.74	0.08
RCADS obsessive compulsive disorder	0.79	0.09
RCADS depressive disorder	0.89	0.10
YSR internalizing problems	0.88	0.10
CBCL internalizing problems	0.63	0.07
TSCC_depression	0.92	0.10
TSCC_anxiety	0.75	0.08
TSCC_PTSD	0.87	0.09
TSCC_dissociation	0.83	0.09
TSCC_sexual concerns	0.56	0.06
A-DES	0.70	0.08

Factor score coefficients were calculated using the regression method (see Table 1). 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 questionnaires. All calculations were performed in SPSS with Principal Component Analysis. See Table S1 and Fig. S1 in the supplemental material for the mean psychopathology scores across the psychopathology groups.

2.4. Data acquisition and analysis

DTI data were collected using a Philips 3.0T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) with an eight-channel SENSE (Sensitivity Encoding) head coil. A single-shot echo-planar imaging sequence was used with the following scan parameters: re- petition time = 11,000 ms, echo time = 56 ms, flip angle = 90°, b- factor = 1000s/mm2, voxel dimensions = 2.3 mm isotropic, number of slices = 73, and no slice gap. DTI data were acquired along 32 directions, together with a baseline image having no diffusion weighting (b = 0). The total scanning time was ~7.5 min. DTI data is not publicly available.

The Oxford Centre for Functional MRI of the Brain (FMRIB) software library was used to preprocess (see supplemental material) and analyze DTI data. Voxel-wise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics (Smith, Jenkinson, Johansen-Berg, Rueckert, Nichols, Mackay, et al., 2006), part of FSL (Smith, Jenkinson, Woolrich, Beckmann, Behrens, Johansen-Berg, et al., 2004) First, FA images were created by fitting a tensor model to the diffusion data using FMRIB's Diffusion Toolbox. All subjects' FA images were then registered to a common space using nonlinear registration (see supplemental material). Next, the mean FA image was created and a mean FA skeleton was created which represents the centers of all tracts common to the group. Each subject's registered FA image was then projected onto this skeleton and the resulting data fed into voxel-wise group analysis.

We performed an ROI analysis in order to examine whether Ud was related to white matter integrity of regions that have previously been associated with childhood adversity, that is, the cingulum, corpus callosum (splenium, body, and genu) and the superior longitudinal fasciculus (Daniels, et al., 2013). A mask containing these three regions was created using the Johns Hopkins University (JHU) white matter atlas provided by FSL (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005). This mask was applied to the mean FA skeleton so that only voxels in the mean FA skeleton were included.

Voxel-wise statistical group analysis was performed using the General Linear Model and inference was performed with Randomise, (see supplemental material). Our model included the GPF as a continuous variable, Unresolved status (Ud versus non-Ud), and covariates of no interest were sex, IQ, and a composite score combining age and pubertal status. 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. We assessed the contrasts 1) Ud > nonUd; 2) Ud < nonUd; 3) positive association with GPF; 4) negative association with GPF. Significant voxels were determined using Threshold-Free Cluster Enhancement (TFCE)(Smith, & Nichols, 2009) with family wise error correction for multiple comparisons ($p < .05$). In order to visualize the associations between GPF, Ud, and white matter integrity in graphs, FA values were extracted using fslmeants for voxels of regions that were significantly related to GPF or unresolved status. In addition to ROI analysis, we also performed whole brain analyses with the same contrasts.

FA is a non-specific marker for WMI, meaning that it gives no information about underlying tissue structure. Therefore, post-hoc analyses were performed to examine mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in the voxels that were significantly related to GPF or unresolved-disorganized attachment in the ROI analysis. Increases in MD and RD reflect demyelination (Alexander, Lee, Lazar, & Field, 2007; Horsfield, & Jones, 2002), whereas decreased AD values reflect axonal loss (Budde, Xie, Cross, & Song, 2009).

Table 2
Mean (SD) general psychopathology scores, age, PDS, and total IQ scores for the Ud versus non-Ud group.

	UD (*N*=12)		Non-UD (*N*=51)	
	M	SD	M	SD
GPF	0.23	1.03	-0.04	1.00
Age	15.58	1.68	15.47	1.75
Total IQ	101.67	7.99	103.63	8.98
PDS-scores	4.25	1.14	4.25	0.74

3. RESULTS

3.1. Clinical characteristics

Clinical assessment (as detailed in Supplemental material) revealed that the mean score found for post-traumatic symptoms was 34.49 (TSCC, SD 23.36; range 0–98), for depression 13.00 (CDI, SD 9.42; range 0–4), for anxiety 25.97 (RCADS, SD 14.93; range 0–70), for dissociation 1.39 (A-DES, SD 1.38; range 0–6.4), for self-report problems by youth 19.10 (YSR, SD 11.03; range 0–44) and for parent reported internalizing problems 13.99 (CBCL; SD 9.08; range 0–37).

Based on the AAI, 34.9% of the adolescents in this sample was classified as secure (N = 22), 46.0% as dismissive (N = 29), 19.0% as Unresolved-disorganized (Ud) (N = 12; CNTR N = 1, DEP N = 5, CSA-PTSD N = 6). Correlational analysis showed that there was no significant relation between Unresolved-Disorganized status and GPF (r = .21, p = .11). Adolescents with Unresolved-Disorganized status did not have higher GPF scores than adolescents without Unresolved-Disorganized status ($t(61)$ = -.84, p = .40). Neither was there a significant difference in puberty phase, age, or IQ between the Ud and non-Ud group (p's > .49, see Table 2) or in the number of male and female participants in the Ud and non-Ud group (Ud: women N = 11, men N = 1, non-Ud: women N = 42, men N = 9, $\chi^2(1)$ = .63, p = .38).

3.2. DTI results

3.2.1. ROI analysis

ROI analysis showed reduced FA values in the splenium in individuals with Unresolved loss and trauma (p < .05, FWE corrected for multiple comparisons, controlling for GPF, age, puberty status, IQ, and sex, see Fig. 1), but no association between Unresolved status and FA values was found in the cingulum or superior longitudinal fasciculus. Furthermore, ROI analysis revealed a negative association between GPF scores and FA values in the genu and body of the corpus callosum (p < .05, FWE corrected for multiple comparisons, controlling for Ud, age, puberty status, IQ, and sex), but not in the splenium

(see Fig. 2). Neither was there an association between GPF scores and FA values in the cingulum or superior longitudinal fasciculus.

3.2.2. Post-hoc analyses

Post-hoc analyses were performed to examine MD, RD, and AD in the voxels that were significantly related to GPF scores or unresolved loss and trauma in the ROI analysis. Unresolved status was not significantly related to MD, RD, and AD. However, we found a positive association between GPF scores and MD, RD, and AD in the body of the corpus callosum ($p < .05$, FWE corrected for multiple comparisons, controlling for Ud, age, puberty status, IQ, and sex). Additional analyses were performed to examine the relation between FA, MD, RD, AD and GPF and unresolved status in girls only because of sex differences in white matter integrity (Inano, Takao, Hayashi, Abe, & Ohtomo, et al., 2011). In the sample with only girls, the association between FA, MD, RD and GPF scores remained significant (controlling for Ud, age, puberty status, and IQ), but AD was not significantly related to psychopathology (see supplemental material). In addition, girls with an unresolved status showed significantly lower FA values than girls without Unresolved status, controlling for GPF, age/ puberty, and IQ ($F_{(1,48)} = 16.57$, $p < .001$).

3.2.3. Whole brain analysis

The whole brain voxel-wise analysis showed that adolescents who were classified as Unresolved had reduced FA values in the splenium and the inferior fronto-occipital fasciculus (IFOF) (whole brain analysis, $p < .05$, FWE corrected for multiple comparisons, controlling for GPF, age, puberty status, IQ, and sex) (see Fig. 1). Whole brain analysis did not reveal an association between GPF scores and FA values, controlling for Ud, age, puberty status, IQ, and sex.

4. DISCUSSION

The current study is the first to examine white matter correlates of unresolved-disorganized attachment and a measure of general psychopathology (GPF). With DTI, we showed that unresolved-disorganized attachment representation (Ud), i.e. unresolved loss or trauma as assessed with the AAI, and GPF are differentially related to abnormalities in a skeleton representation of white matter tracts. We studied a mixed group of adolescents with CSA-related PTSD, anxiety and depressive disorders and without psychiatric symptoms. We found that unresolved loss and trauma was associated with reduced FA values in the inferior fronto-occipital longitudinal fasciculus and the splenium of the corpus callosum, whereas our ROI analysis showed that GPF was associated with reduced white matter integrity in the

genu and body of the corpus callosum. This is consistent with our hypothesis that a GPF and Ud are differentially related to white matter abnormalities. Our findings provide evidence for a WMI correlate of Ud within the splenium of the corpus callosum ROI, and indicate that reduced white matter integrity in the genu and body is a trans-diagnostic biomarker of multiple psychopathological symptoms.

As white matter develops over at least three decades following birth, it is thought to be a brain structure prone to be influenced by psychopathology as well as childhood maltreatment (Andersen, 2003; Ayling, Aghajani. Fouche, & Van der Wee, 2012). Previous neuroimaging studies found white matter reductions in the corpus callosum in patients with several mental disorders, including PTSD, major de- pression, anxiety disorders, borderline personality disorder and bipolar disorder, for a review see (Thomason, & Thompson, 2011). However, corpus callosum reductions have been found in healthy individuals with a history of maltreatment, regardless of psychopathology (Teicher, & Samson, 2016). It has therefore been suggested that brain abnormalities in each diagnostic group may be restricted to a maltreatment ecophenotype (Teicher, & Samson, 2016). Indeed, a study by Bücker and col- leagues (2014) showed that corpus callosum reductions were associated with bipolar disorder, but were limited to patients with experiences of maltreatment. Thus, in the past few decades, neuroimaging studies may have confounded childhood trauma and psychopathological symptoms (Van der Kolk, 2016). Our findings are consistent with and extend this suggestion and indicate that white matter integrity of the splenium of the corpus callosum is specifically related to unresolved-disorganized attachment, which is a result of childhood loss or trauma, while psychopathology is linked to the genu and body of the corpus callosum.

The corpus callosum is crucial for interhemispheric communication and is the largest white matter tract in the human brain. Thickness of the corpus callosum has been associated with measures of IQ and problem solving (Luders, Narr, Bilder, Thompson, Szeszko, Hamilton, et al., 2007). Although the number of fibers in the corpus callosum is already determined at birth, structural changes continue to occur during childhood and adolescence due to axonal myelination, pruning, and redirection (Luders, Thompson, & Toga, 2010; Galaburda, Rosen, & Sherman, 1990; Luo, & O'Leary, 2005). The same degree of growth is, however, not the same for each subregion. Luders and colleagues (Luders et al., 2010) show a more pronounced growth of the splenium compared to other regions of the corpus callosum in children between 5 and 18 years of age. This is consistent with studies showing greater age-related changes in posterior regions than in anterior regions of the corpus callosum in other age groups (Giedd, Rumsey, Castellanos, Rajapakse, Kaysen, Vaituzis, et al., 1996; Chung, Worsley, Paus, Cherif, Collings, Giedd, et al., 2001). Accelerated development of the splenium during childhood and adolescence may lead to greater vulnerability to childhood stressors, which may explain the association with unresolved-disorganized

attachment related to loss and trauma in the current study. Rodent studies show that these callosal abnormalities are related to imbalance in oligodendrocyte proliferation in reaction to high cortisol stress levels due to chronic exposure to stress (Alonso, 2000; Miyata, Koyama, Takemoto, Yoshikawa, Ishikawa, Taniguchi, et al., 2011).

Our finding that reduced white matter integrity in the splenium of the corpus callosum and IFOF was specific for individuals with Ud (after controlling for the GPF) could be explained in alternate ways. One possibility is that reduced white matter integrity in the splenium of the corpus callosum and IFOF may reflect a pre-existing vulnerability factor that increases sensitivity to deleterious effects of childhood abuse, resulting in unresolved loss and trauma. In fact, reduced callosal size has been negatively associated with IQ and cognitive functioning (Luders, et al., 2007), which may in turn hinder recovery from trauma (Masten, Hubbard, Gest, Tellegen, Garmezy, & Ramirez, 1999; Masten, et al., 2008). Another ex- planation is that a secure parent-child relationship may help in resolving a traumatic experience and may stimulate recovery or compensatory changes. There is some evidence showing that resilience after childhood trauma is associated with compensatory neurobiological mechanisms (Galinowski, Miranda, Lemaitre, Paillere Martinot, Artiges, Vulser, et al., 2015). Future studies should therefore examine WMI in individuals with traumatic childhood experiences with longitudinal intervention designs in order to shed light on trauma- and attachment-related neurobiological changes and which interventions help best to recover in patients with versus without Ud.

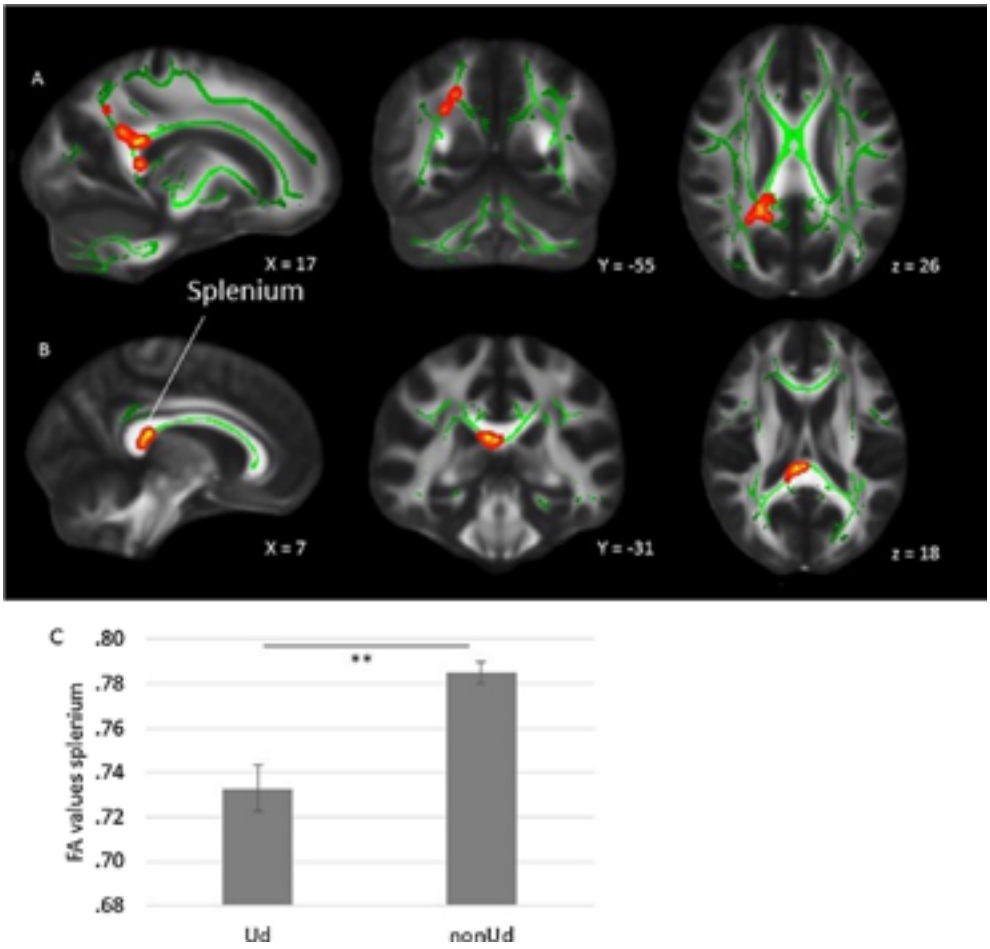

Fig. 1. Reduced FA values in individuals with Ud. Upper panel A: whole brain analysis; lower panel B: ROI analysis. Depicted in green is the white matter skeleton superimposed on the FMRIB58_FA_1 mm standard brain (gray). Depicted in yellow are the regions in which FA values were significantly lower in individuals with Ud (N = 12), compared to individuals without Ud (N = 51), $p < 0.05$, TFCE corrected. The results are thickened (in red) using the "tbss-fill" command. The right side of the image corresponds to the left hemisphere of the brain and vice versa. Panel C shows mean (SE) FA values of the subregion of the splenium that was significantly related to unresolved status (extracted for illustrative purposes) for individuals with and without Ud, controlled for TIQ, composite score age and puberty, sex, and GPF (** $p < .001$).

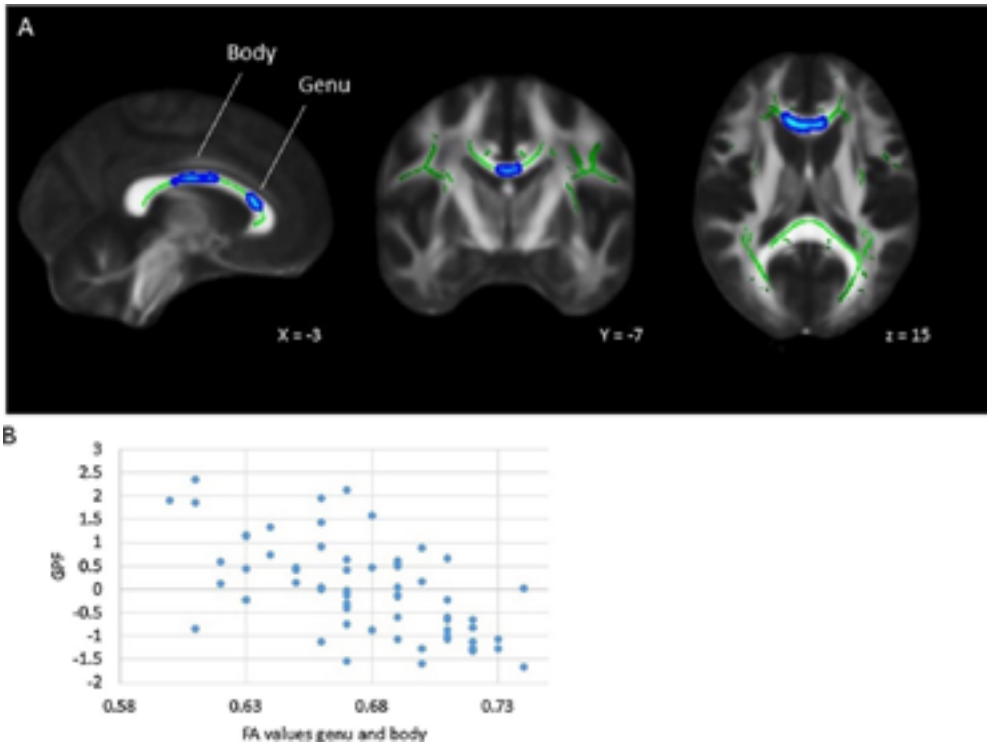

Fig. 2. Panel A: Negative association between general psychopathology factor (GPF) and FA values in the genu and body of the corpus callosum (ROI analysis). Depicted in green is the white matter skeleton superimposed on the FMRIB58_FA_1 mm standard brain (gray). Depicted in light blue are the regions in which FA values were significantly related to GPF, $p < 0.05$, TFCE corrected. Panel B: A scatterplot of extracted voxel values, for illustrative purposes only, showing the negative association between GPF and FA values in the genu and body.

When traumatic childhood attachment experiences remain unresolved it may account for reduced white matter integrity of the splenium, but abnormalities of the genu and body of the corpus callosum may be the consequence of a general vulnerability for psycho- pathology that might be a result of genetic influences (Patel, Kelly, Wright, Gupta, Arias-Vasquez, Perrone-Bizzozero, et al., 2015) or prenatal stress (Jensen, Pangelinan, Björnholm, Klasnja, Leemans, Drakesmith, et al., 2018). Our findings indicated that the smaller FA values in the genu and body were due to increases in AD, RD, and MD. RD and MD are known to reflect demyelinization (Alexander et al., 2007), whereas the positive association between GPF and AD values may reflect altered axonal integrity (Budde et al., 2009). However, caution with interpretation of these WMI indicators is warranted because causality still has to be established.

Some limitations should be mentioned. The generalizability of results may be limited due to the relatively small sample size and the restricted ranges of age, IQ, and gender. Future studies should examine neural correlates of unresolved loss and trauma and a GPF in a more diverse sample with a broader range of psychopathological symptoms, for example including more externalizing symptoms. In addition, the study was cross-sectional which makes conclusions regarding causality speculative. Furthermore, we did not make use of fieldmap corrections for susceptibility artifacts. Lastly, although studies with different age categories (children, adolescents, adults) and countries using different report sources (self-report, parent or teacher report) all confirm the existence of a GPF (see Caspi, & Moffitt, 2018 for a review), it is still unclear what causes the correlation among disorders and symptoms. The GPF has been compared with the general factor in intelligence (the "g" factor) (Caspi, & Moffitt, 2018), which accounts for correlated scores on different cognitive tests, whereas more domain-specific factors explain shared variance among smaller subsets of tests. A similar bifactor model specifying both a general factor and specific internalizing and externalizing factors has been proposed for the structure of psychopathology, although alternative models for the correlation among symptoms should also be tested (Caspi, & Moffitt, 2018). The findings of the current study may suggest that GPF has a neurobiological basis, similar to the "g" factor (Duncan, Seitz, Kolodny, Bor, Herzog, Ahmed, et al., 2000). However, it is still unclear what GPF exactly means and whether it is a g like *causal* factor. Caspi and Moffitt therefore call for a neuroimaging approach in the investigation of GPF. Exploring brain correlates of GPF could potentially be a step forward in the discovery of biological psychiatry as it may be a new route to identify the causes shared by psychiatric disorders (Caspi, & Moffitt, 2018).

5. CONCLUSIONS

In conclusion, we showed that a GPF and unresolved loss or trauma have unique associations with white matter integrity. Our findings indicate that reduced white matter integrity in the genu and body is a trans-diagnostic biomarker of multiple psychopathological symptoms, which may be related to comorbidity and presence of symptoms that transcend specific psychopathological diagnoses. In contrast, reduced white matter integrity of the splenium and IFOF seem to reflect consequences of unresolved childhood loss or other trauma and may account for heterogeneity within diagnostic categories. Together, these findings suggests that a dimensional approach may complement the traditional classificatory approach in clinical research and practice.

DISCLOSURES

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2018.10.014.

SUPPLEMENTAL MATERIAL CHAPTER 5 (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 [A.1] or according to the American Psychiatric Association 'PTSD with dissociative symptoms' [A.2] 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 EPISCA study (Emotional Pathways' Imaging Study in Clinical Adolescents), 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 et al., 2013). AAI (Hesse, 2016) and clinical characteristics of the group and neuroimaging data were reported previously (e.g. Van Hoof et al., 2015; A.3).

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 [A.4](WISC-III) or Adults [A.5](WAIS-III), 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 psychotrauma centres of child and adolescent psychiatric institutes in the Leiden region in 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 the psychotrauma centre. 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 [A.6] and no history of CSA (see [A.7, A.8, A.9]. 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 [A.10], 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 [A.6], 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, 1991] and CBCL: Child Behavior Checklist (Achenbach, 1991), with Dutch translations by Verhulst and colleagues (Verhulst, Van den Ende, & Koot, 1996; 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) [A.7] 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.

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.

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) [A.11], though discriminant validity has been subject to discussion. In this study, the total CDI score had a Cronbach's alpha coefficient of .93.

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 [A.13].

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 [A.4, A.14] and adolescents aged 16 and above and adults, the Wechsler Adult Intelligence Scale, WAIS-III [A.5] 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)[A.15].

A.1.3.9 PDS: The Pubertal Development Scale (Petersen, Corckett, Richards, Boxer, 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 [A.16]. 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

A.1.4.1 Preprocessing. The Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) version 5.0.9 was used to preprocess and analyze DTI data. First, non-brain tissue was removed, using the Brain Extraction Tool [A.17]. DTI data were corrected for distortion and motion artifacts, induced by eddy currents, using affine registration of each diffusion weighted image to the b=0 reference image.

A.1.4.2 Analysis. Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics, (Smith, et al., 2006). First, FA images were created by fitting a tensor model to the diffusion data using FMRIB's Diffusion Toolbox, and then brain-extracted using BET [A.17]. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT [A.18, A.19], which uses a b-spline representation of the registration warp field [A.20]. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. Voxel-wise statistical group analysis was performed using the General Linear Model and inference was performed with Randomise, FSL's tool for nonparametric permutation inference on neuroimaging data [A.21].

A.1.5 RESULTS

The association between GPF scores and FA, MD, RD and remained significant in the sample with only girls (controlling for Ud, age, puberty status, and IQ, FA: $F_{(1,48)} = 22.31$, $p < .001$, MD: $F_{(1,48)} = 5.17$, $p < .05$, RD: $F_{(1,48)} = 6.86$, $p < .05$), but AD was not significantly related to psychopathology ($F_{(1,48)} = 2.34$, $p < .12$)).

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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
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

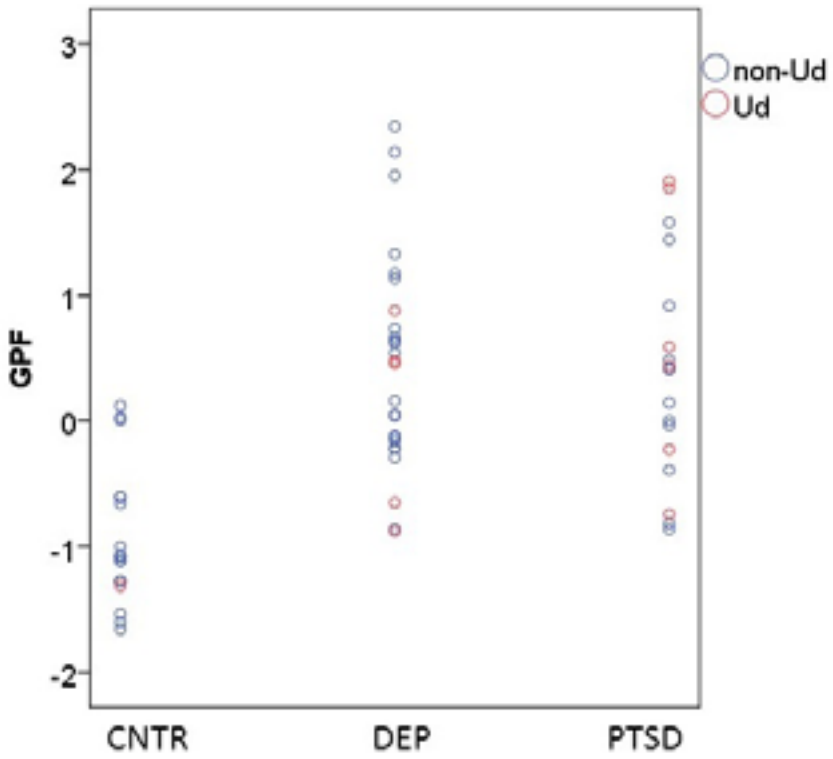

Figure A.1. Scatterplot of general psychopathology scores for the Ud, non-Ud, anxiety/depression (DEP), PTSD, and control group (CNTR).