Interpersonal Traits of Psychopathy Linked to Reduced Integrity of the Uncinate Fasciculus

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Abstract: Psychopathy is a personality disorder characterized by callous lack of empathy, impulsive antisocial behavior, and criminal recidivism. Here, we performed the largest diffusion tensor imaging (DTI) study of incarcerated criminal offenders to date ($N = 147$) to determine whether psychopathy severity is linked to the microstructural integrity of major white matter tracts in the brain. Consistent with the results of previous studies in smaller samples, we found that psychopathy was associated with reduced fractional anisotropy in the right uncinate fasciculus (UF; the major white matter tract connecting ventral frontal and anterior temporal cortices). We found no such association in the left UF or in adjacent frontal or temporal white matter tracts. Moreover, the right UF finding was specifically related to the interpersonal features of psychopathy (glib superficial charm, grandiose sense of self-worth, pathological lying, manipulativeness), rather than the affective, antisocial, or lifestyle features. These results indicate a neural marker for this key dimension of psychopathic symptomatology. *Hum Brain Mapp 36:4202–4209, 2015.* © 2015 Wiley Periodicals, Inc.

Key words: psychopathy; antisocial personality disorder; diffusion tensor imaging; uncinate fasciculus; prefrontal cortex; amygdala; crime

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INTRODUCTION

Psychopathy is a personality disorder characterized by a callous lack of empathy and impulsive antisocial behavior. Present in roughly a quarter of adult prison inmates, psychopathy is a significant predictor of violent crime and recidivism [Hare, 2003; Harris et al., 1991]. Identifying the psychological and neurobiological mechanisms underlying this disorder could thus have profound implications for the clinical and legal management of psychopathic criminals, as well as for the basic understanding of human emotion and social behavior. However, due to the logistical challenges associated with performing brain imaging research with psychopathic criminals, to date this line of research has commonly been beset by relatively small sample sizes, inconsistent diagnostic criteria, and consequently, a lack of replication of major findings [Koenigs et al., 2011]. One notable exception is an association between psychopathy and reduced microstructural integrity of the right uncinate fasciculus (UF; the major white matter pathway connecting ventral frontal and anterior temporal cortices). The UF is believed to play a critical role in social-affective function and decision-making [Olson et al., 2013; Von Der Heide et al., 2013]. Four different diffusion tensor imaging (DTI) studies have found reduced fractional anisotropy (FA) of the right UF in psychopathic and/or antisocial offenders, relative to nonpsychopathic individuals [Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012]. However, because each of these studies included relatively small groups of highly psychopathic versus nonpsychopathic individuals, the extant DTI data leave two critical questions unanswered. First, is this brain-behavior relationship continuous across the full spectrum of psychopathy severity, or is it only observed as a categorical difference for cases of extreme psychopathy severity? Second, does reduced integrity of the right UF relate to any specific subsets of psychopathic traits? These outstanding questions reflect an evolving nosology in psychiatry in which mental illnesses are increasingly viewed in terms of dimensions of distinct psychological or behavioral characteristics, which are underpinned by distinct neural circuits, rather than as unitary categorical entities [Insel, 2014].

Symptoms of psychopathy can be disaggregated into two main "factors", or dimensions, of traits. Factor 1 corresponds to the unique interpersonal/affective traits of psychopathy (e.g., callousness, egocentrism, pathological lying), whereas Factor 2 corresponds to the more general lifestyle/antisocial features (e.g., impulsivity, irresponsibility, criminal versatility) that are shared with other externalizing disorders [Hare et al., 1990]. Each factor can be further subdivided into a total of four distinct "facets" (Table I). Linking right UF integrity to a particular psychopathy factor or facet would thus provide a more specific neurobiological marker for a key dimension of social-affective dysfunction, but to do so would require a large sample with a wide range of severity on both factors

TABLE I. Dimensions of psychopathic traits, based on the psychopathy checklist-revised (PCL-R)

Total PCL-R					
Factor 1 interpersonal-affective		Factor 2 lifestyle-antisocial			
Facet 1 interpersonal	Facet 2 affective	Facet 3 lifestyle	Facet 4 antisocial		Neither
Glibness/Superficial charm	Lack of remorse or guilt	Need for stimulation/proneness to boredom	Poor behavioral controls		Many short-term marital relationships
Grandiose sense of self-worth	Shallow affect	Parasitic lifestyle	Early behavioral problems		Promiscuous sexual behavior
Pathological lying	Callous/lack of empathy	Lack of realistic long-term goals	Juvenile delinquency		
Conning/manipulative	Failure to accept responsibility for own actions	Impulsivity	Revocation of conditional release		
		Irresponsibility	Criminal versatility		

TABLE II. Participant characteristics

	Nonpsychopathic ($n = 50$)	Intermediate ($n = 47$)	Psychopathic ($n = 50$)
Age	31.26 (6.82)	30.94 (6.83)	29.84 (7.48)
Race (Cauc/Af Am)	36/14	19/28	33/17
Years Education	10.96 (1.23)	10.60 (1.23)	10.00 (1.78)
IQ	99.30 (12.64)	96.16 (12.41)	100.86 (10.82)
Anxiety	11.14 (8.43)	10.43 (5.53)	17.06 (8.73)
Violent Offenses	3.63 (3.68)	5.35 (7.28)	6.14 (4.89)
Substance Use Disorder	18/50	39/47	41/50
PCL-R Total Score	14.41 (3.50)	25.54 (2.42)	31.90 (1.57)
Factor 1	5.11 (2.24)	9.43 (2.07)	12.10 (1.84)
Interpersonal Facet	1.26 (1.14)	3.60 (1.39)	5.08 (1.50)
Affective Facet	3.85 (1.87)	5.83 (1.32)	7.02 (1.04)
Factor 2	7.83 (2.76)	14.11 (1.88)	17.00 (1.52)
Lifestyle Facet	4.52 (1.85)	7.36 (1.36)	8.41 (1.20)
Antisocial Facet	3.17 (2.02)	6.65 (1.82)	8.46 (1.41)

of psychopathic traits. To accomplish this aim, we collected DTI data using a unique mobile MRI scanner from a large sample ($N = 147$) of incarcerated criminal offenders with a broad range of psychopathy severity.

METHODS

Participants

Participants were adult male inmates at a medium-security Wisconsin correctional facility. Participants were scanned between 2010 and 2013. Inmates were eligible if they met the following criteria: 18–45 years of age, IQ > 70, free of psychotropic medication use, no history of loss of consciousness lasting longer than 30 minutes, and no history of psychosis or bipolar disorder. The final sample ($N = 147$) included 22 inmates ($n = 13$ psychopathic and $n = 9$ nonpsychopathic) who participated in a previous DTI study from our group in which we reported group differences in right UF integrity between relatively small groups of psychopathic and nonpsychopathic inmates [Motzkin et al., 2011]; however, these individuals were rescanned for this study. Participant characteristics for this study are presented in Table II. All participants provided oral and written informed consent.

Assessments

Psychopathy was assessed by trained research staff using the Psychopathy Checklist-Revised (PCL-R) [Hare, 2003]. The PCL-R is a clinical measure of psychopathy, completed based on a 60–90 min clinical interview and review of institutional files used to assess the presence of 20 psychopathy-related traits (Table I), assigning a score of 0, 1, or 2 for each item. Inter-rater reliability ratings were available for 13 participants and yielded a high intraclass correlation ($r = 0.99$) for PCL-R total scores. Factor and facet scores were calculated according to published

guidelines [Hare and Neumann, 2005; Harpur et al., 1989]. Scores for Factors 1 and 2 were moderately correlated ($r = 0.66$). Further, scores for related facets were moderately correlated (Interpersonal and Affective, $r = 0.55$; Lifestyle and Antisocial, $r = 0.52$). For categorical analyses participants were identified as psychopathic if they scored 30 or greater on the PCL-R ($n = 50$), nonpsychopathic if they scored 20 or lower ($n = 50$), and intermediate if they scored between 20 and 30 ($n = 47$) [Hare, 2003].

Substance use disorder was assessed using the Structured Clinical Interview for DSM-IV (SCID) [First et al., 2012]. To minimize the number of covariates used in statistical models, a composite variable was calculated for substance use; participants who met criteria for abuse or dependence on any substance (alcohol, cannabis, cocaine, opioids, stimulants, sedatives, or hallucinogens) earned a substance use disorder score of "present," and all other participants were scored as "absent." IQ was estimated using the Wechsler Adult Intelligence Scale [Wechsler, 2008]. Trait negative affect was assessed using the Welsh Anxiety Scale [Welsh, 1956]. Finally, the number of violent offenses for each participant was quantified as the count of charges for murder, assault, robbery, sexual assault, weapon-related offenses, and kidnapping.

MRI Data Acquisition

Diffusion-weighted echo-planar MRI was acquired on correctional facility grounds using the Mind Research Network's Siemens 1.5 T Avanto Mobile MRI System equipped with a 12-element head coil. Diffusion sensitizing gradients were applied along 30 noncollinear directions (b value = 800 s/mm^2). Five interleaved nondiffusion-weighted (b value = 0 s/mm^2) volumes were collected during each run to enable corrections for motion and eddy current distortions. Images were collected with the following parameters: repetition time (TR) = 9200 ms, echo time (TE) = 84 ms, field of view = 256 × 256 mm, matrix
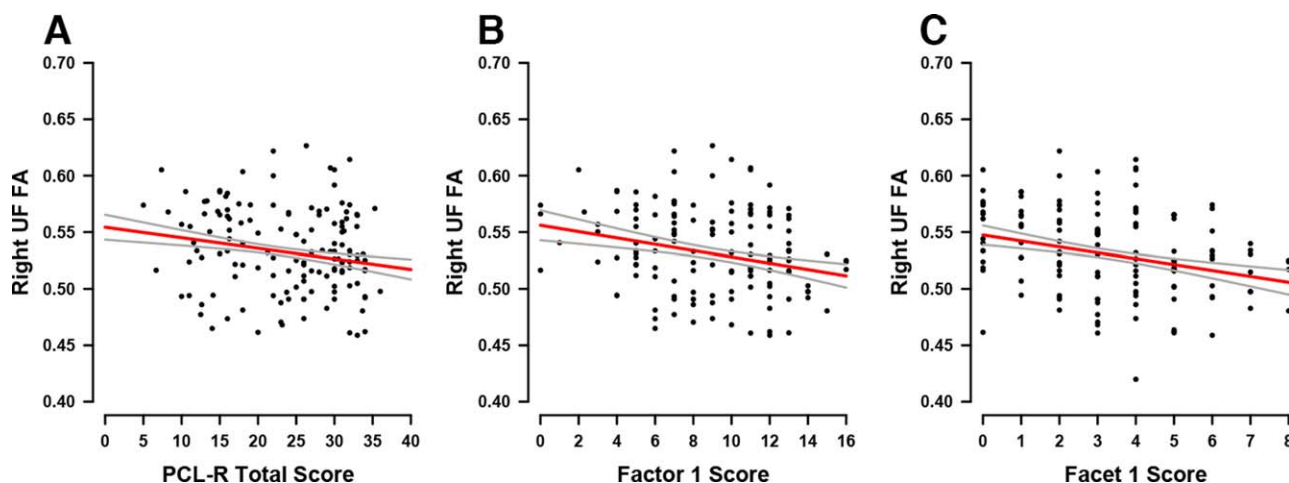
Figure 1.

Inverse relationships between right UF FA and (**A**) PCL-R Total scores ($P = 0.047$), (**B**) Factor 1 scores ($P = 0.040$), and (**C**) Facet 1 scores ($P = 0.021$). Scatter plot points are raw data. Gray lines indicate ± 1 standard error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

size = 128 × 128, slice thickness = 2 mm, no gap, voxel size = 2 × 2 × 2 mm³, 70 slices. The sequence was repeated twice and the data combined to improve signal-to-noise ratio. Head motion was limited using padding and restraint.

DTI data were processed using FSL [Smith et al., 2004, 2006] and Camino [Cook et al., 2006]. Eddy current and subject motion were corrected via affine registration to the first nondiffusion-weighted (i.e., b0) volume. Brain extraction to remove nonbrain tissue was performed on the b0 image. Masks were eroded and quality checked before being applied to the remainder of nondiffusion-weighted volumes. The resultant images were used for nonlinear diffusion tensor estimation [Alexander and Barker, 2005]. Extreme outlier voxels were then identified and masked. Finally, voxels that led to tensors that were not symmetric positive-definite were identified and forced to meet this criterion [Barmpoutis and Vemuri, 2010] before FA maps were calculated.

FA maps were nonlinearly registered to the MNI152 FA template and resampled to 1 mm³ using FSL's tract-based spatial statistics workflow [Smith et al., 2006]. Alignment quality was visually confirmed for all subjects. A grand mean FA image was used to calculate a white matter skeleton, which was used for all subsequent analyses to minimize the partial volume effect. Tract average FA was computed across voxels in the intersection of the white matter skeleton and Johns Hopkins University white matter atlas labels [Mori et al., 2005].

Statistical Analysis

Average FA within a given tract was the primary dependent measure for linear regressions performed in R [R Development Core Team, 2014]. All statistical models included participant age, race, and presence of substance use disorder as covariates. Left and right UF were selected as a priori tracts of interest, while comparison tracts were selected based on either proximity to the UF or on previous studies identifying psychopathy-related abnormalities in these tracts [Hoppenbrouwers et al., 2013; Raine et al., 2003]. Left and right UF FA were separately regressed on PCL-R Total scores, as well as on categorical psychopathy diagnoses. To determine the relationship between specific psychopathic traits and UF integrity, FA values were also regressed on PCL-R factors and facets. In some cases, items for specific factors or facets are omitted during the PCL-R interview because the individual's life history is not conducive to accurate assessment (e.g., no history of conditional release, thus revocation of such is not possible); a total of 10 subjects with such omitted items were excluded from factor and facet analyses. Because PCL-R factor and facet scores are correlated with each other, these subscore analyses were conducted by first running separate models for each individual factor or facet, and then including all factors or facets in a single model to assess the unique relationship between FA and each factor or facet.

To assure accuracy of regressions, we performed model case analysis. This consisted of plotting a histogram of Cook's distances for each model [Cook, 1977], identifying and excluding individuals that had values that were discontinuous with the rest of the distribution (i.e., had disproportionately large influence on the model), and rerunning the model. This exclusion criterion was adopted as a means to minimize the error in regressions, which is inflated by influential cases that are outliers with substantial leverage. Based on this criterion, $n = 8$ were excluded
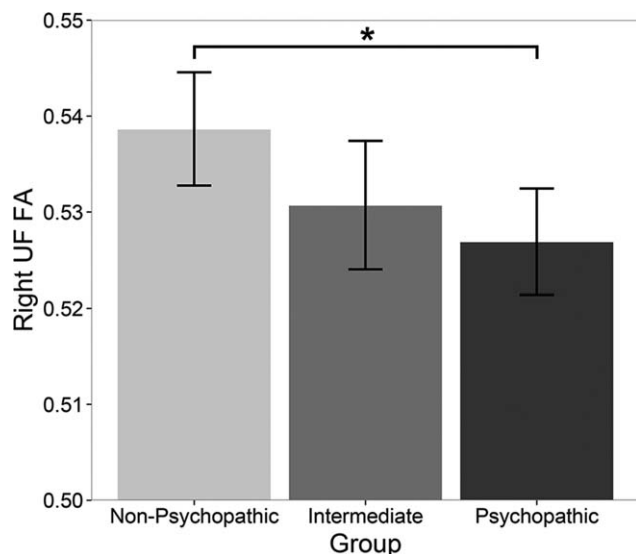
Figure 2.

Right UF FA by psychopathy category. Error bars indicate ± 1 standard error. * Psychopathic participants had lower right UF FA than nonpsychopathic participants ($P = 0.013$).

from the Total PCL-R regression, $n = 7$ were excluded from the between-group analysis, $n = 9$ were excluded from the Factor regression, and $n = 9$ were excluded from the Facet regression.

RESULTS

Relationship of PCL-R Total Scores and Regional FA

Consistent with previous findings, PCL-R Total scores were inversely related to right UF FA ($t_{(134)} = -2.00$, $P = 0.047$, partial $\eta^2 = 0.029$; Fig. 1A), but had no significant association with left UF FA ($P = 0.31$). The finding in right UF was highly specific; PCL-R Total scores were unrelated to FA of comparison tracts (cingulum bundle, anterior internal capsule, thalamic radiation, or genu or body of the corpus callosum; all $P > 0.42$). Further, PCL-R Total scores were unrelated to whole-brain FA ($P = 0.29$), suggesting that the effect observed in the right UF was not driven by a general relationship between PCL-R Total score and overall white matter integrity.

Relationship of Psychopathy Diagnosis and UF FA

In addition, participants meeting traditional categorical criteria for psychopathy also had lower right UF FA than nonpsychopathic participants ($t_{(88)} = -2.54$, $P = 0.013$, partial $\eta^2 = 0.068$; Fig. 2). There was no significant difference between groups for left UF FA ($P = 0.19$).

Relationship of PCL-R Factor Scores and Right UF FA

To determine whether right UF integrity was specifically related to one of the two primary dimensions of psychopathy, we regressed FA in this area on Factor 1 (Interpersonal-Affective) and Factor 2 (Antisocial-Lifestyle) scores, with the aforementioned covariates, in separate models. Factor 1 scores were inversely related to right UF FA ($t_{(133)} = -2.35$, $P = 0.021$, partial $\eta^2 = 0.040$). There was also a trend toward a negative relationship between Factor 2 scores and right UF FA ($t_{(123)} = -1.79$, $P = 0.076$, partial $\eta^2 = 0.025$).

To determine the unique relationship between each factor score and right UF integrity, we regressed FA in this area in a single model that included Factor 1 scores, Factor 2 scores, their two-way interaction, and aforementioned covariates. Factor 1 scores were inversely related to right UF FA ($t_{(121)} = -2.07$, $P = 0.040$, partial $\eta^2 = 0.034$; Fig. 1B), while the unique contributions of Factor 2 scores and the interaction of the two Factor scores were unrelated to right UF integrity (both $P > 0.46$).

Relationship of PCL-R Facet Scores and Right UF FA

To further parse the association between right UF integrity and subdimensions of psychopathy, we regressed FA in this area on scores for the four facets, with the same covariates, in separate models. Consistent with the Factor analyses, there was a significant inverse relationship between Facet 1 (Interpersonal) scores and right UF FA ($t_{(133)} = -3.12$, $P = 0.002$, partial $\eta^2 = 0.068$). Facet 2 (Affective) scores were not related to right UF FA ($P = 0.47$). Facet 3 (Lifestyle) trended towards a significant relationship with right UF FA ($t_{(124)} = -1.88$, $P = 0.063$, partial $\eta^2 = 0.028$). Finally, Facet 4 (Antisocial) scores were not related to right UF FA ($P = 0.34$).

To determine the unique relationship between each Facet score and right UF integrity, we regressed FA in this area on the four Facets, and aforementioned covariates, in a single model. Facet 1 scores were significantly and inversely related to right UF FA ($t_{(117)} = -2.35$, $P = 0.021$, partial $\eta^2 = 0.045$; Fig. 1C), but no other facet was significantly associated with right UF integrity (all $P > 0.24$).

Relationship of Substance Use, Psychopathy, and FA

As expected, the prevalence of substance use disorders differed across psychopathy categories ($\chi^2(2, N = 147) = 9.94$, $P = 0.007$), with a smaller proportion of nonpsychopathic individuals meeting DSM-IV criteria (36%) than intermediate (83%) or psychopathic individuals (82%). Likewise, presence of substance use disorder was positively correlated with PCL-R Total scores ($r_{(145)} = 0.46$, $P < 0.0001$). Although the presence of substance use

disorder was associated with increased whole-brain FA in a model including PCL-R Total score, age, and race ($t_{(142)} = 3.07$, $P = 0.003$, partial $\eta^2 = 0.062$), there was not a significant influence of substance use disorder on the specific associations between psychopathy severity and right UF FA. In the same model reported above for the relationship between PCL-R Total score and right UF integrity, there was no significant relationship between presence of substance use disorder and right UF integrity ($P = 0.27$). In the contrast reported above for the relationship between of psychopathy diagnosis and right UF integrity, there was no significant relationship between presence of substance use disorder and right UF integrity ($P = 0.31$). In the same models reported above for the relationship between Factor 1 scores and right UF integrity, there was no significant relationship between presence of substance use disorder and right UF integrity (all $P > 0.42$). Finally, in the same models reported above for the relationship between Facet 1 scores and right UF integrity, there was no significant relationship between of presence of substance use disorder and right UF integrity (all $P > 0.30$).

DISCUSSION

In the largest DTI study of incarcerated criminal offenders to date, we have identified an anatomically specific neural characteristic of psychopathy: reduced microstructural integrity of the right UF. Our finding of an inverse relationship between Total PCL-R score and right UF FA across our entire inmate sample corroborates previous findings based on group comparisons with smaller samples, showing lower FA in right UF in psychopathic offenders versus non-psychopathic individuals [Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012]. However, the large sample and wide range of psychopathy severity in this study has afforded us the unique opportunity to examine whether this particular neurostructural characteristic relates to specific symptoms of the disorder. Our follow-up factor and facet analyses provide novel insight in this regard; reduced right UF integrity was specifically related to the interpersonal traits of psychopathy (e.g., pathological lying, glibness, manipulativeness, egocentricity). This finding supports a multi-dimensional model of psychopathy, in which specific components of the disorder are underpinned by distinct neurobiological substrates.

Here, we discuss further the relation of our findings to the extant literature as well as implications for future translational research. In the first DTI study of psychopathy, which compared 9 adult male forensic inpatients with relatively high PCL-R scores (range $24 - 34$) to 9 healthy comparison subjects, Craig et al. [2009] found reduced FA in the right UF, but not in the left UF or in comparison tracts (the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus). In a previous study, our group made a remarkably similar finding in a sample of 14 psychopathic adult male inmates (PCL-R range 30–36), as compared with 13 nonpsychopathic adult male inmates (PCL-R range 11–19): reduced FA in the right UF, but not in the left UF or any other comparison tract (inferior longitudinal fasciculus/inferior fronto-occipital fasciculus, superior longitudinal fasciculus, superior fronto-occipital fasciculus) [Motzkin et al., 2011]. In a third study that focused more on antisocial personality disorder (ASPD), Sundram et al. [2012] compared 15 adult male forensic inpatients with ASPD (PCL-R range 13–34) to 15 healthy comparison subjects, finding reduced FA in right UF, but also in several adjacent tracts in frontal lobe. Although Sundram et al. performed factor score correlations in this small sample, they found no relationship between Factor 1 scores and white matter abnormalities. A fourth study of 11 psychopathic offenders (PCL-R range 23–34) and 11 healthy comparison subjects found reduced FA in right UF as well as several adjacent tracts [Hoppenbrouwers et al., 2013]. The present study included 147 adult male inmates with PCL-R scores ranging from 5 to 36, including 50 psychopathic (PCL-R score ≥ 30) and 50 nonpsychopathic (PCL-R score ≤ 20) subjects. As this is by far the largest DTI study of psychopathy to date, the results provide a definitive confirmation of the association between psychopathy and reduced FA in the right UF. Not only do the present results replicate the between-group differences in right UF FA in much larger groups of psychopathic and nonpsychopathic inmates, but they also demonstrate a significant link between right UF FA and psychopathy across virtually the entire spectrum of psychopathy severity. In addition, our findings highlight the neuroanatomical specificity of this relationship; we observed a significant inverse relationship between psychopathy and FA in right UF, but not in left UF or in neighboring white matter tracts. Moreover, this study offers a unique opportunity to determine whether this neurostructural characteristic relates to any specific dimensions of psychopathic personality.

Indeed, we found that reduced FA in the right UF was specifically related to the interpersonal traits of psychopathy (Factor 1/Facet 1), which include glib superficial charm, grandiose sense of self-worth, pathological lying, conning, and manipulativeness. It is noteworthy that these traits are unique to psychopathy, whereas the antisocial and lifestyle traits (Factor 2) are more generally characteristic of externalizing behavior, such as ASPD. Accordingly, the present results demonstrate a neurobiological marker of a specific and distinct dimension of psychopathic personality. To date, few studies have linked Factor 1 scores to structural neuroimaging measures. Factor 1 traits have been associated with decreased amygdala volume [Yang et al., 2009] and increased caudate volume [Glenn et al., 2010], although larger studies have not found consistent relationships between Factor 1 traits and regional gray matter volume [Cope et al., 2012; Ermer et al., 2012]. Our results suggest that Factor 1 traits may be underpinned partly by deficient fronto-temporal connectivity. This

assertion is consistent with the psychological and behavioral functions normally subserved by two key brain areas interconnected by the UF—the amygdala and ventromedial prefrontal cortex (vmPFC). This circuit is believed to underlie a host of social, cognitive, and affective functions relevant to psychopathy, such as moral judgment, empathy, aggression, value representation, and stimulus-reinforcement learning [Blair, 2007, 2008; Koenigs, 2012]. Tractography analyses could potentially help identify the specific neural connections within the UF that are most closely associated with particular psychopathic traits.

Although the current study data link psychopathic traits to right UF integrity, there are several caveats to bear in mind for the interpretation of these results. One caveat is that the observed relationships between psychopathy and right UF FA are strictly correlational; at present it is unclear whether reduced right UF FA is a cause or consequence of psychopathic behavior. Secondly, the psychopathic offenders in this study had elevated rates of substance use disorder relative to non-psychopathic offenders. Since drug abuse has been associated with white matter abnormalities, including reduced or increased FA [Bava et al., 2009; Schlaepfer et al., 2006; White et al., 2008] in certain tracts, we specifically considered the potential impact of substance use history on our main results. We observed a positive relationship between substance use history and whole-brain FA. Importantly, we found that the diagnosis of substance use disorder was not related to right UF integrity in any of the regression models. Finally, it is noteworthy that reduced UF FA has been observed in psychiatric disorders besides psychopathy. For example, reduced UF FA has been found in patients with generalized anxiety disorder [Tromp et al., 2012] as well as major depression [de Kwaasteniet et al., 2013]. This combination of results suggests that the integrity of the UF is related to some aspect (or aspects) of neuropsychological function that is germane to multiple types of social and affective disorders.

The ultimate challenge for future research will be to capitalize on these findings to generate more effective strategies for preventing, diagnosing, and treating psychopathy. If the brain-behavior relationship identified here reflects a distinct etiopathological mechanism for a specific cluster of psychopathic traits, then the development of interventions may benefit from targeting these traits separately. Furthermore, it is possible that neuroimaging measures could improve prognosis by supplementing the standard interview assessment of traits and behaviors [Aharoni et al., 2013].

In summary, here we have reported a novel relationship between the interpersonal features of psychopathy and reduced structural integrity of the UF. These results indicate a neural marker for a key dimension of psychopathic behavior.

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