White-matter tract abnormalities and antisocial behavior: A systematic review of diffusion tensor imaging studies across development

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Abstract
Antisocial behavior (AB), including aggression, violence, and theft, is thought to be underpinned by abnormal functioning in networks of the brain critical to emotion processing, behavioral control, and reward-related learning. To better understand the abnormal functioning of these networks, research has begun to investigate the structural connections between brain regions implicated in AB using diffusion tensor imaging (DTI), which assesses white-matter tract microstructure. This systematic review integrates findings from 22 studies that examined the relationship between white-matter microstructure and AB across development. In contrast to a prior hypothesis that AB is associated with greater diffusivity specifically in the uncinate fasciculus, findings suggest that adult AB is associated with greater diffusivity across a range of white-matter tracts, including the uncinate fasciculus, inferior fronto-occipital fasciculus, cingulum, corticospinal tract, thalamic radiations, and corpus callosum. The pattern of findings among youth studies was inconclusive with both higher and lower diffusivity found across association, commissural, and projection and thalamic tracts.

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1. Introduction

Antisocial behavior (AB), a complex behavioral phenotype that includes violence, aggression, and rule-breaking, is central to the psychiatric diagnoses of Antisocial Personality Disorder (APD) in adults and Conduct Disorder (CD) in youth. AB encapsulates a striking failure to respect the rights of others and conform to societal laws, and predicts a host of negative sequelae, including crime, substance use, and poor physical and mental health (Fergusson et al., 2005; Shaw and Gross, 2008). Moreover, AB is harmful and financially costly to victims, families, and communities (Scott et al., 2001). To improve the efficacy of prevention and treatment efforts, neuroimaging techniques have increasingly been applied to better understand the neural mechanisms underlying the etiology of AB.

1.1. Neural correlates of antisocial behavior

AB is characterized by impairments in affective processing, reduced capacity to learn from reward and punishment, heightened impulsivity, emotional dysregulation, and risk-taking (Blair, 2001; Byrd et al., 2014). AB is theorized to arise from dysfunction in brain areas linked to inhibitory and reward, including the orbitofrontal and ventromedial prefrontal cortices, as well as dysfunction in areas that process emotion and reward, including the orbitofrontal and ventromedial prefrontal cortices, as well as dysfunction in areas that process emotion and reward (Blair, 2001; Hyde et al., 2013). Functional magnetic resonance imaging studies support these theories by demonstrating decreased prefrontal cortex functioning during reward-based and reinforcement learning tasks among adults and youth with AB (Finger et al., 2011; Yang and Raine, 2009). Abnormal amygdala reactivity to threatening stimuli has also been established as a neural marker of AB (Coccaro et al., 2007; Hyde et al., 2014; Kiehl et al., 2001; Viding et al., 2012).

Together, these findings suggest that AB arises from dysfunction in a network of regions critical to emotion processing, reward, and learning (Blair et al., 2014; Kiehl et al., 2001). Thus, a better understanding of the neural underpinnings of AB may be gained by moving beyond a focus on regionally-specific activation to examine regional connections (Insel et al., 2010). In support of this idea, studies have reported reduced functional connectivity between prefrontal and limbic structures among adults and youth high on AB (Finger et al., 2012; Marsh et al., 2008; Mostkin et al., 2011). However, impairments in the functioning of networks may be the result of disruptions to the physical structures connecting different brain regions (Hyde et al., 2013). By investigating microstructural abnormalities in the white-matter tracts that connect brain regions, we may gain better understanding of the neurobiological basis of AB.

1.2. Diffusion tensor imaging (DTI)

Diffusion tensor imaging (DTI) is a non-invasive method that assesses water diffusion to index microstructural properties of white-matter tracts (Beaulieu, 2009; Winston, 2012). Specifically, DTI measures how freely water molecules can move within white-matter tracts based on microstructural features (e.g., fiber diameter, fiber density, and myelination) that restrict perpendicular diffusion and constrain water movement to certain directions. Tracts that force water molecules to move in the direction of the main orientation of fibers are often described as having higher microstructural “integrity” (Thomason and Thompson, 2011). To measure the diffusivity within white-matter tracts, studies compute fractional anisotropy (FA), which represents the ratio of diffusivity across different directions of the tract, ranging from 0 to 1 (Beaulieu, 2009; Winston, 2012) with higher FA values indexing lower diffusivity within tracts, which is interpreted as “greater integrity” (Basser et al., 1994; Thomason and Thompson, 2011). A second value of interest is mean diffusivity (MD), which represents the mean diffusion value across all directions of movement. Both FA and MD values are informed by axial diffusivity (AD) and radial diffusivity (RD) values. AD values represent longitudinal diffusion along the main fiber direction, with higher values thought to index lower diffusion, described as “greater integrity” (Buddde et al., 2009). Radial diffusivity (RD) values represent perpendicular diffusion of water, with higher values thought to index “reduced integrity” (Klawiter et al., 2011). Examining AD and RD in addition to FA or MD values may help to precisely pinpoint the nature of diffusion differences and thus microstructural white-matter differences.
1.3. DTI and antisocial behavior

To examine whether there are white-matter microstructural abnormalities related to AB, studies have typically employed region-of-interest (ROI) analyses that identify specific tracts a priori. In an ROI approach, DTI indices are extracted and averaged from regions defined using automated atlases (Mori et al., 2005) or via manual dissection of specific tracts, allowing values to be compared across subjects. Based on the findings of functional and structural imaging studies, DTI studies adopting a ROI approach have focused on the uncinate fasciculus (UF), an association tract that connects the amygdala and prefrontal regions (Pandya et al., 2015). However, the link between AB and altered white-matter microstructure of the UF has not been consistently replicated, with studies reporting lower FA, no difference in FA, or higher FA among individuals high on AB relative to healthy controls (e.g., Finger et al., 2012; Motzkin et al., 2011; Passamonti et al., 2012).

One possible explanation for this mixed picture in the direction of findings centers on the type of sample examined. In particular, the presence of psychopathic traits represents a potential moderator of effects. Psychopathic traits identify adults with more severe and violent forms of AB, as well as deficits in empathy and guilt, and a callous interpersonal style (Patrick, 2007). Similarly, callous-unemotional (CU) traits identify children with AB who show empathy and guilt deficits, reduced concern for others, and particularly severe AB across the lifespan (Frick and White, 2008). Previous research has established divergent patterns of amygdala reactivity and affective processing contingent on the level of psychopathic or CU traits, such that individuals high on AB and psychopathic/CU traits exhibit reduced threat responsiveness, whereas those high on AB without concurrent psychopathic/CU traits show exaggerated threat-related responses (Blair et al., 2014; Hyde et al., 2014). These functional differences suggest there could also be divergence in white-matter microstructural abnormalities in tracts connecting the amygdala with prefrontal regions. Among forensic samples, there are also high rates of psychopathy, which could account for the mixed pattern of findings noted between AB and FA in the UF. However, this question has yet to be systematically explored within a review. A second factor that could affect the direction of findings across DTI studies of AB is age, especially given increases in FA within white-matter tracts that become evident during early adulthood (Westlye et al., 2009). Thus, it is crucial to consider the influence of age when evaluating DTI studies of AB. A third factor that could explain mixed findings is analytic approach. In contrast to the ROI-based approaches described above, whole-brain voxel-based approach methods, including tract-based spatial statistics (TBSS), register DTI values into a common space and use voxel-wise statistical analytic methods to examine differences across the whole brain (e.g., Bach et al., 2014). Interestingly, when studies have adopted whole-brain approaches, they typically report white-matter microstructural differences in many other tracts beyond the UF in both adult (Sundram et al., 2012) and youth samples (Haney-Caron et al., 2014). Given the prevailing view in the field that the UF is specifically critical to the development of AB (e.g., Craig et al., 2009), a review is needed to evaluate whether the mixed findings arise because of differences in methodology (i.e., ROI vs. whole-brain approach) and whether or not AB is marked by specific deficits in the microstructure of the UF.

1.4. Current review

This systematic review evaluated findings from DTI studies of AB among both youth and adult samples. Our goal was to examine links between AB and the microstructure of association pathways (i.e., tracts connecting structures within the cerebral cortex within the same hemisphere), with a focus on tracts connecting frontal and temporal lobe regions implicated in functional and structural imaging studies of AB. We also evaluated evidence from studies examining white-matter microstructural abnormalities in commissural pathways (i.e., connecting similar regions across hemispheres) and projection and thalamic pathways (i.e., connecting cortical and subcortical structures). Our second aim was to examine the influence of sample age on findings and whether abnormalities in white-matter were specific to individuals high on psychopathy or CU traits. Finally, we evaluated whether method (ROI vs. whole-brain) coincided with the identification of specific versus widespread white-matter microstructural differences in tracts. Finally, because research demonstrates that other DTI indices beyond FA capture more specific microstructural abnormalities, we included results for AD, RD, and MD values when reported by studies to aid in the interpretation of findings.

2. Methods

2.1. Study selection

We included peer-reviewed, empirical studies published in English that examined associations between AB, psychopathy, and/or CU traits, and DTI measures of brain white-matter tracts. To capture a narrow behavioral phenotype, we excluded studies where participants were recruited based on criteria that did not specifically assess AB (i.e., excluding studies that assessed aggression arising in the context of another disorder). Thus, we excluded studies where the primary inclusion criterion was a diagnosis of ADHD (but see van Ewijk et al., 2012 for a systematic review of white-matter tract abnormalities in ADHD), schizophrenia (Hopman et al., 2002), alcohol/substance use and dependence (Thayer et al., 2013), and bipolar disorder (Saxena et al., 2012). Online searches were performed in the databases OVID (Medline), EMBASE, EBSCO (PsycINFO, PsycARTICLES, Child Development & Adolescent studies, Criminal Justice Abstracts, and Violence & Abuse Abstract), and NCBI (PubMed) on April 4th 2016. We used search terms relating to AB, focusing on a wide range of terms to capture similar constructs across domains, including criminology (e.g., delinquency; crime; violence), psychiatry (e.g., APD; CD; psychopathy), and developmental psychopathology (e.g., aggression; CU traits). Thus, the search was sensitive to studies that assessed clinical diagnoses of childhood CD and adult APD, as well as continuous behavior scales. We combined terms assessing AB or CU traits/psychopathy with those assessing DTI (see Supplemental Table 1 for search terms used).

3. Results

3.1. Retrieved studies

The flow of studies through the screening is summarized in Fig. 1. We identified 456 publications, of which 117 were duplicates. After removing duplicates, we screened 339 reports, 300 of which were excluded based on title or abstract. Full texts of the remaining 39 reports were screened in detail; 17 were excluded, most commonly for the following reasons: (1) no measure of AB, (2) structural MRI only (i.e., no DTI), and/or (3) not published in a peer-reviewed journal (i.e., conference proceedings) (Supplemental Table 2 summarizes why studies were excluded at this stage). Twenty-two publications that met inclusion criteria were included in the review (Fig. 1).

3.2. Sample, methodological, and analytic features of included studies

3.2.1. Sample types

Of the ten adult studies, the majority compared forensic samples to community samples of men only. Exceptions were two studies of community and high-risk males (Beyer et al., 2014; Sobhani et al., 2015), one study of a community sample with equal numbers of men and women (Karlsdot et al., 2015), and one study of clinic-referred women who were compared to controls drawn from the community (Lindner et al., 2016) (Table 1). Of the 12 studies of youth, 11 assessed community samples or children at risk for AB, and 1 assessed a forensic sample. Youth were almost exclusively assessed during mid-to-late adolescence (e.g., 14–18), with the exception of one study that assessed...
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### 3.2.2. DTI approach

DTI measures can be extracted using tractography or voxel-wise whole-brain analysis. First, tractography involves the construction of fiber trajectories and connection patterns based on the successive orientations associated with adjacent voxels. Defining the points or “seeds” to begin fiber construction (e.g., seeding) can be determined using an ROI approach (placing of seeds in ROIs that are manually drawn or extracted automatically) or using a whole-brain approach (e.g., automatic seeding for the whole brain) (Cercignani, 2010; Jones et al., 2013; Soares et al., 2013). Tractography itself is divided into deterministic versus probabilistic tractography, with the former tracking fiber, and the latter estimating probability maps based on the possibility of multiple fibers passing through one voxel. Second, DTI can be analyzed using voxel-wise whole brain analysis, such as voxel-based analysis (VBA) or TBSS, which involve the registration of DTI maps into standard space to allow for the comparison of diffusion parameters of voxels between subjects by ensuring anatomical correspondence among subjects (for fuller descriptions of these different DTI methodologies, see Cercignani, 2010; Jones et al., 2013; Soares et al., 2013).

Across included studies, six of the 10 adult studies and 5 of 12 youth studies adopted an ROI-only approach (Tables 1 and 2). Of the six adult studies that used an ROI-only approach, three studies utilized automated methods to identify ROIs, while three studies analyzed manually-dissected tracts. Four of the adult ROI studies used deterministic tractography, one used TBSS, and one used both deterministic tractography and a voxel-based approach. Of the five youth studies that used an ROI-only approach, four used automated methods to identify ROIs, while one study analyzed manually-dissected tracts. Two of the ROI studies in youth used deterministic tractography, two used TBSS, and one used both deterministic tractography and an alternate voxel-based approach. In addition, four of 10 adult studies and 4 of 12 youth studies adopted whole-brain approaches. Of the four whole-brain adult studies, three used TBSS, while one used an alternate voxel-based approach. Of the four youth studies that used a whole-brain only approach, three used TBSS, and one study used an alternate voxel-based approach. Finally, three youth studies combined both ROI- and whole-brain approaches (Tables 1 and 2).

### 3.2.3. Measurement approach

Three adult studies examined associations using only a case-control approach (e.g., classifying individuals as being high AB/high psychopathy vs. healthy controls). Three studies examined associations dimensionally (i.e., the extent to which individual differences in AB covaried with differences in DTI measures) and four studies adopted both dimensional and case-control approaches. Adult studies examined self-report- or interview-assessed or self-reported psychopathy. Items assessing psychopathy were often summed to create a total psychopathy score, but were also examined as subscales reflecting separable factors within the psychopathy construct (Hare, 2006; Table 1). Thus, studies distinguished between subscales assessing deficits in affective and interpersonal traits (e.g., callousness, low interpersonal affiliation; “Factor 1”) versus the harmful, antisocial behaviors associated with psychopathy (e.g., impulsivity, deviant lifestyle, violence; “Factor 2”) (Hare, 2006). Five youth studies examined associations with DTI measures using a case-control approach only; two youth studies examined associations using a dimensional approach only. Five youth studies used both case-control and dimensional approaches. Youth studies most commonly employed self-reported, parent-reported, or teacher-reported measures of AB, aggression, or other forms of externalizing behavior problems, as well as measures of psychopathic or CU traits (Table 2).

### 3.3. Aim 1: is AB related to brain white-matter tract abnormalities measured by DTI?

To aid in the interpretation of findings, we present the results of studies within three broad tract classifications: association, commissural, and projection and thalamic pathways. Within these classifications, we separate by adult versus youth findings. Because of heterogeneity in methods, sample types, and analytic approaches across studies, we
### Table 1
Summary of sample characteristics and main findings for studies examining AB and white-matter tract abnormalities in adults measured by DTI.

| Study                          | N  | Type | Key criteria or covariates | Behavioral measures: dimensional or categorical analysis | Method          | Key findings                                                                 |
|-------------------------------|----|------|----------------------------|----------------------------------------------------------|-----------------|-------------------------------------------------------------------------------|
| Beyer et al., 2014            | 93 | 1    | Exclusions: other psychiatric or neurologic disorder, Covariates: | AB: Buss Perry Aggression (S) & Taylor Aggression Paradigm (O) | ROI-A: (DT)     | Dimensional: no significant associations                                      |
| Craig et al., 2009            | 18 | 1 & 4 | Exclusions: other psychiatric or neurologic disorder, psychotropic medication Covariates: IQ & age-matched HC | AB: male offenders from specialist forensin inpatient units Psychopathic traits: PCL-R (I) | ROI-M: (DT)     | Categorical: AB + P+ vs. HC; FA right UF. No significant differences          |
| Hoppenbrouwers et al., 2013   | 22 | 1 & 4 | Exclusions: other psychiatric or substance use disorders, head trauma, seizures Covariates: age-matched male HC | AB: male offenders convicted for assault, homicide, human trafficking, & kidnap Psychopathic traits: PCL-R (I) | Whole-brain (TBSS) | Dimensional: interpersonal-affective: FA left UF, IFOF, & ATR; Lifestyle-antisocial: FA right ATR, UF, & IFOF |
| Karlsgodt et al., 2015        | 45 | 1 & 46 | Exclusions: Axis I disorder Covariates: age & gender Exclusions: bipolar disorder, psychosis, neurologic disorder Covariates: Axis I disorders, physical & sexual abuse | AB: Buss Perry Aggression (S) | Whole-brain (TBSS) | Categorical: AB + P vs. HC; FA left right SFL                                      |
| sundram et al., 2016          | 67 | 1 & 3 | Exclusions: other psychiatric or substance use disorders, head trauma, reading age < 10 Covariates: alcohol & cocaine dependency | AB: SCID-I | Whole-brain (TBSS) | Categorical: AB + vs. HC; AD bilateral corpus callosum, CG, Fmin, and IFOF, and left CR (controlling for depression, anxiety, substance dependence and experience of abuse) AB + vs. clinical comparison; FA left cortical callosum, forceps minor |
| Motzkin et al., 2010          | 27 | 4    | Exclusions: age > 45, IQ < 70, history of psychosis & psychotropic medication Covariates: | AB: Adult male inmates at a medium-security correctional facility Psychopathic traits: PCL-R (I) | ROI-A: (VBA & DT) | Categorical: AB + P vs. AB + P--; FA right UF (relative to overall reduction in whole brain FA). No significant differences in SLF, IFOF, IFOF |
| Sethi et al., 2015            | 26 | 3    | Exclusions: other psychiatric or substance use disorders, head trauma, reading age < 10 Covariates: alcohol & cocaine dependency | AB: Offenders incarcerated for violent crime Psychopathic traits: PCL-R (I) | ROI-M: (DT)     | Dimensional: interpersonal-affective: FA left & right dorsal CG |
| Sobhani et al., 2015          | 24 | 1 & 2 | Exclusions: other psychiatric or neurologic disorder Covariates: IQ, age | Psychopathic traits: Current (age 24): Psychopathic Personality Index (PPI), Prior (age 14–15): CPS, APSD, PCL:YV to form composite score | ROI-M: (DT)     | Dimensional: current PPI score psychopathy scores and prior psychopathy composite score: FA right UF |
| Sundram et al., 2015          | 30 | 1 & 4 | Exclusions: other psychiatric or neurologic disorder Covariates: age & IQ-matched HC | AB: ICD-10 ASPD diagnosis (I) | Whole-brain (VBA) | Dimensional: Total PCL-R & Lifestyle-Antisocial factor: FA in frontal lobe. Lifestyle-Antisocial factor: MD in frontal lobe. Categorical: AB + P vs. HC; FA bilateral CC, IC, IFOF, right ACR, right UF, left IF, right PTR. MD right IFOF, UF, CC, & ACR |
| Wolf et al., 2015             | 147| 1 & 4 | Exclusions: IQ < 70; psychotropic medication; psychiatric disorder; head trauma Covariates: age, race, substance use disorder | AB: Adult male inmates at a medium-security correctional facility Psychopathic traits: PCL-R (I) | ROI-A: (TBSS)   | Dimensional: total psychopathy scores: FA right UF (no association with left UF & unrelated to comparison tracts, CC, IC, TR, fR CC & whole-brain FA); Interpersonal-affective factor: FA right UF (controlling for Factor 2). Interpersonal Facet: FA right UF |

Note that we report findings from the most stringent analyses carried out by included studies, including models controlling for multiple comparisons or overlap of outcome variables. Type of sample: 1 = community; 2 = high-risk; 3 = clinic; 4 = forensic. DTI acronyms: ACR = anterior corona radiata; AD = axial diffusivity; ATR = anterior thalamic radiation; CC = corpus callosum; CG = cingulum/cingulate gyrus; CT = corticospinal tract; Fmaj = forceps major; Fmin = forceps minor; FA = fractional anisotropy; IC = internal capsule; IFOF = inferior fronto-occipital fasciculus; IFOF = inferior longitudinal fasciculus; PTR = posterior thalamic radiation; RD = radial diffusivity; SCR = superior corona radiata; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus. Categorical findings based on studies adopting a case-control versus dimensional approach, although these distinctions are summarized in full in Tables 1–3.

3.4. Association pathways

3.4.1. Uncinate fasciculus (UF)

The UF reciprocally connects structures in the frontal lobe, including the cingulate gyrus, frontal pole, and orbitofrontal cortex, to structures in the temporal lobe, including the amygdala and temporal pole (Leng et al., 2016).

3.4.1.1. Adults. Six of nine studies of adults reported that AB was related to white-matter microstructural differences in the UF, and specifically to greater diffusivity. Three studies reported non-significant findings.

Using a case-control design, adults high on AB and psychopathy had lower FA in the right UF (Craig et al., 2009; Sundram et al., 2012), higher MD in the right UF (Sundram et al., 2012), and lower FA bilaterally in UF (Hoppenbrouwers et al., 2013) compared to healthy controls. Adults with high AB and psychopathy also showed lower FA in the right UF.
Table 2
Summary of sample characteristics and main findings for studies examining AB and white-matter tract abnormalities in youth measured by DTI.

| Study | N | Type & age | %P | Exclusion criteria or covariates | Behavioral measures | Method | Key findings |
|-------|---|------------|----|---------------------------------|--------------------|--------|--------------|
| Breeden et al., 2015 | 47 | 1 | M (SD) = 14 (3) | 47 Exclusions: IQ < 80 Covariates: age & IQ | AB: SDQ & CRCL (P) Psychopathic/CU traits: ICU (PC) | ROI-A: (TBSS) | Dimensional: CU traits; ↓ FA bilateral UF, & right fornix, controlling for overlapping externalizing and similar when examining only within AB+ group AB: No associations found controlling for CU traits Categorical: AB+ vs. HC: ↓ FA right UF, left fornix; AB+ + CU+ vs. HC: ↓ FA bilateral UF, bilateral fornix; AB+ + CU+ vs. AB− + CU−: no significant differences |
| Decety et al., 2015 | 110 | 1 & 2 | M (SD) = 10 (1) | 52 Exclusions: developmental disorder, head trauma Covariates: age, gender & race (also explored as moderators) | AB: DISC (P&S) | Whole brain (TBSS) | AB− vs. subAB: no significant differences subAB + vs. HC: no significant differences AB+ vs. HC: no significant differences but gender & race interactions (AD & RD) - regions comparable to above |
| Finger et al., 2012 | 31 | 1 & 3 | M (SD) = 14 (2) | 10 Exclusions: psychiatric or neurological disorder, head trauma, IQ < 80 Covariates: age, IQ | AB: KSADS DSM-IV (I) Psychopathic/CU traits: ASPD (P) & PCL-YV (I) | Whole brain (VBA) & ROI-A: (DT) | Categorical: AB+ vs. HC: no significant differences |
| Haney-Caron et al., 2014 | 41 | 1 & 2 | M (SD) = 16 (1) | 39 Exclusions: any other psychiatric disorder Covariates: gender, CD age of onset, & IQ | AB: KSADS DSM IV (I) | Whole brain: (TBSS) | Dimensional: CD symptoms: ↓ FA right ACC, bilateral SCR, & left CC & PCC; ↑ FA bilateral ATR similar controlling for CD onset age, gender, & IQ |
| Hummer et al., 2015 | 66 | 1 | M (SD) = 14 (1) | 27 Covariates: Age (also examined as moderator) | AB: KSADS DSM-IV (I) | ROI-A: (TBSS) | AB+ vs. HC: ↓ FA bilateral UF; ↓ FA left UF; ↓ FA left ATR; ↑ FA left ACR; ↑ FA left CC; ↓ FA left IFOF; ↓ FA left ILF; ↓ FA right CC; ↓ FA right IFOF; ↓ FA right ILF; ↓ RD bilateral UF; ↓ RD bilateral IFOF; ↓ RD bilateral ILF; ↓ RD left CC; ↓ RD left IFOF; ↓ RD left ILF |
| Li et al., 2005 | 76 | 1 | M (SD) = 14 (1) | 39 Exclusions: HC: no psychiatric disorder Covariates: age | AB: KSADS DSM-IV (I) | Whole brain: (VBA) | Dimensional: CU traits: ↓ FA bilateral CT Grandiose-manipulative traits: ↑ FA and ↓ RD bilateral ATR, CT, Fmin, IFOF, UF, CC, ↓ RD bilateral CC, Fmaj, SLF & RD left IFOF; ↓ RD left ILF |
| Pape et al., 2015 | 145 | 4 | M (SD) = 18 (2) | 14 Covariates: age & IQ | Psychopathic/CU traits: YPI (S) | Whole brain (TBSS) | Dimensional: CU traits: ↓ FA bilateral CT Grandiose-manipulative traits: ↑ FA and ↓ RD bilateral ATR, CT, Fmin, IFOF, UF, CC, ↓ RD bilateral CC, Fmaj, SLF & RD left IFOF; ↓ RD left IFOF; ↓ RD left CC; ↓ RD left SCR; ↓ RD left ATR |
| Passamonti et al., 2012 | 26 | 1 & 2 | M (SD) = 18 (1) | 0 Exclusions: developmental disorder, physical illness, IQ < 80; HC with IQ > 115 Covariates: ADHD | AB: KSADS DSM IV (I) Psychopathic/CU traits: YPI (S) | Whole brain (VBA) & ROI-M (DT) | Dimensional: CU traits: ↓ FA bilateral CT Grandiose-manipulative traits: ↑ FA and ↓ RD bilateral ATR, CT, Fmin, IFOF, UF, CC, ↓ RD bilateral CC, Fmaj, SLF & RD left IFOF; ↓ RD left IFOF; ↓ RD left CC; ↓ RD left SCR; ↓ RD left ATR |
| Peper et al., 2015 | 258 | 1 | M (SD) = 14 (3) | 52 Exclusions: neurological, psychiatric or endocrine illness. Covariates: age | AB: Buss Perry Aggression (S) | ROI-A (DT) | Dimensional: Age: ↑ FA overall Verbal aggression: ↑ MD temporal-temporal Hostility: ↑ MD in subcortical-temporal & temporal-temporal Dimensional: SDQ (total & conduct problem scales); ↑ FA bilateral UF; APSP (total & CU traits scales); ↑ FA bilateral UF |
| Sarkar et al., 2013 | 43 | 1 & 2 | M (SD) = 16 (2) | 0 Exclusions: IQ < 80 Covariates: age | AB: KSADS DSM IV (I), SDQ (P&S) Psychopathic/CU traits: PCL-YV (I) & APSD (P&S) | ROI-M: (DT) | Dimensional: SDQ (total & conduct problem scales): ↑ FA bilateral UF; APSP (total & CU traits scales): ↑ FA bilateral UF Categorical: AB+ vs. P+ + HC: ↑ FA left UF |
| Zhang et al., 2014b | 69 | 1 & 3 | M (SD) = 15 (1) | 0 Exclusions: psychiatric disorder, head trauma, past year substance abuse, IQ ≤ 80 | AB: SCID DSM IV (I), SDQ & BIS (S) Psychopathic/CU traits: APSD (S) | Whole brain (TBSS) & ROI-A (DT) | Dimensional: CU traits: ↓ FA bilateral CC, left ACR, right SCR; ↓ RD bilateral CC, left ACR |
| Zhang et al., 2014a | 56 | 1 & 3 | M (SD) = 14 (1) | 46 Exclusions: psychiatric disorder, substance use, head trauma, IQ ≤ 80 Covariates: gender tested as moderator | AB: SCID DSM IV (I) & SDQ (S) | Categorical: AB+ vs. HC: no significant differences |

Note that we report findings from the most stringent analyses carried out by included studies, including models controlling for multiple comparisons or overlap of outcome variables.

Type of sample: 1 = community; 2 = high-risk; 3 = clinic; 4 = forensic.

DTI acronyms: ACR = anterior corona radiata; AD = axial diffusivity; ATR = anterior thalamic radiation; CC = corpus callosum; CG = cingulum/cingulate gyrus; CT = corticospinal tract; Fmaj = forceps major; Fmin = forceps minor; FA = fractional anisotropy; IC = internal capsule; IFOD = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; PFR = posterior thalamic radiation; RD = radial diffusivity; SCR = superior corona radiata; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus.

Behavior acronyms: AB = antisocial behavior; CU = callous-unemotional; P = psychopathy; S = self-reported; P = parent-reported; I = structured interview.

Behavior groupings: AB + P+ = high on AB and psychopathy; AB + P− = high on AB and low on psychopathy; AB + CU + = high on AB and callous-unemotional traits; HC = healthy controls.

DTI method acronyms: DT = deterministic tractography; ROI-A = region of interest automatic generation; ROI-M = region of interest, manually drawn; TBSS = tract-based spatial statistics; VBA = voxel based analyses.
Table 3
Summary of DTI findings by tract across studies youth and adults.

| Tract and Description | Diagram of tracts | Adult findings | Youth findings |
|-----------------------|-------------------|----------------|----------------|
| **Association pathways** |                   |                |                |
| Cingulum (CG): Connects frontal & temporal lobes, cingulate & medial gyri of frontal, parietal, occipital, & temporal lobes | ![Diagram](image1.png) | Greater diffusivity | Greater diffusivity |
|                        |                   | FA bilateral CG: interpersonal-affective traits (Sethi et al., 2015), AB + P+ vs. HC (Hoppenbrouwers et al., 2013) | AB + vs. HC (Haney-Caron et al., 2014) |
|                        |                   | AD bilateral CG: AB + P+ vs. HC (Sethi et al., 2015) | Lower diffusivity |
| Inferior fronto-occipital fasciculus (IFOF): Connects temporal lobe (medially) & frontal lobe (inferiorlally) | ![Diagram](image2.png) | Greater diffusivity | Greater diffusivity |
|                        |                   | FA bilateral IFOF: AB + P+ vs. HC (Hoppenbrouwers et al., 2013; Sundram et al., 2012) | FA bilateral IFOF: CD symptoms, AB + vs. HC (Haney-Caron et al., 2014) |
|                        |                   | FA left IFOF: Interpersonal-affective traits (Hoppenbrouwers et al., 2013) | AD bilateral IFOF: AB + vs. HC (Haney-Caron et al., 2014) |
|                        |                   | FA right IFOF: Lifestyle-antisocial traits (Hoppenbrouwers et al., 2013) | Lower diffusivity |
|                        |                   | MD right IFOF: AB + P+ vs. HC (Sundram et al., 2012) | FA & RD bilateral IFOF: psychopathic traits (Pape et al., 2015) |
| Inferior longitudinal fasciculus (ILF): connects temporal pole & occipital pole | ![Diagram](image3.png) | Greater diffusivity | Greater diffusivity |
|                        |                   | FA left ILF: AB + P+ vs. HC (Sundram et al., 2012) | FA bilateral ILF: CD symptoms, AB + vs. HC (Haney-Caron et al., 2014) |
| Superior longitudinal fasciculus (SLF): connects frontal lobe & parietal, occipital, & temporal lobes | ![Diagram](image4.png) | Greater diffusivity | Greater diffusivity |
|                        |                   | FA & RD right SLF: aggressive acts (Karls godt et al., 2015) | RD right SLF: CD symptoms (Decety et al., 2015) |
| UF = uncinate fasciculus (UF): connects temporal pole & orbitofrontal cortex. | ![Diagram](image5.png) | Greater diffusivity | Greater diffusivity |
|                        |                   | FA bilateral UF: AB + P+ vs. HC (Hoppenbrouwers et al., 2013) | FA bilateral UF: CU traits, AB + CU+ vs. HC (Breeden et al., 2015) |
|                        |                   | FA right UF: psychopathy (Wolf et al., 2015; Sobhani et al., 2015), interpersonal-affective traits (Wolf et al., 2015) & lifestyle-antisocial (Hoppenbrouwers et al., 2013), AB + P+ vs. HC (Craig et al., 2009; Sundram et al., 2012), AB + P+ vs. AB + P (Motzkin et al., 2011) | FA right UF: AB + CU- vs. HC: (Haney-Caron et al., 2015) |
|                        |                   | FA left UF: lifestyle-antisocial (Hoppenbrouwers et al., 2013) | AD bilateral UF: AB + vs. HC (Haney-Caron et al., 2014) |
|                        |                   | AB + P+ vs. HC: FA right UF (Craig et al., 2009; Sundram et al., 2012), MD right UF: AB + P+ vs. HC (Sundram et al., 2012), MD right UF: AB + P+ vs. HC (Haney-Caron et al., 2014) | FA bilateral UF: behavior problems: (Sarkar et al., 2013), psychopathic traits (Sarkar et al., 2013) |
|                        |                   |                             | FA & RD bilateral UF: psychopathic traits (Pape et al., 2015) |
|                        |                   |                             | FA left UF: AB + P+ vs. HC: (Sarkar et al., 2013); FA, AD, & RD bilateral UF: AB + vs. HC (Passamonti et al., 2012) |
|                        |                   |                             | RD & MD right UF: CU traits (Zhang et al., 2014a) |
| Commissural pathways |                   | Greater diffusivity | Greater diffusivity |
| Corpus callosum (CC), forceps major (Fmaj) & forceps minor (Fmin): Connects cerebral hemispheres: anterior (Fmin) & posterior (Fmaj) | ![Diagram](image6.png) | AD bilateral CC & Fmin: AB + vs. HC & clinical comparison (Lindner et al., 2016) | AD left CC: CD symptoms (Haney-Caron et al., 2014) |
|                        |                   | MD right CC: AB + P+ vs. HC: (Sundram et al., 2012) | AD bilateral CC & Fmin: AB + vs. HC (Haney-Caron et al., 2014) |
|                        |                   | AD bilateral CC & Fmin: AB + vs. HC (Sundram et al., 2012) | Lower diffusivity |
|                        |                   | AD bilateral CC & Fmin: AB + vs. HC (Haney-Caron et al., 2014) | FA & RD bilateral CC & Fmin: psychopathic traits (Pape et al., 2015), AB + vs. HC (Zhang et al., 2014b) |
|                        |                   | AD right CC & Fmin: CD symptoms (Decety et al., 2015) | AD right Fmin: CD symptoms (Decety et al., 2015) |
|                        |                   | AD bilateral CC & Fmin: psychopathic traits (Pape et al., 2015) | RD Fmin: psychopathic traits (Pape et al., 2015) |

(continued on next page)
compared to adults with high AB without psychopathy (Motzkin et al., 2011). Dimensionally, lower FA in the right UF was related to higher psychopathy total scores (Sobhani et al., 2015; Wolf et al., 2015), as well as higher subscale scores for interpersonal-affective (Wolf et al., 2015) and lifestyle-antisocial (Hoppenbrouwers et al., 2013) traits.

3.4.1.2. Youth. Six out of 11 studies reported that AB was significantly related to white-matter microstructural abnormalities of the uncinate fasciculus (UF), although in mixed directions. Youth with AB were reported to show higher FA in the UF compared to healthy controls (Passamonti et al., 2012). Higher FA in the UF was also related to more reported to show higher FA in the UF compared to healthy controls (Sundram et al., 2012). However, two studies reported the opposite pattern in terms of tract diffusivity: within a case-control design, youth with high AB had lower FA in the right UF (Zhang et al., 2014a). Finally, within a subsample of boys with CD, CU traits were related to lower RD in the right UF compared to healthy controls (Haney-Caron et al., 2014). Dimensionally, higher CU traits were uniquely related to lower FA bilaterally in the UF, after accounting for these studies, only two studies adopting a whole-brain approach identified significant relationships between AB and white-matter microstructure of the cingulum, IFOF, and ILF. However, the direction of the findings of these two studies was contrasting. Haney-Caron et al. (2014) found AB to be associated with lower FA, while Pape et al. (2015) reported higher FA in the UF compared to healthy controls (Haney-Caron et al., 2014). Dimensionally, higher CU traits were higher on AB also showed lower AD in the UF compared to healthy controls (Haney-Caron et al., 2014).

3.4.2. Cingulum, inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF)

In addition to the UF, AB was linked to abnormal white-matter microstructure in other association tracts, including the cingulum, inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF) (Table 3). The cingulum, SLF, and ILF connect regions within the limbic system, including the posterior cingulate, medial prefrontal cortex, and medial temporal lobe (Teipel et al., 2010). Additionally, the ILF and IFOF share projections at the posterior temporal and occipital lobes and connect visual association areas of the occipital lobe, auditory and visual association areas, and prefrontal cortex (Catani et al., 2013). Disconnection of the ILF has been linked to impaired communication between the occipital and temporal lobes, including the amygdala (Fox et al., 2008).

3.4.2.1. Adults. Eight studies investigated white-matter microstructure within association pathways, with four studies utilizing a whole-brain approach, two studies using ROIs for the SLF, ILF, and IFOF, and two studies using an ROI of the cingulum. In general, AB and psychopathy were associated with greater diffusivity in white-matter tracts, indexed by lower FA in the cingulum (Hoppenbrouwers et al., 2013; Sethi et al., 2014), IFOF (Hoppenbrouwers et al., 2013; Sundram et al., 2012), ILF (Sundram et al., 2012), and SLF (Karlsfogd et al., 2015). Additionally, AB and psychopathy was associated with higher MD in the IFOF (Sundram et al., 2012) and aggression was associated with higher RD in the SLF (Karlsfogd et al., 2015). Finally, women with CD had lower AD in the cingulum and IFOF compared to healthy controls (Lindner et al., 2016) (Tables 1 & 3).

3.4.2.2. Youth. Eight youth studies investigated white-matter microstructural abnormalities in association pathways beyond the UF. Of these studies, only two studies adopting a whole-brain approach identified significant relationships between AB and white-matter microstructure of the cingulum, IFOF, and ILF. However, the direction of the findings of these two studies was contrasting. Haney-Caron et al. (2014) found AB to be associated with lower FA, while Pape et al.
(2015) found AB to be associated with higher FA and AD, as well as lower RD. For the SLF specifically, four studies reported white-matter microstructural differences among youth with AB, but again in contrasting directions with two studies finding AB to be associated with higher FA in the SLF (Haney-Caron et al., 2014; Liu et al., 2005), but another reporting lower RD in the SLF (Pape et al., 2015). Interestingly, one study found evidence in both directions, reporting higher RD and higher AD of the right SLF (Decety et al., 2015) (Table 2).

3.5.2. Summary of commissural pathways
Among adults, two of four whole-brain studies reported that individuals with high AB showed disrupted white-matter microstructure bilaterally in the corpus callosum. Among youth, findings were mixed with three of seven studies reporting that AB and psychopathic traits were related to higher FA, higher AD, or lower RD in the corpus callosum, but one study reporting that AB was related to lower FA and AD of the corpus callosum, and forceps minor and major (Table 3).

3.6. Projection & thalamic pathways
3.6.1. Fornix
The fornix is one of the main tracts connecting the hippocampus with other subcortical regions, including the anterior nuclei of the thalamus and contralateral hippocampus.

3.6.1.2. Youth
One youth study adopting an ROI approach reported that AB was related to white-matter microstructural differences in the fornix. Within a case-control design, youth with high AB had lower FA in the fornix when compared to healthy controls. Dimensionally in the same study, higher CU traits were specifically related to lower FA in the right fornix, controlling for AB (Breeden et al., 2015).

3.6.2. Corticospinal tract, internal and external capsules, peduncle, and corona radiata
The corticospinal tract represents the major descending pathway for motor function connecting the motor cortex to the spinal cord, which converges on the internal and external capsules and peduncle, and passes through the corona radiata (Jang, 2011).

3.6.2.1. Adults
Two of four adult studies that used whole-brain approaches reported greater diffusivity in projection pathways originating with the corticospinal tract, while the others reported null findings. First, Sundram et al. (2012) found that men with AB and psychopathy had lower FA in the internal capsule and right anterior corona radiata compared to healthy controls. Second, women with CD had lower AD in the left corona radiata compared to healthy controls, notably at the intersection with the IFOF (Lindner et al., 2016).

3.6.2.2. Youth findings
Five of seven studies of youth that used whole-brain approaches reported abnormal white-matter microstructure in projection pathways originating with the corticospinal tract, with four studies reporting lower diffusivity in these tracts. Using a case-control design, youth with AB showed higher FA, higher AD, and lower RD in the right external capsule (Passamonti et al., 2012), higher FA in the right superior corona radiata (Zhang et al., 2014b), and higher FA and lower RD in the left anterior corona radiata (Zhang et al., 2014b) when compared to healthy controls. Examined dimensionally, CD symptoms were related to higher AD in the left corticospinal tract and right superior corona radiata (Decety et al., 2015), and psychopathic traits were related to higher FA and AD and lower RD in the corticospinal tract (Pape et al., 2015). In contrast, one study reported that CD was related to lower FA in the right anterior corona radiata, bilateral superior corona radiata, and left posterior corona radiata (Haney-Caron et al., 2014) (Tables 2 & 3).

3.6.3. Anterior and posterior thalamic radiations
Thalamic radiations extend from different nuclei of the thalamus and project to visual, somatosensory, and visual cortices via the peduncle and internal capsule. Portions of the posterior thalamic radiation of
the internal capsule connect fibers of the optic radiation and are involved in the visual system (Sherbundy et al., 2008). Physical disruption of these networks is thought to affect the detection and processing of facial expressions of emotion, which is compromised in individuals high on AB (Marsh and Blair, 2008).

3.6.3.1. Adults. Two of five studies reported greater diffusivity in white-matter tracts in thalamic radiations, and two studies reported null findings (see Table 3). Within a case-control design, adults high on AB and psychopathy showed lower FA in the anterior thalamic radiation (Hoppenbrouwers et al., 2013) and in the left posterior thalamic radiation (Sundram et al., 2012) relative to healthy controls. Dimensionally, higher interpersonal-affective scores were related to lower FA in the left anterior thalamic radiation, and higher lifestyle-antisocial scores were related to lower FA in the right anterior thalamic radiation (Hoppenbrouwers et al., 2013).

3.6.3.2. Youth. Of seven studies of youth adopting whole-brain approaches, two studies reported that AB was associated with lower diffusivity of the anterior thalamic radiation. CD symptoms were associated with higher FA in the anterior thalamic radiation (Haney-Caron et al., 2014) and psychopathic traits were related to higher FA and lower RD in the anterior thalamic radiation (Pape et al., 2015).

3.6.4. Summary of projections and thalamic pathways

Among adults, there was some consistency across studies reporting AB to be related to greater diffusivity in projection and thalamic pathways, indexed via lower FA or lower AD. Among youth, there were mixed findings as to the nature of white-matter microstructural differences in projection and thalamic pathways, including reports of both lower and higher FA in the corticospinal tract, internal and external capsules, anterior and superior corona radiata, and anterior thalamic radiations (Table 3).

3.7. Aim 2: are white-matter tract abnormalities specific to AB with psychopathic traits?

3.7.1. Adults

Six of ten studies examined forensic samples of adults with high AB and psychopathy, consistently demonstrating greater diffusivity in tracts among these individuals relative to healthy controls. Thus, there is evidence that the white-matter tract microstructural deficits are more pronounced among antisocial individuals with psychopathy. The most compelling evidence to support this conclusion comes from a study of incarcerated males, among whom the lower FA found in the right UF was specific to those with psychopathy versus those without psychopathy (Motzkin et al., 2011). This case-control approach inherently accounted for AB, enabling microstructural deficits to be uniquely linked to psychopathy. Moreover, Sobhani et al. (2015) demonstrated that psychopathic traits in a high-risk sample were related to lower FA in the UF. In further support of potential specificity of white-matter microstructural deficits in the UF to psychopathy, Beyer and colleagues examined aggression and anger among a community sample, where rates of psychopathy are likely lower, and reported no difference between a high AB versus low AB group (Beyer et al., 2014). At the same time, in another community sample, aggressive acts were related to lower FA and higher RD in the SLF (Karlgodt et al., 2015). However, without an assessment of psychopathic traits, it is difficult to ascertain whether individual differences in psychopathy would have accounted for this finding.

3.7.2. Youth

Only seven of the 12 studies of youth included measures of CU or psychopathic traits, which limits the extent to which we could evaluate whether these traits accounted for white-matter tract microstructural differences. Of these seven studies, one study that examined a community sample of youth found that CU traits were specifically related to lower FA in the UF and fornix within a dimensional analysis that controlled for concurrent AB (Breeden et al., 2015). However, two studies that investigated CU/psychopathic traits in isolation (i.e., without controlling for concurrent AB) found that they were related to higher FA, lower RD, and higher AD in various commissural, projection, and association tracts (Pape et al., 2015; Sarkar et al., 2013). CU traits were also found to be specifically related to lower RD and MD of the right UF among males with CD (Zhang et al., 2014a). Finally, among a clinic-referred and community sample, no differences were found in white-matter microstructure for youth high on AB and psychopathic traits compared to healthy controls using both whole-brain and ROI approaches (Finger et al., 2012). Moreover, of the five studies that examined AB without assessing concurrent CU or psychopathic traits, the direction of findings was mixed, and two studies reporting no association between AB and white-matter microstructure. Thus, it is difficult to ascertain the extent to which differences noted in these latter studies are specific to AB in general or whether they were accounted for unmeasured levels of CU or psychopathic traits.

4. Discussion

The included DTI studies demonstrate that adult AB is related to greater diffusivity (i.e., “poorer integrity”) within association, commissural, and thalamic and projection pathways, as indexed via lower FA and AD, and higher RD values. By integrating across studies, this review implicates greater diffusivity in a wider range of tracts than previously thought, contradicting the hypothesis that AB is characterized by specific white-matter microstructural deficits of the UF. In contrast to adult findings, DTI studies of youth identified a mixed pattern of white-matter microstructural differences among youth with AB compared to healthy controls. We discuss the DTI findings for AB in relation to abnormalities within specific tracts and attempt to reconcile the conflicting findings from youth studies. We also situate findings within an emerging science that focuses on the organization of the brain into intrinsic functional networks (Menon, 2011).

4.1. What are the white-matter tract abnormalities in adult AB?

Among adults, evidence from ten studies suggests that AB is associated with greater diffusivity within white-matter tracts across commissural, association, and projection and thalamic pathways, including the corpus callosum, cingulum, IFOF, ILF, SLF, UF, corticospinal tract, corona radiata, and thalamic radiations, as indexed via lower FA and AD and higher RD values. These findings contradict the notion that AB arises from a specific abnormality in UF microstructure, suggesting instead that AB reflects dysfunction in white-matter across regions and hemispheres. This widespread dysfunction is consistent with behavioral characteristics associated with AB that encompass deficits in affective, cognitive, attentional, and reward processing. The greater diffusion within white-matter tracts emerged in both dimensional and case-control analyses, suggesting that, rather than characterizing only severe AB within forensic samples, greater diffusivity (i.e., “poorer integrity”) within white-matter tracts is associated with the full dimensional range of AB. However, we did not find evidence that abnormal microstructure was related to any one microstructural component specifically, as findings emerged across FA, AD, and RD values.

It was striking that the majority of adult studies assessed forensic male samples. At the same time, this is a population where rates of APD and psychopathy are well-established as being higher, making them a logical target of investigation given their impact on crime, violence, and harm to society (Hare, 2006). However, one study examined white-matter microstructure in a female-only sample with a novel design that enabled comparison of women with CD, clinical comparison women with similar rates of depression, anxiety, substance use, and experience of physical and sexual abuse, and healthy controls (Lindner et al., 2016). The study found that lower AD of the corpus callosum was
null
AB beginning early in childhood (Shaw and Gross, 2008). The mixed findings noted in the current review suggest that future studies of white-matter maturation among youth with AB should consider accounting for the influence of environmental and social variables. For example, by adopting the case-control approach of Lindner and colleagues and comparing groups with versus without AB who are matched based on experience of maltreatment, abuse, or other negative exposures, studies could isolate the white-matter deficits specific to AB, rather than deficits that may be reflective of risky social or emotional experiences.

4.3. Network-based functional implications of white-matter tract abnormalities in AB

Adopting a network approach is useful for integrating evidence across included studies because it helps conceptualize AB as the consequence of abnormalities in multiple brain areas. Indeed, while the majority of neuroimaging research to date has been driven by a focus on regionally-specific neural correlates, the current review provides an opportunity to evaluate several distinct systems, which underpin diverse functional processes. Given that AB and psychopathy are defined by deficits in a range of social, cognitive, and affective processes, we hypothesize that three ways in which impaired physical connectivity of the networks contributes to these processes. In relation to commissural pathways, abnormalities in white-matter microstructure among individuals high on AB and CU/psychopathic traits were found in the corpus callosum and forceps minor. In particular, greater diffusivity within white-matter tracts (i.e., lower FA) is thought to cause an imbalance in interhemispheric communication, which has been further hypothesized to promote approach behaviors linked to AB, such as impulsivity and aggression, as well as undermine the ability to integrate information about the thoughts and emotions of others with behavior (Lindner et al., 2016; Schutter and Harmon-Jones, 2013).

Greater diffusivity was also reported among association pathways, including the cingulum, fornix, SLF, UF, and ILF. Interestingly, many of these tracts connect regions within the default mode network (DMN). The DMN is typically more active under conditions of rest (i.e., mind-wandering, day-dreaming), but less active during cognitively-demanding tasks (Fox et al., 2005; Raichle et al., 2001). Of relevance to AB, the DMN is active when participants engage in socio-affective processing (Buckner et al., 2008), moral judgement making (Greene et al., 2001), and evaluations of self- and other-emotional states (Ochsner et al., 2004). Abnormalities in the physical connections between DMN regions as measured by DTI may contribute to the emotional detachment and violence seen in highly antisocial and psychopathic individuals by limiting their capacity for introspective social, moral, and affective processing (Sethi et al., 2014). This assertion is supported by findings of a recent study where reduced DMN functional connectivity was related to higher interpersonal-affective traits scores (i.e., “Factor 1” of psychopathy) among 142 adult male prison inmates (Philippi et al., 2015).

Finally, there were white-matter tract abnormalities among association and thalamic and projection pathways linked to AB, including ILF, IFOF, internal capsules, and thalamic radiations. These pathways connect visual association areas of the occipital lobe, auditory and visual association areas, and the prefrontal cortex (Catani et al., 2013). Physical disruption of this network of tracts is thought to affect the detection and processing of expressions of emotion, which is compromised in individuals high on AB, who show deficits in recognizing fearful and sad facial expressions (Marsh and Blair, 2008) and in individuals high on psychopathy, who show impairments in the processing of both facial and vocal expressions across several emotions (i.e., not only fear and sadness) (Dawel et al., 2012). Moreover, the ILF and IFOF connect regions of the “salience” or cingulo-opercular network and “executive control” or fronto-parietal network, which act together in the integration of salient emotional and cognitive information to facilitate goal-oriented behavior (Dosenbach et al., 2006; Menon, 2011). Diminished physical connectivity of these functional networks could contribute to the behavioral dysfunction seen in AB by impairing detection and mapping of salient external stimuli and internal events, with consequences for cognition, affective processing, and attention.

4.4. The influence of CU/psychopathic traits on white-matter tract abnormalities in AB

It is difficult to draw conclusions about the contribution of CU/psychopathic traits to relationships between white-matter tract abnormalities and AB. A major issue was that most studies investigated relationships between white-matter microstructure and AB or CU/psychopathic traits simultaneously, making it challenging to establish unique links. Importantly, previous research examining task-related reactivity or functional connectivity provides support for unique and divergent neural mechanisms of psychopathic traits, and in some cases, CU traits (Hyde et al., 2014; Viding et al., 2012). Future studies that investigate associations between microstructural abnormalities of white-matter tracts and psychopathic/CU traits while accounting for AB, and vice versa, and either using dimensional (cf. Breeden et al., 2015) or case-control analyses (cf. Motzkin et al., 2011; Viding et al., 2012), are needed to understand differences in underlyng neural circuitry for these separate constructs.

A second issue relevant to interpreting the associations between CU traits/psychopathy and white-matter microstructure abnormalities centers on the role of DTI method: ROI versus whole-brain analysis. Early studies provided evidence that psychopathy may be related to more diffuse white-matter microstructure (e.g., lower FA) of the UF, which is borne out in four of the included adult studies. However, all four employed ROI-analysis (Craig et al., 2009; Motzkin et al., 2011; Sobhani et al., 2015; Wolf et al., 2015). Among four studies that employed whole-brain analysis, two failed to find that AB or psychopathy were related to lower FA values of the UF (Karlsgard et al., 2015; Lindner et al., 2016). Moreover, while the other two studies confirmed UF reduced integrity (Hoppenbrouwers et al., 2013; Sundram et al., 2011), they also reported greater diffusivity within white-matter (i.e., lower FA) across a range of other tracts. Thus, a major finding from this review is that the previously-purported specificity of white-matter abnormalities to the UF may have been contingent on studies using a ROI-focused analysis, which challenges current etiological models of AB. At the same time, the UF is in a region of many intersecting tracts and whole-brain analyses may be limited in power to detect differences. Thus future studies could employ the “hybrid” approach of Motzkin and colleagues, who used an ROI, but contrasted UF findings with those for the SLF, ILF, and IFOF, still finding specificity of abnormalities to the UF (Motzkin et al., 2011; also see Passamonti et al., 2012).

4.5. Other future directions

In addition to contrasting findings from ROI versus whole-brain approaches, future studies of AB more broadly should contrast different techniques within ROI versus whole-brain approaches. In particular, the deterministic tractography methods adopted by many included studies may be limited in terms of the accuracy with which directions and pathways of fibers can be determined, especially in regions of the brain where multiple fiber bundles of different orientations are crossing each other (e.g., SLF and UF). Even when included studies addressed this potential limitation by comparing DTI measures using a voxel-wide approach (i.e., rather than reconstructing fiber tracts), there is the possibility of normalization or skeletonization errors (for a more in-depth discussion of the strengths and weaknesses of these methods, see Cercignani, 2010; Jones et al., 2013; Soares et al., 2013). Both tractography and voxel-wise approach were represented within included studies, but we did not identify a clear pattern of findings related to one or other type of methodology. Importantly, however, very few studies employed the same techniques, particularly within the youth
studies (e.g., only three of 12 youth studies used an identical analytic approach). Inconsistencies in methodology thus likely contributed to the mixed findings among the youth studies, highlighting the importance of future studies including a clear rationale for using a specific technique and incorporating a range of different techniques to enable better comparison across studies.

Finally, an important implication of this review is that future studies need to isolate the neurobiological meaning of white-matter microstructural differences and what the functional consequences are for socioemotional, neurocognitive, or behavioral functions (i.e., do differences in white-matter microstructure predict functional reactivity in regions implicated in youth AB/CU traits?), for an example of a study testing this question, see Breeden et al., 2015). We have also remained cautious in our interpretation of DTI measures, and have focused our presentation of results on specific measures (i.e., focusing on higher versus lower FA) or the nature of diffusivity within tracts. In particular, we note the persuasive arguments of Jones and colleagues who suggest that terms such as “lower white-matter integrity” or “lower connectivity” of tracts, while popular in the literature, are highly problematic (Jones et al., 2013). Indeed, several possible explanations exist for why DTI measures, including FA, may be different in one group relative to another. Importantly, many of these reasons have nothing to do with purported “integrity” of white-matter tracts, such as axon diameter, packing density, branching of tracts, myelination, or other microscopic changes to axonal structure (Beaulieu, 2002; Hoelt et al., 2007; Jones et al., 2013). As outlined by Jones and colleagues, part of the ambiguity surrounding the interpretation of DTI measures arises from the nature of the measures themselves and the fitting of a tensor model. Accordingly, future studies of white-matter microstructural differences in AB could be informed by incorporating approaches that are more sensitive to microstructural changes, including Diffusion Kurtosis Imaging (Jensen and Helpern, 2010) and Magnetization Transfer Imaging, which is highly sensitive to potential demyelination as a cause of altered DTI parameters (Wozniak and Lim, 2006). Combining these alternative approaches with DTI may lead to a better understanding of the specific microstructural alterations that underpin AB.

4.6. Limitations

The emerging literature on structural connectivity in AB suggests that differences in white-matter microstructure contribute to AB. However, several limitations both of included studies and the current review undermine the conclusions that can be drawn about white-matter microstructure abnormalities in AB. First, due to heterogeneity in methodology (e.g., sample, age, measures, analyses), we were unable to perform a meta-analysis and could not determine the magnitude of effect sizes. Second, this review was likely limited by the “file-drawer problem” (Reyns, 2006) in that we could not account for unpublished findings, particularly given that only five included studies found no significant effects (4 in youth; 1 in adults). Third, a major limitation in all but two of the included studies was that samples invariably included individuals who were extreme on both AB and CU/psychopathic traits or among whom the level of CU/psychopathic traits was unknown. Thus, the findings of many included studies may confound severity of AB with the presence of interpersonal-affective deficits associated with CU/psychopathic traits. Future studies need to examine unique associations of psychopathy or CU traits with white-matter microstructure abnormalities, parsing variance in overall AB severity or overlapping constructs of aggression and impulsivity, or by using a case-control approach that compares individuals high on AB with versus without psychopathy (for examples of this type of analytic approach, see Breeden et al., 2015; Motzkin et al., 2011; Philippi et al., 2015). Fourth, only two of the included studies examined demographic moderators (Decety et al., 2015; Zhang et al., 2014a). In terms of moderation by gender, these two youth studies reported findings in opposite directions— one reported increased AD in white-matter tracts that was specific to girls (Decety et al., 2015) and the other reported lower RD in the UF that was specific to boys (Zhang et al., 2014b). It is interesting that in one adult study that examined only women, the direction of the relationship between AB and white-matter abnormalities was consistent with findings from studies of only men (i.e., lower AD: Lindner et al., 2016). Nevertheless, future research is needed to expand our knowledge of sex-specific effects of white-matter abnormalities on AB across development.

Additionally, only one study examined race as a moderator, reporting that white-matter microstructure abnormalities, indexed by higher AD, were more strongly related to AB among African-American children compared to Caucasian/Hispanic children (Decety et al., 2015). Other studies were inconsistent in reporting of the racial and/or ethnic group membership of participants, which is relevant to understanding AB as previous research has found that many of the most consistently-reported relationships between psychopathy and brain reactivity fail to replicate in African-American samples (Baskin-Sommers et al., 2011; Hyde et al., 2015; Lorenz and Newman, 2002). Finally, this review emphasizes the need for future research to consider the context in which participants grow up, given evidence of the influence of exposure to environmental stressors or abuse on relationships with white-matter integrity (Lindner et al., 2016), and to examine samples of individuals from different economic strata, who may have specific neurodevelopmental pathways toward AB (Raine, 2002).

4.7. Conclusion

Despite these limitations, the research presented in the 22 reviewed studies demonstrates significant associations between diffusivity of white-matter tracts and AB. Specifically, lower FA in association, commissural, and projection and thalamic pathways was found among adults with AB and psychopathic traits. Importantly, the review found that AB across the lifespan was associated with widespread white-matter microstructure differences rather than specific deficits to the UF, as previously thought. These findings demonstrate the importance of utilizing both whole-brain and ROI approaches to identify abnormalities in the structural networks underlying AB. Among youth studies, the evidence was mixed with different studies reporting both greater and reduced diffusivity of white-matter tracts, or no differences in white-matter microstructure of youth with AB versus healthy controls. The review supports the existence of an association between AB and altered microstructure of brain white-matter tracts, and guides future research by highlighting the need to focus on a wider range of tracts beyond the UF alone, adopt a more developmentally-focused approach by examining samples with narrower age range, and account for environmental risk and pubertal stage.

Conflict of interest statement

No conflicts declared.

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Appendix A. Supplementary data

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