Review

A systematic review of diffusion weighted MRI studies of white matter microstructure in adolescent substance users

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ABSTRACT

Recent studies using diffusion weighted magnetic resonance imaging (DW-MRI) have provided evidence of abnormal white matter microstructure in adults with substance use disorders (SUDs). While there is a growing body of research using DW-MRI to examine the impact of heavy substance use during adolescence, this literature has not been systematically reviewed. Online databases were searched for DW-MRI studies of adolescent substance users, and 10 studies fulfilled the inclusion and exclusion criteria. We identified consistent evidence for abnormal white matter microstructure in neocortical association pathways as well as in projection and thalamic pathways. Dose-dependent relationships between DW-MRI measures and patterns of substance use were also observed. The consistency of these findings with DW-MRI research in adults suggests that white matter microstructure is impacted in the early stages of heavy substance use. However, given the largely cross-sectional nature of the available data, important questions remain regarding the extent to which white matter abnormalities are a consequence of adolescent exposure to alcohol and other drugs of abuse or reflect pre-existing differences that increase risk for SUDs.

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1. Introduction

Over the past three decades, magnetic resonance imaging (MRI) has provided considerable *in vivo* evidence that abnormalities in the structure of brain white matter are associated with heavy and prolonged exposure to most drugs of abuse. Conventional MRI demonstrates several forms of white matter abnormality (e.g., altered volume and density, and hyperintensities) in individuals with a range of substance use disorders (SUDs), including those related to alcohol, cannabis, amphetamines, cocaine, inhalants, and opioids (Batalla et al., 2013; Berman et al., 2008; Lyoo et al., 2004; Monnig et al., 2012; Schlaepfer et al., 2006; Yücel et al., 2008). More recently, newer MRI technology (i.e., diffusion weighted MRI [DW-MRI]; Le Bihan and Johansen-Berg, 2011) has provided evidence of abnormal white matter microstructure and altered patterns of anatomical connectivity in association with a range of SUDs (Arnone et al., 2006; Batalla et al., 2013; Bora et al., 2012; Gruber et al., 2011; Lane et al., 2010; Pfefferbaum et al., 2009; Tobias et al., 2010; Zalesky et al., 2012). At the same time, MRI has revolutionised our ability to characterise changes in brain structure across the life span (Giedd et al., 1999; Paus et al., 1999). DW-MRI, in particular, has been instrumental in demonstrating that the development of white matter in healthy individuals accelerates through adolescence and continues into young adulthood (Lebel and Beaulieu, 2011). Together, these lines of evidence suggest that heavy substance use may be particularly harmful during adolescence when white matter is still developing (Clark et al., 2008; Lubman et al., 2007). Indeed, this notion is supported by evidence from DW-MRI studies in adults with SUDs (e.g., Gruber et al., 2011; Zalesky et al., 2012), which have found an earlier age of onset to be associated with more severe white matter abnormalities.

Several recent DW-MRI studies (e.g., Bava et al., 2009; Jacobus et al., 2009; Yücel et al., 2010) have sought to address this issue further by investigating white matter microstructure in adolescent substance users. A cursory examination of this emerging literature suggests the presence of widespread microstructural abnormalities in heavy users of alcohol and/or other drugs such as cannabis, with lower Fractional Anisotropy (FA; see Table 1) often detected in multiple white matter fibre tracts.

Yet, despite these observations, there has been no synthesis of the existing evidence in terms of the consistency with which microstructural abnormalities are found in specific white matter tracts and across different adolescent substance-using populations. Furthermore, the extent to which abnormalities in white matter microstructure relate to specific patterns of substance use (e.g., age of onset, duration, dose/quantity, frequency, abstinence) among adolescents remains largely undetermined. Finally, whether microstructural abnormalities identified in adolescent substance users are similar to those reported in DW-MRI studies of adults with SUDs also requires further investigation. Such analyses are critical to determining the relative impact of substance use on developing white matter.

In this paper, we provide a systematic review of studies that have used DW-MRI to investigate white matter microstructure in adolescent substance users. Our aims are to (a) identify tracts that consistently show signs of abnormal white matter microstructure, (b) examine these abnormalities in relation to patterns of substance use, and (c) consider such findings in the context of DW-MRI research in adults with SUDs.

2. Methods

The systematic review was conducted in line with the QUORUM (Moher et al., 1999) and AMSTAR (Shea et al., 2007) guidelines. An overview of the procedure used for study selection is provided in Fig. 1.

2.1. Literature search

Online searches of the PubMed (United States Library of Medicine), MEDLINE (Thomson Reuters Web of Knowledge), and PsycINFO (Wolters Kluwer Health OvidSP) databases were initially performed in June 2012 and repeated in January 2013 using several relevant search terms (e.g., '[diffusion AND weighted] AND [substance AND abuse]') and search limits (e.g., 'Ages: Adolescent, Young Adult'; for further details, see Fig. 1). Abstracts were examined for references to DW-MRI, SUDs, and adolescents, and if the study appeared relevant, then the full text was retrieved. Reference lists of downloaded articles were searched for additional studies.

2.2. Inclusion and exclusion criteria

Criteria for inclusion were (a) use of DW-MRI, (b) case-control group comparison, where cases were adolescents with past or current SUDs or a history of heavy substance use, (c) peer-reviewed journal article, and (d) written in English. Furthermore, studies were included if participants were aged between 12 and 24 years. The age range was extended beyond the typical limit for adolescence (approximately 18 years of age) to accommodate studies with participants in late adolescence transitioning to young adulthood. Comparisons of individuals with and without prenatal exposure to alcohol or other drugs of abuse were not included. One study (Bava et al., 2010) was excluded because it examined correlations between neuropsychological measures and previously published group comparison data already selected for the review (Bava et al., 2009).

One hundred and fifty-eight articles were retrieved from the database searches, of which 10 met the inclusion criteria (see Fig. 1). Eight were cross-sectional studies (Ashtari et al., 2009; Bava et al., 2009; Clark et al., 2012; De Bellis et al., 2008; Jacobus et al., 2009; McQueeny et al., 2009; Thatcher et al., 2010; Yücel et al., 2010), one was a prospective study (Jacobus et al., 2012), and one was a longitudinal study (Bava et al., 2013).

2.3. Data collation

Pertinent details from each study were recorded, including methodological information regarding sample characteristics, substance use, and DW-MRI, the details of which are described below and shown in Table 2. In terms of findings, the neuroanatomical locations (i.e., white matter tract or region) of noteworthy differences in DW-MRI measures between adolescent substance users and control participants were recorded. Locations of relationships between DW-MRI measures and patterns of substance use (e.g., age of onset, duration, dose/quantity, frequency, abstinence) were also recorded. Neuroanatomical categories from a DW-MRI atlas of human white matter (Oishi et al., 2011) provided the framework for organising these findings into sets of meaningfully related locations; tracts were classified as one of the following types: brainstem and cerebellar, projection and thalamic, association, or

Table 1
Select tensor-based scalar measures of white matter microstructure derived from diffusion weighted magnetic resonance imaging data.

Measure	Abbreviation	Description
Fractional Anisotropy	FA	The fraction of diffusion that is directionally dependent (or anisotropic; see main text). Lower FA might reflect damage to the myelin sheath surrounding axons, enlarged axonal diameter, reduced axonal packing density, or increased membrane permeability. The presence of myelin is not essential to observe diffusion anisotropy (i.e., FA is not myelin specific).
Axial Diffusivity	AD	The magnitude of diffusion parallel to fibre tracts. Lower AD might reflect reduced axonal calibre or less coherent orientation of axons. There is evidence that AD is not influenced by myelin.
Radial Diffusivity	RD	The magnitude of diffusion perpendicular to fibre tracts. RD may be relatively more sensitive to myelin, but higher RD might reflect myelin loss or loss of axons and/or reduced axonal packing density.
Mean Diffusivity (or Trace)	MD/Tr	Directionally averaged (i.e., overall) magnitude of diffusion. Higher MD/Tr is associated with many types of brain abnormalities and could be due to axonal or myelin degradation.

Described is a selection of scalar measures derived from the eigenvalues of the diffusion tensor (see main text; Jones, 2009) that have been proposed to characterise white matter microstructure. Note, however, that the relative contribution of specific axonal components (e.g., membrane, cytoskeleton, myelin) and architectural characteristics (e.g., geometry) to these measures continues to be debated (Beaulieu, 2009) and that tensor-based approaches have limited capacity to resolve microstructural properties in voxels with complex axonal geometries (Jones et al., 2012; Tournier et al., 2011).

commissural. We did not perform a formal meta-analysis of the data due to the limited number of studies available, high prevalence of overlapping samples, and differences in analysis methods used.

2.4. Sample characteristics

Participants in seven of the ten studies were drawn from two distinct cohorts: (a) University of California San Diego (UCSD;
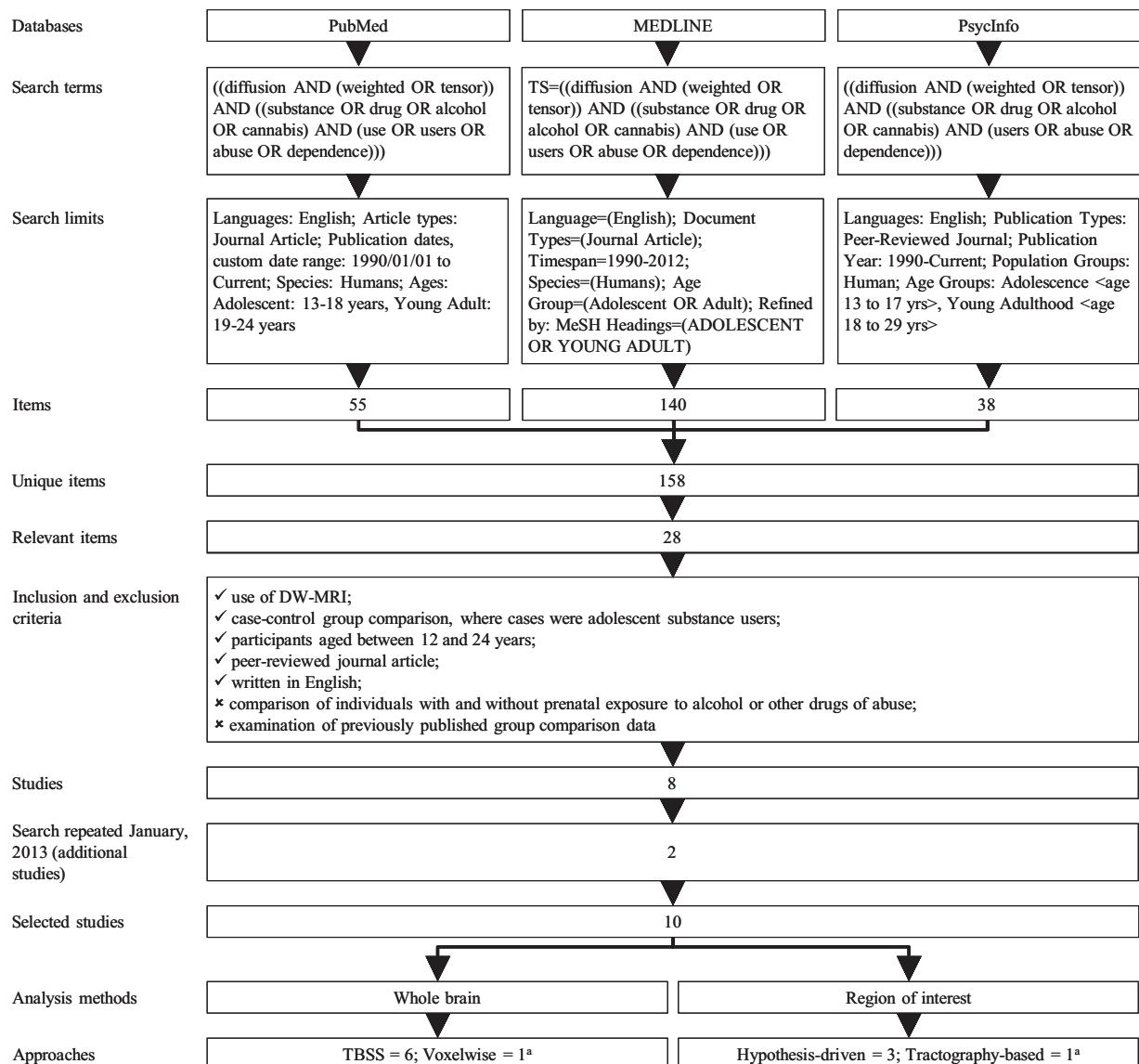

Fig. 1. Procedure used for study selection. *Abbreviations*: DW-MRI, diffusion weighted magnetic resonance imaging; TBSS, Tract Based Spatial Statistics (see Smith et al., 2006). [a]Ashtari et al. (2009) used two approaches: (a) whole brain voxelwise and (b) tractography-based region of interest.

Table 2

Sample characteristics, substance use details, and diffusion weighted magnetic resonance imaging methods for all studies (n = 10).

Author (year)	Cohort	Control participants Male N	%	Age (years) M	SD	Range	Adolescent substance users Male N	%	Age (years) M	SD	Range	Alcohol Dose, M (SD)	Frequency, M (SD)	Cannabis Dose, M (SD)	Frequency, M (SD)	Processing and analysis Method	Measure
Ashtari et al. (2009)	ind	14	[100]	18.5	1.4	17.3–21.5	14	[100]	19.3	0.8	18–21.2		[≤4 days p.m.]	5.8 (NR) joints p.d.[h]		See[o]	FA; AD; RD; MD/Tr
Bava et al. (2009)	UCSD	36	[72.2]	17.8	0.8	[16–19]	36	[72.2]	17.9	0.9	[16–19]	52.9 (52.4) drinks p.m., past 3 months; See also[b]			11.6 (8.4) days p.m., past 3 months; See also[i]	TBSS	FA; MD/Tr
Bava et al. (2013)	UCSD	51	73	17.88	1.07	[16–21]	41	63	18.42	1.2	[16–21]		See[c]		See[j]	TBSS	FA; AD; RD; MD/Tr
(18-month follow-up)	–	–	–	19.25	1.08	[17–22]	–	–	19.81	1.13	[17–22]		[22.67 occasions p.m. over follow-up]		[36.22 occasions p.m. over follow-up]	TBSS	FA; AD; RD; MD/Tr
Clark et al. (2012)	Pitt	20	[45]	16.2	1.0	[14–19]	35	[54]	16.8	1.2	[14–19]		1.8 (2.9) days, past 30 days			ROI	FA; AD; RD
De Bellis et al. (2008)	ind	28	[61]	15.9	1.1	13.3–17.7	32	[78]	16.9	1.2	13.6–19.3	[51.6 (20) drinks p.m.]				ROI	FA; MD/Tr
Jacobus et al. (2009)	UCSD	14	86	17.3	0.8	[16–19]	14	86	18.1	0.7	[16–19]	19.6 (13.3) drinks p.m., past 3 months	See[d]		[0.37 occasions p.m., past 3 months]; See also[k]	TBSS	FA; MD/Tr
		–	–	–	–	–	14	79	18.2	0.7	NR	26.1 (16.1) drinks p.m., past 3 months	See[e]		[50.97 occasions p.m., past 3 months]; See also[l]	–	–
Jacobus et al. (2012)	UCSD	49	73	17.6	0.8	[16–19]	47	59	18.0	0.9	[16–19]		See[f]		See[m]	ROI	FA
(18-month follow-up)	–	–	–	19.0	0.9	[17–20]	–	–	19.5	0.9	[17–20]		[11.8 occasions p.m. over follow-up]		[14.7 occasions p.m. over follow-up]	–	–
McQueeny et al. (2009)	UCSD	14	[85.7]	17.95	0.88	[16–19]	14	[85.7]	18.09	0.69	[16–19]	15.43 (7.82) drinks p.m., past 3 months	See[g]		See[n]	TBSS	FA
Thatcher et al. (2010)	Pitt	12	[50]	16.68	1.08	[14–18]	24	[50]	16.7	1.01	14–18	10.38 (23.97) drinks, past 30 days	1.79 (3.19) days, past 30 days		7.96 (12.5) days, past 30 days	TBSS	FA; AD; RD; MD/Tr
Yücel et al. (2010)	ind	8	25	19.7	2.7	NR	11[a]	45.5	18.2	1.6	NR	2.61 (6.1) standard drinks, typical day		1.6 (2.5) g, typical day		TBSS	FA
		–	–	–	–	–	11	66.7	19.4	1.9	NR	1.7 (2.6) standard drinks, typical day		0.8 (0.5) g, typical day		–	–

Studies are listed in alphabetical order by first author surname. Values enclosed in square brackets were extrapolated from published data. Regarding alcohol and cannabis use, lifetime dose and frequency are not presented because age of onset and duration of use vary across studies making it difficult to compare lifetime substance use; however, see footnotes b–g and i–n. *Abbreviations*: AD, Axial Diffusivity; FA, Fractional Anisotropy; ind, independent; MD/Tr, Mean Diffusivity (or Trace); NR, not reported (and unable to be extrapolated); OHSU, Oregon Health and Science University; Pitt, University of Pittsburgh; p.m., per month; p.w., per week; RD, Radial Diffusivity; ROI, region of interest; TBSS, Tract Based Spatial Statistics; UCSD, University of California San Diego.

[a] For inhalant users, M = 1.61 (SD = 1.3) cans in a typical day.

[b] 195.3 (152.7; range: 25–736) lifetime alcoholic drinks.

[c] Lifetime alcohol use occasions: 224.71 (179.75).

[d] Lifetime alcohol use occasions: 54.6 (48.8).

[e] Lifetime alcohol use occasions: 152.9 (116.4).

[f] Lifetime alcohol use occasions: 233.1 (234.7).

[g] Lifetime alcohol use occasions: 54.57 (48.80).

[h] In the 1 year prior to the current period of abstinence.

[i] Lifetime cannabis use occasions: 551.7 (481.2; range: 180–1844).

[j] Lifetime cannabis use occasions: 453.07 (309.60).

[k] Lifetime cannabis use occasions: 2.2 (3.1).

[l] Lifetime cannabis use occasions: 549.5 (479.2).

[m] Lifetime cannabis use occasions: 471.0 (357.1).

[n] Lifetime cannabis use occasions: 2.21 (3.09).

[o] Two approaches were used: (a) whole brain voxelwise and (b) tractography-based ROI (see Ashtari et al., 2009).

Table 3
Eligibility criteria for screening participants.

Author (year)	DSM Axis I[a]	Developmental disorder[c]	Medical condition[e] or head injury	Psychotropic medication	Prenatal exposure[f]	Family history of psychiatric disorder
Ashtari et al. (2009)	Yes	Yes	Yes	Yes		
Bava et al. (2009)	Yes		Yes	Yes	Yes	Yes[g]
Bava et al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes[h]
Clark et al. (2012)		Yes	Yes			
De Bellis et al. (2008)		Yes[d]	Yes			
Jacobus et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes[g]
Jacobus et al. (2012)	Yes	Yes	Yes	Yes		
McQueeny et al. (2009)	Yes	Yes	Yes	Yes	Yes	
Thatcher et al. (2010)		Yes	Yes			
Yücel et al. (2010)	Yes[b]		Yes	Yes		

Studies are listed in alphabetical order by first author surname.

[a] Past or current *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) Axis I psychiatric disorder other than a substance use disorder (e.g., schizophrenia and other psychotic disorders, and major depressive disorder and other mood disorders).

[b] Psychotic disorder only.

[c] For example, intellectual and learning disabilities, and attention-deficit and disruptive behaviour disorders.

[d] Intelligence quotient below 80.

[e] Clinically significant medical/physical or neurological condition.

[f] Prenatal exposure to a drug of abuse (including alcohol).

[g] Bipolar I or psychotic disorder.

[h] Bipolar I, psychotic, or antisocial personality disorder.

five studies: Bava et al., 2009, 2013; Jacobus et al., 2009, 2012; McQueeny et al., 2009); and (b) University of Pittsburgh (Pitt; two studies: Clark et al., 2012; Thatcher et al., 2010). The other three studies recruited independent samples (Ashtari et al., 2009; De Bellis et al., 2008; Yücel et al., 2010).

Two main recruitment strategies were used: (a) recruitment of local high-school students, allowing the five studies that were based on the UCSD cohort to characterise adolescent substance users in the general population; and (b) targeted recruitment of treatment-seeking individuals, allowing the other five studies to characterise adolescents with a history of relatively heavy substance use.

A range of eligibility criteria were used for screening participants (for further details, see Table 3). Importantly, in nine studies (Ashtari et al., 2009; Bava et al., 2009, 2013; Clark et al., 2012; De Bellis et al., 2008; Jacobus et al., 2009, 2012; Thatcher et al., 2010; Yücel et al., 2010), the majority of cases met diagnostic criteria for a SUD in accordance with the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM IV*; American Psychiatric Association, 1994). The remaining study (McQueeny et al., 2009) examined adolescents who reported binge drinking alcohol but did not meet diagnostic criteria for SUD.

Most samples were small, with the number of adolescent substance users ranging between 10 and 47, and they were characterised by a higher proportion of males, consistent with sex differences in the distribution of SUDs (Kessler et al., 2007). The average age of users across studies ranged from approximately 17 to 19 years, capturing a period when substance use (alcohol and cannabis use in particular) increases in prevalence and severity (Australian Institute of Health and Welfare, 2011; Johnston et al., 2012).

2.5. Substance use

Alcohol and/or cannabis were the primary focus, reflecting the fact that these are two of the most commonly used and abused substances by adolescents (AIHW, 2011; Johnston et al., 2012). Specifically, two studies examined alcohol use (De Bellis et al., 2008; McQueeny et al., 2009), two studies examined cannabis use (Ashtari et al., 2009; Yücel et al., 2010 [also investigated inhalant use]), and six studies examined combined use of alcohol and cannabis (Bava et al., 2009, 2013; Clark et al., 2012; Jacobus et al., 2009, 2012; Thatcher et al., 2010). Patterns of substance use

varied accordingly, with heavy and binge alcohol use combined with heavy cannabis use featuring prominently among cases except in studies focusing on inhalant and/or cannabis use, for which alcohol use was minimal to moderate. However, there was considerable polysubstance use among cases. Tobacco use was prevalent across all 10 studies, and some use of amphetamines (or similar, including ecstasy), cocaine, or opioids was documented in six studies (Bava et al., 2009, 2013; Clark et al., 2012; De Bellis et al., 2008; Jacobus et al., 2009; McQueeny et al., 2009).

Duration and frequency of substance use and the dose/quantity of substances consumed were quantified in various ways, including age of initiation (i.e., first use) or age of onset (i.e., first weekly or regular use, or first diagnosed with SUD), and number of use occasions or number of units (e.g., grams of alcohol or cannabis, drinks, joints, or cans) per day, week, month, or lifetime. In addition, periods of abstinence, where reported, varied considerably between studies (ranging from 24 h to 11 months). To assist cross-study comparisons of substance use patterns, alcohol and cannabis consumption data were converted into similar units (i.e., occasions or units per month; see Table 2).

2.6. Diffusion weighted MRI

Diffusion weighted magnetic resonance imaging (DW-MRI) is a neuroimaging technique that enables the non-invasive mapping of the diffusion of water molecules in brain tissue. The magnitude of this diffusion varies with direction (termed *anisotropic*) because of restrictions imposed by physical barriers (e.g., axonal architecture; Beaulieu, 2009). In white matter, water molecules diffuse to a greater extent along the axis parallel rather than perpendicular to the trajectory of axons. This anisotropic diffusion can be modelled as a three-dimensional ellipsoid defined by a 3×3 matrix known as the diffusion tensor (Jones, 2009). Several scalar measures derived from the eigenvalues of the diffusion tensor have been proposed to characterise white matter microstructure, and the most commonly used in the studies reviewed are summarised in Table 1.

Between-subjects analysis of these DW-MRI measures is typically carried out using either (a) a whole brain white matter skeleton based approach called Tract Based Spatial Statistics (TBSS; Smith et al., 2006), (b) a hypothesis-driven region of interest (ROI) approach, or (c) a whole brain voxelwise approach. An important consideration in using any of these approaches is the accurate

Table 4
Group differences in diffusion measures between adolescent substance users and control participants.

Pathway or region	Tract or location	FA ↓	FA ↑	AD ↓	AD ↑	RD ↑	MD/Tr ↓	MD/Tr ↑
Neocortical association	Superior longitudinal fasciculus	R[1,a,8,9,10,b]	R[2]	R[9]		R[1,a,3,9]		R[1,a,3]
		L[2,6,c,8]				L[1,a,3]		L[1,a,3]
	Inferior longitudinal fasciculus	R[2,6,c,d]				R[3,e]		
		L[8]					L[2]	
	Inferior fronto-occipital fasciculus	L[2,6,c]						
Callosal	Corpus callosum	Genu[8]						
			Rostral-body[5,f]					
		Body[8]						
		Posterior-midbody[5,f,g]						
			Isthmus[5,f]				Isthmus[5,f]	
		Splenium[2,3,e,10,h]						
Projection and thalamic	Thalamic radiation	R-anterior[3]				R-anterior[3]		R-anterior[3]
						R-posterior[3]		R-posterior[3,e]
	Corona radiata	L-inferior[2]						
		R-anterior[8]						
		L-anterior[8]						
		R-posterior[3,e]						R-posterior[3]
		L-posterior[8]			L-posterior[3]			
		L-superior[6,d]						
	Motor fibres			R[1,a]				
				L[1,a]				
	Internal capsule		R-anterior[2]					
		R-posterior[1,i]		R-posterior[1,i]		R-posterior[1,i]		R-posterior[1,i]
		L-posterior[1,i,8]		L-posterior[1,i]		L-posterior[1,i]		L-posterior[1,i]
	External capsule	R[8]						
		L[8]						
	Cerebral peduncle	R-anterior[2]						
		L-anterior[2]						
Cerebellar	Cerebellar peduncle	L-superior[8]						
		L-middle[6,c,d]						
		L-inferior[8]						
Subcortical association	Fornix and stria terminalis	R[10,h]						
		L[8,10,h]						
Prefrontal[4,f]	Frontal gyrus	R-inferior[2]						
Parietal[4,f]	Post central gyrus	L[2]						
Temporal[4,f]	Temporal gyrus	R-superior[1,i,2]		R-superior[1,i]		R-superior[1,i,2]		R-superior[1,i]
		L-middle[1,i]				L-middle[1,i]		L-middle[1,i]
Occipital	Cuneus		R[2]					R[2]

Neuroanatomical locations of lower (↓) and higher (↑) group differences ($p < 0.05$) in diffusion measures between adolescent substance users and control participants. Studies are numbered 1–10 in alphabetical order by first author surname: [1]Ashtari et al. (2009), [2]Bava et al. (2009), [3]Bava et al. (2013), [4]Clark et al. (2012), [5]De Bellis et al. (2008), [6]Jacobus et al. (2009), [7]Jacobus et al. (2012), [8]McQueeny et al. (2009), [9]Thatcher et al. (2010), [10]Yücel et al. (2010). *Abbreviations*: AD, Axial Diffusivity; FA, Fractional Anisotropy; L, left hemisphere; MD/Tr, Mean Diffusivity (or Trace); R, right hemisphere; RD, Radial Diffusivity.

[a] Tractography-based region of interest (ROI) analysis (see Ashtari et al., 2009).
[b] Cannabis users < controls when a post hoc analysis was performed (see Yücel et al., 2010).
[c] Binge drinkers < controls (see Jacobus et al., 2009).
[d] Binge drinkers with heavy cannabis use < controls (see Jacobus et al., 2009).
[e] Exhibited group difference at both Time 1 and Time 2 (see Bava et al., 2013).
[f] ROI study (Clark et al., 2012; De Bellis et al., 2008; Jacobus et al., 2012 [the findings of which are not shown because prospective associations, not between-group differences, were examined]).
[g] Female cases < female controls (see De Bellis et al., 2008).
[h] Inhalant users < controls (see Yücel et al., 2010).
[i] Whole brain voxelwise analysis (see Ashtari et al., 2009).

alignment of voxels and tracts across multiple subjects because it reduces misclassification and variability of data, which, in turn, increases robustness and sensitivity. The whole brain voxelwise approach is most problematic in this regard, but its strength is in providing an unbiased analysis of the entire brain. ROI approaches, on the other hand, minimise alignment/registration errors, but they provide only a partial analysis of the brain and with it the potential for researcher bias in region selection. TBSS attempts to redress these limitations by testing for group differences in voxels comprising a central skeleton of white matter at the whole brain level, although its failure to use all available data remains a consideration.

Across the 10 studies, DW-MRI data were acquired on 3 Tesla (T) systems (except Ashtari et al. (2009), 1.5 T) using a single-shot echo-planar imaging sequence with a range of echo times (TE = 77–106 ms), repetition times (TR = 7200–14,000 ms), slices (36–50), slice thicknesses (3 mm, except Ashtari et al. (2009), 2.5 mm), gradient directions (6–48), and *b*-weights (independent

Table 5
Correlations between Fractional Anisotropy and patterns of substance use.

Pathway or region	Tract or location	Negative correlation	Positive correlation
Neocortical association	Superior longitudinal fasciculus	R: tobacco use[9,a,b]; days of abstinence prior to scan[9]	R: lifetime alcohol use[2]
		L: recent alcohol use[8,c]	L: lifetime drinking occasions[6]; recent cannabis use[2,d,6,e]
	Inferior fronto-occipital fasciculus		L: lifetime alcohol use[2]; years of regular drinking[2]; lifetime cannabis use[2]
Callosal	Corpus callosum	Genu and body: lifetime hangover symptoms[8]	
		Body: lifetime hangover symptoms[8]; recent alcohol use[8,c]	
		Anterior-midbody: age of onset of AUD[5,f]	Anterior-midbody: duration of alcohol use[5,f]
		Splenium: lifetime alcohol use[2]; lifetime cannabis use[2,g]	
Projection and thalamic	Corona radiata	L-posterior: recent alcohol use[8,c]	
		R&L-superior: follow-up substance use[7,f,h]	L-superior: lifetime cannabis use[6]
	Internal capsule		R-anterior: lifetime alcohol use[2]
	External capsule	R: recent alcohol use[8,c]	
		L: recent alcohol use[8,c]	
	Cerebral peduncle	R-anterior: lifetime alcohol use[2]	
		L-anterior: lifetime alcohol use[2]	
Subcortical association	Fornix and stria terminalis	R&L-fornix: follow-up substance use[7,f,h]	
Prefrontal[4,f,i]	Frontal gyrus	R-inferior-frontal-gyrus: lifetime alcohol use[2]; years of regular drinking[2]	
Parietal[4,f,i]	Post central gyrus	L-post-central-gyrus: lifetime alcohol use[2]	
Occipital	Cuneus		R: lifetime alcohol use[2]

Neuroanatomical locations of negative and positive correlations ($p < 0.05$) between Fractional Anisotropy (FA) and substance use measures. Studies are numbered 1–10 in alphabetical order by first author surname: [1]Ashtari et al. (2009), [2]Bava et al. (2009), [3]Bava et al. (2013), [4]Clark et al. (2012), [5]De Bellis et al. (2008), [6]Jacobus et al. (2009), [7]Jacobus et al. (2012), [8]McQueeny et al. (2009), [9]Thatcher et al. (2010), [10]Yücel et al. (2010). *Abbreviations*: AD, Axial Diffusivity; AUD, Alcohol Use Disorder; FA, Fractional Anisotropy; L, left hemisphere; MD/Tr, Mean Diffusivity (or Trace); R, right hemisphere; RD, Radial Diffusivity.

[a] Cigarette use days (see Thatcher et al., 2010).
[b] Total number of cigarettes (see Thatcher et al., 2010).
[c] Estimated peak blood alcohol concentration, past 3 months (see McQueeny et al., 2009).
[d] Marijuana use days per month, past 3 months (see Bava et al., 2009).
[e] Marijuana use episodes, past 3 months (see Jacobus et al., 2009).
[f] Region of interest study (Clark et al., 2012; De Bellis et al., 2008; Jacobus et al., 2012).
[g] For particularly heavy users of cannabis ($n = 9$; see Bava et al., 2009).
[h] Lower FA at baseline predicted more days of substance use, past month, at follow-up ($N = 96$), and in cases ($n = 47$) baseline FA predicted follow-up past month substance use days above and beyond covariates and baseline past month substance use days (see Jacobus et al., 2012).
[i] FA was negatively related to the frequency of diagnostic criteria for cannabis abuse/dependence ('cannabis symptom count'; see Clark et al., 2012).

and Pitt studies, $1000 \, s/mm^2$; UCSD studies, $2000 \, s/mm^2$). As shown in Table 2, all 10 studies compared at least one measure of diffusivity (Axial Diffusivity [AD], $n = 4$; Radial Diffusivity [RD], $n = 4$; Mean Diffusivity or Trace [MD/Tr], $n = 6$) and anisotropy (FA, $n = 10$) between adolescent substance users and control participants. For these analyses, six studies used TBSS, three studies used a ROI approach, and one study (Ashtari et al., 2009) performed both whole brain voxelwise and tractography-based ROI analyses (see Fig. 1).

3. Results

At the whole brain level, differences in DW-MRI measures between adolescent substance users and control participants were detected throughout the white matter of the brain (see Table 4). The most common finding was lower FA. Neuroanatomical locations of correlations between FA and patterns of substance use are shown in Table 5; most commonly, lower FA in association with greater levels of substance use. Using a defined neuroanatomical framework (Oishi et al., 2011), the most consistently implicated pathways were projection and thalamic, association, and commissural. Of the association and commissural pathways, microstructural abnormalities were most commonly observed along tracts that connect neocortical areas within and between the cerebral hemispheres (i.e., intrahemispheric and callosal, respectively; see Section 3.1).

Several areas that contain ascending or descending tracts were also implicated (see Section 3.2). We report the findings of whole brain and ROI studies separately due to differences in analysis methods used.

3.1. Neocortical association pathways

3.1.1. Intrahemispheric

Six of the seven whole brain studies found evidence for abnormal white matter microstructure in tracts that connect multiple cortical areas within each cerebral hemisphere, including the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), and inferior fronto-occipital fasciculus (IFOF). Lower FA and diffusivity differences were most commonly observed in the SLF (left: Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009; right: McQueeny et al., 2009; Thatcher et al., 2010; Yücel et al., 2010 [cannabis users cf. controls]), a large tract comprising four subdivisions which together connect the frontal, parietal, temporal, and occipital lobes (Makris et al., 2005). Four studies (Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009; Thatcher et al., 2010) found an association of FA in intrahemispheric pathways (e.g., SLF, ILF) with substance use (e.g., alcohol, cannabis), although the most frequently reported pattern was higher (not lower) FA in association with greater levels of substance use.

3.1.2. Callosal

Four whole brain studies (Bava et al., 2009, 2013; McQueeny et al., 2009; Yücel et al., 2010 [inhalant users cf. controls]) found lower FA in the corpus callosum, which connects corresponding left and right cortical areas. Lower FA was most commonly observed in the posterior corpus callosum (i.e., splenium), which contains commissural fibres between parietal, temporal, and occipital areas (Hofer and Frahm, 2006). For this and other subdivisions of the corpus callosum (e.g., genu and body, projecting into prefrontal and motor areas, respectively), two studies (Bava et al., 2009; McQueeny et al., 2009) found that FA was negatively associated with alcohol use. These findings suggest that heavy alcohol consumption and possibly inhalant use may negatively impact callosal microstructure.

3.2. Projection and thalamic pathways

Across five whole brain studies (Ashtari et al., 2009; Bava et al., 2009, 2013; Jacobus et al., 2009; McQueeny et al., 2009), evidence was found for abnormal white matter microstructure (predominantly lower FA) in the thalamic radiation (anterior, posterior, and inferior), corona radiata (anterior, posterior, and superior), internal capsule (anterior limb and posterior limb), external capsule, and cerebral peduncle (anterior), which variously contain axonal projections between the cerebral cortex, thalamus, brainstem, and spinal cord (Oishi et al., 2011). Two of these studies also found evidence for lower FA in association with greater levels of alcohol use, firstly in the left posterior corona radiata and external capsules (McQueeny et al., 2009), and secondly in the anterior cerebral peduncles (Bava et al., 2009). Longitudinal changes of diffusivity in projection and thalamic pathways were also observed, including increased AD in the left posterior corona radiata, which was predicted by more alcohol use over an 18-month interscan interval (Bava et al., 2013). These findings suggest that heavy alcohol use may adversely affect white matter microstructure in several areas predominantly containing sensory and motor pathways.

3.3. Region of interest

The four studies that used ROI approaches provided evidence for microstructural abnormalities in areas largely consistent with locations identified at the whole brain level, including lower FA in the SLF (Ashtari et al., 2009) and in prefrontal, parietal, temporal (Clark et al., 2012), and callosal (De Bellis et al., 2008) white matter (see also higher FA in the rostral body and isthmus of the corpus callosum, projecting into motor and sensory areas, respectively; De Bellis et al., 2008). Two of the ROI studies (Clark et al., 2012; Jacobus et al., 2012) also found lower FA in association with greater levels of substance use or related problems, including prospective associations between lower FA in the fornix and superior corona radiata at 16–19 years of age and more days of substance use (in the past month) 1.5 years later (Jacobus et al., 2012). ROI selection differed between these studies, making direct comparisons difficult. Collectively however, the findings demonstrate that the examination of specific regions or tracts can be used to highlight areas with abnormal white matter microstructure in adolescent substance users.

4. Discussion

Ten DW-MRI studies comparing white matter microstructure in adolescent substance users with control participants were systematically reviewed. Nine studies found lower FA and five studies found diffusivity (AD, RD, or MD/Tr) differences, consistent with the notion that heavy substance use during adolescence is associated with white matter abnormalities or, more specifically, altered white matter microstructure. These microstructural abnormalities

were detected using both whole brain and ROI analysis approaches, and were predominantly located in putative neocortical association pathways, particularly intrahemispheric tracts, such as the SLF, but also the corpus callosum. Several projection and thalamic pathways were also implicated. Seven studies found an association of FA with patterns of substance use across multiple neuroanatomical locations, including six studies that found *lower* FA in association with greater levels of alcohol and/or cannabis use or related problems, and three studies that found *higher* FA to be associated with heavier substance use. While the former pattern (i.e., a negative association) is often expected because lower FA is typically thought to represent white matter in relatively poor condition (see Table 1), higher FA has also been found in some clinical populations (e.g., individuals with affective disorders and attention deficit/hyperactivity disorder; for reviews, see Sexton et al., 2009; van Ewijk et al., 2012), suggesting that both patterns may reflect the dose-dependent negative effects of substance use during adolescence.

Such findings are consistent with the adult literature, particularly in terms of neuroanatomical locations, with several studies of adults with SUDs also showing microstructural abnormalities in neocortical association (intrahemispheric and callosal) pathways as well as projection and thalamic pathways. Additionally, studies of adults (e.g., Bora et al., 2012; Gruber et al., 2011; Pfefferbaum et al., 2009; Zalesky et al., 2012; see also Arnone et al., 2006) have also found DW-MRI measures to be associated with patterns of substance use, particularly lower FA in association with heavier substance use. These similarities suggest that heavy substance use affects white matter microstructure early on, which is consistent with the notion that the developing brain may be especially vulnerable to the damaging effects of psychoactive drugs (Lubman et al., 2007). Further support for this notion comes from a recent longitudinal study that examined individuals with significant exposure to alcohol and cannabis by mid-adolescence (Bava et al., 2013). After identifying baseline abnormalities in white matter microstructure (see also Bava et al., 2009; Jacobus et al., 2009, 2012), greater alcohol consumption over the subsequent 18 months predicted higher diffusivity in the SLF (RD and MD/Tr) and posterior corona radiata (AD and MD/Tr) in the absence of cannabis-related effects. Interestingly however, neither adolescent alcohol or cannabis use predicted changes in FA, suggesting that the impact of different levels of substance use on specific indices of white matter microstructure may vary (particularly as other studies have identified altered FA in association with heavy substance use).

An alternative explanation for the convergence of findings between adolescent and adult substance users is the possibility that some of the observed abnormalities in white matter microstructure may precede substance use onset as well as increase risk for the later development of SUDs. There are two lines of evidence that partially support this notion. First, abnormal white matter microstructure is evident among substance-naïve adolescents with a family history of AUD; a study using TBSS and follow-up ROI analyses (Herting et al., 2010) reported lower FA in several white matter tracts, including the SLF, ILF, and anterior superior corona radiata, showing a striking similarity to the pattern of findings reported in adolescent and adult substance users. These adolescents also had slower reaction times (cf. controls) when choosing between immediate and delayed rewards on a delay discounting task, with the relationship between family history status and slower reaction times mediated by lower FA in the left ILF (a neocortical association pathway) and right optic radiation (a thalamic pathway). Second, abnormal white matter microstructure is prospectively related to substance use; as mentioned previously, a prospective ROI study (Jacobus et al., 2012) found that lower FA in the fornix and superior corona radiata at 16–19 years of age predicted a greater propensity for risk-taking behaviours 18 months later, including more frequent

substance use in the past month. Although in this study the adolescents already had significant exposure to alcohol and cannabis prior to baseline DW-MRI, the findings suggest that abnormal white matter microstructure in corticosubcortical pathways may be a risk factor for the development of SUDs.

Both lines of evidence are consistent with the notion that the risk conferred by abnormalities in white matter microstructure for SUDs may occur indirectly, through impairment of cognitive and affective functioning (Clark et al., 2008). For example, microstructural abnormalities in pathways that putatively subserve the frontal mediation of attention (e.g., SLF) or behaviour (e.g., anterior corona radiata) could contribute to deficits in the ability to focus and shift attention or inhibit inappropriate behavioural responses, respectively; such deficits have been identified among at-risk adolescents and individuals with SUDs (for reviews, see Lubman et al., 2004; Koob and Volkow, 2010). Similarly, abnormal white matter microstructure in subcortical association pathways (such as the fornix, as identified in two of the studies reviewed) could alter interactions between affect and memory, and thereby contribute to affective dysregulation; this is a known risk factor for SUDs and is commonly observed among addicted individuals (see Cheetham et al., 2010). Alterations to these pathways also may underpin maladaptive patterns of learning, memory, and motivation that are also commonly observed among people with SUDs (see Robbins et al., 2008). The consistency of findings across at-risk, adolescent substance-using, and chronic SUD populations suggests that some white matter abnormalities may not entirely be a consequence of exposure to alcohol and other drugs of abuse. However, the extent to which abnormal white matter microstructure precedes substance use onset and increases risk for the development of SUDs remains largely unknown, and is further complicated by uncertainties regarding the relative contribution and temporal precedence of impaired cognitive and affective functioning in relation to white matter abnormalities and substance use.

4.1. Methodological considerations

Studies of white matter microstructure in adolescent substance users should be interpreted in the light of some important methodological considerations. Above all, most studies to date have been limited to cross-sectional designs. Thus, we cannot ascertain whether substance use during adolescence impacts developing white matter (with implications for subsequent regulation of substance use behaviour), or whether some abnormalities in white matter microstructure precede substance use onset and increase the risk of developing SUDs. The studies were also susceptible to several challenges inherent in SUD research, including inconsistent measures of substance use, heterogeneity of substance use (in terms of duration, dose/quantity, frequency, and polysubstance use), and high rates of co-occurring psychological disturbances and psychiatric symptomatology. Additional issues common to mental health research included inconsistent eligibility criteria, loss of statistical power due to small and heterogeneous samples, and limited assessment of background psychosocial factors.

From a neuroimaging perspective, there was considerable variation in acquisition protocols/parameters known to influence the reliability of DW-MRI data (e.g., number of gradient directions, *b*-weight; Jones, 2009; Jones et al., 2012). Furthermore, since the publication of the majority of studies selected for this review, experts have highlighted a number of limitations concerning the quantification of DW-MRI data, especially those arising from the application of tensor-based approaches (Jones et al., 2012). It is now widely acknowledged that tensor-based models can be problematic, primarily because of their limited capacity to resolve microstructural properties in voxels with complex fibre tract arrangements (it has been estimated that approximately 90% of

white matter voxels contain multiple fibre orientations). Possible consequences of this approach include the inaccurate segmentation or spurious reconstruction of fibre trajectories and, within these, the inaccurate parameterisation of the condition of white matter (Jeurissen et al., 2012). For example, voxels with crossing fibres have lower FA than voxels with single fibre orientations. As such, a finding of lower FA within a voxel may reflect the fact that one group has a more complex fibre tract arrangement in that voxel than another group, and is not necessarily indicative of poorer white matter microstructure.

4.2. Current challenges and future directions

This area of research faces a couple of major challenges that will require ambitious solutions. Foremost is the dearth of prospective, longitudinal, and long-term follow-up data. Future research using DW-MRI in the same individual at multiple time points during adolescence (e.g., Bava et al., 2013) would be especially informative for understanding the complex interplay between white matter microstructure and substance use as a function of risk, exposure, and abstinence, respectively. To fully understand these relationships, repeated and comprehensive assessments of bio-psycho-social factors, including psychopathology and psychiatric symptomatology, will also be required.

Secondly, while tensor-based approaches have established DW-MRI as a valuable research tool and clinically useful technique that is capable of detecting abnormalities in white matter microstructure, this area of research is confronted by the formidable challenge of interpreting existing results in the light of current thinking on the limitations of these approaches. Furthermore, with recent advances in techniques for the acquisition, processing, and analysis of DW-MRI data, a new challenge is considering the impact that different protocols/parameters, data processing conditions, and analytical approaches can have on novel research findings and their integration with earlier data. Nevertheless, these recent advances in DW-MRI provide an opportunity for researchers to better characterise individual variation in human brain anatomical connectivity and explore its relationship with patterns of substance use. In this regard, we suggest that future studies utilise higher order models of diffusion and advanced tractography algorithms (see Tournier et al., 2011, for review) in combination with novel measures of brain connectivity (e.g., Iturria-Medina et al., 2007; Zalesky and Fornito, 2009). Although these methods have particularly demanding acquisition and processing requirements, which currently hinder their clinical use, they hold promise for advancing our understanding of the neural circuits related to substance use.

5. Conclusions

Research using DW-MRI in adolescent substance users provides evidence for abnormal white matter microstructure in putative neocortical association pathways and in projection and thalamic pathways, largely in line with research using DW-MRI in adults with SUDs. This consistency, along with evidence for dose-dependent relationships between DW-MRI measures and patterns of substance use, suggests that white matter microstructure is impacted in the early stages of heavy substance use. However, there is also evidence to suggest that some abnormalities in white matter microstructure may precede substance use onset and increase risk for the development of SUDs, rather than being entirely a consequence of substance use exposure. In order to understand the temporal precedence of white matter abnormalities in relation to SUDs, prospective, longitudinal, and long-term follow-up research will be essential. Such future research will also need to capitalise

on recent advances in DW-MRI acquisition, processing, and analysis techniques to better characterise white matter *in vivo* and, with unparalleled detail, reveal the nature of the relationship between white matter and substance use.

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