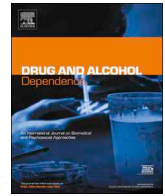




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Review

Substance abuse and white matter: Findings, limitations, and future of diffusion tensor imaging research

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ABSTRACT

Individuals who abuse substances often differ from nonusers in their brain structure. Substance abuse and addiction is often associated with atrophy and pathology of grey matter, but much less is known about the role of white matter, which constitutes over half of human brain volume. Diffusion tensor imaging (DTI), a method for non-invasively estimating white matter, is increasingly being used to study addiction and substance abuse. Here we review recent DTI studies of major substances of abuse (alcohol, opiates, cocaine, cannabis, and nicotine substance abuse) to examine the relationship, specificity, causality, and permanence of substance-related differences in white matter microstructure. Across substance, users tended to exhibit differences in the microstructure of major fiber pathways, such as the corpus callosum. The direction of these differences, however, appeared substance-dependent. The subsample of longitudinal studies reviewed suggests that substance abuse may cause changes in white matter, though it is unclear to what extent such alterations are permanent. While collectively informative, some studies reviewed were limited by methodological and technical approach. We therefore also provide methodological guidance for future research using DTI to study substance abuse.

1. Introduction

There has been recent upsurge of neuroimaging research seeking to examine the risk-factors, neural mechanisms, and neuropathological outcomes of addiction and substance abuse. Neuroimaging studies of drug-abusing and drug-dependent individuals have revealed significant alterations in both brain structure (Franklin et al., 2002; Matochik et al., 2003) and brain activity (Goldstein and Volkow, 2002; Suckling and Nestor, 2017). Such studies have provided converging evidence that substance abusing behaviors involve the neural circuitry relating to reward, memory, motivation, executive function, affect, and metacognition (Koob and Volkow, 2016; Noël et al., 2013). These constructs have in turn been tied to specific grey matter brain regions including the ventral striatum (and component nucleus accumbens), ventral tegmental area, ventral pallidum, extended amygdala, prefrontal cortex, and thalamus (Kalivas and Volkow, 2005).

Despite this progress, our ability to predict, diagnose, and track addiction in humans based on brain images has been relatively limited. The difficulty elucidating such outcomes may be partly due to a relative dearth of research considering neural white matter, which constitutes over half of human brain volume and plays a vital role in governing communication between cortical areas (Fields, 2008). Diffusion magnetic resonance imaging has emerged as a method to non-invasively

examine white matter in the human brain and relate such connectivity to substance abuse and addictive behaviors (Suckling and Nestor, 2017).

1.1. Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique that estimates white matter *in vivo* (Bihan et al., 2001) and is increasingly being used to study the biology of addiction. DTI data can be used to infer information about white matter macrostructure, microstructure, and connectivity. White matter macrostructure is typically measured in terms of total volume, or volume of particular tracts of white matter fibers, i.e. bundles of axons. Using additional analytic techniques that model the direction of water movement, DTI can also capture the microstructural properties of white matter. The most commonly reported measure of white matter microstructure is fractional anisotropy (FA). FA is a composite measure of the extent to which water diffusion is constrained along a particular direction. Axons and their myelinated sheaths restrict water diffusion such that it is greater in the axis parallel to the main direction of axons (Soares et al., 2013). FA is often used as a general index of white matter “coherence”, with lower numbers often reported as “worse” (e.g. Kubicki et al., 2005). Changes in FA signal one or many microstructural alterations,

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such as Wallerian degeneration (Pierpaoli et al., 2001; Thomalla et al., 2004) or decreased neuronal membrane permeability (Jones et al., 2013).

Several other indexes of microstructure, including mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) are also often reported in DTI studies. MD corresponds to the molecular diffusion rate, with higher values corresponding to higher diffusivity, which is often observed in damaged tissues (Jones et al., 2013). RD has been used to infer demyelination or dysmyelination, with greater RD indicating more severe of either of the former (Song et al., 2005; Wozniak and Lim, 2006). AD increases potentially indicate axonal degradation (Song et al., 2005), while AD decreases are often associated with healthy brain maturation (Tamnes et al., 2010). Together, these measures have the potential to offer critical insight into substance-related brain alterations to white matter microstructure.

1.2. Review motivation and aims

In this review, we survey the past decade of DTI research with the goal of examining the relationship, specificity, and directionality, of substance-related differences in white matter microstructure. We attempt to synthesize the results from following major substance categories: alcohol, cannabis, cocaine, nicotine, and opiates. To augment this review, we conduct a mini meta-analysis of the overlapping findings, and compare the relative effect sizes of various abused substances on human white matter. We organize this review into sections examining cross-sectional and longitudinal research of substance-related differences in white matter microstructure. We then discuss the possible mechanisms of these findings, the limitations of the studies reviewed, and offer guidance for future research.

1.3. Literature selection and exclusion criteria

We searched the Web of Science database (<http://apps.whoofknowledge.com/>) and PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) using the following Boolean criteria: “white matter” AND (“DTI” OR “DWI” OR “diffusion” OR “dMRI”) AND “[substance of abuse]”. The substances of abuse in this case were “alcohol”, (“cannabis” OR “marijuana”), “cocaine”, “nicotine”, and (“opiates” OR “heroin”). This search included articles published through December of 2018. Inclusion criteria were: (i) employed diffusion weighted or tensor magnetic resonance imaging; (ii) published no earlier than 2008; (iii) sample size sufficiently powered to conduct at least group level statistics.

It was critical to our review that we only include research with methodologies appropriate to address our aims, leading to several exclusion criteria. First, we aim to examine if consistent relationships exist between *individual* substances of abuse and white matter microstructure. As studies of polydrug users obfuscate such one-to-one relationships, studies examining polydrug use were excluded. Second, studies using participants intentionally drawn from clinical populations, aside from substance abuse or addiction, were also excluded; the white matter differences observed in such studies could be due to clinical disorder, rather than substance-related. Studies that met our inclusion and exclusion criteria were then grouped by substance of abuse and details of each study were extracted (Table 1). In the following sections, we first review the cross-sectional studies, and then the longitudinal DTI research on substance abuse.

2. Cross-sectional research

The first natural question we might ask is whether abuse of an addictive substance is associated with consistent, significant differences in white matter? In this section, we review the cross-sectional research for each substance individually to address this question. When appropriate, we also sub-divide studies by age group examined and severity of abuse

studied.

2.1. Alcohol

Gross anatomical estimations indicate that alcohol-abusing individuals have lower white matter volume (Arnone et al., 2008; Pfefferbaum et al., 2006). However, such macrostructural differences are not always detectable in those with mild alcohol use disorder or a shorter history of alcohol abuse (Asensio et al., 2016), underscoring the value of the more fine-grained microstructural measures possible with DTI. The DTI studies of alcohol abuse reviewed varied in both the participant age and type of drinking behavior being studied.

A subgroup of these alcohol-related studies examined binge, or otherwise heavy, drinking in adolescent populations. Two independent research groups found that binge-drinking adolescents—compared to controls—had lower FA (Badsberg Jensen and Pakkenberg, 1993; McQueeney et al., 2009). FA also seems differentiate between high and low severity of heavy adolescent drinkers, such that those with higher Alcohol Use Disorder scores tends to have lower FA (Thayer et al., 2013). Although one large study in younger adolescents found *higher* FA in individuals with higher Alcohol Use Disorders scores (Cardenas et al., 2013), this result did not stand after correction for multiple comparisons.

Mirroring the general finding among adolescents, alcohol-abusing adults also exhibit lower FA than controls (Harris et al., 2008; Schulte et al., 2010). Consistent with previous FA findings, measures of AD showed a positive relationship with alcohol abuse. That is, alcohol was associated with higher AD in alcohol abusing groups (Pfefferbaum et al., 2014; Topiwala et al., 2017). At variance with the aforementioned studies finding linear relationships, one recent and well-powered ($n = 377$) study suggests that there may be an inverted-u relationship between alcohol use and white matter microstructure. Specifically, light and moderate alcohol consumption was associated with increased FA, whereas heavy consumption (28 drinks or more within a two-week period), was associated with marked decreases in FA (McEvoy et al., 2018). Together these results highlight the importance of both age and dosage in determining the relationship between alcohol and white matter.

2.2. Cannabis

Studies examining the relationship between cannabis abuse and white matter microstructure have yielded conflicting results (Cousijn et al., 2012). One preliminary study (Arnone et al., 2008) found no white matter differences between users and non-users, leading the authors to conjecture that cannabis use does not result in neurotoxic outcomes. However, several shortcomings in the methods of this study (e.g. only partial control of alcohol intake, and low magnetic field strength) should temper any strong conclusions. These limitations, and others, are addressed in more depth in the *Discussion* section and are summarized in *Box 1*.

Contrary to this null finding, studies of *heavy* cannabis users have tended to find significant differences in white matter microstructure. For instance, Ashtari and colleagues found that heavy users of cannabis exhibited lower FA (Ashtari et al., 2009). This association between heavy cannabis use and lower FA was subsequently replicated by an independent research group (Gruber et al., 2011). In addition to the research on heavy users, recreational or “regular” cannabis use has also been studied using DTI. Two such studies found that regular cannabis to be associated with lower FA (Jakabek et al., 2016; Shollenbarger et al., 2015). Contrasting with these findings of linear relationships, other research points to a quadratic relationship. Specifically, higher FA has been observed following regular initial marijuana use, but FA then decreases with extended use (Filbey et al., 2014). The relationship between RD and cannabis use is similarly mixed, with studies finding higher (Ashtari et al., 2009; Becker et al., 2015; Jakabek et al., 2016),

Table 1
 A summary of recent diffusion imaging studies examining the relationship between white matter microstructure and addictive substances. ROI = region of interest; ns = not significant; np = not reported; Δ = FA-change measure; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; IFOF = inferior longitudinal fasciculus; UF = uncinate fasciculus.

Substance no.	Author(s)	n	Field strength (Tesla)	Gradient directions	Specificity	Approx. age range	Other substance controlled	FA	RD	MD	AD	Locus of microstructural difference
Alcohol												
1	Cardenas et al., 2013	100	3	30	whole brain	13 to 15	yes	↑	nr	ns	nr	formix, stria terminalis
2	Harris et al., 2008	30	3	6	ROI	33 to 76	partial	↑↑	nr	nr	nr	SLF, orbitofrontal cortex, cingulum
3	Jacobus et al., 2013	16	3	15	whole brain	16 to 18	no	↓	nr	nr	nr	superior corona radiata, splenium, forceps major
4	Jacobus et al., 2009	42	3	15	whole brain	16 to 19	partial	↓	nr	nr	nr	corona radiata, ILF, IFOF, SLF
5	McEvoy et al., 2018	377	3	N/A	ROI	56 to 66	no	↓↑	↑	ns	nr	UF, forceps minor, IFOF, SLF, anterior thalamic radiation
6	McQueeny et al., 2009	28	3	15	whole brain	16 to 19	partial	↓	nr	nr	nr	SLF, ILF, corona radiata, internal and external capsules, corpus callosum, cerebellum, and limbic projection fibers
7	Pfefferbaum et al., 2014	103	1.5	N/A	whole brain	20 to 60	partial	↓	nr	nr	↑	genu of corpus callosum, body of corpus callosum, anterior and superior projection fibers
8	Topiwala et al., 2017	527	3	30	N/A	14 to 18	no	↓	↑	↑	↑	anterior corpus callosum, genu and anterior body
9	Thayer et al., 2013	125	3	30	whole brain	14 to 18	partial	↓	nr	ns	nr	corona radiata, SLF
10	Arnone et al., 2008	22	1.5	12	whole brain	19 to 29	partial	ns	nr	↑	nr	prefrontal sub-region of corpus callosum
11	Ashtari et al., 2009	14	1.5	15	whole brain; ROI	18 to 21	partial	↓	↑	↑	↓	arcuate fasciculus, internal capsule/thalamic radiation, corpus callosum, motor tracts, and regions of the prefrontal cortex
12	Becker et al., 2015	60	3	30	whole brain	15 to 23	partial	↓	↑	nr	nr	SLF, superior frontal gyrus, corticospinal tract, thalamic radiation
13	Filbey et al., 2014	110	3	32	ROI	20 to 36	yes	↑	↓	ns	ns	forceps minor
14	Gruber et al., 2011	30	3	6	ROI	16 to 34	partial	↓	nr	nr	nr	frontal lobe
15	Gruber et al., 2014	25	3	48	whole brain; ROI	15 to 30	partial	↓	nr	↑	nr	genu of corpus callosum, internal and external capsules
16	Jakabek et al., 2016	56	3	54	whole brain	18 to 55	partial	↓	↓↑	nr	↓↑	forceps minor, left ILF, right cingulate gyrus, left angular bundle, left anterior thalamic radiation
17	Orr et al., 2016	466	3	N/A	ROI	22 to 35	no	↓	↑	ns	ns	SLF, ILF, and forceps major and minor
18	Shollenbarger et al., 2015	67	4	12	ROI	18 to 25	yes	↓	ns	↑	ns	UF, forceps minor, anterior thalamic radiation
Cocaine												
19	Azadeh et al., 2016	39	3	21	whole brain	22 to 54	no	↓	nr	nr	nr	corpus callosum
20	Lim et al., 2008	42	3	12	whole brain; ROI	22 to 54	yes	↓	nr	nr	nr	inferior frontal, corpus callosum
21	Ma et al., 2017	11	3	21	whole brain	18 to 55	no	Δ	ns	ns	ns	splenium of the corpus callosum
22	Morie et al., 2017	39	3	32	whole brain; ROI	12 to 18	partial	↓↑	ns	ns	ns	SLF, cingulum
23	Romero et al., 2010	33	1.5	6	ROI	20 to 45	partial	↓↑	nr	nr	nr	inferior frontal, anterior cingulate
24	Baeza-Loya et al., 2016	31	3	71	ROI	25 to 51	no	↓	nr	nr	nr	anterior cingulum bundle
25	Huang et al., 2013	21	3	32	whole brain; ROI	18 to 40	partial	↓	nr	nr	nr	anterior cingulum bundle
26	Hudkins et al., 2012	36	1.5	6	ROI	20 to 50	partial	↑	nr	nr	nr	prefrontal, cingulum, genu of corpus callosum
27	Liao et al., 2011	88	3	30	voxel	19 to 31	yes	↑	nr	nr	nr	SLF
28	Lin et al., 2013	68	3	12	whole brain	38 to 56	partial	↓	↑	↑	↓	genu and rostral body corpus callosum
29	Paul et al., 2008	20	1.5	12	ROI	25 to 40	yes	↑	nr	nr	nr	corpus callosum
30	Wang et al., 2017	19	3	20	whole brain	22 to 42	yes	↑	↓	ns	ns	SLF, left anterior corona radiata, left superior corona radiata, left posterior corona radiata, left external capsule, left IFOF, and sagittal stratum
31	Yu et al., 2016	45	3	30	whole brain; ROI	17 to 23	yes	↑	↓	ns	↑	corpus callosum, SLF, internal capsule, external capsule, corona radiata, thalamic radiata
32	Yuce et al., 2016	176	3	20	ROI	22 to 44	yes	↓	↑	↑	↓	hippocampus
33	Zhang et al., 2011	96	3	12	whole brain; ROI	20 to 40	no	↓	nr	nr	nr	prefrontal cortex
34	Zhang et al., 2018	109	3	60	ROI	16 to 24	yes	↑	nr	nr	nr	prefrontal cortex, supplementary motor cortex, anterior cingulate gyrus

(continued on next page)

Table 1 (continued)

Substance no.	Author(s)	n	Field strength (Tesla)	Gradient directions	Specificity	Approx. age range	Other substance controlled	FA	RD	MD	AD	Locus of microstructural difference
35	Bora et al., 2012	59	3	28	whole brain	23 to 40	partial	↓	↑	nr	↓	corpus callosum, UF, ILF, thalamic radiation; parietal, frontal, temporal, cerebellar tracts
36	Li et al., 2013	32	3	25	whole brain	28 to 40	partial	↓	↑	nr	ns	frontal lobe sub-gyrus, frontal gyrus, temporal lobe sub-gyrus, cingulate gyrus and extra-nuclear, left temporal lobe
37	Liu et al. 2008	32	1.5	13	whole brain	18 to 45	yes	↓	nr	nr	nr	frontal sub-gyral, precentral gyrus, middle cingulate gyrus
38	Qui et al. 2013	52	1.5	32	whole brain	33 to 42	partial	↓	↑	ns	↓	corpus callosum, thalamic radiation, IFOF, ILF, UF, cortical spinal fasciculus, cingulate gyrus; parietal, frontal, temporal tracts
39	Wang et al., 2011	48	3	25	ROI	21 to 48	partial	↓	↑	nr	↓	corpus callosum

lower (Filbey et al., 2014; Jakabek et al., 2016), or nonsignificant (Shollenbarger et al., 2015) differences in cannabis users relative to controls.

These inconsistent findings in the relationship between cannabis use and white matter may be in part due to age of onset. Specifically, lower FA values have been connected with earlier onset of among cannabis users (Gruber et al., 2014). Complimenting this empirical finding, a large meta-analytical study using the Human Connection Project data also found that the earlier the age of onset of marijuana use, the “worse” the white matter microstructural values (Orr et al., 2016). Together, the cross-sectional research on points to a complex relationship between cannabis use and white matter governed by an array of factors including age and age of onset, duration of use, and usage severity.

2.3. Cocaine

Previous structural MRI studies have demonstrated that cocaine use is associated with lower grey matter volume (Narayana et al., 2010). Several recent DTI studies have found that cocaine users had lower white matter FA relative to controls (Azadeh et al., 2016; Romero et al., 2010). This negative association between cocaine use and white matter microstructure is echoed by other research indicating that cocaine-dependent individuals exhibit attenuated increases in white matter volume typical during brain maturation (Bartzokis et al., 2002). Such a negative association has not always been found, however. Interestingly, cocaine abuse is associated with higher FA in certain regions of the brain, and lower FA in other areas (Morie et al., 2017; Romero et al., 2010). Although preliminary, such studies raise the possibility that the mechanism by which cocaine affects the brain may be different than that of other substances. We briefly discuss a mechanism by which cocaine might affect white matter in Section 5.

2.4. Nicotine

Heavy nicotine use in the form of smoking tobacco has been linked to neuropathy (Brody, 2006), often manifesting as prefrontal gray matter atrophy (Gallinat et al., 2006; Zhang et al., 2011). Conversely, consumption of nicotine via smoking has been associated with higher white matter volume (Gazdzinski et al., 2005; Yu et al., 2011). Studies examining nicotine use via DTI have found similarly conflicting results. In chronic nicotine users, heavy consumption has been associated with lower FA (Lin et al., 2013) and higher FA (Paul et al., 2008), as well as both lower RD (Wang et al., 2017) and higher RD (Lin et al., 2013). The results of studies examining non-chronic, regular nicotine use are similarly split. Regular nicotine use has been associated with lower FA (Huang et al., 2013; Liao et al., 2011; Zhang et al., 2011) and higher FA (Hudkins et al., 2012; Wang et al., 2017). These seemingly conflicting nicotine results may be partly accounted for by the developmental stage in which it is consumed, with higher FA more commonly observed in younger nicotine users (Hudkins et al., 2012; Jacobsen et al., 2007). Alternatively, it maybe that the association between nicotine use and higher FA in adolescents is temporary, and eventually leads to microstructural declines with chronic use. Future longitudinal studies could formally address this theory.

2.5. Opiates

Opiate abuse has been associated with changes in cortical blood flow (Fu et al., 2008; Lubman et al., 2009), grey matter loss (Lyoo et al., 2006) and impaired connectivity (Schmidt et al., 2015). More recently, several studies have examined the relationship between opiate and white matter microstructure. Relative to non-using controls, opiate-abusing individuals consistently exhibit both lower FA (Bora et al., 2012; Fu et al., 2008; Li et al., 2013; Qiu et al., 2013; Wang et al., 2011) and lower AD (Bora et al., 2012; Qiu et al., 2013). Turning to RD, again

the findings are consistent, with opiate users exhibiting higher RD. Within opiate users, FA has also been shown to reliably dissociate short- and long-term users, with the latter having significantly lower FA (Qiu et al., 2013). Together the results suggest that longer durations of opiate dependence are associated with more extensive and severe white matter abnormalities.

2.6. Specificity

Our review of the literature suggests that there is a relationship between substance abuse of addictive substances and white matter microstructure. A logical next question is does substance abuse broadly affect white matter or does it systematically affect certain white matter pathways?

Across substance of abuse, the majority of the studies reviewed found differences in major white matter fiber pathways such as the corpus callosum, superior and inferior longitudinal fasciculi. Table 1 includes a summary of neuroanatomical loci of changes in white matter microstructure for each substance. Overall, there was poor consistency in the neuroanatomical loci of significant microstructural differences. In interpreting these findings, however, it is important to note that many of the studies reviewed performed whole-brain analysis of white matter microstructure using TBSS. This approach is limiting in several ways that we discuss further in Section 6. Nonetheless, there did seem to be one consistent finding across substance of abuse: nearly half of the studies reviewed found at least one significant microstructural difference in the corpus callosum, as measured by FA. We therefore conducted a mini meta-analysis to compare the relationship between each substance and corpus callosum FA values, relative to control.

2.7. Mini meta-analysis: Corpus callosum and substance abuse

In this meta-analysis, we seek to compare the relative relationship of different substances on callosal white matter microstructure, as indexed by FA. That is, we aim to address if some substances are associated with greater differences in white matter than are others. To do this, we extracted effect sizes from the studies reviewed (Table 1) in terms of R^2 for any significant difference in the white matter pathway most consistently implicated across substance—the corpus callosum. If effect size was given in terms of R^2 , we recorded it. If effect size was given in another format, we converted it to R^2 . If no effect size was given, but adequate mean FA information was provided, we calculated R^2 . If there was more than one significant finding in the corpus callosum, we took the average of the R^2 values. If a study did not report sufficient information to determine effect size, we excluded it from this analysis.

None of the cocaine studies reviewed provided enough information to extract effect size. In fact, across substance fewer than half of the studied reviewed contained the necessary information to evaluate effect size in the corpus callosum.¹ Accordingly, there was insufficient power to conduct between-group level statistics. However, a visual inspection (see Fig. 1) of the direction and effect size of the FA differences across substances is nonetheless interesting for several reasons. First, users of alcohol, cocaine and opiates exhibited consistently lower FA in the corpus callosum. Within this group, alcohol and opiate use appeared to have a higher magnitude of effect, relative to controls. For cannabis and nicotine, the results were mixed both in terms of direction and effect size. Future research with appropriate statistical power could formally test the veracity of the trends observed here.

¹ We would like to emphasize that effect size is critical for interpretation of results (Ferguson, 2009), and thus advise that it is included in future DTI studies of substance abuse.

² Cocaine is absent from this figure because none of the studies reviewed examining cocaine included sufficient information to calculate effect size.

3. Longitudinal research

In the previous sections we provide evidence for a fairly robust, albeit weakly-specific, relationship between substance abuse and white matter microstructure. We now examine longitudinal research that better speaks to issues of causality, prediction, and permanence.

3.1. Causality and tracking

In this subsection, we review longitudinal evidence and related research that examines the extent to which substance abuse may cause changes in white matter microstructure, and whether DTI can be used to track substance abuse or treatment.

For alcohol, longitudinal research hints at a causal relationship between alcohol abuse and white matter microstructure. In one corroborative study, alcoholic and control groups had their white matter and drinking habits monitored over the course of several years. While both groups showed age-related declines of FA in white matter, alcoholics exhibited lower FA irrespective of age (Pfefferbaum et al., 2014). Similarly, longitudinal research of adolescent drinkers has shown decreases in FA in major white matter pathways following the onset of alcohol use (Jacobus et al., 2013). Together, these results support the notion that alcohol abuse likely induces white matter changes, not vice versa.

For cannabis, the only longitudinal study in this literature similarly suggests that cannabis use causes white matter changes, not the reverse. In this study, heavy cannabis users exhibited significant declines in white matter FA during the two year period for which they were monitored (Becker et al., 2015).

For cocaine, there is also evidence that cocaine use affects white matter microstructure. Compared to adolescents who had not been exposed to cocaine prenatally, exposed adolescents had lower FA in the cingulum and superior longitudinal fasciculus (Morie et al., 2017). The notion that cocaine induces microstructural white matter changes is corroborated by a recent preliminary longitudinal study. Ma and colleagues found that the more times an individual tested positive for cocaine between the two scanning sessions, the more an individual's FA decreased. Similarly, they found that lifetime cocaine use negatively predicts callosal FA. Together, these studies provide fairly consistent evidence that cocaine abuse negatively impacts white matter microstructure (Ma et al., 2017). Finally, white matter FA also seems to track treatment outcome, with higher FA significantly predicting the number of successful days of abstinence from cocaine (Bell et al., 2011; Xu et al., 2010).

For nicotine, none of the studies reviewed utilized an longitudinal design. Despite the lack of longitudinal research, the current evidence suggests that FA may be a valuable measure for tracking progression of nicotine addiction. Specifically, there seems to a negative relationship between FA with daily usage (Baeza-Loya et al., 2016), duration of usage (Wang et al., 2017; Yu et al., 2011; Yuce et al., 2016), and addiction severity (Yu et al., 2011). That is, lower FA values were associated with higher and longer usage, and higher addiction severity.

Finally, for opiates, longitudinal white matter and opiate addiction research is lacking. However, as with nicotine, longer duration of opiate addiction has been associated with lower FA throughout the brain (Qiu et al., 2013) and more specifically with lower FA in SLF and frontal white matter (Bora et al., 2012). Further, FA values reliably dissociate short- and long-term users of opiates, with the latter having significantly lower FA (Qiu et al., 2013). Together the results suggest that longer durations of opiate dependence are associated with more extensive and more severe white matter abnormalities.

4. Possible mechanisms

We intentionally circumscribed this review to diffusion MRI research. Although this approach allows for the estimation of the

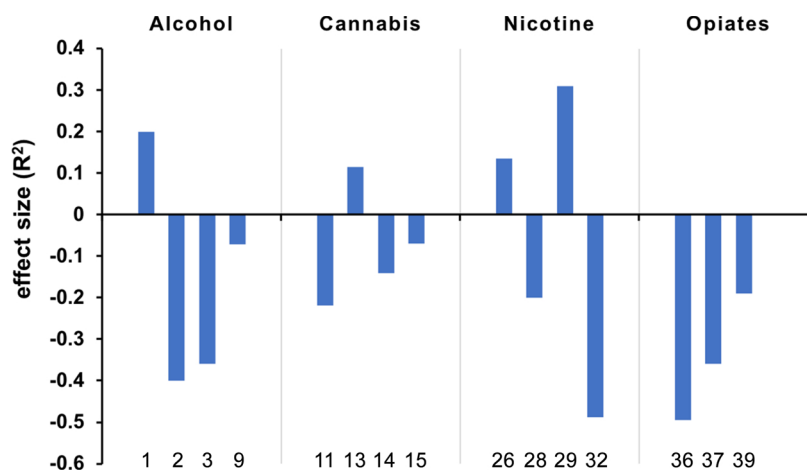


Fig. 1. Mini meta-analysis of the relative effect of substance abuse on corpus callosum white matter microstructure. Only studies that contained sufficient information to record or calculate effect size were included.² All bars are r-squared effect size. Bars below the x-axis indicate substance use group had a mean FA value lower than controls. Bars above the x-axis indicate substance group had a mean FA value higher than that of controls. Numeric bar labels correspond to the study number in Table 1.

microstructural properties of human white matter, it does not tell us *how* substance abuse might affect white matter (for a recent review of environment effects on myelination, see Forbes and Gallo, 2017). Though diverse, most of the proposed mechanisms concern changes to neuronal myelination in some capacity.

Alcohol-induced white matter differences, though not fully understood, may partly stem from liver disease and nutritional deficiencies (Mi et al., 2000). Alcoholism often leads to thiamine deficiency that, in rodent models, can cause thinning of the corpus callosum and death of cortical pyramidal axons. Thiamine deficiency can also lead to demyelination even when overall white matter volume does not decline (Langlais and Zhang, 1997).

Broadly, cannabis may alter white matter via interaction with the cannabinoid receptors that are present in numerous neuronal substrates and cell processes important to myelination (Bava et al., 2009). A particular subtype, CB-1, receptor present in several myelin-related cells including astrocytes (Sánchez et al., 1998), oligodendrocytes (Molina-Holgado et al., 2002), and microglia (Walter et al., 2003). Accordingly, cannabis use may cause microstructural shifts in white matter via CB-1, and other white matter glial cannabinoid receptors.

For cocaine, several mechanisms have been proposed to explain its relationship with white matter. Broadly, cocaine use causes vasoconstriction and hypoperfusion, which in turn affects myelination (e.g. Lim et al., 2008). Specifically, cocaine abuse leads to decreased expression of several myelin-related genes, resulting in lower production of proteolipid protein (PLP), myelin basic protein (MBP), myelin-associated oligodendrocyte basic protein (MOBP), as well as fewer MBP-immunoreactive oligodendrocytes (Albertson et al., 2004; Lehrmann et al., 2003). Neurobiological markers of healthy myelination such as *N*-acetylaspartate are also lower in cocaine users, corroborating the notion cocaine cause neuronal or axonal damage (Li et al., 1999). Cocaine may also induce reactive glial proliferation and hypertrophy (Chang et al., 1999), as well as changes in the cytoskeletal membrane of white matter (Meyerhoff et al., 1999). Together these theories suggest that the measured DTI differences in white matter microstructure, e.g. reductions in FA, are likely due to changes in myelination.

For nicotine, the higher FA observed in some studies may be the result of cholinergic stimulation, which is known to induce myelination (Bartzokis, 2007). Broadly, white matter (Ding et al., 2004) as well as oligodendrocyte precursor cells (Bartzokis et al., 2002) are known to have nicotinic acetylcholine receptors. Nicotine may therefore act on nicotinic acetylcholine receptors that then promote glial proliferation or activity (Garrido et al., 2003; Opanashuk et al., 2001).

Opiate use causes respiratory suppression and vasculitis, leading to hypoperfusion, (Büttner et al., 2000; Kurumatani et al., 1998), which in turn may cause myelination and axonal damage (Kurumatani et al., 1998). Oligodendrocytes appear particularly sensitive: hypoperfusion

and hypoxia triggers apoptosis in oligodendrocytes, which in turn can lead to demyelination (Yin et al., 2013). Such changes in myelination plausibly explain the lower FA often observed in opiate users.

5. General discussion

An increasing number of researchers are using diffusion weighted imaging to study substance abuse and addiction. Our review of the literature indicates that there is a relationship between substance abuse and white matter microstructure. The preponderance of evidence indicates that individuals who abuse alcohol or opiates generally exhibit lower coherence of connective white matter, most often in the corpus callosum or other major white matter pathways. However, several factors such as age, dosage, and duration of use likely influence this relationship. Longer durations of use and heavier use tended to be associated with a larger reductions in FA. The association between either cannabis or nicotine use and white matter microstructure is less clear; some studies reported higher, and others lower FA values in users, relative to non-users. Our review also supports the perspective that substance abuse may cause change in white matter microstructure. The direction of these changes was generally negative, i.e. substance abuse tended to lead to reduced FA, though this appeared to be substance-dependent.

5.1. Does substance abuse affect particular white matter pathways?

The majority of the studies reviewed found differences in major white matter fiber pathways such as the corpus callosum, superior and inferior longitudinal fasciculus. While these observed differences between addicted individuals and healthy controls in these pathways may be valid, such findings do little to tie anatomy to addictive behaviors since the function of these white matter pathways is unclear. That is, it is unclear how lower FA in the corpus callosum would manifest in everyday life. While such white matter changes could, for example, lead to further addictive behavior, altered FA in the corpus callosum has also been associated with a host of other variables such as age (Lebel et al., 2010), gender and handedness (Westerhausen et al., 2004), autism (Hermann et al., 2007), traumatic brain injury (Kumar et al., 2009), schizophrenia (Foong et al., 2000), and bipolar disorder (Barnea-Goraly et al., 2009). Given this, an alternative possible explanation is that some findings were restricted to the most prominent white matter pathways due to the methodological approach. We discuss some limitations of the studies we reviewed in Section 6.

Several studies did find more regionally-specific differences in white matter. These differences were often somewhere in the frontostriatal network, i.e. the white matter that connects the striatum and the frontal lobe (Chudasama and Robbins, 2006). These findings are consistent

with other neuroimaging research suggesting that addiction is partly mediated by dopaminergic and glutamatergic projections among the aforementioned brain regions (Koob and Volkow, 2016). It is plausible that the decision-making observed in addiction might be partly due to, or the result of, aberrant communication caused by altered or damaged white matter between key brain regions (Hampton et al., 2017; Zhang et al., 2011).

5.2. Substances likely affect white matter via different mechanisms

It is tempting to assume that all substances interfere with the myelination process at some stage, leading to demyelination or dysmyelination. While FA and other DTI indices are associated with such changes, it is important to remember that these measures are also affected by many other factors such as transient changes in neuronal membrane permeability (Jones et al., 2013). We therefore recommend cautious interpretation of DTI findings with respect to the underlying mechanisms.

5.3. Substance-related alterations to white matter may not be permanent

Given that our the central nervous system is an intricately balanced, complex network of billions of neurons and supporting cells, some might imagine that extrinsic substances could cause irreversible brain damage. Our review paints a less gloomy picture of the substances reviewed, however. Following prolonged abstinence, abusers of alcohol (Pfefferbaum et al., 2014) or opiates (Wang et al., 2011) have white matter microstructure that is not significantly different from non-users. There was also no evidence that the white matter microstructural changes observed in longitudinal studies of cannabis, nicotine, or cocaine were completely irreparable. It is therefore possible that, at least to some degree, abstinence can reverse effects of substance abuse on white matter. The ability of white matter to “bounce back” very likely depends on the level and duration of abuse, as well as the substance being abused. This theory could be tested in future well-controlled longitudinal studies. If true, this also underscores the need for addiction interventions that are able to induce periods of prolonged abstinence.

6. Limitations of the current literature and suggestions for best practices

Many of the studies that we reviewed were limited in several ways by methodology or design (see Box 1). First, several studies used a 1.5 T MRI scanner. This is likely because 3 T scanners were less widely available even ten years ago. Nonetheless, 3 T scanners have superior signal-to-noise ratio and therefore are preferable (Gonen et al., 2001). Second, the number of channels in the MRI head coil also affects the signal-to-noise ratio, with more channels producing a better ratio (Wiggins et al., 2009). Many of the studies reviewed here did not report head coil information. Relating to the head coil, many of the reviewed studies used as few as 8 gradient directions (see Table 1). The more gradient directions used during image acquisition, the better the white matter tract estimations, with contemporary DTI studies using 64 directions or more. These limitations of the scanner hardware and set-up likely contributed to the notable lack of regional specificity of white matter differences observed in some of the studies reviewed.

Many of the studies reviewed also used whole-brain analyses of white matter microstructure. Whole-brain analyses are typically conducted in the absence of *a priori* hypotheses. The most common analytic technique used in the studies reviewed is a whole-brain analysis technique called Tract Based Spatial Statistics (TBSS). One advantage of TBSS is that it is automated, making it fairly quick and easy to implement. It also gives you whole-brain coverage which is useful in discovery-based science. However TBSS has a number of pitfalls including poor misalignment correction (Zalesky, 2011), and issues with specificity (Bach et al., 2014) and sensitivity (Keihaninejad et al., 2012).

Consistent with this notion, many of the differences in white matter observed in the reviewed literature were in the corpus callosum, corona radiata and other very large white matter pathways.

ROI, or tract of interest analyses, examine specific white matter tracts, often that of two or more grey matter regions—typically based upon the known function of such regions or tracts. Connectivity among ROIs can be obtained via deterministic or probabilistic tractography. Such tractography techniques allow the researcher to examine white matter pathways between two or more predefined regions of interest. Probabilistic tractography is recommended as it has greatly improved robustness to the many kissing and crossing white matter fibers of the brain (Behrens et al., 2007). Probabilistic tractography is often conducted using FMRIB Software Library (FSL) software (Smith et al., 2004); this group provides guides on tractography analyses (<https://fsl.fmrib.ox.ac.uk/fslcourse/lectures/practicals/fdt2/index.html>). Some groundwork for such studies has been laid by probabilistic tractography in other clinical populations including Alzheimer's (Douaud et al., 2011), schizophrenia (Cho et al., 2015; Kubicki et al., 2005), and autism (Ikuta et al., 2014). Specifically, we encourage future study of tracts that connect addiction-related brain areas (Kalivas and Volkow, 2005) such as the ventral striatum, ventral tegmental area, ventral pallidum, the extended amygdala, orbitofrontal cortex, and thalamus. Within this subset, connectivity between the striatum and frontal lobe, i.e. frontostriatal connectivity, may be of particularly interest: frontostriatal connectivity has been consistently linked to reward and impulsive decision making behaviors (Hampton et al., 2017; Peper et al., 2012; van den Bos et al., 2014, 2015).

Behaviorally, some of the studies reviewed were also limited by their lack of control of potential confounds. When probing for the neurobiological basis of a disorder such as addiction, it is critical to select for individuals only taking the substance of interest. Many of the studies, for example, did not adequately control for alcohol use when studying the effect of a second substance. This is problematic as many studies have shown that alcohol use alone is associated with significant differences in white matter microstructure (see Section 2.1). In cases that polydrug use cannot always be controlled for in sample populations, it should at least be controlled for in the ensuing statistical analysis (see Figs. 2 and 3).

These points, among others, are summarized in Box 1. Diffusion weighted imaging is a powerful tool for studying addiction and substance abuse and investigators in the planning phase of a study should try to optimize the pulse sequence and analytic pipeline, which will give them robust and replicable effects. Training in this method can be obtained by going through the FSL tutorial, attending a structural connectivity short course or workshop (<https://www.nmr.mgh.harvard.edu/training/connectivity>), and collaborating with an investigator versed in this technique. We recommend purchasing anatomy reference books since most graduate students and post-doctoral fellows will not learn about white matter through their coursework. Two essential texts are Schmahmann and Pandya *Fiber Pathways of the Brain* (Schmahmann and Pandya, 2009) and Catani and Thiebaut de Schotten's *Atlas of Human Brain Connections* (Catani and Thiebaut de Schotten, 2012).

In terms of future research, diffusion imaging has the potential to answer several “big” questions such as how individual differences in structural circuitry might predispose some individuals to substance abuse and addiction (Box 2). We can also examine whether individual differences in structural circuitry governs the ability to quit without relapse. Importantly, it is possible—and probable—that white matter microstructure is also a predictive risk factor such that certain white matter configurations may predispose individuals to abuse substances. Current research has established the importance of white matter as a component of addiction pathology, but has been limited by methodological and technical approach. Future diffusion imaging research that leverages technological and methodological advances will likely be key in understanding the neural basis and consequences of addictive behaviors.

1. **Study design.** If a study seeks to determine a causal relationship between substance abuse and white matter, a longitudinal design is ideal. Longitudinal designs control for between-subject variance by testing the same participants at different time points and thus have greater inferential value. This design is also useful for questions pertaining to recovery and relapse.
2. **Diffusion imaging acquisition.** 3T scanners are highly preferred to 1.5T scanner, which produce data of significantly lower quality. Similarly, we recommend collection of a minimum of 30 diffusion orientations (although 64 is better) for accurate interpretation of white matter microstructure. Also, several b0s should be included in the protocol and additional “shells” will be required for higher order diffusion models. Finally, head movement is a significant problem in diffusion imaging since the dependent measures are also measures of movement, albeit on a minute scale. This is particularly important in certain clinical populations that are more likely exhibit problematic movement, compromising the quality of the data. This issue can be mitigated by training study participants in a mock-scanner prior to actual scanning. Although not optimal, movement can also be account for in the analysis phase.
3. **Controls.** (1) *polydrug use*: though understandably difficult to control, polydrug use can make it difficult to interpret findings relating specific drugs to specific white matter differences; (2) *age*: white matter is known to vary with age, with some white matter tracts not maturing until age 30 (Libel et al., 2012). Participants should therefore be age-matched to controls; and (3) *gender*: similarly, potential gender differences in white matter should also be considered, even if gender is not a variable of direct interest. Significant gender differences in microstructural indices have been observed in samples of healthy young adults (see Alm et al., 2016).
4. **Comorbidity.** Most diffusion imaging studies do not control for psychiatric disorders even though certain illnesses, such as depression, occur at higher rates in substance abuse populations. As these disorders are known to also be related to altered white matter, they should be accounted for statistically before drawing overarching conclusions.
5. **Modeling white matter.** The issue of kissing and crossing fibers is a problem when using traditional DTI analytical techniques. The diffusion tensor model often has difficulty accurately modeling neural areas where two or more fiber pathways cross. Consideration should be given to techniques more robust to such intersections, such as probabilistic tractography, HARDI imaging, or diffusion spectral imaging.
6. **Neural Specificity.** Sustained drug abuse likely has global physiological effects on white matter that would be instantiated in altered whole brain white matter volume as well as altered whole-brain FA, as observed in this review. However, it may be wise to do hypothesis testing on specific tracts as damage to particular fiber pathways may be predictive of cognitive differences that accompany addiction, as well as behaviors of clinical interest, such as relapse. For instance, white matter microstructure between the ventral striatum and medial prefrontal cortex has been shown to predict reward impatience in neurologically normal young adults (Hampton et al., 2017). Individuals who suffer from substance abuse, which is characterized by impatient responding to rewards, likely have altered microstructure in this circuit.
7. **Interpretation of white matter indices.** FA is a valuable summary measure of microstructure. However, as a composite measure, it is less specific than component measures. Therefore, we recommend that researchers assess radial (RD) and axial diffusivity (AD) in addition to FA. Further, we recommend that future studies interpret the meaning of higher versus lower FA values with caution, and examine interhemispheric differences, as direction of effect can vary between hemisphere.

Fig. 2. Box 1. Best practices in conducting diffusion imaging studies on substance abuse.

1. To what extent are white matter differences observed in substance users the cause or effect of such use?
2. If the cause, to what degree can white matter altered by drug abuse regenerate and repair after drug cessation? Does this capacity interact with age and other health indices such as nutritional status?
3. How much of the variance in white matter microstructure is genetically determined, making a subset of individuals more prone to addiction? This causality dilemma may require special experimental designs, such as a twin study.
4. Can individual differences in white matter microstructure be linked to specific differences in cognition and behavior that accompanies substance abuse?
5. Can responsiveness to drug cessation treatment be predicted or tracked by individual differences in white matter microstructure?
6. Can specific white matter tracts, e.g. those connecting addiction-related brain areas such as the ventral striatum, ventral tegmental area, amygdala, and orbitofrontal cortex, account for addictive behaviors?
7. If specific tracts are identified as predictive of addictive behaviors, what is the relative predictability of this measure?

Fig. 3. Box 2. Questions for Future Research.

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Conflicts of interest

Authors declare no conflicts of interest.

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