Drug and Alcohol Dependence 201 (2019) 29–37

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Regional differences in white matter integrity in stimulant use disorders: A meta-analysis of diffusion tensor imaging studies

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ARTICLE INFO

Keywords:
Stimulant use disorder
White matter integrity
Diffusion tensor imaging
Meta-analysis
Cocaine
Methamphetamine

ABSTRACT

Background: Converging lines of evidence from diffusion tensor imaging (DTI) studies reveal significant alterations in white matter (WM) microstructure in the prefrontal cortex of chronic stimulant users compared to controls, suggesting compromised axonal microstructure and/or myelin.
Methods: A meta-analysis of DTI-based WM integrity was conducted for white matter regions across the corpus callosum and association fibers. Articles were sourced and selected using PRISMA guidelines for systematic review and meta-analysis. Inclusion and exclusion criteria were determined by the authors in order to best capture WM integrity among individuals with primary stimulant use in comparison to healthy control subjects.
Results: Eleven studies that focused on region-of-interest (ROI)-based analysis of WM integrity were extracted from an initial pool of 113 independent studies. Analysis across ROIs indicated significantly lower fractional anisotropy (FA) values in stimulant use groups compared to controls with a small to moderate overall effect (Hedges' g = -0.37, 95% CI [-0.54, -0.20]). Eigenvalues were also analyzed, revealing a significant effect for radial diffusivity (RD; Hedges' g = 0.24, 95% CI [0.01, 0.47]) but not axial diffusivity (AD; Hedges' g = 0.05, 95% CI [-0.20, 0.29]) or mean diffusivity (MD; Hedges' g = 0.20, 95% CI [-0.01, 0.41]). Subgroup analyses based on specific ROIs, primary substance use, poly-substance use, and imaging technology were also explored.
Conclusion: Results of the present study suggest a consistent effect of compromised WM integrity for individuals with stimulant use disorders. Furthermore, no significant differences were found between cocaine and methamphetamine-based groups.

1. Introduction

Cocaine (CO) and methamphetamine (MA) are the two most commonly abused psychostimulants. In the United States, these stimulants rank third in prevalence behind marijuana and misuse of prescription opiates, with approximately 2.8 million individuals reporting past month use (Hughes et al., 2013). Of the stimulants, cCO presents the largest burden to the healthcare and criminal justice systems in terms of mortality, morbidity, violent crime, and unemployment– and this trend has not declined significantly for decades (SAMHSA, 2014). Regions of the US are facing what appears to be a resurgence of cocaine abuse, with more overdose deaths in the US in 2015 to 2017 than any other period since 2000 and a 61% increase in new users from 2013 to 2015 (Hughes et al., 2013; U.S. Department of State, 2017). Similarly, according to recent epidemiological reports, rates of MA use disorder are on the rise (Courtney and Ray, 2014). Over 535,000 individuals were estimated to meet MA dependence criteria in 2012 as compared to 329,000 in 2011 (SAMHSA, 2014). In 2017, MA accounted for more than 10,700 drug-related overdose deaths in the US, ranking third behind deaths related to opioids and CO (Kariisa et al., 2019). Stimulant use disorder is a chronic relapsing condition that produces an allostatic load on the brain and body, resulting in key neurobiological alterations (Courtney and Ray, 2014).

The last two decades of neurobiological research have yielded brain imaging evidence for both functional and structural impairments associated with stimulant use disorder. Neuroimaging studies, including

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https://doi.org/10.1016/j.drugalcdep.2019.03.023
Received 14 February 2019; Received in revised form 20 March 2019; Accepted 25 March 2019
Available online 29 May 2019
0376-8716/

Table 1
Inclusion and exclusion criteria.

Item	Inclusion Criteria	Exclusion	Rationale
1.	Illicit Substance use/dependence disorder based on DSM-IV, DSM-5, ICD-9, or ICD-10 criteria.	Self-reported use or other lack of formal diagnostic evaluation.	**Generalizability.** Relevant to individuals who meet diagnostic criteria for abuse.
2.	Stimulant use/dependence identified as the primary disorder in the stimulant use group.	Axis 1 mental health or other non-stimulant substance use disorders identified as primary.	**Generalizability.** Aimed at reducing confounding variables that may be responsible for WM impairment.
3.	Inclusion of one or more major white matter tracts (e.g., corpus callosum, association fibers).	Individual anatomical structures; no association tracts	**Methodological and Data Quality.** Aimed at reducing heterogeneity due to lack of standardization related to ROI identification
4.	Experimental or quasi-experimental designs with comparison of individuals who use stimulants to controls.	Non-experimental designs; lack of a control group.	**Methodological.** Inclusion of control groups. Baseline differences between conditions (if unmatched) can be statistically controlled.
5.	Fractional anisotropy as ROI outcome.	TBSS methods.	**Methodological.** Outcome of interest.
6.	Data in article or provided by authors sufficient for effect size calculation.	Ambiguous data (e.g., bar graphs without exact numbers); Unable to receive data from the authors after contact	**Analysis.** Necessary for data synthesis and analysis.
7.	Publications sourced from a peer-reviewed journal	Unpublished findings; articles from other journals; dissertations; poster/conference presentation	**Data Quality.** Peer review process may add somewhat to risk of bias, but studies that have been subjected to peer-review are thought to have potentially higher methodological quality.
8.	English Language Text		**Accessibility.** Necessary for data extraction and synthesis.
9.	Adult human participants (18 +)	Animal studies; participants < 18 years old.	**Generalizability.** Necessary for analysis on substance use in adulthood. Reduces possible differences based on developmental factors.

positron emission tomography (PET) and single-photon emission computed tomography (SPECT), have reliably identified various prefrontal cortex regions of activation that relate to core clinical symptoms of addiction (Goldstein and Volkow, 2011; Volkow et al., 2003). A recent meta-analysis of human in vivo PET and SPECT imaging studies suggests altered dopamine receptor density and release is associated with long-term exposure to the effects of stimulants; however, causal inferences cannot be drawn from this dataset (Ashok et al., 2017). Neuroimaging studies have also revealed broad structural abnormalities, including volume differences in prefrontal cortical regions subserving several important cognitive functions related to impulsivity, decision-making, and working memory (Kwako et al., 2018). Diffusion tensor imaging (DTI) is the most common imaging modality for brain white matter (WM) structure (Beaulieu, 2002).

DTI is an imaging technique that allows for the evaluation of WM fibers by quantifying the diffusive properties of water within tissue. Fractional anisotropy (FA) provides a general index of axonal integrity by measuring the degree to which water diffusion is constrained in the brain (Alexander et al., 2007). Principal eigenvalues represent mean, axonal, and radial diffusivity directions. Increases in radial diffusion (perpendicular to the direction of the fiber tract) have been associated with altered myelin integrity in cocaine users (Albertson et al., 2004; Moeller et al., 2005) and many other CNS-related diseases, including multiple sclerosis, leukodystrophies, Alzheimer's, and HIV (Acosta-Cabronero et al., 2012; Hoare et al., 2012).

Converging lines of evidence from DTI studies reveal significant alterations in WM microstructure in prefrontal regions of chronic stimulant users compared to controls, suggesting compromised fiber and/or myelin. WM tracts within the corpus callosum have been shown to be particularly susceptible to the chronic effects of stimulant use (Lim et al., 2008; Ma et al., 2009; Moeller et al., 2007, 2005). Region-specific microstructural alterations in WM have been associated with impaired performance on laboratory measures of cognitive control, decision-making (Lane et al., 2010), impulsivity (Moeller et al., 2005), and working memory (Tang et al., 2015) in chronic stimulant users. WM microstructural deficits are positively associated with severity and amount of substance use (Kaag et al., 2017; van Son et al., 2016v) and inversely related to duration of abstinence from stimulant use (Bell et al., 2011).

Studies of WM abnormalities have been meta-analytically reviewed for other substance use disorders, including alcohol (Monnig et al., 2013) and heroin (Wollman et al., 2015), but not CO or MA use disorders (versus control populations). Thus, the objective of this study was to obtain an averaged effect size (ES) for WM integrity, as indexed by FA metrics, associated with stimulant use disorder. Considering WM tissue may be vulnerable to the neurotoxic effects of chronic stimulant use, an improved understanding of the extent and focal regions of impairment may help to identify previously under recognized targets and medications for neuroprotection.

The present study evaluated the overall effect of psychostimulant use on WM integrity across individuals with stimulant use disorders in comparison to healthy controls (HC). The stimulant users (SU) group was defined as individuals with diagnoses of stimulant use disorder for methamphetamine or cocaine. Studies included baseline measurements of DTI for SU and HC groups, regardless of treatment status. Comparisons of WM integrity included a primary outcome of fractional anisotropy (FA) as well as eigenvalues where provided (AD, RD, MD). WM regions across the corpus callosum and association fibers were included in a meta-analytic design by deriving a grand mean effect size of FA for each study across regions-of-interest (ROI). Subgroup analyses were conducted in order to determine differential WM disruption based on demographic and study characteristics as well as stimulant type (cocaine, methamphetamine).

2. Methods

2.1. Eligibility criteria

Inclusion and exclusion criteria were determined by the authors in order to best capture WM integrity in individuals with primary stimulant use (SU) in comparison to healthy control subjects (HC). Terms were derived to capture categories of substance, problematic use, DTI imaging, and methodology (Appendix A), as agreed upon by the committee of authors.

2.2. Search and information sources

Articles were sourced and selected using PRISMA guidelines for systematic review and meta-analysis (Moher et al., 2009). Inclusion and exclusion criteria are included in Table 1 as well as rationale for each inclusion/exclusion choice (i.e., methodological considerations, generalizability, and relevance).

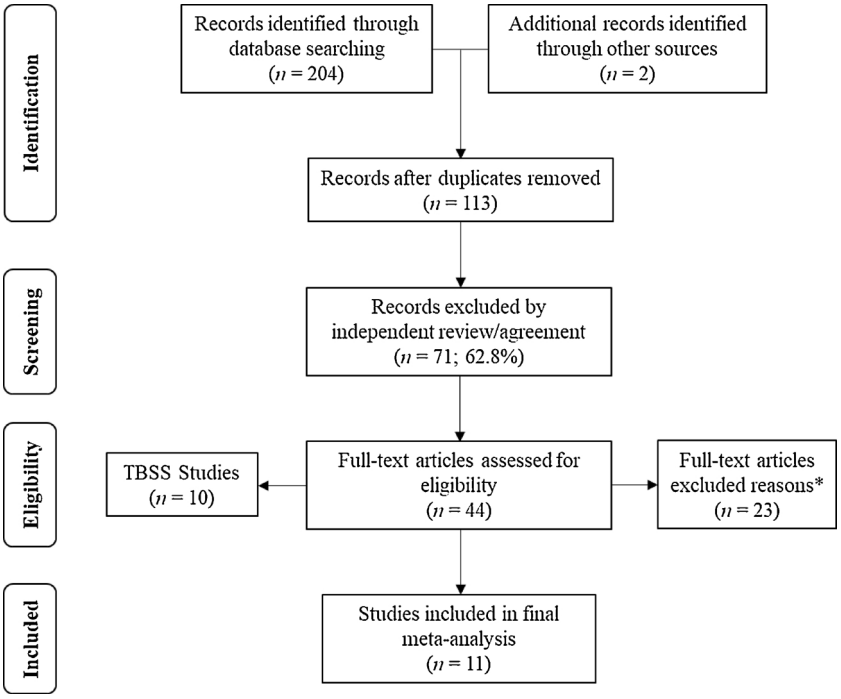

Fig. 1. Prisma flow diagram for study selection.
Note. Lack of healthy control group (n = 2); lack of major white matter tract (n = 3); dissertation/conference paper/abstract (n = 10); duplicate data set (n = 5); insufficient information (n = 3).

2.3. Study selection

Study selection was conducted by two independent reviewers (Authors CB and HS) following the recommendations of the PRISMA group (Moher et al., 2009). Information regarding the article search is included in Fig. 1 with full search terms available in Appendix A[1]. The search was conducted using Pubmed, Embase, and PSYCHINFO databases. Search terms were adjusted based on the formatting of each database for target terms within the journal text (text words). Individual search terms were constructed for cocaine (CO) and methamphetamine (MA) studies.

2.4. Risk of Bias

Risk of bias at the individual study level was addressed through the process of determining methodological quality. Methodological quality was assessed using an author-adapted rating scale from a prior study (Hirst et al., 2017) (Appendix B). Domains evaluated included: study design (3 items), comparability of groups (2 items), participant characteristics (2 items), measurement of stimulant use disorder (3 items), DTI methodology (3 items), and statistical analyses (2 items). Methodological quality was assessed using total number of affirmative responses by calculating the Intra-class correlation with a two-way mixed design (Hallgren, 2012).

Three studies were ultimately excluded due to lack of information. One article that was not included reported *no significant difference* on DTI metrics between individuals with stimulant use disorders and controls (Kelly et al., 2011). The other studies found mixed results based on region of interest (Andres et al., 2016; Chung et al., 2007). These potential findings were considered in the risk of bias analysis, where bias was assessed at the study level, including funnel plot analysis with Egger's regression and publication-level *Fail-Safe N* (Borenstein, 2006; Rosenthal, 1979).

2.5. Summary measures and data extraction

All analyses were conducted using Hedges' adjusted *g*, a standardized difference method with correction for small sample sizes (Hedges and Olkin, 1985). Standardized differences were calculated for SU groups in comparison to HC. Negative effect size outcomes indicate decreased WM integrity in the SU group. Data were extracted from articles and subsequently checked for accuracy in reporting. Where possible, means and standard deviations were extracted (n = 9 studies). However, one study provided data in an alternate form (Lim et al., 2008); thus, effect sizes were calculated based on the standard difference (frontal inferior white matter) and sample size with p-value (other measured areas). Another provided median and range values (Lederer et al., 2016), which were converted using the recommendations of Hozo and colleagues (Hozo et al., 2005). Data were entered into Comprehensive Meta-Analysis (Borenstein et al., 2013) for analysis.

2.5.1. DTI outcomes

Fractional anisotropy (FA) was identified as a primary measurement outcome. All studies provided results for FA for both SU and HC groups across WM association and callosal tracts, and a grand mean effect size was calculated as the primary outcome. Additional outcomes for DTI eigenvalues were also extracted, including mean diffusivity (MD), radial diffusivity (RD), and axonal diffusivity (AD) (Hasan et al., 2011).

2.5.2. Regions-of-interest

Regions-of-interest were derived from the articles based on inclusion and exclusion criteria, specifically to address aims of evaluating WM integrity in association and callosal fiber tracts (Wakana et al., 2004). The decision regarding ROIs was based on author consensus with respect to regions that clearly specified WM versus regions with high fiber crossing and potential involvement of grey matter (Abhinav et al., 2014). As a result, structural regions or regions not identified as callosal or association tracts were excluded (e.g., cingulate, hippocampus, cingulum, insula). The supplementary material includes an exhaustive list of regions included in the analysis. Some regions were

consistently identified across studies (i.e., three or more studies referenced the same region). These areas, including the corpus callosum genu, splenium, and body, as well as frontal WM, were extracted for individual analysis in order to determine the degree of WM group differences within different areas of the brain.

2.5.3. Secondary analyses

Additional subgroups were identified based on study characteristics, including polysubstance use, type of substance (CO vs. MA), and DTI-methodology related outcomes such as magnet strength and brand (see supplemental information)[1]. Where information was available, these features were compared across studies with a grand mean effect size based on all relevant regions. Finally, chronicity of use (i.e., average years of use per study) was entered into a meta-regression to determine the moderating effect of chronicity.

3. Results

Text word search yielded 118 articles from Embase (66 CO, 52 MA), 29 articles from PsychINFO (21 CO, 8 MA), and 57 from PubMed (Fig. 1). The total number of articles sourced from all databases was 204. De-duplication was conducted by using automated and suggested de-duplication reference management software (n = 87) as well as title screening (n = 4). Two authors (CB and HS) reviewed the remaining 113 abstracts using Rayyan web-app for systematic reviews (Ouzzani et al., 2016). The authors demonstrated an overall agreement of 86.7%. Disagreements were resolved with collaborative review in the full-text review process. Rationale for disagreements was explored per the recommendation of (Higgins and Deeks, 2008), and exclusions were due to select reasons, including conference presentations or dissertations (8 articles), inclusion of gray matter only (2 articles), and lack of control group (2 articles). Forty-four articles were selected for full-text review based on abstract review and ancillary articles (n = 2).

Inclusion and exclusion were based on study criteria, and studies with overlapping authors or institutions were screened by the study team to protect from non-independence due to overlapping participant pools. Those studies with the most relevant data for the largest number of participants were chosen for inclusion. Authors were contacted for studies with insufficient information for a full analysis (Andres et al., 2016; Chung et al., 2007; Kelly et al., 2011); however, additional information was not provided, and these articles were subsequently excluded from analysis. After review and de-duplication, the process yielded a pool of 21 studies that evaluated WM via extracting regions of interest (n = 9), tract-based analysis (TBSS; n = 10), or both methods (n = 2). Data for TBSS outcomes were not included, as tract-based studies are beyond the scope of the present analysis due to differences in data processing and presentation. These studies represent a "hold out" sample with plans to analyze TBSS outcomes in the future.

3.1. Study characteristics

Study characteristics are presented in Table 2. All studies included in the final analyses were performed on adults with average ages ranging from 25-45. Average chronicity (i.e., years of stimulant use) ranged from 6 to 19 years. Due to high frequencies of polysubstance use in those with SUDs, we included studies that allowed current or past diagnoses of other substance use disorders. Of the 11 studies, 6 studies excluded individuals if they had a current diagnosis of other substance use disorders (excluding nicotine), whereas 5 studies allowed other diagnoses as long as stimulants were the primary drug of abuse. Nicotine, alcohol, and cannabis were the most commonly reported secondary substances used in these samples. Timing of the scan with respect to last use was variable across studies, with 6 studies indicating that the participants had to be abstinent (ranging from 72 h to several years). While most studies excluded individuals with HIV (n = 5), one chose not to perform the test for ethical reasons (n = 1) and others did not mention HIV as an exclusion criterion (n = 3). Two studies specifically included individuals with HIV: one included an HIV-negative stimulant-use-disorder-positive group, and another only included an HIV-positive and stimulant-use-disorder-positive group.

3.2. Methodological quality

Evaluator responses tended to have a restricted range such that one evaluator provided a small range of scores (Rater 1 Range: 12–14) and another provided a larger, though still restricted, range (Rater 2 Range = 9–16). Scores in this range on the 15-point measure suggest excellent quality overall across studies. Due to the restricted range, article quality was reviewed by examining frequencies. The average score for article quality across studies was within the top third of possible scores, and 90.0% (10 studies) had scores in the top quartile (> 11.25).

3.3. Primary analysis

A grand mean effect size was derived for FA values across all reported regions. Using this method, each study provided one overall effect size, which statistically combined the regions reported in the study. A fixed-effects model was used due to a non-significant amount of heterogeneity in the model (χ^2 (10) = 15.51; p > 0.05). This suggests that the studies demonstrated consistency in measurement and outcome. A forest plot of effect sizes is included in Fig. 2. The primary analysis for FA yielded an effect size in the small to moderate range (g = -0.37, 95% CI: [-0.54, -0.20]; Cohen 1988), indicating FA was lower in the SU compared to the HC group across the corpus callosum and association fibers (Table 3).

3.4. Secondary analysis: eigenvalues

Further effect sizes were calculated based on DTI eigenvalues, including MD (n = 7 studies), AD (n = 5 studies), and RD (n = 6 studies) (Table 3). Though these values were not present across all studies, this secondary measurement analysis was conducted in an exploratory fashion. Overall, a significant effect was found for RD (g = 0.24, 95% CI: [0.01, 0.47]) but not for AD (g = 0.05, 95% CI: [-0.20, 0.29]) or MD (g = 0.20, 95% CI: [-0.01, 0.41]). Note that higher RD values represent decreased WM integrity (the opposite of FA), accounting for the difference in the sign of Hedges' g between FA and RD.

3.5. Regional differences

Results from the subgroup analyses based on reported region of interest are included in Table 4. Frontal WM was evaluated across a number of studies, and identified areas of the Anterior-Commissure Posterior-Commissure Plane (AC-PC Plane), inferior and superior frontal lobes, and frontal WM were included. As with the grand mean effect size, studies that included multiple regions of interest within frontal WM (e.g., left and right regions, various measurements across the AC-PC plane) received an overall effect size for frontal WM that collapsed across regions and laterality. Frontal areas were included in 6 studies and demonstrated a large overall effect using a random effects model (g = -0.71, 95% CI: [-1.36, -0.07]; χ^2 (5) = 36.04, p < 0.05).

Further analyses were conducted for regions of the corpus callosum. Identified regions across studies included the anterior and posterior mid-body, body, corpus, genu, isthmus, rostral body, and splenium. An overall effect size for the corpus callosum was calculated by combining across these regions in 10 studies, yielding a small to moderate effect under the fixed effects model (g = -0.27, 95% CI: [-0.45, -0.09]; χ^2 (9) = 16.43, p = 0.06). Further areas were explored, indicating a moderate effect in the genu (g = -0.42, 95% CI: [-0.76, -0.08]; χ^2 (9) = 31.68, p < 0.05), but failed to find significant effects in the splenium (g = -0.16, 95% CI: [-0.38, 0.06]; χ^2 (6) = 7.04, p = 0.32) or

Table 2
Study Characteristics.

ROI Studies									
First Author	Year	Drug	*n* Patients (Controls)	Age Patients (Controls, years)	Years Use	MRI Tesla	Brand	Timing of Scan	Other Substances
Alicata	2009	MA	30(30)	33.3(32.7)	N/I	3	Siemens	N/I	N
Cordero	2017	CO	37(35)	45.5(41.3)	17.8	3	GE	CUR	Y
Kim	2009	MA	11(13)	34.4(35.5)	10.6	3	GE	ABS	N
Lederer	2016	MA	40(40)	25.5(25.0)	6.5	3	Siemens	ABS	N
Romero	2010	CO	32(33)	31.6(29.1)	11.4	1.5	Siemens	ABS 72hrs	N
Salo	2009	MA	37(17)	36.3(32.2)	11.6	1.5	GE	ABS > 3wk	Y
Tang	2015	ST	21(22)	37.5(39.55)	N/I	3	Phillips	N/I	Y
Tobias	2010	MA	23(18)	32.2(33.3)	8.0	1.5	Siemens	ABS 7-13 day	Y
Ma	2009	CO	19(18)	39.1(35.1)	10.7	3	Phillips	N/I	Y
Lim	2002	CO	12(13)	44.2(40.4)	17.3	1.5	Siemens	N/I	N
Lim	2008	CO	21(21)	42.5(40.9)	18.9	3	Siemens	ABS 4 days	N

Note. PT: Patients; CTL: Controls; ST: Stimulants; CO: Cocaine; MA: Methamphetamine; ABS: Abstinent; CUR: Current Users; N/I: Not Included; Other substances: Y- refers to studies that included participants with current diagnoses of other substance use disorders, N – refers to studies that did not include participants with current diagnoses of other substance use disorders (with the exception of nicotine).

other areas of the body (including areas identified as: the anterior and posterior mind-body, rostral body, corpus, body, and isthmus; g = 0.07, 95% CI: [-0.22, 0.37]; $\chi^2(2) = 2.64$, p = 0.27).

3.6. Substance use analysis by type

In order to determine group differences based on substance of use, a subgroup analysis was conducted to contrast CO and MA studies (Table 5). One study was excluded, as the article included a mixed group (i.e., broad stimulant use) (Tang et al., 2015). Results for each substance group were congruent, though heterogeneity was present in the CO group (χ^2 (4) = 9.95, p = 0.04) but not the MA group (χ^2 (4) = 2.65, p = 0.62). Thus, a random-effects model was conducted for the CO group, and a fixed-effects model was used for the MA group. When using a random effect, WM impairment was not significant for CO use (g = -0.37, 95% CI: [-0.79, 0.05]) and was significant for methamphetamine use (g = -0.32, 95% CI: [-0.57, -0.07]). However, no significant differences were found between the stimulant use groups (χ^2 (1) = 0.04 p = 0.83), and Hedge's g was highly similar for both drugs. Due to heterogeneity on the cusp (p = 0.049) and a lack of significant differences between drugs, a fixed-effects model was employed to further explore the CO group. Under that model, a significant effect was found for CO use (g = -0.34, 95% CI: [-0.60, -0.08]). Thus, it was judged that differences in study measurement (Inconsistency = 59.82%) with a small sample size may have underestimated the effect of CO use in the random-effects model.

3.7. Polysubstance use analysis

Studies varied in the extent to which participants were screened in or out for co-occurring use of non-stimulant substances. As seen in Table 2, five studies included participants who used other substances, while six excluded for polysubstance use. A subgroup analysis was conducted (Table 5), and no difference in subgroups was found (χ^2 (1) = 0.07, p = 0.80). Both groups were similar to the overall effect and demonstrated a small to moderate effect for WM disruption for the SU group compared to HC (Table 5).

3.8. Substance use chronicity

Chronicity of use was explored using meta-regression to determine the effect of number of years of use on WM integrity. Stimulant use was reported in nine studies and ranged from 6.5 to 18.9 years (mean = 12.53). Chronicity did not emerge as a significant predictor of WM impairment (β = 0.02 95% CI [-0.02, 0.06], z = 0.84).

3.9. Risk of Bias

Study bias was evaluated using three measures. First, an analysis of funnel plot symmetry was conducted to determine the extent to which studies' overall effect was captured in the grand mean effect. Fig. 3 includes the plot, for which study precision is measured by the y-axis (standard error) and effect size measured on the x-axis. The overall effect is represented by the diamond shape and midline of the plot (Borenstein, 2006). Overall, most studies appeared to cluster around the mean; however, some of the more precise studies (i.e., relatively lower standard errors) were represented outside of the margin (Cordero et al., 2017; Romero et al., 2010), suggesting reliable studies with differing results. To test for funnel plot asymmetry, Egger's regression was derived (Egger et al., 1997), which measures asymmetry based on differences in study precision (i.e., determining if more precise studies have larger effect sizes). The regression did not indicate significant asymmetry (t (9) = 1.77, p = 0.11); thus, study-level risk of bias was determined to be non-significant.

Finally, risk of publication bias was conducted by calculating *Rosenthal's Fail-Safe N,* a measure of the number of non-significant studies needed in order to nullify the observed overall grand mean to a non-significant value. The present analysis indicated that 48 studies (more than four times the studies included in the analysis) would be needed in order to remove the estimated total effect.

Table 3
Summary effect size for FA, MD, RD, and AD for all ROIs by study.

			95% Confidence Interval			
Outcome	$N_{Studies}$	g	Lower	Upper	z	Test of Homogeneity
Fractional Anisotropy	11	−0.37	−0.54	−0.20	**−4.22****	χ^2 (10) = 15.51 (ns)
Mean Diffusivity	7	0.20	−0.01	0.41	1.87	χ^2 (6) = 3.40 (ns)
Radial Diffusivity	6	0.24	0.01	0.47	**2.03***	χ^2 (5) = 3.01 (ns)
Axial Diffusivity	5	0.05	−0.20	0.29	0.39	χ^2 (4) = 1.22 (ns)

* $p < .05$; **$p < .01$; *g: Hedges' g.*

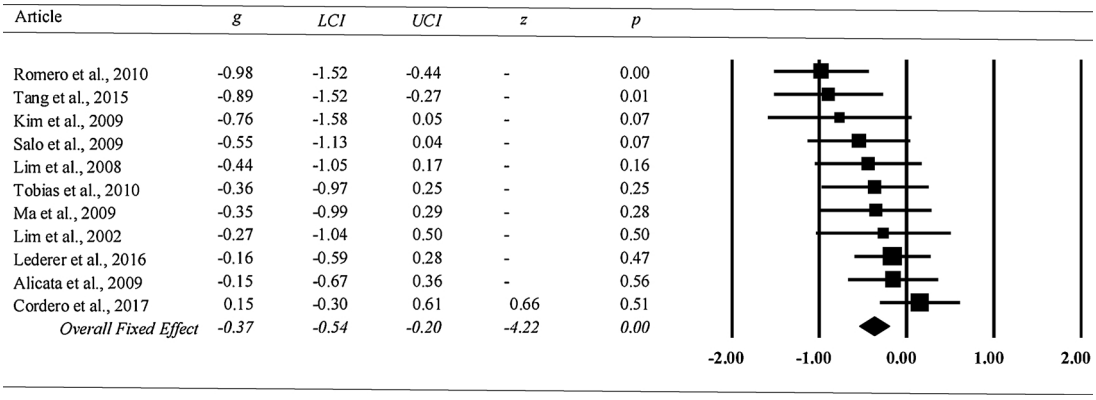

Fig. 2. Forest plot for FA across regions of interest.
Note. Effect sizes are based on a fixed-effect model. Study weights are represented by blocks, with confidence intervals as lines through the blocks. Negative values indicate white matter integrity lower in stimulant use participants in comparison to health controls. Confidence intervals at the "0" line indicate no significant difference between groups. The overall fixed effect is represented as a diamond.

4. Discussion

The aim of the present analysis was to provide an overview regarding the effect of stimulant use on WM disruption. This was accomplished via a comprehensive meta-analysis using PRISMA guidelines in order to derive a summary of the overall effect. The methodological quality of the reviewed studies fell within the top quartile of possible scores. Regions of interest were collapsed across 11 studies, resulting in an overall effect size of WM integrity for stimulant use disorder versus HC subjects. Taken together, stimulant use was found to have a small to moderate effect on WM integrity as measured by DTI outcomes. Overall effects on FA values and eigenvalues (where provided) were assessed, resulting in a significant effect for RD but not for MD or AD. Further subgroup analyses were conducted in an exploratory fashion for five studies of CO-specific and five studies of MA-specific groups, and no significant differences were found. CO-based studies had greater heterogeneity, suggesting more variance between studies and possible population differences. Thus, a random-effects estimator was used, which indicated no significant difference between groups. This outcome should be considered cautiously in light of potential underestimation of WM disruption as a result of a small, heterogeneous sample.

Overall the present report offers verification of white matter impairment in stimulant use disorders via meta-analysis of the extant literature. A previous meta-analysis of gray matter volume in > 2000 individuals with dependence on a range of different substances and > 1000 controls provides robust evidence of reduced cortical and subcortical gray matter volumes in substance use disorders (Mackey et al., 2018). That analysis concluded that the greatest ES on gray matter volume was related to alcohol use disorder. Considerably less data are available for white matter integrity in substance use disorders, and to our knowledge this is the first meta-analysis focused on white matter in CO and MA. Previous meta-analyses provide evidence for white matter disruption in alcohol use disorder (Monnig et al., 2013) and opiate use disorder (Wollman et al., 2015). One meta-analysis examined whole brain volume and ROIs (including WM) in chronic marijuana use but did not report outcomes independently for WM volume or WM ROI, thereby precluding ES estimation of WM in cannabis users (Rocchetti et al., 2013). The estimated ES for the influence of alcohol on white matter integrity is $g = 0.30$, based on a sample of 19 studies and focusing on white matter volume as the primary metric (Monnig et al., 2013). For opiate use disorder, the estimated ROI-based ES is $g = 0.35$ based on DTI FA values (Hedges' g converted from SMD z score = 4.001 and total N = 135); however, this estimate was limited to only four studies that met the meta-analysis inclusion criteria (Wollman et al., 2015). From these available meta-analytic studies, ES estimates for stimulants (methamphetamine and cocaine), alcohol, and opiates are quite similar (small-medium ES between 0.30 and 0.37) with the caveat that outcome metrics were different across the studies. Interestingly, while the results from each drug class suggest possible neurotoxicity to brain white matter resulting from chronic use, there are likely both shared and unique mechanisms of insult across the different drug classes. An extensive review of these mechanisms across drug classes is beyond the scope of this report.

Corroborating previous DTI studies of WM in stimulant use, the present meta-analysis found significant effects for the RD metric but not AD. A prevailing interpretation of this observation is compromised myelination, commonly associated with neurological pathology (Jelescu et al., 2016; Sbardella et al., 2013; Song et al., 2003; Yao et al., 2018). Additionally, preclinical work in CO-exposed rodents indicates that RD changes reflect altered myelin integrity (Narayana et al., 2014). Psychostimulants are known to induce neuroinflammation, thus inducing the activation of the glial system (Beardsley and Hauser, 2014; Clark et al., 2013; Harricharan et al., 2017). Chronic neuroinflammation and overactivation of neuroimmune responses provide a putative mechanism by which psychostimulants may compromise myelin

Table 4
Effect sizes for FA outcomes by region of interest (ROI).

Region of Interest	$N_{Studies}$	g	95% Confidence Interval		Z	Test of Homogeneity
			Lower	Upper		
Corpus Callosum	10	−0.27	−0.45	−0.09	**−2.98****	χ^2 (9) = 16.43 (ns)
Splenium	7	−0.16	−0.38	0.06	−1.39	χ^2 (6) = 7.04 (ns)
Genu	10	−0.42	−0.76	−0.08	**−2.42***	χ^2 (9) = 31.68*
Body^	3	0.07	−0.22	0.37	0.47	χ^2 (2) = 2.64 (ns)
Frontal Cortex^^	6	−0.71	−1.36	−0.07	**−2.18**	χ^2 (5) = 36.04**

Note: Effect size estimates are included for outcomes with greater than two studies. * p < .05; ** p < .01; g: Hedges' g. ^Includes: Body, anterior mid-body, posterior mid-body, isthmus, and rostral body ^^Includes: AC-PC plane, inferior and superior frontal lobes, frontal white matter (left and right).

Table 5
Subgroup Analyses for FA in combined ROIs.

			95% Confidence Interval			
	$N_{Studies}$	*g*	Lower	Upper	*Z*	Test of Homogeneity
Polysubstance Abuse Included	5	−0.32	−0.58	−0.07	**−2.48***	χ^2 (4) = 7.94 (ns)
Polysubstance Abuse Excluded	6	−0.41	−0.64	−0.18	**−3.45***	χ^2 (5) = 7.32 (ns)
Polysubstance Overall Between						**χ^2 (1) = 0.07 (ns)**
Random Effects						
Cocaine Use	5	−0.37	−0.79	0.05	**−1.74**	χ^2 (4) = 9.95*
Methamphetamine Use	5	−0.32	−0.57	−0.07	**−2.49**	χ^2 (4) = 2.65 (ns)
Fixed Effects						
Cocaine Use	5	−0.34	−0.60	−0.08	**−2.58***	
Methamphetamine Use	5	−0.32	−0.57	−0.07	**−2.49***	
Stimulant Type Overall Between						**χ^2 (1) = 0.04 (ns)**

integrity. Indeed, changes in FA and RD values can reflect alterations in astrocyte and oligodendrocyte structure (Budde et al., 2011; Franklin and Ffrench-Constant, 2017). The foregoing suppositions will require confirmation via more extensive and systematic investigation, including preclinical, in vitro, and post-mortem research.

Several limitations were evident in the present study. First, the overall effect size was derived from a small group of studies (n = 11), which was particularly concerning for the exploratory subgroup analyses. This small number of studies hinders the generality of conclusions that may reasonably be drawn and calls for further work in this area. Furthermore, some factors were considered for separate analysis but were not clear across studies and thus remain unanswered, such as the relative contribution of HIV. The authors therefore decided to include groups within studies that best matched the comparisons of interest, but this may have introduced potential sources of heterogeneity. While acute effects of psychostimulants are unknown and not well-established in white matter disruption, information regarding the timing of each scan in proximity to substance use may have also contributed to the study as a covariate in the analyses. Future studies should include data regarding prior use in order to rule-out acute effects as a possible moderator. Finally, a conservative approach to defining regions of interest was taken in the present study, which limited white matter regions to association and callosal fibers. Other regions, such as those in areas of the limbic system and projection fibers, may be relevant. However, these were beyond the scope of the present study due to considerable variability identifying particular regions and in data reporting practices across studies.

Because WM integrity is critical for efficient cognitive functioning, it is likely that WM abnormalities account in part for the cognitive impairments observed in chronic stimulant using individuals. In CO or MA use disorder, WM integrity has been associated with performance on attention, working memory, and impulse control tasks, with greater impairment predicting worse treatment outcome (Lane et al., 2010; Moeller et al., 2005; Xu et al., 2010). As such, pharmacological interventions with cognitive-enhancing effects have been recommended to improve response to treatment (Sofuoglu, 2010). None of the candidate medications tested to date have targeted WM structure, with one exception. In a recent proof-of-concept study we found that the activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) by pioglitazone resulted in measurable improvement (pre-to-post treatment changes) in WM integrity (FA values) compared to no change with placebo (Schmitz et al., 2017). Pioglitazone, as well as other novel anti-inflammatory and neuroprotective agents, e.g., ibudilast (Ray et al., 2017), merit further investigation given their potential to enhance WM integrity as a target for improving treatment outcome. Cognitive enhancement may show promise irrespective of whether the source of white matter impairment was directly due to drug-induced neurotoxicity or other factors. Indeed, most structural brain changes related to substance use are likely due to a confluence of factors that accompany a substance abusing lifestyle (Tannous et al., 2019).

In conclusion, the present study supports existing research regarding the association between stimulant use disorder and decline in WM integrity observed in callosal and association fibers. Further summative research on WM tracts and whole-brain WM integrity is warranted.

Role of funding source

Funding for this study was provided by the National Institute on Drug Abuse (NIDA P50 DA009262). The NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of data; in the writing of the report; or in the decision to

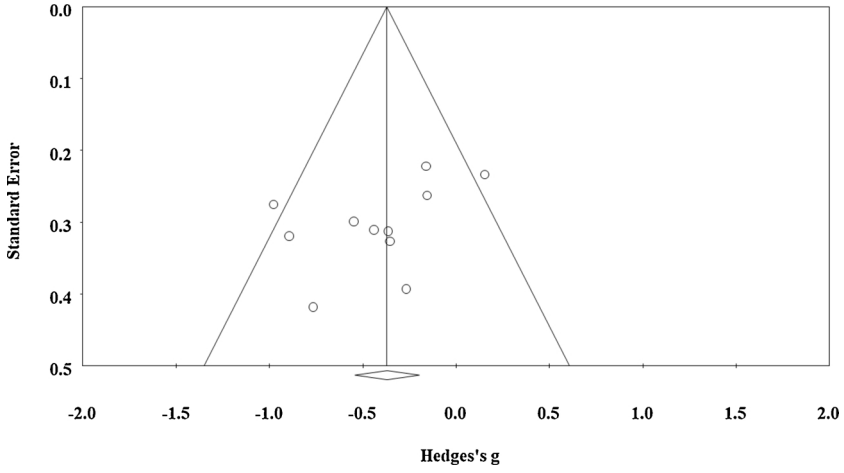

Fig. 3. Funnel plot.

submit the paper for publication.

Contributors

Authors Beard, Schmitz, Soder, Suchting, Yoon and Lane assisted in conceptualizing and designing the study. Author Beard took the lead in applying PRISMA as the basis for conducting and reporting the research process. Author Soder and Yoon assisted in article selection and evaluation of quality. Author Suchting assisted in data extraction and analyses. Authors Hasan, Narayana and Moeller provided expertise on subject matter. All authors contributed to editing and re-writing of the manuscript and provided final approval of the submission.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

Supported by NIDAP50 DA009262 (FGM, JMS, SDL) and the UTHealth Louis A. Faillace Endowment (SDL).

References

Abhinav, K., Yeh, F.C., Pathak, S., Suski, V., Lacomis, D., Friedlander, R.M., Fernandez-Miranda, J.C., 2014. Advanced diffusion MRI fiber tracking in neurosurgical and neurodegenerative disorders and neuroanatomical studies: a review. Biochim. Biophys. Acta Mol. Basis Dis. 1842, 2286–2297.

Acosta-Cabronero, J., Alley, S., Williams, G.B., Pengas, G., Nestor, P.J., 2012. Diffusion tensor metrics as biomarkers in Alzheimer's disease. PLoS One 7, e49072.

Albertson, D.N., Pruetz, B., Schmidt, C.J., Kuhn, D.M., Kapatos, G., Bannon, M.J., 2004. Gene expression profile of the nucleus accumbens of human cocaine abusers: evidence for dysregulation of myelin. J. Neurochem. 88, 1211–1219.

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2007. Diffusion tensor imaging of the brain. Neurotherapeutics 4, 316–329.

Andres, T., Ernst, T., Oishi, K., Greenstein, D., Nakama, H., Chang, L., 2016. Brain microstructure and impulsivity differ between current and past methamphetamine users. J. Neuroimmune Pharmacol. 11, 531–541.

Ashok, A.H., Mizuno, Y., Volkow, N.D., Howes, O.D., 2017. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: a systematic review and meta-analysis. JAMA Psychiatry 74, 511–519.

Beardsley, P.M., Hauser, K.F., 2014. Glial modulators as potential treatments of psychostimulant abuse. Adv. Pharmacol. 69, 1–69.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system: a technical review. NMR Biomed. 15, 435–455.

Bell, R.P., Foxe, J.J., Nierenberg, J., Hoptman, M.J., Garavan, H., 2011. Assessing white matter integrity as a function of abstinence duration in former cocaine-dependent individuals. Drug Alcohol Depend. 114, 159–168.

Borenstein, M., 2006. Software for publication bias. In: Rothstein, H.R., Sutton, A.J., Borenstein, M. (Eds.), Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments. Wiley, Hoboken, NJ.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2013. Comprehensive Meta-analysis, Version 3. Biostat, Englewood, NJ.

Budde, M.D., Janes, L., Gold, E., Turtzo, L.C., Frank, J.A., 2011. The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained tissue sections. Brain 134, 2248–2260.

Chung, A., Lyoo, I.K., Kim, S.J., Hwang, J., Bae, S.C., Sung, Y.H., Sim, M.E., Song, I.C., Kim, J., Chang, K.H., Renshaw, P.F., 2007. Decreased frontal white-matter integrity in abstinent methamphetamine abusers. Int. J. Neuropsychopharmacol. 10, 765–775.

Clark, K.H., Wiley, C.A., Bradberry, C.W., 2013. Psychostimulant abuse and neuroinflammation: emerging evidence of their interconnection. Neurotox. Res. 23, 174–188.

Cordero, D.M., Towe, S.L., Chen, Nkuei, Robertson, K.R., Madden, D.J., Huettel, S.A., Meade, C.S., 2017. Cocaine dependence does not contribute substantially to white matter abnormalities in HIV infection. J. Neurovirol. 23, 441–450.

Courtney, K.E., Ray, L.A., 2014. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol Depend. 143, 11–21.

Egger, M., Smith, G.D., Schneider, M., Minder, C., Tabuso, M., Dunlop, A., Arasaradnam, R., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Franklin, R.J.M., Ffrench-Constant, C., 2017. Regenerating CNS myelin— from mechanisms to experimental medicines. Nat. Rev. Neurosci. 18, 753–769.

Goldstein, R.Z., Volkow, N.D., 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat. Rev. Neurosci. 12, 652–669.

Hallgren, K.A., 2012. Computing inter-rater reliability for observational data: an overview and tutorial. Tutor. Quant. Methods Psychol. 8, 23–24.

Harricharan, R., Abboussi, O., Daniels, W.M.U., 2017. Addiction: a dysregulation of satiety and inflammatory processes. Prog. Brain Res. 235, 65–91.

Hasan, K.M., Walimuni, I.S., Abid, H., Hahn, K.R., 2011. A review of diffusion tensor magnetic resonance imaging computational methods and software tools. Comput. Biol. Med. 41, 1062–1072.

Hedges, L.V., Olkin, I., 1985. Statistical Methods for Meta-analysis. Harcourt Brace, Orlando.

Higgins, J.P., Deeks, J.J., 2008. Selecting studies and collecting data. In: Higgins, J.P.T., Deeks, J.J. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. Wiley, Hoboken, NJ.

Hirst, R.B., Beard, C.L., Colby, K.A., Quittner, Z., Mills, B.M., Lavender, J.M., 2017. Anorexia nervosa and bulimia nervosa: a meta-analysis of executive functioning. Neurosci. Biobehav. Rev. 83, 678–690.

Hoare, J., Fouche, J.-P., Spottiswoode, B., Donald, K., Philipps, N., Bezuidenhout, H., Mulligan, C., Webster, V., Oduro, C., Schrieff, L., Paul, R., Zar, H., Thomas, K., Stein, D., 2012. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors". J. Neurovirol. 18, 205–212.

Hozo, S.P., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5, 13.

Hughes, A., Williams, M.R., Lipari, R.N., Van Horn, S., 2013. State Estimates of Past Year Cocaine Use Among Young Adults: 2014 and 2015, the CBHSQ Report. Substance Abuse and Mental Health Services Administration, Rockville, MD.

Jelescu, I.O., Zurek, M., Winters, K.V., Veraart, J., Rajaratnam, A., Kim, N.S., Babb, J.S., Shepherd, T.M., Novikov, D.S., Kim, S.G., Fieremans, E., 2016. In vivo quantification of demyelination and recovery using compartment-specific diffusion MRI metrics validated by electron microscopy. Neuroimage 132, 104–114.

Kaag, A.M., van Wingen, G.A., Caan, M.W.A., Homberg, J.R., van den Brink, W., Reneman, L., 2017. White matter alterations in cocaine users are negatively related to the number of additionally (ab)used substances. Addict. Biol. 22, 1048–1056.

Kariisa, M., Scholl, L., Wilson, N., Seth, P., Hoots, B., 2019. Drug overdose deaths involving cocaine and psychostimulants with abuse potential – united States, 2003-2017. MMWR Morb. Mortal. Wkly. Rep. 68, 388–395.

Kelly, C., Zuo, X.N., Gotimer, K., Cox, C.L., Lynch, L., Brock, D., Imperati, D., Garavan, H., Rotrosen, J., Castellanos, F.X., Milham, M.P., 2011. Reduced interhemispheric resting state functional connectivity in cocaine addiction. Biol. Psychiatry 69, 684–692.

Kwako, L.E., Bickel, W.K., Goldman, D., Kwako, L.E., Bickel, W.K., Goldman, D., 2018. Addiction biomarkers: dimensional approaches to understanding addiction. Trends Mol. Med. 24, 121–128.

Lane, S.D., Steinberg, J.L., Ma, L., Hasan, K.M., Kramer, L.A., Zuniga, E.A., Narayana, P.A., Moeller, F.G., 2010. Diffusion tensor imaging and decision making in cocaine dependence. PLoS One 5, e11591.

Lederer, K., Fouche, J.P., Wilson, D., Stein, D.J., Uhlmann, A., 2016. Frontal white matter changes and aggression in methamphetamine dependence. Metab. Brain Dis. 31, 53–62.

Lim, K.O., Wozniak, J.R., Mueller, B.A., Franc, D.T., Specker, S.M., Rodriguez, C.P., Silverman, A.B., Rotrosen, J.P., 2008. Brain macrostructural and microstructural abnormalities in cocaine dependence. Drug Alcohol Depend. 92, 164–172.

Ma, L., Hasan, K.M., Steinberg, J.L., Narayana, P.A., Lane, S.D., Zuniga, E.A., Kramer, L.A., Moeller, F.G., Ma, L., Hasan, K.M., Steinberg, J.L., Narayana, P.A., Lane, S.D., Zuniga, E.A., Kramer, L.A., Moeller, F.G., 2009. Diffusion tensor imaging in cocaine dependence: Regional effects of cocaine on corpus callosum and effect of cocaine administration route. Drug Alcohol Depend. 104, 262–267.

Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., Allen, N.B., Alia-Klein, N., Batalla, A., Blaine, S., Brooks, S., Caparelli, E., Chye, Y.Y., Cousijn, J., Dagher, A., Desrivieres, S., Feldstein-Ewing, S., Foxe, J.J., Goldstein, R.Z., Goudriaan, A.E., Heitzeg, M.M., Hester, R., Hutchison, K., Korucuoglu, O., Li, C.-S.R., London, E., et al., 2018. Mega-analysis of gray matter volume in substance dependence: general and substance-specific regional effects. Am. J. Psychiatry 176, 119–128.

Moeller, F.G., Hasan, K.M., Steinberg, J.L., Kramer, L.A., Dougherty, D.M., Santos, R.M., Valdes, I., Swann, A.C., Barratt, E.S., Narayana, P.A., 2005. Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. Neuropsychopharmacology 30, 610–617.

Moeller, F.G., Hasan, K.M., Steinberg, J.L., Kramer, L.A., Valdes, I., Lai, L.Y., Swann, A.C., Narayana, P.A., 2007. Diffusion tensor imaging eigenvalues: preliminary evidence for altered myelin in cocaine dependence. Psychiatry Res. 154, 253–258.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J.A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J.J., Devereaux, P.J., Dickersin, K., Egger, M., Ernst, E., Gøtzsche, P.C., Grimshaw, J., Guyatt, G., Higgins, J., Ioannidis, J.P.A., Kleijnen, J., Lang, T., et al., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.

Monnig, M.A., Tonigan, J.S., Yeo, R.A., Thoma, R.J., McCrady, B.S., Monnig, M.A., Tonigan, J.S., Yeo, R.A., Thoma, R.J., McCrady, B.S., 2013. White matter volume in alcohol use disorders: a meta-analysis. Addict. Biol. 18, 581–592.

Narayana, P.A., Herrera, J.J., Bockhorst, K.H., Esparza-Coss, E., Xia, Y., Steinberg, J.L., Moeller, F.G., 2014. Chronic cocaine administration causes extensive white matter damage in brain: diffusion tensor imaging and immunohistochemistry studies. Psychiatry Res. 221, 220–230.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan— a web and mobile app for systematic reviews. Syst. Rev. 5, 210.

Ray, L.A., Bujarski, S., Shoptaw, S., Roche, D.J., Heinzerling, K., Miotto, K., 2017. Development of the neuroimmune modulator ibudilast for the treatment of alcoholism: a randomized, placebo-controlled, human laboratory trial. Neuropsychopharmacology 42, 1776–1788.

Rocchetti, M., Crescini, A., Borgwardt, S., Caverzasi, E., Politi, P., Atakan, Z., Fusar-Poli, P., 2013. Is cannabis neurotoxic for the healthy brain? A meta-analytical review of

structural brain alterations in non-psychotic users. Psychiatry Clin. Neurosci. 67, 483–492.
Romero, M.J., Asensio, S., Palau, C., Sanchez, A., Romero, F.J., 2010. Cocaine addiction: diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter. Psychiatry Res. 181, 57–63.
Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638–641.
Substance Use and Mental Health Services Administration, 2014. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48. Substance Use and Mental Health Services Administration, Rockville, MD.
Sbardella, E., Petsas, N., Tona, F., Prosperini, L., Raz, E., Pace, G., Pozzilli, C., Pantano, P., 2013. Assessing the correlation between grey and white matter damage with motor and cognitive impairment in multiple sclerosis patients. PLoS One 8, e63250.
Schmitz, J.M., Green, C.E., Hasan, K.M., Vincent, J., Suchting, R., Weaver, M.F., Moeller, F.G., Narayana, P.A., Cunningham, K.A., Dineley, K.T., Lane, S.D., 2017. PPAR-gamma agonist pioglitazone modifies craving intensity and brain white matter integrity in patients with primary cocaine use disorder: a double-blind randomized controlled pilot trial. Addiction 112, 1861–1868.
Sofuoglu, M., 2010. Cognitive enhancement as a pharmacotherapy target for stimulant addiction. Addiction 105, 38–48.
Song, S.-K., Sun, S.-W., Ju, W.-K., Lin, S.-J., Cross, A.H., Neufeld, A.H., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 20, 1714–1722.
Tang, V.M., Lang, D.J., Giesbrecht, C.J., Panenka, W.J., Willi, T., Procyshyn, R.M., Vila-Rodriguez, F., Jenkins, W., Lecomte, T., Boyda, H.N., Aleksic, A., Macewan, G.W., Honer, W.G., Barr, A.M., 2015. White matter deficits assessed by diffusion tensor imaging and cognitive dysfunction in psychostimulant users with comorbid human immunodeficiency virus infection psychiatry. BMC Res. Notes 8, 515.
Tannous, J., Mwangi, B., Hasan, K.M., Narayana, P.A., Steinberg, J.L., Walss-Bass, C., Moeller, F.G., Schmitz, J.M., Lane, S.D., 2019. Measures of possible allostatic load in comorbid cocaine and alcohol use disorder: brain white matter integrity, telomere length, and anti-saccade performance. PLoS One 14, e0199729.
U.S. Department of State, 2017. International Narcotics Control Strategy Report. U.S. Department of State, Washington, D.C.
van Son, D., Wiers, R.W., Catena, A., Perez-Garcia, M., Verdejo-García, A., 2016v. White matter disruptions in male cocaine polysubstance users: associations with severity of drug use and duration of abstinence. Drug Alcohol Depend. 168, 247–254.
Volkow, N.D., Fowler, J.S., Wang, G.J., 2003. The addicted human brain: insights from imaging studies. J. Clin. Invest. 111, 1444–1451.
Wakana, S., Jiang, H., Nagae-Poetscher, L.M., van Zijl, P.C.M., Mori, S., 2004. Fiber tract–based atlas of human white matter anatomy. Radiology 230, 77–87.
Wollman, S.C., Alhassoon, O.M., Stern, M.J., Hall, M.G., Rompogren, J., Kimmel, C.L., Perez-Figueroa, A.M., Wollman, S.C., Alhassoon, O.M., Stern, M.J., Hall, M.G., Rompogren, J., Kimmel, C.L., Perez-Figueroa, A.M., 2015. White matter abnormalities in long-term heroin users: a preliminary neuroimaging meta-analysis. Am. J. Drug Alcohol Abuse 41, 133–138.
Xu, J., Devito, E.E., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Potenza, M.N., 2010. White matter integrity is associated with treatment outcome measures in cocaine dependence. Neuropsychopharmacology 35, 1541–1549.
Yao, Y., Nguyen, T.D., Pandya, S., Zhang, Y., Hurtado Rua, S., Kovanlikaya, I., Kuceyeski, A., Liu, Z., Wang, Y., Gauthier, S.A., 2018. Combining quantitative susceptibility mapping with automatic zero reference (QSM0) and myelin water fraction imaging to quantify iron-related myelin damage in chronic active MS lesions. Am. J. Neuroradiol. 39, 303–310.