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Structural imaging for addiction medicine: From neurostructure to neuroplasticity

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Abstract

Quantitative morphometry and diffusion tensor imaging have provided new insights into structural brain changes associated with drugs of abuse. In this chapter, we review recent studies using these methods to investigate structural brain abnormalities associated with excessive use of marijuana, stimulants, and opiates. Although many brain regions have been associated with structural abnormalities following abuse of these drugs, brain systems underlying inhibition, mood regulation, and reward are particularly involved. Candidate pathological mechanisms underlying these structural abnormalities include the direct toxic effects of the drugs, neuroinflammation, ischemia, hemorrhage, and abnormal brain development. Returning damaged brain areas to neural health would involve enhancing neuroplasticity. Behavioral, environmental, pharmacological, and cell-based therapies have been correlated with enhanced neuroplasticity following brain injury, providing a basis for new treatments of brain changes associated with excessive drug use. When testing new treatments, structural imaging may prove useful in selecting patients, monitoring recovery, and perhaps, tailoring interventions.

Keywords

Marijuana; Stimulants; Opioids; Quantitative morphometry; Diffusion tensor imaging

1 INTRODUCTION

Many imaging studies of the impact of substance abuse on brain structure have been published over the past six decades. Imaging methods used in these studies varied from pneumoencephalography to high-resolution magnetic resonance (MR) imaging (Barini and de Silva, 1959; Thompson et al., 2004). Despite having been harvested for many years, the information that can be reaped from structural brain imaging has not yet been exhausted. Rather, structural brain imaging remains an evolving and informative source of information about brain correlates of addiction. The development of quantitative morphometric imaging tools based on advances in tissue segmentation, anatomical labeling, and assessment of properties of brain geometry, such as gyral shape, cortical thickness, tissue volume, and gray matter density, have driven structural imaging's novel contributions to brain studies of substance use disorders. When quantitative morphometry of structural images is combined with diffusion tensor imaging (DTI), structural imaging studies can span cellular to brain

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system levels of neural organization. In addition to providing localization information for functional brain imaging, structural imaging contributes information in its own right to multimodal imaging research into disorders of addiction.

The initial use of imaging to investigate the brain correlates of addictive disorders typically reported on visual descriptions of the images. More recent investigations use quantitative methods based on T1- or T2-weighted contrast or DTI to investigate brain structure and tissue integrity. Studies using T1- or T2-weighted imaging typically report data on brain volume, cortical thickness, or tissue density at a gross anatomical level. In contrast, DTI studies derive information from MR signal attenuation related to the diffusion of water. In biological samples, the isotropic diffusion expected in a pure sample of water is restricted by large proteins and cell membranes (Beaulieu, 2002). For large fiber bundles, such as those occurring in white matter, the restricted diffusion can be dominated by a single diffusion direction, producing strong anisotropic diffusion. The starting place for interpreting DTI data is a standard view that when tissue is lost, diffusion is less constrained thereby increasing the rate of diffusion and creating a more isotropic state of diffusion. Thus, two measures commonly reported in the DTI literature are mean diffusion (MD) rate averaged over three directions of diffusion and fractional anisotropy (FA), the degree to which diffusion deviates from an isotropic state standardized by total diffusion. MD is roughly $0.001 \text{ mm}^2/\text{s}$ in human brain and FA varies from 0 to 1.

Structural imaging research on addictive substances forms a large and diverse literature. In this chapter, we will limit our review to magnetic resonance imaging (MRI) studies of brain structure involving three commonly used categories of substances leading to addiction—marijuana, stimulants, and opiates. This chapter focuses on T1- and T2-weighted MRI images and DTI. We selected papers through January 2015 by searching PubMed crossing the search terms “magnetic resonance imaging, brain structure, and diffusion tensor imaging” with each of the categories of addictive substances just mentioned. We did not further limit the search by the method used to analyze structural or diffusion images. Rather, learning what methods of analysis are used in the field was one of the aims of the review. When the literature was sufficiently detailed, we separately discussed the structural brain effects of prenatal, adolescent, and adult exposure to addictive substances.

2 MARIJUANA

Marijuana is the most widely used illicit drug in the United States (Johnston et al., 2013, 2015). Although prevalence rates have remained stable, perceived risk of harm is decreasing, and marijuana sales will likely increase with legal relaxation (Johnston et al., 2015; Karnes, 2014; Miron, 2010). Cannabinoid receptors in the central nervous system (CB_1) are found in high density in cerebral cortex, hippocampus, hypothalamus, and basal ganglia (Iversen, 2003). The endogenous cannabinoid system is believed to modulate the inhibitory actions of neurotransmitters (Atakan, 2012; Iversen, 2003). ⁹ tetrahydrocannabinol is the principal psychoactive compound found in marijuana (Mechoulam, 1970) and acts as a partial agonist at the CB_1 receptor (Matsuda et al., 1990). Disruption of the endogenous cannabinoid system via repeated marijuana consumption likely results in a cascade of neurochemical and structural brain changes, with adolescents particularly vulnerable to disruption (e.g.,

compromised myelination, cortical thinning) (Rubino and Parolaro, 2008; Stiles and Jernigan, 2010). Marijuana-related neural substrate changes may alter neurocognitive and psychosocial functioning. Structural brain changes associated with marijuana use in adolescent and adult samples are particularly important since: (1) structural brain changes are protracted throughout late adolescence and young adulthood (Giedd, 2008; Lebel and Beaulieu, 2011), (2) marijuana use peaks in late adolescence (Caldeira et al., 2012; Johnston et al., 2013), and (3) age of onset of regular marijuana use (<17 year old, approximately) predicts poorer neural outcomes (Lisdahl et al., 2013).

3 ADOLESCENCE (AVERAGE SAMPLE AGE 21)

3.1 QUANTITATIVE MORPHOMETRY

Early cross-sectional studies by Medina and colleagues (2007, 2009, 2010) examined the hippocampus, prefrontal cortex, cerebellar morphometry, and global white matter volume in adolescent marijuana users following 28 days of monitored abstinence. The authors identified decreased global white matter and larger prefrontal cortex volume in female marijuana users compared to nonusing female counterparts, however, the opposite relationship was found for males. In these cross-sectional samples, decreased white matter volume was associated with more reported depression symptoms, and smaller prefrontal cortex volume was associated with better executive functioning. Marijuana users (male and female) were found to have larger posterior inferior vermis volume in the cerebellum, also associated with poorer executive functioning (Medina et al., 2007, 2009, 2010).

In 2010, Churchwell and colleagues examined subdivisions of the orbitofrontal cortex and found smaller medial orbital volumes compared to matched controls; smaller volume was related to early age of marijuana initiation. Churchwell's findings are similar to morphological analysis conducted by Wilson and colleagues (2000) in which smaller global and regional gray matter volume were linked with marijuana use onset prior to age 17. However, the authors did not observe a differential impact on subregions for males and females as found by Medina and colleagues in global prefrontal cortex volume (Medina et al., 2009).

Several studies have focused analysis on limbic system structures. McQueeney et al. (2011) found larger amygdala volume in female adolescent marijuana users compared to nonusing females; larger amygdala volumes were associated with more internalizing symptoms (McQueeney et al., 2011). Ashtari and colleagues (2011) found smaller hippocampal volume, bilaterally, in adolescent marijuana users. A dose-dependent effect was found between more joints used and smaller hippocampus volumes in the right hemisphere (Ashtari et al., 2011). In a recent study by Gilman and colleagues, the authors found that marijuana users had greater gray matter density of the left nucleus accumbens, which was related to increased marijuana use severity (Gilman et al., 2014).

Two recent studies have found no differences between adolescent and young adult marijuana users and matched controls on structural imaging estimates. The authors report no discrepancies between corpus callosum morphology, as well as limbic and cerebellum

regions between marijuana users and matched controls (Weiland et al., 2015). Limitations of these studies include small sample size and limited substance use history assessment.

Two studies have focused on cortical thickness exclusively. Jacobus et al. (2014) and Lopez-Larson et al. (2011) identify increased cortical thickness estimates in temporal and posterior cortical regions in marijuana users compared to controls, yet thinner cortices with increased severity of use in frontal brain regions present both pre- and post-28 days of monitored abstinence (Jacobus et al., 2014). Both studies identified associations between thickness estimates and age of marijuana use onset (Jacobus et al., 2014; Lopez-Larson et al., 2011). Cortical thickness estimates may be unique compared to volume and density, in that volume may be driven more by surface area in the early phase of life, but thickness as one gets older (Storsve et al., 2014). The authors suggest thicker estimates may reflect altered developmental trajectories, while thinner cortices may be associated with tissue remodeling or marijuana-related neurotoxicity.

The majority of studies show alteration in macrostructure, including smaller limbic structures, differential impact of gender on cortical estimates, and alterations in cortical thickness that may result from interference with myelination and synaptic refinement. Nevertheless, preexisting differences cannot be ruled out. Cheetham and colleagues (2012) identified smaller bilateral orbitofrontal volume at age 12 in those adolescents that initiate cannabis use by age 16 (Cheetham et al., 2012). Jacobus et al. (2013b) followed adolescents pre- and postinitiation of marijuana use and reported differences in tissue integrity (e.g., white matter health) despite preexisting vulnerabilities (Jacobus et al., 2013b). Preexisting vulnerabilities, combined with exposure, likely interact to influence neural health outcomes.

3.2 DIFFUSION TENSOR IMAGING

Studies in adolescent and young adult samples have generally found decreased FA in marijuana users in widespread tracts throughout the brain (see Table 1). Medina and colleagues (2007) identified differences in global white matter volume that were associated with increased depressive symptoms. Several studies since 2007 have examined FA and MD to examine more subtle changes influenced by regular marijuana use. Bava et al. (2009, 2010) and Jacobus et al. (2009, 2013a,b,c) examined adolescent heavy marijuana users compared to matched controls in longitudinal investigations spanning 3 years (ages 18–22). This program of research typically found decreased FA and increased MD in both association and projection fiber tracts (medium to large effect sizes), suggesting poorer white matter integrity in fibers located in all four lobes of the brain bilaterally (e.g., superior longitudinal fasciculus, fronto-occipital fasciculus) and bundles important for cortico-limbic projections (e.g., corona radiata, uncinate fasciculus, thalamic projections, internal capsule, fornix, cingulate projections) (Bava et al., 2009, 2010; Jacobus et al., 2009, 2013a,b).

DTI research with varying abstinence periods has revealed similar findings both acutely (no reported abstinence period) (Yucel et al., 2010), and following up to 3 months of abstinence (Ashtari et al., 2009), suggesting that differences in diffusion estimates among adolescent marijuana users might represent an enduring “longer-term” effect. Clinical correlations have found increased FA associated with improved processing speed, visuospatial functioning, and complex attention and executive functioning performance, as well as general global

cognitive functioning and fewer reported risk-taking behaviors (Bava et al., 2010; Jacobus et al., 2013b,c).

4 ADULthood (AVERAGE SAMPLE AGE 22, ON AVERAGE)

4.1 QUANTITATIVE MORPHOMETRY

Early adult MRI studies reported inconsistent evidence of structural brain changes. Block and colleagues (2000), Tzilos and colleagues (2005), and Jager and colleagues (2007) all failed to find differences when examining global and regional gray matter volume, hippocampal volume, and parahippocampal density. However, Matochik and colleagues (2005) found divergent relationships between controls and marijuana users in gray and white matter density estimates. Decreased density was found in parahippocampal gyrus and parietal white matter, while increased density was identified in precentral gyrus, right thalamus, and parahippocampal and fusiform white matter. Interestingly, increased white matter density in the frontal lobe (precentral) was associated with more reported years of marijuana use (Block et al., 2000; Jager et al., 2007; Matochik et al., 2005; Tzilos et al., 2005).

In more recent studies, limbic system and cerebellum structures have been evaluated (see Table 2). Yucel et al. (2008) reported smaller hippocampal and amygdala volumes, while Cousijn et al. (2012) reported increased anterior cerebellar volume (both report similar findings discussed in the adolescent literature). Similar to Medina et al., larger cerebellum volumes for marijuana users were identified (Cousijn et al., 2012). Cousijn and colleagues also found that more reported weekly cannabis use was associated with smaller hippocampus volumes, and smaller amygdala volumes were associated with more cannabis-dependence symptoms. Similarly, Yucel identifies smaller hippocampus volumes with more reported cannabis exposure in the past 10 years.

Mata et al. (2010) found decreased concavity (more flattening) in frontal, parietal, and temporal lobes, and thinner sulci in the right frontal lobe (Mata et al., 2010). The authors suggest that several forces may influence curvature and the folding process (which continues throughout adolescence), including thickness, volume, and white matter connectivity. Age was not related to curvature indices in the users (as was the case with controls), suggesting that there may be a premature alteration in gyrification that resembles a degenerative process.

4.2 DIFFUSION TENSOR IMAGING

The adolescent literature on white matter health is more consistent compared to the adult literature. For example, DeLisi and colleagues (2006) is one of few to find *increased* FA and *decreased* MD in cannabis users compared to controls, which is opposite the DTI pattern suggesting toxicity to the brain (DeLisi et al., 2006). While this finding is in the unexpected direction, other studies (Bava et al., 2010) have reported discrepancies in the unanticipated direction, which could be reflective of a compensatory mechanism, complex geometry, or axonal changes (e.g., crossing fibers) that are independent of myelination changes (Jones et al., 2013). Gruber and colleagues have identified differences in diffusion estimates (e.g.,

decreased FA and increased MD) in heavy marijuana users after using more advanced alignment approaches compared to their earlier investigations (Gruber and Yurgelun-Todd, 2005). Their results included decreased white matter integrity (lower FA and higher MD) in the corpus callosum and cingulate projections, as well as multiple projection and association fiber tracts. The authors report poor white matter integrity among marijuana users is associated with young age of regular marijuana initiation and increased impulsivity (Gruber et al., 2011, 2014). The majority of diffusion studies with adult population have not required an extensive abstinence period (~12 h, on average); therefore, it is difficult to say if effects would be detected following several weeks to months of abstinence. Nevertheless, studies suggest a deleterious impact on microstructural integrity in heavy adult marijuana users, which has clinical correlates, similar to adolescent studies.

4.3 SUMMARY

While differences in structural integrity are frequently reported, some argue results are equivocal. Weiland and colleagues (2015) have suggested that varied effect sizes per structure indicate no effect within the bounds of sampling error (Cohen's d range across structure and hemispheres = -1.2 to $+1.4$), consistent with their lack of findings in limbic and cerebellum regions. However, their sample was recruited from the criminal justice system and identified adolescent users or nonusers based on past 3 months use patterns. Nevertheless, it does remain unclear what varying observations in neuroimaging estimates of gray and white matter reflect in the context of neurobiology (e.g., changes in neuropil, neuronal size, dendrites, axonal arborization, intra/extracellular fluid, myelination, coherence of fiber tracts).

More information on consumed marijuana (cannabinoid ratios) and objective use markers (better toxicology measures) will help disentangle findings that are likely complicated by bias in self-report measures. Future longitudinal studies can account for preexisting vulnerabilities, which will help with development of neuroscience-informed interventions that target vulnerable neural circuitry such as cortico-limbic regions (e.g., orbitofrontal and cingulate cortex projections) that modulate reward response and attentional biases for conditioned drug use stimuli.

5 STIMULANTS

The primary pharmacological actions of many stimulants, especially those in the amphetamine class, are to release dopamine into the synapse or to inhibit dopamine reuptake (Stahl, 2000). Stimulants also have weaker releasing actions on noradrenergic and serotonergic systems (Stahl, 2000). Several stimulants modulate dopamine activity through the cocaine–amphetamine regulatory transcript system (Vicentic and Jones, 2007). In addition to their effects on neurotransmission, stimulants can damage the brain through vascular, inflammatory, and direct neurotoxic mechanisms (Geibprasert et al., 2010). Vascular damage can be caused by hemorrhage, vasculitis, or ischemia. Ischemic damage may be due to vasoconstriction, thrombosis, or cardiac disease and the damage can alter either gray or white matter (Geibprasert et al., 2010).

6 PRENATAL EXPOSURE

6.1 QUANTITATIVE MORPHOMETRY

Studies of children prenatally exposed to cocaine have frequently found loss of gray matter in frontal cortex (Grewen et al., 2014). Most studies have also found smaller basal ganglia volumes (Liu et al., 2013). Loss of gray matter volume has been observed as early as 5 weeks following birth and appears to persist through adolescence (Grewen et al., 2014; Rando et al., 2013). Unlike the cocaine findings, increased cortical thickness has been observed among children exposed to methamphetamine prenatally, although the effect varies regionally across studies and is at times only observed among girls (Derauf et al., 2012; Roos et al., 2014). Findings involving basal ganglia volumes have been inconsistent among children prenatally exposed to methamphetamine with one study reporting larger volumes and others smaller volumes (Chang et al., 2007; Gilman et al., 2014; Roos et al., 2014).

6.2 DIFFUSION TENSOR IMAGING

Findings from DTI studies of children exposed to cocaine *in utero* have produced inconsistent results. In one study, exposed children showed significantly higher average diffusion in the left frontal callosal and right frontal projection fibers (Warner et al., 2006). A second study also found higher MD in the splenium of the corpus callosum, as well as lower FA in the right arcuate fasciculus (Lebel et al., 2013). Yet, a third study found no callosal differences in either FA or MD (Liu et al., 2011). The pattern of DTI results in children prenatally exposed to cocaine appears to be moderated by prenatal tobacco and alcohol exposure (Lebel et al., 2013; Liu et al., 2011).

The two DTI studies investigating children with prenatal exposure to methamphetamine found lower MD in anterior corona radiata and frontal and parietal white matter (Cloak et al., 2009; Colby et al., 2012). Colby et al. (2012) also found larger FA values in the left internal and external capsules and corona radiata, whereas Cloak et al. (2009) observed a trend toward greater FA in left frontal white matter.

7 EXPOSURE IN ADOLESCENCE AND ADULTHOOD

7.1 QUANTITATIVE MORPHOMETRY

Most structural imaging studies of individuals with histories of cocaine abuse have reported less gray matter density or smaller volume in frontal cortex, although the effects of cocaine abuse on brain structure appears to involve a wider range of cortical area than seen in the abuse of amphetamine-like drugs (Moreno-Lopez et al., 2012). When found, frontal lobe changes in cocaine abuse or dependence have been associated with longer duration of use (Ersche et al., 2011).

There is no consistent evidence of global gray matter atrophy following methamphetamine exposure. Moreover, global increase of ventricular volume does not frequently occur. The apparent contradiction between the lack of evidence for wide spread global gray matter atrophy in humans and the evidence of neurotoxic effects of methamphetamine in rodents (Cadet et al., 2005) might be due to differences in dosing patterns, to differences in drug

purity, or to interspecies differences in the balance of neurotoxicity and neuroplasticity. However, some evidence exists for regional ventricular enlargement, especially in the anterior horn of the right lateral ventricle (Jeong et al., 2013). Interestingly, white matter volume appears to be increased with evidence of white matter abnormalities (Berman et al., 2008). Moreover, abuse of amphetamine-type stimulants is typically associated with increased volume of basal ganglia (Berman et al., 2008; Jernigan et al., 2005), even among occasional users (Mackey et al., 2014). Although global atrophy of gray matter does not occur with methamphetamine exposure, lower cortical gray matter density or smaller cortical volume has been reported in the frontal cortex or insula of individuals using amphetamine-like drugs (Daumann et al., 2011). Although lower gray matter density or volume has been consistently reported in frontal cortex, the subregion of frontal cortex involved varies across studies. Nonetheless, when frontal lobe involvement is found following abuse of amphetamine-like drugs, length, and intensity of use is associated with more abnormal findings (Daumann et al., 2011; Kim et al., 2006).

7.2 DIFFUSION TENSOR IMAGING

DTI studies of postnatal exposure to cocaine have commonly found reduced FA, increased MD, or increased diffusivity in directions perpendicular (radial) to the prominent diffusion direction in sections of the corpus callosum (Lane et al., 2010; Ma et al., 2009; Moeller et al., 2005). Less consistently, DTI signs of abnormal white matter have also been observed in frontal and parietal white matter. Variations in the patterns of abnormal DTI values associated with cocaine abuse or dependence is partly accounted for by comorbid alcohol consumption and by route of cocaine administration with smoking cocaine associated with lower FA and higher perpendicular diffusivity than intranasal administration (Ma et al., 2009). Length of abstinence of cocaine use was associated with larger FA and smaller MD values in one study (Xu et al., 2010).

All DTI studies of methamphetamine abuse or dependence we reviewed investigated *a priori* selected regions of interest. No study found smaller FA and greater diffusivity in the same region. When lower FA was found, it was observed in frontal white matter pathways or in the genu of the corpus callosum without significant changes in MD (Alicata et al., 2009; Chung et al., 2007; Tobias et al., 2010). Increased diffusion, when observed, was found in the basal ganglia without significant changes in FA (Alicata et al., 2009). We observed a considerable degree of variability in findings across studies.

7.3 SUMMARY

Stimulant abuse or dependence appears to have its most consistent structural effects on frontal and striatal cortex and their pathways, although even these findings are variable across studies. Structural alterations in the fronto-striatal system can be seen in children exposed to cocaine prenatally. An intriguing finding in structural studies of methamphetamine dependence is evidence of large basal ganglia volumes. Whether large basal ganglia volume is a premorbid characteristic of methamphetamine abusers or occurs as a result of methamphetamine use is unknown. When found smaller gray matter volumes in the fronto-striatal system associated with stimulant use is correlated with greater impulsivity

and executive dysfunction (Kim et al., 2006; Moreno-Lopez et al., 2012; Schwartz et al., 2010).

8 OPIATES

Opioid drugs offer beneficial analgesic properties, but many of the compounds, such as heroin, are some of the most addictive substances in the world leading to tolerance, withdrawal, and relapse (Gruber et al., 2007; Kalant, 1997). The underlying cellular mechanisms that cause the addictive properties of opiates have been studied in detail, although the impact upon neural systems is less clear. Opiates cause their reinforcing actions via binding to a family of G-protein-coupled receptors, particularly the μ (and to a lesser extend δ) opioid subtypes (Le Merrer et al., 2009). Although these receptors are found in a large number of brain structures, the direct reinforcing effects of opioids appear to be limited to a select number of brain regions, including dopamine cell bodies within the midbrain ventral tegmentum area (Wise, 1989), which project to the nucleus accumbens forming part of the brain reward system. In addition to dopaminergic pathways, opioid binding to their receptors cause upregulation of the cAMP pathway in neurons from the locus coeruleus (reviewed by Nestler and Malenka, 2004) and nucleus accumbens (Chieng and Williams, 1998). Similar to stimulants, opioids can change brain morphology through vascular, metabolic, and direct neurotoxic mechanisms as detailed below (Cunha-Oliveira et al., 2008).

9 QUANTITATIVE MORPHOMETRY

Opiate abuse leads to a cascade of events from cellular to neural systems to behavior. A small, yet instructive, literature has examined structural abnormalities in human opiate users using quantitative *in vivo* structural MRI in order to better understand changes to the neural systems that mediate behavior. Quantitative morphometric studies using a variety of techniques, such as voxel-based morphometry, have demonstrated changes to the volume of brain regions important for reward processing and associated cognitive functions that are altered in opiate abusers, such as executive functions and memory (Ornstein et al., 2000). Structural MRI studies of the cerebral cortex often find reduced gray matter densities in the prefrontal cortex, anterior cingulate, insula, and temporal cortex of opiate/heroin abusers (Lyoo et al., 2006; Yuan et al., 2009). Importantly, duration of heroin use has been found to negatively correlate with gray matter density in many of these brain regions, even after other possible confounding factors, such as alcohol consumption, cigarette smoking, and abstinence time of heroin use, were controlled (Yuan et al., 2009). This finding suggests that continued and prolonged use of opiates such as heroin may lead to neuronal damage or death (Büttner, 2011). Further, opioids are specifically known to decrease dendritic spine density, and this decrease could explain the smaller volumes (Liao et al., 2005, 2007). Reduced gray matter density in prefrontal cortex is consistent with MRI studies reporting cerebral blood flow changes to the prefrontal cortex and associated behavioral changes (Daglish et al., 2001; Sell et al., 1999). Other regions underlying reward processing that also show smaller volumes include the nucleus accumbens (Seifert et al., 2014) and amygdala (Upadhyay et al., 2010). The amygdala-related alterations may, in part, facilitate vulnerability to risky behaviors (Love et al., 2009). Also, the nucleus accumbens, in particular, is involved in

drug-seeking behaviors (Carlezon and Thomas, 2009). This role is consistent with the observed association between nucleus accumbens volumes and depression among heroin users such that more neuronal damage (e.g., smaller volumes) is associated with increased depressed mood (Seifert et al., 2014).

10 DIFFUSION TENSOR IMAGING

In addition to morphometric studies, DTI has been used to examine microstructural abnormalities in white matter of opiate users. These studies find diminished white matter integrity in frontal, temporal, and parietal regions (Bora et al., 2012; Liu et al., 2008; Qiu et al., 2013), as well as specific tracts connecting neuronal regions (Upadhyay et al., 2010). Associations between duration of use and FA in these white matter regions have been observed such that the longer the duration of opioid abuse the more damage to the tissue. Additionally, examination of white matter tracts has implicated a number of pathways where decreased FA in opiate abusers have been observed including the stria terminalis, ventral amygdalofugal fibers, and uncinate fasciculus that connect the amygdala with other subcortical and cortical structures, including the nucleus accumbens and insula (Upadhyay et al., 2010). Some researchers have explained these white matter changes as damage to only myelin (Bora et al., 2012), whereas others have found evidence for both myelin pathology and axonal injury (Qiu et al., 2013), possibly due to opioid-induced leukoencephaly (Liu et al., 2008). There is also evidence for increased ischemic lesions in heroin abusers (Andersen and Skullerud, 1999), which may result from perfusion deficits and/or ischemia related to respiratory suppression, overdoses, disturbance of consciousness, vasculitis, and rhabdomyolysis in heroin abusers (Qiu et al., 2013). White matter damage is not surprising given that cell types such as oligodendrocytes express opioid receptors and blocking opioid receptor activity alters myelin production. It is quite plausible that chronic opioid exposure would induce changes in white matter integrity (Foote, 1987; Persson et al., 2003). Alternatively, long-term hypo- or hyperactivity and hypo- or hypertrophy within neuronal circuits (related to metabolic alterations in the neurons) involved in drug addiction may lead to gray matter changes discussed earlier, which in turn affect white matter tracts (Gilbertson et al., 2002; Roozendaal et al., 2009).

10.1 SUMMARY

Consistent with the cellular underpinnings of opioid use, structural MRI studies have found alterations to gray and white matter within the frontal-subcortical networks underlying the reward system. However, findings are somewhat inconsistent due to studies of different specific opiates (e.g., heroin, morphine, and oxycodone) and to subject-selection and study design features common to many structural studies of addiction disorders.

11 TREATMENT IMPLICATIONS

In addition to their effects on neurotransmitter systems, drugs of addiction are associated with structural brain abnormalities. These abnormalities involve cortical and subcortical gray matter structures and their white matter connections. Although many brain regions have been associated with structural abnormalities, brain systems underlying inhibition, mood regulation, and reward are particularly involved. The mechanisms causing these structural

abnormalities are not firmly established. Candidate mechanisms include the direct toxic effects of the drugs, neuroinflammation, ischemia, hemorrhage, and alterations of processes underlying brain development. In addition to prevention and abstinence or moderation of drug use, what other treatments might mitigate the impact of addictive drug use on brain structure? Prevention and medical treatment of conditions contributing to vascular or infectious disease might lessen the vascular and inflammatory consequences of addictive substance use. Once structural brain injury has occurred, interventions aimed at compensatory reassignment—where behaviors associated with an intact brain system are strengthened in order to take over lost function—have led to improved functioning in other brain disorders (Raymont and Grafman, 2006). Improved neural health of damaged structures must rely on neuroplasticity. Animal research provides evidence that behavioral, environmental, pharmacological, and cell-based therapies are correlated with some functional improvement following brain injury (Kolb and Muhammad, 2014). For example, animal studies have shown that exercise may have positive effects on brain structure by increasing neurotrophic factors and elevating the expression of anti-inflammatory cytokines (Svensson et al., 2015). When studying the treatment effects of new biological or behavioral interventions, structural imaging will be useful in selecting patients, monitoring recovery, and perhaps, tailoring interventions to optimally treat an individual's brain disorder following abuse of addictive drugs.

12 CONCLUSIONS AND FUTURE DIRECTIONS

The results described above varied considerably across studies. This variability was associated with age and gender effects, variation in patterns of use, and with the abuse of multiple drugs, including alcohol and nicotine (Agosti et al., 2002; Terry-McElrath et al., 2013). Variation in results might also be due to a balance between a drug's neurotropic and neurotoxic effects. It is intriguing, for example, that treatment with amphetamine has been associated with enhanced neuroplasticity when administered to brain-injured animals in combination with physical therapy (Kolb and Muhammad, 2014). Some of the variation in results is due to method variance. Further analytical and empirical research is needed to determine how cortical volume, thickness, area, and density relate and to establish their relative sensitivity to brain abnormalities. Moreover, the validity of DTI measures as markers of specific cellular changes needs to be established by immunohistochemical measures in animal and human autopsy studies. The possibility that premorbid differences in brain structure might place an individual at risk for abusing addictive drugs complicates separating cause and effect from the essentially correlational literature reviewed above. The field needs better controlled neuroscience studies of the structural effects of drugs of addiction that are feasible with animal research. However, most critically, longitudinal studies are needed to determine how the brain changes in response to ingestion of drugs of abuse.

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Table 1
Structural Imaging and Marijuana Use, Adolescent Sample (Sample Age 21, on Average)

Author (Year)	Method	Mean Age (Approx.)	Image Analysis	Abstinence Period	Primary Result	Primary Clinical Correlations
Medina et al. (2007)	MRI 1.5T	18	Hippocampal and global white matter volume ROIs	28 days	MJ < CON, global white matter volume	↓ White matter volume = ↑ Depressive symptoms
Medina et al. (2009)	MRI 1.5T	18	PFC volume ROIs	28 days	↓ PFC total volume male MJ vs. CON ↑ PFC total volume in female MJ vs. CON	↑ PFC total volume (CON) and ↓ PFC total volume (MJ) = ↑ Ex Fx
Medina et al. (2010)	MRI 1.5T	18	Cerebellum volume ROIs	28 days	MJ > CON, posterior inferior vermis volume	↑ Posterior vermis volume = ↓ Ex Fx
Churchwell et al. (2010)	MRI 3T	17	PFC volume ROIs	Not required	MJ < CON, right moPFC volume	↑ moPFC total volume = ↑ Age of MJ initiation
McQueeney et al. (2011)	MRI 3T	18	Amygdala volume ROI	28 days	↑ Amygdala volume in female MJ vs. CON	↑ Amygdala volume = ↑ Internalizing Sx
Ashtari et al. (2011)	MRI 1.5T	19	Medial temporal volume ROIs	30 days	MJ < CON, left and right hippocampus volume	↑ Joints smoked = ↓ Right hippocampus volume
Lopez-Larson et al. (2011)	MRI 3T	17	156 Bilateral cortical thickness ROIs	Not required	MJ > CON, temporal, parietal, paracentral, lingual MJ < CON, middle and superior frontal; insula	↓ Superior frontal thickness = ↑ Age of MJ onset
Cheetham et al. (2012)	MRI 3T	12 and 16	Cortical and subcortical limbic volume ROIs	Preinitiation	MJ < CON, left and right OFC volume at age 12 (preinitiation)	None identified
Takagi et al. (2013)	MRI 3T	18	Corpus callosum ROIs	Not reported	MJ = CON in corpus callosum morphology	None identified
Jacobus et al. (2014)	MRI 3T	18	34 Bilateral cortical thickness ROIs	28 days	MJ > CON, left entorhinal thickness ↓ Frontal thickness = ↑ Lifetime MJ use	↑ Frontal and temporal thickness = ↓ Global cognition ↑ Frontal and temporal thickness = ↑ Age of MJ onset
Gilman et al. (2014)	DTI 3T	21	Whole brain and ROIs	1 day	MJ > CON, density and shape change left nucleus accumbens and right amygdala	↓ Amygdala and nucleus accumbens density and shape difference = ↑ MJ use severity
Weiland et al. (2015)	MRI 3T	17	Limbic and cerebellum volume ROIs	Not reported	No differences identified	None identified
Ashtari et al. (2009)	DTI 1.5T	19	Whole-brain voxelwise	3 months	MJ < CON fronto-temporal connections, FA	None identified

Author (Year)	Method	Mean Age (Approx.)	Image Analysis	Abstinence Period	Primary Result	Primary Clinical Correlations
Jacobus et al. (2009)	DTI 3T	18	Whole-brain voxelwise	23 days	MJ < CON, FA multiple projection and association tracts	↑FA = ↑Cannabis use severity measures
Bava et al. (2009)	DTI 3T	18	Whole-brain voxelwise	24 h	MJ < CON, FA; MJ > CON, MD multiple projection and association tracts	None significant
Bava et al. (2010)	DTI 3T	18	Whole-brain voxelwise	24 h	MJ < CON, FA; MJ > CON, MD projection and association tracts	↑FA = ↑Attention, working memory, processing speed
Yucel et al. (2010)	DTI 3T	19	Whole-brain voxelwise	Not reported	MJ < CON, FA hippocampus, superior longitudinal fasciculus	None identified
Jacobus et al. (2013a)	DTI 3T	18, 19, 21	Whole-brain voxelwise	28 days each visit	MJ < CON, FA projection and association tracts over 3 years	↑FA = ↑Cognitive performance
Jacobus et al. (2013b)	DTI 3T	18 and 21	Whole-brain voxelwise	Pre/postinitiation 28 days each visit	MJ < CON, FA projection and association tracts postinitiation	↑FA = ↑Cognitive performance

Table 2

Structural Imaging and Marijuana Use, Adult Sample (Sample Age 22, on Average)

Author (Year)	Method	Mean Age (Approx.)	Image Analysis	Abstinence Period	Primary Result	Primary Clinical Correlations
Block et al. (2000)	MRI 1.5T	22	Global and regional volume ROIs	Not reported	No differences identified	None identified
Tzilos et al. (2005)	MRI 1.5T	30	Total gray, white, and hippocampus volume ROIs	Not reported	No differences identified	None identified
Matochik et al. (2005)	MRI 1.5T	26	Whole-brain gray, white, and hippocampus density ROIs	20 days	MJ < CON, right parahippocampal gyrus, left parietal WM MJ > CON, precentral gyrus, right thalamus, parahippocampal WM, and fusiform gyrus WM	↑MJ use years = ↑Left precentral white matter density
Jager et al. (2007)	MRI 1.5T	24	Parahippocampal density ROIs	Negative tox screen, days not reported	No differences in GM density identified	None identified
Yucel et al. (2008)	MRI 3T	36	Hippocampus and amygdala volume ROIs	10 h	MJ < CON, hippocampal and amygdala volumes	↑Past 10 years cannabis exposure = ↓Left hippocampus volume
Mata et al. (2010)	MRI 1.5T	26	GM volume and gyrfication whole brain estimates	Not required	MJ < CON, concavity and thickness of sulci in right frontal lobe	CON only: ↑Age = ↓Gyrification and thickness
Cousijn et al. (2012)	MRI 3T	22	Limbic and cerebellum volume ROIs	24 h	MJ > CON, anterior cerebellum volume	↓Amygdala volume = ↑Cannabis dependence score ↓Hippocampus volume = ↑Weekly cannabis use
Gruber and Yurgelun-Todd (2005)	DTI 3T	26	Corpus callosum and cingulate projections ROIs	Not required	No differences	None identified
DeLisi et al. (2006)	DTI 1.5T	22	Whole-brain voxelwise	Not reported	MJ > CON, frontal and parietal FA MJ > CON, frontal and parietal ADC	None identified
Amone et al. (2008)	DTI 1.5T	24	Corpus callosum tractography segmentation	Not required	MJ > CON, MD prefrontal subregion corpus callosum	↑MD = ↑Months of use
Gruber et al. (2011)	DTI 3T	26	Corpus callosum and cingulate projection ROIs	12 h	MJ < CON, FA; MJ > CON, MD frontal WM and genu	↓FA = ↓Impulsivity ↓FA, ↑MD = ↓Age of MJ initiation

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Gruber et al. (2014)	DTI 3T	23	Corpus callosum, corona radiata, internal/external capsule ROIs	12 h	MJ < CON, FA; MJ > CON, MD genu, corpus callosum	↓FA = ↓Age of MJ initiation ↓FA = ↑Impulsivity scores