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Are there Volumetric Brain Differences Associated with the Use of Cocaine and Amphetamine-Type Stimulants?

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Abstract

While a large number of studies have examined brain volume differences associated with cocaine use, much less is known about structural differences related to amphetamine-type stimulant (ATS) use. What is known about cocaine may help to interpret emerging information on the interaction of brain volume with ATS consumption. To date, volumetric studies on the two types of stimulant have focused almost exclusively on brain differences associated with chronic use. There is considerable variability in the findings between studies which may be explained in part by the wide variety of methodologies employed. Despite this variability, seven recurrent themes are worth noting: 1) loci of lower cortical volume (approximately 10% on average) are consistently reported, 2) almost all studies indicate less volume in all or parts of the frontal cortex, 3) more specifically, a core group of studies implicate the ventromedial prefrontal cortex (including the medial portion of the orbital frontal cortex) and 4) the insula, 5) an enlarged striatal volume has been repeatedly observed, 6) reports on volume differences in the hippocampus and amygdala have been equivocal, 7) evidence supporting differential interaction of brain structure with cocaine vs. ATS is scant but the volume of all or parts of the temporal cortex appear lower in a majority of studies on cocaine but not ATS. Future research should include longitudinal designs on larger sample sizes and examine other stages of exposure to psychostimulants.

Keywords

MRI; Volumetric; Voxel-based morphometry; Grey matter volume; Stimulants; Cocaine; Amphetamine-type stimulants; Amphetamine; Methamphetamine; MDMA

1. Introduction

Cocaine and amphetamine-type stimulants (ATS) are psychoactive compounds that have profound effects on brain and body e.g. appetite suppression, intense feelings of well-being, and increased energy, heart rate, and mental alertness. Amphetamine-type stimulants, which include l-amphetamine, d-amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), methylphenidate, methcathinone, ephedrine, and pseudoephedrine among others, share common elements in their chemical structure (Sulzer *et al.*, 2005). Although cocaine has a markedly different chemical composition than

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ATS, both act on the nervous system by increasing the synaptic availability of catecholamines (e.g. dopamine, norepinephrine) and serotonin. Cocaine and methylphenidate specifically block the reuptake of neurotransmitters via transmembrane transporters. Most ATS, in addition, catalyze the release of presynaptically stored neurotransmitters into the synaptic cleft (Woolverton and Johnson, 1992). While the medical use of cocaine is limited to topical anesthesia, ATS are prescribed to treat a variety of neurological diseases ranging from attention deficit hyperactivity disorder (ADHD) to narcolepsy and obesity. Non-medical use of these drugs is widespread and the economic burden of abuse in terms of health and criminal service costs as well as lost productivity is substantial (Executive Office of the President, 2004). A significant number of individuals who experiment with stimulants will develop problematic patterns of use. For example, it is estimated that 15% of those who consume cocaine recreationally will become addicted within 10 years of first use (Wagner and Anthony, 2002). The National Survey on Drug Use and Health (2010) indicates that 1 million persons in the U.S. are currently dependent on cocaine in addition to 350 thousand persons who are dependent on some other type of stimulant. An understanding of how these drugs affect the brain is critical to the development of interventions which could address the negative consequences of non-medical stimulant use.

The present article will review data collected by magnetic resonance imaging (MRI) on the interaction of brain structure with cocaine and ATS consumption and will concentrate primarily on differences in regional grey matter. It should not be assumed that cocaine and ATS have entirely identical effects on the brain. However, multiple independent lines of investigation point to several convergent a priori regions-of-interest for both cocaine and ATS. This review will emphasize commonalities between cocaine and ATS because the limited amount of volumetric data available and the high degree of variability between studies make it difficult to identify differences reliably at this time. Acute cocaine and ATS intoxication produces an increase in intracellular dopamine in the striatum, especially in its ventral anterior part (Di Chiara and Imperato, 1988; Drevets et al., 1999; Volkow et al., 1996). These acute effects are believed to mediate the reinforcing properties of stimulants but are unlikely the sole factor in the development of compulsive drug-taking behaviors (Volkow *et al.*, 2009). Neural activity may be impaired in other parts of the brain which, in healthy individuals, would otherwise protect against substance abuse (Everitt *et al.*, 2008; Goldstein *et al.*, 2009). Such impairments could either be the result of stimulant use or could predate substance use in a population of individuals at-risk. In animal models, chronic exposure to cocaine and ATS produces long-lasting alterations in markers of dopamine, norepinephrine and serotonin activity in many parts of the brain, including the striatum, thalamus, hippocampus, midbrain and cortex (Gould et al., 2011; Krasnova and Cadet, 2009; Porrino et al., 2004). Similarly in humans, in vivo positron emission tomography (PET) studies have shown alterations of catecholamine and serotonin signaling in association with chronic cocaine and ATS use (Ding et al., 2010; McCann et al., 1998; Sekine et al., 2003; Sekine et al., 2006; Volkow et al., 2001; Volkow et al., 1993). Markers of dopamine activity are decreased in the striatum of chronic methamphetamine users postmortem (Kitamura et al., 2007; Wilson et al., 1996) and lower levels of dopamine transporter availability in cocaine and ATS users correlates with glucose metabolism in the orbitofrontal cortex (Volkow et al., 2001; Volkow et al., 1993). fMRI studies further indicate that there is abnormal activity in the frontal, parietal, and insular cortex of chronic stimulant users (Paulus et al., 2003; Paulus et al., 2002; Paulus et al., 2005). Taken together, the diversity of findings suggest that extensive neuroadaptations occur throughout the brain in response to stimulant intoxication (Koob and Volkow, 2010).

The time course of these neuroadaptations may be reflected in the volume of the brain at several stages of interest: 1) prenatal exposure, 2) differences in brain structure before initial

use that might bias at-risk individuals toward use or abuse/dependence, 3) effects of occasional/recreational use which represents the most prevalent pattern of drug consumption, 4) effects of chronic use associated with abuse/dependence, 5) structural markers that could predispose individuals to relapse after rehabilitation, and 6) the effects of abstinence. To date, the literature on the interaction of brain structure with stimulants has focused almost exclusively on stage 4, the effects of chronic use. Studies on the effects of chronic cocaine use are catalogued in sections 2.1 (current or recent chronic use) and 2.2 (more than 2 months abstinence). The few studies pertaining to the other stages of interest of cocaine use are grouped together in section 2.3. Since more studies have examined volumetric effects associated with cocaine, these studies provide a framework to interpret the smaller number of studies that have examined ATS (section 3). Studies that have examined regional volumetric differences associated with chronic ATS use are catalogued in sections 3.2 (current or recent chronic use) and 3.2 (more than 2 months abstinence) while studies on the other stages of interest are grouped in section 3.3. One goal of sections 2 and 3 is to draw attention to the variability of results that have been reported in the literature. Most parts of the brain have been implicated in at least one study. In order to properly interpret the significance of individual findings, it is necessary to view them against this background of variability. Awareness of variability in the literature is also a precondition of understanding its source. Methodological considerations which could account for some of the differences in findings between studies are considered in section 4. Despite a large number of apparent contradictions, many consistent findings do emerge when this body of work is considered as a whole. Seven recurrent themes in the literature are summarized in section 5 and discussed at length in section 6. The summary and discussion sections are followed by speculation on future directions of the field.

2. Volumetric Effects of Cocaine Use

2.1. Active or Recently Abstinent Chronic Users

Several magnetic resonance imaging studies have examined the relationship between brain volume and chronic cocaine use in populations that are either currently using the drug or recently abstinent (Table 1). Subjects in these studies on recent or active use meet the criteria for a clinical diagnosis of cocaine dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) and a positive urine test is frequently required for inclusion. The substance dependent subjects described in this section have consumed cocaine at least once within the previous 20 days on average.

The earliest of these studies relied on manual identification of predetermined regions of interest and generated several conflicting results (Table 1). Liu *et al.* measured the volumes of prefrontal and anterior temporal cortex in a group of poly-substance abusers most of whom primarily abused cocaine (23 out of 25 subjects) (Liu *et al.*, 1998). While there was no difference between substance users and controls in terms of total brain volume, users had significantly less grey matter volume in the prefrontal cortex bilaterally (11.5% and 13.7% in the right and left hemispheres, respectively). In addition, the number of years of cocaine use was negatively correlated with prefrontal volume. Bartzokis *et al.* (2000), however, observed lower temporal but not frontal lobe grey matter volume in cocaine using subjects. Grey matter volume in both lobes decreased with age but, intriguingly, the age-related loss was accelerated in the temporal lobes of cocaine users compared to controls (Bartzokis *et al.*, 2000). A subsequent study by the same group of investigators using a similar experimental design but with a substantially larger sample was unable to replicate these results. Rather, it was reported that age-related white matter increases observed in the frontal and temporal lobes of control subjects did not occur in cocaine dependent subjects (Bartzokis *et al.*, 2002), leading the authors to suggest that chronic cocaine use may block

normal white matter maturation that continues into late middle age. Numerous studies have investigated foci of hyper-intensity in the white matter of MR-images which are believed to represent demyelination indicative of a lesion. The concentration of these hyper-intensity foci is greater in the brains of cocaine dependent subjects than healthy controls (Bartzokis *et al.*, 1999; Lyoo *et al.*, 2004; Tobias *et al.*, 2010). Consistent with the hypothesis that cocaine use alters normal age-related white matter volume effects, Bartzokis and colleagues *et al.* (1999) noted that the concentration of white matter hyper-intensities in their sample of cocaine dependent subjects was equivalent to a drug naïve population that was 20 years older. These findings could be important because, if it is true that cocaine has differential structural effects at various developmental time-points, comparisons of cross-sectional volumetric studies on cocaine use should consider the differences in the average age of subjects between studies. To date, longitudinal data which could address this issue has not been reported.

Early volumetric studies that manually identified the amygdala and hippocampus also produced conflicting evidence. Jacobsen *et al.* found no differences in the volume of the whole brain, amygdala or hippocampus between cocaine users and normal control subjects (Jacobsen *et al.*, 2001b) while Makris *et al.* reported that the volume of the amygdala but not the hippocampus was significantly lower in cocaine users (Makris *et al.*, 2004). The right and left amygdala were reduced by 23% and 13%, respectively, relative to the control subjects and a volume asymmetry between the left and right sides noted in controls was absent in users. Since the size of the amygdala in cocaine users did not correlate with indicators of total use and even the subjects with limited experience (1–2 years) exhibited lower amygdala volumes, the authors argued that structural changes to the amygdala represent either a unique early effect of cocaine use or a developmental marker that could predispose individuals to drug abuse. Most subsequent studies have not observed lower amygdala volume in chronic cocaine users with one notable exception described later in this section (Barros-Loscertales *et al.*, 2011).

Jacobsen and colleagues, who manually identified components of the striatum, found that the caudate nucleus was 3.4 % larger and the putamen was 9.2% larger in cocaine dependent subjects compared to controls (Jacobsen *et al.*, 2001a). Volumetric differences in the striatum of chronic stimulant users are potentially interesting because alterations in striatal dopamine neurotransmission have been repeatedly observed with PET in human cocaine users (McCann *et al.*, 1998; Volkow *et al.*, 1997) and in animal models (Wilson *et al.*, 1994). Martinez and colleagues generated partially related data on the volume of striatum which they divided into an anterior and a posterior part. The anterior part was smaller and the posterior part larger in chronic cocaine users (Martinez *et al.*, 2004), although these differences did not reach the threshold of significance possibly due to the small sample size. In summary, the early manual studies provided interesting but often contradictory results in terms of the volume of the cortex, striatum, amygdala and hippocampus. Many of these studies were limited by relatively small samples (Table 1) which may be related to the considerable effort required to manually identify structures in individual brains.

More recently, *voxel-based morphometry* (VBM) has been applied to study the structural brain effects associated with substance abuse. Since VBM is an automated protocol, it is less time consuming than the older manual methods which, in turn, facilitates efficient whole brain analyses. In the standard VBM protocol, all brains are spatially normalized to a common stereotactic space which eliminates global shape differences between individual brains while sparing regional differences in grey and white matter density (Ashburner and Friston, 2000). Grey and white matter are automatically segmented, spatially smoothed and voxel-wise statistical tests are applied to generate statistical parametric maps. Because the standard VBM protocol may misclassify tissue types due to systematic structural differences

between groups, an optimized VBM protocol has been developed (Good *et al.*, 2001). The optimized protocol uses an iterative approach to segmentation and normalization that results in a more accurate identification of grey and white matter. An additional processing step that can be added to either the standard or optimized VBM protocols is modulation of the segmented images by the Jacobian determinants produced during spatial normalization. This will be referred to simply as modulation in the tables and the remainder of the text. Modulation preserves information about the absolute volume of the brain tissue while unmodulated analyses compare the relative local concentrations of grey and white matter (Mechelli *et al.*, 2005).

Franklin *et al.* (2002) first used standard VBM without modulation to analyze subjects with a current diagnosis of cocaine dependence. While no differences in white matter were discovered, cocaine dependence was associated with a 5–11% reduction of grey matter concentration in the ventromedial, orbitofrontal, anterior cingulate, anteroventral insula and superior temporal cortex compared to controls. Lower grey matter concentration in the ventromedial prefrontal cortex is clinically interesting because of poor real-life decision making displayed by patients with lesions in that part of the brain (Eslinger and Damasio, 1985). Patients with lesions in the ventromedial frontal cortex engage in risky financial and social behaviors that often have disastrous personal consequences. They are impaired on the Iowa Gambling task which was designed explicitly to mimic the conditions of real-life decision making that challenges such patients (Bechara *et al.*, 1994) (Bechara *et al.*, 1999). Since substance abusers also exhibit deficits on the Iowa gambling task compared to controls (Grant *et al.*, 2000), the authors suggest that disruption of the evaluative computations which underlie performance on the Iowa gambling task and depend upon the integrity of the ventromedial frontal cortex may also play an important role in the poor decision-making that perpetuates substance abuse (Franklin *et al.*, 2002). Matochik and colleagues (2003) obtained similar results in an examination of 14 cocaine abusers. Thirteen small manually drawn anatomical regions of the frontal cortex were compared following simple VBM processing without modulation. Voxel clusters of reduced grey matter concentration were found in 10 of the 13 regions of interest including the cingulate gyrus, lateral prefrontal cortex, and medial and lateral aspects of the orbitofrontal cortex. Although the samples were quite small in the studies by Franklin *et al.* and Matochik *et al.*, the observation of lower volume in the insula and ventromedial frontal cortex are noteworthy as they have been frequently repeated.

Sim *et al.* (2007) examined a larger sample using the optimized VBM protocol with modulation by the Jacobian determinants. The reported stereotactic coordinates of significant clusters in this study indicate that the cocaine group had less grey matter volume (13.4–16.6%) bilaterally in the cerebellum, premotor, and temporal cortex as well as the thalamus and the right anterior lateral prefrontal cortex compared to a control group (Sim *et al.*, 2007). White matter in the right cerebellum was also lower by 10%. An innovative aspect of this report was the correlation of volumetric effects with behavioral tasks in order to improve the interpretation of results. Motor ability as measured by the Grooved Pegboard Test (Matthews, 1964) was significantly correlated with grey and white matter volume of the cerebellum while executive function as measured by the Trail Making Test B (Reitan *et al.*, 1992) and the Color-Word Stroop Test (Golden, 1978) were significantly correlated with cerebellar grey matter volume alone. Since cerebellar grey matter volume was also negatively correlated with years of drug use, this data suggests that cocaine related damage to the cerebellum may mediate some of the neuropsychological deficits observed in drug dependent individuals. Consistent with the earlier report by Bartzokis *et al.* (2000), an age related decline was observed in parts of the temporal lobe grey matter of drug users alone, but unlike Bartzokis *et al.* (2002), a relation between white matter and age was not observed. The cerebellum and bilateral premotor cortex also declined with age in both drug users and

controls underscoring once again the potential importance of subject age in the comparison of volumetric studies. The significance of the cerebellar findings in this study and their relation to function are unclear as they have received very little support from similar volumetric investigations (but see Barros-Loscertales et al., 2011; O'Neill et al., 2001).

The anatomical information provided by VBM can be complemented by diffusion tensor imaging (DTI) which measures the microstructure of white matter fiber tracts. DTI is based on the diffusion of water molecules through the brain. In grey matter, water molecules typically move in all directions equally (isotropic diffusion). In white matter, water molecules are constrained by axonal membranes and tend to move in the direction of the fiber axes (anisotropic diffusion). Fractional anisotropy is an estimate of anisotropic diffusion derived from diffusion tensors representing the direction of water molecules at each voxel. Higher fractional anisotropy (FA) indicates greater fiber organization and integrity (Taber *et al.*, 2002). DTI in cocaine dependent subjects has exposed a lower FA in the inferior frontal cortex compared to controls in several studies (Lim *et al.*, 2002; Lim *et al.*, 2008; Romero *et al.*, 2010). Lim and colleagues found lower FA in the inferior frontal white matter of cocaine dependent subjects (N=21) compared to controls in a study that combined DTI with a volumetric analysis (Lim *et al.*, 2008). Grey and white matter volume and FA were estimated in three pre-defined brain regions that were fitted to individual brains on the basis of visually identified landmarks. The three regions of interest were the superior and inferior frontal cortex and the entire cerebrum (forebrain). The volumes of these three regions were not significantly different between cocaine users and controls, although there was a trend toward lower inferior frontal grey and white matter volume in the inferior frontal region. The subjects were also scored on the Barratt Impulsivity Scale (BIS-11) (Patton *et al.*, 1995) Although it has been repeatedly demonstrated that substance abusers score significantly higher than normal controls on the Barratt Impulsivity scale (BIS-11) (Moeller *et al.*, 2002; Patkar *et al.*, 2004), the cocaine dependent subjects' scores in this study did not correlate with grey matter, white matter or FA in any of the defined frontal regions of the interest. In a separate whole brain voxel-wise analysis, impulsivity was negatively correlated with FA in the body and genu of the corpus callosum and the internal capsule, i.e. more impulsive individuals had less FA. By contrast, Romero and colleagues found FA in the corpus callosum was not lower in chronic cocaine users and that individual scores on the BIS-11 were negatively correlated with FA in the inferior frontal white matter (Romero *et al.*, 2010). They also reported higher FA in the white matter of the anterior cingulate region. Both differences in the FA of the inferior frontal cortex and anterior cingulate white matter were matched by parallel differences in regional white matter volume quantified by optimized VBM with modulation. Moeller *et al.* (Moeller *et al.*, 2005) who examined the corpus callosum alone observed lower FA in the rostrum/genu of the corpus callosum of cocaine dependent subjects that also correlated with BIS-11 scores and the Immediate and Delayed Memory Tasks (Dougherty *et al.*, 2002). Several other studies have also reported altered FA in the corpus callosum of chronic cocaine users (Lane et al., 2010; Ma et al., 2009; Moeller et al., 2007). With regard to whether FA is lower in the inferior frontal white matter or the rostrum/genu of the corpus callosum of chronic cocaine users, it should be noted that these two structures are closely related anatomically. Wallerian degeneration of the axonal fibers comprising the anterior corpus callosum occurs subsequent to lesions of the anterior frontal cortex (de Lacoste *et al.*, 1985). Thus, lower FA in both white matter regions are consistent with damage to the frontal cortex that might result from cocaine use.

A further avenue of investigation that has been little explored but is likely to provide a wealth of information on substance abuse in the future is the relationship of brain volume to genetic variability. Alia-Klein and colleagues have recently examined the relation of chronic cocaine abuse with the MAO-A gene which encodes monoamine oxidase-A, an enzyme

involved in the metabolic regulation of monoamine neurotransmitters including dopamine and norepinephrine (Alia-Klein *et al.*, 2011). A variant of the MAO-A gene with a low number of allele repeats (MAO-A*Low) increases risk for anti-social behavior and alcohol addiction (Caspi *et al.*, 2002; Saito *et al.*, 2002). In a VBM analysis with modulation, cocaine use was associated with a reduction of approximately 5–10% of the volume of the orbitofrontal, dorsolateral frontal, hippocampal and temporal cortex in 40 cocaine dependent individuals compared to normal controls. Hierarchical regression analysis to determine the unique effects of different measured features indicated that cocaine use and MAO-A*Low contributed the greatest unique variability to orbitofrontal grey matter volume loss whereas lifetime alcohol consumption explained more of the variability in the dorsolateral frontal cortex and the hippocampus. The design of the study does not determine whether diminished volume of the orbitofrontal cortex is a cause or an effect of cocaine use. Since MAO-A is critical for catabolic degradation of dopamine and norepinephrine during prenatal development, it is possible that MAO-A*Low may impair grey matter maturation of the orbitofrontal cortex establishing a later behavioral vulnerability for cocaine abuse. It is also possible that MAO-A*Low aggravates damage to the cortex caused by cocaine exposure. These results are difficult to interpret at present because the MAO-A polymorphism is not directly related to the level of MAO-A activity in the brain (Fowler *et al.*, 2007).

In another study with important genetic implications, Ersche and colleagues (2012) examined brain and behavioral markers of addiction in 50 biological siblings, one of whom was dependent on stimulants. Compared to controls, dependent subjects and their siblings performed poorly on the Stop Signal Reaction Time Task which is a predictive factor for drug dependence in adolescents (Nigg *et al.*, 2006). FA was reduced in dependent subjects and their siblings but not in the controls. Furthermore, FA in the ventral frontal white region was significantly correlated with performance on the stop signal reaction time task. Grey matter as measured by VBM with modulation was reduced in both substance dependent users and their siblings relative to controls in left posterior Sylvian fissure including parts of the postcentral gyrus, insula, superior temporal gyrus. Also, the left putamen and left amygdala were enlarged relative to unrelated controls. The similar findings in sibling pairs suggest that there is a strong genetic predisposition toward drug taking behavior that could be detected with structural neuroimaging. Unlike their siblings, dependent subjects exhibited lower volume in medial orbital and ventromedial frontal cortex, the anterior and middle parts of the insula and medial occipital cortex (Ersche *et al.*, 2012). These additional regions may reflect structural changes resulting from drug use.

Three other recent studies have used VBM to examine brain volumetric effects associated with chronic cocaine use. Barros and colleagues have produced the only evidence of lower striatal grey matter volume (14.8%) in cocaine users relative to controls (Alfonso Barros-Loiscertales, 2011). Interestingly, these data were smoothed with a Gaussian kernel of 8 mm FWHM. Less spatial blurring is recommended in situations where the structure of interest is small relative to the spatial blurring kernel. When a larger blurring kernel (12mm) was applied, the group difference in the volume of the striatum was no longer significant. Consistent with previous reports that have noted loci of lower cortical volume, the volume of the supramarginal gyrus was 12.1% lower in cocaine users and years of cocaine use was negatively correlated with the grey matter volume of the middle and superior frontal gyrus, the parahippocampal gyrus, the posterior cingulate, amygdala, insula, right middle temporal gyrus, and cerebellum. A VBM study with a much larger sample by Ersche and colleagues also found lower volumes in widespread regions of the cortex including the orbitofrontal, medial frontal, anterior cingulate, insular, temporoparietal and parts of the cerebellar cortex (Ersche *et al.*, 2011a). But unlike Barros *et al.*, this study observed higher grey matter volumes in the striatum and parts of the cerebellum. Regions of significant difference between users and controls were applied as a mask in a further analysis of voxel-wise

correlations with behavioral measures of impulsivity and cocaine related compulsivity as well as duration of cocaine use. Compulsivity for drug use was measured by the Obsessive/Compulsive Drug Use Scale (Franken *et al.*, 2002). Impulsivity was quantified by several different measures: the Barratt Impulsivity Scale, the Behavioral Inhibition/Activation System Scale (Carver and White, 1994), the Stop Signal Reaction Time Task (Logan *et al.*, 1997) and the Rapid Visual Information Processing Tasks (www.camcog.com). Principal components analysis identified five principal components among these measures. Two of these components, Inattention and Impulsive Reward Seeking, were significantly different in the dependent group compared to controls. The size of the caudate was positively correlated while the insula and middle temporal gyrus were negatively correlated with the Inattention component. The ventromedial frontal cortex was negatively correlated with cocaine related compulsivity. Cocaine associated changes in the insula, inferior frontal gyrus, anterior cingulate gyrus, and temporal cortex and left caudate nucleus and cortex were also positively related to duration of cocaine use (Ersche *et al.*, 2011b).

Lastly, Narayana and colleagues examined the brains of 34 cocaine dependent subjects using VBM with and without modulation as well as tensor based morphometry (Narayana *et al.*, 2010). Tensor based morphometry (TBM) detects regional structural differences on the basis of the deformation fields which spatially normalize brain images to a common template (Ashburner and Friston, 1999) i.e. statistical maps are generated from the deformation fields rather than grey and white matter segmented images as in VBM. This is the only published study using automated whole brain techniques that found no significant results or trends. The authors entertain several possibilities with regard to why no differences were detected in their study. These included stricter selection criteria and the use of family-wise error correction rather than spatial extent inference to establish a significance threshold.

Investigations of the volumetric brain effects associated with current or recent chronic cocaine use have produced a variety of results. Almost all studies that measured the volume of the cortex showed lower volume in some part of the cortex in cocaine users compared to controls (Alia-Klein *et al.*, 2011; Barros-Loscertales *et al.*, 2011; Bartzokis *et al.*, 2000; Ersche *et al.*, 2011a; Ersche *et al.*, 2012; Franklin *et al.*, 2002; Lim *et al.*, 2008; Liu *et al.*, 1998; Matochik *et al.*, 2003; Sim *et al.*, 2007). In addition, most studies implicated the frontal cortex with several noting, in particular, volume effects in the ventromedial/medial orbitofrontal prefrontal cortex (Alia-Klein *et al.*, 2011; Ersche *et al.*, 2011a; Ersche *et al.*, 2012; Franklin *et al.*, 2002; Matochik *et al.*, 2003). In an effort to improve understanding of the functional significance of these structural effects, ongoing research has started to relate volumetric differences to behavioral (e.g. Ersche *et al.*, 2011a; Romero *et al.*, 2010) and genetic measures (Alia-Klein *et al.*, 2011). Although these studies examined chronic users, longitudinal data is absent which could indicate whether volume differences occurred before or subsequent to chronic use of cocaine. Consequently, it is unknown whether the reported findings are direct/indirect causes or effects of chronic consumption.

2.2. Long-term abstinence in chronic cocaine users

Beyond the immediate effects of chronic cocaine use, several studies have examined the structural response of the brain during abstinence (Table 2). It is worth noting that all these studies are cross-sectional in design. Thus, at present, it is not possible to differentiate structural brain changes that might be associated with chronic use from those associated specifically with abstinence. However, insofar as the findings are consistent with studies of active users, it does suggest that these structural differences are independent of potential acute intoxication effects.

Di Sclafani and colleagues, identified the hippocampus manually on serial coronal MR sections (Di Sclafani *et al.*, 1998b). Subjects were also assessed by the MicroCog

Assessment of Cognitive Functioning which measures aspects of spatial attention, executive function, spatial processing, immediate/delayed memory for stories and reaction time (Powell, 1993). Dependent subjects were less proficient on all neuropsychological domains relative to normal controls. Despite a hypothesized relation between the hippocampus and memory ability as measured by the MicroCog test battery, no significant difference in the volume of the hippocampus was observed between dependent subjects and healthy controls. In a second related study, intracranial volume which includes both brain and cerebrospinal fluid was quantified in cocaine and alcohol dependent and cocaine only dependent subjects (Di Sclafani et al., 1998a). Cocaine subjects were significantly impaired globally on MicroCog scores and specifically in the domains of abstraction, spatial abilities, memory and learning, but did not differ from normal controls on intracranial volume. Intracranial volume did though explain 14.1% of the variance in the global MicroCog score for the drug using subjects. The authors interpreted these results in terms of the concept of functional reserve which holds that individuals with a larger reserve of brain volume will continue to function in the face of neurodegeneration longer than those who start off with less brain volume.

O'Neill 2001 *et al.* investigated subjects dependent on cocaine alone or dependent on both cocaine and alcohol. An operator blind to the experimental condition used a semiautomated algorithm to segment brain tissue into five categories: cortical grey matter, white matter, sulcal and ventricular cerebrospinal fluid, subcortical grey matter and white matter lesions. Overall, cocaine users had 4.8% less cortical grey matter and 3.2% less white matter compared to healthy control subjects. In the prefrontal cortex, grey matter volume was lower by 6% relative to controls and by 8.8% on average in the temporal lobes, cerebellum and brainstem (O'Neill *et al.*, 2001). Only the occipital region appeared to be larger (4.6%) in cocaine users than controls. With regard to the significance of this study, it is worth noting that only 8 cocaine dependent subjects were examined. In a similar study comparing cocaine dependent subjects with cocaine and alcohol dependent subjects, both groups exhibited less grey matter volume in the prefrontal cortex of approximately 10% compared to controls but did not differ significantly from each other (Fein *et al.*, 2002). Subjects were assessed by the MicroCog test battery. In contrast to Sclafani et al. (1998), dependent subjects performed less well than controls in all domains except immediate/delayed memory. Scores on the executive domain in dependent subjects correlated with prefrontal cortical volume which was also negatively correlated with age.

A recent VBM study with modulation was conducted on polysubstance abusers who were dependent on two or more substances, mainly cocaine, alcohol, amphetamine and cannabis (Tanabe *et al.*, 2009). The polysubstance abusers had significantly less grey matter volume bilaterally in the ventromedial frontal cortex. Although the polysubstance abusers were more likely to select a suboptimal strategy in a modified version of the Iowa Gambling Task, this failed to reach the threshold of significance. Consistent with the hypothesis of Franklin *et al.* (2002), performance on the Iowa Gambling Task was correlated with the volume of the ventromedial frontal cortex. Better performance was associated with larger volume.

Like current/recent cocaine users discussed in the previous section, individuals who have been abstinent for more than a month possess less frontal cortical volume than controls (Fein *et al.*, 2002; O'Neill *et al.*, 2001; Tanabe *et al.*, 2009). Lower volume may be due specifically to the ventromedial frontal cortex. Interestingly the volume of this region correlates with performance on the Iowa Gambling Task (Tanabe *et al.*, 2009) which suggests that dependent subjects have difficulty selecting the optimal strategy in contexts that offer differential risk and reward contingencies. Also like the studies on current/recent cocaine users, the absence of longitudinal data makes it impossible determine whether differences between abstinent users and controls are a cause or an effect of cocaine use.

2.3. Other Volumetric studies on Cocaine Use

A small number of volumetric cocaine studies have investigated issues beyond differences between chronic users and controls. In a study that identifies a potential risk factor for cocaine abuse, Bartzokis and colleagues explored the relationship between brain volume and euphoria following acute cocaine administration (Bartzokis et al., 2004). Cocaine dependent subjects were infused with 40 mg of cocaine hydrochloride and subsequently requested to rate the level of euphoria experienced at 3, 10 and 30 minutes post-delivery on a verbal scale ranging from 1–10. Grey and white matter volumes of the frontal and temporal lobes were estimated from a series of manually segmented MR-images. Controlling for age and height, the largest correlations between euphoria and grey matter volume occurred in the frontal and temporal lobes at 10 minutes post-delivery. These results suggest that grey matter volume, at least in part, mediates euphoria. The authors speculated that individuals with more grey matter volume might be at greater risk for abuse because they would experience more intense drug reinforcement.

A few studies have also examined the effects of prenatal exposure to cocaine in adolescents. Avants and colleagues measured the caudate nucleus in children with intrauterine exposure to cocaine by automated mapping of a brain template to each individual (Avants *et al.*, 2007). The caudate was smaller in children who had been exposed to cocaine compared to a non-exposed control group. The authors speculated that the volume difference may contribute to deficits in attention and impulse control that have been noted repeatedly in these children (Accornero *et al.*, 2007). A subsequent volumetric study on the effects of intrauterine exposure to cocaine involving an automated whole brain analysis in prenatally exposed children indicated that there were significant decreases in cortical and total brain volume compared to controls but that these changes could not be separated from the effects of concomitant exposure to alcohol and cigarettes (Rivkin *et al.*, 2008). A DTI study on intrauterine exposure found no significant difference in white matter FA in children exposed to cocaine prenatally relative to a control group (Liu *et al.*, 2011b).

3. Volumetric Effects of Amphetamine-Type Stimulant Use

The interaction of brain structure with ATS has not been examined by MRI as extensively as it has been with cocaine (Tables 3 and 4). Similar to volumetric investigations of cocaine use, the majority of the studies on ATS that have been published target *chronic* use. These studies also tend to focus on methamphetamine users. The few exceptions -- including two studies on occasional use of amphetamine and MDMA, and one study on prenatal exposure -- are presented in section 3.3. Despite the smaller literature, there are several important points of convergence with reports on the structural effects of cocaine.

3.1. Active or Recently Abstinent Chronic Amphetamine-Type Stimulant Users

Similar to studies on the effects of chronic cocaine use, white matter hyperintensities are present more in chronic methamphetamine users than healthy controls (Bae *et al.*, 2006). Several DTI studies have reported diminished FA in either the frontal white matter (Alicata et al., 2009; Chung et al., 2007; Tobias et al., 2010) or anterior portion of the corpus callosum (Kim *et al.*, 2009; Salo *et al.*, 2009; Tobias *et al.*, 2010) in methamphetamine dependent subjects compared to controls. Alicata and colleagues also found changes in the striatum, consistent with a loss of myelinated axons, which correlated with age of drug initiation and the amount of lifetime consumption. By contrast, chronic MDMA use (>1 year) has been reported to affect white matter integrity in the anterior limb of the internal capsule, the cortical spinal tract, and the thalamus bilaterally (Liu *et al.*, 2011a).

The reported grey matter volumes in three studies on current/recent chronic ATS use also resembles those reported for cocaine dependent subjects (Table 3). A study by Bartzokis and

colleagues described in section 2.1 which examined active cocaine users also included a group of subjects who were dependent on amphetamines. The temporal lobe was significantly diminished relative to control subjects in both substance dependent groups (Bartzokis *et al.*, 2000). The difference was largely driven by lower grey matter volume which was statistically significant in cocaine users but only approached the threshold of significance in the amphetamine users. Note, however, that the sample was exceptionally small in this study (N=9). In a second study, surface-based volume was investigated in subjects with a diagnosis of methamphetamine dependence (Thompson *et al.*, 2004). Brain volumes were spatially registered by alignment to 80 manually defined anatomical landmarks within a template average of healthy control brains. Tissue classes were categorized on the basis of differences in signal intensities then the cortical surface was rendered as a 3D volume. Group differences were established by cortical pattern matching (Thompson *et al.*, 2003). Unlike VBM, this technique incorporates gyral variation into its estimation of regional volume differences. It is also more labor intensive and dependent on accurate manual identification of sulcal landmarks. Grey matter in the cingulate, limbic and paralimbic cortex was lower by 11.3% in methamphetamine users compared to controls while white matter was higher globally by 7%. The hippocampus, which was manually identified on serial sections, was significantly reduced (7.8%) in methamphetamine users. Subjects were interviewed on the Repeated Memory Test (Simon, 1999) which measures both recall and recognition of pictures and words. Word recall was correlated with total volume and volume of the right hippocampus. In the third study, Nakama and colleagues investigated grey matter volume changes in automatically identified regions of interest (6 lobes and 17 subregions) in methamphetamine dependent subjects (Nakama *et al.*, 2011). The grey matter volumes of the dorsolateral prefrontal, orbitofrontal, superior temporal cortex and a subregion that the study figures suggest is the insula were significantly smaller by 4–5% adjusted for total cranium volume in methamphetamine dependent subjects compared to healthy controls. While there was a gradual age related decline in grey matter in all subjects in all regions examined, the loss of grey matter was significantly accelerated in frontal, temporal, occipital, and insular lobes in the methamphetamine dependent subjects compared to healthy controls. Extrapolating from these data, the authors estimate that the average grey matter decline per decade in chronic methamphetamine users would be 6.4–8.5% but in normal controls would be only 0.1 to 3.5%. In summary, as noted with regard to chronic cocaine studies, lower volume in the frontal cortex is observed in volumetric studies of current chronic amphetamine use and the ventromedial/medial orbital frontal cortex, in particular, is identified (Nakama *et al.*, 2011; Thompson *et al.*, 2004). Again, the data suggest that age may be an important factor to consider when comparing cross-sectional data (Nakama *et al.*, 2011).

3.2. Long-term Abstinence in Chronic Amphetamine-Type Stimulant Users

With regard to the effects of long-term abstinence in chronic ATS users, interpretation can also be informed by findings on cocaine use (Table 4). Chang and colleagues traced the thalamus, midbrain, caudate nucleus, putamen, globus pallidus, cerebellum, and whole brain on serial MR-images obtained from abstinent methamphetamine users and healthy controls (Chang *et al.*, 2005). A semi-automatic algorithm was also used to segment the corpus callosum into four parts. The globus pallidus (10%) and putamen (8%) were significantly larger in methamphetamine users. The volume of the putamen was correlated with verbal fluency and both the putamen and the globus pallidus correlated with performance of the non-dominant hand in the grooved Pegboard Task. The lifetime amount of methamphetamine consumed was negatively correlated with the volume of the putamen and the globus pallidus. Together these results suggest that the enlargement of the putamen and the globus pallidus may protect cognitive abilities from damage associated with chronic use.

The authors propose that the volume change could be due to neuroinflammation or glial mediated trophic effects that occur during early phases of drug use.

A similar study published in the same year compared methamphetamine dependent subjects with and without HIV to HIV positive and negative controls (Jernigan *et al.*, 2005). Structures of interest were manually identified including: the frontal, temporal, parietal, and occipital lobes and the caudate nucleus, nucleus accumbens, lenticular nucleus (globus pallidus/putamen), thalamus, amygdala and hippocampus. Methamphetamine use was associated with higher grey matter volume in all lobes. This however reached the threshold of significance only in the parietal lobe. The three compartments of the striatum identified were also significantly larger in methamphetamine dependent subjects than healthy controls. There was a significant age-related decrease in the volume of the cortical lobes, the striatum and the thalamus. Interestingly, the largest striatal volumes were observed in the youngest methamphetamine users. This may indicate that methamphetamine does not increase the size of the striatum but rather interferes with a normal age-related decline in volume from adolescence to early adulthood.

Optimized VBM with modulation was performed on a large sample of abstinent methamphetamine dependent subjects (Schwartz *et al.*, 2010). The abstinent subjects had significantly less volume in the bilateral insula (9.6%) and left middle frontal gyrus (12.6%) than controls. A delay discounting task (Hoffman *et al.*, 2008) which measures the likelihood that a subject will select smaller immediate rewards rather than larger delayed rewards was also administered to study participants. The inability to delay gratification for larger rewards is an indicator of impulsivity. Methamphetamine dependent subjects were significantly more impulsive on the delayed discounting task and, in all subjects, this correlated positively with the grey matter volume of the posterior cingulate and ventral striatum and negatively with the left superior frontal gyrus. The amygdala was larger in those with a longer period of abstinence from cocaine use and the intracranial volume was negatively correlated with age of initial use.

Kim and colleagues compared healthy controls with methamphetamine dependent individuals who had been abstinent for a short (30 days on average) or a long period (930 days on average) (Kim *et al.*, 2006). A standard VBM analysis without modulation revealed lower grey matter concentration in the right middle frontal gyrus which was correlated with errors on the Wisconsin Card Sorting Task. Although long-term abstinent subjects displayed less frontal cortical volume loss and committed fewer errors on the card sorting task than short-term abstinent subjects, they were deficient on both these measures compared to normal controls. The intermediate level volume loss and cognitive performance in the long-term abstinent group suggest that there may be some recovery associated with long periods of the abstinence. In light of the comparable findings on the volumetric effects associated with chronic cocaine use, it is notable that the volume of the frontal cortex is lower in formerly ATS dependent subjects who have been abstinent for a prolonged period (Kim *et al.*, 2006; Schwartz *et al.*, 2010).

3.3. Other Volumetric Studies on Amphetamine-Type Stimulant Use

Little attention has been paid to the interaction of ATS with brain volume at stages of interest beyond chronic dependence in adults. Chang *et al.* (2004) investigated the effects of methamphetamine on development in 13 children (average age 6.9 years) who were exposed to the drug prenatally. Total brain size was estimated by an automated algorithm that separated brain tissue from cerebrospinal fluid (Itti *et al.*, 1997). The midbrain, thalamus, globus pallidus, caudate, putamen, cerebellar hemispheres and hippocampus were manually identified in the MR-images. While total brain, midbrain, thalamic, and cerebellar volumes were similar in methamphetamine exposed children compared to healthy age matched

controls, the globus pallidus (28.5%), putamen (17.7%) and hippocampus (19.5%) were significantly smaller bilaterally. The volume of the caudate nucleus was also lower in methamphetamine exposed children but this did not reach the threshold of statistical significance. The methamphetamine exposed children demonstrated deficits on tests of visual motor integration, attention, and verbal and spatial memory. Attention scores were correlated with all of the significantly affected structures while verbal memory scores were correlated only with the volume of the globus pallidus and putamen. More evidence is required but these results suggest that amphetamine has significant effects on development.

Two studies have examined the effects of *occasional* use of ATS on grey matter volume. The first is also the only volumetric study to focus primarily on MDMA use. VBM without modulation was applied to MR-images of 31 individuals with a history of recreational MDMA use and a comparison group of MDMA naïve individuals (Cowan *et al.*, 2003). Polydrug use was present in both groups but was more extensive in those who had experience with MDMA. Other substances consumed included: cannabis, alcohol, cocaine, and hallucinogens. Compared to other studies on chronic stimulant use in dependent subjects described in sections 2.1, 2.2, 3.1, and 3.1, the subjects who used MDMA in this study were much younger (21.7 years old on average) and consumed quantities which suggest a more occasional pattern of use. Subjects were abstinent from MDMA for at least three weeks prior to participation in the study. Significantly less grey matter density was observed bilaterally in the occipital cortex and in the left temporal and frontal cortex as well as in the brain stem and cerebellum. Statistical removal of nuisance covariates, namely age, sex, handedness and other drug use, revealed the same pattern of results. The reduced statistical threshold, introduced in these analyses to avoid an increase in type II error, also unmasked an additional robust grey matter density reduction in the anterior cingulate cortex.

A similar region of reduced grey matter density was detected in the only other investigation of volumetric effects in occasional users of ATS (Daumann *et al.*, 2011). Healthy controls were compared to a group of low exposure users who had consumed less than 5 doses and a group of experienced users who had consumed more than 100 units MDMA or 50g of amphetamine. A VBM analysis without modulation indicated that there were no grey matter regions in the brains of individuals with low exposure to ATS that were significantly different from controls. Experienced users, however, possessed significantly less grey matter volume in the perigenual/subgenual frontal cortex and medial orbital frontal cortex than low-exposure users and controls (see Figure 1). No white matter differences in FA as measured by DTI were observed in this study or in a study by Moeller and colleagues (2007), however, other DTI studies on occasional users of MDMA have shown lower FA in the thalamus (de Win *et al.*, 2008; Liu *et al.*, 2011a) and frontoparietal white matter (de Win *et al.*, 2008) and less myelination of the globus pallidus (Reneman *et al.*, 2001), anterior limb of the internal capsule (Liu *et al.*, 2011a), and rostral body of the corpus callosum (Moeller *et al.*, 2005).

4. Methodological Considerations

Although there are some consistent findings across a majority of studies (see section 5 Summary), numerous discrepancies exist between the various studies that have been described in the preceding sections. In part, these discrepancies may be explained by the different protocols that have been employed to measure the macrostructural brain effects associated with stimulant use. These include several different manual segmentation methods, a surface based method as developed by Thompson and colleagues, tensor-based morphometry, and multiple VBM protocols. The relative benefits and disadvantages of each are not yet entirely known. While the flexibility of manual methods may arguably produce more accurate results for some brain structures provided defining anatomical criteria are

appropriate, automatic methods eliminate concerns about subjective bias and are less time consuming which, in turn, facilitates efficient whole brain analyses. But VBM remains a novel technique and a fuller understanding of its ideal parameters and methodological limitations is still evolving. Recently, guidelines for reporting experimental VBM parameters have been suggested that should facilitate the comparison of data between studies and will likely generate insight on the correct usage of this technique and the interpretation of its results (Ridgway *et al.*, 2008). Some parameters are known to have dramatic effects on the data produced. The investigator's decision whether or not to modulate the results of a VBM analysis by the Jacobian determinants generated during spatial normalization will produce different information (Mechelli *et al.*, 2005). Non-modulated images are an estimate of regional concentration relative to other tissue types while modulated images represent absolute volume. For example, a difference would be detected in modulated but not in unmodulated images between healthy controls and a patient group with lower total temporal lobe volume but equivalent relative proportions of white and grey matter. Interesting differences also potentially exist between the output of VBM protocols and the surface based method developed by Thompson and colleagues. The surface based method accounts for gyral variation in its estimation of regional volume differences while VBM does not (Thompson *et al.*, 2003). In VBM, cortical thickness is confounded with cortical folding (Mechelli *et al.*, 2005). That is, thick cortex could produce the same VBM result as thinner cortex with more cortical folds. Thus, the inherent differences between various measurement protocols that have been used may explain some of the variability in the published results.

There are several other potential sources of variability. One important issue is polydrug use. The interpretation of studies that explicitly include polydrug users (e.g. Cowan *et al.*, 2003; Tanabe *et al.*, 2009) is problematic because it can be difficult to disentangle the individual effects of the various substances consumed. This problem is almost certainly present in all studies to varying degrees although it is not always adequately reported. For instance, there is a disproportionate use of cannabis, alcohol, and nicotine in regular users of cocaine and ATS relative to non-users. One way to limit the issue of polydrug use would be to establish strict selection criteria that focus the membership of the experimental groups. Although the study of pure chronically using populations would be scientifically interesting (e.g. long-term abuse of amphetamines exclusively with no exposure to nicotine or alcohol), such subjects are so rare that this is not practical in humans. Consumption can be restricted to specific stimulants in animal models but, it should be noted, the individuals in these studies are assigned randomly to groups. In humans, preference for subjects that have exposure to one drug exclusively would introduce a selection bias that could interfere with the extrapolation of findings to the general clinical population. The alternative is to document the co-use of other substances so that their effects can be separated during statistical analysis. A related problem is that most studies rely on self-reports without independent verification to establish substance use patterns. Such self-reports may deviate substantially from more objective measures. As with any symptom based syndrome, there is also the possibility that stimulant dependent subjects do not represent a homogenous grouping and may be more meaningfully described as two or more distinct groups. Additionally, individuals who abuse stimulants tend to have fewer years of education, inferior access to health care and greater exposure to environmental stressors than control subjects which could contribute to volumetric brain differences not directly related to substance use.

All of these issues may play a role in the variability apparent between studies, but we argue that the two most important current methodological problems are: the small number of subjects in most studies, especially the earliest, and the absence of longitudinal data. Kim and colleagues (2006) have compared short- and long-term abstinent chronic methamphetamine users, however, no study has been published with a longitudinal within

subjects design. Longitudinal studies are more difficult to coordinate but eliminate considerable between subject variability. More significantly, while the initial cross-sectional studies have indicated that there are structural differences between substance dependent groups and healthy controls, only longitudinal observations make it possible to determine whether differences predate or are a consequence of substance use.

5. Summary

Structural brain imaging studies of individuals with cocaine and ATS use disorders have yielded a significant number of contradictory results. Nearly every part of the brain seems to have been implicated in at least one study (Tables 1–4). There are, however, several consistent findings worth noting. For convenience of referral, these are each listed briefly in this section. This is followed by a more detailed point by point discussion in section 6.

1. Loci of lower cortical volume (approximately 10% on average) are consistently reported in chronic users of cocaine and ATS.
2. Almost all studies indicate less volume in some part of the frontal cortex.
3. More specifically, a core group of studies have implicated the ventromedial prefrontal cortex.
4. An interesting number of studies also implicate the insula.
5. An enlarged striatal volume has been repeatedly observed.
6. Reports on volume differences in the hippocampus and amygdala have been equivocal.
7. While there is little direct evidence of differential structural brain effects between various types of ATS or between ATS and cocaine, a majority of studies on chronic use of cocaine (but not ATS) have found lower volume in some part of the temporal cortex.

6. Discussion

Although there are several stages of potential interest in the interaction of brain structure with cocaine and ATS consumption as mentioned in the introduction (section 1), to date most studies have concentrated on the effects associated with chronic intoxication reviewed in sections 2.1, 2.2, 3.1, and 3.2 (Tables 1–4). The somewhat confusing diversity of findings on chronic stimulant users may be explained in part by several methodological factors (section 4). Chief amongst these are the application of different measurement protocols, a frequent reliance on small sample sizes and the absence of longitudinal within-subjects study designs. Despite the many differences between studies, there are seven themes in the literature worth noting.

First, among the 23 studies that measured either absolute volume or concentration of cortical grey matter, only 4 did not report a region of significantly less grey matter associated with cocaine or amphetamine-type stimulant use in some part of the cortex (namely, Bartzokis *et al.*, 2002, 2004; Lim *et al.* 2008; Narayana *et al.*, 2010) and only 2 reported higher regional cortical volume (Jernigan *et al.*, 2005; O'Neill *et al.*, 2001). It is noteworthy that, in the Lim *et al.* paper, chronic cocaine users possessed less frontal cortical volume than control subjects. The failure of this trend to reach the threshold of significance was due to an insufficient sample size (N=21) according to the authors. The number of cocaine dependent subjects examined in Bartzokis *et al.*, (2004) was also relatively small (N=17). Based on studies that provided estimates of absolute volume, the average magnitude of the reported cortical volumetric differences between stimulant users and controls is approximately 10%

with a range of 4 – 17%. Several reports have indicated that these loci of lower cortical volume occur in the absence of lower total cerebral volume (e.g. Jacobsen *et al.*, 2001b; Thompson *et al.*, 2004; Alia-Klein *et al.*, 2011). There are multiple plausible explanations for why lower cortical volume is observed in chronic stimulant users. These remain speculative because none of the volumetric studies performed in humans to date supply direct evidence with regard to a cause. Consequently, biological mechanisms that could affect volume are supported principally by experimental studies in animals. These mechanisms overlap substantially with proposed causes of neurodegeneration in unsuccessful aging (e.g. Alzheimers disease or Parkinson's disease)' including: oxidative stress, mitochondrial degradation, vasoconstriction, neuroinflammation, disruption of the ubiquitin proteasome system and glutamate – mediated excitotoxicity (Block *et al.*, 2007; Kaufman *et al.*, 1998; Neiman *et al.*, 2000; Yamamoto *et al.*, 2010). Several of these processes are suspected to be mutually reinforcing so that volumetric effects associated with stimulant use may involve a combination of related cellular factors that promote cell loss.

Second, 16 out of 23 studies that have quantified cortical grey matter have reported that all or parts of the frontal cortex are significantly lower in chronic cocaine (Tables 1 and 2) or ATS users (Tables 3 and 4) relative to normal controls. As noted in the last paragraph, some studies may not have been able to detect significant differences due to a lack of statistical power. For example, Bartzokis *et al.* (2000) included only 10 cocaine users and 9 amphetamine users. Lim *et al.* (2008) observed a trend toward lower frontal cortical volume in 21 cocaine dependent subjects that did not reach significance. Barros *et al.* (2011) did not find significant differences in the frontal cortex when comparing 20 cocaine dependent subjects with normal controls but did find that, within the dependent subjects, the amount of lifetime cocaine use was negatively correlated with the volume of the middle frontal gyrus bilaterally and the left superior frontal gyrus. In contrast to differences observed in the frontal lobes, foci of lower grey matter volume or concentration were found less consistently in the other cortical lobes. Only 2 of 18 studies that measured occipital grey matter reported less grey matter in stimulant users compared to controls in that region of the brain (Cowan *et al.*, 2003; Ersche *et al.*, 2012). Similarly, few studies have found grey matter differences in the parietal lobe (Barros-Loscertales *et al.*, 2011; Jernigan *et al.*, 2005) or cerebellum (Barros-Loscertales *et al.*, 2011; Cowan *et al.*, 2003; O'Neill *et al.*, 2001; Sim *et al.*, 2007). Lower temporal lobe volume has been reported more in studies on cocaine than on amphetamine-type stimulants which will be taken up below in a separate discussion on the differential volume changes associated with cocaine and ATS. Loss of frontal grey matter volume has been corroborated by numerous reports of white matter deficits either in the frontal lobe white matter (Alicata *et al.*, 2009; Chung *et al.*, 2007; Lim *et al.*, 2002; Lim *et al.*, 2008; Romero *et al.*, 2010) or in the anterior part of the corpus callosum which connects the left and right frontal lobes (Kim *et al.*, 2009; Ma *et al.*, 2009; Moeller *et al.*, 2005; Salo *et al.*, 2009; Tobias *et al.*, 2010).

Third, not all parts of the frontal cortex appear to be equally implicated. A core group of studies indicate that the volume of the ventromedial frontal cortex specifically is affected in stimulant users (Figure 1) (Alia-Klein *et al.*, 2011; Daumann *et al.*, 2011; Ersche *et al.*, 2011a; Ersche *et al.*, 2012; Franklin *et al.*, 2002; Kim *et al.*, 2006; Matochik *et al.*, 2003; Nakama *et al.*, 2011; Tanabe *et al.*, 2009; Thompson *et al.*, 2004). Lower volume of the ventromedial frontal cortex has also been observed in studies on nicotine (Liao *et al.*, 2010) and opiate use (Lyoo *et al.*, 2006) although a comprehensive review of volumetric studies on abuse of other substances is beyond the scope of the present review. Comparative studies in the human and macaque indicate that there are two distinct hierarchically organized networks of architectonically defined areas in the ventral and medial regions of the frontal cortex of the primate brain (Mackey and Petrides, 2010). The more medial of these two networks, the ventromedial region, is located medial to the medial orbital gyrus on the

orbital surface and continues over onto the medial surface extending dorsally towards the corpus callosum. The human ventromedial network is assumed to possess a pattern of brain connectivity resembling the medial network as described by Price and colleagues (Price, 2007) and the mediodorsal trend as described by Barbas and colleagues (Barbas, 2007) in the macaque brain which includes rich reciprocal innervation of the amygdala, thalamus, hypothalamus, medial temporal lobe structures and neurotransmitter-specific systems of the brain stem. The ventromedial frontal cortex also sends a unidirectional projection to the rostral striatum. This input is processed locally and relayed through the basal ganglia to the thalamus which then projects back to the ventromedial frontal cortex forming a corticostriatohalamocortical loop called the limbic circuit (Alexander *et al.*, 1986). The limbic circuit which regulates the initiation of goal directed behavior is one of several parallel modules connecting the frontal cortex with anatomically comparable basal ganglia-thalamocortical circuits. These parallel circuits organize distinct aspects of goal directed behavior e.g. reward orientation (lateral orbitofrontal cortex), executive planning (dorsolateral prefrontal cortex) and motor commands (frontal motor cortex). The limbic circuit can influence the other circuits via feed forward mechanisms mediated by the thalamus and midbrain dopamine neurons that propagate information from adjacent corticostriatal circuits in a “spiral” moving outward from the limbic circuit to cognitive circuits which in turn interact with the motor pathways that execute action (Haber, 2003). Substance abuse may be conceptualized as a disease of the basal ganglia where initiation of drug taking involves maladaptive processing in the anterior limbic circuit that in later stages spreads to more posterior circuits involved in the maintenance of habitual behaviors (Robbins *et al.*, 2012). Within this anatomical and functional context, it is tempting to speculate that lower volume in the ventromedial frontal cortex reflects an alteration in its normal function that might play a role in the initiation of drug consumption. It is not yet clear whether lower ventromedial cortical volume is a cause or an effect of chronic stimulant abuse. It has been reported that lower ventromedial prefrontal cortex volume occurs in individuals with high exposure but not low exposure to ATS (Daumann *et al.*, 2011). While this could suggest that ventromedial frontal cortex volume is altered by the amount of exposure, the cross sectional design of the study does not eliminate the possibility that those subjects with more experience may have had reduced volume prior to exposure which may have encouraged heavier stimulant use.

Fourth, a fewer but still interesting number of studies on stimulant users have observed lower grey matter volume in the insula (Alfonso Barros-Loscertales, 2011; Ersche *et al.*, 2011a; Ersche *et al.*, 2012; Franklin *et al.*, 2002; Nakama *et al.*, 2011; Schwartz *et al.*, 2010). It is worth noting that the agranular cortex in the posterior part of the ventromedial frontal region shares reciprocal projections with the anterior agranular insula (Carmichael and Price, 1996). Further anatomical studies of the insula place it at the center of a network of brain structures involved in the perception and regulation of the internal body state (Craig, 2002). It has been proposed that disruption of the physiological sense of the body in substance abuse may drive consumption in a maladaptive attempt to return the body to a state of homeostasis (Paulus *et al.*, 2009). Consistent with this hypothesis, damage to the insula has been reported to produce cessation of smoking without effort in patients who were previously dependent (Naqvi *et al.*, 2007). In rats with prior amphetamine experience, inactivation of the insula disrupts amphetamine seeking in a place preference task (Contreras *et al.*, 2007). Thus, the lower insula volume observed in chronic stimulant users may interfere with normal functioning of the interoceptive system that, in turn, could influence drug seeking behavior.

Five, in contrast to reduced cortical grey matter, the striatum is frequently reported to be larger in chronic stimulant users (Chang *et al.*, 2005; Ersche *et al.*, 2011a; Ersche *et al.*, 2012; Jacobsen *et al.*, 2001a; Jernigan *et al.*, 2005). Martinez and colleagues also measured

the volume of the striatum in cocaine addicts and, although their data did not reach significance, the striatal structures rostral to the anterior commissure were smaller in cocaine dependent subjects than healthy controls while the post-commissural putamen was larger. The one study that found lower striatal volume in stimulant users had a smaller sample size than the other studies and the effect disappeared with greater standard blurring during preprocessing (Barros-Loscertales *et al.*, 2011). Higher striatal volume has primarily been observed in studies that relied on manual segmentation of the structure. It is possible that voxel-based morphometry is unable to resolve the striatum due to its shape or size except when the sample size is very large (e.g. Ersche *et al.*, 2011a; Ersche *et al.*, 2012). The changes in striatal volume are interesting in terms of the conceptualization of drug abuse as a disease of the basal ganglia. Related findings in three other patient populations may be instructive: attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder, and schizophrenics treated with antipsychotics. ADHD symptoms can be controlled pharmacologically by oral doses of ATS, namely amphetamine (e.g. Adderall, Dexedrine) and methylphenidate (e.g. Ritalin, Concerta). Although it has been reported that children with ADHD have smaller caudate volumes than controls (Filipek *et al.*, 1997), children diagnosed with ADHD who have been treated with methylphenidate for a prolonged period exhibit smaller striatal volumes than those who have not been treated. (Bussing *et al.*, 2002). While ADHD children suffer from impulsivity and lack of focus, OCD patients are unable to resist stereotyped activities despite negative consequences, a behavioral symptom that bears some resemblance to the habitual abuse of substances despite negative feedback in dependent individuals. It is interesting then that a recent meta-analysis of volumetric studies in OCD patients found enlarged striatal volumes compared to controls (Rotge *et al.*, 2010). The increase in extracellular dopamine that results from intoxication with cocaine or ATS may contribute to the volume changes observed in the striatum. Like methylphenidate, typical antipsychotics prescribed to treat schizophrenia increase the synaptic availability of dopamine by blocking D₂ receptors. A longitudinal study of schizophrenia spectrum patients who had been treated with typical antipsychotics for 2 years found that these subjects had larger putamen volumes following treatment but that a comparable increase was not observed in those treated with atypical antipsychotics that do not block the D₂ receptor (Corson *et al.*, 1999). It is not apparent at the moment whether the volume of the putamen is a result or a marker of risk in stimulant use. Chang and colleagues reported that the putamen and caudate were smaller in children exposed to methamphetamine prenatally (Chang *et al.*, 2004) which suggests that exposure could alter volume developmentally. However, a study that included methamphetamine dependent subjects and their non-dependent siblings found that the putamen was enlarged in both siblings compared to healthy non-related controls indicating that an enlarged striatum could be a genetic marker of risk (Ersche *et al.*, 2012).

Six, most studies have not found a difference in the volume of the amygdala and hippocampus. While failure to observe a difference may be due to difficulties that the size and shape of these structures, like the striatum, pose to automated methods, the four studies that manually segmented the hippocampus found no difference in volume between stimulant users and healthy controls (Bartzokis *et al.*, 2002; Jacobsen *et al.*, 2001b; Jernigan *et al.*, 2005; Makris *et al.*, 2004). Only two studies, employing automated whole brain techniques, detected a size reduction in the hippocampus (Alia-Klein *et al.*, 2011; Thompson *et al.*, 2004). Studies on amygdala volume have been even more varied. Two of the studies based on manual segmentation found no effect (Jacobsen *et al.*, 2001b; Jernigan *et al.*, 2005) while a third observed lower volume (Makris *et al.*, 2004). Generally automated methods have not detected a change in the volume of this structure although one study with a relatively large sample size did find a larger volume (Ersche *et al.*, 2012). It is worth noting, however, that these same researchers did not detect this difference in an earlier study with an even larger sample of cocaine dependent subjects (Ersche *et al.*, 2011a). By contrast Barros and colleagues have reported that the amygdala is not enlarged but rather decreases in size as a

function of the amount of stimulant use (Barros-Loscertales *et al.*, 2011). One study has also reported that the size of the amygdala is correlated with the length of abstinence (Schwartz *et al.*, 2010). The majority of studies have found no difference. On balance, the available evidence does not support the conclusion that the volumes of the hippocampus and amygdala are affected by chronic amphetamine use.

Seven, there is scant direct evidence for a difference in structural effects between different types of ATS or between cocaine and ATS. The reason for this may be simply because not enough studies have been completed. The two studies which have examined the effects of MDMA use include only occasional users (Cowan *et al.*, 2003; Daumann *et al.*, 2011) and so are difficult to compare to the many studies that have looked at the effect of chronic methamphetamine use in dependent individuals (see Table 3). Only Bartzokis and colleagues have examined both cocaine and amphetamine dependent subjects in the same study (Bartzokis *et al.*, 2000). While the temporal lobes were significantly smaller in both cocaine and amphetamine dependent groups compared to normal controls, only the cocaine group had a significant negative correlation with age. The results of this study should be approached with caution not only because of the small sample size but also because 5 of the 9 subjects in the amphetamine group had a past history of cocaine dependence. Despite the lack of direct evidence, it is remarkable that the majority of the volumetric studies that have measured the temporal lobe following chronic cocaine abuse have found less cortical grey matter in all or parts of this structure (Alia-Klein *et al.*, 2011; Barros-Loscertales *et al.*, 2011; Bartzokis *et al.*, 2002; Bartzokis *et al.*, 2000; Ersche *et al.*, 2011a; Ersche *et al.*, 2012; Franklin *et al.*, 2002; O'Neill *et al.*, 2001; Sim *et al.*, 2007) while a majority of studies on ATS have not (Daumann *et al.*, 2011; Jernigan *et al.*, 2005; Kim *et al.*, 2006; Nakama *et al.*, 2011; Schwartz *et al.*, 2010; Thompson *et al.*, 2004).

6.1. Future Directions

A compelling body of evidence as summarized in section 5 indicates that there are reliably reproduced volumetric differences in the brains of *chronic* stimulant users relative to control subjects, notably in the ventromedial frontal cortex, insula and striatum. Considerably less, however, is known about the other stages of stimulant experience listed in the introduction (section 1), namely prenatal exposure, structural differences before initial use, effects of occasional/recreational use, predictors of relapse after rehabilitation and the effects of abstinence. The few studies that do exist were grouped together in sections 2.3 and 3.3. The initial evidence drawn from the small number of studies that have examined prenatal exposure to cocaine or ATS suggests that there could be important effects on the developing brain but the exact regions involved need to be replicated in much larger samples (Avants *et al.*, 2007; Chang *et al.*, 2004; Rivkin *et al.*, 2008). The significance of the effects would be easier to interpret if brain volumes were related in the same children to specific behavioral measures of cognitive or life adjustment outcome. Likewise, few studies have examined occasional stimulant use. Since the predominant pattern of non-medical stimulant use is occasional, it would appear to be an important matter of public policy to establish the dangers to health, if any, beyond the risk of addiction that attach to infrequent use. Two already published studies suggest that there may indeed be volumetric brain differences associated with infrequent use (Cowan *et al.*, 2003; Daumann *et al.*, 2011). Longitudinal studies will be required to know if these differences are a result or a cause of stimulant use. Structural predictors of risk would be useful in the development of abuse prevention programs. Volumetric MRI data may also be able to help predict those individuals who are more likely to relapse after treatment. In the future, prognostic volumetric factors could be used to shape individualized therapies based on a risk profile. Finally, it is also important to understand to what extent the brain can be expected to *repair* itself during periods of prolonged abstinence. The only study specifically designed to examine the effects of

abstinence compared methamphetamine abusers who had been abstinent for a short (< 6 months) or long period (> 6 months) (Kim *et al.*, 2006). The frontal cortex in long-term abstinent subjects presented an intermediate volume between healthy controls and short-term abstinent subjects indicating that volume of the frontal cortex may be at least partially restored by abstinence. Since other studies that examined individuals after prolonged abstinence were not longitudinal in design, it cannot be determined whether relief from chronic exposure to psychostimulants had a restorative effect in those individuals.

The interaction of age and stimulant use on the structure of the brain suggests that, in addition to static explanations of the effects of drug use, dynamic lifetime models should be considered that include obstruction of healthy maturational stages in younger drug using subjects and, in older subjects, an exacerbation of processes related to unsuccessful ageing. Bartzokis and colleagues found that the decline in volume of the temporal lobe white matter was accelerated in cocaine dependent subjects (Bartzokis *et al.*, 2002). Sim and colleagues also found an age accelerated decline in the temporal lobes of cocaine dependent subjects though the decline was located in the grey matter not the white matter (Sim *et al.*, 2007). Similarly in methamphetamine users, Nakama and colleagues have reported an enhanced age-related decline in grey matter volume in the insula and the frontal, occipital, and temporal lobes. With regard to age specific structural effects in youth, Jernigan *et al.* found that, while the volume of the putamen was enlarged relative to age matched controls, it was the same size as younger drug naïve subjects. This suggests that a maturationally normal reduction in the volume of the putamen from adolescence to adulthood in the control group might be partially blocked in the young cocaine users. Thus, age may play an important role in the volumetric effects of stimulant use and should be considered when making comparisons between studies. Further research will be required to develop a more comprehensive understanding of the volumetric interaction of brain structure with psychostimulants across the full life cycle.

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Highlight

Major themes in the literature on the volumetric brain effects of chronic use of cocaine and amphetamine-type stimulants as measured by MRI:

1. loci of decreased cortical volume are consistently reported
2. almost all studies indicate decreased volume in all or parts of the frontal cortex
3. a core group of studies implicate the ventromedial prefrontal cortex and the insula
4. an enlarged striatal volume has been repeatedly observed
5. reports on volume differences in the hippocampus and amygdala have been equivocal

Figure 1. Illustration of the perigenual/subgenual region in the ventromedial frontal cortex that is frequently implicated in volumetric studies on chronic psychostimulant use. Here, in red, regions of lower grey matter density in experienced recreational users compared to those with low exposure to amphetamine-type stimulants. From Daumann *et al.* (2011) with permission.

Table 1

Volumetric studies on current or recent (2 weeks) cocaine users.

Reference	Image Acquisition Parameters	Image Processing Method	Number Dependent & Control Subjects	Dependence Status	Age, Mean $\pm$ Standard Deviation (years)	Grey Matter Volume/ Density Differences between Cocaine Users & Controls
Liu <i>et al.</i> 1998	1.5T, Spoiled GRASS, matrix=256 $\times$ 192, FOV=24cm, S=124, ST=1.5mm	Semi-automated tissue segmentation; manually identified frontal & temporal lobes	25 POLY (23 primarily COC) 14 NC	>15 days abstinent	33.5 $\pm$ 3.8	Reduced prefrontal grey matter volume
Bartzokis <i>et al.</i> 2000	1.5T, IR, matrix=256 $\times$ 192, FOV=25cm, S=not stated, ST=3mm	Manual segmentation, sampled frontal & temporal lobes in 7 contiguous slices	10 COC 16 NC	Not stated	31.4 $\pm$ 3.8	Reduced temporal lobe volume
Jacobsen <i>et al.</i> 2001	1.5T, SPGR, matrix=256 $\times$ 192, FOV=24cm, S=not stated, ST=1.9mm or 3mm	Manual segmentation hippocampus	27 COC 16NC	Average 13.2 days abstinent	34.8 $\pm$ 5.5	No difference volume of amygdala, hippocampus, or whole brain
Jacobsen <i>et al.</i> 2001	1.5T, SPGR, matrix=256 $\times$ 192, FOV=24cm, S=not stated, ST=1.9mm or 3mm	Manual segmentation striatum	25 COC 20 NC	Average 15.3 days abstinent	35.6 $\pm$ 5.7	Increased volume putamen and caudate
Bartzokis <i>et al.</i> 2002	1.5T, IR, matrix=256 $\times$ 192, FOV=25cm, S=not stated, ST=3mm	Manual segmentation, sampled frontal & temporal lobes in 7 contiguous slices	37 COC 52 NC	Current	37.5 $\pm$ 6.1 COC subjects significantly older than NC	No difference
Franklin <i>et al.</i> 2002	1.5T, IRP-SPGR, matrix=256 $\times$ 192, FOV=24cm, S=128, ST=1mm	VBM (SPM99) without modulation	13 COC 16 NC	Current	42 $\pm$ 6.3 COC subjects significantly older than NC	Reduced density frontal ventromedial, anterior cingulate, anteroventral insular and superior temporal cortex
Matochik <i>et al.</i> 2003	1.5T, SPGR, matrix=256 $\times$ 256, FOV=24cm, S=124, ST=1.5mm	VBM (SPM99) without modulation	14 COC 11 NC	20 days abstinent	36.3 $\pm$ 4.7	Reduced density bilateral frontal subgenual and perigenual cortex, medial and lateral orbitofrontal cortex, right middle/dorsal cingulate gyrus
Makris <i>et al.</i> 2004	1.5T, SPGR, matrix=256 $\times$ 256, FOV=24– 26cm, S=60, ST=3.1 or 2.8mm	Manual segmentation amygdala & hippocampus	27 COC 27 NC	Current	33.9 $\pm$ not stated [age-range 26– 45]	Reduced volume of amygdala but not hippocampus
Martinez <i>et al.</i> 2004	1.5T, Spoiled GRASS, matrix=256 $\times$ 192, FOV=22cm, S=124, ST=1.5mm	Manual segmentation striatum	17 COC 17 NC	Current	38.7 $\pm$ 3.8	Non-significant trend toward reduced volume anterior striatum, increased volume posterior striatum
Sim <i>et al.</i> 2007	1.5T, SPGR, matrix=256 $\times$ 192, FOV=24cm, S=124, ST=1.5mm	VBM (SPM) with modulation	40 COC 41 NC	Current	41.4 $\pm$ 6.9	Reduced volume bilateral premotor cortex, right anterior frontal cortex, bilateral temporal cortex, left thalamus and bilateral cerebellum

Reference	Image Acquisition Parameters	Image Processing Method	Number Dependent & Control Subjects	Dependence Status	Age, Mean $\pm$ Standard Deviation (years)	Grey Matter Volume/ Density Differences between Cocaine Users & Controls
Lim <i>et al.</i> 2008	3T, SPGR, matrix=256 $\times$ 176, FOV=not stated, ST=1mm	Preprocessing and initial tissue segmentation with FSL, template-derived regions of interest	21 COC 21 NC	>4 days abstinent	40.9 $\pm$ 7.4	Non-significant trend toward reduced inferior frontal cortex
Narayana <i>et al.</i> 2010	3T, SPGR (Turbo Field Echo), matrix=256 $\times$ 256, FOV=24cm, S=132, ST=1mm	VBM (SPM8) with and without modulation; TBM	34 COC 36 NC	Current	41 $\pm$ 9.1 COC subjects significantly older than NC	No difference
Alia-Klein <i>et al.</i> 2011	4T, MDEFT, matrix=256 $\times$ 256, FOV=24cm, S=not stated, ST=1mm	VBM (SPM5) with modulation	40 COC 42 NC	Current	45 $\pm$ not stated; COC subjects significantly older than NC	Reduced volume orbital and dorsolateral frontal cortex, temporal cortex and hippocampus
Barros- Loscertales <i>et al.</i> 2011	1.5T, GRE, matrix=256 $\times$ 176, FOV=24cm, S=not stated, ST=1mm	VBM (SPM5) with modulation	20 COC 16 NC	>2 days abstinent	33.3 $\pm$ 6.9	Reduced volume striatum and right supramarginal gyrus
Ersche <i>et al.</i> 2011	3T, MPFRAGE, matrix=240 $\times$ 256, FOV=240mm $\times$ 256mm, S=176, ST=1mm	VBM (FSL) with modulation	60 COC 60 NC	Current	32.5 $\pm$ 8.5	Reduced volume orbitofrontal, cingulate, insular temporoparietal and cerebellar cortex
Ersche <i>et al.</i> 2012	3T, MPFRAGE, matrix=240 $\times$ 256 FOV=240mm $\times$ 256mm, S=176, ST=1mm	VBM (FSL) with modulation	50 COC or AMPH (47 primarily COC) 50 NC	Current	34.5 $\pm$ 7.4	Increase volume putamen and amygdala Decrease volume insula, posterior sylvian fissure, medial orbital and ventromedial frontal cortex, medial occipital cortex

T = Tesla, FOV = field of view, S = slices, ST = slice thickness, GRASS = Gradient-Recall Acquisition at Steady State, IR = Inversion-Recovery, SPGR = Spoiled Gradient Recalled, IRP-SPGR = Inversion-Recovery SPGR, MDEFT = Modified Driven-Equilibrium Fourier Transform, GRE = Gradient Echo, MPFRAGE = Magnetically Prepared Rapid Acquisition Gradient Echo, SPM = Statistical Parametric Mapping, TBM = Tensor Based Morphometry, FSL = FMRIB Software Library, POLY = polysubstance COC = cocaine, AMPH = amphetamine, NC = normal control; age is stated only for stimulant users (controls were not statistically different in age from the users in any of the studies except where noted). As noted in the text, "with modulation" refers to the modulation by Jacobian determinants produced during transformation to standardized space.

Table 2

Volumetric studies on long-term abstinent cocaine users.

Reference	Image Acquisition Parameters	Image Processing Method	Number Dependent & Control Subjects	Dependence Status	Age, Mean $\pm$ Standard Deviation (years)	Grey Matter Volume/Density Differences between Cocaine Users & Controls
Sclafani <i>et al.</i> 1998a	1.5T, Spin Echo Sequence (proton density and T ₂), matrix=not stated, FOV=not stated, S=not stated, ST=3mm	Automated segmentation of intracranial volume (in-house software)	19 COC 28 COC+ALC 19 NC	Average 72.1 days (COC) & 95.2 days (COC+ALC) abstinent	39.2 $\pm$ 7 (COC) 41.4 $\pm$ 7.2 (COC +ALC) subjects significantly older than NC	No difference
Sclafani <i>et al.</i> 1998b	1.5T, MPAGE, matrix=not stated, FOV=not stated, S=164, ST=1.4mm	Manual segmentation hippocampus	19 COC 18 COC+ALC 18 NC	Average 69.3 days (COC) & 83.3 days (COC+ALC) abstinent	38.7 $\pm$ 6.9 (COC) 41.3 $\pm$ 7.5 (COC +ALC)	No difference in hippocampus
O'Neill <i>et al.</i> 2001	1.5T, MPAGE, matrix=not stated, FOV=not stated, S=not stated, ST=1.5mm	Semi-automated tissue segmentation, template-derived regions of interest	8 COC 17 COC+ALC 12 ALC 13 NC	Average 131.6 days (COC) & 113.4 days (COC+ALC) abstinent	41.8 $\pm$ 6.2 (COC) 41.8 $\pm$ 6.6 (COC +ALC) ALC subjects significantly older than non-ALC subjects	Reduced volume prefrontal and temporal cortex, and cerebellum, increased volume occipital cortex in COC & COC+ALC compared to NC & ALC
Fein <i>et al.</i> 2002	1.5T, MPAGE, matrix=not stated, FOV=not stated, S=not stated, ST=1.5mm	Semi-automated tissue segmentation, template-derived regions of interest	17 COC 29 COC+ALC 20 NC	Average 42 days (COC) & 42 days (COC+ALC) abstinent	39 $\pm$ 7 (COC) 42 $\pm$ 6 (COC+ALC)	Reduced volume prefrontal cortex in combined COC & COC +ALC compared to NC
Tanabe <i>et al.</i> 2009	3T, IR-SPGR, matrix=256x256, FOV=24cm, S=not stated, ST=1.7mm	VBM (SPM5) with modulation	19 POLY (including 17 COC disorder) 20 NC	60 days	35 $\pm$ 7	Reduced volume medial orbitofrontal cortex

T = Tesla, FOV= field of view, S = slices, ST= slice thickness, IRP-SPGR = Inversion-Recovery Spoiled Gradient Recalled, MPAGE = Magnetically Prepared Rapid Acquisition Gradient Echo, SPM= Statistical Parametric Mapping, POLY = polysubstance COC = cocaine, ALC = alcohol, NC = normal control; age is stated only for stimulant users (controls were not statistically different in age from the users in any of the studies except where noted). As noted in the text, "with modulation" refers to the modulation by Jacobian determinants produced during transformation.

Table 3

Volumetric studies on current or recent amphetamine-type stimulant users.

Reference	Image Acquisition Parameters	Image Processing Method	Number Dependent & Control Subjects	Dependence Status	Age, Mean $\pm$ Standard Deviation (years)	Grey Matter Volume/ Density Differences between ATS Users & Controls
Bartzokis <i>et al.</i> 2000	1.5T, IR, matrix=256x192, FOV=25cm, S=not stated, ST=3mm	Manual segmentation, sampled frontal & temporal lobes in 7 contiguous slices	9 AMPH 16 NC	Not stated	27.8 $\pm$ 4.3	Reduced temporal lobe volume
Thompson <i>et al.</i> 2004	3T, SPGR, matrix=256x256, FOV=not stated, S=not stated, ST=1.22mm	Semi-automated cortical pattern matching (FreeSurfer)	22 METH 21 NC	Average 6.6 days abstinent	35.3 $\pm$ not stated; standard error of the mean = 1.7	Reduced grey matter in the right posterior, middle and subgenual cingulate cortex, paracingulate cortex, and right and left hippocampus
Nakama <i>et al.</i> 2011	3T, MPRAGE, matrix=256x208, FOV=not stated, S=144, ST=1mm	Preprocessing and initial tissue segmentation with FSL, template-derived regions of interest	34 METH 31 NC	Average 18 days abstinent	33.1 $\pm$ 8.9	Reduced volume dorsolateral, orbital frontal cortex, insula and superior temporal cortex

T = Tesla, FOV = field of view, S = slices, ST = slice thickness, IR = Inversion-Recovery, SPGR = Spoiled Gradient Recalled, MPRAGE = Magnetically Prepared Rapid Acquisition Gradient Echo, FSL = FMRIB Software Library, METH = amphetamine, AMPH = amphetamine, NC = normal control; age is stated only for stimulant users (controls were not statistically different in age from the users in any of the studies except where noted).

Table 4

Volumetric studies on long-term abstinent amphetamine-type stimulant users

Reference	Image Acquisition Parameters	Image Processing Method	Number Dependent & Control Subjects	Dependence Status	Age, Mean $\pm$ Standard Deviation (years)	Grey Matter Volume/ Density Differences between ATS Users & Controls
Chang <i>et al.</i> 2005	1.5T, Fast IR, matrix=not stated, FOV=24cm, S=not stated, ST=3.5mm	Manually identified regions of interest	50 METH 50 NC	Average 120 days abstinent	32.1 $\pm$ 7.1	Increased volume putamen and globus pallidus
Kim <i>et al.</i> 2006	3T, IRP-SPGR, matrix=256 $\times$ 256, FOV=22cm, S=248, ST=0.7mm	VBM (SPM99) without modulation	11 METH (short- term abstinent) 18 METH (long- term abstinent) 20 NC	< 182.5 days (short- term) > 182.5 days (long-term)	37.9 $\pm$ 6.0 (short-term) 35.6 $\pm$ 5.2 (long- term)	Reduced density right middle frontal gyrus, frontal polar and medial orbital frontal cortex (combined short-term + long-term abstinent)
Jernigan <i>et al.</i> 2005	3T, SPGR, matrix=not stated, FOV=24cm, S=not stated, ST=1.2mm OR Spiral FSE, matrix=not stated, FOV=24cm, S=not stated, ST=1.3mm	Semi-automated tissue segmentation, manually identified regions of interest	21 METH 30 METH+HIV 22 HIV 30 NC	93.6 days	38.2 $\pm$ 7.7 (METH) 39.0 $\pm$ 6.7 (METH+HIV)	Increased volume striatum (nucleus accumbens, caudate nucleus and lenticular nucleus – putamen and globus pallidus) and parietal cortex (combined METH & METH+HIV)
Schwartz <i>et al.</i> 2010	3T, MPRAGE, matrix=208 $\times$ 256, FOV=208 $\times$ 256mm, S=144, ST=1mm	VBM (FSL) with modulation	61 METH 44 NC	Average 63.7 days abstinent	33.4 $\pm$ 8.4	Reduced volume bilateral insula and left middle frontal gyrus

T = Tesla, FOV= field of view, S = slices, ST= slice thickness, IR = Inversion-Recovery, IRP-SPGR = Inversion-Recovery Prepared Spoiled Gradient Recalled, SPGR= Spoiled Gradient Recalled, FSE = Fast Spin Echo, MPRAGE = Magnetically Prepared Rapid Acquisition Gradient Echo, SPM = Statistical Parametrical Mapping, FSL = FMRIB Software Library, METH = amphetamine, AMPH = amphetamine, NC = normal control; age is stated only for stimulant users (controls were not statistically different in age from the users in any of the studies except where noted).