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Chronic Methamphetamine Abuse and Corticostriatal Deficits Revealed by Neuroimaging

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Abstract

Despite aggressive efforts to contain it, methamphetamine use disorder continues to be major public health problem; and with generic behavioral therapies still the mainstay of treatment for methamphetamine abuse, rates of attrition and relapse remain high. This review summarizes the findings of structural, molecular, and functional neuroimaging studies of methamphetamine abusers, focusing on cortical and striatal abnormalities and their potential contributions to cognitive and behavioral phenotypes that can serve to promote compulsive drug use. These studies indicate that individuals with a history of chronic methamphetamine abuse often display several signs of corticostriatal dysfunction, including abnormal gray- and white-matter integrity, monoamine neurotransmitter system deficiencies, neuroinflammation, poor neuronal integrity, and aberrant patterns of brain connectivity and function, both when engaged in cognitive tasks and at rest. More importantly, many of these neural abnormalities were found to be linked with certain addiction-related phenotypes that may influence treatment response (e.g., poor self-control, cognitive inflexibility, maladaptive decision-making), raising the possibility that they may represent novel therapeutic targets.

Keywords

methamphetamine; addiction; corticostriatal circuitry; positron emission tomography; magnetic resonance imaging; diffusion tensor imaging

Methamphetamine use disorder constitutes a major public health problem, associated with high rates of attrition, crime, relapse, and mortality. Although the prevalence of illicit methamphetamine use in the U.S. declined sharply in the late 2000s following legislation

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limiting access to precursors, the estimated number of current users has increased since 2010, totaling 595,000 in 2013 (SAMHSA, 2014a)). Furthermore, with 144,000 Americans estimated to have tried methamphetamine for the first time in 2013 (SAMHSA, 2014a) and established supply connections to Mexican cartels (Shukla et al., 2012), the problem may continue to grow. Methamphetamine has also become more prevalent throughout Asia and the Pacific region in recent years, leading to it being ranked as the primary or secondary drug of use in 13 of the 15 countries from that region surveyed in 2012 (UNODC, 2013). While many users seek treatment for methamphetamine abuse, which accounts for well over 100,000 admissions to drug treatment facilities annually in the U.S. alone (SAMHSA, 2014b), the vast majority relapse (Brecht and Herbeck, 2014; McKetin et al., 2012). Still, despite their poor therapeutic efficacy, generic behavioral interventions (e.g., cognitive behavioral therapy, contingency management, motivational interviewing) remain the mainstay of treatment for methamphetamine use disorder.

Chronic abuse of methamphetamine is often associated with a constellation of behavioral problems (e.g., Cartier et al., 2006; Cohen et al., 2003; McKetin et al., 2008; Zweben et al., 2004), including mood disturbances (London et al., 2004; Newton et al., 2004; Shen et al., 2012), persistent craving (Zorick et al., 2010) and psychosis (Grant et al., 2012). Cognitive deficits are also common among individuals with a history of methamphetamine abuse, particularly involving executive functions (e.g., mental flexibility, self-control), which are important for suppressing habitual behaviors (Dean et al., 2012; Monterosso et al., 2005; Scott et al., 2007; Simon et al., 2010). As outlined below, neuroimaging studies have demonstrated that methamphetamine abusers also typically display several signs of corticostriatal dysfunction. Moreover, these studies provide suggestive evidence that many of these corticostriatal abnormalities may underlie certain cognitive and behavioral phenotypes that can serve to promote compulsive drug use, raising the possibility that they may represent novel therapeutic targets.

Structural Brain Imaging of Methamphetamine Users

Structural magnetic resonance imaging has provided evidence for cortical and striatal gray- and white-matter abnormalities associated with methamphetamine abuse. A substantial number of studies have linked structural brain abnormalities with cognitive dysfunction in methamphetamine users.

Methamphetamine users generally exhibit smaller cortical but larger striatal gray-matter volumes than non-users (Berman et al., 2008a). Following brief abstinence (< 3 weeks), gray-matter volumes in anterior cingulate cortex (ACC), dorsolateral prefrontal (DLPFC), orbitofrontal (OFC), and superior temporal cortices as well as the hippocampus are smaller than in never-users (Nakama et al., 2011; Thompson et al., 2004); and a bilateral deficit in gray-matter density of the insula has been observed with abstinence up to 6 months (Schwartz et al., 2010). In contrast, subjects who are abstinent from methamphetamine for an average of 3-4 months show greater gray-matter volume in the parietal cortex, caudate nucleus, lenticular nucleus, nucleus accumbens (Jernigan et al., 2005), putamen and globus pallidus (Chang et al., 2005) than never-users. Putamen volume also is larger among non-abstinent users than non-users (Jan et al., 2012b).

Cortical gray-matter deficits appear to reverse with protracted abstinence from methamphetamine. Supporting this view is the observation that gray-matter volume increased in inferior frontal, angular, and superior temporal gyri, precuneus, insula, and occipital pole in methamphetamine users following one month of abstinence (Figure 1) (Morales et al., 2012). In addition, participants abstinent for 6 months or more have higher gray-matter density in the bilateral middle frontal gyrus than those abstinent for shorter periods (Kim et al., 2006).

Factors other than methamphetamine use *per se* may contribute to cerebral structural abnormalities. For example, while only 22% of the general population comprises smokers, smoking is more prevalent among methamphetamine users (87-92%) (Weinberger and Sofuoglu, 2009). One study found that smokers, both those who did and those who did not use methamphetamine, had smaller gray-matter volume in the OFC and caudate nucleus than nonsmokers who did not use methamphetamine (Morales et al., 2012). Participants who engaged in both behaviors, however, had smaller gray-matter volumes in superior and inferior temporal, supramarginal, and precentral gyrus than smokers who did not use methamphetamine. Thus, while some cortical deficits appear to result from either methamphetamine use or its combination with smoking, gray-matter volume deficits in the OFC and caudate may be in part attributable to cigarette smoking or pre-morbid conditions in methamphetamine users.

White matter abnormalities have also been linked to methamphetamine use. Fractional anisotropy, a measure of the extent to which water diffusion is restricted to a single direction, depends on axon caliber, fiber density and organization, and myelination (Beaulieu, 2009). Methamphetamine users have lower fractional anisotropy in prefrontal white matter (Chung et al., 2007; Tobias et al., 2010), the genu of the corpus callosum (Kim et al., 2009; Salo et al., 2009a; Tobias et al., 2010), midcaudal superior corona radiata, and the perforant path (Tobias et al., 2010). These findings are consistent with drug-induced white-matter damage. Prominent generalized white-matter hypertrophy, found in early abstinent methamphetamine users (Thompson et al., 2004), may result from altered myelination and adaptive changes, including gliosis secondary to neuronal damage. Significant effects are observed in temporal and occipital cortices, adjacent to some of the regions where hippocampal and cortical gray-matter changes are detected; and right cingulate gray-matter loss accompanies frontal horn expansion in the right lateral ventricles (Thompson et al., 2004).

Although human studies generally do not allow assignment of structural abnormalities to methamphetamine use *per se*, this question can be addressed in animal studies. In vervet monkeys, exposure to a methamphetamine-dosing regimen that resembles a common pattern of human drug-taking results in increased gray-matter volume in the putamen, and this increase is associated with reductions in D_2-type dopamine receptor and dopamine transporter (DAT) availability, and decrements in cognitive flexibility (Figure 2) (Groman et al., 2013). These observations suggest that at least the gray-matter abnormalities detected in the putamen in human methamphetamine users may partly be a consequence of drug exposure.

As structural features of the brain (Peper et al., 2007; Thompson et al., 2002; Thompson et al., 2001) and addiction (Agrawal and Lynskey, 2008; Li and Burmeister, 2009; Uhl et al., 2008) are both heritable, methamphetamine users may differ in brain structure from drug non-users before they initiate drug use, and the differences may be linked to genetic vulnerability for drug use. In a test of this hypothesis, 50 cocaine- or amphetamine-dependent individuals and their siblings without histories of chronic drug use were compared to healthy controls (Ersche et al., 2012). Stimulant-dependent individuals and their unaffected siblings had greater gray-matter volume in putamen, amygdala and hippocampus than controls, but only the stimulant-dependent individuals showed smaller volumes of OFC and anterior insula than controls. Stimulant-dependent individuals and their unaffected siblings also had lower fractional anisotropy than healthy controls, suggesting that white-matter abnormalities shared by individuals with familial history of substance use disorders predispose them to drug abuse. Collectively, these findings suggest that some but not all of the structural brain abnormalities in methamphetamine users may predate drug use.

Deficits in Brain Structure and Impaired Executive Functions

Considerable evidence indicates that structural integrity of the prefrontal cortex contributes to cognitive control. The *pars opercularis* of the right inferior frontal gyrus (IFG) has been linked to inhibitory control (Aron et al., 2004), and gray-matter structural deficits in this region occur in methamphetamine users (Tabibnia et al., 2011; Thompson et al., 2004). Moreover, white-matter integrity, inferred from fractional anisotropy in fiber tracts proximal to the right IFG, is positively related to motor inhibitory control capacity on the Stop-signal task in stimulant users, their unaffected siblings, and healthy controls with no familial history of stimulant dependence (Ersche et al., 2012). Gray-matter integrity of the *pars opercularis* has also been linked with capacity for motor response inhibition on the Stop-signal task and with success in an emotion-regulation task in healthy adults (Tabibnia et al., 2011). Methamphetamine users show impairment on this task, their performance being negatively correlated with methamphetamine craving, which is negatively associated with gray-matter volume in the *pars opercularis* (Monterosso et al., 2005). A positive association between putamen volume and performance on a test of psychomotor inhibitory control also has been observed in methamphetamine users (Jan et al., 2012b).

Other dimensions of inhibitory control include the ability to suppress or resist irrelevant information, commonly measured using the Stroop task, and the ability to respond flexibly to changes in the environment, which can be tested using the Wisconsin Card Sorting Task (WCST). On the Stroop task, methamphetamine users exhibit greater interference, measured as the Stroop reaction time, than controls (Salo et al., 2009b). And on the WCST, methamphetamine users make more errors and achieve fewer categories (Hosak et al., 2012; Kim et al., 2006). These deficits have been found to be correlated with increased fractional anisotropy in the genu of the corpus callosum, a white-matter bundle carrying fibers originating in the prefrontal cortex (Kim et al., 2006; Salo et al., 2009a). Gray-matter density in the middle frontal gyrus of methamphetamine users is also associated with errors on the WCST (Kim et al., 2006).

The pattern of smaller gray-matter volume in prefrontal cortex and larger striatal volumes has been linked both to impulsive choice and impulsive action. Temporal discounting paradigms measure the rate at which the subjective value of a reward diminishes with time, assessing preference for smaller rewards available sooner over larger, more delayed alternatives. Methamphetamine users exhibit steeper temporal discounting than healthy controls (Monterosso et al., 2007; Schwartz et al., 2010); and this characteristic has been associated with lower gray-matter density in the superior frontal gyrus but greater gray-matter density in putamen, ventral striatum and posterior cingulate in methamphetamine-dependent individuals as well as non-users (Schwartz et al., 2010).

Molecular Imaging of Methamphetamine Users

Studies employing positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) have identified neurochemical abnormalities in the cortices and striata of individuals with a history of methamphetamine abuse. These include markers of deficient monoaminergic signaling capacity, poor neuronal integrity, neuroinflammation, and abnormal glucose metabolism.

Monoamine systems

Methamphetamine is a psychostimulant that acts to increase release and sustain extracellular concentrations of dopamine, serotonin and norepinephrine (rev. Sulzer et al., 2005). These actions primarily underlie effects of the drug on mood, cognition and physiology, including its addictive properties and, in part, its capacity to induce neurotoxicity (rev. Cadet et al., 2010; Panenka et al., 2013). Accordingly, much of the relevant molecular imaging research has focused on neurochemical markers for monoaminergic, particularly dopamine, systems.

Extending findings from animal studies and postmortem human brain analyses indicating that methamphetamine alters monoaminergic nerve terminals (rev. Seiden and Ricaurte, 1987), PET has been used to assess presynaptic neurochemical markers *in vivo*. Striatal levels of DAT were generally lower in abstinent methamphetamine users than in matched non-users: deficits of 11-28% were measured using [^{11}C]WIN-35,428 and [^{11}C]d-threo-methylphenidate (Johanson et al., 2006; McCann et al., 1998; McCann et al., 2008; Sekine et al., 2001; Volkow et al., 2001b; Volkow et al., 2001d). Although some participants in these studies were abstinent for up to 25 years (rev. McCann et al., 2008), a Tc-99nm TRODAT SPECT study found evidence of up to a 38% DAT recovery in the first two weeks of abstinence among five methamphetamine abusers (Chou et al., 2007), and another with PET and [^{11}C]d-threo-methylphenidate found that DAT availability increased 19% and 16% in the caudate and putamen, respectively, in five individuals between early (< 6 months) and later abstinence (12-17 months) (Volkow et al., 2001b). Notably, in some (McCann et al., 2008; Volkow et al., 2001d) but not all (Johanson et al., 2006) of these studies, measures of DAT availability were correlated with cognitive and psychomotor performance, and there is preliminary evidence that DAT recovery with abstinence may correspond to recovery of executive function, as indicated by improved performance on the WCST (Chou et al., 2007). Lower DAT availability has also been found in the anterior prefrontal cortex (PFC), OFC, DLPFC and amygdala of methamphetamine users (Sekine et al., 2001; Sekine et al., 2003).

DAT availability in the striatum and PFC were negatively associated with psychiatric symptoms and duration of methamphetamine use (Sekine et al., 2001; Sekine et al., 2003).

The serotonin and type-2 vesicular monoamine transporters (SERT and VMAT2, respectively) are other presynaptic markers that have been measured using PET in methamphetamine users. Consistent with laboratory rodent (Kovachich et al., 1989; Reichel et al., 2012) and postmortem human findings (Kish et al., 2009), a study using [^{11}C]trans-1,2,3,5,6,10-beta-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]isoquinoline ([^{11}C](+)McN-5652) to measure SERT levels showed lower availability in cortical and subcortical structures, including the striatum, among methamphetamine users abstinent for less than one year; reductions in the OFC, temporal cortices, and ACC were related to a measure of aggression (Sekine et al., 2006). Findings pertaining to VMAT2 are less clear, with one study using [^{11}C]dihydrotetrabenazine finding that striatal availability was higher (+22%, caudate; +12%, putamen; +11%, ventral striatum) in methamphetamine users during early abstinence (< 3 weeks) compared to controls, the group differences diminishing with longer abstinence (Boileau et al., 2008), and another finding 10% lower striatal availability among users who were abstinent for over 3 months than non-users (Johanson et al., 2006). The former finding fits with work in rats showing reductions in striatal VMAT2 protein following an excitotoxic methamphetamine dosing regimen; although, no change was found following a behaviorally sensitizing regimen (Frey et al., 1997), and a postmortem brain analysis found no difference in striatal VMAT2 levels between methamphetamine users and non-users (Wilson et al., 1996). Molecular imaging studies of norepinephrine transporters or markers of monoamine synthesis in methamphetamine users have not been conducted in vivo.

In addition to assessments of monoaminergic nerve terminal integrity, PET studies have shown deficits in dopamine D_2-type receptor availability, a putative biomarker of postsynaptic dopamine function. One study using the D_2/D_3-preferring ligand [^{11}C]raclopride demonstrated lower striatal availability among methamphetamine users who were abstinent for between 2 weeks and 35 months (−16%, caudate; −13%, putamen; −8%, nucleus accumbens) (Volkow et al., 2001b), and similar results have been obtained with [^{18}F]fallypride among individuals abstinent for 4-10 days (Lee et al., 2009). Furthermore, striatal D_2-type receptor availability was positively correlated with regional glucose metabolism in the OFC, measured with [^{18}F]fluorodeoxyglucose (Volkow et al., 2001b), and with trait impulsivity (Lee et al., 2009). D_2-type receptor availability also has predicted treatment outcome, in that high baseline D_2-type receptor availability in the caudate and putamen predicted the maintenance of abstinence for participants in an outpatient rehabilitation program, and low baseline D_2-type receptor availability predicted relapse to methamphetamine abuse during a nine-month follow-up period (Wang et al., 2011). Preliminary evidence also suggests that low striatal D_2-type receptor availability is associated with steeper temporal discounting among methamphetamine users (Ballard et al., 2014). There is some evidence that striatal D_2-type receptor availability recovers with protracted abstinence in rodents (Segal et al., 2005) and nonhuman primates (Groman et al., 2012), although longitudinal studies investigating D_2-type receptor availability with methamphetamine abstinence over time not been conducted in humans.

A PET study with [^{11}C](+)4-propyl-3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-*b*][1,4]oxazin-9-ol ([^{11}C]-(+)-PHNO), which shows higher differential binding at D_3 than at D_2 dopamine receptors (Wilson et al., 2005) showed that individuals with a history of methamphetamine use exhibited only a slight reduction in binding in striatal regions compared to controls, a finding interpreted as evidence that increased D_3 receptor levels overshadowed the reduction in D_2 receptor levels (Boileau et al., 2012). Most of the individuals sampled in that study, however, had abused drugs in addition to methamphetamine, limiting the conclusions that can be drawn regarding the effects of methamphetamine. Aside from a study that found no difference in binding of a ligand that selectively binds both D_2 and type-2 serotonin receptors ([^{11}C]-N-methylspiperone) between six men with a history of methamphetamine psychosis and healthy non-user controls (Iyo et al., 1993), no other molecular imaging studies have yet investigated levels of D_1-like, serotonin, or norepinephrine receptors in methamphetamine users.

Neuronal integrity and neuroinflammation

Mounting evidence that repeated exposure to methamphetamine can produce neurotoxicity (rev. Cadet et al., 2010; Jan et al., 2012a) has prompted evaluation of chemical markers of neuronal integrity and neuroinflammation with MRS in methamphetamine users. These studies have shown lower levels of *n*-acetyl-aspartate (NAA) metabolites and a lower ratio of NAA to creatine and phosphocreatine (Cr) metabolites – indicating poorer neuronal integrity and viability – among methamphetamine abusers relative to healthy controls in frontal brain regions, particularly the ACC (Ernst et al., 2000; Nordahl et al., 2002; Nordahl et al., 2005; Sailasuta et al., 2010; Sung et al., 2007). Moreover, the NAA/Cr ratio in the ACC is positively correlated with attentional control (Salo et al., 2007) and negatively correlated with years of methamphetamine use (Nordahl et al., 2005) among methamphetamine users, and appears to recover, albeit slowly, with extended abstinence (Nordahl et al., 2005; Salo et al., 2011). Higher levels of choline (Cho) metabolites have been found in frontal regions and the basal ganglia of methamphetamine users than non-users (Ernst et al., 2000; Nordahl et al., 2002; Nordahl et al., 2005; Sekine et al., 2002), and evidence that the level of frontal glutamate is increased (Ernst and Chang, 2008; Sailasuta et al., 2010) implicates glutamate excitotoxicity as a potential contributing factor. Inverse correlations between months of abstinence and Cho/Cr and Cho/NAA ratios in the ACC suggest that some recovery is possible after prolonged abstinence (Nordahl et al., 2005). In addition, higher *myo*-inositol in frontal gray matter – indicative of glial cell proliferation – has been found using MRS in methamphetamine users compared to non-users (Ernst et al., 2000; Sung et al., 2007). Corroborating MRS findings, a PET study that used [^{11}C]N-butan-2-yl-1-(2-chlorophenyl)-N-methylisoquinoline-3-carboxamide ([^{11}C]PK11195), a ligand for the translocator protein, found more binding, suggestive of increased neuroinflammation, in the midbrain, striatum, thalamus, OFC, and insular cortex among abstinent methamphetamine abusers than non-users (Sekine et al., 2008). As well, a longer duration of abstinence from methamphetamine was inversely associated with binding in the midbrain, striatum, and thalamus (Sekine et al., 2008). Methamphetamine-induced inflammation and neurodegeneration are likely behaviorally relevant, as peripheral markers of immune activation are associated with impaired cognitive functioning (Loftis et al., 2011), and Cr/Cho ratios in the basal ganglia are positively correlated with duration of

methamphetamine use and the severity of residual psychiatric symptoms (Sekine et al., 2002).

Regional Brain Function

The radiotracer [^{18}F]fluorodeoxyglucose is used with PET to map regional cerebral metabolism of glucose, an index for local brain function (Phelps et al., 1979; Reivich et al., 1977; Sokoloff et al., 1977). This procedure has been used to compare methamphetamine users with non-users and to evaluate how functional abnormalities are related to mood, and how they change over time. In the first of these studies, global metabolic rate was higher among methamphetamine users, who had a range in duration of abstinence from 2 weeks to 35 months; with an elevation in normalized metabolism in the parietal cortex reaching statistical significance (Volkow et al., 2001c). In the same study, deficits in normalized metabolism were observed in subcortical regions that have dopaminergic innervation (thalamus, caudate, putamen), consistent with the notion of disrupted dopaminergic function.

When the abstinence period was limited to the first week, a different pattern emerged, with methamphetamine users exhibiting less relative glucose metabolism in the ACC and insula but greater relative regional glucose metabolism in the amygdala, ventral striatum, and OFC (London et al., 2004). In another study, glucose metabolism in the OFC was positively correlated with personality measures of inhibitory control, as indexed by the harm avoidance scale and constraint superfactor of Tellegen's Multidimensional Personality Questionnaire, among recently abstinent methamphetamine users (Goldstein et al., 2002), suggesting that OFC function contributes to stable personality predispositions in methamphetamine users. Recently abstinent methamphetamine users also perform more poorly than non-users on tests of sustained attention; and their performance on these tasks correlates negatively with metabolic activity in the anterior and middle cingulate gyri and the insula, suggesting that PFC and insular dysregulation in the early abstinence period could underlie some of the cognitive deficits (London et al., 2004).

A subset of the methamphetamine users who were tested in early abstinence were re-tested after another month of abstinence, when greater variance in task performance accompanied a global increase in cerebral glucose metabolism in the parietal cortex, as well as other cortical regions and the thalamus (Berman et al., 2008b). Considering the earlier study of participants who were abstinent for up to about 2.5 years (Volkow et al., 2001c), these findings suggest either that cortical abnormalities in glucose metabolism evolve after the first week of abstinence, or that a chronic elevation in glucose metabolism is masked by residual effects of the drug during early abstinence. The change may reflect adaptive processes, such as reactive proliferation of glial cells (which have a higher metabolic demand than neurons) in response to cortical (especially parietal) damage. In both studies, parietal metabolism in the methamphetamine users correlated with task performance (Grooved Pegboard Task (Volkow et al., 2001c) or Continuous Performance Task (Berman et al., 2008b)), suggesting that this dysregulation of both dopaminergic and non-dopaminergic systems contributes to the cognitive, motor, and mood deficits observed with long-time methamphetamine abuse.

There is also evidence that cerebral glucose metabolism remains abnormal throughout protracted abstinence. Significantly greater thalamic, although not striatal, metabolism was seen following 12 – 17 months of abstinence compared to values after less than 6 months, and this increase was associated with improved performance in motor and verbal memory tests (Wang et al., 2004). In addition, lower glucose metabolism in PFC white matter has been observed among male methamphetamine users abstinent 19 months (SD = 27), compared to non-users, and the severity of this deficit correlated with impairment on the WCST, which relies on prefrontal integrity (Kim et al., 2006). Still, a study employing technetium-99m-hexamethyl-propyleneamineoxime ([^{99m}Tc]HMPAO) SPECT that showed lower relative regional cerebral blood flow, another functional index, in the right ACC among abstinent methamphetamine users than in healthy controls found signs of recovery with abstinence. In that study, binding was lower among the subset of 13 users who had been abstinent an average of 3 months (SD = 2) than 27 users who were abstinent an average of 36 months (SD = 40) (Hwang et al., 2006).

Functional Imaging of Brain Activation Using fMRI in Methamphetamine Users

The use of functional magnetic resonance imaging (fMRI) has greatly advanced the understanding of brain function as it provides a non-invasive approach to indirectly measure neuronal activity. Consistent with the reports that chronic methamphetamine use results in changes in biological markers of neuronal function in cortical and subcortical areas (London et al., 2004), fMRI studies have shown that methamphetamine users have impairments in prefrontal and striatal activation during tests of executive functioning.

On the Stroop task for example, methamphetamine users exhibit less activation than controls in the right IFG, supplementary motor cortex/ACC and the anterior insular cortex during the incongruent condition relative to rest but greater activation in the ACC, medial PFC and frontal pole than control subjects in the incongruent than congruent conditions (Nestor et al., 2011). These results, in combination with findings that impaired Stroop performance was related to a deficit in integrity of white-matter fibers originating in the prefrontal cortex (see above), suggest that loss of integrity and connectivity of PFC regions may underlie deficits in executive function in methamphetamine users.

Methamphetamine users show functional deficits while performing tasks that assess decision-making in the presence of varying likelihoods of risk and reward magnitude. An fMRI study found a link between greater temporal discounting and abnormality in neural recruitment within the left DLPFC and intraparietal sulcus of methamphetamine users (Monterosso et al., 2007). While non-users showed increasing BOLD signal with more difficult choices, methamphetamine users showed similar recruitment for easy and difficult choices (Monterosso et al., 2007). In another study, healthy controls exhibited greater activation in DLPFC, ACC and caudate nucleus than methamphetamine users while choosing between immediate and delayed alternatives (Hoffman et al., 2008). The results suggest that discounting of delayed rewards in methamphetamine users may represent reward-driven behavior due to impairments in frontostriatal activation.

Stimulant users also show impairments in brain activation during risky decision-making, drug users consistently showing impairments in the striatum and in the OFC, DLPFC, medial frontal cortex and ACC (Gowin et al., 2013). In a recent study, a linear relationship between level of risk and activation in the DLPFC during decision-making was greater among non-user controls than methamphetamine users, but the relationship with the ventral striatal activation was greater among the methamphetamine users (Figure 3) (Kohno et al., 2014). Inasmuch as frontostriatal circuitry plays a critical role in integrating motivational and cognitive processes to produce optimal behavior (Jentsch and Taylor, 1999), frontostriatal impairments may contribute to deficits in executive functioning that have been observed in methamphetamine users (Dean et al., 2012; Jentsch and Taylor, 1999; Nordahl et al., 2003).

Methamphetamine-related impairments in frontal function have also been linked with dysregulated mood and emotional processing deficits. Threatening or fearful visual scenes have shown to evoke less activation in bilateral DLPFC and insula of methamphetamine users than in non-user controls (Kim et al., 2011). Methamphetamine users also exhibit less activation in the IFG during the presentation of fearful and angry faces (Payer et al., 2011) and while performing an empathy task (Kim et al., 2010). As methamphetamine users exhibit less empathy (Kim et al., 2010) but greater aggressive behavior (Payer et al., 2011), the results suggest that impairments in PFC control may contribute to deficits in the evaluation of internal states, and that they precipitate dysregulated emotional processing in methamphetamine-abusing individuals.

Not only is activation in frontal and striatal systems central to decision-making and emotional processing, it has been associated with success of treatment for methamphetamine abuse. An fMRI study of decision-making using a 2-choice prediction task, found that activation of the insula, DLPFC, as well as parietal, and temporal cortices predicted maintained abstinence from methamphetamine, with lack of activation heralding relapse (Paulus et al., 2005). In another study, differences in activation of the striatum, insula and IFG between abstainers and relapsers were obtained while participants performed the paper-scissors-rock task (Stewart et al., 2013). These findings provide evidence that corticostriatal and limbic dysfunction relate to impaired higher-order cognitive and motivational functions that promote the maintenance of addiction (Goldstein and Volkow, 2002)

Resting-state Functional Abnormalities in Brain Demonstrated Using fMRI

Advances in assessing network dynamics through resting-state functional connectivity (RSFC) have contributed to new insights in the functional organization of brain systems (Greicius, 2008), and recent studies have interrogated RSFC within the mesocorticolimbic system in individuals with various substance use disorders (Gu et al., 2010; Tomasi et al., 2010; Upadhyay et al., 2010; Wilcox et al., 2011). These studies have indicated various differences in mesocorticolimbic RSFC between drug users and nonusers, presumably in part as a function of drug use history and recency of drug taking (Konova et al., 2013) . In another study, abstinent methamphetamine users exhibited stronger RSFC than controls of the midbrain with amygdala, hippocampus, striatum, insula and PFC (Kohno et al., 2014). It is plausible that this effect contributes to psychostimulant sensitization (Robinson and

Berridge, 1993). As RSFC was related to brain function during decision-making (Kohno et al., 2014), the study has important implications for mesocorticolimbic sensitization on brain function and behavior (Figure 4).

In addition to the aforementioned evidence for dopamine system dysfunction, increases of local tonic dopamine concentrations, presynaptic glutamate release and reduction of long-term depression in dopamine neurons (Jones et al., 2000) disrupt striatal and cortical function. Dopaminergic efferents from the ventral tegmental area (VTA) and glutamatergic efferents from the PFC often terminate on the same postsynaptic cell in the ventral striatum (Beaulieu and Gainetdinov, 2011) and efferents from the PFC contact dopaminergic neurons of the VTA that project to the nucleus accumbens directly (Bunney et al., 1991). As adaptive decision-making would require a balance between behavioral control and reward-seeking behavior, impairments in the corticostriatal circuit of methamphetamine users may attenuate PFC regulation of ventral-limbic response to reward. Thus, the functional deficits during risky decision-making (Gowin et al., 2013; Lane and Cherek, 2000) and temporal discounting (Hoffman et al., 2008; Monterosso et al., 2007) seen in methamphetamine abusers could be attributed to a disruption in the corticostriatal circuit leading to abnormal evaluation of a stimuli and the assignment of value.

Implications for Therapy

Dopamine system deficiencies and associated behavioral phenotypes may be a critical barrier to success in treating methamphetamine use disorders. As reviewed above, the effects of methamphetamine on dopaminergic markers and associated signaling pathways may promote dysfunctions of cognitive control and decision-making. In line with this view, low striatal D_2-type receptor availability has been linked with poor inhibitory control (Monterosso et al., 2005) and impulsivity (Lee et al., 2009) in methamphetamine users, as well as with decreased activity in prefrontal regions important for executive functioning (Volkow et al., 2001a).

Direct and indirect dopamine agonists, including modafanil, methylphenidate and d-amphetamine have not consistently proven to be efficacious (Brensilver et al., 2013; Miles et al., 2013). This may in part be due to methamphetamine-induced neurotoxicity to dopamine nerve terminals. Consistent with studies in animals, neuroimaging studies have detected evidence for neuroinflammation in humans with chronic methamphetamine exposure (Ernst et al., 2000; Sekine et al., 2008). Given the evidence that minocycline, a powerful anti-inflammatory drug, ameliorates methamphetamine-induced neurotoxicity to dopamine nerve terminals and behavioral changes (Zhang et al., 2006), anti-inflammatory agents may be considered in the treatment of methamphetamine dependence.

Another therapeutic approach might be to augment dopaminergic signaling using nonpharmacological methods. Given relationships between striatal D_2-type receptor availability and decision-making (Kohno et al., 2013), inhibitory control (Ghahremani et al., 2012) and trait impulsivity (Buckholtz et al., 2010) in healthy controls, an upregulation of D_2 receptors may provide clinical improvements in executive function for individuals affected with stimulant-use disorders. In patients with Parkinson's disease intensive exercise

leads to increased D_2-type receptor BP_{ND} (Fisher et al., 2013), and preliminary findings suggest a positive finding in methamphetamine users as well (Robertson et al., 2013). Future studies may also benefit from therapeutic approaches targeted at novel targets in the dopamine system, such as the D3 receptor (Baladi et al., 2014; Paterson et al., 2014), as chronic methamphetamine exposure is associated with reduced levels of D_2 receptors but elevated levels of D_3 receptors (Boileau et al., 2012; Payer et al., 2014).

Despite high rates of attrition and relapse (Rawson et al., 2004; Smout et al., 2010), cognitive behavioral therapy, contingency management, and motivational interviewing (Carroll and Onken, 2005; Rawson et al., 2006) are the mainstay of treatment for methamphetamine users. As cognitive impairment is related to poorer treatment outcomes for drug dependence, cognitive remediation may augment the efficacy of behavioral therapy for drug dependence (Vocci, 2008). Cognitive remediation therapies requires the practice of skills that are essential for daily functioning such as attention, memory, executive skills, visuoperceputal skills and problem-solving (Kurtz et al., 2007). Improvements with cognitive remediation therapies have been shown in patients with schizophrenia (Bell et al., 2001), attention-deficit hyperactivity disorder (O'Connell et al., 2006), and anorexia nervosa (Wood et al., 2011). The potential of cognitive remediation for treatment of methamphetamine dependence lies in the probability of transfer of improvement in one cognitive task to another task that uses similar underlying neural structures. As an emerging literature suggests experience-dependent neural plasticity can be detected in vivo using magnetic resonance imaging (Ilg et al., 2008; May and Gaser, 2006; May et al., 2007; Scholz et al., 2009), future studies might address whether cognitive remediation can facilitate recovery of brain structure and function in methamphetamine users.

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Highlights

- Chronic methamphetamine abuse is linked to abnormalities in frontostriatal circuitry
- Neural abnormalities linked with methamphetamine exposure, abstinence, and executive control
- Brain structure, chemistry and function are potential therapeutic targets

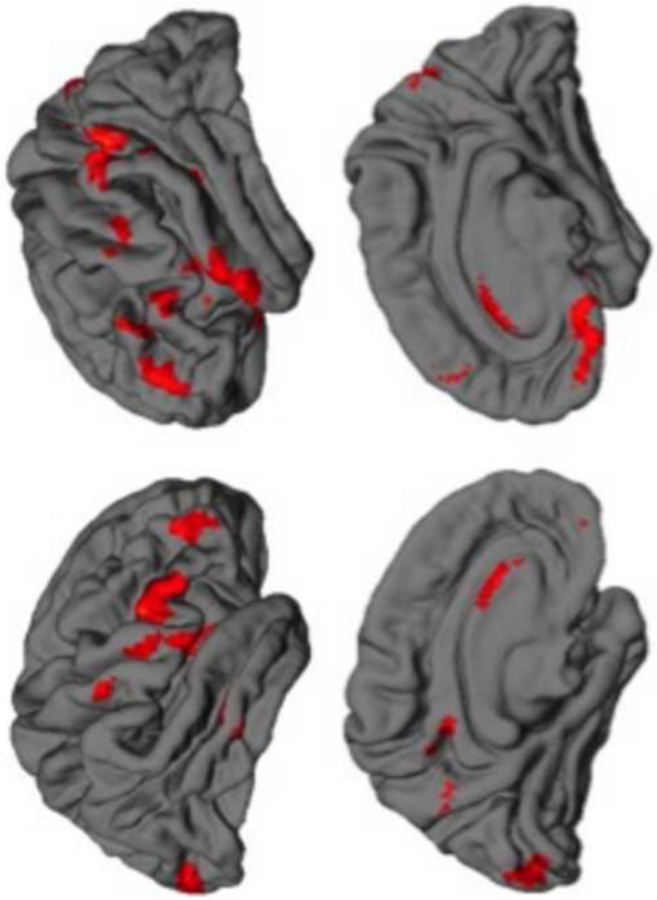

Figure 1. Changes in gray matter during early abstinence from methamphetamine

In methamphetamine-dependent individuals, gray matter increased between the first and fourth weeks of abstinence from methamphetamine (results displayed at a statistical threshold of $p < 0.005$ uncorrected with a cluster extent > 200 voxels). No changes in gray matter were detected in healthy control participants who underwent two scanning sessions approximately 1 month apart. The left hemisphere is displayed on the left side of the image.

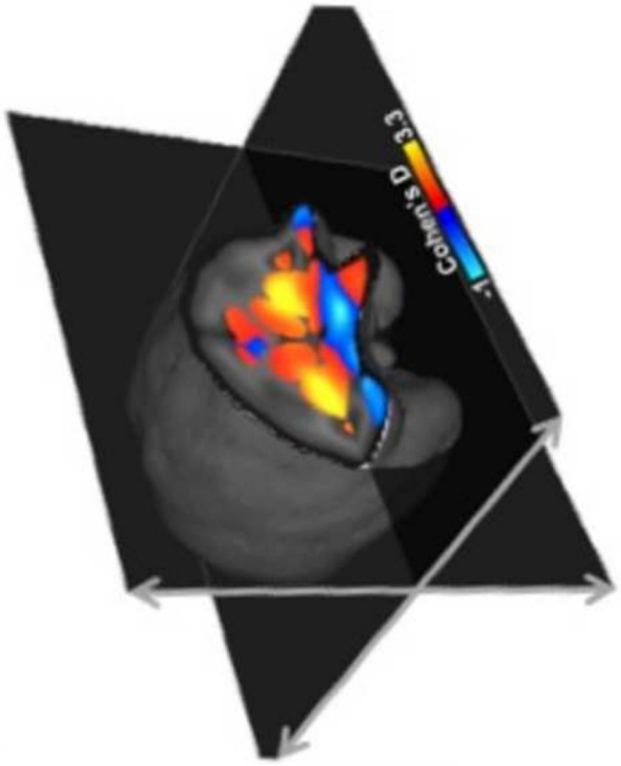

Figure 2. Exposure to escalating methamphetamine causes structural changes in the vervet monkey brain

In the effect size (Cohen's d) map, positive values (warmer colors) indicate brain regions where gray matter increased in the methamphetamine-exposed group relative to the saline controls; negative values (cooler colors) depict the converse relationship. Methamphetamine exposure produced a significant increase in gray matter in the striatum compared to saline ($p < 0.05$ corrected for multiple comparisons). The left hemisphere is depicted right side of the image.

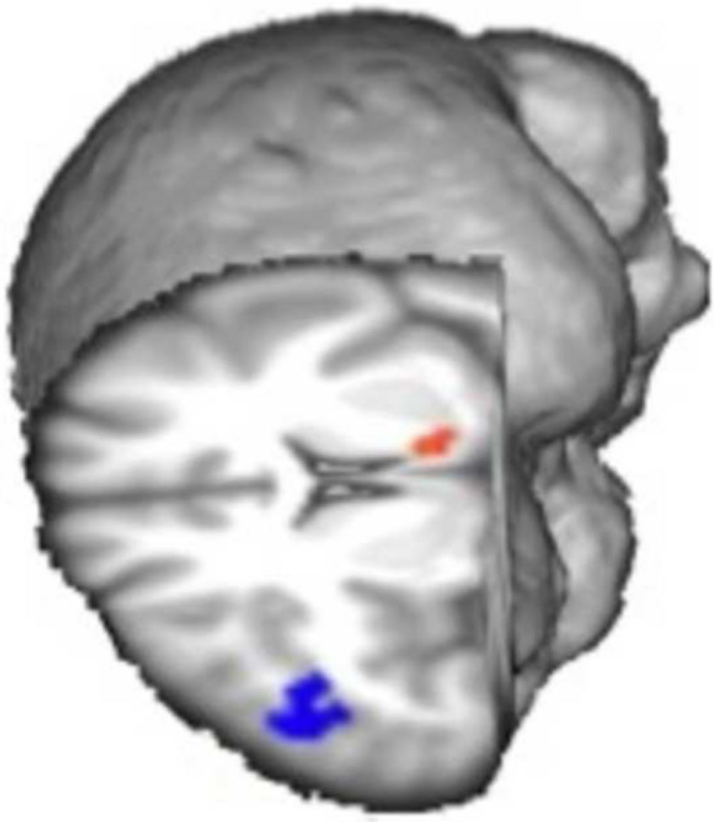

Figure 3. Differences in brain function during risky decision-making between methamphetamine-dependent and healthy control participants

The linear relationship between risk levels and activation in the dorsolateral prefrontal cortex (blue) was greater in control group than in the methamphetamine-dependent group; however, the opposite relationship was found in the greater in the ventral striatum (red) ($p < 0.05$, cluster corrected). Results were controlled for age, sex, smoking status, and marijuana use.

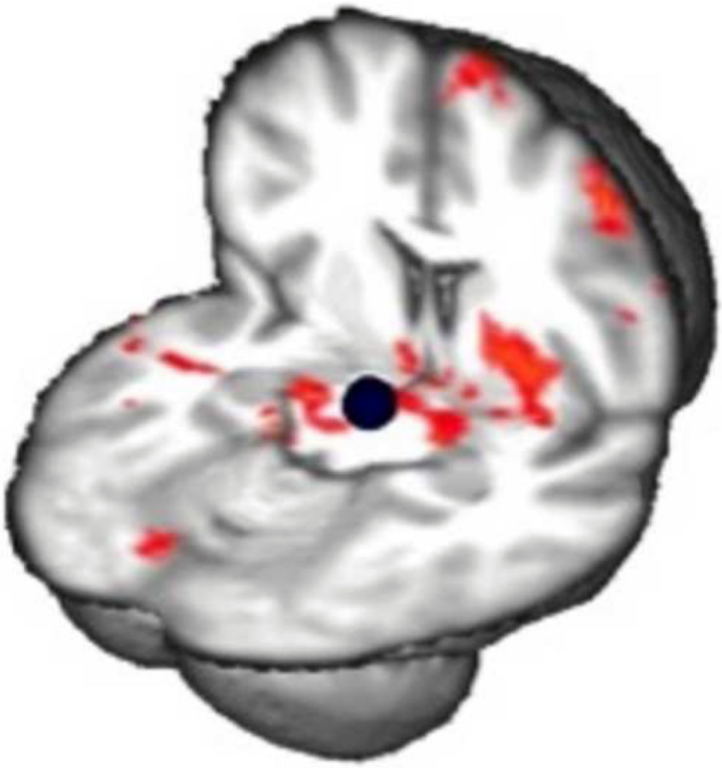

Figure 4. Relationship between prefrontal brain function during risky decision-and resting-state connectivity of the midbrain in methamphetamine-dependence

Connectivity maps show a negative correlation between modulation of activation in right dorsolateral prefrontal cortex during risky decision-making and the connectivity between midbrain seed (shown in blue) and nucleus accumbens, putamen, amygdala, hippocampus, orbitofrontal cortex, anterior cingulate, and superior frontal gyrus in methamphetamine-dependent individuals ($p < 0.05$, whole-brain cluster corrected). Results controlled for age, sex, smoking status and marijuana use.