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Molecular, Behavioral and Physiological Consequences of Methamphetamine Neurotoxicity: Implications for Treatment

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ADHD; attention hyperactivity disorder; CNS, central nervous system; DA, dopamine; DAergic, dopaminergic; GABA, gamma-aminobutyric acid; METH, methamphetamine; PD, Parkinson's disease

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Abstract

Understanding the relationship between the molecular mechanisms underlying neurotoxicity of high-dose methamphetamine (METH) and related clinical manifestations is imperative for providing more effective treatments for human METH users. This article provides overview of clinical manifestations of METH neurotoxicity to the CNS and neurobiology underlying the consequences of administration of neurotoxic METH doses, and discusses implications of METH neurotoxicity for treatment of human abusers of the drug.

1. Introduction

METH is a central nervous system stimulant, chronic abuse of which continues to be a significant problem in the USA and worldwide. METH has powerful addictive properties and, therefore, has devastating effects on health and other aspects of life of people who abuse it. METH is a schedule II drug, which can only be prescribed for attention deficit hyperactivity disorder (ADHD), extreme obesity, or to treat narcolepsy (as Desoxyn), with amphetamine being more often prescribed for these conditions due to amphetamine having lower reinforcing potential than METH (Lile et al., 2013). Even though amphetamine is less potent than METH, it can also be neurotoxic when taken at high doses and has the same molecular mechanisms of action as METH. Molecular mechanisms underlying neurotoxicity of amphetamine and METH are complex and they ultimately lead to severe dysfunction of dopaminergic (DAergic) and, in most species, serotonergic (5HTergic) neurotransmission. There is no treatment for some neurologic complications associated with chronic METH use such as cognitive impairments.

Understanding the relationship between the molecular mechanisms underlying neurotoxicity of METH and related clinical manifestations may help to develop pharmacological treatment for neurological impairments associated with METH use as well as to improve therapies aimed against METH dependence and relapse.

2. Prevalence of METH abuse

Per the 2015 report form the United Nations Office on Drugs and Crime, METH dominates global market for synthetic drugs (UNODC, 2015). Thus, METH confiscations grew ~1.5 fold from 34 tons in 2009 to 88 tons in 2013. In recent years, METH abuse increased dramatically in East and South-East Asia but not in North America. The number of METH users in the USA has been stable in most states among 12-64 year-olds between 2008 and 2014. Approximately 0.3% percent of USA population used amphetamines chronically between 2008 and 2014. Nevertheless, increases in METH abuse has been reported in Minnesota, Ohio and California. In 2015, approximately 897,000 people were current users of METH in the United States (SAMHSA, 2016).

3. Medical use of METH

METH is a methylated amphetamine, more potent in the CNS than amphetamine likely due to the addition of the methyl group (Lake and Quirk, 1984) and a consequent higher lipophilicity (Gulaboski et al., 2007b). The half-life of METH in humans is between 9 and 12 hours, depending on route of administration (Cook et al., 1992; Cook et al., 1993b), with oral METH having the shortest half-life and intravenous METH having the longest. The general pharmacodynamic effects of types of amphetamines

are similar, and indeed humans trained to discriminate METH will respond to *d*-amphetamine, however *d*-amphetamine does not produce the alterations to blood pressure and heart rate to the degree observed with METH (Sevak et al., 2009). Likewise, human self-reporting of the subjective effects of METH and amphetamine are similar, though METH is typically rated as producing a larger "high" (Kirkpatrick et al., 2012). This is possibly due to METH having a higher lipophilicity and higher ability to release DA via DAT and to inhibit DA uptake than amphetamine (Gulaboski et al., 2007a; Goodwin et al., 2009). Amphetamine is a metabolite of METH, produced via *N*-demethylation of METH by the CYP2D6 enzyme (Lin et al., 1997). The half-lifes of amphetamines varies widely depending on both the isoform and the route of administration. The elimination half-life of amphetamine is reported to be between 15 and 25 hours, whereas the elimination half-life for METH is reported to be between 9 and 15 hours (Mendelson et al., 2006) (Carvalho et al., 2012, for a review).

Both amphetamines have two active optic isoforms, *d*-enantiomer and *l*-enantiomer (Hensley and Cody, 1999) with similar pharmacokinetics in humans (Mendelson et al., 2006). At high doses, intoxication produced by METH is similar for both enantiomers; however, the psychodynamic effects of *l*-METH are shorter-lived than those of *d*-METH (Mendelson et al., 2006) and, therefore, less desired by human users of the drug. In rodents, *d*-enantiomers of both amphetamines produced few times greater central stimulant effects than *l*-METH due to a higher potency to release DA (Heikkila et al., 1975; Jackson et al., 1975; Kuczenski et al., 1995; Easton et al., 2007). Interestingly, Easton and colleagues found that areas mediating pleasurable effects in the rat brain differ for each amphetamine isomer. In addition, *d*-amphetamine is a more potent

agonist of TAAR1 receptor (which regulates DAergic neurotransmission (Miller, 2011) than *l*-amphetamine (Lewin et al., 2011). These findings could explain stronger than *l*-isomer reinforcing properties of *d*-isomer. Unsurprisingly, animals self-administer *d*-amphetamine at a higher rate than *l*-amphetamine (Balster and Schuster, 1973), indicating that the stronger CNS effects extend to abuse potential.

There is evidence for the *l*-isomer of METH or amphetamine contributing more to the peripheral effects e.g. heart rate, with *d*-isomer contributing more to the CNS effects (e.g., heart rate; Smith, 1979) (Goodman and Gilman, 2001). There is also evidence to the contrary (Mendelson et al., 2006). The *d* - and *l*-isomer peripheral effects may vary with the doses administered. *l*-Amphetamine was reported either as potent, or more potent, than *d*-amphetamine as a releaser of noradrenaline (NE) *in vivo* (Heikkila et al., 1975; Easton et al., 2007). NEergic fibers originate in the parabrachial area and project to the pons and medulla oblongata, which could explain the aforementioned finding because these CNS regions are involved in autonomic functions such as breathing and heart rate. Amphetamines may also activate alpha-adrenergic receptors by releasing NE from peripheral sympathetic terminal.

As mentioned previously, amphetamines are prescribed for ADHD, narcolepsy and severe obesity. Their therapeutic doses range from 5-60 mg/day (usually in divided doses) and come as *d*-enantiomer or a mixture of the two, *d*- and *l*- isomers. As discussed above, the *d*-enantiomer has stronger CNS effects but it is metabolized more quickly than the *l*-enantiomer, which is longer lasting due to the slower breakdown (Cody et al., 2003). As a result, drugs that contain *d*-/*l*- mixture (e.g. Adderall) were reported to result in better clinical response in some children with ADHD (Patrick et al.,

2009). The initial strong central effect of Adderall comes from the *d*- enantiomer, while prolonged effect is provided by *l*-enantiomer (Cody et al., 2003). This allows a patient to take the medication less frequently than a medication containing *d*-amphetamine only (e.g. Dexedrine). The maximum therapeutic dose is 60 mg *d*-amphetamine (equivalent to ~120 mg 'pure' illicit amphetamine which is usually an equal mix of two stereoisomers), but even therapeutic doses can give rise to negative side effects such as insomnia, loss of appetite and anxiety (Medscape).

l-METH, a vasoconstrictor, is the active constituent of the Vicks Inhaler decongestant, an over-the-counter product containing about 50 mg of the drug (Smith et al., 2014). Desoxyn, which is *d*-METH, is rarely medically prescribed due to its strong reinforcing properties. Therapeutic doses of Desoxyn are 20-25 mg daily, taken every 12 hours, with dosing not exceeding 60 mg/day (Medscape).

4. Behavioral and physiological effects of METH

4.1. Short-term behavioral and physiological effects of METH: dose dependence

DA and 5HT pathways regulate a variety of functions and behaviors. Consequently, the repeated release of these monoamines in the CNS METH is responsible for several neurological problems in METH users. There is clear evidence for a dose-dependent pharmacodynamic profile (Nash and Yamamoto, 1992; Boireau et al., 1995; Wallace et al., 1999), with higher doses of METH resulting in more severe and deleterious consequences brought on by disruption of these pathways. For example, chronic or high dose METH exposure can lead to the development of psychotic features (Bell, 1973), likely due to excessive DAergic activity (Hsieh et al., 2014). Dysregulation of

glutamatergic (GLUergic), GABAergic, cholinergic, and opioidergic signaling by neurotoxic METH doses contributes to other symptoms in a dose-dependent manner (Seiden and Sabol, 1996; Courtney and Ray, 2014; Moratalla et al., 2015), including aggression, depression, motor impairments and sleep disruption.

Short-term behavioral effects of METH and amphetamine at low to moderate doses include: euphoria, “rush”, alertness, wakefulness, anti-fatigue effect, increased confidence, hyperactivity, and loss of appetite (Comer et al., 2001; Mendelson et al., 2006; Pike et al., 2016). Higher doses will also cause talkativeness, aggressiveness, restlessness, and repetitive behavior (Hart et al., 2008). Consumption of METH at very high doses (e.g. in a binge) will trigger the appearance of some or all of the following symptoms: agitation, confusion, anxiety, irritability, dysphoria, violent behavior, impairment of psychomotor and cognitive skills, stereotypy (punding), auditory hallucinations, panic, formication (delusions of parasites or insects on the skin), and paranoia (Richards et al., 1999a; Zweben et al., 2004). During the end stage of a METH binge, known as “tweaking,” euphoria is gradually replaced by negative feelings (e.g., anxiety, feelings of emptiness) and the appearance of most or all of the symptoms described above (Newton et al., 2005). A “crash” phase, synonymous with early withdrawal, which follows METH binge, is characterized by intense fatigue, uncontrollable sleepiness and catnapping (Gossop et al., 1982).

Short-term physiological effects of METH and amphetamine include loss of appetite, increased heart rate, blood pressure, and breathing rate as well as dilation of the pupils and raised body temperature. At higher doses fever, sweating, headache, blurred vision, dizziness, stomach cramps, muscle fatigue and cramps, chest pains and

shaking, dehydration, nausea and vomiting can occur. Very high doses induce a variety of negative effects such as hyperthermia, hypertension, cardiac arrhythmia, seizures, cerebral hemorrhage, ischemic infarct, renal failure, rhabdomyolysis, and wakefulness to the point of collapse and temporary blindness, coma or death (Richards et al., 1999a; Richards et al., 1999b; Mendelson et al., 2006; Cloutier et al., 2013; Jones and Rayner, 2015; Nakagawa et al., 2015).

4.2. Long-term behavioral and physiological effects of METH: dose dependence

Medically prescribed doses of METH have some of the adverse effects described above (e.g. dysphoria, insomnia, tremors) and can lead to drug addiction due to the pleasurable effects. Even the lowest dose (5 mg; 0.06–0.08 mg/kg) is capable of resulting in reinforcing drug effects in patients (Hart et al., 2001).

Humans abuse METH in different patterns (once a week, once a day, in a binge) and by different routes of administration (oral, intranasal, intravenous; Cook et al., 1993a; Mirecki et al., 2004; Newton et al., 2005). Doses of recreationally taken METH are estimated to be between 20 and 40 mg, which for a 60–80 kg person equals to a 0.25–0.67-mg/kg doses. A report from the U.S. National Highway Traffic Safety Administration states: “purity of METH is currently very high, at 60-90%”, i.e. the illicit METH is predominantly *d*-METH and that “common abused doses are 100-1000 mg/day, and up to 5000 mg/day in chronic binge use”. The results from several surveys and research studies on chronic METH abuse within the US agree with this report; the self-reported chronic METH use was on average 0.25–1.6 g/day (Volkow et al., 2001b; Chang et al., 2007; Volkow et al., 2015b).

Chronic METH abuse, particularly at high doses, has a variety of cardiovascular, gastrointestinal, neurological, and physiological effects, which resemble acute effects of high-dose METH (Perez-Reyes et al., 1991; Mendelson et al., 2006). The latter include cerebral vasculitis as well as intracerebral, subarachnoid or intracranial hemorrhage. Behavioral consequences of chronic METH use include dependence on the drug, cognitive impairments, anxiety or depression, violent behavior (often risk-taking), insomnia, repetitive movements (stereotypy), and psychosis. Cognitive impairments, disturbed sleep or insomnia, depression, anxiety as well as intense drug craving are the most prominent symptoms of METH withdrawal (Zweben et al., 2004; McGregor et al., 2005). Depression and anxiety in withdrawn METH users can lead to suicidal thoughts. These neurological effects can come directly from neuronal alteration and/or damage (London et al., 2004), and there is evidence that some METH withdrawal symptoms can be remediated by pharmacotherapy (Mizoguchi and Yamada, 2011). In addition, chronic METH users may be at higher risk for developing Parkinson's disease (PD) than non-users due to the toxic effects of the drug in the nigrostriatal DA pathway (Garwood et al., 2006; Callaghan et al., 2010; Curtin et al., 2015; Todd et al., 2016). Indeed, postmortem evidence suggests that METH users show higher risk of a later PD diagnosis than matched controls or matched cocaine users, suggesting a strong link between METH toxicity and later PD diagnosis that is not generalized to other psychostimulants (Callaghan et al., 2012).

5. Pharmacology of METH

METH is an indirectly acting sympathomimetic amine. It releases DA, 5HT, noradrenaline, and adrenaline from nerve terminals in the central and peripheral nervous system thus increasing their neurotransmission. Due to high lipophilicity, METH easily crosses the blood brain barrier and distributes throughout the brain (Kalasinsky et al., 2001). Due to chemical structure similar to monoamines, METH is recognized as a substrate by DA, 5HT, and noradrenaline plasma membrane transporters in the brain and transported into neurons and neuronal terminals (Zaczek et al., 1991; Fleckenstein et al., 1997; Volz et al., 2007; Yamamoto et al., 2010). Higher concentrations of METH can cross the membranes *via* passive diffusion (Mack and Bönisch, 1979). It is hypothesized that once in the monoaminergic terminals, METH acts on the monoamine storage vesicles and depletes them of neurotransmitters by reversing the vesicular monoamine transporter 2 (VMAT2) and collapsing the pH gradient across the vesicular membrane (Sulzer and Rayport, 1990; Sulzer et al., 1995; Brown et al., 2000). In addition, METH inhibits monoamine metabolism *via* inhibition of monoamine oxidase (Suzuki et al., 1980; Egashira and Yamanaka, 1993; Santillo, 2014). The net result of these actions is an increase in intracellular levels of cytoplasmic DA and other monoamines. Low pH within the DA storage vesicles keeps DA from autoxidation. METH also inhibits and triggers a reversal of the monoamine transporters, leading to massive release of monoamines into the synaptic cleft (Volz et al., 2007; Yamamoto et al., 2010). The net result of this METH action is overstimulation of the monoaminergic pathways in the central and peripheral nervous system that can lead to severe dysfunction or even neuronal degeneration in several brain areas, including the striatum, prefrontal cortex (PFC) and hippocampus (Volz et al., 2007; Yamamoto et al.,

2010). In addition, acting via the striato-nigro-thalamo-cortical loop, METH triggers an increase in glutamate (GLU) in the striatum, which results in excitotoxicity at higher doses of the drug (Mark et al., 2004). METH has minimal effect as an agonist at postsynaptic DA receptors and it activates them indirectly via released DA. In addition to damaging DAergic and serotonergic terminals, METH also damages cell bodies in the striatum and few other brain areas (Cadet et al., 2003; Moratalla et al., 2015, for a review).

6. METH neurotoxicity in the CNS

6.1. What is neurotoxicity?

Neurotoxicity is most often defined as actual physical damage to neurons. Neurotoxicity can be more broadly defined as a permanent or reversible adverse effect of a substance on neuronal structure or function (definition used by Environment Protection Agency for regulatory purposes), causing loss of neuronal components, loss of entire neuron, histological signs of neuronal damage, and/or behavioral abnormalities. Consequently, throughout this review, we include under this term neuronal degeneration/damage and also alterations in neuronal structure, morphology and function. Available animal and human data critically evaluated by Kish and colleagues indicates that although medium-to-high doses of METH damage DAergic and 5HTergic neurons in experimental animals, recreational use of METH does not appear to damage (degenerate) these neurons in humans (reviewed in (Kish et al., 2017)). However, some human METH users suffer from persistent DA deficits as well as from brain structural and metabolic abnormalities (Cadet et al., 2003; Chang et al.,

2007; Berman et al., 2008; Hall et al., 2015) as well as from persistent mild cognitive impairments (Scott et al., 2007; Dean et al., 2013). In experimental animals, METH neurotoxicity is dose-dependent (Seiden and Sabol, 1996) whereas in humans there is not clear correlation between total METH consumed and cognitive impairments (discussed below). This; however, may be due to a variety of confounding factors characteristic for studies in humans. Recovery of monoaminergic markers does not exclude a possibility of degeneration of monoaminergic pathways as such damage may increase synthesis of monoaminergic markers and upregulation of function of monoaminergic signaling as observed in PD (Brotchie and Fitzer-Attas, 2009). These adaptive modifications, e.g. axonal sprouting, may result in abnormal functioning of neurons (Arkadir et al., 2014).

6.2. Clinical manifestations of METH neurotoxicity

There are numerous manifestations of METH neurotoxicity in the CNS, including cognitive and psychomotor impairments as well as mental illnesses. Per meta-analytic summary of seventeen cross-sectional studies, most common cognitive impairments in abstinent chronic METH users are impairments in episodic memory, executive function, language skills, and visuoconstructional abilities as well as decreased speed of information processing (Scott et al., 2007). Specifically, learning, executive function, and memory appear to be the most consistently impaired, followed by attention/working memory and overall motor function, while visuoconstruction impairments are inconsistently reported in the literature (Scott et al., 2007). In addition to the impairments reported above, the meta-analysis revealed that chronic METH users also

display impairments in fine motor skills. Another meta-analysis identified three regions of significant gray matter reduction in the temporal, frontal and parietal cortex as well as in the putamen in METH-dependent individuals as compared to healthy controls (Hall et al., 2015). The findings from several qualitative studies were mixed and sometimes contradictory (Nordahl et al., 2003; Cherner et al., 2010; Hart et al., 2012; Dean et al., 2013) but overall suggested that that chronic METH abuse causes a cognitive decline. Motor deficits in METH users typically do not involve alterations in gross motor skills (Moszczynska et al., 2004b); however, impaired gait (Volkow et al., 2001d) and increased risk for developing PD have been reported (Callaghan et al., 2010; Callaghan et al., 2012; Curtin et al., 2015; Todd et al., 2016). Other motor impairments include stereotypic behavior, choreoathetoid movements, and dyskinesias that in some cases can persist for long time after cessation of METH use (Rylander, 1972; Lundh and Tunving, 1981; Sperling and Horowitz, 1994; Morgan et al., 2004). Mental illnesses that can persist after cessation of chronic METH use include anxiety, depression, and psychosis (Tong et al., 2014). Psychosis develops more readily in drug users taking METH in high doses and for long periods of time; therefore, is regarded as a direct consequence of METH neurotoxicity by some scientists. Indeed, METH psychosis is related to the severity of other cognitive impairments, further suggesting that it is a manifestation of METH toxicity (Chen et al., 2015). An alternative hypothesis regarding METH-induced psychosis states that METH use triggers underlying psychosis or schizophrenia. In fact, the symptoms of METH-induced psychosis are like those observed in patients with schizophrenia (Zweben et al., 2004; McKetin et al., 2006). Of

note, formication is one of the specific manifestations of METH-induced paranoia or psychosis.

6.3. Molecular mechanisms and loci of METH neurotoxicity

6.3.1. METH neurotoxicity to DAergic and 5HTergic terminals in experimental animals

As aforementioned, METH enters DAergic terminals via the DAT and passive diffusion, and releases DA from the storage vesicles. Once in the cytoplasm, DA quickly autoxidizes, an event followed by the formation of several reactive oxygen species and DA quinones (Graham et al., 2008). These species trigger oxidative stress and damage to protein and lipid components within the DAergic terminals (Yamamoto and Zhu, 1998; Fitzmaurice et al., 2006; Park et al., 2006; Moszczynska and Yamamoto, 2011). The molecular mechanism(s) underlying METH neurotoxicity to 5HTergic terminals is not clear but is known to depend on DA (Johnson et al., 1987; Gross et al., 2011). METH-induced biochemical and structural changes in striatal monoaminergic terminals are dependent on normal DAergic functions. Specifically, DA D_1 and D_2 receptors antagonists were shown to attenuate the toxic effects of METH on DA and 5HT systems (Sonsalla et al., 1986; Xu et al., 2005). In addition to increasing DA, 5HT and NE, METH induces increased release of GLU in the striatum and other brain areas (Nash and Yamamoto, 1992; Rocher and Gardier, 2001), which contributes to the toxicity of the drug via excitotoxic pathway (Mark et al., 2004). Additional molecular mechanisms contributing to monoaminergic terminal degeneration are hyperthermia, mitochondrial dysfunction, inflammatory response, ubiquitin-proteasome system impairment, and impairment of axonal transport (Ali et al., 1994; Moszczynska and Yamamoto, 2011;

Killinger and Moszczynska, 2016) (reviewed in (Cadet et al., 2003; Yamamoto et al., 2010)).

In rats and non-human primates, high doses of binge or chronic METH cause selective degeneration of DAergic terminals in the striatum (Hotchkiss and Gibb, 1980; Ricaurte et al., 1982; Woolverton et al., 1989; Moszczynska et al., 1998; Harvey et al., 2000a), while sparing NEergic terminals (Wagner et al., 1980). METH damages DAergic terminals primarily in the striatum, whereas DAergic terminals in the PFC, hippocampus, olfactory bulb, hypothalamus, thalamus, perirhinal cortex, amygdala, and nucleus accumbens are minimally affected or unaffected (Morgan and Gibb, 1980; Ricaurte et al., 1980; Wagner et al., 1980; Eisch et al., 1992; Broening et al., 1997; Harvey et al., 2000a; Guilarte et al., 2003; Anderson and Itzhak, 2006; Granado et al., 2010; Chuang et al., 2011). In contrast to DA terminals, 5HT terminals in various brain regions including the hippocampus, PFC, amygdala, and striatum are similarly sensitive to the toxic effects of METH (Morgan and Gibb, 1980; Ricaurte et al., 1980; Seiden et al., 1988). METH-induced changes in the hippocampus and PFC are particularly important given their role in learning, memory and executive functioning.

At the molecular level, METH neurotoxicity to DAergic and 5HTergic terminals is manifested by persistent (long lasting after METH cessation) reductions in DAergic and 5HTergic markers (DA, 5HT and their metabolites, DA and serotonin transporters (DAT and SERT), VMAT2, tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH)) (Wagner et al., 1980; Preston et al., 1985; Sonsalla et al., 1986; Mooney et al., 1994; Broening et al., 1997; Harvey et al., 2000b), morphological and structural abnormalities (e.g. swollen axons) (Lorez, 1981; Ricaurte et al., 1982; Sharma and Kiyatkin, 2009) as

well as microglial activation and gliosis (Pu et al., 1994; Thomas et al., 2004). It is worth noting that the effect of METH exposure in rodents depends partly on the pattern of exposure. Binge exposure typically results in more severe or longer-lasting effects (including reductions in DAergic function) than a chronic model (Keller et al., 2011; Kesby et al., 2017) of comparable cumulative dose, suggesting development of tolerance to METH toxic effects. To some extent, the loss of DAT, TH, DA and its metabolites is due to a physical loss of axons (Bowyer and Schmued, 2006). However, extended abstinence from METH results in recovery of these DAergic markers in experimental animals and humans (Bowyer et al., 1992; Friedman et al., 1998; Cass and Manning, 1999; Harvey et al., 2000b; Volkow et al., 2001b; Volkow et al., 2015a), suggesting compensatory changes within the nigrostriatal DA pathway.

6.3.2. METH neurotoxicity to neuronal perikarya in experimental animals

In rats and non-human primates, METH appears to spare DA cell bodies in the substantia nigra *pars compacta* (SNc) from which they originate (Hotchkiss and Gibb, 1980; Ricaurte et al., 1982; Woolverton et al., 1989; Moszczynska et al., 1998; Harvey et al., 2000a; Harvey et al., 2009). In mice, DA neurons of the SNc degenerate (Deng et al., 2001; Zhu et al., 2005; Ares-Santos et al., 2013) as do multiple other brain areas (Yu et al., 2004; Xu et al., 2005). Administration of high METH doses can also result in toxicity to neuronal, or glial, perikarya in the striatum, parietal cortex, and amygdala, which are GABAergic, cholinergic and/or GLUergic neurons (Pu et al., 1994; Jayanthi et al., 2004; Xu et al., 2005; Kuczenski et al., 2007; Simoes et al., 2007; Beauvais et al., 2011; Fujikawa et al., 2016; Thanos et al., 2016). METH toxicity in cell bodies is

manifested by the presence of apoptosis and necrosis, astrocyte or microglia activation as well as by abnormal alterations in cell morphology or structure. METH-induced apoptosis of striatal GABA neurons and frontal cortical neurons depends on GLU and DA and involves mitochondrial dysfunction, endoplasmic reticulum stress and calcium-influx activation of the calpain pathway (Deng et al., 2001; Jayanthi et al., 2004; Warren et al., 2005; Warren et al., 2007; Tokunaga et al., 2008; Gold et al., 2009; Beauvais et al., 2011; Shiba et al., 2011). In the hippocampus, in addition to inducing apoptosis, which is often followed by blebbing of pyramidal neuron dendrites and death of pyramidal neurons and granular cells, METH inhibits neurogenesis and reduces hippocampal volume (Teuchert-Noodt et al., 2000; Deng et al., 2001; Thompson et al., 2004; Kuczenski et al., 2007; Mandyam et al., 2008; Kochman et al., 2009; Hori et al., 2010). The cortical damage produced by METH occurs via an excitotoxic mechanism (Eisch et al., 1996). METH-induced glial cells death is mediated via oxidative stress and mitochondrial damage pathway (Stadlin et al., 1998; Jumnongprakhon et al., 2014).

6.3.3. Cognitive impairments in experimental animals

A common animal model of METH toxicity is the binge exposure model. Animals exposed to single-day high dose exposure paradigms show a host of behavioral abnormalities, including object (Schroder et al., 2003; Belcher et al., 2005; He et al., 2006; Herring et al., 2008; Siegel et al., 2010) and spatial (Acevedo et al., 2007; Vorhees et al., 2009) memory impairments. Issues with more executive tasks have also been noted, including reversal learning (Izquierdo et al., 2010) and working memory (Mizoguchi et al., 2011). These memory impairments, at least, have also been observed

in repeated exposure ("chronic") paradigms; rodents exposed to chronic METH have displayed impairments in both object (Ito et al., 2007; Arai et al., 2009; Noda et al., 2010) and working (Nagai et al., 2007; Lee et al., 2011) memories. These impairments persist for an extended period (North et al., 2013; Braren et al., 2014), strongly suggesting that these deficits are the result of toxicity rather than withdrawal.

An interesting issue with these models of METH toxicity is evidence that prior exposure to METH provides a protective effect against some of the toxicity observed in binge and chronic models (e.g., Belcher et al., 2008), which suggests tolerance to METH neurotoxicity in animal and human METH abuse, which typically features escalating usage (Simon et al., 2002). However, animals given prolonged access to METH over an extended amount of time in a self-administration paradigm, resulting in a stepwise increase in use, do still show behavioral impairments consistent with human METH toxicity literature. Rodents that self-administer METH display impaired memory function (Recinto et al., 2012; Le Cozannet et al., 2013), especially object recognition performance (Rogers et al., 2008; Reichel et al., 2011; Reichel et al., 2012; Reichel and See, 2012; Scofield et al., 2015). Impaired object recognition in rodents primarily implicates the perirhinal cortex, but may also involve impaired hippocampal function (Olarte-Sanchez et al., 2015). Interestingly, these effects persist even in the face of an escalating dose regimen (Rogers et al., 2008; Reichel et al., 2011) mimicking the pre-exposure, which provided protective effects in Belcher et al., 2008. This lends increased validity to the self-administration model and further suggests that the cognitive symptoms observed in human subjects may indeed be the result of METH toxicity, rather than withdrawal.

Self-administration models have also demonstrated impairments to spatial memory tasks, including object location (Le Cozannet et al., 2013) and Y-maze tasks (Recinto et al., 2012), more directly implicating the impairments to the hippocampus. Like human METH toxicity, self-administration in rodents also results in impaired attentional set shifting, a PFC mediated executive/attentional task analogous to aspects of the human Wisconsin Card Sorting Task (Parsegian et al., 2011). In addition, rats trained to self-administer METH display impaired reversal learning in a visual attention-set task (Cox et al., 2016), a measure of cognitive flexibility ,further implicating dysregulation of the PFC and larger frontal circuits. While there is some evidence that METH self-administration results in prolonged impulsivity, these results were transient and should more appropriately be viewed as the result of METH withdrawal (Dalley et al., 2007). Similarly, as seen with humans (discussed below) METH self-administration produces a depressive-like and anxiety-like phenotype in rats during early post-exposure periods (Jang et al., 2013) consistent with METH withdrawal. When taken together, there is significant evidence that METH self-administration results in impairments to multiple cognitive systems, including memory (both spatial and object) and executive function (including attention, planning, and flexibility). It is worth noting that the impairments in inhibitory control at least have also been observed in non-human primate models of METH abuse (Groman et al., 2013; Kangas and Bergman, 2016).

6.3.4. Molecular markers of METH neurotoxicity in human METH users

The METH-mediated neurotoxic effects and their manifestation in METH users are similar to those observed in experimental animals; however, actual degeneration of

DAergic and 5HTergic nerve terminals, or cell bodies, is questionable (Kish et al., 2017). Nevertheless, most human METH users suffer from persistent DA deficits as well as from brain structural and metabolic abnormalities in the same brain areas as those affected by METH in experimental animals, suggesting dysregulation of these areas. Studies in autopsied human brains determined that three DAergic markers (DA, DAT and TH, but not in 3,4-dihydroxyphenylalanine decarboxylase and VMAT2) are decreased in the caudate, putamen, and nucleus accumbens in METH users compared to matched controls; DA deficit was more pronounced in the cognition mediating caudate than in the motor activity mediating putamen (Wilson et al., 1996; Moszczynska et al., 2004b; Kitamura et al., 2007). *In vivo* imaging techniques (PET and MRI) revealed reduced density of DAT (McCann et al., 1998; Volkow et al., 2001b; Volkow et al., 2001d; Sekine et al., 2003; Volkow et al., 2015a), dopamine D2 receptor (Volkow et al., 2001a), VMAT2 (Johanson et al., 2006; Kitamura et al., 2007) (but see (Boileau et al., 2008; Boileau et al., 2016)) SERT (Sekine et al., 2006; Kish et al., 2009), and GLU+glutamine (Ernst and Chang, 2008; O'Neill et al., 2015) in abstinent (weeks-months) human abusers of METH. The DAT was decreased in the orbitofrontal cortex, dorsolateral prefrontal cortex, dorsal striatum, nucleus accumbens and amygdala whereas the SERT was decreased in the orbitofrontal and occipital cortices the midbrain, thalamus, caudate, putamen, cerebral cortex, and cerebellum. Several neuronal metabolites or their ratios were found altered (increased or decreased) in basal ganglia, anterior cingulate and frontal cortex white matter of METH users using proton magnetic resonance spectroscopy (MRS) (Ernst et al., 2000; Nordahl et al., 2002; Sekine et al., 2002; Chang et al., 2005b; Nordahl et al., 2005). Measurement of

glucose metabolism in METH users by PET has observed increased global metabolism but showed lower relative levels of striatal and thalamic metabolism (Volkow et al., 2001c; Wang et al., 2004; Chang et al., 2007). Other CNS abnormalities detected in brains of abstinent METH users were apoptosis and microglial activation as measured by PET (Sekine et al., 2008). Microglial activation was detected in the midbrain, striatum, thalamus, orbitofrontal cortex, and insular cortex and correlated inversely with the duration of methamphetamine abstinence in the midbrain, striatum, and thalamus. On the other hand, METH users who died of dug overdose did not displayed microglial activation or apoptosis (Kitamura et al., 2010). Postmortem tissue studies also did not detect significant activation of astrocytes in METH users (Kitamura et al., 2010; Tong et al., 2014). However, oxidative stress and decreased phospholipid metabolism were detected in autopsied striatum of chronic METH users (Ross et al., 2002; Mirecki et al., 2004; Fitzmaurice et al., 2006).

Several structural abnormalities (grey matter volume, fiber structure/connectivity) were detected in a variety of affected areas comprehensively reviewed by several groups (Berman et al., 2008; Tobias et al., 2010; Dean et al., 2015; London et al., 2015). Specifically, grey matter deficits were present in cingulate, limbic and paralimbic cortex, and hippocampus, while white matter was hyperthophic in temporal and occipital cortex. In abstinent METH users, grey matter was smaller in insular and frontal cortex, while in the dorsal striatum, nucleus accumbens and globus pallidus it was enlarged. White matter and grey matter abnormalities were detected in the are of PFC and hippocampal formation As in rodents, the frontal cortex was affected by METH exposure, as smaller medial PFC volumes have been detected in METH and

amphetamine users, which correlated with errors in the WCS test (Kim et al., 2006; Daumann et al., 2011). Reductions in grey matter volume the cingulate cortex, along with corresponding impairments to glucose metabolism negatively correlated with task error rates in METH users (London et al., 2005). The substantia nigra *pars compacta* also had abnormal morphology in METH users (Todd et al., 2013). These neuronal alterations, specifically alterations to mesolimbic, prefrontal, hippocampal, and nigrostriatal structures have been shown to correlate with behavioral neurological consequences of METH neurotoxicity (Table 1).

6.3.5. Behavioral markers of METH neurotoxicity in human METH users

There is evidence that METH abusers display altered reward preference (Monterosso et al., 2007; Hoffman et al., 2008; Schwartz et al., 2010), indicated by an increased preference for smaller immediate rewards over greater delayed rewards. This task constitutes a type of impulsivity thought to both precipitate and result from drug use (de Wit, 2009). This preference for immediate reward is compounded by evidence suggesting an increase in risky decision making (Kohno et al., 2014), possibly the result of a circuit-based bias towards reward, as well as increased drug craving/anxiety (Yuan et al., 2015). This craving at least, is likely related to decreased striatal DA, which in turn has been shown to precipitate METH relapse in humans (Wang et al., 2012). Taken as a whole, there is evidence that METH toxicity results in lasting functional alterations to human decision-making, impulsivity, and reward circuitry.

As aforementioned, there is extensive evidence that human METH users display impairments to executive functioning (particularly as assessed by the Wisconsin Card

Sorting Task; Simon et al., 2002; Kim et al., 2005; Monterosso et al., 2005; Kim et al., 2009; Rendell et al., 2009; Simon et al., 2010). Considering this impairment, it is unsurprising that several studies had found that METH abusers showcase impairments in top-down inhibitory tasks (e.g., the Stroop task), further indicative of impaired executive control (Simon et al., 2000; Fillmore and Rush, 2002; Salo et al., 2002; Salo et al., 2009; Weafer et al., 2014). These impairments strongly implicate structural disruption of the PFC and greater executive circuits (Tabibnia et al., 2011), indicating that these impairments are likely due to METH toxicity rather than pharmacological withdrawal. This is consistent with animal literature data suggesting that METH toxicity results in functional impairments in the PFC (Kuczenski et al., 2007). In addition, these individuals show reductions in overall task processing speed (Simon et al., 2000; Kalechstein et al., 2003), reaction time (Lawton‐Craddock et al., 2003), and motor speed (Volkow et al., 2001d).

METH abusers consistently show dysfunction in learning (McKetin and Mattick, 1998; Kalechstein et al., 2003; Henry et al., 2009) and memory tasks (Boileau et al., 2008; Rendell et al., 2009). This is not surprising, as METH abusers have shown reductions in hippocampal volume (Thompson et al., 2004) and alterations to functional connectivity between the midbrain and hippocampus (Kohno et al., 2014). Studies have also noted impairments to working memory (Chang et al., 2002; Gonzalez et al., 2007; Rendell et al., 2009). This is interesting, as recent evidence has suggested that cognitive training using the N-back task may be an effective adjunct for treating the symptoms of METH toxicity (Brooks et al., 2016). Unlike spatial or object memory tasks, working memory is a global process, involving multiple circuits (see D'Esposito and

Postle, 2015 for a review). However, the dorsolateral PFC is particularly important in working memory function (Rogasch et al., 2015), and evidence suggests that METH abusers show decreased PFC activity compared to healthy controls (Salo et al., 2013).

As previously indicated METH users also display affective symptoms, including depression (London et al., 2004), psychotic symptoms (Sekine et al., 2002; Sekine et al., 2003), impulsivity (Andres et al., 2016), or aggressive behavior (Sekine et al., 2006). Sensitization to METH psychosis could be functionally related to neurotoxicity because psychiatric symptoms correlated inversely with DAT density in the striatum and PFC (Sekine et al., 2003). With extended abstinence from METH, METH neurotoxicity-associated brain abnormalities and neurological problems may partially recover (McCann et al., 1998; Volkow et al., 2001d; Chang et al., 2007). Some papers have suggested that this is particularly true for the cognitive aspects of METH toxicity (Iudicello et al., 2010). However, several other papers have shown persistent deficits in cognitive skills with little improvement over time (Volkow et al., 2001d; Johanson et al., 2006). This discrepancy is likely related to the individual factors that underlie METH use (use pattern, dosage; genetics, age, demographics, education, poly-drug use). As such, cognitive recovery from METH toxicity is an open and ongoing research topic. Some manifestations of METH neurotoxicity and related molecular mechanisms are presented in Table 1. However, the relationship between METH toxicity and cognitive impairments is not necessarily clear: prior work has suggested that METH use parameters predict motor impairment but not cognitive impairment, suggesting that personal vulnerabilities are involved in the cognitive symptoms of METH toxicity (Cherner et al., 2010). This is consistent with the aforementioned discrepancy in recovery following METH toxicity.

As previously discussed, METH toxicity results in a host of effects at the molecular level, including a decline in DAergic markers similar to the pathology of PD. These changes, while not causative for PD *per se* do suggest similarities between METH toxicity and PD pathogenesis (Moszczynska et al., 2004a). For example, humans with a history of stimulant use have abnormal morphology of the SN that is itself consistent with increased risk for PD (Todd et al., 2013; Todd et al., 2016). In light of this, it appears that there are several phenotypic responses to METH neurotoxicity, depending in part of the frequency and magnitude of use, with some individuals seeing recovery, others stabilized at their current impairment, and still others experiencing further damage/degeneration.

There are marked similarities between human and animal studies of METH toxicity. These studies report similar behavioral effects, including affective dysregulation (London et al., 2004; McGregor et al., 2005; Jang et al., 2013; Silva et al., 2014), memory impairment (Recinto et al., 2012; Braren et al., 2014; Brooks et al., 2016), and disruption of executive functioning (Izquierdo et al., 2010; Kohno et al., 2014). It appears that the mechanisms for these impairments are relatively well conserved between species, as well—humans and animals showcase reductions in DAergic and 5HTergic signaling (Wilson et al., 1996; Friedman et al., 1998; Graham et al., 2008; Kish et al., 2009; Hensleigh and Pritchard, 2015), and do so in a variety of brain regions including the striatum, frontal cortex, and hippocampus. Both species seem to show conflicting evidence for spontaneous recovery of lost function (Johanson et al., 2006). There are, however, functional differences between the two species. First, as previously noted, while mice remain a popular tool for assaying METH toxicity, mice see

widespread cell loss not seen in humans or rats (Deng et al., 2001), which limits the direct translational value of this model. Second, though there have been advances in the field in the last 10 years, many studies of animal toxicity still rely on single-day binge exposure models, which (as discussed above) can have different outcomes that longer chronic models that feature a gradual build-up in dosing to better mimic human abuse (Graham et al., 2008). Despite these shortcomings, animal research into METH toxicity has suggested several promising targets for remediating cognitive impairments observed in METH toxicity.

Molecular markers (e.g. DAT, GLU) may return to normal or close to normal levels during protracted abstinence but may not be paralleled by normalization of neurological problems (Volkow et al., 2001b; O'Neill et al., 2015; Volkow et al., 2015b). Several cross-sectional and longitunal studies have indicated that cognitive impairments partially recover with prolonged abstinence (Volkow et al., 2001b; Wang et al., 2004; Jaffe et al., 2005; Kim et al., 2006; Salo et al., 2009) or recover in some but not all individuals (Iudicello et al., 2010), with a potential exception of episodic memory and cognitive inhibition (Johanson et al., 2006). For example, prefrontal grey matter volume was more decreased in early than late abstinence from METH but still significantly lower than in the control subjects (Kim et al., 2006). Lower metabolism in the striatum (most accentuated in the caudate and nucleus accumbens) was detected in METH users withdrawn from the drug at least for a year (Wang et al., 2004). These changes could be associated with the effect of METH on episodic memory and executive functions. Among other indices of METH neurotoxicity, putamen and globus pallidus enlargement lasted for at least two years (Chang et al., 2005a). As smaller putamen volume was

associated with poorer performance on verbal fluency and dexterity test its enlarged volume was hypothesized to represent a compensatory response to the METH exposure driven by inflammation (Chang et al., 2005a). In support, microglial activation was long-lasting (~2 years on average) in several brain areas in abstinent METH users, including the striatum (Sekine et al., 2008). Increased grey matter volume might also result from *de novo* axonal sprouting (Arkadir et al., 2014) or neuronal cell swelling (Rungta et al., 2015).

7. Implications of METH neurotoxicity for treatment

While there is some evidence for spontaneous recovery of cognitive functioning following METH neurotoxicity, most evidence indicates that cognitive impairments resulting from METH toxicity, albeit mild and variable between individuals, are long lasting, if not permanent. These impairments interfere with their every day functioning (e.g., financial functioning, communication, transportation), health and well being, including taking medications and, importantly, adherence to anti-addiction programs (Henry et al., 2010). Moreover, METH-dependent participants with mild or greater cognitive deficits are more likely to be unemployed than the cognitively unimpaired individuals (Weber et al., 2012). Some compensatory mechanisms might not be beneficial for brain function (e.g. axonal sprouting (Arkadir et al., 2014)). Importantly, strength of craving for METH can be reduced by cognitive strategies (Lopez et al., 2015); therefore, improvement of cognitive abilities of abstinent METH is important.

7.1. Current treatments of cognitive impairments

While there are treatments for the individual symptoms of METH neurotoxicity, there are no current interventions for the underlying pathology. However, there are several promising lines of inquiry. Some potential interventions for cognitive impairment have focused on physical interventions. For example, there is evidence that electroconvulsive shock restores object-related memory in mice in a chronic METH paradigm (Chao et al., 2012). A separate group has shown that cognitive training may remediate some of the executive impairments in human METH users (Brooks et al., 2016). Most interventions, however, are pharmacological, and focus on manipulating the DAergic and 5HTergic systems. Silibinin, a flavonoid with 5HTergic and DAergic releasing properties, has been shown to increase cognitive performance on memory tasks in METH-treated mice (Lu et al., 2010), possibly through inhibition of MAO. Likewise, ZSET1446, which increases extracellular acetylcholine, has been shown to reverse memory impairments induced by METH toxicity (Ito et al., 2007), most likely through indirect activation of D1 dopamine receptors. The stimulant modafinil has been the subject of several clinical trials as a possible intervention for METH dependence and as a booster of cognitive performance in METH dependent individuals. However, it may also be beneficial in the treatment of METH toxicity, as modafinil has been shown to improve working memory performance (N-back task) in abstinent METH-dependent individuals who showed baseline impairments in working memory indicative of toxicity (Kalechstein et al., 2010). This report is corroborated by animal studies showing that modafinil reverses object memory impairments induced by sub-chronic METH treatment in mice (González et al., 2014), possibly by restoring ERK signaling in the PFC. These results appear to be independent of GLUergic signaling (Reichel et al., 2014), and may extend to protecting against other

neurological markers of METH toxicity (Raineri et al., 2012). While these methods show promise, more and larger clinical trials are required to demonstrate their efficacy in reversing or protecting against METH neurotoxicity.

7.2. Potential new approaches for treatment of METH-dependent individuals

Neurobehavioral abnormalities in METH users vary between individuals with use pattern, dosage, age, demographics, education, poly-drug use, and genetic factors. Moreover, they may be linked to pre-existing abnormalities (68 in Cadet). Many molecular mechanisms underlying cognitive impairments in METH-dependent individuals are different in early than late abstinence. Consequently, treatment of METH users should be developed on the individual basis and involve neuropsychological and neuroimaging assessments as well as careful examination of health histories and histories of drug use. This approach will allow for the development of specific approaches that would the most benefit each individual. Therapeutic approaches may be the most effective if combining cognitive or pharmacological treatments. For example, currently used treatments with cognitive-behavior therapy and contingency management could be combined with administration of DA, 5HT and acetycholine releasing pharmaceuticals (see section 7.1 for details). METH neurotoxicity is not progressive in nature and takes place during administration of the drug. In experimental animals, only a few compounds were able to attenuate METH neurotoxicity when administered *after* METH binge, namely DA uptake inhibitors, nicotinic receptor ligand lobeline (Eyerman and Yamamoto, 2005), and trophic factors (e.g. GDNF) (Cass et al., 2000); they are potential candidates for treatment of cognitive impairments in METH-

dependent patients. Another options include stimulation of endogenous defense/repair mechanism (e.g. DNA repair (Brooks, 2002) as well as protein and mitochondria repair via degradation pathways (Castino et al., 2008; Narendra et al., 2008; Liu et al., 2013)), administration of anti-inflammatory medications (Asanuma et al., 2003), reversal of epigenetic changes induced by METH (epigenetic changes are triggered by neurotoxic METH doses (Cadet et al., 2014; Moszczynska et al., 2015), and/or targeted delivery of ion gated Na+ channel inhibitor (neuronal swelling, which may contribute to enlarged brain areas, depends on Na^+ and Cl^- influx (Rungta et al., 2015)); however, benefits of these approaches remained to be tested.

8. Summary

METH dependence is a chronic and debilitating illness with no current pharmacological treatment. Chronic METH users often co-abuse other drugs. Therefore, it is imperative to understand molecular mechanisms and manifestations of METH neurotoxicity as well as drug-drug interaction between METH and other drugs that may have fatal consequences. The bulk of clinical efforts are focused on METH dependence, however this review has demonstrated that the toxic effects of METH are serious, long lasting and presently have no empirically validated remediation. Few clinical trials have investigated or intervened in the cognitive-behavioral consequences of METH toxicity directly. This is interesting, as there is a wealth of preclinical and human-subjects data suggesting both physiological and neurochemical targets for intervention. This review has demonstrated that METH toxicity is primarily one of dysfunction of neurotransmission in the striatum, PFC, and hippocampus. Additionally,

we have argued that while spontaneous remission of cognitive impairments may be possible, there is far more evidence that METH toxicity results in either long-lasting deficit or further decline into PD pathology. There is a present need for interventions targeted specifically at the toxic loss of DA and 5-HT systems and the broad spectrum cognitive impairments they underpin.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: A. Moszczynska and S.P. Callan.

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Table 1. Manifestations of METH neurotoxicity in human subjects *vs.* experimental animals, brain areas mediating the manifestations and underlying molecular mechanisms. The focus is on the studies that compared early (up to 6 months) to late abstinence (>6 months) and the studies that compared clinical manifestations with molecular or morphological changes in the brain.

Manifestation	**Dose**	**Effect and Molecular Mechanism (Current use/ Early abstinence)**	**Effect and Molecular Mechanism (Late abstinence)**	**Human Studies**	**Animal Studies**
Anxiety, Dysphoria	> 30 mg	▲ Adrenergic alpha1 stimulation (PFC) ▲5-HT receptor, DA receptor stimulation (striatum) Altered glucose metabolism (multiple areas)	▼ DA and 5-HT neurotransmission	(Martin et al., 1971; Tong et al., 2003; London et al., 2004; Filip et al., 2005; Newton et al., 2005; Berridge, 2006)	(Jang et al., 2013)
Elevated body temperature	> 30 mg	▲ DA, serotonin, noradrenaline release (hypothalamus)		(Martin et al., 1971)	(Bowyer et al., 1992; Bowyer et al., 1994)

Talkativeness	> 50 mg	▲ Anterior cingulate cortex, ventral striatum activity		(Bell, 1973; Vollm et al., 2004)	
Paranoia / Psychosis	> 55 mg	▲ DA release, D2 receptor, DAT dysfunction (striatum), ▼ Grey matter (anterior PFC, left perisylvian structures), ▼ White matter volume (OFC, amygdala, hippocampus)		(Bell, 1973; Ujike et al., 2009; Orikabe et al., 2011; Aoki et al., 2013; Mash, 2016)	
Hallucinations (auditory, visual)	> 55 mg	Auditory: ▲ thalamus, ventral striatum activity. Visual: ▲ paralimbic system, primary motor cortices activity		(Bell, 1973; Silbersweig et al., 1995; Drevets et al., 2001)	
Stereotypy (punding)	High	D1/D2 receptor imbalance (dorsal striatum)		(Rylander, 1972)	(Ujike et al., 1989)
Choreoathetosis, Dyskinesia	High	▲D2 receptor activity (dorsal striatum)		(Sperling and Horowitz, 1994)	(Ujike et al., 1989)
Working memory	2-5 g/week	▼Working Memory	▼Working Memory	(Ornstein et al., 2000; Chang et al., 2002; Scott	(Mizoguchi et al., 2011)

			▼ Dorsolateral PFC activity, ▼ regional CBF (putamen, insula & parietal cortex)	et al., 2007; Rendell et al., 2009)	
Learning	2-5 g/week	▼Learning ▼Hippocampal volume ▼Frontal / Cingulate circuitry	▼Learning	(Scott et al., 2007; Henry et al., 2009; Ghahremani et al., 2011)	(Gutierrez et al., 2017)
Recall Memory	~3 g/week, 0.25-1.6 g/day	▼ Memory ▼ Hippocampal volume ▼ Hippocampal grey matter ▼ DAT, VMAT2 (striatum) ▼ Glucose metabolism (thalamus, striatum)	▼ Memory (▲ Memory & ▲ Thalamic glucose metabolism *vs.* short abstinence)	(Rylander, 1969; Volkow et al., 2001b; Thompson et al., 2004; Wang et al., 2004; Johanson et. 2006)	(Schroder et al., 2003; He et al., 2006; Reichel et al., 2012; Thanos et al., 2016)
Executive function	>50 g cumula-tive use	▼ Executive functioning ▼ Decision Making ▼ PFC activation ▼ Frontal DAT	▲Executive f. (*vs.* short abstinence) ▼Frontal grey matter (▲ *vs.*	(Paulus et al., 2002; Sim et al., 2002; Kim et al., 2005; London et al., 2005; Kim et al., 2006;	(Izquierdo et al., 2010; Parsegian et al., 2011)

		▼ Frontal white matter ▼ Grey matter volume (PFC) ▼ Glucose metabolism (PFC white matter) ▼ Frontal white matter ▼ SERT (orbitofrontal) ▼ Auditory vigilance ▲Parietal glucose metabolism ▼ Cingulate glucose metabolism	short abstinence) ▼ Frontal glucose metabolism ▼ DAT (▲ *vs.* short abstinence) ▼ Attention ▼NAA-Cr ▲ Cho-NAA (cingulate)	Chou et al., 2007; Chung et al., 2007; Salo et al., 2007; Scott et al., 2007; Berman et al., 2008; Han et al., 2008; Kish et al., 2009; Salo et al., 2009; Nestor et al., 2011; Uhlmann et al., 2016)	
Reward preference / Impulsivity	>0.5 g/day	▼ Reward decision-making ▼ D2 receptor (striatum) ▼ Prefrontal grey matter volume with ▲ Striatal grey matter volume ▲ Striatal volume	▲ Decision-making (*vs.* short abstinence)	(Jernigan et al., 2005; Monterosso et al., 2007; Hoffman et al., 2008; Wang et al., 2013; London et al., 2015)	(Richards et al., 1999; Dalley et al., 2007)
Motor skills	1.6 g/day	▼ D2 receptor (striatum) ▼ DAT (striatum)	▼ Motor (▲ *vs.* short abstinence)	(Volkow et al., 2001a; Volkow et al., 2001b;	(Wallace et al., 1999)

		▼ Glucose metabolism (thalamus) ▼ Glucose metabolism (caudate)	▲ Thalamic glucose metabolism	Wang et al., 2004; Cherner et al., 2010)	
Verbal skills	4.6 g/day	▼ Verbal fluency ▼ Putamen volume Dysregulation of temporal lobe	▼ Verbal fluency	(Chang et al., 2005; Scott et al., 2007; Chen et al., 2015) (Osipowicz et al., 2016)	
Information processing speed	1.0 g/day	▼ Processing speed ▼ White matter integrity (global)	▼ Processing speed	(Scott et al., 2007; Kalechstein et al., 2014) (Penke et al., 2010)	(Dalley et al., 2007)
Visuospatial ability	>0.5 g/day	▼ Visuospatial ability ▼ DAT and VMAT2 (striatum) ▼ Cerebral blood flow (striatal / parietal) ▲ Parietal cortex volume	▼ Visuospatial ability ▼ Cerebral blood flow (striatal / parietal)	(Lawrence et al., 2000; Chang et al., 2002; Kalechstein et al., 2003; Johanson et al., 2006; Scott et al., 2007)	

BOLD: Blood Oxygen Level Dependent activity; CBF: Cerebral Blood Flow; Cho-NAA: Choline *N*-acytl aspartate; DA: Dopamine; DAT: Dopamine Transporter; Glu/Gln: Glutamate and Glutamine; 5-HT: Serotonin Receptor; NAA-Cr: *N*-acetyl aspartate creatine and phosphocreatine; OFC: Orbitofrontal Cortex; PFC: Prefrontal Cortex; SERT: Serotonin Transporter; VMAT2: Vesicular Monoamine Transporter 2. ▲/▼: Increased / Decreased *vs.* control subjects or long abstinence *vs.* short abstinence (when indicated).