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The Effect of Methamphetamine Abuse on Brain Structure and Function

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I hereby certify that all material in this final year project which is
not my own work has been identified and that no work is included for
which a degree has already been conferred on me.

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Abstract

The great amount of METH abuse all over the world causes enormous social and criminal justice problems. In the human brain the abuse of METH causes implications on both structures and functions given rise to acute as well as long term symptoms. In this essay the effects of METH abuse is described in the manner of the drug mechanism such as the impact on neurotransmitters, structural deficits with decreased and increased volumes and the implication on attention, memory, decision making and emotions. Results from studies showing brain structural and cognitive impairments in METH abusers and in prenatal METH exposed children.

Keywords: METH, DAT, grey matter, white matter, cognitive skills

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1. Introduction

Methamphetamine (METH) is a highly addictive psychostimulant drug (Barr, Paneka & MacEwan, 2006), the abuse of which has reached epidemic proportions in western countries (Rose & Grant, 2008). A number of findings suggest that its chronic abuse can lead to serious cognitive, psychiatric and neurological impairments in the user and can have negative consequences on the development of children exposed to METH in utero as well as to children raised by parents addicted to METH (Rose & Grant, 2008). Moreover, METH toxication can be lethal (Kalasinsky, 2000). Currently there are no pharmacological treatments available to treat METH dependence (Aron & Paulus, 2007). In order to develop necessary treatments a greater understanding of the drug's mechanism of action and of the way its abuse can affect the brain of the user is needed.

The aim of the essay is to describe and discuss the effect of METH on brain structure and function. In what follows, first a brief overview of METH as a substance is given providing a description of the mechanism of its action. Next, the symptoms and consequences following acute and long- term abuse of METH are described. Then, studies investigating the effect of the drug on different brain structures are reviewed followed by the presentation of research results demonstrating which brain functions METH abuse can affect. The essay ends with a discussion bringing together all the diverse effects of METH abuse for a general evaluation.

2. Methamphetamine as a Substance

2.1. Background

Methamphetamine (METH) belongs to a group called “amphetamines” and was introduced in 1893, six years after the first compound in this group – amphetamine - was synthesized. The substances in this group have similar biological properties and structures. Although the illicit manufacture of the drug began already in the 1960s (Berma, O’Neill, Fears, Bartzokis, & London, 2008), it is the great expansion of the METH market in the 1980s that made it one of the most wide-spread illicit drugs of abuse and has developed into an epidemic across the world (Rose & Grant, 2008). One reason lying behind the wide-spread use of METH is its relative ease and low cost of synthesis (Cadet, Krasnova, Jayanthi, & Lyles, 2007). The most common precursors for producing METH in amateur laboratories are ephedrine and pseudoephedrine (Sulzer, Sonders, Poulsen & Galli, 2005) which can be found in nonprescription allergy medicines. Manuals for METH production are readily available in the internet (Barr et al., 2006).

The spread of the drug on such a large scale constitutes a serious social health care and criminal justice concern, both in the US and in Europe (Rose & Grant, 2008). Even though most of the production of METH occurs in East and South-East Asia and in Northern America, some of the METH labs can also be found in Europe, mostly in the Czech Republic, Slovakia and Lithuania. In 2006 alone, 154kg of METH was confiscated in 17 European countries, with greatest amounts discovered in Norway and Sweden. The finding that in many countries, such as Slovakia and the Czech Republic, METH users are the most frequent group of drug addicts seeking treatment, demonstrates the magnitude of the problem concerning METH abuse (EMCDDA, 2008).

2.2.Mechanism of Action

Methamphetamine (*N*-methyl-*O*-phenylisopropylamine) is a molecule with a strong influence on the sympathetic and the central nervous system (CNS). Although METH is structurally very similar to its parent molecule, amphetamine, it is more highly lipophilic, meaning that the drug crosses the blood brain barrier (BBB) more easily. The BBB is an astrocytic barrier between the blood vessels and nervous tissues in the CNS, protecting the brain from various chemical compounds and blood- bourne agents (Gazzaniga et al., 2002). Due to its ease in crossing the BBB, METH is more potent than amphetamine and is hence classified as a highly addictive psychostimulant drug (Barr et al., 2006).

The addictive nature of METH is achieved through its effect on the brain's reward system mediated by the rapid and sustained increases in monoamine (mostly dopamine) levels immediately after the drug has been consumed. After crossing the BBB and entering the brain, the drug enters monoaminergic terminals, interacts with the vesicular monoamine transporters, enters the vesicles and induces the release of monoamines from the vesicles after which the neurotransmitters are released into respective synaptic clefts (Cadet et al., 2007). In addition to the displacement of monoamines from the vesicles to the cytosol, METH also interferes with the plasma membrane transporters by reversing the transportation of neurotransmitters. Also, similarly to its group members cocaine and methylphenidate, METH blocks the activity of monoamine reuptake transporters. Moreover, the drug inhibits the activity of monoamine oxidase (MAO), a major enzyme responsible for the degradation of extracellular monoamines. Through all these mechanisms METH induces a significant increase in extracellular monoamine levels (Rose & Grant, 2008).

In a study conducted by Han et al. (2008) Addiction Severity Index, Wisconsin Card Sorting test, the NS (novel seeking) subscale in the Temperament and Character

Inventory was used with the attention to measure frontal executive functions, severity of addiction and novelty seeking (NS) temperament. The background thesis consisted of previous findings that frontal executive functions and NS temperamental nature patterns shows a relationship with the polymorphism of DA receptors (specifically type 2 (DRD2)–TaqI A1). The participants in the study was METH abusers and healthy controls, all generalized by (DRD2)–TaqI A1. Results shows that the METH abusers in contrast to the control group showed a higher score of NS and a lower score of frontal executive functions and also had a higher frequency of (DRD2)–TaqI A1 allele polymorphism. Overall the METH abusers with higher frequency of (DRD2)–TaqI A1 allele polymorphism, showed higher scores of NS and a lower score of frontal executive functions compared with the METH abuser that was not (DRD2)–TaqI A1 carrier. The authors draw the conclusion based on the findings that METH abusers might have a genetic and biogenic vulnerability for METH.

2.3.Symptoms of METH Use and Abuse

As a result of METH's mechanism of action, that is, a sudden increase in the levels of monoamines, after the acute use of the drug a person experiences increased well being characterized by such positive states as increased motivation, confidence, energy, alertness, and excitation. The drug also increases focused attention and decreases appetite (Rose & Grant, 2008). The negative side-effects of acute METH use include restlessness, insomnia, paranoia, anxiety, and behavior characterized by aggression and suspiciousness as well as irritability of unprovoked manner. Physiological METH use symptoms include increased blood pressure and heart rate as well as tremor, increase in body temperature,

sweating, loss of vision and headache (De La Garza, Shoptaw, & Newton 2008; Rose & Grant, 2008).

Chronic abuse of METH which is characterized by compulsive drug use and loss of control over drug intake induces neurobiological changes, such as reduced levels of dopamine and dopamine transporters (Lingford-Hughes, 2005). Chronic abuse of METH has been shown to correlate with increased aggressiveness (Sekine et al., 2006), deficits in manual dexterity, executive functions and short term memory (McCann et al., 2008; Hoffman et al., 2008) as well as with increased prevalence of anxiety and mood disorders (London et al., 2004).

Moreover, drugs that affect dopaminergic neurotransmission are known to have an impact on sleep. As such, METH use can cause dose-related insomnia and after chronic abuse, hypersomnia with an increased amount of nightmares. The drug also reduces sleep duration, increases sleep latency, decreases both rapid eye movement (REM) sleep and slow wave sleep (SWS) (Ashton, 2002).

3. The Effect of METH Abuse on Brain Structure

3.1. Grey and white matter alterations from METH abuse

Chronic METH abuse has been associated with a number of structural deficits in the human brain as indicated by alterations in both, the grey and white matter. Due to the drug primarily influencing dopaminergic neurotransmission, many magnetic resonance imaging (MRI) studies have demonstrated structural changes in brain areas rich in dopamine receptors. For example, Chang and colleagues showed (Chang et al., 2005) that compared to healthy controls, striatal structures, such as the putamen and globus pallidus, were enlarged in

the brains of abstinent METH abusers. As the cognitive functions of METH abusers with larger striatal structures were relatively normal, the authors of the study suggest that the enlarged putamen and globus pallidus might represent a compensatory response to maintain function. Possible mechanisms leading to the enlarged striatal structures include glial activation and inflammatory changes associated with METH-induced injury.

In addition to striatal regions, the drug has been demonstrated to affect other brain areas as well. Using magnetic resonance imaging (MRI) and computational brain mapping techniques Thompson and colleagues (Thompson et al., 2004) demonstrated a severe reduction in the volume of grey matter in the paralimbic, limbic and cingulate cortices of METH abusers, as compared to healthy controls. The loss of grey matter in the right cingulate cortex made the frontal horn of the right lateral ventricle to expand, a phenomenon often found in psychotic and neurodegenerative disorders. The METH abusers also had smaller hippocampal volumes, which correlated with poor memory performance on word-recall test. In addition, enlargement of the white matter was found in the temporal and occipital regions, close to areas with reduced grey matter. According to the authors, this kind of enlargement may result from altered myelination processes and adaptive glial changes (such as gliosis after neuronal damage).

Another study investigating white matter changes in METH abusers indicated a greater prevalence and severity of structural white matter abnormalities in METH abusers relative to healthy controls. However, these findings were only demonstrated in male but not in female METH abusers. According to the authors, the gender difference may be explained by the female hormone estrogen which can have a protective role against the neurotoxicity of METH (Bae et al., 2006)

Prenatal exposure of METH can have a detrimental effect on subsequent brain development. For example, Chang and colleagues (Chang et al., 2004) showed that in

comparison with healthy children, children exposed prenatally to METH had smaller subcortical brain volumes. More specifically, METH-exposure resulted in smaller caudate bilaterally, smaller hippocampal volumes, smaller globus pallidus and smaller putamen bilaterally (Chang et al., 2004).

Altogether, these findings suggest that METH can lead to significant abnormalities in the grey and white matter of the brains of the abusers. Moreover, in addition to having a negative influence on the brain structures of adult abusers, the drug can also damage the brain of children exposed to the substance prenatally. The next chapter will consider the neurotoxicity of METH which may be the mechanism underlying the structural changes seen in the brains of METH abusers.

3.2. Neurotoxicity of METH

The neurotoxicity of METH has been widely demonstrated in animals but an increasing number of studies indicate the detrimental effect of the drug on human abusers, as evidenced by abnormalities in dopaminergic and serotonergic function.

Many studies have demonstrated alterations in the number of dopamine transporters (DAT) in the striatum of METH abusers. For example, McCann and colleagues (McCann, Wong, Yokoi, Villemagne, Dannals, & Ricaurte, 1998) showed in a positron emission tomography (PET) study that there is reduced density of striatal DAT in methamphetamine abusers. The reduction of DAT density indicates reductions of dopamine in the axons and axon terminals as well as loss of dopamine terminals themselves. The latter is confirmed by findings from a postmortem study demonstrating great reductions in dopaminergic terminal markers in the brains of long-term METH abusers (Kitamura,

2009). Such an alteration may in time lead to neuropsychiatric conditions like Parkinson's disease (McCann et al., 1998). In addition to the striatum, significantly lower levels of DAT density in METH abusers have also been documented in the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC) as well as the amygdala (Sekine et al., 2003).

According to Volkow, Fowler, Wang, Baler, & Telang (2009) drug abusers have a decreased number of dopamine D2 receptors and reduced dopamine release. Reduced regional activity in the orbitofrontal cortex, cingulate gyrus and dorsolateral prefrontal cortex is associated with the decreased dopamine function. In the dlPFC, an area important for executive functions, the impact of decreased dopamine function results in impaired regulation of intentional actions.

In addition to dopaminergic cells and receptors, alterations in serotonergic cells in the brains of METH abusers have been studied. For example, Sekine and colleagues (2006) found that the serotonin transporter (5-HTT) density in global brain regions (such as thalamus, caudate, putamen, the midbrain, cerebellum and cerebral cortex) of METH abusing subjects, was significantly reduced in contrast to healthy controls. This reduction was shown to be negatively correlated with the duration of drug abuse, that is, the longer a person had used METH, the lower the density of 5-HTT in his or her brain. Furthermore, METH abusers showed increased levels of aggression. As such, by reducing the density of the serotonin transporter in the brain of drug abusers, METH can lead to increased levels of aggression.

As to the recovery from the neurotoxic damage induced by METH, it has been shown that abstinence from the drug can have a positive effect. Volkow and colleagues (Volkow et al., 2001) carried out a study in which they compared METH abusers with a protracted versus short abstinence period. The results revealed that the protracted abstinence abusers had a significantly higher DAT than the short abstinence group. This can be taken as

evidence that protracted abstinence can induce a significant recovery in DAT levels.

However, even if DAT levels seem to recover from METH abuse during protracted abstinence there seems to be limited, if any, recovery in neuropsychological functions.

Concerning the protective effects against METH neurotoxicity, a few studies have suggested that certain substances, such as N-acetyl-L-cysteine, ascorbic acid and vitamin E, have the ability to protect the destruction of monoaminergic terminals by the drug. Protection against METH toxicity can also be provided by selenium and melatonin (Cadet et al., 2007).

In sum, the studies reviewed above demonstrate that long-term METH abuse is neurotoxic to dopamine and serotonin neurons leading to several functional impairments associated with the drug abuse.

4. The Effect of METH Abuse on Brain Function

4.1. Decision -Making

Decision-making is a type of executive function thought to involve two distinct neural systems comprising specific brain structures dedicated to the processing of different aspects of the decision and its outcomes. The “cognitive” circuit involves the dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), posterior parietal cortex (PPC) and superior temporal gyrus (STG) and is thought to be concerned with the evaluation of outcomes and comparison of different alternatives for the outcomes. The “affective” circuit includes the amygdala, ventral striatum, ventrolateral prefrontal cortex (vlPFC), ventral anterior cingulate cortex (vACC) and the anterior insula and is specialized on the

salience and immediacy of the stimulus. It has been hypothesized that drug addicted individuals have difficulties in reflecting over the consequences of their decision and that they over evaluate immediate rewards. Results from studies suggest that addicts prefer to choose relatively smaller immediate gratifications over large delayed ones. For example, Hoffman and colleagues (Hoffman et al., 2008) made use of a delay discounting task in which subjects were required to evaluate immediate and delayed options, compare the choices and select preferred option as well as a motor response. The authors showed that in both, the healthy and METH abusers, hard choices induced greater cortical activation in several structures involved in cognitive and affective circuits involved in decision-making than easier choices. Drug abusers, however, exhibited more activation in these structures in easy tasks than did controls demonstrating that their brain activation levels do not differ to a great degree in these different conditions. The authors claim the finding suggests that METH abusers have difficulties in general decision-making, irrespective of the relative ease or difficulty or the choice.

Kim and colleagues (2005) used positron emission tomography (PET) and the Wisconsin card sorting test (WCST) to investigate changes in relative regional cerebral glucose metabolism during executive function. The WCST was used to measure such executive functions as strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responding.. Results showed that in comparison with a control group, METH abusers had reduced activation in the right prefrontal cortex and also reduced reaction times while performing the WCST task. Thus, METH users demonstrated frontal executive malfunction suggesting they have problems in applying earlier experiences to new situations (Salo, Ursu, Buonocore, Leamon, & Carter, 2009b).

4.2.Attention

Salo and colleagues (2007) carried out a study investigating attentional control and its relationship to the levels of brain metabolism in subjects with a diagnosis of lifetime methamphetamine dependence. Attentional control was tested by using the Stroop Attention Task and brain metabolite levels were measured by proton magnetic resonance spectroscopy (MRS). The results revealed that in comparison to healthy controls, the METH abusers exhibited reduced attentional control (as evidenced by increased Stroop interference). The reduction in attentional control was found to correlate with the levels of NAA (N-acetyl aspartate, a marker of cellular integrity that is found in processes of dendrites and axons in neurons) in anterior cingulate cortex (ACC), with subjects displaying impaired attentional control having low levels of NAA . The results are thought to indicate impaired anterior cingulate cortex (ACC) after long-term METH abuse and subsequent problems in attentional control.

In another study investigating cognitive control in METH addicts again Stroop test was administered while white matter microstructure in callosal regions was measured. The results showed that METH abusers performed worse on the Stroop test (as indicated by slower reaction times), which can be interpreted as reduced cognitive control. The microstructure of white matter in the genu of corpus callosum showed abnormalities and correlated with attentional deficits (Salo et al., 2009a)

In another study by Salo and colleagues (2008) a difference in implicit and explicit attentional processes caused by long term use of METH was demonstrated. Long-term METH abuse seems to have a greater impact on explicit attentional functions than implicit attention.

As to the effect of METH on prenatally exposed children, Chang and colleagues (2004) carried out a study using a combination of 11 neuropsychological tasks involving visual motor integration, motor function, sustained attention, verbal memory, visual attention/visual motor tasks, spatial memory, naming word/ retrieval, comprehension vocabulary, verbal fluency, intelligence and mood and a fMRI. The authors showed that children influenced by the drug *in utero* scored lower than healthy controls in a sustained attention task.

4.3. Memory

Rendell and colleagues (Rendell, Mazur, & Henry, 2009) set out to investigate prospective memory deficits, that is deficits in the memory for future intentions, in METH abstinence patients with a history of addiction. The subjects were required to perform tasks in a board game called “Virtual week”, a game in which a token is moved around the board with the circuits on the board representing a typical day including daily activities and the participant is supposed to make choices about those activities as well as to remember them. The results of the study demonstrated that people with a history of METH addiction had impairments in prospective memory suggesting that METH abuse leads to everyday memory deficits.

Further studies on memory deficits affected by METH use have been conducted. In one of them, Simon, Dacey, Glynn, Rwason & Ling (2004) investigated differences in memory among METH abusers at different stages of abuse. Three groups of subjects were studied: one group consisting of individuals with continuous abstinence, a second of people with initial abstinence but later relapse and the third of those with

continuous drug use. The group that performed best was the ones of continuing using subjects, worse in episodic memory test were the group with relapse group.

With the aim to investigate regional cerebral blood flow and cognitive skills in METH abusers, Chang and colleagues (Chang et al 2002) demonstrated that despite normal performance in most neuropsychological tests, METH abusers had slower reaction time in working memory tests relative to healthy controls. fMRI revealed that in the METH abuser the relative regional blood flow was increased in right posterior parietal region area, bilaterally in the left tempoparietal white matter and also the left occipital brain area, , though in right lateralparietal brain area, bilaterally in putamen cortex and insular cortex the blood flow was decreased.

4.4.Emotion

Studies have shown that the same networks ,both cortical and subcortical areas such as the amygdala, orbifrontal cortex, anterior cingulate cortex (ACC) and dIPFC, are activated and involved in emotion processing in healthy individuals also activated in drug abusers. Not only are the limbic regions activated, but they respond more intensely to drug-related cues than to other cues. For example, when addicts were shown drug related items and movies about drug use, they experienced intense craving for the drug. In addition, the exposure of drug-related cues activated cortical and subcortical regions known to be involved in the creation of emotional memory and emotional processing: the amygdala, the anterior cingulate cortex, orbifrontal cortex and dorsolateral prefrontal cortex (Grant et al. 1996).

Payer and colleagues (Payer et al., 2008) were interested whether METH abusers respond abnormally to social cues and if so, how is this related to cortical activations. In their study, subjects were required to carry out an affect matching tack while being

exposed to faces conveying different facial expressions, such as fear and anger. The results demonstrated no differences in the behavioral performance between the healthy controls and METH abusers. However, the METH subjects did exhibit more task-related activity in the dorsal anterior cingulate cortex than the control subjects. The task-related activity in control subjects was more in the ventrolateral prefrontal cortex, temporoparietal junction, right hemisphere fusiform gyrus, left hemisphere cuneus and both anterior and posterior temporal cortices. The findings thus indicate that the socially inappropriate behavior that can be seen in METH abuser can have a correlation to the cortical abnormalities found in this study.

Additional evidence for the effect of METH abuse on mood dysregulation comes from the study by London and colleagues (London et al., 2004). Two groups of women were used in this study, one group consisting of 17 abstinent METH abusers and one group consisting of 18 healthy controls. The subjects performed a vigilance task while mood and cerebral glucose metabolism was measured and then compared between the two groups. Global and relative metabolism in the amygdala, cerebellum, striatum, orbitofrontal cortex, cingulate cortex, insular cortex, lateral prefrontal cortex was measured by PET. Additionally, symptoms of anxiety and depression were measured by self-report questionnaires. The results revealed that compared to healthy controls, the regional glucose metabolism in METH abusers was reduced in the insula and in the anterior cingulate cortex, while it was higher in the orbitofrontal cortex, the cerebellum, the amygdala, ventral striatum, posterior and middle part of the cingulate cortex. As to the self-reported measures of mood, the METH abusers reported more symptoms of depression and anxiety. Thus, the findings suggest a relationship between mood disorders and brain abnormalities influenced by METH.

5. Discussion

Taken together studies made on METH use and abuse, the experience of the acute symptoms of METH use seems to be in a positive manner. The feeling of being alert and in a great mood, have the self confidence and a lot of energy with no feeling of depression or dejection (Rose & Grant, 2008) is probably a quite delightful sensation. Perhaps this might be one reason why the great amount of citizens abuses METH due to its negative costs.

When METH crosses the barrier, which is suppose to protect the brain from unwanted and toxic substances, it affects the CNS and the reward centre of the brain (Cadet et al., 2007), it is not out of the ordinary that states of mind in that moment is extreme positive. The state of mood is not the only factor affected by METH. What is happening inside the body and particularly in the brain has a more severe and long term effect in contrast to the short acute experience of the drug. According to the results in studies taken under investigation in this essay, brain structures does change in volume of METH abuse, leading to modifications of their functions. Whereas grey matter areas of the brain were decreased in volume in METH abusers just similar to brain abnormalities in neurodegenerative and psychotic disorders, while white matter areas was found to be increased in volume reminding of the process of neuronal injuring (Thompson et al, 2004) the changes are obvious. Not only is METH affecting the user per se, prenatal exposed children were proving to have smaller volume in a great among of brain structures with correlating cognitive deficits (Chang et al., 2004). Those changes point towards the affects METH causes and to what the dimension of damage are.

Moreover, transmitter substances like serotonin and dopamine do alter in the impact of METH. Density of DAT have been proven to be abated as a affect of METH use in several studies (Sekine et al, 2006, Kitamura, 2009, McCann et al., 1998, Volkow et al., 2009) and even though some recovery of DAT seems to be possible in abstinence METH abusers the neuropsychological functions does not seem to have the same capability (Volkow et al., 2001). Though a few studies claim that substances like selenium, melatonin and estrogen have a provided effect on METH, (Cadet et al., 2007, Bae et al., 2006).

Changes in brain structure have an impact on associational function and outcome. In cognitive skills like attention, decision making, memory and emotion, deficits have been correlated to METH use. Skills like apply former experiences to new situation (Salo et al. 2009b), reduced attentional control (Salo et al.,2007), lessened explicit attentional functions (Salo et al., 2008), prospective memory deficits (Rendell, Mazur, & Henry, 2009), working memory impairment (Chang et al 2002). Emotional alterations could also be seen in METH abusers pointing toward a greater ability for feeling depression or anxiety (London et al., 2004), aggression, suspiciousness and paranoia (De La Garza, Shoptaw, & Newton 2008; Rose & Grant, 2008). Brain activity when performing social cue tests differ in METH abusers even if the outcome does not show any signify differences from normal people's reactions (Payer et al., 2008).

Despite being considered as a highly addictive drug, METH is used in medical contexts for treating obesity as well as attention deficit hyperactivity disorder (ADHD) (Kish, 2008). METH is even used in the treatment for narcolepsy. Because of the drugs high potential to abuse that often leads to psychological and physiological addiction, it has been classified in Schedule II by Drug Enforcement Agency (DEA) meaning it is being highly controlled as a medical treatment (Berman et al., 2008).

Writing this essay which includes reading all those studies made in the area of METH use, have given a broader perspective of the harm the drug causes. Taken for example such a petite part as the subjects in each study consist of METH abusers and none of the studies mentioned any problems in finding the amount of participants indicates how common the drug is. Not only has this essay mentioned the highly addictive nature of the drug but also the long term affects both in behavior and brain structure.

As a end closer of this essay some future study proposal in the topic of METH use perhaps might be more directly to the core of treatment. Even though most of former studies based on METH use, are done in the approach of treatment, a suggestions is to investigate already mentioned substances and their ability for METH protection. Perhaps in the future a method to take control over the drug and the abuse can be offered.

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