Methamphetamine & The Brain
“A neuropsychiatrist investigates how drugs work and specifically how methamphetamine effects the brain.”

1. INTRODUCTION

The media item presented for analysis is a promotional clip (excerpt) from one of the episodes of the National Geographic Channel's new television mini-series Drugs Inc. and provides a summary into the illicit drug methamphetamine and its effects on the brain. According to the National Geographic, the series Drugs Inc. 'provides a 360 view of our society's most abused drugs: cocaine, methamphetamine, heroin and marijuana'. Methamphetamine is a psychostimulant drug, which triggers the psychological reward system in the brain, leading to feelings of euphoria and increased self-confidence. The physical and psychological affects leads to a high chance of abuse and addiction to this psychoactive drug by users. It is known by many street names, such as meth, ice, speed, and crystal.

This short clip presents an interview with a current Meth user and a discussion from Dr. Edythe London, a neuropharmacologist from University of California in Los Angeles, who studies the effects of methamphetamine on the brain. Short-termed and permanent effects of this drug on the brain are discussed, specifically the release of dopamine in the brain (which causes the feelings of intense competence) and the high negative correlation between the number of dopamine receptors in the brain and impulsivity in prolonged Meth users.

This subject is of great interest because of the high risk of abuse and addiction associated with Methamphetamine users, especially with young adults. In Australia in 2007, the National Drug Strategy Household Survey found that 23% of people between the ages of 15 and 24 used illicit drugs within the past year, methamphetamines being the third most common form of drug abused. We are interested in discovering why so many people find such pleasure from this drug that they are willing to risk almost everything to continue the abuse of the substance. The role of neurotransmitters, specifically dopamine, and the psychological reward system are fascinating. Also, the complex mechanisms by which tolerance to
methamphetamine occurs, which is still not completely understood by scientists is a fascinating area of interest. It is interesting to note the fact that the brain is capable of changing and possibly repairing itself, which is consistent with the modification of brain maps that we had learned about in lectures.

2. NEUROSCIENTIFIC CONTEXT

2.1 Methamphetamine

Methamphetamine is a white, odorless crystalline powder that dissolves easily in liquids. Its IUPAC name is \( N \)-methyl-1-phenylpropan-2-amine. It is a stimulant to the nervous system, which causes the user to have an increase in alertness, concentration, and energy. This cationic lipophilic molecule that has dramatic effect on sympathetic and parasympathetic pathways and is more potent than its parent compound amphetamine due to its lipophillic nature and thus, has a greater ability to penetrate the CNS (Homer et al., 2008).

After ingestion of Meth, users experience an intense sense of euphoria which is caused by the increased level of dopamine, together with other highly desirable effects including increased productivity, a heightened sense of attention/awareness, hypersexuality, increased energy and decreased anxiety (Cretzmeyer, 2003; Meredith et al., 2005). It increases the production of dopamine in the brain while suppressing the levels of adrenaline. The result is a highly euphoric feeling while the drug is active, but this is faced with high tension and irritability when the effects wear off due to this chemical imbalance (Facts on Meth).

2.1.1 Neurotoxicity of Methamphetamine:

Through a wide number of animal studies, METH has been found to have neurotoxic effects on both the dopaminergic and serotonergic transmitter systems, with the potential of damaging nerve terminals and neuron cell bodies (Cho & Melega, 2002). As summarised in primary literature, primates treated with regimens of a typical abuse pattern support the above findings. With the evidence of positron emission topography (PET) studies, it is clear that there is damage to dopamine nerve terminals as well as cell bodies in chronic METH abusers, even if they've abstained from the substance for a prolonged period of time (McCann et al., 1998).

PET images showing accumulation of a dopamine transporter ligand in the stratum of a control subject and an abstinent methamphetamine subject. Thus, this is evidence of reduced density of striatal ligand labelled DAT sites in living humans with a history of methamphetamine abuse (McCann et al., 1998). The damage that Meth abuse can cause to the serotonin and dopamine systems can lead to an imbalance in
the equilibrium of these systems and thus affect the behaviour of chronic abusers. It is well known that serotonin plays an important role in a wide range of physiological systems from respiration to cardiovascular regulation and is involved in the regulation of functions from appetite to pain sensitivity to sexual behaviour to circadian rhythm synchronisation (Meredith et al., 2005). In addition, dopamine is crucial in physiological functions, for example, the regulation of emotional responses and the reward system, as well as the cardiovascular, central nervous and hormonal system (Homer et al., 2008). Thus, a disturbance of any one of these systems through the abuse of Meth can critically effect behaviour and have serious physiological consequences (Cho & Melega, 2002).

Additionally, according to an fMRI study conducted in abstinent METH-dependent individuals examining neuronal activation during decision making, there was evidence of localized brain damage, with individuals showing less prefrontal cortex activation when having to engage and make decisions (Paulus et al., 2002). Similar findings have been replicated in further studies and indicate that using Meth can ‘lead to impaired brain functioning in ways that have significant ramifications for certain cognitive abilities’ (Homer et al., 2008).

Many areas of the brain are affected by Methamphetamines. Damage to the mid brain by prolonged Meth use causes the user to become irritable, anxious, or moody. The occipital lobe, which processes visual information, is affected, causing some Meth users to hallucinate. The frontal lobe processes emotions, moods, and it is the area for planning and reasoning. Damage to this area by Meth can cause impaired judgment, impulsive thinking, and strong unprovoked emotions, i.e. feelings of rage without cause. The cerebral cortex of the frontal lobe is also the area where most of the dopamine-sensitive neurons are located.

From the information already presented, it is evident that methamphetamine is a highly addictive drug of abuse that has significant effects on the CNS and has been known to damage monoaminergic systems in the brain, cause significant impairments in social cognitions as well as physiological changes in brain structure and functioning in areas such as the frontal lobe (Homer et al, 2008). There are a wide range of human and animal studies that have found numerous negative consequences associated with METH abuse, "including neurological damage, and altered cognitive and behavioural function" (Homer et al, 2008).

### 2.2 Dopamine

Dopamine (abbreviated as DA) is a catecholamine neurotransmitter present in both vertebrates and invertebrates. Its IUPAC name is 4-(2-aminoethyl)benzene-1,2-diol. When DA comes in contact with
Dopamine receptors, it affects the sympathetic nervous system, causing increased heart rate and blood pressure. In addition to its role as an important neurotransmitter, dopamine also serves as a precursor to adrenaline and noradrenaline (MedicineNet 2004). It has a large effect on many physical and mental processes, including those “that control movement, emotional response, and ability to experience pleasure and/or pain (University of Texas, 1999).

Dopamine is a monoamine that is synthesized from the amino acid tyrosine, being formed though the decarboxylation of L-dihydroxyphenylalanine (L-DOPA) with help from the enzyme aromatic amino acid decarboxylase, as depicted below (Bioslutions, 2008).

2.2.1 The "pleasure neurotransmitters":

Dopamine has a significant role with regards to the psychological reward and motivation pathway. This reward system alters behaviour by inducing pleasurable feelings in the brain. This pleasurable feeling encourages more attempts at the behaviour that originally produced the pleasing effect, thereby creating a reinforcing mechanism of that behaviour. There are many ways by which researchers can stimulate the feeling of pleasure in the brain; namely, there are three different circuits which activate the psychological reward system: electrical brain stimulation reward, psychomotor stimulant reward, and opiate reward. All of these reward mechanisms show heavy involvement of dopamine (Bozarth, 1994). Techniques, such as electrical stimulation, help to identify the activation of the medial forebrain bundle, which is coupled to the mesolimbic and ventral tegmental dopamine systems (Bozarth, 1994). Dopamine is the most consistently affected neurotransmitter when psychomotor stimulant drugs affect the brain, and it is dopamine that “may be related to the intense craving associated with withdrawal in drug dependent humans” (Bozarth, 1994).

2.2.2 Effects on dopamine by methamphetamine:

Meth stimulates the release of newly synthesized catecholamines in the CNS and partially blocks the presynaptic reuptake of these neurotransmitters (Cho & Melega, 2002). Specifically, Meth has significant effects on the dopamine neuronal system. With the support of animal studies it has been shown that that METH targets the "dopamine transporter which regulates dopaminergic transmission by facilitating dopamine reuptake" and as a result "inhibits the re-uptake of dopamine by reversing the direction of the dopamine transporter", leading to an increase release of dopamine (Giros et al, 1996). The reinforcing properties of Methamphetamine are mediated by this increased dopamine transmission (Carati and Schenk, 2011). The increased dopamine transmission occurs due to a reversal of the mechanism of the dopamine transporter (DAT), by preventing the action of DAT to translocate dopamine from the extracellular space to the presynaptic terminals. This then leaves an increase of dopamine in the extracellular space. As dopamine is intricately associated with the psychological reward system, this high release of dopamine causes the individual to feel very pleasurable, competent, and euphoric—a very good feeling, and a great incentive to continue the intake of this drug.

Studies have shown that individuals “with the highest levels of dopamine release [after being given amphetamine] reported subjectively stronger cravings after we gave them the drug” (Harmon, 2010). This
suggests that the increased levels of dopamine in the brain, which were originally caused by methamphetamine, actually causes the individual to want *more* of that drug, which would cause continued increase of dopamine levels in the brain. This is simply a vicious cycle and then addiction to this dangerous drug is just all too easy.

### 2.2.3 Damage to dopamine receptors by toxins in methamphetamine:

Studies have shown that toxins in methamphetamine can lead to the damage to dopamine receptors. The neurotoxic effects of long-term methamphetamine use have been associated with dopamine receptor damage and eventual depletion. There are five main types of dopamine receptors currently known, abbreviated as D1, D2, D3, D4, D5. Studies have shown that long-term methamphetamine users have a decreased level of dopamine receptor availability in the brain, specifically D2 receptors (Volkow, 2003).

The graph below depicts the difference in dopamine receptor availability in a Meth abuser and a comparison subject. The dopamine D2 receptors were labeled with [11C]raclopride, which shows up as the red regions in the PET scans below. It can be clearly seen that the Comparison Subject (non-drug-abusing individual) has a significantly greater level of D2 receptors than its Meth abuser counterpart (Volkow, 2003).

The decreased levels of dopamine receptors in the brain of methamphetamine abusers “suggests that D2 receptor-mediated dysregulation of the orbitofrontal cortex could underlie a common mechanism for loss of control and compulsive drug intake in drug-addicted subjects” (Volkow, 2003).

### 2.2.4 Dopamine receptor levels correlated to impulsivity:

The involvement of dopamine in the reward and motivation system may lead to serious adverse effects when the natural chemical levels of dopamine are altered. Research findings suggest that “the ventral tegmental dopamine system serves as an appetitive motivation system for diverse behaviors […] this dopamine system represents one important mechanism for the control of both normal and pathological behaviors” (Bozarth, 1994).

The connection between dopamine and impulsivity has been recently shown. Researchers at Vanderbilt University in the U.S. “proposed that people who were more impulsive might have less active dopamine receptors in their midbrain but their brains wold be more likely to fire off large quantities of the neurotransmitter when stimulated” (Harmon, 2010). This stimulation would be easily found in impulsive actions. These researchers used PET scans on healthy and psychiatrically normal adults with varying impulsivity and observed their dopamine receptors with and without amphetamine, and the results of which verified the hypothesis. This finding gives some explanations as to why Meth addicts are likely to become very impulsive and violent, and why they so easily lose control.

### 2.3 Brain and Neurogenesis:

The video realises the possibility of neurogenesis in areas affected by methamphetamine. One approach was put forward by Northrop, Smith, Yamamoto, and Eyerman (2011). They proposed that the regulation
of glutamate release is a significant mechanism mediating the excitotoxic damage to the dopamine and serotonin neurons observed after methamphetamine exposure. This interpretation is possible when the positive influence of glutamate in learning, memory and cognition is taken into account. The study showed that meth administration increased extracellular glutamate which could be associated with its excitotoxic effect that long-term meth use can then result to eventual decrease in dopamine and serotonin neurons.

In another study (Segovia, Yague, Garcia-Verdugo, & Mora, 2006), neurogenesis was exhibited in rats when housed in an enriched environment (two running wheels, rearrangeable plastic tunnels, elevated platforms and toys) compared to the controlled rats, that were housed in a wire mesh cage. Interestingly, this enriched group also showed heightened levels of glutamate and GABA in the hippocampus compared to controls.

Overall, it is apparent that there is a possibility of brain repair. Studies have just been on its initial stage and it is too early to conclude which brain areas are destroyed by methamphetamine and which of these areas hold the possibility of brain repair. Further research is needed for isolating certain effects and its location in the brain. Until then, other psychological interventions, such as, behavioral and group therapy have been useful tools in addressing the issue of narcotic abuse in the community.

3. ANALYSIS

The National Geographic Society (NGS) is a well-acclaimed organization that is known worldwide as one of the largest non-profit scientific and education organizations in the world. Generally speaking the followers of National Geographic are a somewhat older crowd, so as part of an NGS document this clip is targeted to more of an adult audience. Due to the broadcasting situation in Australia, the National Geographic channel is not free to air, and requires subscription from pay TV suppliers (e.g. Foxtel), making it less accessible to a wider audience. In contrary, in the United States it is broadcast free-to-air making it accessible to viewers of all ages and backgrounds, not only those that have subscribed to a pay TV service.

That being said, the information given in this video is portrayed in a considerably simplistic manner. At the onset of the media item, a professional (a leading neuro-pharmacologist, Dr. Edythe London) discusses methamphetamine abuse and its effects which helps enforce the points made, adds credibility to the information and increase the validity of the media item. The material, however, does not go into much depth and leaves quite a lot of holes in one's understanding of methamphetamine. This is most likely due to its purpose as a promo clip for the full episode to be aired at a future date. While it does a sufficient job in discussing the role of the main neurotransmitter, dopamine, it does not touch on any further details regarding the chemical composition of the drug or its effects on the body in general. It explains that the drug increases the release of neurotransmitters, leading to compulsive behavior but does not mention how this increase in neurotransmitters goes on to increase heart rate and blood pressure levels, as well as sensations of pleasure, self-confidence, energy and alertness, loss of appetite, sleeplessness, and increased body temperature.

Ultimately, it can be gathered from the film that METH is a highly addictive drug and long-term use can result in the failure of dopamine receptors. It does not, however, disclose the symptoms of long-term use.
Physical symptoms include decayed teeth, weight loss, skin lesions, stroke, and heart attack. By presenting a gloomy picture of a METH user in front of the camera, it gives the viewer an image of how METH can alter one's appearance, change their lifestyle, and ultimately, their demeanor. As evident by the METH user's recount of situations presented in the media item, behavioral symptoms include aggressiveness, violence, and isolation. The story of this METH abuse victim, personalizes the promo clip, engages the viewer on an emotional level as a means for better communicating the information and the message that methamphetamine is a dangerous drug with severe effects and lifestyle consequences. In the conclusion of the clip, the narrator states that there is no effective medication for METH abuse, and behavioral therapy such as drug counseling is the only real option for addicts. Despite the truth behind this statement, it is a generalized opinion that focuses on one of the treatment options that has been tried. Furthermore, there is no mention how there are certain medications that can reduce the "high" associated with METH and the reduce the cravings associated with withdrawal. Nor is there any mention about clinical trials with selective serotonin re-uptake inhibitors. However, this is understandable due to nature of the clip as a promotional media item and that the clip is engaged at a wider audience of viewers and not focused on academics but informing the general public and wider community. Currently, as simplistically stated in the promo clip, there are no medications to prevent relapse.

4. APPENDIX

Search Strategy: the focus clip originates from the National Geographic Channel's new series, Drugs Inc. and was accessed directly from the National Geographic TV website (http://natgeotv.com/ca/drugs-inc/videos/meth-brain).

Research will aim to provide information on the overall effects of methamphetamine on the brain, mechanisms of action, side-effects, and add to the information introduced in the clip, especially the role of dopamine in substance abuse by Meth users.

Originally, the group decided to focus on neuro-degenerative disorders such as Alzheimer's due to our own personal knowledge that had been acquired in other courses such as Neuropharmacology. Several clips were sourced from 'youtube' but due to the difficulty in finding appropriate contextual research for the information been presented in the clip to be selected (due to the nature of the novel research been conducted), the group decided to choose a clip from a second search which widened the subject criteria to include the effect of illicit drugs of the brain. This subject was of interest to all group members, and so, we focused on clips associated with Meth abuse and its effects on the brain.

The focus clip was ultimately selected due to the reputation of the source providing valid information in all its media that was backed up by scientific evidence. Also, the clip provides a generalized understanding that can be easily understood by all viewers not only academics, and thus, would be a good starting point for further research into Meth abuse and its effect on the brain. Research into this field was conducted via SIRIUS (database) in which both review articles and primary articles were found relevant to the topic. Supplementary information was gathered from credible websites to reinforce the information provided in primary articles.
5. REFERENCES


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