Literature Review

Craving: the Neurotoxic and Social-cognitive Effects of Drugs Consumptions of Adults, Adolescences, including Prenatal Exposure to Drugs of Abuse

Author: Hada Fong-ha Ieong

MSc, Forensic Toxicology, Department of Forensics Vet Medicine/Forensics Pharmacy, Health Science Center, University of Florida, USA

Abstract: Substances of abuse affect cognition in a number of ways. One of its indirect effects include craving, which has been an important factor to relapse to substance abuse. Peer-induced craving is a powerful form of this construct. The brain mechanisms involved in drug craving or the urge have been studied in recent years. As the social contagion and wrong association in peer groups are the main causes to substance abuse and relapse, understanding the mechanisms involved in processing a peer’s thought and behavior will be beneficial in the rehabilitation treatment. This literature review highlights the short-term neurotoxicity of drugs of abuse and its long-term consequence of cognitive deficits in the brain and mind of abusers, including adults, adolescences and prenatal exposure of drugs of abuse, as well as the genetic factors associated. The review also provides a window into complex social-cognitive relations in which drug abusers not only try to think of what the other abusers are thinking or behaving, but also attempt to measure and seek craving responses to external and internal related stimuli – i.e. why and what the others’ craving reaction affect one’s thoughts and behaviors.

Keywords: addiction; craving; cognition; neurotoxicity; social cognition

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1 Author for correspondence (hada@ufl.edu)

Note: This review is to present on The 8th Mainland, Hong Kong and Macau Conference on Prevention of Drug Abuse - 29 October – 1 November 2013 (Grants: Activity A2013500610 – Social Welfare Bureau).
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CHAPTER 1

Introduction

General statement

Drugs such as heroin are highly addictive substances. Drug craving has been an important factor to relapse to its abuse, and peer-induced craving is a powerful form of this construct. To watch a person to inject an illicit drug by a syringe and a needle may not be a pleasurable experience for most people. However, it may be contagious for drug addicts. That is, accurately knowing what another is feeling and experiencing for something, anticipating of its reinforcing effects being felt by another, and feeling an urge to follow the same behaviors to experience similar effects are elements of craving (Tiffany, 1990), and they could create a phenomenon of social contagion (Ennett, Flewelling, Lindrooth & Norton, 1997), as well as chronic vulnerability to relapse (Weiss, 2010). But is the mechanism of the desire or craving the same, when the target is intrinsically versus extrinsically triggered?

Statement of Problem

The term “craving” should be defined in this study. Prior neuroscientific studies on craving in addiction among researchers have had diverse definitions of craving. Some investigators restrict its definition to a desire for drug use, while others define craving somewhat differently. For example, some have defined craving as behavioral intention to use a drug is the target (Buydens-Branchey et al., 1997); whereas others, like West & Schneider (1987) restricted craving to an experience characterized by extreme desire. One the other hand, some investigators argue that the term “craving” encompasses a more broad range of phenomena, including the expectation of a drug’s reinforcing effects, intention to engage in drug use and the desire for the drug (Tiffany & Drobes, 1991). Marlatt (1985) suggested that the term “craving” be restricted to the desire for the effects of a drug while using the term “urge” could be used to describe its behavioral intention.

Previous studies on craving have also focused less on its classification as distinct from mental or psychological obsession (Silkworth, 2013; Baker, 1998; Pelchat, 2009). A computational neuroscience study (Redish & Johnson, 2007) suggested that a model of
craving is based on the recognition of a path to a high-value outcome, whereas, obsession is based on a value-induced limitation of the search process. Craving is considered to be a subjective, internal feeling or experience when one is aware of a desire (Niaura et al., 1988; Kassel & Shiffman, 1992), and may or may not always be reflected in external action, i.e. the high-value outcome (expectation) can only occur in the planning system but not the habit system (Redish & Johnson, 2007). However, craving could then lead to a recurring search of the planning system, which would appear as cognitive blinding or obsession – requiring a forward search component and a memory retrieval process. Perhaps as a result of such differing definitions of craving, brain regions of interests (ROI) in craving similarly vary in previous studies.

**Statement of Purpose**

Understanding the changes in the brain which occur during craving and obsessive thoughts while processing the addictive behavior of others as a stimulus not only has major implications in the rehabilitation treatment therapy and the prediction of relapse, but also for a better understanding of addictive behaviors because of its emphasis on active cognitive processing, conscious reasoning, and decision-making in using drugs, quitting drugs, and relapsing to drug use (Niaura, 2000).

The first two reasons of drug abuse are reported to be the lack of restraint or boundaries in the abuser’s life and the wrong associations with peers who themselves promote destructive behavior (Maisto & O’Farrell, 1988; Carbb, 2011; Norregaard, Tonnesen & Petersen, 1993). According to the central tenets of cognitive social learning theory (CSLT) as they apply to addictive behaviors, human beings live in a social and cognitive world where behavior is largely associated with the ability to manipulate cognitively and store symbolic representations of the environment (Bandura, 1977; Campbell, 1963; Niaura, 2000) – i.e. what and how we think affects what and how we behave – described as reciprocal determinism (Bandura, 1969; Bandura, 1986), and what we believe also affects what we think of the others’ thoughts – i.e. Theory of Mind (ToM), whose neural network includes bilateral temporo-parietal junctions (TPJ), precuneus (PC), and medial prefrontal cortex (mPFC) regions (Saxe & Kanwisher, 2003). Regions of ToM are recruited when thinking about others’ mental experience.
Assumptions and Limitations

One assumption is that there is an overlap between the regions of ToM and the neural and neuroendocrine mechanisms implicated in drug desire evoked by drug cues and stress in the complex cognitive functioning.

The limitation is that there is not yet a study in measuring epigenetic and proteomic changes in living human brains. In terms of molecular and epigenetic studies, more animal studies are needed to investigate the correlation between genes, proteins and subtracts associated with addiction. In terms of cognitive functions, brain-imaging techniques are suggested.
CHAPTER 2

Literature Review

History of the Measuring Drug Craving in Addiction

Researchers have long posited a relationship between craving and addiction (Wilker, 1948; World Health Organization, 1995). However the critical elements of this relationship, and the very nature and validity of craving as a construct, have been vigorously debated (Mello, 1978; Tiffany, 1990; Kassel & Shiffman, 1992). There has been a recent increase in the study of craving from a variety of biological and psychological perspectives (Pickens & Johanson, 1992; Lowman et al., 2000). Nevertheless, the manner in which craving is measured does not receive sufficient attention, in addition with the further advancement in craving research is hampered by divergent conceptualizations and inconsistent measures (Kozlowki & Wilkinson, 1987). Because there is not a standardized measure of craving, the challenge is to select the optimal measure(s) for a particular research or clinical application. This review begins with a brief summary of the principal definitions of craving and related conceptual issues, the historical self-report measures approaches, mainly the non-verbal measures such as neurobiological responding and cognitive processing. Second, we review the neurotoxic effects of acute drug administration. Included in this section is a review of the “Dopamine hypothesis” in regarding the neurotransmitter dopamine, reward, and learning. Third, we explore the cognitive deficits in chronic drug abuse regarding cognition in the frontal lobe and emotion in the mesolimbic lobe. Further, this review includes the findings of drugs of abuse and the development brain, including prenatal and adolescent exposures. Finally, factors that may influence the choice of drug use are addressed in hope of seeking better understanding of the brain network and better treatment.

Although drug craving has been defined in many ways, it is generally been regarded as a desire to use a drug (Sayette et al., 2000). Craving is usually considered to be a subjective experience, that is, one must be aware of a desire in order to crave (Niaura et al., 1988; Kassel & Shiffman, 1992). With few exceptions, like Tiffany (1992), craving has been conceptualized as “reflecting a drug drug-acquisitive state which motivates drug use”. In spite of the general appeal of craving as a construct, there are a number of issues defining craving (Sayette et al., 2000). They are:
Different scope of craving definitions among researchers (Buydens-Branchey et al., 1997; Marlatt, 1985; Tiffany & Drobes, 1991; Kozlowski et al., 1996)

Debatable time frame of a craving experience (West, Hajek & Belcher, 1989; Anton, Moak & Latham, 1995; Gawin, 1991; Shiffman et al., 1996)

Different characterizations in assessments to craving - a broad continuum of desire or restriction to extreme desire (West & Schneider, 1987)

Debatable the fact that craving might exist in the absence of awareness (Miller & Gold, 1994; Berridge & Robinson, 1995)

The degree to which craving and drug use should be associated (Sayette et al., 2000)

Nearly all conceptualizations of craving assume that drug-motivational can be indexed through self-report measures of subjective experience (Sayette et al., 2000). As a matter of fact, the measures are popular due to their high displayed degree of face validity, and they can easily to be collected.

However, it is problematic to view self-reports of craving, whose interpretation of the meaning has been described as the correspondence view of test meaning (Buchwald, 1961; Wiggens, 1973), as providing a direct readout of a person’s craving state, assuming that a one-to-one mapping of verbal reports to hypothetical internal states. As noted by Wiggens (1973), in order to achieve “accurate” measurement from the perspective of the correspondence view, four conditions should be hold. They are:

- Craving item(s) have common meaning among participants and between participants and researchers.
- The participant must be able to accurately assess his/her internal state.
- The participant must report their internal states honestly to the tester.
- The craving item(s) is related to the concept of “craving” as used by the researcher.

If self-reports of craving are considered to be the gold standard for assessment, six non-verbal responses, as researcher Sayette (2000) argues, should be considered merely as behaviors or reactions that are associated with (self-reported) craving. The non-verbal measures of craving used in research have included reinforcement “proxies”, drug self-
administration, psychophysiological responding, neurobiological responding, cognitive processing, and expressive behavior (Sayette et al., 2000).

Drug Reinforcement proxies. For researchers who consider carving as to motivation to engage in drug use, the degree to which anticipated drug use is perceived to be reinforcing can be used as a parameter. It often involves assessment of choice behavior leading to drug administration. Historically craving has been inferred by determining the cost, such as the amount of work or pain, that an animal or human will assume in order to obtain a desired drug (Garden & Lowinson, 1993).

Drug self-administration. For researchers who consider craving primarily to reflect a behavioral intention to use a drug, direct assessment of drug use may be advisable to self-report measures of craving (Hughes, 1987). Researchers like Berridge & Robinson (1995) also emphasize measures of drug self-administration in studies where drug use can be influenced by other forces other than drug craving. For example, one may experience a strong craving but if the drug is unavailable, or if one wants to quite, drug use may ensue. Conversely, one might use a drug in the absence of a craving.

Psychophysiological responding. Changes in heart rate, skin temperature, blood pressure, skin conductance and salivation have been included in craving studies. Because these responses have often differed (Niaura et al., 1988; Glautier, Drummond & Remington, 1992; Carter & Tiffany, 1999), these measures are presumably less vulnerable to conscious control and thus may be more sensitive than self-report measures to detecting craving (Bake & Brandon, 1990).

Neurobiological responding. Prior studies have been using both animals and human to investigate brain structures and processes that may underlie craving (Wise, 1988; Robinson & Berridge, 1993). Measures of glucose metabolism with human subjects reveal metabolic increases during craving manipulations in particular brain structures associated with both emotional (e.g. amygdala) and cognitive (e.g. hippocampus) aspects of memory (Everitt, 1997). It is to note that imaging studies such as using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) can indicate that a specific craving manipulation produces increases in indices of brain activation where neurobiological changes may be correlated with craving (Sayette et al., 2000), and that it has been a trend in recent years.
Cognitive processing. Craving and the changes in cognitive processing have a long history of association (Sorokin, 1942; Key et al., 1950). One approach is to assess the redistribution of cognitive resources during craving involves divided attention tasks. The secondary response time (RT) is an example of this approach. RT paradigms have been used to measure the degree a primary task draws on limited-capacity cognitive resources by recording performance decrements on a secondary RT task (Sayette et al., 2000). Studies using both smokers and alcoholic subjects have provided evidence that there are increases in secondary RTs during peak craving periods, relative to non-craving baseline periods (Sayette et al., 1994; Sayette & Hufford, 1994; Cepeda-Benito & Tiffany, 199; Juliano & Brandon, 1998).

Another cognitive performance approach to assess craving involves explicit memory tasks such as cued recall (Sayette et al., 2000). Words, for example, that are most salient to a person, can be presumably to be recalled readily from a previously learned list. Researchers like Zeitlan, Potts and Hodder (1994) concludes that consistent with the formulation, abstinence appears to increase ability to recall already presented smoking-related words. One argument may be raised form this approach is that increased recall of drug-related words may be caused by encoding strategies rather than the salience produced by craving.

Some implicit memory tasks have assessed process associated with craving. The functions of these tasks are to examine the salience of drug-related messages for individuals without making them aware of the assessments. For example, stem completions, perceptual identification, categorization tasks and color-naming variants of the Stroop task have been used for studies of implicit memory providing conflicted findings, with drug deprivation leading to facilitation (Litz, Payne & Collett, 1987; Jarvik et al., 1995; Zeitlin et al., 1994; Gross et al., 1993) as well as inhibition (Zeitlin et al., 1994) in the selective processing of drug-related information.

Expressive behavior. Interesting enough, analysis of facial expressive behavior is also considered to be a measuring tool of emotional response (Darwin, 1872; Darwin, 1965; Barlow, 1988). The use of a standard and anatomically based facial coding system may prove useful for detecting craving because craving itself can be affective in nature (Baker et al., 1987). Advantages of such objective facial coding systems include the
capacity to comprehensively measure immediate responses, to assess positive and negative affects as orthogonal dimensions, and to discriminate between different emotions (Ekman & Rosenberg, 1997). Sayette and Hufford (1995) found that high craving ratings could be linked to both positive affect-related signals when expecting to smoke and negative affect-related signals when not permitted to smoke by using the Facial Action Coding System (FACS: Ekman & Friesen, 1978) to code subjects’ responses to smoking cues under two experimental condition. The limitations of using FACS include reliance on expressions visible to humans and the restriction to brief craving coding intervals. As a matter of fact, future studies may need to identify specific facial action patterns that are associated with craving.

In sum, cognitive tasks have proven useful in suggesting cognitive processes that may change during craving as well as memory structures associated with craving. Thus, the appropriate experimental procedures, in which factors such as drug use history of an individual, level of drug abstinence and presence of drug-related stimuli are identified, measured or controlled.

**Reward and reinforcement: the “Dopamine Hypothesis’**

In 2007, neuroscientist celebrated the 50th anniversary of the discovery of the key neurotransmitter, dopamine, by Arvid Carlsson who won the Nobel Prize for Medicine in 2000 (Bjorklund & Dunnet, 2007). Dopamine is a central neurotransmitter that serves a variety of functions, including the fine-tuning of mother control and cognitive function; modulating the salience of events and attention, learning and memory; bonding and attachment in relationships; and the planning and motivation of behavior. It is widely accepted that dopamine also plays a significant role in addiction to most drugs of abuse (Volkow & Li, 2004). Current researches prove that addiction also involves changes within a number of neurochemicals and neurotransmitter systems such as the endogenous opioids, glutamate and gamma-aminobutyric acid (GABA), and thus it appears to exert their influence through the dopaminergic reward circuits (Goodman, 2008).

Amphetamines, cocaine, alcohol, nicotine and cannabis act on a forebrain structure known as the nucleus accumbens (NAcc) producing large and rapid release of dopamine (DA) (Robbins et al., 2007). The effects produced by these drugs originate in
the neurons of the midbrain ventral tegmental area (VTA), which deliver DA into synapses into the NAcc (Wise & Bozarth, 1987; Koob & Bloom, 1988; Di Chiara, 1998). Cocaine, amphetamines, and ecstasy directly increase the amount DA available for postsynaptic cleft by increasing the release or by reducing dopamine reuptake from the synapse (Hutcheson et al., 2001); whereas alcohol, cannabis and nicotine increase DA activity indirectly by signaling neurons that influence dopaminergic neurons (Koob & Le Moal, 1997; Nisell et al., 1994).

The neural system involved in learning, reward and motivation has important association with the NAcc. Addictive drugs produce over 10 times more dopamine in the NAcc than natural reinforces, in which this excess release of DA by the drugs is suggested to make drug abuse more appealing than everyday rewarding activities (Hyman, 2005). Imaging of brain function during intoxication shows that the increase in DA signaling in the NAcc was believed to give drugs their euphoric or rewarding affects (Volkow et al., 2004a), that is the greater the DA release in the NAcc, the greater the euphoria that is reported (Laruelle et al., 1995; Drevets et al., 2001). However, it does not always happen. Some studies conducted by Robinson and Berirdge (2000) also reflects that there is a poor correlation between subjective state of pleasure and drug-taking behavior.

**Neurotoxic Effects of Acute Drug Administration**

Neurotransmission-associated neurotoxicity. Neurotransmission constitutes an important part of the functioning central (CNS) and peripheral nervous system (PNS) through connection of two neurons or nerves via a synapse. Release of chemical signaling molecules, commonly called neurotransmitters, causes not only signal transduction but also diverse actions that might alter the physiological response. Interference with neurotransmission is possible on multiple levels. Moreover, the sole interaction between the toxicant with the neurotransmitter receptor might not correspond to the resulting neurotoxicity.

Nicotine is widely available in tobacco products and as a pesticide and as such causes a significant number of neurotoxicity. It is the main sympathetic and parasympathetic neurotransmitter in the CNS by binding as an agonist to nicotinic
acetylcholine receptors. It also is responsible for signal transduction on the neuromuscular junction in the PNS controlling muscle contractions. The rare occurrence of acute nicotine overdose therefore results in widespread disturbances of the nervous system with confusion, reduced heart rate, hypotension, and further may lead to coma and death by respiratory paralysis. Low chronic exposures on the other hand are a considerable epidemiologic concern due to the widespread use of tobacco products but it has been difficult to separate specific nicotine effects from the other substances contained in tobacco smoke. Cancer, respiratory disorders, cardiovascular diseases, and attention deficit disorders in children have been associated with tobacco smoke. Exposures of tobacco smoke components after inhalation by the mother to the fetus may result in complex neurological disorders or even result in loss of the fetus (Klaassen, 2008).

Cocaine and amphetamines are widely abused and mostly illegal drugs (cocaine has a few special therapeutically applications). It is a central stimulant that increases heart rate and leads to vasoconstriction by inhibiting the reuptake of the sympathetic neurotransmitters dopamine and norepinephrine (a stress neurotransmitter and hormone released from the sympathetic neurons to affect the brain and heart) as well as serotonin (a neurotransmitter associates with mood, sleep, well-being and awareness). The high degree of addiction and feeling of euphoria mainly result from the stimulation of dopamine release and its action on post-synaptic dopamine D1 receptors. Due to the stimulatory effects, cocaine abusers are at a greater risk of developing cardiovascular complications as well as suffering from strokes and intracranial hemorrhage due to increased cerebrovascular resistance and development of neurodegenerative disorders in chronic abusers. Similar to cocaine, amphetamines are CNS stimulants that prevent reuptake of neurotransmitters but in addition directly damage both dopaminergic and serotonergic axons causing distal axotomy of such neurons. The mechanism of amphetamine-induced neurodegeneration is not known in detail, but the generation of reactive species as a consequence of excess dopamine that is oxidized to a Quinone that might lead to damage and loss of neurons as is the case in Parkinson’s disease (Klaassen, 2008).

N-methyl-D-aspartate (NMDA) receptor or kainic acid (KA) receptor have been implicated in neural and behavioral plasticity ranging from development to learning
Excitatory amino acids mainly acidic amino acids similar to glutamate, the main excitatory neurotransmitter in the brain and also an additive in many food products to enhance and preserve taste. The effects of glutamate are mediated through binding to ion channels or G-protein coupled receptors. Specific agonists have defined the name of the specific receptor such as KA receptor or NMDA receptor. Glutamate entry into the brain is controlled by active transporter processes in the blood-brain barrier but in addition it can enter the brain through the circumventricular organs. Within this susceptible area glutamate damages and kills neurons through activation of ion channels and therefore leads to uncontrolled leakage of glutamate into the brain. KA is a potent excitotoxin through activation of specific glutamate receptors and selective damage to dendrites and neurons. Chronic damage and loss of neurons may result from such highly specific glutamate receptor agonists that lead to selected cell death which progresses with loss of memory and ultimately complete neurodegeneration due to the widespread glutamate receptor distribution in the brain. Other excitotoxins have been identified as food poisonings and require chronic ingestion to cause the neurodegenerative disorders observed.

Not surprisingly, it has been well reported that clinicians often observed that patients undergoing treatment for addiction become highly vulnerable to relapse when they return to environments where they develop addiction (Hyman, 2005; see 2005). Clinical studies indicate that cues associated with substance abuse elicit physiological responses and cravings for drugs (Franklin et al., 2007). Laboratory animals also develop strong associations and cue-response behaviors in the presence of drug-related stimuli. A phenomenon called conditioned place preference has been demonstrated in studies using nicotine, ethanol, amphetamine, methamphetamine, cocaine, morphine, cannabis, and caffeine – showing the animals given a drug in one compartment of a double cage subsequently will gravitate to that compartment more than to the alternative compartment (Bardo & Bevin, 2000). And thus, it is important to understand the formation of drug-stimulus association and the persistence of drug-stimulus associations in addiction (Gould, 2010).

The formation of drug-stimulus association. Addiction as mentioned above in the dopamine hypothesis where NAcc produces rewarding experience caused by a drug,
attributes addicted individuals’ strong responses to drug cues to a learning process that inculcates powerful drug-stimulus associations (Robinson & Berridge, 2000). In this view, the individual taking a drug perceives his or her present surroundings as highly significant (salient) and makes exceptionally strong mental connections between features of those surroundings and the intense rewarding experience of the drug. And thus when the individual re-encounters those features, the strong and powerful association reassert themselves, are experienced as prompts for drug seeking and drug taking. Studies conducted by Franklin and his colleagues (2007) and Volkow (2006) suggest that exposing addicted individuals to cues that they associate with drug abuse elicits changes in the activity levels of brain regions involved in learning and memory (i.e., stratum, amygdala, orbitofrontal cortex, hippocampus, thalamus, and left insula). The acute effects of amphetamine, nicotine, and cocaine fit straightforwardly into this scenario.

The persistence of drug-Stimulus association. Recent research has brought to lights to the strikingly long-lasting ability of maladaptive drug-stimulus associations to influence behavior and provoke relapse. Studies have shown that many abused substances can reshape the communication pathways between neurons (synaptic plasticity) – contributing to both the formation and the persistence of maladaptive drug-stimulus associations. Cocaine and nicotine can directly induce one form of synaptic plasticity, the strengthening of neural connections via a process known as long-term potentiation (LTP) (Argilli et al., 2008; Kenny & Gould, 2008). Amphetamine can enhance LTP (Delanoy, Tucci & Gold, 1983). Marijuana activates the endocannabinoid system, resulting in inhibition in some instances and facilitation in others of both LTP and long-term depression (LTD), another form of synaptic plasticity in which connections between neurons become less responsive (Carlso, Wang & Alger, 2002; Nugent & Kauer, 2008; Sullivan, 2000). Morphine inhibits LTP of neurons that exhibit inhibitory control of neural activity via GABA (Nugent & Kauer, 2008), whose activities could lead to a net increase in neural activity throughout the brain – leading to the formation of stronger associations including maladaptive drug-context associations (Gould, 2010).

Cognitive Deficits in Chronic Drug Abuse

Drug addicts progress to the withdrawal stage when they initiate abstinence.
Many drugs produce cognition-related withdrawal symptoms that may make abstinence harder (Gould, 2010). These include:

- **Opioids** – deficits in cognitive flexibility (Lyvers & Yakimoff, 2003);
- **Cocaine** – deficits in cognitive flexibility (Kelley et al., 2005);
- **Amphetamine** – deficits in attention and impulse control (Dalley et al., 2005);
- **Alcohol** – deficits in working memory and attention (Moriyama et al., 2006);
- **Nicotine** – deficits in working memory and declarative learning (Kenney & Gould, 2008).

While the cognitive deficits associated with withdrawal from drugs are often temporary, long-term use can also lead to lasting cognitive decline. Long-term cannabis users have impaired learning, retention, and retrieval of dictated words, and both long-term and short-term users show deficits in time estimation (Solowij et al., 2002), although how long these deficits persist is unknown. Chronic amphetamine and heroin users, on the other hand, show deficits in a range of cognitive skills, including verbal fluency, pattern recognition, planning, and the ability to shift attention from one frame of reference to another (Ornstein et al., 2000). The deficits in decision-making resembled those observed in individuals with impairment of the prefrontal cortex, suggesting that both drugs alter function in the brain area (Rogers et al., 1999).

A pair of neuropsychological studies suggests that some methamphetamine-induced cognitive loss may be partially recouped with extended abstinence (Volkow et al., 2001; Wang et al., 2004). Evaluated when abstinent for less than 6 months, chronic methamphetamine abusers scored lower than unexposed controls on motor function testing, memory for spoken words, and other cognitive tasks. The deficits were believed to be associated with a comparative scarcity of DA transporters and reduced cellular activity in the thalamus and NAcc. When being retested after twelve to seventeen months of abstinence, the drug abusers’ motor function and verbal memory had risen back to control group’s level, and the gains correlated with a return toward normal transporter levels in the striatum and metabolic levels in the thalamus; nevertheless, along with depressed activity in the NAcc, other neuropsychological deficits remained.
In another study, abusers of ecstasy continued to score relative poorly in tests of immediate and delayed recall of spoken words even after two and a half years of abstinence (Thomasius et al., 2006). In a study of cocaine-and-heroine abusers, it shows that it causes deficits in executive functions (e.g. changes in fluency, working memory, reasoning, response inhibition, cognitive flexibility, and decision-making) remained after up to five months of abstinence (Verdejo Garcia & Perez-Garcia, 2007).

An important question is thus raised: does an abused drug’s cognitive deficit persists as the addictive behaviors shifts from sporadic to chronic?

In some studies with animals, chronic nicotine administration improved cognitive capacities such as attention, but other found that initial improvement waned with chronic treatment (Kenny & Gound, 2008). Furthermore, other recent studies have shown that smoking and a past smoking history are associated with cognitive decline (Nooyen, van Gelder & Verschuren, 2008). Laboratory studies have also demonstrated nicotine-related alterations in neuronal functioning that could underlie cognitive decline that persists even after prolonged abstinence. For example, rats’ self-administration of nicotine was associated with a decrease in cell adhesion molecules, a decrease in new neuron production, and an increase in cell death in the hippocampus (Abrous et al., 2002). Such changes could lead to long-lasting cognitive changes that contribute to poor decision-making and addiction.

**Cognition: the Pre-frontal Cortex**

Brain regions of interests (ROI) vary in previous studies. Drugs abused by humans increase dopamine in the reward circuit, conditioning and habit formation (Wise, 1996; Chiara & Imperato, 1988; Goldstein & Volkow, 2011), and thus many clinical studies in addiction pay more attention on the brain area involved reward, including the midbrain dopamine area, i.e. the ventral tegmental area (VTA) and substantia nigra, and the basal ganglia, i.e. the ventral and the dorsal striata. Moreover, some investigators suggested that the central to theories of drug addiction have been involved the nucleus accumbens (NAcc) and amygdala, which are responsible to functions of reward and emotion, may be crucial to initiate drug self-administration (Volkow & Fowler, 2000).

More advanced current studies have brought to light to clarify the role of the
prefrontal cortex (PFC), which is involved in a whole range of high level cognitive functions such as decision-making, planning, social interaction, understanding other people, and self awareness (Blakemore & Frith, 2005), and it is the last part of the human brain to develop maturely (Gogtay, 2004; Blakemore, 2007). More particularly, the brain regions of interest (ROI) in PFC, including the anterior cingulated cortex (aCC), the dorsolateral prefrontal cortex (DLPFC), and the orbitofrontal cortex (OFC) have been selected and highlighted based on the preclinical literature on drug-seeking behavior and the current addictive cue studies (Robinson & Berridge, 1993; Wise, 1988; Galvan et al., 2005; Brody et al., 2002; Childress et al., 1999; Smolka et al., 2006; Due et al., 2002; Goldstein & Volkow, 2002; Goldstein et al., 2007; Wilson, Sayette & Fiez, 2004; Volkow et al., 2009). That helps explain the disruption of PFC in addiction could negatively affect a wide range of behaviors such as im/com-pulsivity, risk taking, reduced satiety, enhanced stress reactivity and inability to suppress emotional intensity, impaired self-monitoring, drug-related anticipation, and choice of immediate reward over delayed gratification (Goldstein & Volkow, 2011).

**Drugs of Abuse and the Development Brain**

The human brain continues to develop and learn important neural pathways from the prenatal period through adolescence. Throughout these years, the brain is highly vulnerable and susceptible to the insult of drugs, and drug-induced alterations of neural plasticity may deflect the normal course of brain maturation.

**Prenatal exposure**

Prenatal exposures to a number of drugs have significant deleterious effects on cognition and behavior that may not rise to the level of mental retardation. A study shows a 5-year-olds whose mothers had used alcohol, cocaine, and/or opiates while pregnant ranked below unexposed controls in language skills, impulse control and visual attention, although there were no significant difference between the two groups of children in intelligence, visual/manual dexterity, or sustained attention, both groups placed below the normative means on these measures (Pulsifer et al., 2008). Another similar study documented memory deficits in 10-year-old children who had been exposed prenatally to
alcohol or marijuana (Richardson et al., 2002).

Clinical and laboratory research has implicated prenatal exposure to methamphetamine in both cognitive deficits and altered brain structure. One study correlated shorted attention span and delayed memory with reduced volume in the putamen (-18%), globus pallidus (-27 to -30%), and hippocampus (-19 to -20%) among 15 children who were 3 to 16 years prenatally exposed to the stimulant, compared with controls (Chang et al., 2004).

Cognitive deficits following prenatal exposure to smoking may reflect structural brain changes. In one study, prenatally exposed adolescent smokers had greater visuospatial memory deficits in conjunction with changes in parahippocampal and hippocampal functions compared with adolescent smokers not prenatally exposed (Jacobsen et al., 2006). Brain imaging of adolescent smokers and nonsmokers who were prenatally exposed to smoking has revealed reduced cortical thickness (Toro et al., 2008) and structural alterations in cortical white matter (Jacobsen et al., 2007). Furthermore, in rats, prenatal exposure to nicotine decreased memory-related neural activity in the hippocampus and resulted in deficits in active avoidance learning, with male and female prenatally exposed rats showing significantly fewer correct responses as young adults (Vaglenova et al., 2008).

**Adolescent exposure**

Adolescence is a high-risk period for substance abuse. Most addicted smokers initial formed the habit during adolescence (Khuder, Dayal & Mutgi, 1991). Some studies show that adolescent smokers scored worse than age-matched nonsmokers on tests of working memory, verbal comprehension oral arithmetic, and auditory memory (Fried, Watkinson & Gray, 2006; Jacobsen et al., 2005). In addition, adolescent rates treated with nicotine had long-lasting changes in the sensitivity of the adenylyl cyclase cell-signaling cascade, a second messenger pathway involved in many processes, including learning and memory (Slotkin et al., 2008).

Adolescent smoking can foster cognitive decline with other disorders. For example, a study shows that adolescent cigarette use is associated with future episodes of depression (Choi et al., 1997), a malady which in turn is associated with negative effects
on cognition (Thomas & O’Brien, 2008). A laboratory investigation shed light on this relationship: Adult rats that had been exposed to nicotine during their adolescence proved less sensitive than controls to rewarding/appetitive stimuli and more responsive to stress and anxiogenic stimuli (Iniguez et al., 2009).

Moreover, adolescent exposures to alcohol, cannabis, and MDMA also cause persistent disruption of cognition (Brown et al., 2000; O’Shea, McGregor & Mallet, 2006; Piper & Meyer, 2004; Stiglick & Kalant, 1982). These findings prove that the adolescent brain is susceptible to insult from drug use and abuse, which can result in long-lasting changes in cognition.

**Gene, Drugs and Cognition**

While the cognitive deficits associated with withdrawal from drugs are often temporary, long-term use can also lead to lasting cognitive decline. The nature of deficits varies with the specific drug, the environment, and the user’s genetic makeup. For example, an individual’s cognitive response to acute amphetamine depends in part on which of alternative forms of the catechol-O-methyltransferase (COMT) gene, which is responsible for the degradation of catecholamines such as dopamine, epinephrine, and norepinephrine, the person has inherited. This gene encodes a protein that metabolizes DA and norepinephrine, among other molecules. A person inherits two sets of copies of COMT, one from a father, another from a mother, and each copy has either a valine or a methionine DMA triplet at codon 158, thus a heterozygous pair (Val/Met), the homozygous (Met/Met) or (Val/Val) of codons at this location. Administration of acute amphetamine to individuals with the Val/Val pairing improved their performance on test of cognitive flexibility that activates the dorsolateral prefrontal cortex and increased efficiency in their prefrontal cortex function (Mattay et al., 2003). Furthermore, smokers with the Val/Val pairing were more sensitive to the disruptive effects of nicotine withdrawal on working memory and exhibited a greater cognitive response to tobacco (Loughead et al., 2009).

These findings are important not only because they demonstrate a link between the effects of drugs of abuse on cognition and behavioral traits associated with addiction, but also because they provide examples of how genotype contributes to the addictive
phenotype (Gound, 2010). More research is needed to understand the extent of individual vulnerabilities in drug addiction versus the effect of cumulative exposure, a greater understanding of vulnerability phenotypes, as well as the addictive resilient phenotype that recovers normal plasticity in the NAcc, could ultimately lead to new therapies for addiction (Piazza, 2013).

**Preclinical research and Clinical Implications**

The literature reviewed here highlights the importance of considering past, present and possible future cognitive functions when treating patients for addiction, as drug-related cognitive changes may cause patients and family bias toward responses and actions that continue to the cycle of addiction. While clinicians face the challenges of helping patients master adaptive strategies to overcome the strong association that contribute to relapse after patients return to environment where they used to associate with their prior substance use habit, pre-clinical researchers also face the challenges of understanding the brain networks of drug abusers. As being knowing what another is feeling and experiencing for something, anticipating of its reinforcing effects being felt by another, and feeling an urge to follow the same behaviors to experience similar effects are elements of craving (Tiffany, 1990), whilst having the ability to attribute the mental states such as beliefs, intents, desire, to oneself and others and to understand that others have beliefs, desire and intentions that are different from one’s own is called Theory of mind (ToM) and it is one of the elements of empathy (Batson, 2009).

This review is to provide a window in future research into the complex social relations in which drug abusers not only try to think of what the other abusers are thinking or behaving in orders to make sense to themselves, but also attempt to measure and seek craving responses to external and internal related stimuli – i.e. why and what the others’ craving reaction affect one’s thoughts, while making a moral judgment, and also a better understanding in addiction.

This project does not specifically deal with the treatment of craving in addiction; however, no work such as this can be complete without at least a brief mention of treatment. Several treatments exist to help drug abusers recover from addiction. These include cognitive behavioral therapy, medication and behavioral therapy, and
motivational interviewing. Easing withdrawal symptoms can be important in the initiation of treatment; prevent relapse is necessary for maintaining its effects.

The key factor is a continuum of care that includes an effective treatment regimen to maintain medical and mental health of an individual; but for those who do not, avoid treatment can have detrimental side-effects that can lead to terrible aftermaths. Follow-up like community or family recovery support can be crucial to a person’s success in achieving and maintaining a drug-free lifestyle.

Acknowledgments
To Dr. Emile Bruneau, who lighted my passion for cognitive neuroscience and his heart to guide every one in the world who deserves to be educated. To Dr. Charles Zaroff, who ignited my passion for research and his advise to my path. To Dr. Ian Tebbett, who helped me to map my quest. To Dr. John Roll, who gave me encouragement to pursue the study in substance abuse. To Dr. Wen Chao Bai, who showed me the operation of the Imaging Department. To my parents Kam-Sen Ieong and Mon Fong Chan for giving me their unconditional love, and to all the friends who have helped me along the way. I dedicate my study and future studies to all of you, particularly to those who suffers from the battle of addiction.

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