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Chapter 2

STIMULANTS: NEUROIMAGING AND TREATMENTS

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ABSTRACT

Psychostimulant abuse is an epidemic of global proportion; the associated medical, social and economic consequences have become a major problem worldwide. Stimulant drugs such as cocaine and amphetamine have approved medical use but are well documented to cause addiction. Recent advances in neuroimaging techniques have enabled research into the effects of stimulants on the human brain; positron emission tomography and magnetic resonance imaging studies confirm that stimulant addiction results in structural, functional and neurochemical damage. This chapter provides a review of neuroimaging research in human cocaine and methamphetamine users, and trials of medications for stimulant addiction with an emphasis on agonist replacement therapy and medications modulating related neurotransmitter systems.

1. INTRODUCTION

Drug addiction, or dependence, is one of the most pervasive, costly and challenging health and social problems [1]. The associated cost to society is prodigious when medical, economic, criminal and social factors are combined. The estimated overall costs of substance abuse in the USA, related health and crime consequences, loss of productivity, foster care and other social problems, exceed $600 billion annually which includes $181 billion for illicit drugs [2], while public expenditure on all aspects of drug phenomena in Europe was estimated at €34 billion in 2005 [3]. Addiction is defined as a chronic relapsing brain disorder characterised by a maladaptive pattern of substance use (the terms ‘addiction’ and ‘dependence’ will be used interchangeably throughout this chapter).

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DSM-IV Diagnostic Criteria for Alcohol and Drug Dependence

Tolerance	A need for markedly increased amounts of the substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of the substance.
Withdrawal	The characteristic withdrawal syndrome for a substance; or the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
Impaired control	The substance is often taken in larger amounts or over a longer period than was intended. A persistent desire or unsuccessful efforts to cut down or control substance use.
Time spent	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
Neglect of activities	Important social, occupational, or recreational activities are given up or reduced because of substance use.
Continued use despite problems	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

The diagnostic criteria for addiction have evolved over the past three decades with a shift from the emphasis and necessary criteria of tolerance and withdrawal to other factors more focused on compulsive use [4]. The Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) outlines seven criteria and states that addiction is as a "maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following occurring in the same 12-month period" [5]. The number of criteria met by drug users can vary with the severity of addiction, the stage of the addiction process and the substance being used [6]. From a psychiatric perspective, drug addiction includes aspects of impulse control and compulsive disorders. Impulse control disorders are characterised by tension or arousal before committing an impulsive act, and pleasure, gratification or relief at the time of committing the act which may or may not be accompanied by feelings of regret, self-reproach or guilt [5]. In contrast, compulsive disorders are characterised by anxiety and stress beforehand, and relief from the stress by performing the compulsive behaviour. As an individual moves from impulsive to compulsive behaviour, there is a shift from positive reinforcement driving the motivated behaviour to negative reinforcement [7]. Drug addiction has been conceptualised as a disorder that evolves from impulsivity to compulsivity, and this shift often occurs either when there is increased access to the drug or when a more rapid route of administration is employed.

The onset and intensity of the 'high' and the subsequent dysphoria are dependent on the route of administration; for example, smoking cocaine is associated with a more rapid and intense high and dysphoria than the intranasal and oral routes [8-10]. All drugs of abuse act on the central nervous system and largely affect dopamine, noradrenaline and serotonin, as well as acetylcholine, glutamate and γ-amino butyric acid (GABA) [11]. Of these, dopamine has been consistently associated with reinforcing effects and is involved in the regulation of

movement, reward, cognition, psychosis and numerous other functions [12]. Although different drugs of abuse have different acute mechanisms of action, there is evidence that they all converge on a common pathway in the limbic system [13-17]. Research has focused on the mesolimbic dopamine pathway, which projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), amygdala, hippocampus and prefrontal cortex (18). The VTA-NAc pathway, along with other limbic regions, mediate the positive emotional effects of natural rewards, such as food, water and social interactions [19, 20]. It is also one of the most important substrates for the acute rewarding effects of all drugs of abuse. Drugs of abuse cause excessive release of dopamine, often surpassing the magnitude and duration of dopamine release that is triggered by natural rewards [21]. While dopamine increases induced by natural rewards undergo habituation, those produced by drugs of abuse do not [22]. This chapter will focus on cocaine and amphetamines – psychostimulants that have high abuse potential and are well documented to produce addiction. It will outline findings from studies of dependent participants using various neuroimaging techniques, as well as trials of pharmacological agents to treat amphetamine addiction.

2. STIMULANTS

Stimulant drugs such as cocaine, amphetamine and methamphetamine are approved for medical use, but also have considerable abuse potential [4]. These drugs act by increasing the amount of synaptic monoamine neurotransmitters in the synaptic cleft by blocking the reuptake of dopamine, noradrenaline and serotonin [23]; amphetamines also enhance the release of these neurotransmitters [24].

2.1. Cocaine

Cocaine, derived from the coca plant (*Erythroxylon coca*), has been a popular recreational drug for decades and has a long history of misuse. The powdered hydrochloride salt form can be snorted or dissolved in water then injected. ‘Crack’ is the street name given to cocaine that has been processed to make a rock crystal, which, when heated, produces vapours that are inhaled [25]. It was used early on as a local anaesthetic for ophthalmological work and today, the only accepted medical uses are local anaesthesia and vasoconstriction for some ear, nose and throat surgeries [26]. After the opiates and heroin, cocaine is the most problematic drug worldwide and the United Nations Office on Drugs and Crime estimated the prevalence of cocaine use in 2008 to be 0.3-0.4% of the adult population, or between 15 and 19 million people [27].

Cocaine acts by blocking synaptic reuptake mechanisms; this prevents reabsoprtion of the neurotransmitters dopamine and noradrenaline, resulting in higher concentrations of neurotransmitter in the synaptic cleft which then bind to postsynaptic receptors [28]. Acute administration of cocaine is associated with feelings of energy, decreased fatigue, a sense of wellbeing and increased confidence and talkativeness while prolonged cocaine use can cause depletion of neurotransmitters, which may account for the depression and craving associated with the cessation of drug use.

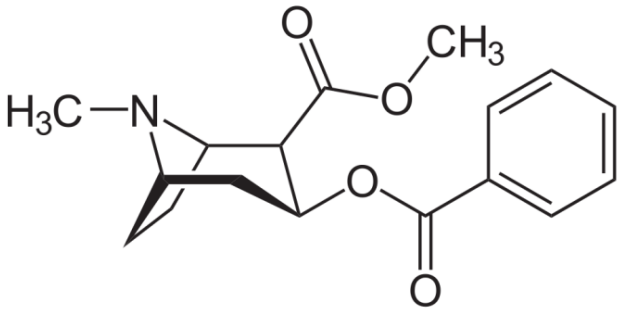

Figure 1. Chemical structure of cocaine.

2.2. Amphetamine-Type Stimulants

Amphetamine-type stimulants refer to a group of synthetic substances comprised of simple phenethylamines (primarily amphetamine, methamphetamine and methcathinone) and substituted phenethylamines i.e. the ecstasy-group substances (3, 4-methylenedioxymethamphetamine or MDMA and its analogues). While ecstasy-group substances are chemically related to the amphetamines, they differ structurally in terms of the methylenedioxy (-O-CH_2-O-) group attached to the ring of the phenethylamine molecule. In this respect, they more closely resemble the structure of mescaline – a hallucinogenic substance and, as a result, increase serotonin release and inhibit its reuptake to a greater extent than dopamine; their pharmacological effects are a blend of those seen following amphetamine and mescaline administration. It has been claimed that dependence on MDMA is unlikely to become a serious problem because the decrease in pleasurable or rewarding effects and contrasting increase in unpleasant effects following frequent drug use would diminish the incentive to use the drug in a manner that could give rise to dependence. This phenomenon occurs with the classical hallucinogens such as lysergic acid diethylamide or LSD, which have not proven to cause dependence to the same extent as drugs such as alcohol and the opioids [29]. Therefore, this chapter will primarily focus on simple phenethylamines D-amphetamine (or dexamphetamine) and methamphetamine; MDMA addiction will not be discussed. Amphetamines were originally synthesised for the treatment of asthma and used by the military for their anti-fatigue properties [30]. After the Second World War, an epidemic of methamphetamine abuse occurred in Japan when military stockpiles of amphetamines were released to the Japanese market [31]. Amphetamines are currently approved for use as adjuncts for short-term weight loss and in the treatment of narcolepsy and attention deficit-hyperactivity disorder (ADHD).

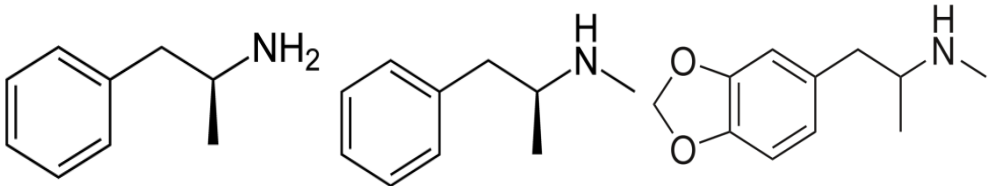

Figure 2. From left to right: the chemical structures of dexamphetamine, methamphetamine and MDMA.

Unlike the coca leaf or opium poppy, the manufacture of illicit amphetamines is not affected by geographical or environmental factors; laboratories can operate anywhere and be relocated. Furthermore, amphetamines can be synthesised from a variety of starting materials using a range of methods, consequently they are the second most commonly used illicit drugs. The global number of users is likely to exceed the number of opiate and cocaine users combined [27].

Similarly to cocaine, amphetamines increase synaptic concentrations of monoamines and have greater effects on noradrenaline than dopamine or serotonin [32]; however, the primary neuropharmacological action responsible for the psychostimulant and reinforcing effects appears to be the dopamine system [4]. In addition to blocking monoamine reuptake, amphetamines also stimulate the presynaptic release of neurotransmitters [28] and inhibit monoamine oxidase [33]. The stimulant effects of amphetamines are similar to those produced by cocaine, with a much longer duration of action due to an unusually long half-life – 1.1 hours when smoked, to 12.2 hours when used intravenously [34]. By contrast, the half-life of cocaine ranges from 48 to 75 minutes [35].

3. NEUROIMAGING

Neuroimaging encompasses a wide variety of techniques that enable assessment of the structure, function and pharmacology of the brain, and includes techniques that use X-rays (computed tomography or computed axial tomography), infrared light (diffuse optical imaging and event-related optical signal), magnetic fields and radioactively labelled chemicals.

This chapter will focus primarily on one radiotracer technique – positron emission tomorgraphy (PET)–and one magnetic resonance imaging (MRI) technique, with four different modalities–functional MRI (fMRI), structural MRI, diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (MRS).

3.1. Positron Emission Tomography

Radiotracer studies are used in the measurement of molecular targets such as receptors, transporters and enzymes; they are the only techniques that allow for the direct assessment of blood flow, metabolism or neurochemical reactions in a particular region of the living brain. PET is a molecular imaging technique that has been used to capture markers of brain activity such as drug uptake, oxygen use, regional blood flow and the rate of glucose metabolism. The underlying technical principle involves a radiotracer administered into the blood stream that emits high-energy gamma-rays when a positron combines with an electron. The disintegration of particles from the positron-emitting radiotracer is recorded by sensors placed around the head, and reconstructed images reflect the location and concentration of the isotope for a given place. PET can locate activity changes in spatial resolution of 6 mm for all part parts of the brain and, although it is progressively being replaced by fMRI, PET remains necessary for molecular, receptor, neurotransmitter and gene imaging [36]. PET can be used to study drugs of abuse in a number of ways [37]:

1. Using radiolabelled drug to ascertain drug distribution in the brain and other organs
2. Using tracer doses of drug (where only a small fraction of binding sites is occupied) to investigate local concentrations of drug binding sites
3. Determining the degree of binding site occupancy by a drug
4. Measuring competitive binding between a radiolabelled drug and endogenous neurotransmitter
5. Examining the effects of drugs of abuse on other neurotransmitter systems
6. Investigating the activity of enzymes that transform the radiolabelled drug into a labelled product that is 'metabolically trapped' in tissues

A number of radiotracers are available to image neurochemistry relating to drug addiction, including ^{3}H-SCH23390 for dopamine D_1 receptors, ^{11}C-raclopride for D_2 receptors and ^{11}C-methylphenidate or ^{11}C-WIN35428 (a cocaine analogue) for dopamine transporters. SCH23390 has also been shown to interact potently with serotonin 5-HT_2 receptors as well as D_2 receptors [38]. Levels of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) can also be measured with PET radiotracers ^{11}C-clorgyline and ^{11}C-deprenyl respectively. MAO-A is located predominantly within neurons while MAO-B is largely localised to glial cells and is involved in the metabolism of dopamine [39]. 2-^{18}F-fluoro-2-deoxy-D-glucose (FDG) can be used to measure brain glucose metabolism [40], which is considered a marker of brain function. PET has been used extensively in both preclinical and clinical research and can also be used for functional imaging during tasks; however, only human PET studies of dopaminergic function and cerebral metabolism in drug addiction will be discussed.

3.1.1. Cocaine

The role of dopamine in the psychostimulant actions of cocaine have been thoroughly investigated by animal studies, therefore PET studies of cocaine addiction have predominantly been centred around dopaminergic transmission. An early study by Volkow et al. [41] assessed the effects of chronic cocaine use on postsynaptic dopamine receptors in cocaine users with ^{18}F-N-methylspiroperidol (NMS). The ratio index represents the slope of the ratio of radioactivity in the striatum to radioactivity in the cerebellum, and is used as an index of postsynaptic dopamine receptor availability. Analysis of ratio index values found that non-detoxified cocaine users showed lower than normal uptake of NMS in the striatum but values of the participants who had been detoxified for four to five weeks did not differ from controls, suggesting that decreased receptor availability may be temporary and associated with the period of time since last cocaine use.

Volkow et al. [42], [43] then investigated the patterns of regional brain metabolism and D_2 receptor availability using FDG and NMS respectively, to determine whether regional brain function may be related to cocaine dependence and withdrawal. Participants in the early trial were studied within one to four weeks after their last dose of cocaine. Recently abstinent users displayed higher glucose metabolism rates than both longer abstinent users and controls, particularly in the orbitofrontal cortex and basal ganglia regions; however, no differences were observed between the longer abstinent group and controls. The selectivity of changes in glucose metabolism suggested that the regional metabolic abnormalities seen in cocaine users during the detoxification phase may be related to alterations in dopamine activity [42]. In the later trial, cocaine users exhibited significantly lower NMS uptake, indicating decreases in D_2

receptor availability, which persisted for up to three months after drug withdrawal. Correlational analysis showed that these decreases were significantly associated with lower metabolic rate in several frontal brain regions, most prominently in the orbitofrontal cortex and the cingulate gyri, suggesting that dopamine dysregulation of regions involved in motivational drive and affect may result in the loss of control that is responsible for drug-taking behaviour [43].

The relationship between dopamine transporter occupancy, blockade by cocaine and the subsequent subjective effects has also been evaluated. Volkow et al. [44] tested the ability to block or attenuate the high elicited by prior dopamine transporter blockade by administering two doses of methylphenidate 60 minutes apart and comparing responses in healthy drug-naïve male participants. Although pre-treatment with methylphenidate significantly reduced ligand binding, no association was found between the level of transporter occupancy and the subjective perception of a 'high'. However, a negative correlation was observed when transporter occupancy was close to 100% suggesting that greater than 80% transporter blockade needs to be achieved in order to prevent the high induced by cocaine [44]. These findings were extended in another study using ^{11}C-cocaine to measure the direct relationship between dopamine transporter blockade and the subjective effects of cocaine in current cocaine users [45]. Intravenous cocaine administration (0.3-0.6 mg/kg) resulted in 60-77% dopamine transporter blockade, and the magnitude of self-reported 'high' correlated with the degree of transporter occupancy in the striatum. Furthermore, the temporal course of self-reported feelings of 'high' paralleled that of cocaine concentration within the striatum, a region implicated in the regulation of motivation and reward. These findings suggest that a substitution medication for cocaine addiction would only be effective if given at doses that achieve almost complete dopamine transporter blockade [45]. The results of studies evaluating the potential for methylphenidate as a pharmacological substitute for stimulant addiction will be discussed further in later sections of this chapter.

The mechanisms involved in craving and the role of drug-related cues in addiction and relapse have also been investigated using FDG. Long-term cocaine users showed regional increases in metabolism within the cortex and medial temporal lobe when presented with cocaine-related cues [46]. Furthermore, there was a significant correlation between self-reported craving and regional glucose metabolism in the dorsolateral prefrontal cortex, medial temporal lobe – particularly in the amygdala – and cerebellum that was not seen in healthy control participants, suggesting that the effects of such cocaine-related stimuli are dependent upon a history of cocaine use. These regions correspond to a distributed neural network that links emotional and cognitive aspects of memory; therefore it is possible that the association between environmental cues and cocaine craving is mediated by this network [46]. Similar findings were observed in a later study by Bonson et al. [47] using neutral and cocaine-related visual cues and an evocative cocaine-related script. Cocaine-related stimuli elicited increased self-reported feelings of craving in cocaine users, which correlated with greater brain activations in the left amygdala/rhinal cortex, left lateral orbitofrontal cortex, right superior frontal cortex and left posterior insula. These results suggest that induction of drug craving involves a neural network which assigns incentive motivational value to environmental stimuli via activation of regions that process information about memories and emotions [47]. The identification of specific regional activation associated with craving may be important for directing future investigations into the mechanisms and therapeutic targets for relieving craving in drug addiction [46].

3.1.2. Methamphetamine

In animals, methamphetamine administration is well known to cause damage to dopamine terminals [48], and post-mortem data from human methamphetamine abusers indicate deficits in striatal dopamine markers [49]. McCann et al. [50] carried out the first PET study in living humans using ^{11}C-WIN35428 to investigate decrements in striatal dopamine transporter density in abstinent methamphetamine and methcathinone users. Results were compared to control participants and patients with early Parkinson's disease. Analysis revealed a significantly reduced density of ^{11}C-WIN35428-labelled dopamine transporter binding sites in the caudate nucleus and putamen of participants with a history of methamphetamine and methcathinone use compared to controls, though these decreases were not as pronounced as those observed in Parkinson's patients. A later longitudinal study using the dopamine transporter radioligand ^{11}C-methylphenidate provided evidence that losses in dopamine transporter density recover with abstinence [51]. Abstinent methamphetamine users were tested within six months of last methamphetamine use and again at least nine months later if they remained drug-free [52]. The results showed significantly higher ^{11}C-methylphenidate binding in the caudate and putamen of methamphetamine users following protracted abstinence suggesting significant recovery of dopamine transporter density in those who stayed drug free for at least nine months after the initial testing session. Furthermore, the period between test sessions positively correlated with dopamine transporter binding, indicating that the recovery of transporter binding may be, in part, a function of the duration of abstinence [51].

Previous PET studies of methamphetamine users have reported losses in dopamine transporters; however, the first study to investigate D_2 receptor density was carried out by Volkow et al. [53] using ^{11}C-raclopride. PET measures of D_2 receptors predominantly reflect levels of postsynaptic receptors [54]. Estimates of D_2 receptor availability in methamphetamine users were significantly lower than those in controls in the caudate and putamen, which may reflect receptor down regulation in response to high extracellular dopamine content secondary to the acute pharmacological effects of methamphetamine, as well as a methamphetamine-induced loss of dopamine transporters [49]. Reductions in D_2 receptor numbers have been reported in users of other drugs, including cocaine, alcohol and heroin, which suggest that reduced D_2 receptor density is not specific to any type of drug addiction but may underlie a common abnormality in addiction or be a common predisposing factor.

Because striatal D_2 receptor levels have been associated with metabolic rates in the orbitofrontal cortex of cocaine users [43], the authors investigated whether a similar dopaminergic dysfunction underlies the compulsive behaviour seen in methamphetamine users. D_2 receptor availability in the putamen of the methamphetamine group correlated significantly with metabolism in the orbitofrontal cortex, which may reflect dopamine-mediated striatal regulation of orbitofrontal activity via striato-thalamo-cortical pathways [55]. These findings are in accordance with previous findings in cocaine users, suggesting that D_2 receptor-mediated dysregulation of the orbitofrontal cortex may underlie a common mechanism for loss of control and compulsive behaviour in drug addiction.

The first study of the non-dopamine neurons in human methamphetamine users was carried out using FDG to assess changes in regions other than those innervated by dopamine [56]. Compared to control participants, global metabolic rate was significantly higher in methamphetamine users, particularly in the parietal cortex, and analysis of relative measures

also showed significantly lower metabolism in the thalamus and striatum. The patterns of hypometabolism in the striatum closely reflect those of dopamine transporter reduction, and the authors propose that hypermetabolism in the parietal cortex – which is not significantly innervated by dopamine – is the result of methamphetamine-induced effects on circuits other than those modulated by dopamine i.e. glutamate and serotonin. These findings provide evidence that methamphetamine induces persistent metabolic changes in brain regions neuroanatomically connected with dopamine as well as in regions that are not innervated by dopamine.

Chronic methamphetamine use is often accompanied by psychiatric symptoms during intoxication or withdrawal; symptoms include psychosis and anxiety and mood disturbances, which can reflect neurochemical abnormalities detectable by PET. The relationship between dopamine transporter density and clinical characteristics was investigated in abstinent methamphetamine users with ^{11}C-WIN35428 [57]. In comparison to controls, methamphetamine users showed significantly lower dopamine transporter binding potentials in the caudate/putamen, nucleus accumbens and the prefrontal cortex. Moreover, significant correlations were observed between dopamine transporter binding potential and clinical measures in the caudate/putamen and nucleus accumbens but not the prefrontal cortex i.e. decreased dopamine transporter density in the caudate/putamen and nucleus accumbens was associated with increased durations of methamphetamine use and greater scores on the positive symptoms subscale of the Brief Psychiatric Rating Scale. These results show parallels between reduced dopamine transporter density in the brain, which was associated with the duration of methamphetamine use, and symptoms of a chronic psychotic state in methamphetamine users. However, transporters are only one part of the dynamics of the dopamine transmission and further study is needed to elucidate the causal mechanisms of methamphetamine-induced psychosis. London et al. [58] conducted a study to investigate whether dysfunction in certain regions may underlie negative affect in recently abstinent methamphetamine users.

The Beck Depression Inventory and State-Trait Anxiety Inventory were used to rate depression and anxiety, respectively, on the day of the PET examination; results were correlated with regional glucose metabolism measure using FDG. Methamphetamine users showed significantly higher self-ratings of depression and anxiety than control participants, and relative regional glucose metabolism also differed in several areas – lower in the anterior cingulate and insula, and higher in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum and cerebellum. Self-reported depressive symptoms correlated significantly with relative glucose metabolism in limbic regions, and ratings of state and trait anxiety correlated negatively with glucose metabolism in the anterior cingulate cortex and left insula. Trait anxiety was also negatively associated with glucose metabolism in the orbitofrontal cortex and positively associated with amygdala activity. These results identified brain substrates of affective dysfunction in recently abstinent methamphetamine users, which may provide potential targets for pharmacological intervention in the treatment of addiction [58].

3.2. Magnetic Resonance Imaging

MRI includes a variety of techniques that do not use ionising radiation but instead use a powerful magnetic field to align the atoms in the body which are then exposed to a beam of radio waves. MRI detects radio signals emitted by the atoms, which differ based on proton composition of tissue and has been an invaluable tool for providing insight into the structure, function and biochemistry of the human brain, in both clinical settings and research.

3.2.1. Functional MRI

fMRI has the ability to detect small magnetic fields induced by increases in blood oxygen that occur in areas of heightened neuronal activity [59]. The most common form of fMRI measures changes in magnetic fields associated with the ratio of oxygenated to deoxygenated haemoglobin, referred to as the blood oxygenation level-dependent or BOLD contrast [60]. During activation of a brain region, this ratio changes as increased delivery of diamagnetic oxygenated blood into that region temporarily surpasses the consumption, consequently decreasing the amount of paramagnetic deoxygenated haemoglobin. Having lower levels of deoxygenated haemoglobin in a region of the brain alters the T2*-weighted magnetic resonance signal and results in less rapid signal decay [61]. The recorded signal is stronger; hence, deoxygenated haemoglobin is sometimes considered an endogenous contrast enhancing agent. This small signal increase – typically about 1% or less – serves as a marker of functional activation and can vary depending on the strength of the applied field [59, 61]. The magnitude of the signal is dependent upon the changes in blood flow and volume within a tissue, as well the change in local oxygen tension so there is no straightforward relationship between signal change and a single physiological parameter [61]. Although, unlike PET, fMRI cannot report absolute changes such as units of blood flow, it allows for visualisation of neural activities with higher spatial and temporal resolution than PET or single-photon emission computed tomography (SPECT) by monitoring changes in blood flow-induced signals in real time. Advances in gradient coil technology have allowed ultra-fast imaging, in which complete cross-sectional images are recorded in 50-100 ms, permitting multi-slice recording of the entire brain within seconds. Different task-related stimuli can be presented to a participant during fMRI and can localise changes in basic functions including primary sensory areas, areas involved in simple motor tasks or higher-order areas responsible for cognitive function. The haemodynamic response to repeated stimuli over a typical experimental time course is recorded as a series of low resolution images which are then mapped onto high-resolution anatomical images and analysed.

3.2.1.1. Cocaine

Functional neuroimaging in cocaine dependence indicates prefrontal deficits, suggesting that cocaine users show attentional biases toward drug-related stimuli, poor inhibitory control and compromised behavioural monitoring and evaluation [62]. Attentional control has been assessed using Stroop tasks where irrelevant information requires participants to engage cognitive control to inhibit a prepotent response and execute a task-relevant response [63]. Typical versions of the Stroop task present words in different font colours and require participants to ignore the word name and respond to the font colour (colour-word Stroop). ‘Emotional’ Stroop tasks present drug-related colour words, or drug-related pictures

surrounded by coloured borders and require participants to ignore the picture and respond to the border colour (colour-word drug Stroop) [64].

The neural mechanisms underlying attentional biases have not been extensively studied. Goldstein et al. [65] conducted an imaging study using with the colour-word drug Stroop to investigate the role of the anterior cingulate and orbitofrontal cortices in the processing of salient cues. The task produced bilateral activation of the anterior cingulate cortex, a region frequently implicated in cognitive dysfunction. Hypoactivation was observed in the rostral anterior cingulate and medial orbitofrontal cortices of cocaine users for drug-related words compared to neutral words, which correlated with more errors committed for drug-related words. These results suggest that the abovementioned regions may contribute to different aspects of drug-related responses. Brewer et al. [66] used the colour-word Stroop to investigate the relationship between regional brain activation and treatment outcomes using behavioural therapy. During the Stroop task, cocaine users activated similar brain regions as those reported in non-addicted individuals – the anterior cingulate cortex, dorsolateral prefrontal cortex, parietal lobe, insula and striatum; however, activation in corticostriatal regions were correlated with reported abstinence and cocaine-free urine toxicology. These findings suggest that the neurocircuitry underlying cognitive control may play a role in behavioural treatment outcomes and that neural activation patterns during cognitive tasks can be predictors of treatment response. Attention switching studies assess switching between externally presented stimuli (e.g. between sensory modalities or between competing stimuli in one modality) [67] or between task sets (e.g. between mathematical operations and language-based operations) [68]. Attentional control of thoughts may be particularly relevant to drug abuse as perseverative thinking is characteristic of many clinical conditions including drug dependence [62]. Garavan [69] operationalised attentional control of thoughts in a task which required participants to switch between items held in working memory. Using such a task, Kübler et al. [70] found evidence of impaired attention switching in cocaine users. These impairments manifested as hypoactivity in the cingulate and prefrontal areas and putamen, while other task-related cortical areas, such as the dorsolateral prefrontal and anterior frontal cortices [71] were unaffected. This finding provides evidence for the neurological basis of impairment in disengaging attention from drug-related thoughts that characterises drug-seeking behaviour and/or contribute to the maintenance of addiction [62, 70].

Frontal lobe functions are thought to be involved in the control and regulation of behaviour in cocaine users [72]. A key function of this region is to control behaviour via inhibitory processes that suppress or terminate prepotent responses [73]. The failure to develop adequate inhibitory control and/or the loss of previously learned inhibitory control may have profound effects on the ability of an individual to gate prepotent behaviours, such as cocaine use [74]. The GO-NOGO task requires the suppression of prepotent behaviours and has been conducted with and without varying working memory demands to assess inhibitory control in active cocaine users [74, 75]. In both studies, cocaine users showed a compromised ability to exert control over strong prepotent urges that was associated with reduced activity in the anterior cingulate cortex, insular regions and the left inferior frontal gyrus. These data demonstrate that midline areas of the anterior cingulate are critical for cognitive control and are less responsive in cocaine users, suggesting that addiction may be accompanied by a disruption of brain structures that are critical for higher-order cognitive control. With higher working memory demands, increased activity was observed in the left cerebellum of cocaine users, which may indicate a compensatory response to diminished

prefrontal activation. The results indicate that cocaine users experience difficulty in inhibiting actions, particularly when working memory demands increase, which is the case during cue-induced craving [47]. This provides support for the importance of cognitive functions in maintaining abuse or predisposing users towards relapse. Improving our understanding of the neural activity associated with stress and stress-induced drug craving could be beneficial for the development of treatments to prevent relapse in cocaine dependence.

3.2.1.2. Methamphetamine

fMRI has also been used to assess the neural substrates of cognitive function relevant to methamphetamine addiction; impairments have been observed in tasks of decision making and cognitive control. Cognitive impairment may contribute to and promote maintenance of the maladaptive actions associated with drug-seeking behaviour and addiction [76]. The orbitofrontal cortex plays a vital role in stimulus-reinforcement association learning and the correction of these associations when contingencies change [77]. Decision making, which involves balancing expectations with stimulus-associated rewards or reinforcing possibilities, is one of three behavioural functions affected by orbitofrontal and dorsolateral cortex dysregulation [78]. The decision making process itself involves several cognitive and non-cognitive functions [79], such as attention, working memory [80], contingency approximation [81, 82], hypothesis testing [82], impulsivity [83, 84] and risk taking [85]. Paulus et al. [79] used a two-choice prediction task to investigate whether methamphetamine users in early abstinence showed altered decision making rules. Analysis revealed that methamphetamine users relied more heavily on an outcome-dependent strategy (win-stay/lose-shift) and the magnitude of these behavioural differences decreased with increasing duration of abstinence. This increased use of win-stay/lose-shift strategy supports the hypothesis that methamphetamine users are more driven by the immediately preceding outcome, even in situations without a priori advantageous or disadvantageous response bias. Furthermore, methamphetamine users displayed more task-related activation in the bilateral prefrontal, parietal and insular cortices but showed no activation in the left prefrontal, bilateral ventromedial prefrontal and right orbitofrontal cortices. The discrepancies in task-related activation between methamphetamine users and controls are consistent with previous studies, which show those areas are essential in the decision making process [85, 86]. A further study using the two-choice prediction task investigated whether methamphetamine users exhibited altered sensitivity to different degrees of success or failure, as well as the influence of stimulus presentation on response during decision making [87]. Recently abstinent methamphetamine users were found to be no more or less sensitive to success or failure than controls. The increase in win-stay/lose-shift consistent responses by methamphetamine users was independent of success rate, rather a result of an increased response to the previous stimulus and not due to altered processing of success or failure. Irrespective of error rate, methamphetamine users showed diminished task-related activation in the bilateral inferior prefrontal and dorsolateral prefrontal cortices, as well as in the bilateral parietal cortex and left superior temporal gyrus. While control participants showed success-related patterns of activation in the left insula, middle frontal gyrus, precuneus and inferior parietal lobe, activation in these areas of methamphetamine users was inversely related to the degree of outcome predictability i.e. highest activation when the outcome was most unpredictable. These findings are consistent with the idea that stimulant addiction is a state where stimuli exert a strong influence on response selective, regardless of associated outcomes [76].

Paulus et al. [88] conducted the first study using fMRI to predict relapse in substance-dependent participants. Performance on the two-choice prediction task was assessed in recently abstinent methamphetamine users, and participants were followed up one year after the imaging session. As hypothesised, methamphetamine users who relapsed during the follow-up period showed less activation in the dorsolateral prefrontal, parietal and temporal cortices and the insula – a network of structures involved in decision making. fMRI activation patterns within the right insular, posterior cingulate and temporal cortices correctly predicted 20 of 22 participants who did not relapse and 17 of 18 participants who did; upon regression analysis, activation in the right middle frontal and middle temporal gyri and posterior cingulate were identified as the best predictors of time to relapse. These results suggest that functional neuroimaging may prove a valuable clinical tool for assessing susceptibility to relapse.

Chronic methamphetamine use is also associated with structural deficits in the frontal and basal ganglia regions that play an important role in inhibitory control, which is closely related to impulsivity. Impulsivity has been operationalised in terms of the inability to inhibit prepotent actions – people who are impulsive have difficulty inhibiting action, whereas people who are not impulsive find it easier to do so [89]. 'Delay discounting', the relationship between the delay and value of reinforcers, has been hypothesised to be the basis of impulsivity [90]. Rewards and punishments are more potent reinforcers when they are immediate rather than delayed; this may be particularly relevant to addiction as the rewarding effects of drug use are relatively immediate and the consequent adverse effects tend to be delayed, and drug users tend to devalue or discount future rewards. The ventromedial prefrontal cortex, including the orbitofrontal cortex, is indirectly involved in the valuation of delayed rewards. Monterosso et al. [91] and Hoffman et al. [92] combined the Delay Discounting Task with fMRI to assess this phenomenon in current and recently abstinent methamphetamine users. Behaviourally, methamphetamine users showed more delay discounting than control participants – the control group was approximately indifferent in choosing between $20 immediately and $28 delayed by one month, whereas the methamphetamine users group was approximately indifferent in choosing between $20 immediately and $47 delayed by one month, showing a greater than normal willingness to trade reward amount for immediacy [91]. Analysis revealed significantly different neural recruitment among methamphetamine users because control participants displayed minimal recruitment during 'easy choice' blocks, while recruitment during 'easy choice' blocks in methamphetamine users was close to the level observed in 'hard choice' blocks which may indicate inefficiency of cortical processing related to decision making. Control participants displayed more robust cortical activation in the anterior cingulate, dorsal anterior cingulate and right dorsolateral prefrontal cortices – the anterior part of a brain system that connects working memory, spatially-directed attention [93, 94] and cognitive control [95]. Interestingly, amygdala activation in methamphetamine users during choice of delayed rewards was associated with a greater degree of discounting, which may represent the aversive nature of picking the deferred option. The authors suggest that methamphetamine users who discount more heavily may be at greater risk of relapse, therefore heavy discounting may provide a target for pharmacological and psychosocial intervention aimed at changing the magnitude of preference for immediate rewards [91].

3.2.2. Structural MRI

The investigation of structural changes in the brain using MRI has become increasingly important for the study of addiction. Pathological changes resulting in cell loss manifest as loss of brain tissue or atrophy, which can be detected by structural MRI [96]. Methods of analysing brain atrophy include visual inspection by experienced radiologists or manual measurement of structures of interest; traditionally, the most commonly employed method was region of interest (ROI)-based volumetric analysis. ROI-based analysis requires manual delineation of the regions and can be very accurate; however, the process is time consuming and researchers must have the requisite anatomical knowledge. More recently, with the advancement of MRI, automated techniques have been developed to enable the rapid exploratory assessment of atrophy across large study groups and circumvent the need for manual delineation and subjective visual inspection. Voxel-based morphometry (VBM) is one such automated tool that is used to investigate changes in brain tissue concentration [97, 98], thus allowing assessment of damage within a structure even if its overall size has not changed. The process involves spatial normalisation of individual data – typically high resolution T1-weighted volumetric images – to the same stereotactic space, extracting and smoothing the grey matter and then performing statistical analysis across all voxels in the image to localise group differences which can then be used to infer the presence of atrophy or tissue expansion [96, 97]. Although VBM can be used to investigate both grey and white matter density, the majority of VBM studies in clinical populations focus on grey matter changes. Abnormalities in white matter may be assessed more accurately with other imaging techniques discussed below.

3.2.2.1. Cocaine

In addition to the functional abnormalities associated with cocaine use, structural abnormalities have also been reported. An early volumetric analysis of the prefrontal lobe of abstinent polysubstance users found that participants displayed significantly lower prefrontal lobe volume with increasing years of cocaine use [99]; however, as participants were polysubstance users, with all participants reporting alcohol use and half of the participants reporting 2-15 year histories of heroin use, these results may not be attributable to cocaine alone. Another study evaluated the relationship between age, and frontal and temporal lobe volumes in young male cohorts of cocaine and methamphetamine users [100]. A significant negative correlation was observed between age and total temporal volume of cocaine users, but not in methamphetamine users or controls. Further segmentation of brain regions into grey and white matter revealed that the negative correlation was predominantly induced by a significant age-related decline in grey matter volume. The magnitude of euphoric effects of cocaine has previously been negatively associated with ventricular-brain ratio [101], suggesting that reductions in cortical grey matter volumes may be related to a diminished capacity to experience the cocaine-induced ‘high’. Therefore, it is possible that utilising cortical grey matter volumes as a marker of individual susceptibility to the euphoric effects of drugs of abuse may be of relevance to the development of pharmacotherapy for addiction [100].

Franklin et al. [102] carried out the first VBM study in cocaine-dependent participants to determine whether cocaine use is associated with structural changes within regions involved in decision-making processes and autonomic arousal. Analysis revealed significant decreases in grey matter density in the ventromedial orbitofrontal, anterior cingulate, anteroventral

insular and superior temporal cortices of cocaine-dependent participants, which may reflect decreased neuronal content. No areas of increased grey matter or white matter differences were observed. Abnormalities in these particular regions may contribute to interrupted or imbalanced cognitive processing and may underlie the characteristic behavioural patterns associated with cocaine addiction [102]. Another study utilised VBM to relate functional impairments to possible structural abnormalities in short-term abstinent cocaine users, with a priori regions based on fMRI data from the same group. Lower grey matter density was observed in the frontal cortex of cocaine users – the cingulate gyrus, lateral prefrontal cortex, and medial and lateral aspects of the orbitofrontal cortex, but no group differences were seen in white matter. These areas overlap with findings from PET studies which showed less activation in the right lateral prefrontal cortex during the Iowa Gambling [103] and Stroop Interference Tasks [104], and greater activation in the cingulate gyrus, suggesting a relationship between structural integrity and functional performance. Recently, Hanlon et al. [105] carried out the first study to directly compare cognitive performance and neuro-structural integrity in recently abstinent cocaine users with both current users and non-drug-using controls. Current users showed significantly lower cortical and subcortial tissue density relative to controls but tissue density of abstinent users did not differ from healthy levels. Furthermore, cortical grey matter density correlated with performance in several tests of cognitive function with superior performance by abstinent users compared to current users. Considered together, the results suggest that individuals who are able to remain abstinent for a period more than one month may have more cortical grey matter and greater cognitive ability than individuals who continue drug use, indicating grey matter normalisation with protracted abstinence.

Sim et al. [106] conducted a study using an optimised VBM technique to study cerebellar structural abnormalities in cocaine users. Optimised VBM [107] incorporates additional spatial processing steps to improve image registration and segmentation to increase sensitivity and reduce voxel misclassification errors compared to standard VBM methods. Cocaine users showed lower grey matter density in the bilateral premotor cortex, right orbitofrontal cortex, bilateral temporal cortex, left thalamus and cerebellum compared to controls, as well as significantly lower white matter density in the cerebellum. The changes in grey and white cerebellar density correlated with deficits in executive function and decreased motor performance, suggesting that the cerebellum is vulnerable to cocaine-induced effects and such deficits may contribute to neuropsychological deficits and motor dysfunction.

Tensor-based morphometry (TBM) is a more recent voxel-based method for estimating changes in brain structure [108], and has been shown to provide methodological improvements over VBM. The Jacobian determinant is one of the main TBM metrics that directly measures tissue growth or atrophy [109]; the main advantage of TBM is that it can be applied directly to Jacobian determinants without the need for tissue segmentation or spatial smoothing [110, 111]. A recent study failed to detect any cocaine-related volume differences in any brain structure with both TBM and VBM [112]. The authors suggest that this lack of difference may be due to variations in cohorts and demographic factors as well as analysis methods. Evidence from studies using other MRI modalities suggests that cocaine use is associated with relatively limited damage to myelin and axonal injury and some gliosis [113-115]. While demyelination and axonal loss can result in reduced tissue volume, gliosis has the opposite effect; therefore, the lack of overall volumetric changes seen here may not be surprising.

3.2.2.2. Methamphetamine

The strongest evidence for stimulant-associated changes in brain structure, and possible stimulant-induced neurotoxicity, has been drawn from studies relating to methamphetamine use. Bartzokis et al. [100] carried out the first controlled study to measure structural differences in methamphetamine users compared to cocaine users and controls. Both methamphetamine and cocaine users displayed significantly smaller temporal lobe volumes but only cocaine users showed a significant age-related decline. The reduction in temporal lobe volume was localised to grey matter suggesting that these drugs may be associated with region- and drug-specific reductions in brain volume that exceed 'normal' age-related loss of cortical grey matter. In a later trial, high-resolution MRI was combined with computational brain-mapping techniques to determine the pattern of structural brain changes associated with chronic methamphetamine use in the cortex, hippocampus, white matter and ventricles [116]. Analysis revealed that methamphetamine-dependent participants had lower grey matter in the cingulate, limbic and paralimbic regions, as well as smaller hippocampal volumes, which correlated with memory performance on a word-recall task, and significant white matter hypertrophy. The authors suggest that chronic methamphetamine use is associated with a selective pattern of cerebral deterioration, particularly in the medial temporal lobe and limbic cortices, and white matter hypertrophy may reflect adaptive glial changes or altered myelination in response to chronic drug exposure [116]. Chang et al. [117] carried out a study in short-term abstinent methamphetamine users and proposed that evaluation of striatal structures may provide insights into methamphetamine-induced brain injury. Methamphetamine users showed enlarged bilateral putamen and globus pallidus but uncompromised cognitive performance relative to controls. However, poor cognitive performance and high cumulative lifetime methamphetamine use were associated with smaller striatal structures, suggesting that striatal enlargement occurs only during early phases of drug dependence as a compensatory response to methamphetamine-induced injury and greater cumulative methamphetamine use eventually leads to reduced striatal volume and poorer cognitive performance [117].

In accordance with previous findings, significantly larger striatal volumes were observed in abstinent methamphetamine users in a study examining the separate and combined effects of methamphetamine dependence and HIV infection on brain morphology [118]. The caudate nucleus, lenticular nucleus and nucleus accumbens showed significant methamphetamine-associated increases, with a larger increase in the nucleus accumbens of younger methamphetamine users without HIV. Significant increases in parietal lobe volume of methamphetamine users were also observed, which correlated with more severe cognitive impairment; however, lower cortical volumes were observed in HIV-positive individuals which also correlated with cognitive impairment suggesting that larger parietal lobe volumes are unlikely to represent an adaptive compensatory mechanism to methamphetamine-induced neurotoxicity as proposed for striatal volume increases.

A study by Kim et al. [119] was the first to use VBM with methamphetamine-dependent participants to assess grey matter density, as well as the first to compare short-term and long-term abstinent users. Significant differences in grey matter were observed between three groups – the short-term abstinent group had lower right middle frontal grey matter density than the long-term abstinent group who had lower grey matter density than healthy controls. This pattern of results was also observed for performance during the Wisconsin Card Sorting Task – a task that assesses the ability to identify abstract categories and shift cognitive sets,

and has been used as a measure of frontal lobe damage [120]. The short-term abstinent group committed the greatest number of total errors relative to long-term abstinent users and controls. The authors proposed that decreases in grey matter density may be related to microscopic neuronal injury from methamphetamine-induced ischaemic changes or dopaminergic neurotoxicity, and that deficits in prefrontal grey matter density may partially recover with long-term abstinence [119]. A more recent study by Schwartz et al. [121] used VBM to relate regional grey matter differences and whole brain segmentation volumes to performance on the Delay Discounting Task. Recently abstinent methamphetamine users displayed higher impulsivity in the task, and had reduced grey matter density in the bilateral insula, which has not previously been reported, and in the left middle frontal gyrus, which has been associated with impaired cognitive control. Length of abstinence was associated grey matter density in several regions – positively correlated with the bilateral amygdala and putamen, and negatively correlated with cortical density in the right middle frontal gyrus which suggests that abstinence from methamphetamine may result in volumetric changes or that volumes in these regions are predictive of the ability to maintain abstinence [121].

There appears to be considerable variability in reports of the location and nature of anatomical changes associated with methamphetamine use, further investigation will lead to better understanding and development of treatment for methamphetamine-induced damage.

3.2.3. Diffusion Tensor Imaging

DTI measures diffusivity of water molecules and shows the preferential orientation of movement in white matter tissue [122]. It provides information about the microstructure and organisation of white matter which is not available with other imaging methods, and allows for quantitative assessment of the integrity of anatomical connectivity in white matter. Isotropic diffusion describes diffusion in the absence of barriers where water molecules undergo Brownian motion in all directions, whereas anisotropic diffusion refers to diffusion where water molecules exhibit directional preference. High anisotropy is observed in organised structures such as fibres in white matter since water diffusion is restricted along the length of tracts. Decreased anisotropy may imply greater diffusivity of water related to white matter pathology or loss of fibre integrity. Fractional anisotropy (FA) is the most commonly used index for quantifying anisotropy [123]; it is a scalar measure ranging from 0 to 1, where 0 indicates isotropic diffusion and 1 represents anisotropic diffusion. FA is mathematically related to the diffusivity values – eigenvalues – of the diffusion tensor along three principal directions. Animal studies have suggested that individual eigenvalues are more specific markers of myelination and axonal morphology than FA or mean diffusivity [124, 125]. Diffusivities perpendicular to axonal fibres are rarely considered separately, and are usually averaged. It has been shown that demyelination increases diffusion perpendicular to the direction of the tract (radial diffusion, $\lambda_2+\lambda_3/2$ or $\lambda_\perp$) with minimal effect on diffusion along the tract (axial diffusion or λ_1); conversely, axonal damage results in decreased λ_1 with relatively little effect on $\lambda_\perp$ [124]. Changes in diffusion eigenvalues could potentially be used to differentiate myelin loss and axonal injury. Diffusion data can also be used to trace brain pathways by calculating the orientation of maximum diffusion at each point and using these orientation estimates to reconstruct a pathway that corresponds to the underlying fibre pathway [126]. To date, no tractography studies have been carried in participants with stimulant addiction.

3.2.3.1. Cocaine

Cocaine dependence is associated with white matter abnormalities which occur in multiple locations; however, it has been suggested that investigating white matter hyperintensities is neither specific nor sensitive enough to identify subtle abnormalities in frontal white matter [127]. Therefore, Lim et al. [127] carried out the first study to show that cocaine dependence may be associated with compromised white matter microstructure *in vivo*. The effects of cocaine were determined in different levels of the frontal and temporal lobes, as well as the corpus callosum. Cocaine-dependent participants showed significantly lower FA in frontal white matter at the anterior-commissure-posterior commissure (AC-PC) plane. Compromised white matter integrity was predominantly observed in the inferior frontal brain regions, and no significant changes in white matter integrity were observed in the temporal lobes or corpus callosum. Disrupted connectivity in inferior frontal regions is consistent with hypothesised anatomical circuits, implicating the orbitofrontal cortex in addiction-related phenomena such as craving and compulsive-repetitive behaviours [77, 128]. In a later study by Moeller et al. [129], reduced FA in the anterior corpus callosum was negatively correlated with impulse control and positively correlated with the ability to discriminate between 'target' and 'distracter' stimuli in a memory task. These findings are consistent with prior theories suggesting frontal cortical involvement in impaired inhibitory control in cocaine dependence [73], but may also suggest reduced corpus callosum function manifested as impaired interhemispheric communication rather than damage to the prefrontal cortex [129].

To gain a more specific understanding of the underlying pathology of white matter changes in cocaine dependence, studies have examined diffusion eigenvalues [114, 115, 130]. Higher $\lambda_{\perp}$ has consistently been observed in frontal and parietal regions, as well as the corpus callosum of cocaine users. Measures of white matter integrity also correlated with decision-making deficits in the Iowa Gambling Task, suggesting that compromised white matter integrity may be related to functional impairments in decision making [130].

Studies have also combined DTI with other imaging techniques to allow for concurrent evaluation of the macrostructural and microstructural correlates of cocaine dependence. Lim et al. [131] showed that cocaine dependence was associated with significantly lower FA in inferior frontal white matter with trends toward smaller white and grey matter volumes in the same region. A later study by Romero et al. [132] also found significantly lower FA values in the bilateral inferior frontal white matter, along with higher FA values in the anterior cingulate white matter of cocaine-dependent participants. Macrostructural analysis also revealed a loss in inferior frontal and anterior cingulate white matter volume [132].

Although white matter abnormalities have been identified in cocaine-dependent participants, the relationship between white matter integrity and treatment outcome is not well understood. Xu et al. [133] directly investigated how measures of white matter integrity related to treatment outcomes in cocaine-dependent participants seeking behavioural therapy. Pre-treatment white matter integrity was assessed in participants who received eight weeks of behavioural therapy; DTI parameters were then correlated with measures of treatment outcome. Multiple DTI measures were correlated with self-reported and urine toxicology-based measures of abstinence, showing that worse white matter integrity at treatment onset is associated with poorer abstinence-based outcomes [133]. Further research into the neurobiological characteristics of successfully abstinent participants showed distinct differences between abstinent cocaine users and controls, as well as among short-, mid- and

long-term abstinent subgroups. Higher FA in the right anterior thalamic radiation and right anterior cingulum, and lower FA in the left superior longitudinal fasciculus was associated with longer abstinence, suggesting that FA differences across abstinence durations may reflect dynamic patterns of brain changes in addiction and recovery [134].

3.2.3.2. Methamphetamine

The first DTI study of methamphetamine-dependent participants was carried out by Chung et al. [135], exploring the changes in frontal white matter integrity of long-term abstinent users. Frontal executive function was also assessed using the Wisconsin Card Sorting Task. Methamphetamine users displayed significantly lower FA in three regions of interest – the left and right frontal white matter at the AC-PC plane and the right frontal white matter above the AC-PC plane. Methamphetamine users also committed more errors during the task but only the right frontal white matter above the AC-PC plane negatively correlated with task errors, supporting the hypothesis that frontal white matter integrity may underlie impaired executive function seen in methamphetamine-dependent participants. In a later trial, Tobias et al. [136] used FA as a possible index of gliosis and investigated white matter abnormalities of methamphetamine users during early abstinence. Methamphetamine users displayed significantly lower FA in the right prefrontal white matter above the AC-PC plane, in the midline genu of the corpus callosum, bilateral midcaudal superior corona radiata and right perforant fibres. Changes in FA appear to be limited to late-myelinating structures and, considered together with evidence from previous studies using different MRI modalities (structural MRI, MRS and PET), these findings suggest that frontal white matter and late-myelinating regions are more vulnerable to the effects of methamphetamine.

Kim et al. [137] also assessed the relationship between white matter integrity and impaired cognitive function using the Wisconsin Card Sorting Task in short-term abstinent methamphetamine users. This was the first study to evaluate microstructural abnormalities specifically in the corpus callosum using diffusion eigenvalues. Methamphetamine users displayed significantly lower FA values in the genu of the corpus callosum, as well as lower λ_1 but higher λ_2 and λ_3. Methamphetamine users also performed significantly worse in the task and demonstrated a significant negative correlation between FA and total errors in the genu. There was also a significant positive correlation between λ_2 in the genu and total errors, but not with λ_3. This interesting finding might suggest that λ_2 is more closely related to myelin integrity and is the main source of FA reduction in the genu of the corpus callosum, which, in turn, is associated with impairment of frontal cognitive function [137]. The relationship between behavioural regulation (i.e. cognitive control) and white matter microstructure has also been investigated in long-term abstinent methamphetamine users using the Stroop task [138]. FA and diffusion eigenvalues were obtained in the corpus callosum and correlated with behavioural measures. No group differences were observed in DTI indices in the corpus callosum; however, behavioural analysis revealed that methamphetamine users exhibited greater Stroop interference compared to control participants, which manifested as longer reaction times. Greater Stroop interference significantly correlated with lower FA in the genu of methamphetamine users suggesting that disruptions in white matter integrity may contribute to maladaptive decision making [138]. The basal ganglia have not been previously investigated with DTI; a recent study evaluated the diffusion tensor properties of white matter and subcortical brain regions in a cohort of chronic methamphetamine users [139]. In comparison to controls, methamphetamine users

exhibited significantly lower FA in the frontal white matter, as well as higher λ_1 and $\lambda_\perp$ in the left caudate. The apparent diffusion coefficient (ADC) describes the three-dimensional mobility of water in brain tissue, with higher values indicating greater diffusivity. Although a higher ADC was observed in the left caudate, this was not associated with any measures of drug exposure; however, the significantly higher ADCs observed in the left and right putamen were associated with earlier initiation of methamphetamine use, greater amounts of methamphetamine used per day and higher cumulative lifetime dose. It is somewhat surprising that methamphetamine users exhibited normal FA within striatal structures but higher diffusivity values; the authors proposed that this reflects increased water content and diffusion in the basal ganglia, which may also be related to inflammatory processes or decreased myelination [139].

Sub-analyses for gender differences have been carried out in some of the abovementioned studies. Results from Chung et al. [135] revealed that lower FA values in frontal white matter and more errors in the Wisconsin Card Sorting Task were found only in male participants relative to control participants of the same gender, suggesting that frontal white matter in males may be more vulnerable to the effects of methamphetamine. However, due to the small number of female participants in the trial, these findings cannot be considered as evidence that methamphetamine use is not harmful to females. In contrast, Salo et al. [138] reported no effect of gender on methamphetamine-induced FA changes in the genu of the corpus callosum and Tobias et al. [136] reported significantly lower FA in all but one of the white matter regions examined in female methamphetamine users but no such difference males. These results suggest that methamphetamine-induced effects can be observed in both males and females, and argue against the possible neuroprotective effects of oestrogen [135]; however, further studies are needed to examine gender differences in white matter microstructure.

3.2.4. Magnetic Resonance Spectroscopy

Proton MRS is a non-invasive imaging technique that allows for the measurement of chemical products without the use of radiotracers. MRS provides a snapshot of the neurochemical environment within a defined volume of interest and, although it provides less sensitivity than other imaging techniques, MRS has the potential for tracking disease and/or treatment progression. The spectral output of MRS depends on the energy absorbed by specific organic molecules, which is determined by the number of hydrogen atoms (protons) in the compound, as well as in the surrounding environment. The most commonly investigated metabolites include *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr) and *myo*-inositol (MI), along with amino acids glutamate, glutamine and GABA. These compounds form a range of markers for cellular integrity and function. With the exception of the water peak, which is frequently suppressed during acquisition, the NAA signal is the most prominent peak on the spectrum (at 2.02 ppm). It is considered a marker of neuronal viability and therefore a measure of the effects of drug use. The Cho peak (at 3.2 ppm) represents a number of choline-containing compounds and indicates cellular density and cell wall turnover [140]; consequently the signal increases with increasing membrane synthesis. It has been suggested that Cho is a marker of glial density and therefore may be an appropriate marker to track neuronal changes associated with drug use and abstinence [141].

The Cr peaks (at 3.03 and 3.94 ppm) are considered markers of high energy metabolism [142] and the first peak is often used as an internal reference metabolite for other peaks as its

concentration is assumed to be relatively constant. However, data have shown that Cr is not homogeneously distributed across the brain and the assumption that the concentration remains constant may be incorrect under both normal conditions and pathological states [143]. The significance of the MI (at 3.56 ppm) is not well understood but it has been proposed to be a glial marker [144]; elevation of MI in conditions associated with neuronal loss has been interpreted as a sign of gliosis [145]. The neurotransmitters GABA, glutamate and glutamine maintain a balance between excitation and inhibition, in addition to regulating neuronal energy metabolism [146]. At 1.5 T glutamate and glutamine peaks overlap (at 2.34 and 2.36 ppm) and cannot be separated without specialised spectral editing and are often considered as a 'Glx complex'. At 3.0 T, glutamate can be adequately separated from glutamine to provide identification [147]. Similarly, the GABA peak (at 3.03 ppm) is obscured by Cr and other macromolecules [148]. Despite the preponderance of evidence for the role of abnormal glutamate and GABA neurotransmission in drug addiction [149, 150], most spectroscopic studies have focused on metabolites that are comparatively easier to resolve [151].

3.2.4.1. Cocaine

One of the first *in vivo* proton MRS studies was carried out in a group of long-term abstinent cocaine users, measuring concentrations of NAA, Cho, Cr, MI and Glx [152]. Significantly increased Cr and MI were observed in the temporoparietal white matter of abstinent cocaine users with no change in NAA or other metabolites. These findings are suggestive of abnormalities in the non-neuronal cells of subcortical brain regions with no significant neuronal damage; however, it is possible that biochemical evidence associated with neuronal damage may be detected in brain regions not evaluated in this study. In a later study, Chang et al. [153] examined the persistent cerebral metabolite abnormalities of abstinent cocaine users and also determined whether these changes were different in male and female users. A significant decrease in NAA and increase in MI was seen in the midfrontal grey matter of all cocaine-dependent participants, while only elevated MI was seen in the frontal white matter. Gender effects were also observed; males displayed higher levels of Cho in the grey matter as well as elevated Cr levels in the white matter, while females showed significantly higher MI/Cr in the white matter. Higher elevation of MI in female participants suggests stronger glial reactive processes compared to males and differences in cocaine-induced brain injury. Li et al. [113] investigated the effects of cocaine use on metabolites in the basal ganglia and thalamic region of current users and observed significantly decreased NAA in the thalamic region only.

The results pertaining to NAA have not been consistent throughout the literature, which may be due in part to different regions being investigated. However, the predominant view regarding NAA suggests that levels of NAA may be dynamic and reflective of ongoing processes within neurons, as reductions in NAA observed in neurological disease and brain injury are known to be reversible [154, 155]. Moreover, decrements in NAA content associated with cocaine use may be a result of primary neuronal loss or damage, a reduction in synaptic density or the direct effects of cocaine on neuronal activity and subsequent depletion of monoamine neurotransmitters [113, 151]. Yang et al. [156] investigated glutamate within the anterior cingulate cortex, suggesting that it may improve understanding of frontal lobe alterations and the functional significance of glutamate in cocaine addiction. The study demonstrated significantly lower glutamate/Cr in the rostral anterior cingulate

cortex of cocaine-dependent participants which correlated with years of cocaine use but no significant differences in other metabolites.

These findings suggest that glutamate dysfunction is associated with cocaine use and provide support for interventions aimed at normalising glutamatergic transmission and function for the treatment of cocaine addiction. Two studies have demonstrated that cocaine-dependent participants have significantly lower GABA levels in the occipital [157] and prefrontal [158] regions compared to controls. The finding of low GABA within the prefrontal cortex is of particular significance as frontal lobe functions including switching of attention and inhibitory control have been found to be impaired of cocaine-dependent participants. Consequently, the GABA system has been a target for pharmacological treatment in cocaine addiction.

3.2.4.2. Amphetamine

MRS studies investigating the effects of dexamphetamine on brain metabolites have not been from a drug abuse perspective; typically, dexamphetamine has been acutely administered to provide a lithium-sensitive model of mania [159-161]. The doses in these studies do not reflect chronic regimens of amphetamine administration so will not be discussed further.

3.2.4.3. Methamphetamine

Ernst et al. [162] carried out the first MRS study in methamphetamine-dependent participants to examine metabolite abnormalities. Methamphetamine-dependent participants showed a significant reduction of NAA and total Cr in the basal ganglia and significantly increased Cho and MI in the frontal grey matter. These findings have been corroborated by other researchers; Nordahl et al. [163] and Salo et al. [164] observed significantly decreased NAA/Cr levels as well as increased Cho/Cr levels in anterior cingulate regions.

A study of the basal ganglia found reduced Cr/Cho with no change in NAA/Cho in the bilateral basal ganglia; the reduction in Cr/Cho was attributed to abnormal Cr levels [165]. Linear regression analyses between metabolite concentrations and measures of drug exposure and cognitive function were also carried out in the aforementioned studies. Ernst et al. [162] demonstrated an inverse relationship between NAA in the frontal white matter and the logarithm of cumulative lifetime methamphetamine use, while the reduction in NAA correlated with reduced levels of attentional control in a Stroop interference test [164]. Decreased levels of Cr/Cho correlated with a longer duration of methamphetamine use as well as the severity of residual psychotic symptoms resulting from methamphetamine use [165]. Although these studies were carried in abstinent methamphetamine users, relatively fewer studies have used MRS to track the neuronal changes associated with drug abstinence. Nordahl et al. [141] recruited abstinent methamphetamine users and for the purposes of analyses, participants were divided into recently abstinent and distantly abstinent users. All methamphetamine users showed significantly lower levels of NAA/Cr within the anterior cingulate cortex regardless of abstinence duration; however, levels of Cho/NAA in the same region were significantly higher in participants who had recently initiated abstinence compared to participants who had been abstinent for longer than one year, suggesting that Cho can normalise with drug abstinence.

In contrast, Sung et al. [166] found no significant differences in NAA between groups relative to abstinence duration; however, grey matter NAA positively correlated with

abstinence duration whereas NAA in white matter did not, suggesting that methamphetamine-induced damage in the grey matter only may recover with prolonged abstinence. Findings from the earlier trial by Nordahl et al. [141] have recently been extended to a larger sample size. With increased statistical power, Salo et al. [167] confirmed the earlier finding of Cho normalisation within the anterior cingulate cortex as a function of drug abstinence, observing abnormally high Cho/NAA values in the short-term abstinent group but no difference between the long-term abstinent group and controls. Evidence of NAA/Cr normalisation was also observed. Considered together with the evidence of improved cognitive function across periods of drug abstinence, these findings suggest that brain metabolites and function may not show signs of normalisation until an extended period of abstinence has been maintained. These results highlight the need for longitudinal follow-up studies to improve understanding of methamphetamine-induced neurotoxicity and elucidate the mechanisms underlying these changes, as well as comparison to studies in current methamphetamine users to gain a better understanding of the timeline of these effects.

Few studies have extended their investigations beyond NAA, Cho, Cr and MI; however, research has found that the effects of methamphetamine are related to glutamate as well as dopamine and serotonin, and that glutamate may be implicated in the oxidative stress-mediated neurotoxicity associated with methamphetamine use [168]. The first study to assess the effects of abstinence from chronic methamphetamine on the Glx complex was carried out in a cross-sectional sample of participants with longitudinal follow-up of a subset of participants, five months later [169].

At baseline, participants with short periods of abstinence showed the lowest levels of Glx in frontal grey matter which positively correlated with duration of abstinence; after five months of abstinence, Glx in the frontal grey matter showed a trend towards correlating inversely with the duration of abstinence, suggesting normalisation over time. Interestingly, participants who reported symptoms of craving had lower levels of Glx in the frontal cortex than those who did not. These findings suggest dynamic abnormalities relating to Glx in recently abstinent methamphetamine users with depletion of the glutamatergic system and progressive normalisation with prolonged abstinence.

Further studies are needed to evaluate glutamate and glutamine separately and further determine whether the severity of the hypoglutamatergic state robustly correlates with craving and withdrawal symptoms. More recently, Sailasuta et al. [170] investigated levels of glutamate in short-term abstinent methamphetamine users, hypothesising that any changes in brain glutamate due to methamphetamine use will be detectable with MRS and persist beyond drug cessation. Significant elevations of glutamate were observed in the frontal white matter of abstinent methamphetamine users with a concurrent reduction in NAA. Although the findings of these two studies are not concordant, they both offer support for glutamatergic dysfunction associated with methamphetamine use and provide an impetus for further research into the role of glutamate in drug abuse.

4. PHARMACOLOGICAL TREATMENT FOR STIMULANT ADDICTION

Behavioural interventions are the current mainstay of stimulant addiction treatment; cognitive behavioural therapy has been effective in decreasing cocaine use and preventing relapse but the success rates are low. Behavioural treatment must be tailored to the needs of the individual and often require a combination of treatment, social support and supplementary services [25]. Research into effective pharmacological treatments is a fast-evolving area and efforts have intensified over the last decade; therefore only pharmacological agents for addiction treatment will be discussed in this chapter.

Currently, there is no pharmacological therapy with established efficacy for the treatment of cocaine and amphetamine dependence; however, animal models of addiction and increased understanding of the neurocircuitry and neuropharmacological mechanisms implicated in stimulant dependence have provided several potential targets for therapy. Pharmacological treatments for stimulant addiction have been selected based on research into the neurobiological mechanisms involved in different stages of the addiction cycle, animal models and medications approved for other indications that overlap with specific components of addiction [171].

Cocaine and methamphetamine share a number of similarities; pharmacologically they both block the reuptake of dopamine at the synaptic cleft of neurons in the reward pathway and produce comparable mood-altering effects and physiological effects. Amphetamines also stimulate the release and inhibit the breakdown of neurotransmitters. Consequently, there is considerable overlap between agents trialled for treatment of cocaine and methamphetamine dependence. As pharmacological treatments for cocaine addiction were discussed in Chapter One, this chapter will focus on agents that have been evaluated in clinical trials for amphetamine addiction and are broadly classified into agonist replacement therapy and drugs affecting monoamine, GABA and glutamate systems.

4.1. Agonist Replacement Therapy

Some research indicates that agonist replacement (or substitution) therapy may be a promising approach for the treatment of addiction. The underlying principle of agonist replacement therapy is using a drug from the same pharmacological family to partially replace the effects of the abused drug, thereby stabilising the patient [172]. This approach has been successfully used for the treatment of opiate and nicotine dependence. Dexamphetamine and methylphenidate are dopaminergic agents that have been trialled as agonist replacement therapy in cocaine and amphetamine addiction. Dexamphetamine promotes the release of dopamine, noradrenaline and serotonin while methylphenidate has affinity for dopamine and noradrenaline transporters, but not the serotonin transporter and, although both agents have some abuse liability (methylphenidate is reported to have less), research with both agents have yielded promising results.

To date, there have been a small number of randomised controlled trials of dexamphetamine maintenance treatment for amphetamine-dependent participants. A small open-label pilot study by Shearer et al. [173] was carried out to determine the feasibility of

conducting a trial providing dexamphetamine to dependent users. Amphetamine-dependent participants were randomised to receive weekly counselling or counselling plus immediate-release dexamphetamine (up to 60 mg/day) over 12 weeks. No difference in amphetamine use was observed between groups; however, the dexamphetamine-treatment group was significantly more likely to attend counselling, receiving twice as many sessions as the control group. Although this study was underpowered, the results suggest that substitution therapy is potentially beneficial in problematic amphetamine use. More recently, Longo et al. [174] conducted a randomised, double-blind, placebo-controlled trial of sustained-release dexamphetamine in methamphetamine users. Treatment was administered under a flexible dosing regimen (up to 110 mg/day) over 12 weeks, with 4 sessions of cognitive behavioural therapy over the trial duration. Analysis revealed significantly higher retention rates and longer time to dropout in the dexamphetamine-treated group, as well as lower self-reported dependence. These results show that maintenance treatment with once daily sustained-release dexamphetamine can engage and maintain methamphetamine-dependent participants in treatment and support further investigation of maintenance pharmacotherapy as an intervention for methamphetamine addiction. The role of methylphenidate substitution therapy in amphetamine addiction is relatively less well established than in cocaine addiction; only one study has been carried out. A 20-week randomised study of sustained-release methylphenidate (54 mg/day), aripiprazole (15 mg/day) and placebo in intravenous amphetamine users yielded promising results for methylphenidate [175]. The trial was discontinued due to one active medication being significantly worse than placebo; however, interim analysis showed that methylphenidate treatment was associated with a significant reduction in amphetamine use. The authors suggest that sustained-release methylphenidate may be superior to the immediate-release formulation as users may start to experience cravings for amphetamine as soon as the effects of the substitute drug wear off [175].

4.2. Dopamine-Modulating Agents

Because the addictive qualities of methamphetamine are thought to be primarily mediated by enhancement of dopaminergic activity in the mesolimbic system of the brain, clinical research has been dedicated to developing pharmacotherapeutic strategies targeting the dopamine system.

Atypical antipsychotics have been investigated as treatments for methamphetamine addiction because of their ability to block dopamine and/or serotonin receptors. Risperidone was shown to attenuate the discriminative-stimulus effects of dexamphetamine as well as some of the self-reported drug effects [176], and therefore may decrease the drive to use methamphetamine in early recovery. In an open-label pilot study, participants received treatment with risperidone (average dose 3.6 mg/day) over four weeks [177]. Participants who completed the trial significantly decreased their methamphetamine use and urinalysis showed that less than 3% of weekly urine screens were positive. Although the sample size of this study was small and lacked a control group, the results suggest that risperidone may be a candidate for the treatment of methamphetamine addiction and warrants further investigation. A study evaluating long-acting injectable risperidone in methamphetamine addiction has been completed (see http://clinicaltrials.gov, identifier NCT00284206) but currently, no results are available.

In laboratory studies, aripiprazole (10 and 20 mg) has been shown to significantly attenuate the discriminative-stimulus, cardiovascular and subject-rated effects of dexamphetamine [178, 179], suggesting that partial D_2 agonists have potential as pharmacotherapy in the management of stimulant dependence. However, the results of a more recent trial were in support of the abovementioned trial by Tiihonen et al. [175] where aripiprazole treatment was associated with a significantly higher number of methamphetamine-positive urine samples than placebo. A randomised, double-blind, placebo-controlled inpatient pharmacology study was carried out to assess potential interactions between intravenous methamphetamine (15 and 30 mg) and oral aripiprazole (15 mg), as well as the effects of aripiprazole on abstinence-related craving and cue-induced craving [180]. Analysis revealed that aripiprazole had no effect on cue-induced methamphetamine craving or daily baseline craving over the treatment period and was associated with increased craving independent of methamphetamine dosing, as well as significantly increased subjective ratings of 'euphoria' and 'amphetamine-like effects' and decreased 'bad effects' on rating scales. The findings indicate that aripiprazole increased some of the rewarding and stimulant effects of methamphetamine and is unlikely to be efficacious for facilitating abstinence from methamphetamine, but its efficacy using lower doses and/or its role in relapse prevention should nevertheless be investigated.

4.3. GABA-Modulating Agents

Modulation of the GABA system, particularly $GABA_B$ receptors, is of great interest for the potential treatment of drug dependence – GABA has been shown to exert an inhibitory effect on the tonic activity of dopamine neurons in the ventral tegmental area [181] and the nucleus accumbens [182].

Medications that promote GABAergic activity may be promising medications for the treatment of cocaine and methamphetamine dependence. Results from preclinical and early clinical studies supported the use of GABA-modulating medications in the treatment of cocaine addiction; therefore it was suggested that, by extension, they may also be effective in methamphetamine addiction.

4.3.1. Baclofen

Baclofen is the only $GABA_B$ agonist available for human use. In animals, baclofen attenuates cocaine-induced dopamine release in the nucleus accumbens [183] and intravenous self-administration [184-186]. Heinzerling et al. [187] conducted a randomised, double-blind placebo-controlled trial comparing two GABAergic agents to placebo in methamphetamine-dependent participants. Treatment consisted of baclofen (60 mg/day), gabapentin (2400 mg/day) or placebo for 16 weeks along with thrice-weekly relapse prevention sessions. Analysis revealed no effects for either medication relative to placebo in retention, adherence, craving, depressive symptoms or urine drug screens. However, post-hoc analysis showed that only baclofen had a significant effect of treatment in participants, with higher rates of medication adherence. These authors suggested that, while gabapentin did not appear to be effective for treating methamphetamine addiction, baclofen may have a small effect and concluded that further studies of baclofen and other GABAergic medications may be warranted.

4.3.2. Gabapentin

Urschel et al. [188] carried out an open-label trial, which was recently extended to a double-blind, placebo-controlled trial of a propriety combination of gabapentin with flumazenil (a benzodiazepine antagonist) in methamphetamine-dependent participants [189]. The combination of medication (gabapentin up to 1200 mg/day, flumazenil 0.1-0.3 mg) was administered over 30 days with weekly psychosocial treatment based on the Matrix™ model. In accordance with the previous trial, participants in the active medication group reported less methamphetamine use and decreased craving. The authors suggest that this combination of medications may offer potential benefit in reducing craving and increasing engagement in psychosocial treatment amongst methamphetamine-dependent individuals.

4.3.3. Vigabatrin

Vigabatrin (γ-vinyl-GABA) is an atypical antiepileptic medication used for the treatment of epilepsy and seizures. It is a specific and irreversible suicide inhibitor of GABA transaminase that acts to increase GABA neurotransmission. In animals, vigabatrin has been shown to reduce cocaine-induced dopamine release in the nucleus accumbens by 25% [190]. However, vigabatrin has been associated with the development of unacceptable visual field abnormalities [191], which may limit its clinical use. An early study by Brodie et al. [192] assessed the safety and efficacy of vigabatrin in participants who were dependent on methamphetamine alone, methamphetamine and cocaine, and cocaine alone. Eighteen of the 30 participants completed the 9-week trial; 15 of the completers were methamphetamine- and cocaine-free for more than 4 weeks. Vigabatrin treatment was not associated with any visual field defects; therefore the authors concluded that it may be an appropriate candidate for the treatment of methamphetamine and/or cocaine addiction. However, a recent double-blind, placebo-controlled laboratory study found that, although vigabatrin was well tolerated, it was not efficacious for attenuating the positive subjective effects of methamphetamine and may have the potential to elevate cardiovascular parameters [193]. To date, no randomised controlled clinical trials have been undertaken to determine whether vigabatrin is effective for the treatment of methamphetamine addiction.

4.4. Glutamate-Modulating Agents

The glutamatergic system is involved in drug addiction; glutamate levels increase in the nucleus accumbens during reinstatement, and glutamate receptor activation is necessary for reinstatement of drug-seeking behaviour [194]. Therefore medications that inhibit glutamatergic activity may also be valuable for the treatment of addiction. Modafinil is chemically and pharmacologically distinct from amphetamine-like and other central nervous system stimulants. It is currently approved for the management of narcolepsy, obstructive sleep apnoea/hypoapnoea syndrome or idiopathic hypersomnia [195, 196]. It has a complex neurobiological mechanism of action involving both dopamine- and glutamate-enhancing effects – modafinil increases the release of glutamate in the hippocampus and ventromedial and ventrolateral areas of the thalamus, which may contribute to its vigilance-enhancing effects [197, 198]. There is some evidence that the effects of modafinil are mediated by adrenergic α_1-receptors. A recent PET study shows that modafinil binds to the dopamine

transporter, thus possesses similar properties to methylphenidate [199], and is well tolerated with a low overdose risk [200]. A recent randomised, double-blind outpatient study evaluated the subjective and reinforcing effects of modafinil (200, 400 and 600 mg) in cocaine users and found no abuse liability in this population [201]; however, these results should be interpreted with caution. A PET study using ^{11}C-raclopride and ^{11}C-cocaine to measure the effects of modafinil (200 and 400 mg) on dopamine transporters and extracellular dopamine levels found that modafinil blocked dopamine transporters and increased dopamine in regions of the human brain – including the nucleus accumbens. Because drugs that increase dopamine in the nucleus accumbens have the potential for abuse, these results highlight the need for increased awareness of potential abuse and dependence on modafinil in vulnerable populations [199]. Modafinil has weak stimulant properties and has therefore been cited as a putative treatment to decrease stimulant seeking and craving. The rationale to use modafinil in methamphetamine withdrawal treatment was guided, in part, by some of the most prominent features of the methamphetamine withdrawal syndrome – hypersomnolence and fatigue [202]. Modafinil, with its wake-promoting properties, was identified as a medication with the potential to alleviate these symptoms during the withdrawal phase [203]. It may also be a cognitive enhancer in methamphetamine-dependent participants and improve the response to behavioural therapies. A trial by McGregor et al. [203] was the first to evaluate modafinil for safety and tolerability. The 10-day open-label trial compared modafinil (400 mg/day) and mirtazapine (60 mg/day) against 'treatment as usual' with pericyazine in inpatient methamphetamine withdrawal. Modafinil-treated participants had lower withdrawal scores and appeared to experience a significantly milder withdrawal syndrome and less sleep disturbance than mirtazapine- and pericyazine-treated patients. Moreover, participants taking modafinil also reported less fatigue, agitation, anxiety, irritability, tension and frequency of methamphetamine craving. Another small 16-week single-blind trial investigated the efficacy of modafinil (up to 200 mg/day) combined with weekly cognitive behavioural therapy for treatment of methamphetamine addiction among HIV-positive gay men. Ten participants successfully completed the trial, and six of these reduced their methamphetamine use by over 50% [204]. In a more recent trial, participants were randomly assigned to receive 200 mg/day of modafinil or placebo under double-blind conditions for 10 weeks [205]. Treatment retention and medication adherence were equivalent between groups and there were no differences in methamphetamine abstinence, craving or severity of dependence, though compliant patients in the modafinil group tended to provide more negative urine samples over the treatment period. These results suggest that although modafinil may not be efficacious as an anti-craving agent, it appears to be safe and non-reinforcing, and warrants further investigation in larger trials and/or higher doses.

4.5. Serotonin- and Noradrenaline-Modulating Agents

The neurotransmitter deficit model [206] has guided focus toward medications with the potential to raise synaptic concentrations of one or more of three neurotransmitters affected by methamphetamine – dopamine, serotonin and noradrenaline. Although dopamine agonists have not been investigated in methamphetamine addiction, studies of direct and indirect dopamine agonists in cocaine addiction have yielded largely negative results; consequently serotonin and noradrenaline have become the neurotransmitters of interest.

4.5.1. Selective Serotonin Reuptake Inhibitors

Early work in animals demonstrated that lesions or neurotoxins inhibiting serotonergic signalling caused increased self-administration of amphetamine [207, 208], suggesting that selective serotonin reuptake inhibitors (SSRIs) may be useful for decreasing the reinforcing effects of methamphetamine. However, trials of SSRIs such as fluoxetine [209] and paroxetine [210], as well as the tricyclic antidepressant imipramine [211] have shown no clear efficacy for reducing methamphetamine use. In a larger randomised double-blind, placebo-controlled trial, sertraline – a potent SSRI with a strong safety profile – was combined with contingency management using a counselling platform of Matrix™ model relapse prevention groups [212]. Participants were randomised to one of four conditions for 12 weeks – sertraline (100 mg/day) plus contingency management, sertraline only (100 mg/day), placebo plus contingency management and placebo only. There were no statistically significant effects for the medication or behavioural therapies in retention, drug craving, depression or medication adherence. In fact, sertraline treatment without contingency management appeared to increase methamphetamine use, as indicated by a greater number of methamphetamine-positive urine samples and the reduced likelihood of achieving three consecutive weeks of drug abstinence compared to those in contingency management conditions. These findings support the use of contingency management for the treatment of methamphetamine addiction; however, they suggest that sertraline, and possibly SSRIs as a class, are ineffective and may be contraindicated for methamphetamine addiction.

4.5.2. Mirtazapine

Mirtazapine is noradrenergic and serotonergic antidepressant; it enhances noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission by causing the blockade of inhibitory α_2-adrenergic autoreceptors on noradrenaline and 5-HT_2 and 5-HT_3 serotonin neurons. The sedative and anxiolytic properties may be mediated by antagonist effects at 5-HT_2 and 5-HT_3 receptors, and/or histamine H_1 receptors [213]. A pilot study of mirtazapine for the treatment of amphetamine addiction showed significantly improved withdrawal scores in participants receiving mirtazapine (15-60 mg titrated according to response), as well as significant improvements in the hyperarousal and anxiety subscales [214]. The abovementioned open-label trial by McGregor et al. [203] comparing mirtazapine and modafinil to placebo, found that mirtazapine (60 mg/day) was safe and well tolerated by participants. Mirtazapine treatment was associated with higher withdrawal scores compared to modafinil; however, mirtazapine-treated participants performed better than the ‘treatment as usual group’, with lower withdrawal scores and overall severity of symptoms. In a later double-blind, randomised placebo-controlled trial by Cruickshank et al. [215], mirtazapine was used in the management of methamphetamine withdrawal in an outpatient setting. Treatment was administered at a lower dose and shorter period than previous trials – 30 mg/day for 14 days, and both mirtazapine and placebo groups were offered narrative therapy counselling in conjunction with treatment. No significant differences were observed between the mirtazapine and placebo groups in retention rate or other symptom measures, suggesting that despite benefits in other settings, mirtazapine does not improve retention or alleviate withdrawal in the outpatient setting within a period of two weeks. More recently, a 12-week randomised, placebo-controlled trial combined mirtazapine (30 mg/day) with weekly counselling in methamphetamine-dependent men who have sex with men. Mirtazapine significantly reduced methamphetamine use and was associated with decreases in sexual risk,

but no difference was observed in depression scores, suggesting that its effects of methamphetamine use are independent of its effects on depression [216]. Although there is no clear evidence for the efficacy of mirtazapine in the management of methamphetamine dependence, the differences in treatment setting and doses suggest that it may be a useful pharmacotherapy in certain populations.

4.5.3. Bupropion

Bupropion is an antidepressant that is also approved as a treatment for smoking cessation. It is a monoamine uptake-inhibitor with stimulant-like effects in animals but does not alter serotonergic neurotransmission. Instead, it inhibits the reuptake of dopamine and noradrenaline, and reduces firing of dopamine and noradrenaline neurons – an effect consistent with an increase in synaptic levels of monoamine that inhibits neuronal firing via an autoreceptor-mediated negative feedback mechanism [217]. It also blocks transporters for dopamine and noradrenaline which enhances dopaminergic neurotransmission – an effect that may ameliorate symptoms of methamphetamine withdrawal. Newton et al. [218] conducted a single-blind, placebo-controlled trial in methamphetamine users to assess the effects of bupropion treatment (300 mg/day for 6 days) on methamphetamine-induced subjective effects and craving. Bupropion treatment was associated with a reduced drug effect and feelings of being 'high' after intravenous methamphetamine administration, as well as reduced cue-induced craving. These data provided rationale for further evaluation of bupropion for the treatment of methamphetamine dependence. Bupropion was then tested for efficacy for increasing weeks of abstinence in a 12-week double-blind, placebo-controlled trial [219]. Participants were randomised to receive either sustained-release bupropion (300 mg/day) or placebo. There was no difference between the bupropion and placebo groups in the probability of a 'non-use week' during the 12-week treatment period; however, subgroup analysis revealed that male participants with low baseline use treated with bupropion were more likely to have a methamphetamine-free week. These results suggest that bupropion may be efficacious for the treatment of methamphetamine-dependent participants who exhibit low-to-moderate levels of use. In a further trial, treatment with sustained-release bupropion (300 mg/day) was compared to placebo for efficacy in reducing methamphetamine use, increasing retention and reducing the severity of depressive symptoms and cravings [220]. Treatment with bupropion was associated with significantly reduced cigarette smoking but did not result in any significant differences in severity of depressive symptoms, craving or retention and was no more effective than placebo in reducing methamphetamine use. Post-hoc analysis showed that bupropion reduced methamphetamine use more than placebo amongst participants with low use at baseline. These findings are consistent with the trial by Elkashef et al. [219], demonstrating greater efficacy in participants with low-to-moderate use. Evidence from these trials may warrant further investigation of bupropion in the treatment of methamphetamine dependence among light levels of use.

4.6. Opioid Antagonists

Although the reinforcing effects of stimulants are principally mediated via the mesocorticolimbic dopamine system, other neurotransmitter systems – such as μ-opioid receptors located on mesolimbic dopamine neurons – modulate dopamine [221]. The important functional interactions between the dopamine and opioid systems in stimulant abuse are evident in preclinical and clinical studies. For example, chronic cocaine administration in rats has been shown to increase brain μ-opioid receptor binding in reward-relevant regions, such as the amygdala and nucleus accumbens; this effect appears to be mediated by dopamine receptors [222, 223]. Furthermore, a PET study in chronic cocaine users demonstrated an increase in μ-opioid receptor binding in limbic areas, which correlated with self-reported cocaine craving [224]. Evidence suggests that this dopaminergic-opioid interaction may provide a potential target for pharmacological intervention.

Naltrexone, a μ-opioid receptor antagonist, has been shown to attenuate the subjective effects of dexamphetamine in dependent patients, as well as decrease craving [225], suggesting that naltrexone may be useful as an adjunct pharmacotherapy for treating amphetamine dependence. This provided the rationale for a clinical trial evaluating the efficacy of naltrexone for preventing relapse in amphetamine-dependent participants [226]. In a double-blind, placebo controlled trial, amphetamine-dependent participants were randomly assigned to either placebo or naltrexone (50 mg) treatment for 12 weeks with weekly relapse prevention therapy. Analysis revealed a significantly higher number of amphetamine-negative urine samples in the naltrexone group compared to placebo, as well as a decrease in craving scores and self-reported amphetamine use. Therefore, naltrexone appears to be a very promising medication for treating amphetamine dependence.

CONCLUSION

Stimulant addiction is an increasing worldwide public health problem. Despite many years of clinical research, no pharmacological agent has proven to be robustly successful; consequently the development of effective treatments for stimulant addiction is now a priority. Recent advances in understanding the underlying neurobiological mechanisms of addiction have led to a number of potentially promising medications. However, knowledge about the effects of stimulants and the differences between drug-dependent participants and healthy non-drug users is critical for the identification of possible pharmacotherapies. Neuroimaging techniques can be used to examine the effects of pharmacological interventions and can provide a link between their mechanisms of action and behavioural responses; however, few trials of potential therapies have been guided by findings from imaging studies.

The convergence of evidence from preclinical and clinical trials in addition to neuroimaging studies may provide more insight into the putative effectiveness of potential pharmacotherapies. For example, preclinical studies confirm that baclofen blocks drug-motivated behaviour by inhibiting dopamine release in the ventral striatum and medial prefrontal cortex; however, this mechanism in humans is less well described. Using arterial spin-labelled perfusion fMRI, Franklin et al. [227] examined the effects of baclofen treatment

(80 mg/day for 3 weeks) on cerebral blood flow to reward-relevant areas in smokers. Baclofen significantly modulated blood flow in regions involved in motivational behaviour – the ventral striatum, orbitofrontal cortex and the superior, inferior and ventral medial cortices. The ability to identify the modulatory effects of potential pharmacotherapies on regions involved in addictive processes could improve our understanding of the underlying mechanisms and inform medication selection and/or development.

Chronic drug abuse is also associated with cognitive impairment; these impairments can interfere with behavioural therapy, leading to poor treatment retention and subsequent outcomes. Therefore cognitive remediation strategies using medicines may become an important part of treatment. Modafinil has been used as a cognitive enhancer; however, its mechanism is complex and involves several neurotransmitter systems. Ghahremani et al. [228] used fMRI determine the effects of modafinil (200 mg) on neural function and learning in methamphetamine-dependent participants. Modafinil enhanced learning performance to levels similar to those seen in control participants, which was accompanied by greater activation in bilateral insula/ventrolateral prefrontal and anterior cingulate cortices – regions important for learning and cognitive control. The identification and evaluation of other cognitive-enhancing medications for treating stimulant addiction may be carried out using a range of MRI methods. For example, MRS could be used to assess changes induced by methamphetamine abuse over time or PET could be used to investigate functional and structural amelioration (or deterioration) following drug withdrawal and abstinence. Moreover, combined with pharmacological treatment, neuroimaging may prove to be an invaluable tool for longitudinal follow-up studies of drug addiction.

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