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Understanding drug craving: evidence from fMRI studies

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ABSTRACT: Drug craving is a major crisis experienced by active or former drug abusers. The experience is characterised by an intense desire to abuse drugs for self-pleasure and satisfaction. This desire appears to be the main culprit behind the skyrocketing relapse rate. Neuroimaging has identified neural substrates associated with drug cravings. Here, we provide a mini-review of functional magnetic resonance imaging (fMRI) studies that have examined the brain regions associated with the common types of drug abuse — heroin, methamphetamine, and cocaine. Most studies use visual cues (that is drug-related images) to elicit brain responses in reward-related pathways. Studies have also focused on comparing brain activities between active drug abusers, drug-abstinent individuals, and healthy controls. Current evidence suggests that the dorsolateral prefrontal cortex (DLPFC) is associated with heroin craving, whereas the ventral striatum and medial prefrontal cortex (mPFC) underpin methamphetamine craving. Meanwhile, the hypothalamus is responsible for cocaine cravings. Compared to active drug abusers, drug-abstinent individuals demonstrated fewer brain activations when viewing drug-related images. The relationship between brain response and drug cravings is discussed in terms of brain functions and drug types. The findings offer valuable insights into the potential role of these brain areas in drug cravings and have important implications for drug addiction treatments.

Keywords: Cocaine; Craving; fMRI; Heroin; Methamphetamine

1.0 INTRODUCTION

Since its establishment in 1990, functional magnetic resonance imaging (fMRI) has become one of the common neuroimaging techniques used to observe brain function directly (Yen et al., 2023). It observes brain activity by measuring the changes in magnetic susceptibility between oxygenated haemoglobin (i.e. diamagnetic) and deoxygenated haemoglobin (i.e. paramagnetic) in the brain (Kim & Bandettini, 2023). When the brain performs a certain cognitive task (e.g. working memory), there will be an increasing demand for oxygen-rich supply to that particular brain area responsible for completing the task (Othman et al., 2019). Thus, the increase in the oxygenated

haemoglobin would result in an elevated blood-oxygen-level-dependent (BOLD) signal (Xue et al., 2010). A common way to elicit brain activity and increase BOLD signal is by asking participants to perform a certain task, an approach known as task-based fMRI (Lundengard, 2017).

One of the favourable characteristics of fMRI is that it produces relatively good spatial and temporal resolution images without using harmful ionising radiation (Sklerov et al., 2018; Hussain et al., 2022). As such, fMRI has been used extensively in the field of neuroscience. For example, fMRI has been used to understand the neural mechanisms underlying drug cravings among active drug abusers, drug-abstinent individuals, and healthy individuals (Xue et al., 2010; Glover, 2011; Zeng et al., 2018; Moeller & Paulus, 2018; Dakhili et al., 2022). Active drug abusers refer to individuals who are currently engaged in drug abuse, while drug-abstinent individuals are those who have refrained from drug abuse. On the other hand, healthy individuals are anyone who has no history of drug abuse.

Drug craving is defined as the uncontrollable strong urge to abuse drugs (Biernacki et al., 2021). The craving is often evoked when a person encounters things or memories related to drugs, which may eventually lead them to seek drugs or relapse. Internal factors (e.g. post-acute withdrawal syndrome) and external factors (e.g. friends or environment) may further contribute to relapse (Amat et al., 2020). It has been shown that reward-related behaviours (e.g. feeding, exercise, sex, drug abuse, and social interactions) promote the release of dopamine, which excites the brain-reward system (Lewis et al., 2021). Previous fMRI studies investigating the brain's reward system underpinning drug cravings have been vastly focused on heroin, methamphetamine, and cocaine. However, these fMRI studies often reported inconsistent findings, even when investigating the same type of drug.

More specifically, the documented brain areas evoked by a drug stimulus differ between studies. For instance, an fMRI study on methamphetamine craving reported higher brain activity in the ventromedial prefrontal cortex (Chen et al., 2019), while another study, also on methamphetamine craving, reported higher brain activity in the fusiform, prefrontal, and visual regions (Dakhili et al., 2022). As for cocaine addiction, a study reported an association between neural activity in the posterior areas of the brain and cocaine-related videos in cocaine-dependent individuals (Regier et al., 2021). Cocaine-related images were also found to evoke responses in the bilateral occipital cortex significantly, bilateral dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (Wiers et al., 2020). On the contrary, an fMRI study on heroin craving reported higher brain activity in the prefrontal regions, mesolimbic system, and visuospatial attention regions (Li et al., 2014). Apart from these brain regions, heightened neural activations in the right thalamus, nucleus accumbens, right cerebellum, and left middle temporal gyrus were also identified in heroin-dependent individuals (Dejoie et al., 2024).

The reasons for the inconsistent findings reported in these studies may be attributed to heterogeneity in the study designs, such as participants' demographic characteristics, sample size, history of drug use, duration of abstinence, type of fMRI experimental paradigm, and method of functional data analysis. Thus, it is difficult to identify reliable patterns of brain activity in response to drug cravings based only on individual studies. Therefore, this mini-review aims to provide an overview of the prominent fMRI findings concerning drug craving. The review also aims to elucidate specific brain areas that may serve as potential neural markers for drug addiction treatment.

By utilising fMRI findings to understand the neural mechanism underlying drug addiction better, clinicians might be able to develop more effective, personalised treatment approaches for individuals struggling with addiction. For instance, if an fMRI scan shows heightened activity in a specific brain area associated with the risk of relapse, the treatment approaches could be tailored to lower neural activation in the particular brain area, potentially improving treatment outcomes and minimising the risk of relapse. It is hoped that this mini-review will provide a comprehensive summary of fMRI findings, offering readers a clear understanding of the neural mechanisms of drug addiction. Additionally, this mini-review identifies specific brain regions that may serve as neural markers for treating drug addiction.

2.0 FMRI FINDINGS OF DRUG CRAVING

2.1 Heroin craving

Several fMRI studies have looked into how the brain responds to drug-related images in drug-dependent individuals to predict relapse (Li et al., 2014; MacNiven et al., 2018; Regier et al., 2021). These images were classified into three categories: (i) drug substances (e.g. white powders and pills), (ii) paraphernalia associated with drug use (e.g. spoons and lighters), and (iii) images depicting drug use action (e.g. injecting drugs into the

vein of the arm) (Zeng et al., 2018). For instance, a study compared the brain activity of 31 abstinent heroin users when they viewed drug-related, sexual, and neutral images during an fMRI scan (Liu et al., 2021). It was found that the former heroin users demonstrated distinct brain activation patterns to the three different types of images, particularly in the left dorsolateral prefrontal cortex (DLPFC), left orbitofrontal cortex (OFC), insula, and bilateral thalamus.

Further investigation was performed by comparing the brain activity of the former heroin users when viewing drug-related and neutral images. The results showed significantly enhanced neural activations in several brain regions, including the thalamus, bilateral posterior cingulate/precuneus (PCC), striatum (putamen), precentral, pallidum, and left DLPFC, in response to drug-related images. From the investigation, Liu and colleagues (2021) found that the DLPFC was constantly activated when abstinent heroin users viewed drug-related images. Although it is well-known that the DLPFC is an important structure for exerting inhibitory control over drug use behaviour, the authors were uncertain about the functional coupling of the DLPFC during a cue-induced craving task in former heroin users (Liu et al., 2021).

To unravel the uncertainty, Liu and colleagues performed the psychophysiological interactions (PPI) analysis by choosing the left DLPFC as the seed region (i.e. a region of interest that drug-related images can evoke). It is worth noting that PPI is an analysis method that uses fMRI data to investigate specific neurological changes associated with brain activity in different parts of brain areas. To be more precise, PPI is a method to determine which brain region increases relatedly with a seed region during a task (O'Reilly et al., 2012). **Figure 1** shows the results of the PPI analysis performed by Liu and colleagues (2021), which demonstrated that the left DLPFC (implicated with cognitive control) had a significantly negative coupling with bilateral thalamus, bilateral putamen, and left OFC (these three regions are associated with reward processing).

This finding suggests that the left DLPFC and three other brain regions exhibit opposing activity patterns. When one region becomes more active, the others decrease in activity. The heightened brain activity in reward processing regions, when exposed to heroin-related images, could weaken self-control in former heroin users, potentially increasing the risk of relapse (Liu et al., 2021). This pattern aligns with a study by Yuan and colleagues (2017), which demonstrated that PPI analysis revealed a negative coupling between the left DLPFC and other brain regions during a smoking cue-induced craving task, with this negative functional coupling positively correlated with the craving score.

Research has also explored the effective interventions for treating heroin-dependent individuals using fMRI (Wei et al., 2021; Edinoff et al., 2023). According to the National Institute on Drug Abuse (NIDA), heroin is a type of opioid drug made of morphine (NIDA, 2022). According to Wei and colleagues (2021), there are mainly two types of methods commonly used to treat heroin-dependent individuals: (i) methadone maintenance treatment (MMT) and (ii) protracted abstinence (PA). MMT is an intervention where authorised clinics provide methadone to heroin-dependent individuals regularly.

Methadone is a medication that reduces opioid cravings without producing the same addictive effects as heroin (e.g. feeling pleasure or euphoria) (Wei et al., 2021). As such, MMT is considered an effective and safe intervention for treating heroin addiction. PA is another common method to treat heroin addiction, where heroin-dependent individuals undergo effective psychological treatments or interventions, such as cognitive-behavioural therapy (CBT) (Jhanjee, 2014; Wei et al., 2021). Heroin-dependent individuals are also prohibited from taking any illegal drugs when undergoing this intervention.

Although MMT and PA are generally implemented in managing heroin cravings and preventing relapse, it remains unclear which of the two interventions is more effective. To answer this question, Wei and colleagues (2021) compared the brain activity of 71 heroin-dependent individuals undergoing MMT and PA using fMRI. The result showed that heroin-dependent individuals undergoing MMT demonstrated higher brain activation when viewing 48 heroin-related images as compared to those undergoing PA intervention (Wei et al., 2021). The fMRI results showed significantly higher brain activation in all of the brain regions, including the reward-related regions (right caudate and left pallidum), mesolimbic region (left hippocampus, cingulate cortex, and amygdala), visuospatial-attention regions (right inferior frontal gyrus triangular (IFG-triangle), left superior parietal lobule (SPL), left inferior parietal lobule (IPL), left middle occipital gyrus, auditory cortex regions (right inferior temporal gyrus), and somatosensory cortex (left postcentral gyrus) in the MMT group compared to the PA group.

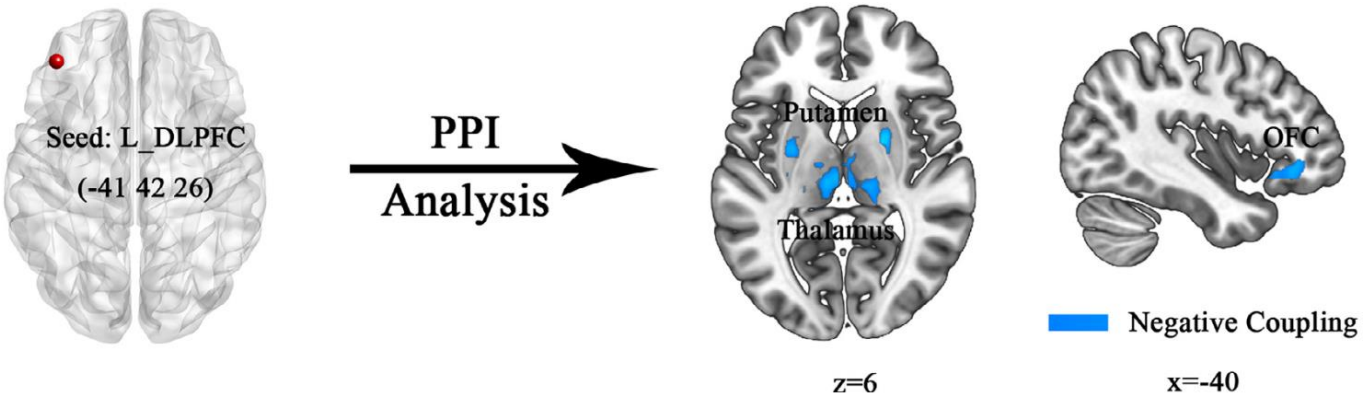

Figure 1. The PPI analysis shows negative coupling between the left DLPFC and left OFC, bilateral thalamus, and putamen (figure adapted from Liu et al., 2021).

In the PA group, the activated brain regions induced by heroin-related images were only the left IPL and left SPL. This fMRI finding suggests that PA is a better intervention approach than MMT to reduce heroin cravings (Wei et al., 2021). Taken together, fMRI may serve as a valuable imaging tool in identifying the best treatment options for treating drug-dependent individuals. This is because fMRI can help to identify neural markers associated with drug addiction, which are strongly correlated with substance dependence and its treatment. These markers offer crucial insights into tailoring and identifying effective treatments for individuals dependent on drugs. For instance, fMRI studies have identified the specific brain areas among drug-dependent individuals. Subsequently, transcranial magnetic stimulation (TMS) has been applied to these areas as a therapeutic intervention. This neuromodulation technique (i.e. TMS) could be targeted at specific brain regions implicated in drug craving and has been demonstrated to reduce drug cravings among cocaine-dependent individuals (Edinoff et al., 2023; Shen & Ward, 2020).

Huang and colleagues (2024) conducted a study utilising the fMRI technique to investigate the brain responses of heroin-dependent individuals to three categories of images: (i) drug-related, (ii) neutral, and (iii) food-related. The study compared the limbic activation patterns between 32 heroin-dependent individuals and 21 healthy controls in response to these images. The study reported that the limbic region of heroin-dependent individuals was intensely activated to drug-related images compared to the healthy controls. Moreover, the findings observed that drug-related images elicited greater activation compared to food-related images. Specifically, the fMRI showed higher activations in the inferior frontal gyrus, anterior cingulate cortex, nucleus accumbens, ventromedial prefrontal cortex, posterior cingulate cortex, and orbitofrontal cortex.

Additionally, the authors identified a positive correlation between these heightened brain responses, specifically in the ventromedial prefrontal cortex, inferior frontal gyrus, and orbitofrontal cortex. These findings were consistent with previous studies that reported drug craving was correlated with limbic hyper-reactivity across various substances, such as cocaine and heroin (Denomme & Shane, 2020; Liu et al., 2021). Conclusively, this positive correlation may serve as an important indicator to predict the risk of drug relapse. In contrast, the authors observed an opposite pattern among healthy control participants, who exhibited higher activations in the orbitofrontal cortex, insula, hippocampus, neostriatum, dorsolateral and ventromedial prefrontal cortex in response to food-related images than by drug-related or neutral images. This finding was expected, considering that the food images depicted palatable foods.

2.2 Methamphetamine craving

Apart from heroin, previous fMRI studies have attempted to understand methamphetamine (MA) craving. For instance, an fMRI study compared the brain activations of 28 individuals with long-term MA abstinence and 27 healthy controls when they viewed three different types of images (i.e. 30 neutral, 30 MA-related, and 30 sexual-related) (Huang et al., 2018). The main purpose of the study was to see the brain activation patterns and craving levels in long-term abstinent MA abusers, as this has not been well studied.

It was found that the MA group showed significantly elevated activity in the right lateral posterior cingulate cortex and bilateral medial prefrontal cortex (mPFC) in response to MA-related images. These brain regions are part of the neural circuits that become activated when the drug abusers encounter drug-related images: (i) reward circuit and (ii) visual attention and planning circuit (Malcolm et al., 2016; Huang et al., 2018). The reward circuit controls the ability to feel pleasure, while a visual attention and planning circuit is responsible for attentional control and plan-making (Huang et al., 2018). In this case, when long-term MA abstinence individuals viewed the MA-related images, these parts of their brains became significantly activated. This finding suggests that drug-related images (i.e. MA-related) may trigger drug craving by activating the brain's reward circuit.

Another interesting finding of the study is that long-term MA abstinence may not necessarily reduce activation in the reward pathway. The study found a positive correlation between increased activity in mPFC and the current degree of cravings in long-term MA abstinence individuals. The finding may indicate that the brains of long-term MA abstinence individuals may still react strongly to drug-related images, and cravings would still be intense. More importantly, using fMRI, Huang and colleagues (2018) have demonstrated that mPFC may serve as a potential neural marker for predicting relapse in long-term MA abstinence individuals.

Other researchers have also studied cue-evoked brain activation in chronic MA-dependent individuals using BOLD fMRI (Malcolm et al., 2016). This study was conducted on nine chronic MA-dependent individuals (i.e. non-treatment-seeking individuals) and nine healthy controls. The authors claimed that their work was the first imaging study to assess cue-elicited craving in chronic MA-dependent individuals who were not seeking treatments. The assessment was done by acquiring the participants' brain activities while lying inside the MRI scanner, viewing neutral and MA-related images for approximately 12 minutes.

As illustrated in **Figure 2**, the fMRI findings showed that the ventral striatum and medial frontal cortex (depicted in colour) were significantly activated when the MA-dependent participants viewed MA-related images relative to neutral ones. The ventral striatum is a part of the brain that is commonly associated with reward and pleasure, while the medial frontal cortex is the brain region involved in thinking and decision-making (Schreuders et al., 2018; Klein-Flugge et al., 2022). Thus, these findings may imply that MA-related images evoke drug craving in chronic MA-dependent individuals by eliciting activity of the ventral striatum and medial frontal cortex (Malcolm et al., 2016). The study has provided valuable insight into the potential role of the ventral striatum and medial frontal cortex in MA cravings. Future works may consider these two brain regions as the neural markers in treating chronic MA-dependent individuals.

Grodin and colleagues (2019) conducted an fMRI study to investigate whether methamphetamine-induced craving responses were associated with brain response to methamphetamine-related images. The study involved 15 non-treatment-seeking MA-dependent individuals. Consistent with a previous study exploring brain responses to methamphetamine-related images, the authors observed activation across various brain regions when participants viewed these images compared to neutral images (Courtney et al., 2016). Specifically, heightened activation was observed in the mesocorticolimbic areas (i.e. ventromedial prefrontal cortex, ventral and dorsal striatum, insula, precuneus, occipital lobe, anterior and posterior cingulate).

Additionally, the authors performed tests to examine the relationship between craving and brain response. They assessed the correlation between peak craving ratings and in-scanner cue reactivity, revealing a positive correlation. They found that methamphetamine-induced craving was positively associated with brain response to these images, particularly in the ventromedial prefrontal cortex, precuneus, and putamen.

2.3 Cocaine craving

Apart from heroin and MA, researchers have also utilised fMRI to understand craving towards other drugs (Prisciandaro et al., 2012; Zhang et al., 2018; Regier et al., 2021). For instance, a study was performed to understand how the brains of drug addicts would respond when they see images related to cocaine (Zhang et al., 2018). They hypothesised that the hypothalamus would be activated when cocaine-dependent (CD) individuals viewed cocaine-related images. The hypothesis was based on the role of the hypothalamus, which produces dopamine (i.e. a chemical that induces pleasure and reward) (National Institute on Drug Abuse, 2020), and that viewing cocaine-related images would lead to a surge of dopamine release in CD individuals.

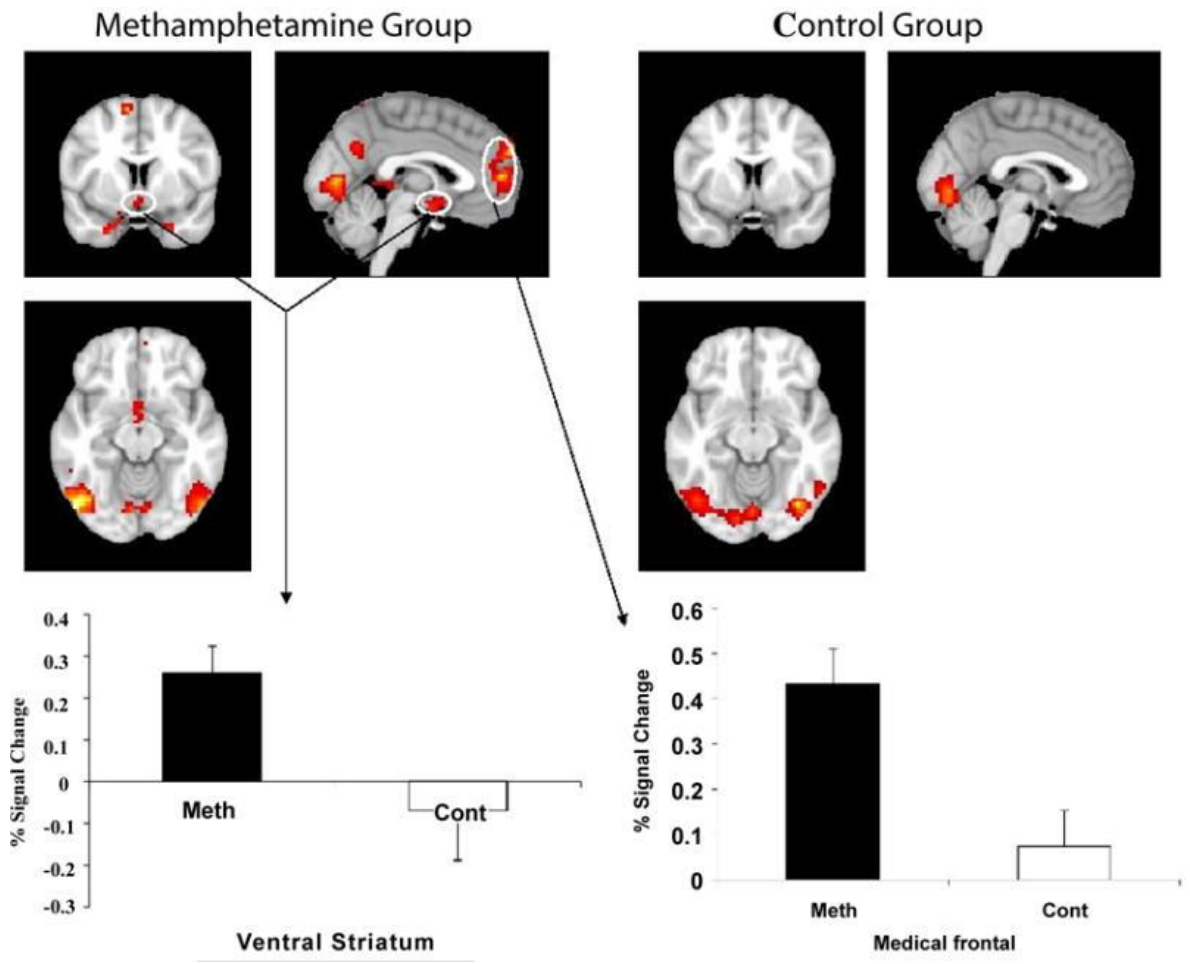

Figure 2. Comparison of brain activation in the ventral striatum and medial frontal cortex between methamphetamine group and healthy controls (figure adapted from Malcolm et al., 2016).

To test the hypothesis, the researchers scanned the brains of 23 recently abstinent, treatment-seeking CD participants while they were viewing neutral and cocaine-related images inside the MRI scanner (Zhang et al., 2018). As tabulated in **Table 1**, the fMRI findings showed significantly increased activations in bilateral visual cortex, bilateral middle frontal gyri (MFG), bilateral inferior parietal cortex (IPC), and hypothalamus among CD participants when viewing cocaine-related images as compared with neutral images—the visual cortex processes visual information (Huff et al., 2023). Therefore, increased visual cortex activation may be due to participants viewing drug-related images (Huff et al., 2023).

Interestingly, a study reported that highly motivated participants (i.e. seeking treatments) demonstrated lower activity in the visual cortex when viewing drug-related images as compared to less motivated participants (i.e. not seeking treatments) (Devoto et al., 2020; Hanlon et al., 2014). This finding suggests that the activity level of the visual cortex may be associated with a person's motivation to undergo drug rehabilitation. As for MFG and IPC, these brain areas are part of a saliency circuit (i.e. a network that regulates one's attentional level) (Zhang et al., 2018). Therefore, it is plausible that the increased activation of MFG and IPC observed in CD individuals may be due to their heightened level of attention towards cocaine-related images.

The researchers found that increased activation of certain brain regions was not strongly linked to participants' craving levels. However, heightened activation of the hypothalamus was strongly associated with craving. The hypothalamus, which regulates pleasure and emotions (Giacolini et al., 2021), maybe more active in individuals with cocaine dependence when they view cocaine-related images, suggesting they experience increased pleasure from such stimuli. Understanding this connection could be crucial for improving cocaine addiction treatment.

Regier and colleagues (2021) also conducted a study to investigate the relationship between brain response to drug-related images and future drug-use outcomes in cocaine-dependent individuals. The study utilised fMRI to examine the brain's response to repeated drug-related images in these treatment-seeking participants. They were presented with cocaine-related, neutral, sexual, and aversive images, in the first half of the task, and then these same images were repeated in the second half. After completing the passive-viewing fMRI task, these 73 participants underwent eight weeks of outpatient treatment that included drug screenings twice a week. The outcomes regarding drug use were defined based on the average percentage of cocaine-positive samples and were classified as good (less than 40%), intermediate (40% to 85%), and poor (more than 85%).

The authors focused on identifying differences in brain response between groups with these three different drug-use outcomes (i.e. good, intermediate, and poor). The results found that the poor outcome group had a sustained response to these repeated drug-related images, while the good outcome group showed a decrease in response to drug-related images in the visual association areas (e.g. fusiform, amygdala, and the parahippocampus). These brain areas could potentially serve as a neural marker for developing targeted treatments.

The authors also highlighted the potential for developing treatments that target these brain areas to facilitate a reduction in the brain response to drug-related images (Regier et al., 2021). To summarise, a comparative analysis of the brain activations among the three drug types (i.e. heroin, methamphetamine, and cocaine) between the three subject groups (i.e. active drug abusers, drug-abstinent individuals, and healthy controls) is shown in **Table 2**.

Table 1. Identification of activated brain region when cocaine-dependent individuals viewed cocaine-related compared with neutral images (table adapted from Huang et al., 2018).

Volume, mm^3	Peak voxel (z)	Montreal Neurological Institute (MNI) coordinates, mm			Side	Identified brain region
		x	y	z		
19 737	6.96	-39	-58	-14	L	Visual cortex
18 036	6.80	42	-82	-8	R	Visual cortex
7 452	6.32	-30	-61	55	L	Inferior parietal cortex
4 914	6.26	33	-46	49	R	Inferior parietal cortex
729	5.39	-54	2	28	L	Middle frontal gyrus
540	5.14	51	8	25	R	Middle frontal gyrus
675	5.14	3	-4	-14	L / R	Hypothalamus

Table 2. Comparative analysis of brain region activation among active drug abusers and drug-abstinent individuals.

Type of drugs	Identified brain regions in different groups of subjects	
	Active drug abusers	Drug-abstinent individuals
Heroin	• Inferior frontal gyrus, anterior cingulate cortex, nucleus accumbens, ventromedial prefrontal cortex, posterior cingulate cortex, and orbitofrontal cortex (Huang et al., 2024)	Dorsolateral prefrontal cortex (Liu et al., 2021)
Methamphetamine	• Ventral striatum and medialfrontal cortex (Malcolm et al., 2016) • Ventromedial prefrontal cortex, precuneus, and putamen (Grodin et al., 2019)	-
Cocaine	• Hypothalamus (Zhang et al., 2018) • Visual association areas (e.g. fusiform), amygdala, and the parahippocampus (Regier et al., 2021)	-

3.0 CONCLUSIONS

Functional MRI has contributed extensively to the field of neuroscience by offering a safe and reliable method for researchers to understand the neural mechanisms underlying drug cravings. With the use of fMRI, researchers have gained an in-depth understanding of the brain regions underpinning heroin, MA, and cocaine cravings in active and former drug abusers. Furthermore, compared to active drug abusers, drug-abstinent individuals exhibit reduced brain activations when exposed to drug-related images, suggesting alterations in neural processing following cessation of drug use. Studies have consistently found that the brain reacts differently to various types of drugs. The brain region responsible for heroin craving is DLPFC, whereas the ventral striatum and medial frontal cortex underpin MA craving. On the other hand, the hypothalamus is involved in cocaine craving. These brain areas may offer a potential neural marker for the treatment of drug addiction.

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