Manuscript Details

Manuscript number	NEUBIOREV_2019_471_R1
Title	Do the effects of cannabis on the hippocampus and striatum increase risk for psychosis?
Article type	Review Article

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Keywords	Cannabis, Psychosis, Schizophrenia, Hippocampus, Striatum, Dopamine, Glutamate, methylazoxymethanol acetate (MAM) rodent model.
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Title: Do the effects of cannabis on the hippocampus and striatum increase risk for psychosis?

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Abstract

Cannabis use is associated with increased risk of psychotic symptoms and in a small number of cases it can lead to psychoses. This review examines the neurobiological mechanisms that mediate the link between cannabis use and psychosis risk. We use an established preclinical model of psychosis, the methylazoxymethanol acetate (MAM) rodent model, as a framework to examine if psychosis risk in some cannabis users is mediated by the effects of cannabis on the hippocampus, and this region's role in the regulation of mesolimbic dopamine. We also examine how cannabis affects excitatory neurotransmission known to regulate hippocampal neural activity and output. Whilst there is clear evidence that cannabis/cannabinoids can affect hippocampal and medial temporal lobe function and structure, the evidence that cannabis/cannabinoids increase striatal dopamine function is less robust. There is limited evidence that cannabis use affects cortical and striatal glutamate levels, but there are currently too few studies to draw firm conclusions. Future work is needed to test the MAM model in relation to cannabis using multimodal neuroimaging approaches.

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1. Introduction

Cannabis is the most used illicit recreational drug with over 192 million users globally (UNODC, 2018). The majority of cannabis users use the drug for the subjective effects that it induces; a feeling of getting 'high' or 'stoned' although there is now increased interest in exploring the medicinal use of cannabis (Grotenhermen and Müller-Vahl, 2016; Hazekamp and Heerdink, 2013; Isaac et al., 2016). Effects of cannabis include feelings of disinhibition or dreaminess and sensations of heightened awareness of music, sounds, colours or tastes (Curran et al., 2016). Experimental and epidemiological research suggests that cannabis use is associated with cognitive impairments (Crean et al., 2011; Meier et al., 2012), which may attenuate with prolonged abstinence (Scott et al., 2018), and an increased risk of experiencing psychotic symptoms. In a small number of cases cannabis use can lead to the development of psychotic disorders such as schizophrenia (Andréasson, Engström, Allebeck, & Rydberg, 1987; Henquet et al., 2005; Moore et al., 2007; Zammit, 2002).

Understanding the relationship between cannabis use and psychosis/schizophrenia is important because schizophrenia is a mental health disorder associated with enormous personal and societal cost (Chong et al., 2016; Rössler, Salize, Van Os, & Riecher-Rössler, 2005). A meta-analysis of the prevalence of schizophrenia shows that about 7 individuals per 1,000 is affected (McGrath et al., 2008). As such, it represents a considerable humanistic and economic burden to society (De Silva et al., 2012; Millier et al., 2014). Epidemiological work indicates that an increased risk of developing psychotic symptoms in adulthood is associated with the early onset of cannabis use (i.e. before 15 years of age) (Arseneault et al., 2002; Konings et al., 2008; Stefanis et al., 2004).

In this review we aim to examine neurobiological mechanisms that may mediate the link between cannabis use and the experience of psychotic symptoms and/or the development of psychosis. We will use an established and influential animal model of psychosis, the methylazoxymethanol acetate (MAM) rodent model (Gomes, Rincón-Cortés, & Grace, 2016; Lisman et al., 2008; Lodge & Grace,

2011) as a framework to interpret studies examining the acute and chronic effects of cannabis (and its constituent components THC and CBD) on the human brain. Specifically, we will examine if the increased risk of psychotic disorders such as schizophrenia in some cannabis users is mediated by the effects of cannabis on the hippocampus and this region's role in the regulation of mesolimbic dopamine (Lodge & Grace, 2011). We will also examine how cannabis affects concentrations of excitatory and inhibitory neurotransmission (i.e. effects on glutamate and GABA) that regulate hippocampal neural activity. Finally, we will discuss whether or not an elaboration of this MAM model can be extended to account for the reported relationship between cannabis use, particularly in adolescence, and the development of psychosis and/or psychotic like symptoms.

2. **Cannabis and how it has changed**

The chemical constituents of cannabis are called cannabinoids. There are at least 140 cannabinoids found in the cannabis plant (Ujváry and Hanuš, 2016). Cannabis research has focused mainly on Δ^9 tetrahydrocannabinol (THC) and cannabidiol (CBD) (Pertwee, 2006). THC is the main psychoactive substance found in cannabis and is responsible for the subjective effects experienced by cannabis users (Wachtel et al., 2002). It exerts its effects by acting as a partial agonist on CB1 endocannabinoid receptors, which are distributed across several cortical and subcortical regions (Herkenham et al., 1990), including the hippocampus, amygdala, striatum and cerebellum (Malone et al., 2010). THC is also responsible for the adverse effects associated with smoking cannabis, including mediating the risk of addiction (Morgan, Freeman, Schafer, & Curran, 2010), cognitive deficits (Oomen et al., 2018) and producing psychotic and anxiogenic effects (Morrison et al., 2009).

CBD is the other main chemical constituent of cannabis often studied in research. This compound has opposing effects to THC and can ameliorate the psychotic mimicking effects of THC (Bhattacharyya et al., 2010; Englund et al., 2013; Morgan, 2009). For this reason it has been trialled as a medication for its antipsychotic (Leweke et al., 2012) and anxiolytic properties (Crippa et al.,

2011) and has been shown to be an effective adjunct therapy in patients with schizophrenia (McGuire et al., 2018). There is also evidence of a restorative effect of CBD on specific sub regions of the hippocampus in cannabis users, most visible in heavy cannabis users (Beale et al., 2018).

At a molecular level THC and CBD differ in their actions at cannabinoid receptors. Cannabinoids are biosynthesized in the cannabis plant as cannabinoid acids and upon heating these acids are decarboxylated to their neutral forms (Kimura and Okamoto, 1970). As stated above THC is a partial CB_1 receptor agonist. The psychomimetic effects of THC are due to its interactions with the CB_1 and CB_2 receptors in the brain (Cascio et al., 2017). Both receptors are g-protein coupled receptors that inhibit adenylyl cyclase and activate mitogen activated protein kinases (Pertwee, 2015). THC can act as both a cannabinoid receptor agonist, and antagonist, this is due to the relatively low cannabinoid receptor efficacy of THC; this means that its action will be dependent on the receptor densities and coupling efficiencies of the cannabinoid receptors (Pertwee, 2008). CB_1 receptor density and efficacy is heterogenous and varies widely in different brain regions. THC also acts at the G-Protein couple receptor GPR55, with different studies reporting opposite effects (Anavi-Goffer et al., 2012; Ryberg et al., 2007; Yin et al., 2009). Like endogenous endocannabinoids, THC acts on presynaptic CB_1 receptors to inhibit ongoing neurotransmitter release; while the effect on the neurons which the receptors are present is inhibitory, this sometimes has the effect of increasing neurotransmitter release from neurons further downstream (Pertwee, 2008).

CBD on the other hand acts as a low potency CB_1 receptor inverse agonist and as a potent CB_1 antagonist (Petitet et al., 1998). Despite a relatively low affinity of CBD at CB_1 and CB_2 receptors CBD acts at lower concentrations than the binding affinity would suggest potentially indicating activity via non CB_1 receptor based mechanisms. It does this by acting as a CB_1 receptor negative allosteric modulator and is able to reduce the efficacy and potency of the endocannabinoid 2-AG and of THC at the CB_1 receptor (Laprairie et al., 2015). A number of the pharmacological actions of CBD take place on non-cannabinoid receptors; including the vanilloid, serotonin and GPR55 receptors

(Bisogno et al., 2001; Russo et al., 2005; Ryberg et al., 2007). A review by Gururajan and Malone demonstrates that the effects of CBD are sensitive to changes in calcium and endocannabinoid homeostasis (Gururajan and Malone, 2016).

FIGURE 1 HERE

There are many forms and strains of cannabis available with varying potencies, depending on the concentration of THC and its balance against the relative concentration of CBD within the particular strain (Potter et al., 2008). High potency cannabis is usually referred to as *Skunk*, *Super Skunk or Sensimilla* (Niesink et al., 2015). These strains have high concentrations of THC of up to 18% (Potter et al., 2018, 2008), showing a steady increase from the 1990's when the average THC content of seized cannabis was around 6-8% (Potter et al., 2018). As well as having higher concentrations of THC, these newer strains of high potency cannabis, also have reduced or negligible concentrations of CBD (Hardwick, 2008; Potter et al. 2018).

The other type of cannabis often found in the UK is *hashish*, *hash or cannabis resin*. Historically, hashish has tended to be a milder form of cannabis, with lower concentrations of THC and a more balanced ratio of THC and CBD (Di Forti et al., 2009). Recent research has shown that police seizures of hashish contain higher levels of THC than they did previously (Potter et al., 2018). This is significant because evidence links higher potency cannabis with increased risk of psychosis, although this may be specific to Skunk type cannabis (Di Forti et al., 2015, 2014). One study showed that users of higher potency cannabis were almost 5 times more likely to develop psychosis compared to non-users; conversely users of low potency cannabis did not have a significantly increased risk for psychosis compared to non-users (Di Forti et al., 2015). Cannabis strains high in CBD may result in a lower risk of psychosis (Morgan & Curran, 2008; Schubart et al., 2011).

To summarise, the relative contents of THC and CBD in street cannabis has changed over the last few decades. In particular, high potency strains of cannabis such as Skunk appear to contain higher amounts of THC and lower amounts of CBD. Importantly, it is these high potency strains of cannabis that are linked to psychosis risk.

3. The Methylazoxymethanol acetate (MAM) model of psychosis

Psychosis covers a range of related conditions in which schizophrenia is the most common. It is associated with alterations in a person's perception, thoughts, moods and behaviour to a significant degree (NICE, 2014). A range of neurobiological changes have been identified in people with schizophrenia including enlarged ventricles, volumetric reductions in the frontal lobes, thalamus and limbic regions including the amygdala and hippocampus (Breier et al., 1992; Honea et al., 2005; Raz and Raz, 1990). Two neurobiological findings that appear particularly robust are: (i) neuroanatomical and physiological alterations in the hippocampus and other medial temporal lobe (MTL) structures (Arnold, 1997; Honea et al., 2005; Karnik-Henry et al., 2012; Tamminga et al., 2010; Van Erp et al., 2016) and (ii) elevated dopamine function in the midbrain and striatum (Brunelin et al., 2013; Howes et al., 2012, 2009).

Experimental work in rodents has begun to shed light on how these factors might be linked and contribute to the development of psychosis. In the MAM rodent model, neurodevelopment is experimentally perturbed by the administration of methylazoxymethanol acetate (MAM) to pregnant rats on gestational day 17 (Lodge & Grace, 2011; Lodge, 2013; Moore et al. 2008, Jentsch, Ghajarnia, Geyer, & Grace, 2006). Work using the methylating agent MAM has highlighted the role of a hippocampal-midbrain-striatal circuit, and suggests that midbrain and striatal dopamine function is elevated as a consequence of *increased neural activity* in descending outputs from the hippocampus to the ventral striatum (Lodge & Grace, 2011). The model postulates that hyperactive hippocampal neural activity results in the increase in striatal dopamine in patients with

schizophrenia (Lodge & Grace, 2007). This increased hippocampal output indirectly increases presynaptic dopamine neuron activity in the ventral tegmental area (VTA) of the midbrain through glutamatergic and GABAergic outputs that project to the ventral striatum (nucleus accumbens) (see Figure 2).

FIGURE 2 HERE

Although the model is derived from animal work, there is substantial evidence in humans of altered hippocampal structure and function as well as elevated dopamine function in the midbrain and striatum in psychosis (See Modinos, Allen, Grace, & McGuire, 2015 for review). What is less clear in humans is how functioning of the hippocampal-midbrain circuit is perturbed in the first instance. A potential mechanism is altered, or imbalanced excitatory and inhibitory neurotransmission i.e. altered GABAergic and glutamatergic concentration in cortical and sub-cortical regions. The MAM model predicts increased glutamate release in the hippocampus and the striatum and reduced cortical GABA levels. MAM-treated rats also show altered densities in cortical GABAergic interneurons (Gastambide et al., 2012; Lodge, Behrens, & Grace, 2009) which may result in the disinhibition of glutamatergic cells (Hammad and Wagner, 2006). This finding in rodents is broadly consistent with evidence that glutamate is altered in schizophrenia and psychosis risk states (Bossong et al., 2018; Bustillo et al., 2011; Fuente-Sandoval et al., 2011; Kraguljac, White, Reid, & Lahti, 2013; Merritt, Egerton, Kempton, Taylor, & McGuire, 2016; Théberge et al., 2002, 2007).

Studies suggest that these glutamatergic changes are a result of impaired GABAergic inhibitory modulation (Benes & Berretta, 2001; Heckers & Konradi, 2015; Marín, 2012). Few *in vivo* studies have examined cortical GABA levels in schizophrenia and only one study has examined cortical GABA levels in people at risk of psychosis (Modinos et al., 2018) and reported no significant differences relative to healthy controls, although the sample size was small. However, a review of imaging

studies examining GABA and schizophrenia, reports that most studies show a reduction in GABA concentration in patients with schizophrenia compared to healthy controls, usually in the medial frontal and occipital cortices (Chiapponi et al., 2016). Post mortem studies have also reported GABAergic alterations in patients with schizophrenia (Benes, Kwok, Vincent, & Todtenkopf, 1998; Benes, Mcsparren, Bird, Sangiovanni, & Vincent, 1991; Benes & Lange, 2001).

Whilst factors such as early stress and trauma are likely to influence the development and function of the hippocampal-midbrain circuit (Froudist-Walsh et al., 2017; Gomes et al., 2016), it is also possible that regular cannabis use in adolescence can perturb the development and functioning of the hippocampal-striatal-midbrain circuit and mediates the association between early onset cannabis use and psychosis/psychotic like experiences (Arseneault et al., 2004). Consistent with this possibility, cannabinoid exposure during adolescence has been shown to exacerbate psychosis-like behaviours in MAM-treated rats (Gomes et al., 2015). The study also showed that pubertal treatment with the a $CB_{1/2}$ receptor agonist in normal animals induced similar changes at adulthood as those observed in the MAM rats, supporting the notion that adolescence exposure to cannabinoids may represent a risk factor for developing psychosis-like symptoms and behaviours. It has also been shown that CB1 receptor mRNA levels are decreased in adolescent and adult MAM-treated rats across a number of brain regions (Gomes et al., 2018).

In summary, the MAM model proposes that the development of psychosis is due to elevated striatal dopamine function that occurs as a consequence of increased neuronal activity in the hippocampus, possibly as a result of altered excitatory and inhibitory neurotransmission that can be affected by early life stress and cannabis use. There is also evidence in experimental animals that cannabinoids, particularly when administered during adolescence, can affect the functioning of the hippocampal-striatal circuit.

4. Evidence from neuroimaging studies in humans

4.1 Effects of cannabinoids on the hippocampus and medial temporal lobe

Most cognitive functions seem to be impaired during acute cannabis intoxication. Impairments in learning and memory, as well as executive function are among the most consistently demonstrated effects (Bossong, Jansma, Bhattacharyya, & Ramsey, 2014; Broyd, van Hell, Beale, Yücel, & Solowij, 2016; Cohen & Weinstein, 2018; Crean et al., 2011; Solowij & Michie, 2007). The medial temporal lobe (MTL) is a system of anatomically related structures including the hippocampus, perirhinal, entorhinal and parahippocampal cortices (Squire et al., 2004). The system plays a major role in learning and memory function (Squire et al., 2004), salience detection (Bunzeck and Düzel, 2006), and emotional processing (Frühholz et al., 2014). Further, MTL dysfunction is linked to a number of pathologies including schizophrenia (Heckers, 2001; Preston et al., 2005), depression (Gorwood et al., 2008) and epilepsy (Spencer, 2002). Altered MTL structure and function in schizophrenia (and in other psychiatric conditions – see Sprooten et al., 2017) is consistent with the marked cognitive and mnemonic deficits seen across different psychiatric illnesses (Karnik-Henry et al., 2012). Although outside the scope of this review, numerous animal studies have shown that cannabinoids impair performance in spatial memory tasks including a delayed non-match to position discrimination task (Mallet and Beninger, 1998) and a radial arm maze task (Lichtman and Martin, 1996; Varvel and Lichtman, 2002). Effects on memory can be reversed however, by administration of the CB1 receptor antagonist SR-141716A (rimonabant), indicating that effects on memory are due to action at the CB1 receptor. Similar effects are seen in animals in which hippocampal tissue has been surgically removed (Hampson and Deadwyler, 1999). We will now review the experimental evidence that acute and chronic cannabinoid administration/use affects function and anatomy in MTL regions (for an extensive review of the effects of cannabis on memory see Bhattacharyya & Schoeler 2013; Jager et al., 2014; Bossong, Jager, Bhattacharyya, & Allen 2014).

In humans, electroencephalogram (EEG) and behavioural studies examining the acute effects of cannabis on working and recognition memory report reductions in item recognition based on Event

Related Potentials (ERP), similar to reductions seen in patients with hippocampal damage (Ilan et al., 2004). Ilan and colleagues report similar performance deficits in casual cannabis users relative to non-cannabis using controls during a word recognition task, with enhanced false recognition in the former. Similarly, a study investigating the acute effects of THC on a number of memory performance measures showed that acute cannabis administration had a dose dependent effect on performance during an episodic memory task, without affecting perceptual priming or working memory (Curran, Brignell, Fletcher, Middleton, & Henry, 2002). These behavioural and ERP studies, along with many others (see Bhattacharyya & Schoeler, 2013 for review) suggest that cannabis is exerting an effect on learning and memory, and specifically episodic memory performance via the hippocampus/MTL. Research on the effects of cannabis on semantic memory has proven less conclusive (Morgan, Rothwell, Atkinson, Mason, & Curran, 2010; Wadsworth, Moss, Simpson, & Smith, 2006). This specific targeting of episodic memory further supports the notion that the effects of cannabis on long term memory are due to its effects on the hippocampus.

The effects of cannabis on the hippocampus are of interest because as already stated, one of the most robust anatomical findings in schizophrenia patients is reduced volume in hippocampus/MTL (Adriano et al., 2012; Honea et al., 2005). A large number of studies also report altered hippocampal and MTL function/perfusion in both psychosis risk states (Allen et al., 2011, 2012, 2016; Schobel et al., 2013; Valli et al., 2011) and in established schizophrenia (Heckers, 2001; Tamminga et al., 2010). The hippocampal formation is rich in CB1 receptors (Mackie, 2005) and patients with psychosis show altered activation in these regions during memory tasks (Achim and Lepage, 2005; Weiss and Heckers, 2001). Here we will review neuroimaging studies which report the effects of both acute (usually defined as a single THC dose administered orally, intravenously or via a vaporizer) and chronic cannabis administration (naturalistic studies in regular or long-term cannabis user) on MTL function and structure.

4.1.1 Acute effects of cannabinoids on MTL function

Using functional Magnetic Resonance Imaging (fMRI) and a verbal paired associate learning task, Bhattacharya and colleagues showed that over subsequent encoding blocks using the same word pairs, there was reduced parahippocampal activation as an effect of learning in a placebo session; this reduced parahippocampal activation was not present after THC administration. As there was no significant difference in task performance between placebo and THC sessions, this suggests that THC results in increased or inefficient neural processing to achieve comparable levels of task performance (Bhattacharyya et al., 2009). Interestingly, higher hippocampal activity during the encoding condition of this task was associated with increased susceptibility to the psychomimetic effects of THC (Bhattacharyya et al., 2018). Similarly, despite the absence of differences in performance on the associative memory task, lower activity in the parahippocampal gyrus during recall of information was significantly related to a higher performance accuracy after placebo but not after THC administration. Together with THC-induced increases in activity in the cuneus and precuneus, this suggests that after THC administration, participants may engage compensatory mechanisms to maintain task performance (Bossong et al., 2012).

Bhattacharyya and colleagues also used an oddball task to examine the acute effects of THC and CBD on salience processing. They showed that THC and CBD had opposing effects on activity in the hippocampus and parahippocampal gyrus, with attenuated activity after THC and augmented activity after CBD compared to placebo. Whereas hippocampal activation was attenuated by THC, it was augmented after single CBD administration. These observations suggest that elevated MTL activity is involved in the acute increase of aberrant attribution of salience after THC administration (Bhattacharyya et al., 2012).

Finally, during processing of facial expressions of emotions, activity in the hippocampus was reduced after THC administration with processing of positive stimuli (happy faces) but increased with processing of negative stimuli (fearful faces). This suggests that administration of THC shifts the

brain's bias for stimuli that have a negative impact towards a bias for stimuli that have a positive impact (Bossong et al., 2013).

Overall, although few studies have been conducted, it has been shown that acute THC administration affects MTL activity and that THC and CBD may have opposing effects on MTL function during the performance of different types of cognitive paradigms.

4.1.2 Chronic effects of cannabis on MTL function

One of the earliest neuroimaging studies to examine the long-term effects of cannabis use on the MTL was conducted by Block and colleagues using [^{15}0] water-PET to examine the effects of regional cerebral blood flow (a proxy of neural activation) during a range of memory tasks. This study found altered hippocampal lateralisation in cannabis users i.e. the left hippocampus was more active than the right during memory tasks in regular cannabis users relative to a non-cannabis using control group (Block et al., 2002). Using fMRI it has also been shown that regular cannabis users show reduced bilateral hippocampal activation relative to non-cannabis users during the encoding phase of an associative learning task, despite no significant difference between groups on task performance (Jager et al., 2007). Nestor and colleagues also conducted an fMRI study with an associative learning task that activates hippocampal regions. Whole brain analysis revealed that the cannabis user group had significantly lower activity during the learning phase of the task than the non-cannabis using control group in a number of cortical regions. However, region of Interest analysis of hippocampal and parahippocampal regions showed that the cannabis group had significantly *greater* activity in the right parahippocampal gyrus during learning (Nestor et al., 2008). Increased parahippocampal activation is the opposite of what was seen in the Jager study discussed above (Jager et al., 2007). Whilst there was no significant difference in task performance, the differences in hippocampal activation between the two studies could be because the associative memory task used by Nestor and colleagues was harder, requiring participants to match pictures to numbers as opposed to matching two pictures, as was the case in the Jager study.

Although findings are equivocal (Scott et al., 2018) it has been reported that regular cannabis use in adolescence can increase the deleterious effects of the drug on cognitive function (Meier et al., 2012) and increase risk for psychosis in adulthood (Arseneault et al., 2004, 2002). To examine the effects of regular cannabis use in adolescence, Jacobsen and colleagues used fMRI in combination with a verbal memory task in 7 abstinent adolescent cannabis users, age matched tobacco smokers and non-smokers. During the memory task, performance accuracy of cannabis users was significantly lower than that of both tobacco smokers and non-smokers. Region of interest analysis revealed that cannabis users failed to deactivate the right hippocampus across working memory task conditions, as opposed to both control groups (Jacobsen et al., 2004). These findings suggest that adolescent cannabis users may have disrupted neural activity when task-focused attention is required, resulting in impaired task performance. However, findings from this study should be interpreted cautiously as the sample size was small and the functional task used did not directly test episodic memory/verbal learning. Furthermore, Jager et al. (2010) report that adolescent cannabis users showed no differences in hippocampal activation during an associative memory task relative to adolescent non-cannabis users.

In summary, there appears to be some evidence for long-term effects of cannabis use on hippocampal/MTL function, but interpretations are hampered by differences in cannabis types and demographic factors such as lifetime cannabis use and abstinence time. There appears to be no particular evidence for stronger effects of adolescent cannabis use on MTL function.

4.1.3 Chronic effects of cannabis on MTL structure

A number of volumetric studies have examined the effects of chronic cannabis use on hippocampal and MTL structure. Preclinical studies have established that THC is toxic to cultured hippocampal

neurons, and that this is mediated through CB1 receptors, with CA1 pyramidal neurons being particularly sensitive (Chan et al., 1998; Lawston et al., 2000). Yucel and colleagues (2008) investigated if long-term heavy cannabis use was associated with anatomical abnormalities in the hippocampus and the amygdala. Long-term cannabis users showed bilaterally reduced hippocampal and amygdala volumes. Furthermore, left hemisphere hippocampal volume was inversely associated with cumulative exposure to cannabis during the previous 10 years. Psychotic symptom scores (hallucinations and delusions) were also associated with cumulative exposure to cannabis.

Although cannabis users showed performance deficits relative to controls on a verbal learning task, performance was not related to regional brain volumes in either group. Lorenzetti et al. (2015) report that heavy cannabis users show smaller hippocampus and amygdala volumes but no alterations of the orbitofrontal and para-cingulate cortices, indicating that chronic cannabis use has a selective and detrimental impact on the morphology of the MTL. Battistella and colleagues (2014) report that regular cannabis use is associated with grey matter volume reduction in the MTL, temporal pole, parahippocampal gyrus, insula and orbitofrontal cortex, regions rich in CB1 receptors and functionally associated with motivational, emotional and affective processing. They also report that the age of onset of regular cannabis use influences the magnitude of these volumetric changes.

Ashtari and colleagues (2011) report that heavy cannabis users show smaller bilateral hippocampal volume but not amygdala volumes compared to controls. In controls, larger hippocampal volumes were significantly correlated with higher verbal learning and memory scores, but these relationships were not observed in cannabis users. These findings in heavy cannabis users, after an average 6.7 months of supervised abstinence, lend support to the idea that cannabis use may impart long-term structural damage to the hippocampus. Alternatively, the observed hippocampal volumetric abnormalities may represent a risk factor for cannabis dependence. Demirakca and colleagues (2011) report similar hippocampal volumetric findings to those reported above but in addition they report that reduced right hippocampal volume in regular cannabis users is associated with the ratio

of THC/CBD in the cannabis being used by their participants. It must be noted however that there are a range of factors other than cannabis use that can play a role in hippocampal damage. For example, a number of environmental risk factors, in particular stress in early life (Paquola et al., 2016) can result in reduced hippocampal volume, increased psychosocial stress (Paus et al., 2008) and increased risk for schizophrenia (Mizrahi et al., 2014). Indeed, stress has been linked to hippocampal damage that may precede cannabis use (Modelli et al., 2010,2011). Such confounding factors should be taken into account when considering the relationship between cannabis and hippocampal function and volume.

To summarise, several studies have linked regular cannabis use to reduced volume in the hippocampus and other MTL regions. However, there is no clear link between cannabis related volumetric reduction in the MTL, cognition, and psychosis like experiences/psychosis risk. It should be noted that some volumetric studies have failed to find differences in hippocampal volume in cannabis users compared to non-cannabis using controls. Studies by Block et al. (2000) and Tzilos et al. (2005) both found no significant difference in hippocampal volume between cannabis users and controls. Using a region of interest approach, Cousijn et al. (2012) found larger bilateral anterior lobes in the cerebellum of cannabis users but no significant differences in the hippocampus or amygdala in heavy cannabis users compared to non-cannabis users. It is possible that mixed results reported by volumetric studies are due to confounders such as lifetime cannabis use, abstinence time and use of other illicit drugs (see Bossong et al., 2014).

4.2 Cannabinoids, striatal function and dopamine

4.2.1 Acute Studies

It is widely established that schizophrenia and psychosis risk states are associated with aberrant striatal neural activity (Fusar-Poli et al., 2011) and increased presynaptic striatal dopamine levels (Howes et al., 2012). There are far fewer studies investigating striatal activity and striatal dopamine levels in relation to cannabis use/cannabinoid administration. A case study by Vorungati and

colleagues was the first to identify an increase in striatal dopamine activity following cannabis use. A drug-free patient with schizophrenia took part in a SPECT (single photon emission computed tomography) study and during a break in the scanning protocol, surreptitiously smoked a cannabis cigarette. The cannabis use led to worsening of psychotic symptoms a few hours later and to a 20% decrease in striatal D2 receptor binding measured on the scan following the break. This suggested an increase in striatal dopamine release following cannabis use, and a role for striatal dopamine in the consequent worsening of psychotic symptoms (Voruganti et al., 2001).

Using Positron Emission Tomography (PET) and the dopamine D2/D3 receptor tracer [^{11}C]-raclopride in healthy participants, Bossong and colleagues found that following administration of inhaled THC, purified from cannabis, there was a significant reduction in [11C]-raclopride binding, indicating an increase in dopamine levels, in the ventral striatum and precommisural dorsal putamen compared to placebo (Bossong et al., 2009). This was a small study, but it was the first group study to show that THC induced elevated striatal dopamine release. In contrast, another study using the same methodology ([11C]-raclopride PET) found no significant effect of oral THC on dopamine release in the striatum relative to placebo in healthy volunteers (Stokes et al., 2009). In a reanalysis of the pooled PET data from the aforementioned studies (i.e. Bossong et al., 2009; Stokes et al., 2009), Bossong and colleagues confirmed the moderate but significant reduction in [^{11}C]-raclopride binding in the ventral striatum (Bossong et al., 2015). Because of this modest effect (-3.65%), the authors concluded that an increase in striatal dopamine was unlikely to be the primary driver of the increased risk of schizophrenia in cannabis users. Moreover, an independent SPECT study by Barkus and colleagues that administered THC intravenously failed to induce any significant elevations in striatal dopamine release (Barkus et al., 2011).

A study by Kuepper and colleagues examined the effects of THC administration on striatal dopamine release in patients with a psychotic disorder, unaffected relatives and healthy controls. This PET

study administered THC extracted from the cannabis plant via inhalation and measured dopamine release by assessing D2 receptor binding using ^{18F}Fallypride (Kuepper et al., 2013). The study reports that the amount of striatal dopamine release was dependent on participants' risk of psychosis, with patients with psychotic disorder and their relatives releasing significantly more dopamine in response to THC than healthy controls, with the biggest difference in the left caudate nucleus.

Functional MRI studies have also shown that the acute administration of THC can affect task-related striatal activation. Bhattacharyya reports that during a paired-associated verbal memory task (also discussed above), THC attenuated the normal linear decrement seen in the striatum after repeated encoding blocks relative to a placebo condition (Bhattacharyya et al., 2009). In the same study cohort THC induced decreases in striatal activity reported during an oddball task (Bhattacharyya et al., 2012), an effect that was reversed by the administration of CBD (Bhattacharyya et al., 2010). Moreover, the effect of THC in the striatum was inversely correlated with the severity of the psychotic symptoms.

In a further exploration of their previous fMRI study with acute THC administration and a verbal associative learning paradigm (in an increased sample), Bhattacharyya et al. (2012b) showed that in healthy volunteers the effects of THC on both behaviour and brain activity were affected by variation in the genes for the dopamine transporter (DAT1, which removes dopamine from central synapses) and the protein kinase B (AKT1, an integral component of the dopamine signalling cascade). Carriers of polymorphisms associated with higher dopamine neurotransmission showed an increased sensitivity to the psychotic effects of THC and to activity in both the striatum during encoding and midbrain during recall (Bhattacharyya et al., 2012b). Reward processing paradigms have also been used to assess acute THC effects on striatal activity, with increased striatal response during reward anticipation after THC compared to placebo in some studies (Jansma et al., 2013) and an absence of THC effects on striatal activity in others (van Hell et al., 2012).

In summary, acute administration studies using PET and fMRI imaging provide evidence for the acute effects of THC on dopamine and striatal function. However, the effects sizes may be small and fMRI studies have provided some equivocal findings. It is possible that the effects of acute THC administration on dopamine and striatal function depend to some extent on the genetic profile for dopamine signaling.

4.2.2 Chronic Studies

Acute studies examining dopamine release have assessed the effects of a single THC administration on dopamine release/striatal activity compared to a placebo condition. PET studies in chronic cannabis users can examine the effect of heavy cannabis use on dopamine release following a stimulant challenge known to cause striatal dopamine release.

Using [^{11}C] raclopride, Volkow and colleagues compared regular cannabis users to non-cannabis using controls to assess striatal dopamine release following a methylphenidate challenge (known to increase extracellular dopamine). The study reports that regular cannabis users showed a significant difference in [^{11}C] raclopride binding in the striatum compared to controls, which suggests a blunted response to methylphenidate. The study concludes that the attenuated response to methylphenidate in regular cannabis users is consistent with decreased brain reactivity to dopamine stimulation that might contribute to negative emotionality and addictive behaviours in cannabis users (Volkow et al., 2014).

Bloomfield and colleagues assessed dopamine synthesis capacity using [^{18}F]-DOPA in cannabis users and non-cannabis using controls (Bloomfield et al., 2014). This study reports that striatal dopamine synthesis capacity was lower in cannabis users compared to controls. This was particularly prominent in subjects that were heavy cannabis users. Van de Giessen and colleagues (2017) also looked at the effects of heavy cannabis use on striatal dopamine release following an amphetamine challenge. The study assessed heavy cannabis users and non-cannabis using controls in a PET study

using a more sensitive $D_{2/3}$ agonist radiotracer [^{11}C] –(+)-PHNO. Similar to findings from the Volkow (2014) study, a deficit in striatal dopamine release (caudate) was seen in cannabis users compared to controls following a stimulant challenge. Consistent with this view, using PET, Leroy and colleagues measured striatal and extra striatal dopamine transporter (DAT) availability (Leroy et al., 2012). DAT availability in the dorsal striatum was significantly reduced in regular cannabis users relative to non-cannabis using controls. One study however, using PET and [^{11}C] raclopride in regular cannabis users reported no changes in striatal dopamine function after amphetamine challenge (Urban et al., 2012).

In summary, findings in chronic users suggest that regular cannabis use is associated with lower striatal dopamine synthesis and reductions in dopamine release. Taken together with the findings from acute administration studies, which suggest the THC may only induce small effects on striatal dopamine, it is possible that the association between cannabis use and psychosis is not entirely due to an *increase* in striatal dopamine release. It is worth noting however that across the schizophrenia literature PET studies that examined [^{11}C] and [^{18}F]-DOPA have also reported conflicting results. This may be because PET and SPECT studies using receptor tracers such as [^{11}C]-raclopride and studies using [^{18}F]-DOPA are measuring dopamine function at post and pre synaptic locations respectively. Furthermore, a number of confounding factors such as antipsychotic medication and illness stage may also affect the findings of PET studies measuring dopamine function in schizophrenia patients. Thus the prediction that the link between cannabis use and psychosis is mediated by increased striatal dopamine function may be simplistic. Finally, it should be considered that genetic factors and environmental factors such as stress (Egerton et al., 2016) known to increase risk for substance use and psychosis (Howes et al., 2017) have also been shown to blunt dopamine release to amphetamine challenge (Casey et al., 2014). This raises the possibility that the blunted dopamine response seen in cannabis users may precede cannabis use rather than be a consequence.

5. Cannabis, Glutamate and GABA

The MAM model of psychosis proposes that changes to cortical GABAergic and glutamatergic neurotransmission results in increased hippocampal neural activity and dysfunction of the hippocampal-midbrain circuit (Moore et al., 2006). It is possible that the acute and chronic effects of cannabis/cannabinoids on hippocampal function and volume are mediated by cannabis-induced changes in excitatory and inhibitory neurotransmitter function. Indeed, the main role of the endocannabinoid system is to regulate excitatory and inhibitory neurotransmission (Wilson and Nicoll, 2002). The CB1 receptor is the most abundant G-protein-coupled receptor in the central nervous system (Cabral et al., 2008; Pertwee, 2006). The two most important endocannabinoid ligands binding to endocannabinoid receptors are anandamide and 2-arachidonylglycerol, which act as retrograde messengers. They are synthesized and released postsynaptically and bind to presynaptic receptors, thereby regulating the release of both inhibitory and excitatory neurotransmitters. This signalling works according to an 'on demand' principle: endocannabinoids are released when and where they are needed (Kano et al., 2009; Katona and Freund, 2012).

Research using both preclinical in-vitro and in-vivo models shows that THC depresses endocannabinoid mediated glutamate synaptic transmission. This affects glutamate release, enzyme activity and also the expression of receptors and transports (for review see Colizzi, McGuire, Pertwee, & Bhattacharyya 2016). At present, there are only a handful of in-vivo studies that examine the effects of cannabis on glutamate function and no studies that look at the effect of cannabis on GABAergic functioning.

Using Magnetic Resonance Spectroscopy (1H-MRS), Chang and colleagues (2006), examined the effects of regular cannabis use in HIV positive patients and healthy controls on brain metabolites. The study found that glutamate metabolite levels in the basal ganglia were reduced in cannabis users relative to non-cannabis user controls. This reduction was seen in a HIV negative group but

was most prominent when both the HIV positive and negative cannabis user groups were analysed together with a 12-13% decrease in basal ganglia glutamate levels.

Muetzel et al. (2013) examined a similar striatal region in heavy cannabis users and non-cannabis using controls. When the whole group was assessed there was a non-significant reduction in striatal glutamate metabolites. However, the study found sex differences such that there was a significant reduction in striatal glutamate metabolites in the female cannabis users compared to female controls. It should be noted that in this study the outcome measure was glutamate + glutamine metabolites (Glx) combined as opposed to just glutamate.

Prescot and colleagues (2011) examined the effects of chronic cannabis use on metabolites in the anterior cingulate cortex of adolescent cannabis users. Using 1H-MRS at 3T they found significant reductions in glutamate metabolites in the ACC in regular cannabis users compared to non-users. The same group carried out another similar study examining the same voxel, comparing an independent cohort of adolescent cannabis users to age-matched non-users. In the second study Prescot and colleagues again reported significantly lower ACC glutamate and GABA concentrations in cannabis users compared to controls (Prescot et al., 2013). Sung and colleagues also used 1H-MRS to examine the effects of regular cannabis use on ACC metabolite levels. However, this group tested concomitant cannabis and methamphetamine users. This study did not find significant difference in glutamate+glutamine metabolites between the users and non-drug using controls in the ACC. It should be noted that this study had quite a small sample size and this may have resulted in the lack of a significant finding (Sung et al., 2013).

Recently however, one study has directly examined the acute effects of THC administration on striatal glutamate levels (Collizi et al. 2019). Compared to placebo, acute administration of THC significantly increased Glx (Combined Glutamine metabolites) in the left caudate head. Furthermore, compared to individuals who were not sensitive to the psychotomimetic effects of THC, individuals

who developed transient psychotic-like symptoms had significantly lower baseline Glx levels. These results show that THC can increase striatal glutamate levels and that lower baseline levels of striatal glutamate metabolites may be a marker of greater sensitivity to its acute psychotomimetic effects.

On a molecular level, the main role of the endocannabinoid system is to regulate synaptic activity via glutamate and GABA-ergic transmission (Wilson and Nicoll, 2002). This is achieved by retrograde inhibition of both GABA-ergic and glutamatergic synapses throughout the brain (Chevaleyre et al., 2006; Marsicano et al., 2003; Schlicker and Kathmann, 2001). Endocannabinoids only affect neurotransmitter release from their accompanying presynaptic site, allowing for protection against excessive glutamate receptor stimulation. However, external cannabinoids may affect the normal endocannabinoid regulatory system by downregulation and desensitization of CB1 receptors (Bossong and Niesink, 2010). These effects have been shown after chronic administration of synthetic cannabinoid agonists and THC (Breivogel et al., 1999; Sim-Selley and Martin, 2002). Disruption of normal endocannabinoid homeostasis of Glutamate and GABA by exogenous endocannabinoids could then result in the differences in these metabolite concentrations in cannabis users. However, as discussed previously, environmental factors such as stress and early life trauma can also perturb glutamate and GABAergic function (Allen et al., 2019), factors that may also increase risk of chronic cannabis use in later life (Schlossarek et al., 2016).

To summarise, the MRS data in regular cannabis users points towards reduced glutamate levels in striatal and cortical regions. However, there are currently too few studies to draw any firm conclusions about the effect of cannabis use on brain glutamate levels although one acute study does provide evidence of a link between exposure to THC, striatal glutamate levels and psychosis proneness. To date, there have been no studies that have explicitly examined GABA levels in cannabis users and no studies have utilised an ‘acute challenge’ design.

6. Discussion & Future work

Using the MAM rodent model as a heuristic framework, in this review we aimed to examine if altered neurobiological functioning in a hippocampal – striatal – midbrain circuit, which regulates mesolimbic dopamine function, mediates the link between cannabis use and the experience of psychotic symptoms and/or increased risk for psychosis. Overall, studies examining the effects of acute THC administration on hippocampal and MTL function indicate that THC can affect hippocampal activation during memory and salience tasks (Bhattacharyya et al., 2009; Sagnik Bhattacharyya et al., 2012) and that increased hippocampal and parahippocampal activity is associated with a susceptibility to the psychotic effects of THC (Atakan et al., 2013; Bhattacharyya et al., 2018). However, studies have reported both increased and decreased hippocampal/MTL activity after acute THC administration. The subtraction methods used in task related fMRI studies (experimental vs. control condition) make these functional findings difficult to interpret. Easier to understand are perfusion and volumetric studies in chronic cannabis users which have reported increased parahippocampal perfusion and reduced hippocampal volume, findings broadly consistent with the MAM rodent model. Furthermore, studies examining the effect of cannabis and cannabinoids on MTL function and volume implicate a number of different MTL regions i.e. posterior and anterior hippocampus and the parahippocampal gyrus. The MAM rodent model however posits that neural hyperactivity is seen in the anterior hippocampus (analogous to the CA1 in humans). This is consistent with human studies in a psychosis risk cohort that report elevated hippocampal perfusion in the CA1 and subiculum subfields of the hippocampus (Schobel et al., 2013). However, the effects of cannabis/THC on hippocampal function and volume appear to be more widespread. This observation may be due to the differential effects of acute and chronic cannabinoid administration on the MTL and differences in study designs used to assess these effects. It should also be noted that studies in chronic cannabis users do not take into account the effects of CBD on brain activity. It has been shown that CBD and THC have opposing effects on brain activity in several regions including the hippocampus (Bhattacharyya et al., 2010). This may be one reason that the

findings from the chronic studies are more equivocal, with chronic cannabis users consuming a range of different cannabis types with differing levels of THC and CBD.

PET studies examining the effects of acute THC administration on striatal D2 receptor binding suggest that THC can increase striatal dopamine function, albeit with a moderate effect size. Studies in chronic users tend to show that cannabis blunts striatal dopamine response compared to non-cannabis using controls. This blunted response could be due to a down regulation of dopamine transporter as seen in other studies (Leroy et al., 2012). fMRI studies have shown an acute impact of THC on striatal activity patterns during paradigms involving learning, reward anticipation and salience processing, with some of these effects depending on genetic profile for dopamine signalling (Bhattacharyya et al., 2012). Taken together, and broadly in line with the MAM rodent model, the findings from PET and fMRI studies suggest that cannabis can affect dopamine and striatal function both in acute administration studies and in chronic users. However, the pattern is complex given the findings of blunted dopamine response in chronic cannabis users. Again, how these findings align with the MAM rodent model of psychosis is difficult to assess. It is possible that, consistent with the MAM model, cannabis initially increases striatal dopamine function and that the longer-term cannabis use causes a blunting of the dopamine function through adaptive mechanisms.

Finally, very few studies have examined how cannabinoids affect cortical and subcortical glutamate levels. Overall, there appears to be some evidence that cannabis use alters glutamate concentrations in striatum and ACC but there is no evidence for increased glutamate concentrations in the hippocampus, as would be predicted by the MAM rodent model. However, a recent MRS study reports that acute THC administration increases striatal Glx levels that were initially lower in subjects more sensitive to the psychosis inducing effects of THC. No studies have examined the effects of cannabinoids on cortical GABA concentrations.

Together, the available evidence provides some support for the notion that the relationship between cannabis use and psychosis risk is mediated through altered hippocampal function, striatal dopamine and glutamate levels. However, much more work is needed to test the predictions of the MAM rodent model systematically in humans and there are a number of environmental factors that may confound this relationship. No studies have examined the effects of cannabis, acutely or chronically, on GABA levels. Regarding cannabis use during adolescence, a recent rodent study reports that adolescent synthetic cannabinoid exposure significantly increased the proportion of susceptible rats displaying a schizophrenia-like hyperdopaminergic phenotype and that this acquired phenotype appears to correspond with alterations in parvalbumin GABAergic interneuron function within the hippocampus (Aguilar et al., 2018). Whilst more animal work is needed to understand the precise mechanisms through which cannabinoids act upon the hippocampal-striatal-midbrain circuit, the findings by Aguilar and colleagues are in line with epidemiological studies in humans that suggest adolescent exposure to cannabis increases risk for psychosis (Arseneault et al., 2002).

To conclude, whilst cannabis and THC clearly affect hippocampal function and structure (chronically), we cannot firmly conclude that these effects are driving the increased risk of psychosis via changes in striatal dopamine function. There is limited evidence that cannabis affects cortical and subcortical glutamate levels. Future work should apply multi-modal neuroimaging approaches that examine the relationship between hippocampal function/volume, striatal dopamine function and cortical and subcortical glutamate and GABA concentrations in order to establish the systematic effects of cannabis/THC on the functioning of the hippocampal-striatal-midbrain circuit. Furthermore, given the increased use of synthetic cannabinoids (Cohen and Weinstein, 2018b) it may also be interesting to examine the effects of synthetic cannabinoids e.g. 'Spice' on dopamine, glutamate, hippocampal and striatal function. This is outside the scope of the current review but it is known that synthetic cannabinoids contain CB_1 and CB_2 receptor agonists, but do not contain CBD

(Martinotti et al., 2017). Worryingly studies have found that synthetic cannabinoids result in more severe clinical outcomes including hallucinations (Forrester et al., 2012).

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FIGURES

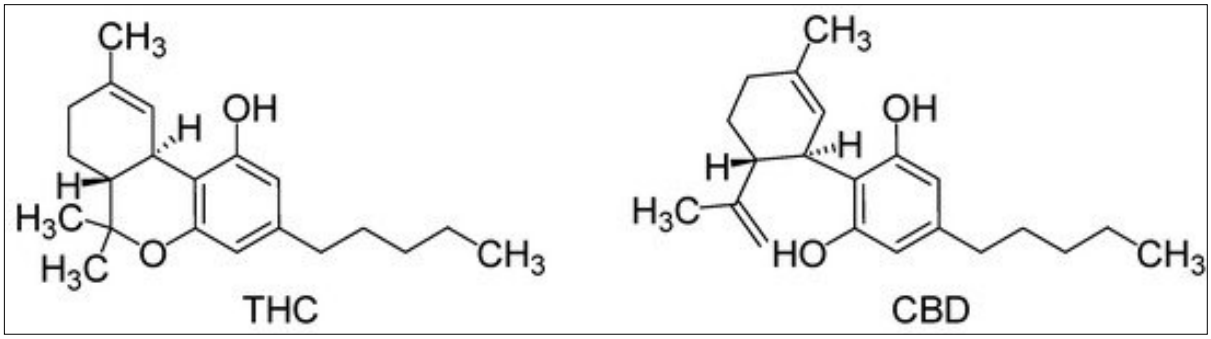

Figure 1: *Chemical structures of Tetrahydrocannabinol (THC) and Cannabidiol (CBD)*

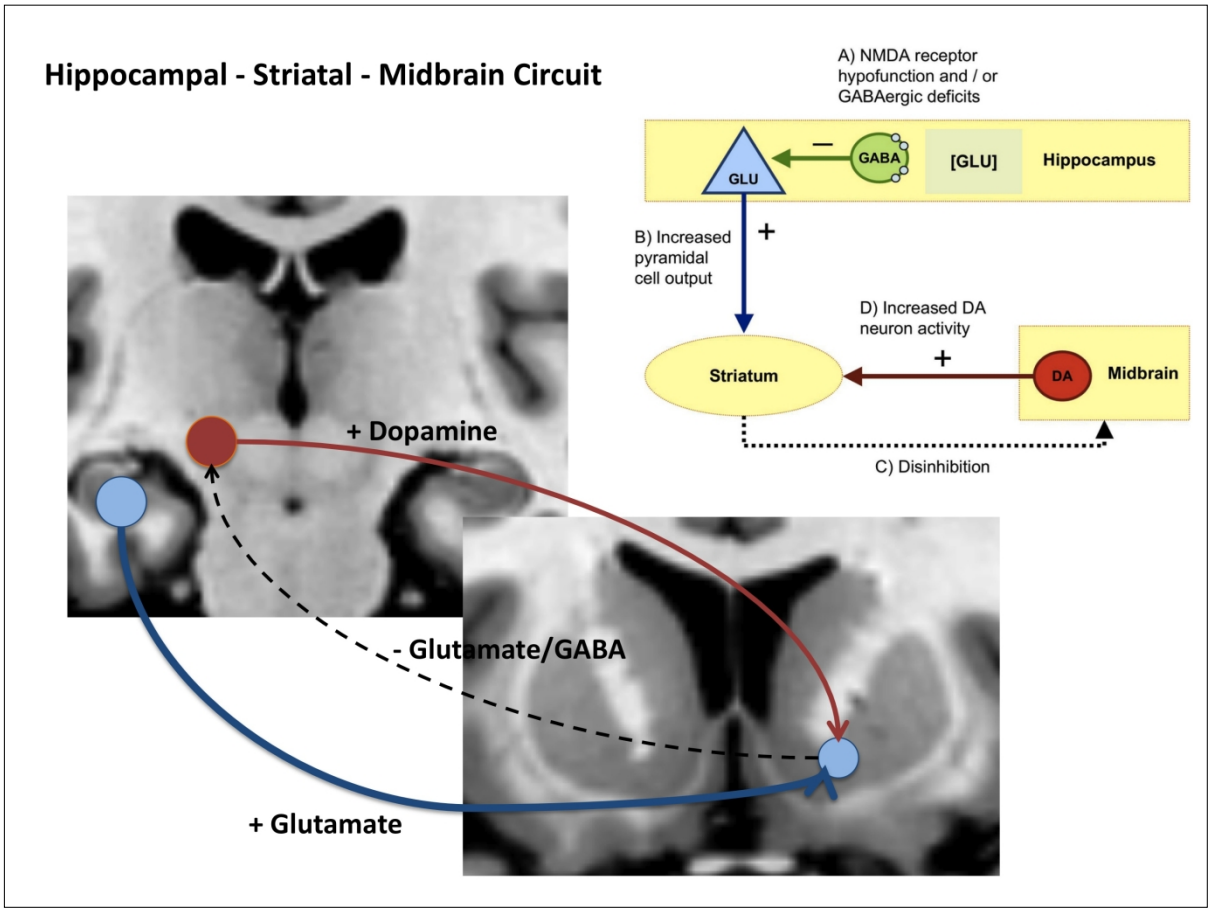

Figure 2: *Diagram showing hippocampal- midbrain- striatal circuit involved in the regulation of striatal dopamine/activity. In psychosis dysregulation of glutamate (due to glutamate/GABAergic imbalances) elevates hippocampal neural activity (hyperperfusion) (A) and output (B, blue line), which alters hippocampal function. Hippocampal hyperactivity leads to increased striatal/dopamine function (C & D, dashed and red lines).*