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Case Report

Similarities and Differences between the Neurobiology of Gambling and Substance Addiction

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Abstract

The DSM-V, published in May 2013, renamed Pathological Gambling (PG) to Gambling Disorder. It was also reclassified from an 'Impulse-Control Disorder Not Elsewhere Classified' to a 'Substance-Related and Addictive Disorder', following results from multiple studies confirming clinical and cognitive similarities between PG and Substance Use Disorders (SUDs), as well as their treatment. As of May 2019, the ICD-11 has opted to remain with PG and other behavioural addictions under the 'Impulse Control Disorders' classification. Both PG and SUD represent considerable burdens across both the UK and globally, with PG costing Great Britain up to £1.16 billion annually, and drug misuse costing society around £15.4 billion. This is further compounded by the lack of clinically proven treatments that have been developed up to now. Thus, a more comprehensive understanding of the pathophysiology of both disorders is urgently required for effective novel therapies to be developed. We can adopt the 3-stage model of addiction with large overlap for both PG and SUD, as neuroimaging studies suggest shared neurocircuitry between the two disorders across multiple neural systems, most importantly the mesolimbic system, the prefrontal cortex (PFC) and orbitofrontal cortex (OFC). Another key aspect in the pathogenesis of addiction as a chronic disorder is the progression from impulsivity to compulsivity, predominantly involving changes to the PFC and ventral striatum. PG and SUD both show activation in these areas corresponding with impulse regulation, although slightly differently. Other similarities of interest include the phenomenon of craving, as well as striatal dopamine (DA) responses to their respective cues. The specific neurotoxic effects of substances of abuse highlight the potential differences in PG and SUD. PG and SUD share the 3-stage model of addiction, along with aberrant responses to stimuli and an impulsive nature, but differ in neurotoxic effects and the recruitment of the reward and other neurotransmitter systems. This critical summary highlights the need for more comprehensive research into the neurotransmitter pathways involved in addiction and impulse control. We suggest that further investigations into the highlighted areas will enable more robust models of addictive pathways and consequently aiding the development of novel based therapies.

Introduction and Background

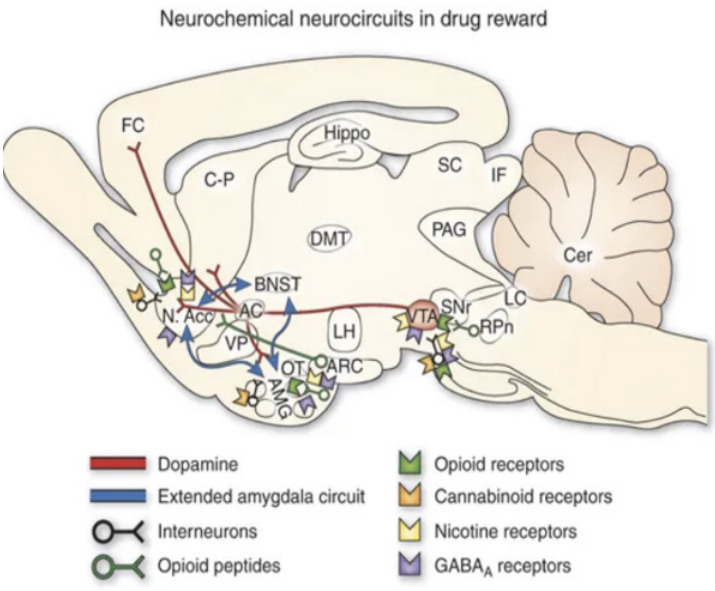
The DSM-V was published in May 2013. Amongst other changes, Pathological Gambling (PG) was renamed to Gambling Disorder and reclassified from an 'Impulse-Control Disorders Not Elsewhere Classified section' to a 'Substance-Related and Addictive Disorder' [1]. Justification came from clinical and cognitive similarities between PG and Substance Use Disorders (SUDs) as well as similarities in their treatment [2,3]. The two have a high co-occurrence as 57.7% of problem gamblers also have a SUD [4]. Changes allow a wider group of patients with clinically significant gambling-related problems to be diagnosed [5]. On the contrary, the

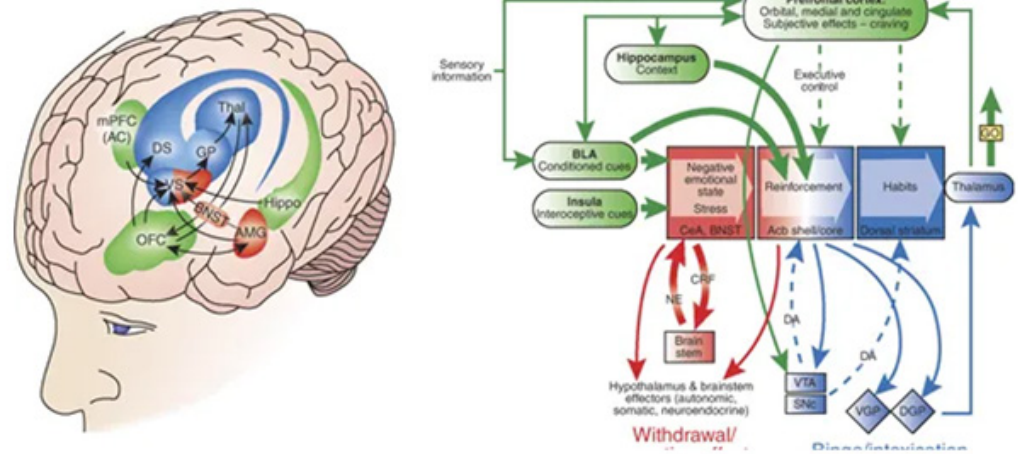
ICD-11, presented to the WHO in May 2019, has opted to keep PG and other behavioural addictions under Impulse Control Disorders [6]. Both PG and SUDs represent major burdens to healthcare systems and society in the UK and worldwide. The Institute for Public Policy Research has reported that treatment of PG costs Great Britain up to £1.16billion annually [7] and drug misuse annually costs society around £15.4billion as reported by the National Treatment Agency [8]. In 2012, 0.5% of the population of England and Scotland met the DSM-IV criteria for PG [9]. Prevalence is far higher in men, a trend shared with SUD, reaching 2.1% in men aged 16-24 [10,11]. In the U.S. in 2015, prevalence for SUDs of elicit substances and alcohol were 8.9% and 6.5% respectively10 and the 2018/19 Crime Survey for England and Wales reported a 10 year high of 9.4% of adults aged 16-59 reportedly taking an illicit substance in the last year [11].

Although reclassification of PG in the DSM-V was based upon common cognitive similarities and treatment, neurobiological mechanisms would arguably be the most valid indicator of whether these disorders are related [12]. There is currently insufficient evidence to justify any classification of other proposed behavioural addictions (internet addiction, kleptomania, video game addiction) [13]. By evaluating the similarities in neurobiology of PG and SUD new targets of future research in these fields may provide this evidence. Similarities in neurobiology open the exploration for research into novel therapeutic agents as well as overlapping pharmacological and behavioral therapy between PG and SUD sufferers [14]. In a trial investigating the safety and efficacy of naltrexone for PG, the most robust clinical measure associated with treatment outcome in individuals was a family history of alcoholism and strong gambling urges at treatment onset demonstrating the potential for this overlap in treatment [3]. This Critical Review aims to compare the similarities and difference between the neurobiology of SUD and PG within this context.

Pathways of Addiction

Drug Addiction is defined as a chronic relapsing disorder comprised of 3 stages: binge/intoxication, withdrawal/negative effect and preoccupation/anticipation, becoming more intense [15]. The progression of addiction involves long-lasting neuroplastic changes [16]. Neuroimaging studies suggest shared neurocircuitry between behavioural and substance addictions [17]. Figure 1 aids in the visualisation of the pathways discussed. The mesolimbic pathway has been implicated in both substance and behavioural addiction, contributing to the binge/intoxication stage [18,19]. Due to general effects of addictive substances on the nucleus accumbens (NAcc), it is considered the node within the memory circuit also involving the medial temporal lobe, hippocampus, anterior thalamic nuclei, regions of the association cortex and prefrontal cortex (PFC) [20]. Cue-induced memory addiction networks have been shown to be triggered by gambling-related cues [21]. Symptoms of acute withdrawal e.g. dysphoria and increased anxiety, involve decreases in the function of the ventral striatum and recruitment of brain stress neurocircuitry [22]. These symptoms of withdrawal are common in both SUD and PG [23]. Dynamic changes in extrahypothalamic Corticotrophin Releasing Factor (CRF) begin with increased release of glucocorticoids. Chronic stress leads to high levels of glucocorticoids, decreasing CRF levels in the periventricular nucleus whilst increasing CRF in the amygdala. Compulsive drug-taking increases CRF in the amygdala, PFC and Ventral Tegmental Area (VTA), contributing to stress-like responses and negative emotional states sustaining the compulsive behaviour [24]. Compulsive drug taking increases dynorphin levels in the NAcc and amygdala contributing to the dysphoric state individuals experience during withdrawal [25]. Other neurotransmitter systems involved in emotional dysregulation include norepinephrine, neuropeptide Y, endocannabinoids and nociception [26]. Increasing levels of stress have been shown to decrease PFC function and increase striatal activity, perpetuating low cognitive control [27].

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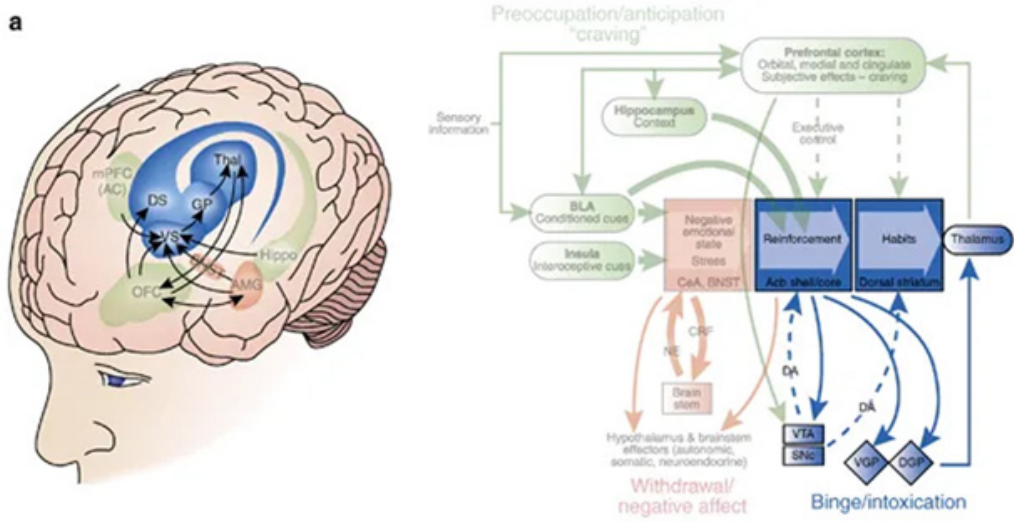
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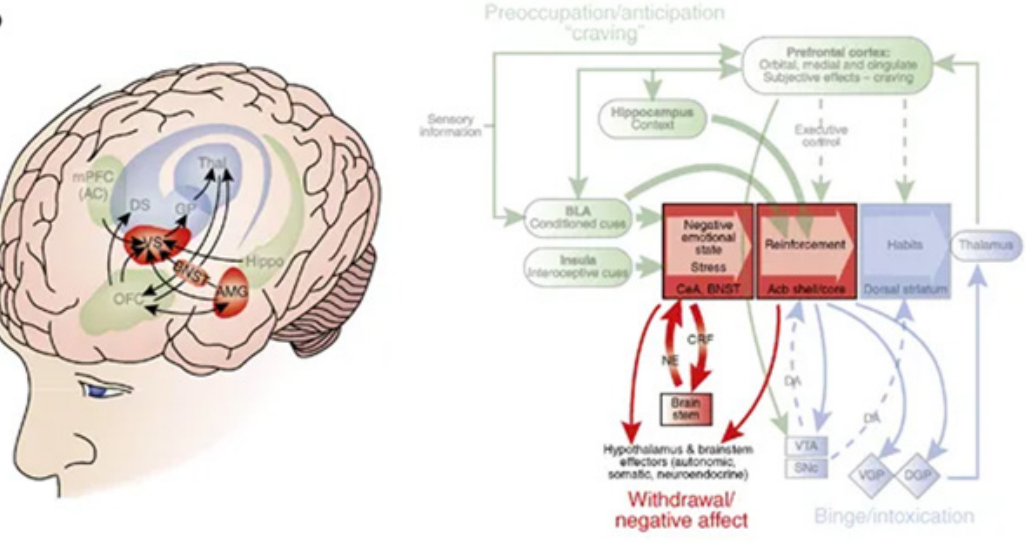
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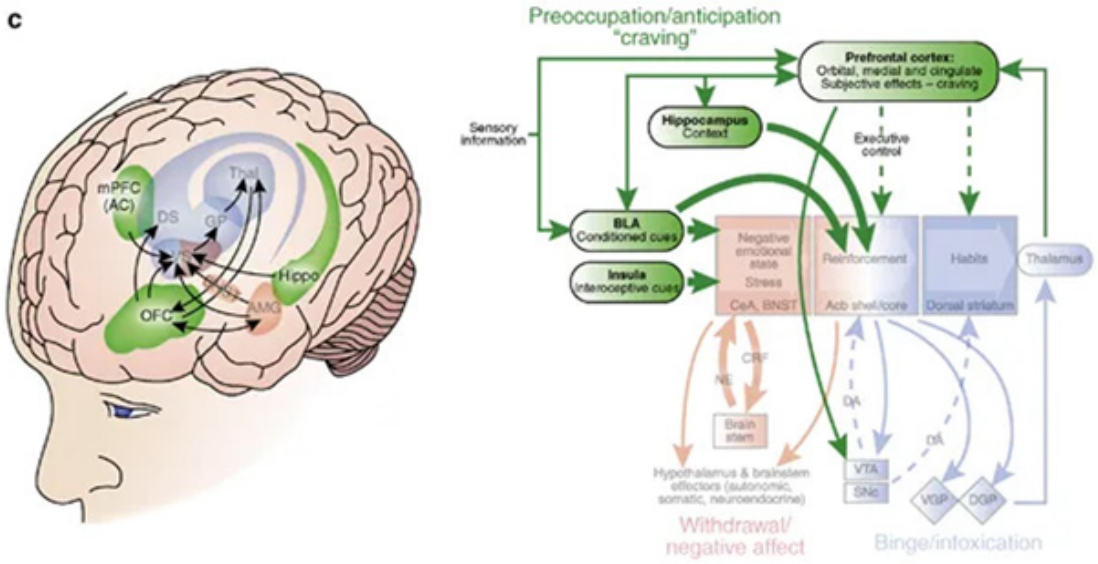

Figure 1: Taken from Koob and Volow's review: the Neurocircuitry of addiction16. Diagrams show the involved brain regions during the 3 stages of addiction namely binge/intoxication, withdrawal/negative affect and preoccupation/anticipation.

The PFC contributes to decision making in disorders of impulse control and addiction, whilst the orbitofrontal cortex (OFC) codes stimuli salience [28]. The inferior frontal gyrus/dorsolateral PFC is important in shifting attention, contributing to the ability to resist intrusive information about drugs/behaviours [29]. Diminished activation of the OFC and cingulate gyrus (CG) have been associated with chronic cocaine use [30], contributing to the preoccupation/anticipation stage. This is reflected in SUD subjects displaying impaired performances in decision-making instruments [31]. In PG, both increased [32] and decreased [33] ventro-medial PFC activity has been reported during simulated gambling/decision-making tasks. Differences in findings may be influenced by small population study or the specific task used.

SUD and PG show similarities most notably during the binge/intoxication and negative withdrawal stages of the 3-stage model of addiction [34]. Overall it appears there are more similarities than differences between SUD and PG neurocircuitry. Research emphasis on addiction has changed from the binge/intoxication stage to include neuroadaptations consequent to drug exposure. These include the mechanisms driving incentive salience, compulsivity, reward-blunting and stress-related hormones during withdrawal [35]. This further research into addiction pathways would allow for more accurate statements on the similarities to be made (Figure 1).

Impulsivity vs Compulsivity

The relationship between impulsivity and compulsivity is not fully defined, they could be described as a dimensional model or more of a spectrum [36]. Models investigating impulsivity and compulsivity together, such as Blanco et al. [37] could further our understanding of the relationship between the two, but these are not commonly used. Generally, Impulsivity is where an action is made often without foresight leading to an unfavourable consequence, and compulsivity is where there is a tendency to repeat an action leading to undesirable consequences. SUDs and other addictions are characterised by a shift from impulsive to compulsive behaviours [38] and, along with overlapping diagnostic criteria, lead to a hypothesis that the same might happen in PG [39].

Patients with PG show many similarities to SUDs in the domains of both impulsivity and compulsivity. Go/no-go and stop signal reaction time task studies have mostly found that response impulsivity is increased in both PG and SUDs relative to controls [40,41]. Choice impulsivity, more specifically delay discounting where more immediate rewards are chosen over those in the future, which is a hallmark sign of SUD and addiction, is also increased in patients with PG [40]. In contrast, attention and working memory deficits are more common in SUD than PG, which could be due to the neurotoxicity of each illicit substances [40,42,43].

Response perseveration, a measure of compulsivity where a person is likely to repeat an action despite a stimulus being stopped, has been demonstrated in PG but only some SUDs [40,41,44]. This suggests compulsivity may be more inherent in PG but again does not consider the various neurotoxic effects of illicit substances. Response perseveration and choice impulsivity lead to negative alterations in risk/reward decision making which has been shown in PG and most SUDs [40,44]. An underlying predisposition to impulsive behaviours is thought to be critical in development of the early stages of both PG and SUD [39] but in SUD there is also evidence that side effects of illicit substances cause an increase in impulsivity [43]. A review concluded that the shift from impulsivity to compulsivity was a trait shared by both PG and SUD [45]. The dopamine reward pathway has been associated with impulse

control, for example Parkinson's Disease patients treated with dopamine agonists have a higher incidence of PG [46]. However unlike in SUD, striatal D2/D3 levels and receptor availability does not differ between PG and healthy controls [47,48] representing a major difference between behavioural and substance addictions. Increased dopamine binding to D2/D3 was correlated with impulsiveness [48], and there may be an ectopic upregulation of D3 in the Dorsal Striatum that is implicated in impulsivity and risky decision making [47]. Compulsivity is often only expressed in the later stages of addition, when the action has become more of a habit, which presents a challenge for research into mechanisms [49]. PG differs from SUD with the lack of the illicit substances' individual neurotoxic effects on pathways involved in the shift from impulsive to compulsive behaviours, including the dopaminergic pathways in the straitum [50]. PG could represent a model of addiction without cofounding factors of acute or chronic SUD [40].

Neurotransmitter Systems Involved in SUD and PG

In the 1970s a potential role for dopamine (DA) was discovered, in an experiment whereby rats would willingly self-stimulate areas in their own brains [51]. These areas were found to be comprised, in part, by dopaminergic neurones. It was also shown that drugs that enhanced dopamine release encouraged further self-stimulation [52]. Since then, the role of dopamine – in particular its dysregulation - has been largely misrepresented as the sole causal factor in the neuropathogenesis of addiction. Substances of abuse's effects on various neurotransmitters and pathways have also been implicated in the development of addiction. Unlike findings in SUD patients, small sample size studies of PG did not display significant volumetric differences in white or gray matter from control [53]. Larger studies have shown smaller amygdala and hippocampal volumes similar to SUD [54] however the contradiction suggests potential differences in PG and SUD induced by the neurotoxic sequelae of chronic drug use.

Psychomotor stimulants

Addiction to cocaine induces specific intermediate and long-term effects. Chronic cocaine exposure as well as numerous other substance addictions including chronic opioid addiction causes accumulation of high levels of the transcription factor ΔFosB [55]. Mice with elevated ΔFosB exhibit behaviours corresponding to human addictive behaviours. Conversely, blocking ΔFosB in mice during a regimen of cocaine exposure reduces these behaviours [56]. Long term neurobiological cocaine addiction induces dendritic branching [57]. This theoretically gives other brain regions enhanced influence over the NAcc potentially driving the long-lived behavioural changes associated with addiction. Although not investigated it is proposed this is an effect of ΔFosB stimulation of CDK5 causing nerve cell growth. As of current literature there is no evidence of PG's effect on gene transcription factors although increased ΔFosB has been observed in mice models showing compulsive running behaviour [58].

Opioids

Opioids modulate mesolimbic DA pathways in the VTA by activating μ opioid receptors on secondary interneurons causing hyperpolarisation and inhibition of GABA release on primary neurons with consequent DA release [59]. Mice that lack the μ opioid receptor gene (OPRM1) show no morphine analgesia or place preference [60]. Opioid molecules link to μ receptors on cells in the Locus Coreleus (LC) suppressing the release of Noradrenaline, resulting in drowsiness, slowed respiration and low blood pressure. With repeated exposure LC neurons adjust leading to enhanced LC activation with excess NA causing symptoms of restlessness, anxiety, muscle cramps and diarrhoea [61]. Increased β-endorphins targeting the same μ opioid receptor have been measured during gambling [62]. Importantly, naltrexone, an opioid antagonist has been shown to be significantly efficacious in the treatment of PG when compared to placebo [63].

Alcohol

Alcohol withdrawal produces decreased DA function in dependent individuals contributing to withdrawal symptoms and relapse [64]. Complete inactivation of the μ-opioid receptor blocks alcohol consumption in mice [65] demonstrating its involvement. Chronic alcohol exposure leads to alterations in the GABA systems including the genes encoding components of the GABAa receptor. Change in subunit composition include decreases in α1 and increases in α4 subunits [65]. Although only reported in a small sample size study, PG patients were shown to have increased GABAa receptor availability in contradiction to lower GABAa receptor availability in an alcohol dependence group [66]. Chronic alcohol use increases NMDA receptors expression. Acamprosate (NMDA receptor antagonist), in combination with psychosocial therapy is clinically effective in maintaining abstinence in alcohol dependence [67]. A small sample size study showed increased NMDA agonists in the CSF of problem gamblers [68]. Research into the role of Glutamate in PG would reveal the extent of similarities. Depletion of serotonin (5-HT) in the basal forebrain has been implicated in mediation of the acute reinforcing actions of ethanol [69]. Rats manipulated to have decreased 5-HT lead to poor decision-making and gambling proneness [70]. Parallels to SUD and PG are limited by the validity of animal studies.

Nicotine

The α4β2 nicotinic acetylcholine receptor is the main receptor mediating nicotine dependence. Knocking out the β2 subunit gene eliminates the behavioural effects of nicotine, including self administration [71]. Repeated exposure to nicotine results in tolerance through receptor desensitisation. Withdrawal symptoms begin in chronic smokers when previously desensitised α4β2 nAChRs become unoccupied and recover to a responsive stage during periods of abstinence. Theα4β2 nicotinic acetylcholine receptor is known to be highly expressed in brain regions implicated in obsessive compulsive disorder (OCD) modifying normal and addictive behavior [72]. As of current literature there is no known effect of PG influence on these receptors.

Tetrahydrocannabinol (THC)

Cannabis Use disorders follow typical SUD patterns with the mechanism for addiction related initially from reward driven use (ventral striatum, medial PFC) to compulsive and habitual

use (dorsal striatum, lateral prefrontal cortex) [73]. Chronic cannabinoid exposure altered PFC structure and impaired cortical synaptic plasticity from reduced long-term potentiation in the hippocampus-PFC circuit [74]. Chronic exposure results in downregulation of CB1Rs with which withdrawal is associated [75]. Rat models have shown stimulation of CB1Rs to improve choice strategy and choice latency in a rat gambling task [76]. The limitations of animal models being misrepresentative of human behaviour is apparent here.

Dopamine Transmission and Function in PG and SUD

Dopaminergic circuits operate at multiple cognitive domains during complex decision making e.g. mesolimbic level and striato-thalamo-cortical circuitry [77]. In PG, mesolimbic DA release has shown positive correlation with symptom severity [78]. Conversely regarding SUD subjects with decreased striatal D2/3 receptor levels experience more pleasurable effects from stimulants [79]. It is hypothesised this difference is due to the over-stimulatory effects of higher receptor levels being unpleasant. Different measures of "pleasure" were used in quantifying pleasant qualia, whereby the quantification of qualitative experience remains difficult for researchers. Furthermore, striatal dopamine release only forms pleasurable effects with regards to certain dopaminergic substances [80] (e.g. stimulants). Opioids and cannabis, show weak associations of striatal dopamine release [81-86], suggesting that striatal dopaminergic activity is not the sole contributor to hedonic experience and further investigations into other biomarkers are indicated.

Another similarity between PGs and SUDs are the dysfunctional dopaminergic responses to respective cues. In PG, we see significantly higher dopamine release in the ventral striatum compared to healthy controls during the Iowa Gambling Task [86]. In another study, intentions to gamble on a football outcome showed greater activations of the higher prefrontal and insular cortex, as well as the striatum, when compared to watching games without the ability to place a bet [87]. In cocaine addicts, 11C-raclopride binding was significantly reduced in the dorsal striatum following cocaine-related cues [88,89], indicating increased DA release at this point. The effect is such that responses to other conditioned stimuli become significantly blunted in those with SUD [90]. This suggests that dopaminergic action in the dorsal striatum is highly implicated in craving experiences.

Dopaminergic circuitry affects psychological performance, thus behaviour in both PG and SUD. In PG, anticipation of monetary gain proportionally correlates with activation in the ventral striatum, potentially promoting irrational decision-making [91]. Risk-aversion was associated with activation of the anterior insula, and a balance between these two circuits may be required for optimal decision making. Studies have shown a link between low DA D2+3 receptor availability and low dopamine release with increases in impulsivity [91]. Addiction, as described by Everitt et al. [38], assumes a dysfunctional transition in the control over drug-seeking and drug-taking, from the PFC towards the striatum. There is also a transition in DA innervation from ventral towards more dorsal areas of the striatum. This behaviour, disregarding long-term consequences of actions has been termed a "myopia for the future" [92], to which dopaminergic circuitry dysfunction assumes a central role amongst both behavioural disorders.

Blunted Responses

fMRI studies have been used in PG and SUD to measure brain activity whilst patients are performing specific tasks. Both conditions are characterised by salience to the conditioned reward and blunting of responses to other rewards [93,94]. There is conflicting evidence as to whether PG show an increased or decreased [93,95] response to monetary rewards whereas cocaine abusers show a decreased response. The striatum is involved in reward and motivation processing [96], and most fMRI studies investigating responsiveness to rewards focus on the ventral striatum's activity and connections. Studies have shown that during anticipation on monetary rewards in PG, the ventral striatum has increased activity when compared to healthy controls [93] and erotic cues [97]. PG also tend to show a higher responsiveness to greater wins through dopaminergic connections to the vmPFC, further implicating dopamine dysfunctions in PG [93]. Cocaine addicts have been shown to lack the complex neuronal response to various increased monetary rewards that healthy controls and PG do [93,94]. Pet scans using D2 receptor radio ligands found that when shown cocaine-cues, cocaine addicts significantly increase dopamine in their striatum [88], suggesting they also have sensitivity to the stimulus of their addiction. The hyposensitivity to rewards is thought to reduce self-control through decreased activity in the prefrontal cortex in cocaine addicts and similar has been found in PG [94,98]. This conditioned sensitivity to relevant rewards could be fundamental in the promotion of addictive behaviours in both PG and SUD. It is important to note that many of these studies have used 11C-Raclopride radioisotope PET tracing to assess for DA release and receptor levels following various forms of stimulation [99]. DA receptors are found in lower densities in the cortex than the striatum [100], and PET tracers often have low levels of background activity, which poses serious challenges in ascertaining meaningful results from studies quantifying DA release/receptor levels in more cortical areas and must be more vigorously scrutinised when looking at data concerning mesocortical DA associations.

Psychological Aspects of Addiction and their Neural Correlates

In the proposed model of addiction, lasting neuroplastic changes closely follow a shift from impulsivity towards compulsivity [101] primarily revolving around the avoidance of negative consequences [102]. This switch from positive reinforcement to negative reinforcement underpins our current understanding of the addiction cycle. In drug addiction (particularly stimulants), impulsivity is characterised by decreases in striatal DA D2/3 receptor availability [103]. Lower 5-HT (serotonin) neurotransmission has also been demonstrated to show increased impulsivity in both human and rat models [104,105], suggesting a more complex involvement of

multiple neurotransmitters. Ventral and dorsal regions of the PFC are also involved in impulsivity [105], with the PFC potentially modulating striatal circuitry involved in impulsive decision making. In PG, the pattern of corticolimbic activation appears to be slightly different, with changes in frontal, paralimbic and limbic neural structures [106].

The withdrawal/negative affect stage involves changes such as, emotional dysregulation, whereby chronic activation of the reward system recruits dysregulated neurotransmitters and hormones that are not found in the fronto-striatal reward pathway [107]. For example, in chronic drug abuse, the hypothalamic-pituitary-adrenal axis becomes dysregulated though chronically-raised CRF, resulting in elevated adrenaline and dynorphin levels and contributing towards the development of negative emotional states and "blunting" of the reward circuitry during protracted abstinence [108,109]. Due to multiple neural systems dynamic involvement, it is difficult to localise and quantify the effect of any one biomarker. This mechanism is a proposed response to limit positive-reinforcing stimuli but may encourage compulsive behaviour by attempting to mitigate these negative emotional and physiological states [110].

Craving is a key factor in promoting relapse. Despite difficulty quantifying craving, and lack of correlative studies with relapse [111], it is considered a key area of focus in the development of novel therapies. Executive cortical areas of the PFC project glutamatergic neurones directly to dopaminergic neurones in the VTA in rat models, modulating firing rate and dopamine release at this loci [112]. The PFC is a key regulator of incentive salience and conditioned behaviour in the presence of salient cues [107]. Common in both drug and non-drug addictions, similar activatory pathways have been noted, including the PFC, Anterior Cingulate Gyrus, dorsolateral PFC, and medial OFC [113-117]. Disruptions in frontal cortical activity have shown disruptions in GABAergic activity [118], which affects decision making, self-regulation, inhibitory control and working memory [119]. The insula is also thought to have an interoceptive function, allowing subjects to integrate autonomic and visceral information with emotion and awareness, allowing for conscious recognition of the urges [120].

Conclusion

Using the well-supported 3-stage addiction model, PG and SUD share aberrant responses to conditioned stimuli and an impulsive nature but differ in neurotoxic effects and the recruitment of neurotransmitter systems. Several studies highlighting similarities in mesolimbic DA transmission in both disorders provide a convincing argument for a similar underlying pathophysiology. However, other presumptive addiction models - such as the DA theory of reward and addiction - appear incomplete. This is accentuated by the discovery of naltrexone as a moderately-effective treatment for both alcoholism and PG, despite its mechanism of action as an opiate antagonist. Currently, no DA-related treatments have shown efficacy in relation to addictive disorders (not including Parkinsonian-related impulsivity), further compounding our lack of understanding into precise neural mechanisms. This critical summary highlights the need for more comprehensive research into the neurotransmitter pathways involved in addiction and impulse control. As our understanding of addiction evolves, it will also be crucially important to investigate the reversibility of neuroplastic changes that are found across addictive disorders. We suggest that further investigations into the highlighted areas will enable more robust models of addictive pathways, and consequently, the development of novel, evidence-based therapies.

Acknowledgement

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Conflict of Interest

No Conflict of interest.

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