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EXPERT REVIEW

Neuroimaging of reward mechanisms in Gambling disorder: an integrative review

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Abstract

Gambling disorder (GD) was reclassified as a behavioral addiction in the DSM-5 and shares clinical and behavioral features with substance use disorders (SUDs). Neuroimaging studies of GD hold promise in isolating core features of the addiction syndrome, avoiding confounding effects of drug neurotoxicity. At the same time, a neurobiologically-grounded theory of how behaviors like gambling can become addictive remains lacking, posing a significant hurdle for ongoing decisions in addiction nosology. This article integrates research on reward-related brain activity (functional MRI) and neurotransmitter function (PET) in GD, alongside the consideration of structural MRI data as to whether these signals more likely reflect pre-existing vulnerability or neuroadaptive change. Where possible, we point to qualitative similarities and differences with established markers for SUDs. Structural MRI studies indicate modest changes in regional gray matter volume and diffuse reductions in white matter integrity in GD, contrasting with clear structural deterioration in SUDs. Functional MRI studies consistently identify dysregulation in reward-related circuitry (primarily ventral striatum and medial prefrontal cortex), but evidence is mixed as to the direction of these effects. The need for further parsing of reward sub-processes is emphasized, including anticipation vs outcome, gains vs. losses, and disorder-relevant cues vs natural rewards. Neurotransmitter PET studies indicate amplified dopamine (DA) release in GD, in the context of minimal differences in baseline DA D2 receptor binding, highlighting a distinct profile from SUDs. Preliminary work has investigated further contributions of opioids, GABA and serotonin. Neuroimaging data increasingly highlight divergent profiles in GD vs. SUDs. The ability of gambling to perpetually activate DA (via maximal uncertainty) may contribute to neuroimaging similarities between GD and SUDs, whereas the supra-physiological DA effects of drugs may partly explain differences in the neuroimaging profile of the two syndromes. Coupled with consistent observations of correlations with gambling severity and related clinical variables *within* GD samples, the overall pattern of effects is interpreted as a likely combination of shared vulnerability markers across GD and SUDs, but with further experience-dependent neuroadaptive processes in GD.

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Background

The DSM-5 reclassification: a landmark decision based on provisional evidence

The fifth edition of the Diagnostic and Statistical Manual (DSM-5) [1] reclassified Gambling Disorder (GD) alongside the substance use disorders (SUDs), from its original classification (as 'pathological gambling') in the Impulse Control Disorders. This decision rested on provisional evidence from the preceding decade showing similarities in the clinical, epidemiological and neurobiological profile of GD and SUDs [2–4]. However, no clear theoretical account was advanced for how behaviors such as gambling can become addictive. This conceptual gap has led to a 'slippery slope' of putative behavioral addictions including Internet Gaming disorder [1], compulsive sexual behavior [5], and binge eating or obesity [6]. As a result, the forthcoming ICD-11 continues to weigh its options regarding classification of non-substance-related impulsive/compulsive behaviors [7, 8].

In response to concerns over the validity of DSM-5, the Research Domain Criteria (RDoC) approach was initiated by the National Institute of Mental Health as a framework to organize mental illnesses based on fundamental neurobehavioral systems instead of symptom-based taxonomies [9]. RDoC proposes that research be centered on key behavioral domains such as the *Positive Valence System*, which includes reward-seeking, consummatory behavior, and reward/habit learning. Reward processing disturbances (either hypo- or hyper-sensitivity) transect psychiatric categories, including addictive disorders, mood disorders [10] and psychosis [11], and may shed light on the functional basis of pervasive comorbidity among these disorders. The present review adopts the RDoC framework to consider structural and functional dysregulation in the Positive Valence System in GD. Application of this framework may inform novel treatment approaches in GD, comorbid GD syndromes, and personalized approaches to treatment.

SUD provides the logical reference point for examining GD [3, 4]. Clinically and phenomenologically, SUD and GD share many features: escalation in use, persistence despite adverse consequences, cravings or urges to use, repeated failures to reduce use, and frequent relapse following a period of abstinence [12]. GD also includes the distinctive symptom of 'loss chasing', persistent gambling despite mounting losses, which may constitute a form of compulsivity as an expression of negative reinforcement [12]. This loss of control over reward-seeking mirrors SUD, in which initially impulsive drug use gradually shifts towards compulsive (relief-oriented) drug-seeking [13]. Because GD lacks exposure to a foreign (potentially neurotoxic) substance in the brain, addiction scientists have become increasingly interested in GD as a means of separating pre-existing vulnerability to addictions from the physiological consequences of drug use [14]. However, this approach assumes not only shared vulnerability but also the absence of any neuroadaptive changes with prolonged gambling, and such plasticity has been demonstrated for other behaviors such as motor skill acquisition [15].

The current review aims to consolidate a surge of research on GD that coincided with the DSM- 5 reclassification, using a systems neuroscience framework to examine the mechanisms underlying gambling as an addictive reinforcer. We synthesize human neuroimaging research in groups with GD (sometimes including subclinical levels of 'problem gambling' or 'disordered gambling') focussing on the Positive Valence System because of its centrality to addictive disorders. The RDoC framework recognizes that the processing of positive valence comprises separable subprocesses, including reward valuation, anticipatory processing vs. responsiveness to outcome delivery, and reward-based choice that further involves delay, probability, and effort representations. We focus on task-related functional magnetic imaging (fMRI) experiments that aim to parse these processes, and the complementary insights that are afforded from positron emission tomography (PET) imaging using radioligands for neurotransmitters that are implicated in reward signalling. We further consider structural MRI, including diffusion tensor imaging (DTI) of white matter integrity, which provides important context for the interpretation of functional disturbances and more directly helps to separate vulnerability mechanisms from neuroadaptive changes. Where possible, we highlight commonalities and differences with SUDs where such markers are established. Neurobiologically, we focus on the striatum and its key modulatory influences: ventral tegmental area/substantia nigra (VTA/SN), anterior cingulate cortex (ACC), ventromedial prefrontal and orbitofrontal cortices (vmPFC; OFC), insula, ventral pallidum, basolateral amygdala and hypothalamus. We acknowledge that functionally dissociable regions exist within these regions, including ventral vs dorsal striatum [16].

How do behaviors become addictive? Reward uncertainty and dopamine sensitization

Public commentary around addiction still widely holds that because drugs of abuse exert a common action on dopamine (DA) transmission, any behavior that drives DA release has the potential to become 'addictive' [17]. However, a key tenet of the original idea that drugs 'hijack' the brain reward system is that drugs perturb this system much more powerfully and persistently than primary rewards [18]. From this perspective, we assert that it is in fact fundamentally

unclear how *any* non-drug-related behavior becomes addictive.

Redish [19] proposed that the ability of drugs like cocaine to activate DA unconditionally distinguishes them from standard non-drug reinforcers, for which the timing of DA release shifts with learning from reward delivery to predictive cues [20]. For non-drug reinforcers, the DA response to the reward (the unconditioned stimulus; US) dissipates with repeated exposure, as the reward becomes fully predicted by its cue (the conditioned stimulus; CS) or the physical reinforcing stimulus itself [21]. In contrast, by pharmacologically activating DA, Redish argued that the DA response to drug delivery persists despite learning, so that the 'new information' imparted by a prediction error signal continues to escalate indefinitely with each dose. Through this 'hyper-learning', drug cues come to dominate motivational approach ('wanting') relative to cues for non-drug reinforcers.

How might this principle apply to gambling? As games of chance, one important feature is that the reinforcement (the monetary wins) is uncertain and never fully predicted. Reward delivery is always a surprise, hypothetically capable of evoking reward prediction errors and concomitant DA release. In primate electrophysiology experiments, uncertainty of reward delivery has a marked effect on DA activation: CSs that predict reward with maximal uncertainty ($p = 0.5$) evoke sustained DA firing during the anticipatory interval [22]. This reward schedule closely matches the pattern found on commercial slot machines [23]. In this way, cues associated with uncertain reward coupled with unpredictable reward delivery may induce in GD the continued escalation in reinforcement learning and DA signalling that drug cues achieve in people with SUDs.

Prominent theoretical accounts of SUD also invoke the concept of DA sensitization in the development of addiction: repeated exposure to drugs drives a hyper-reactivity of the DA system to cues for drug reward and direct pharmacological stimulation [24]. The reward uncertainty model outlined above suggests that sensitization, arising from chronic, unpredictable reinforcement learning could also occur in GD.

Techniques examined

Structural MRI offers a number of distinct protocols for characterizing brain anatomy. Voxel- based morphometry is a widely-used procedure for measuring regional differences in gray matter and white matter volumes, by parcellating the brain into voxels. DTI is a structural MRI protocol that characterizes white matter integrity, based upon the movement of water molecules in myelinated fiber tracts. Fractional anisotropy, the key measure from DTI, quantifies the directionality of the diffusion of water molecules (i.e., within vs. across tracts). fMRI assesses brain activity in terms of the blood-oxygen-level-dependent (BOLD) signal; activity can be measured at rest or in response to psychological tasks tapping specific stimuli (e.g., cues for reward) or processes (e.g., decision-making). We focus on task-related fMRI with reward paradigms, including the Monetary Incentive Delay Task (MIDT) [25], cue reactivity with gambling stimuli (e.g., casino photos), and reward-based decision-making, including the Iowa Gambling Task (IGT) [26] and delay discounting [27]. We do not consider task-related fMRI experiments on non-rewarded tasks, including research on executive functions and other RDoC categories that has been reviewed elsewhere [12, 28, 29].

In contrast to the non-invasive nature of MRI, PET imaging relies on radioactive tracers. This review focusses on PET studies in which specific aspects of neurotransmitter function are measured via selective tracers, such as [11C]-raclopride as a radioligand for the DA $D_{2/3}$ receptor. By further combining PET imaging with a pharmacological or behavioral challenge protocol, it is possible to measure neurotransmitter release based on displacement of the radioligand. Collectively, these techniques provide a diverse set of tools to probe brain morphology and function in the living human brain.

Systematic review methods

Studies were identified in line with PRISMA guidelines [30], applied to the PubMed database on 03/31/2018. To be eligible, a study had to include neuroimaging data from unmedicated participants with GD, pathological or problem gambling, as well as an appropriately-characterized control group. There were no restrictions on date of publication. Search terms were: *gambler, pathological, problem, disorder* and their permutations, cross-referenced with the terms, *imaging, neuroimaging, functional, magnetic, MRI, fMRI, DTI, positron*, and *PET*. For the relatively circumscribed comparison of PET studies in GD vs. SUD (Table 4), we cross-referenced *PET, positron* with (*alcohol / cocaine / methamphetamine / opiate / heroin / nicotine / cannabis) use disorder* or *dependence*. We excluded studies in Parkinson's Disease, where GD-like symptoms can be induced by DA-agonist medications [31], as it remains unclear how this syndrome relates to the primary neuropathology in Parkinson's Disease. For PET studies, we selected those using neurotransmitter tracers in idiopathic GD. Of the fMRI studies, we selected only task-related fMRI delivering monetary rewards or assessing cue reactivity. A total of 2,272 unique studies were found that included at least one search term cross-referenced with gambling or gambler(s). Of these, 179 met inclusion criteria and were incorporated in the review.

We paid particular attention to heterogeneity: *individual differences* within groups of GDs, which may explain inconsistencies between ostensibly similar experiments. We note that neuroimaging studies of GD often vary on a number of sample-related factors, including the following: (i) use of clinically recruited vs. community-recruited samples [32], (ii) variation in gender ratios, with many studies restricted to males with GD (Table 2; c.f. [33]), (iii) differences in preferred forms of gambling [34], and (iv) current gambling involvement versus different lengths of abstinence from gambling [35]. At the same time, disease heterogeneity is important in theories of GD etiology, for example, in the influential Pathways Model [36]. In the neuroimaging literature on GD, systematic variation related to gambling severity, as well as dispositional variables including impulsivity and subclinical mood disturbance, has been observed with a regularity that may exceed the case-control differences that are typically the a priori focus of the experiment [37–40]. Careful consideration of heterogeneity aligns with the idea that (individual differences in) chronic exposure to schedules of unpredictable reward may partly mediate the functional and structural anomalies in GDs.

Structural MRI

Using voxel-based morphometry to assess gray matter and white matter differences, a number of studies have failed to identify any significant group differences between GDs and healthy controls after correcting for multiple comparisons at a whole-brain threshold (see Table 1) [41–44]. In the study by van Holst et al. [41], the lack of structural differences in the GD group ($n = 40$) contrasted with widespread gray matter reductions in an SUD comparison group with alcohol use disorders, thus showing the counterpoint of structural deterioration associated with chronic alcohol consumption [45]. In a similar 3-group design, Yip et al. [44] observed significant gray matter reductions (in vmPFC and ACC) in a group with cocaine use disorder relative to both the GD ($n = 35$) and healthy control groups. The GD and control groups did not differ significantly in whole-brain corrected analysis, but in regression analysis collapsing across all 3 groups, negative relationships were observed between trait impulsivity and gray matter in insula, amygdala and hippocampus. In the largest structural MRI study to date ($N = 107$), Zois and colleagues [46] showed significantly reduced frontal gray matter in a GD group with no SUD comorbidities. Additional reductions were seen in ACC and amygdala gray matter in the GD cases with comorbid alcohol or poly- drug use. Reductions in frontal cortical thickness have been described [47]. Similarly, studies that have applied more focused regions of interest have also indicated gray matter reductions in GD in hippocampus and amygdala [48], putamen and thalamus [43], although increases in frontal and striatal gray matter have also been reported [49]. In SUDs, gray matter reductions in frontal cortex have been related to risky decision making and delay discounting [50, 51]. In GD, gray matter reductions in cerebellum and OFC correlated with risk attitudes (increased loss aversion) [52], but experiments in GD have not directly assessed how structural differences relate to reward processing *per se*.

Studies using DTI in groups with GD have been more consistent in indicating disrupted white matter integrity, although the findings are diffuse [42, 53–55]. In two studies, DTI abnormalities were observed in GD groups that did not show differences with voxel-based morphometry [42, 56]. In Joutsa et al. [42], lower fractional anisotropy was seen in multiple tracts including corpus callosum. Yip and colleagues [56] observed reduced anisotropy in corticolimbic secondary tracts in GD, with similar reductions observed in a third group with cocaine use disorder; the effects in GD were also not explained by comorbid alcohol use. Mohammadi et al. [55] also reported reduced anisotropy in multiple tracts, which were related to a behavioral measure of delay discounting. In people with treatment-resistant GD (lack of response to both cognitive- behavioral therapy and a 12-week naltrexone trial), significant reductions in anisotropy were observed in corpus callosum and superior longitudinal fasciculus [53]. Outside of these tracts, white matter anisotropy was *positively* correlated (indicating more myelinated fibers) with gambling severity. It is unclear at present to what extent these white matter abnormalities pre-date onset of GD and/or arise from neuroplasticity driven by sustained gambling, but Chamberlain et al. [53] interpreted their pattern—an overall *reduction* in GD, combined with a *positive* correlation with GD severity—as reflecting the combination of pre-existing vulnerability and progressive neuroadaptation induced by gambling.

Summary

The structural MRI evidence for gray matter deficits in GD is currently inconclusive, although a conservative statement would be that any reductions are modest in comparison to the reliable deterioration seen in SUDs [57–59]. This conclusion is supported by GD studies employing direct 3-group designs with an SUD comparison group [28, 44]. Nevertheless, individual differences in brain anatomy correlate with vulnerability factors, including impulsivity, which may be transdiagnostic across addictive disorders [44, 46]. DTI studies indicate more consistent reductions in white matter integrity that are of a distributed nature and similar to changes described in SUDs. It is currently unclear whether gray matter or white matter alterations in GD relate directly to reward-based symptom clusters.

Table 1 Summary of structural MRI experiments, including voxel-based morphometry (VBM) of gray matter density, and Diffusion Tensor Imaging (DTI) of white matter integrity in Gambling Disorder (GD)

Reference	Modality	Subjects	Subject matching	Brain region	Finding
Joutsa et al. [42]	Gray matter – VBM[a]	GD 12 / HC 12	Age, education, BMI, monthly income, nicotine use. All male.	—	GD↔HC
van Holst et al. [41]	Gray matter - VBM	GD 40 / HC 54 / SUD 36	Age, IQ, nicotine use, intracranial volume	—	GD↔HC SUD ↓
Rahman et al. [48]	Amygdala and hippocampus volume (ROI)	GD 32 / HC 47	Gender	Amygdala (R), Hippocampus (L)	GD ↓
Fuentes et al. [43]	Gray matter – VBM[a]	GD 30 / HC 30	Age, education	Whole-brain VBM	GD↔HC
				ROIs: Putamen (L), thalamus (R), hippocampus (R)	GD ↓
Koehler et al. [49]	Gray matter - VBM	GD 20 / HC 21	Age, nicotine and alcohol use, education, IQ. All male	ROIs: Ventral striatum (R), anterior PFC	GD ↑
Grant et al. [47]	Cortical thickness	GD 16 / HC 17	Age, gender, education	Frontal cortex (R), supramarginal and post-central gyri (R), IPC (L)	GD ↓
Zois et al. [46]	Gray matter - VBM	GD 107 (47 comorbid SUD) / HC 98	Age. All male.	Medial frontal gyrus, orbital frontal cortex	GD ↓
Mohammadi et al. [55]	Gray matter - VBM	GD 15 / HC 15	Age, nicotine and alcohol use, education, income. All male.	cingulate gyrus, insula (R), putamen, orbitofrontal cortex (R), amygdala (R), hippocampus (R)	GD ↓
Yip et al. [44]	Gray matter - VBM	GD 35 / HC 37 / SUD 37	Age, gender	-	GD↔HC SUD ↓
Takeuchi et al. [52]	Gray matter - VBM	GD 36 / HC 36	Age. All male.	Supramarginal gyrus, cerebellum	GD ↓
Joutsa et al. [42]	White matter - DTI[a]	GD 12 / HC 12	Age, education, BMI, income, nicotine use. All male.	CC, SLF, ILF, IFOF, anterior limb IC, anterior TR	GD ↓
Yip et al. [177]	White matter - DTI	GD 19 / HC 19	Age, gender, ethnicity, education	CC (Genu)	GD ↓
Mohammadi et al. [55]	White matter - DTI	GD 15 / HC 15	Age, nicotine and alcohol use, education, income. All male.	SLF, ILF (L), IFOF (R), Anterior TR	GD ↓
van Timmeren et al. [54]	White matter - DTI	GD 21 / HC 21	Age. All male.	Basal ganglia to prefrontal cortex tracts (L)	GD ↓
Chamberlain et al. [53]	White matter - DTI	GD 16 / HC 15	Gender, education, ethnicity	CC	GD ↓
Yip et al. [56]	White matter - DTI	GD 38 / HC 38 / SUD 38	Age, gender	IC (L), corona radiata, forceps major, posterior TR	GD & SUD ↓

ROI region of interest, *SUD* substance use disorder, *CC* corpus Callosum, *SLF* superior longitudinal fascicle, *ILF* inferior longitudinal fascicle, *IFOF* inferior fronto-occipital fascicle, *IC* internal capsule, *TR* thalamic radiation

↓ Indicates reductions in GD relative to controls; ↑ indicates increases in GD relative to controls; ↔ indicates no significant difference between groups

[a]Studies were run on 1.5T fMRI (all other studies were run at 3T)

Table 2 Summary of task-related fMRI experiments in Gambling Disorder (GD)

Reference	fMRI task	Subjects	Subject matching	Brain region	Finding
Potenza et al. [178]	[a]Gambling videos	GD 10 / HC 11 All male	Age, nicotine use	Cingulate gyrus (B), precuneus, inf parietal (R), sup frontal gyrus (B), OFC, caudate, thalamus	GD ↓
Crockford et al. [179]	Gambling videos	GD 10 / HC 10 All male	Age, ethnicity, nicotine use	Dorsolateral PFC (R), parahippocampal gyrus (R), occipital (L)	GD ↑
Reuter et al. [60]	Card guessing task	GD 12 / HC 12 All male	Age, nicotine use	ventral striatum, mPFC	GD ↓
Tanabe et al. [95]	IGT	GD + SUD 16 / HC 18 / SD 14	Age, gender, ethnicity	vmPFC, superior frontal, frontal pole	GD ↓
de Ruiter et al. [62]	Reversal learning with monetary outcomes	GD 19 / HC 19 / Nic 19 All males	Age, education	Gains: ventrolateral PFC (R)	GD ↓
				Losses: ventrolateral PFC (R)	GD ↓
Goudriaan et al. [83]	Gambling images	GD 17 / HC 17 All male	Age, nicotine use, education	OT cortex, PCC, parahippocampal gyrus, amygdala	GD ↑
de Greck et al. [180]	Gambling, alcohol, food images assessed for personal relevance; reward localizer task	GD 12 / HC 12 All male	Age, intelligence	Ventral striatum (B), putamen (L)	GD ↓
Miedl et al. [181]	Blackjack task	GD 12 / Occasional gamblers 12 All male	Age, nicotine use	Risky choice: Inferior frontal (R), superior temporal (R), thalamus (R)	GD ↑
				Win outcomes: superior frontal (R), parietal (L)	GD ↑
Balodis et al. [61]	MIDT	GD 14 / HC 14	Age, gender, IQ	ventral striatum, mPFC insula	GD ↓
Choi et al. [63]	[a]MIDT	GD 15 / HC 15 / OCD 13 All male	Age, education, IQ	Gain anticipation: Thalamus, caudate	GD ↓
				Loss anticipation: Caudate	GD ↓
Miedl et al. [65]	DDT	GD 15 / HC 15 All male	Age, nicotine use, income, education	OFC (R), ventral striatum, ACC (R), para hippocampal gyrus (L)	GD ↑
Power et al. [94]	IGT	GD 13 / HC 13 All male	Age, ethnicity, nicotine use	Risky vs safe selections: OFC (R), caudate (R)	GD ↑
van Holst et al. [64]	Card guessing task	GD 15 / HC 16 All male	Age, smokers, family history addictions	Dorsal striatum, OFC	GD ↑
Sescousse et al. [72]	[a]MIDT	GD 18 / HC 20 All male	Age, education, income	Ventral striatum, posterior OFC	GD ↔ HC
Fauth-Buhler et al. [40]	Instrumental-motivation task	GD 80 / HC 89 All male	Age, gender, nicotine use	-	GD ↔ HC
Tsurumi et al. [71]	MIDT	GD 23 / HC 27	Age, education	Insula (bilat)	GD ↓
Worhunsky et al. [69]	Slot-machine task	GD 24 / HC 24	Age, gender, IQ	Ventral striatum (reward-anticipation)	GD ↑
				-(reward-receipt)	GD ↔ HC
				Ventral striatum (sequential, near-miss loss)	GD ↓
				Ventral mPFC (non-sequential near-miss loss)	GD ↑
Romanczuk- Seiferth et al. [73]	MIDT	GD 18 / HC 17 All male	Age, gender, nicotine use, handedness, education, IQ	mPFC (R) ventral striatum (R) (loss avoidance)	GD ↓
				ventral striatum (R) (loss anticipation)	GD ↑
Brevers et al. [182]	Risky vs ambiguous gambles	GD 10 / HC 10	Age, gender, education, smoking, depression, alcohol use	Globus pallidus (risky > ambiguous)	GD ↓
				Putamen (risky > safe choices)	GD ↑

Table 2 (continued)

Reference	fMRI task	Subjects	Subject matching	Brain region	Finding
Gelskov et al. [67]	Gain-loss gambling task	GD 14 / HC 15 All male	Age, gender, handedness, general anxiety, alcohol.	Caudate nucleus, DLPFC	GD ↑
Kober et al. [33]	Gambling video	GD 28 / HC 45	Age	mPFC, ACC	GD ↔ HC
Sescousse et al. [66]	Slot-machine task	GD 22 / HC 22 All male	Age, income, BMI, IQ	Ventral striatum	GD ↑
Limbrick-Oldfield et al. [84]	Gambling images	GD 19 / HC 19 All male	Age, IQ	Insula (L), ACC (L), inferior frontal gyrus (R), Cerebellum (L)	GD ↑
Fujimoto et al. [97]	Gambling Quota task	21 GD / 29 HC All male	Age, IQ	dlPFC (L)	GD ↓
Wiehler et al. [92]	DDT with episodic tags	GD 23 / HC 23 All male	Age, education, income, nicotine use	-	GD ↔ HC

MIDT Monetary Incentive Delay Task, *DDT* delay discounting task, *IGT* Iowa Gambling task, *SUD* substance use disorder, *OCD* obsessive compulsive disorder
↓ indicates under-activity in GD relative to controls; ↑ indicates hyper-activity in GD relative to controls. ↔ indicates no significant difference in GD vs. controls
[a]Studies were run on 1.5T fMRI (all other studies were run at 3T)

Functional MRI

Neuroscience theories of addiction describe *blunted* reward processing as a vulnerability marker for addictions ('reward deficiency') [6], but also *enhanced* processing of cues that predict drug rewards (sensitization, also termed 'incentive salience') [24]. These accounts are not mutually exclusive, as the former is an account of vulnerability and the latter is an account of the illness progression, but they are hard to disambiguate using case-control designs. Perhaps as a consequence, fMRI studies of reward processing in GD currently indicate a complex and inconsistent pattern (see Tables 2 and 3).

Early studies found a seemingly clear-cut profile of reduced striatal and medial PFC responsivity to monetary reward processing in GD [60–63]. However, subsequent work using ostensibly similar procedures found increased responsivity within the same regions [64–67]. These inconsistencies may be at least partly due to features of the GD samples (see above). In addition, Table 1 reveals that more than half of the fMRI experiments to date have used GD groups smaller than 20, and we also recognize ongoing controversy regarding appropriate correction thresholds in fMRI [68]. Of relevance to our focus on reward mechanisms, conflicting fMRI findings may also arise from the fMRI task design. One key distinction is between neural activity to the *anticipation* of reward and the *delivery* of reward. Using a Wheel of Fortune game with a relatively long (4 s) anticipatory interval, neural activity in dorsal striatum was *increased* in GDs during expectation of large (vs. small) gains [64]. Similar anticipatory hyper-activity in striatum and medial/inferior PFC was observed by Worhunsky et al. [69] using a simulated slot machine task. Group increases during the reel spin emerged in both GD and a cocaine-dependent group, although only the GD group resembled the pattern shown by van Holst [64]. A recent meta-analysis in SUD and GD [35] separated fMRI studies modelling anticipatory and outcome-related activity. Anticipatory hyper-activity was not substantiated in the GD meta-analysis; rather, across both SUD and GD, anticipatory activity in the striatum was reduced. The SUD and GD groups diverged at outcome processing: dorsal striatal underactivity was observed in GD, and VS hyperactivity was observed in SUD.

Manipulating the nature of reward

Most experiments in the Luijten et al. meta-analysis [35] used variants of the seminal MIDT. In this procedure, visual cues signal availability of monetary rewards of varying sizes (e.g., $0, $2, $5), conditional upon the participant responding rapidly to a target. Intuitively, monetary gains are a relevant cue for GDs. That said, the MIDT bears little

Table 3 Individual Differences in fMRI studies in Gambling Disorder (GD)

Reference	Individual differences tested	Task / contrast	Brain regions	Case-Control Effect	Correlational Effect
Reuter et al. [60]	Severity	Win–loss	ventral striatum, vmPFC	GD ↓	Negative
Goudriaan et al. [83]	Cravings, depression, ADHD	Gambling – neutral cues	Craving: Ventrolateral PFC, ant insula (L), caudate (L)	GD ↑	Positive
de Greck et al. [180]	Severity, controlling for depression	Personally-relevant cues (high – low)	Left ventral striatum	GD ↓	Negative
Balodis et al. [61]	Impulsivity	MIDT reward anticipation	Ventral striatum	GD ↓	Negative
Choi et al. [63]	Severity	MIDT loss anticipation	Ant Insula	GD ↓	Positive[a]
Miedl et al. [65]	Severity	Delayed value parameter	Ventral striatum, vmPFC, midbrain	GD ↑	Negative[a]
van Holst et al. [64]	Severity	Gain Expected Value	Amygdala (R)	GD ↑	Negative[a]
Fauth-Buhler et al. [40]	Depression	Win – loss feedback	Insula (L), dorsal striatum	GD ↔ HC	Positive
Tsurumi et al. [71]	Illness duration	MIDT reward anticipation	Insula (L)	GD ↓	Negative
Romanczuk- Seiferth et al. [73]	Severity	MIDT loss avoidance	mPFC, striatum	GD ↓	Negative
Gelskov et al. [67]	Severity	Extreme ratio gambles	Precuneus	GD ↑	Positive
Kober et al. [33]	Gender	Gambling – neutral videos	Dorsal mPFC, post Insula/caudate	GD ↑	Enhanced in females
Limbrick-Oldfield et al. [84]	Cravings, depression, alcohol use, severity	Gambling – neutral cues	Craving: Insula (L/R), cerebellum	GD ↑	Positive
			Depression: Frontal pole (L), postcentral gyrus (L), cerebellum	GD ↑	Positive
Fujimoto et al. [97]	Time abstinent	Quota sensitivity	Ant Insula	GD ↓	Negative

ADHD attention deficit hyperactivity disorder, *MIDT* Monetary Incentive Delay Task

↓ Indicates under-activity in GD relative to controls; ↑ indicates hyper- activity in GD relative to controls. ↔ indicates no significant difference in GD vs. controls

[a]In these studies, the correlational findings run contra to the case-control difference; for example, increased brain activity in the GD group relative to controls might be offset by a negative correlation between brain signal and gambling severity

resemblance to real-world gambling and typically lacks overt gambling cues; e.g., outcomes are revealed using text "Win $5" rather than an image of a $5 bill. Leyton and Vezina [70] argued that the discrepancies among fMRI experiments on GD may be explained by variability in these ecological cues. Of the five studies in Table 1 using MIDT-style tasks, 3 found evidence for hypo-reactivity to reward in the GD group [61, 63, 71], and 2 found no group differences in the monetary reward condition [72, 73]. Meanwhile, studies using more realistic gambling games have indicated hyper-reactivity of striatal, dopaminergic midbrain, and medial/orbital PFC in GD [64, 66, 67]. This emerging line of research has also enabled the investigation of psychological variables ('structural characteristics') that vary across gambling products. Clark et al [74] developed a simulated slot machine game to deliver unpredictable wins but also 'near-misses': stimulus configurations that closely approximate winning combinations but yield no reward. These events are widespread in gambling and known to motivate continued play, and also elicit neural responses in reward circuitry that overlaps with the response to monetary wins [74]. Comparing these fMRI responses between GD and healthy control groups, male GDs showed *heightened* striatal responses specifically to near misses [66]. Two other studies show similar hyper-reactivity, one using a continuous design as a function of problem gambling symptoms [75], and the other using magnetoencephalography (MEG)[76]. Provocatively, in the recent paper by Sescousse et al [66], striatal reactivity was not modulated by the DA $D_{2/3}$ antago neurotransmitters, see below).

The reward deficiency and sensitization accounts diverge in their predictions concerning non-drug (or non-gambling) reward cues, with reward deficiency predicting a generalized hypo-reactivity, and sensitization predicting hyper-reactivity only to cues related to the addictive reinforcer. One experiment formally compared reactivity across reward types in GD. Presenting cues that predicted money (as a putative gambling reinforcer) and another cue that predicted presentation of an erotic picture, GDs showed an *imbalance* across reward cues in the striatum and orbitofrontal cortex, with greater responses to the monetary cues relative to the erotic cues [72]. Notably, the GD and control groups did not differ significantly in the response to the monetary cues *per se*. Similar attenuated responses to natural (non-drug-related) rewards are seen in cocaine [77] and nicotine dependence [78]. Within the OFC region, the study in GD indicated a posterior–anterior axis in reward responsivity: In healthy participants, posterior OFC was responsive to primary (erotic) rewards, while anterior OFC was responsive to secondary (money) rewards (but see also [79]). This discrimination was absent in the GD group, for whom the monetary rewards recruited posterior OFC, suggesting that in GD, money may become elevated to a 'primary' reward.

The cue reactivity paradigm provides a further means of testing these questions, as a well-established procedure from SUD research that has also been applied to GD. In SUD, drug cues (e.g., drug-taking paraphernalia) activate reward-related regions, including medial frontal cortex, OFC, insula and VS [80–82]. Gambling images and videotapes yield similar effects in GD [33, 83, 84]. Kober et al. [33] showed overlapping recruitment of medial PFC by gambling cues in GDs and by cocaine cues in cocaine-dependent individuals. Limbrick-Oldfield et al. [84] recently showed a positive relationship between cravings reported during the scan and gambling cue-related activity in bilateral insula and VS. These and other correlational effects are summarized in Table 3.

Loss processing and choice-related activity

Some of the gambling tasks described above also involve loss outcomes, which may shape the interpretation of reward signalling. Aversive processing has received comparatively limited attention in addictions research (and represents a distinct RDoC category, Negative Valence), but a logical hypothesis is that sustained behavior in the face of negative consequences may entail reduced sensitivity to punishment [85]. Using an MIDT where distinct cues signalled availability of monetary gains or avoidance of monetary losses, Romanczuk-Seiferth et al [73] found minimal differences in reward processing in GD, but a diminished response in VS and medial PFC to loss avoidance; this was further complicated by an enhanced response to loss anticipation. Increased activity during loss anticipation was also observed in another GD study, in the caudate, and loss-related activity in the anterior insula correlated positively with gambling severity [63]. These findings may reflect a temporal difference shift in aversive learning similar to that proposed for appetitive conditioning, except in this case, cues previously associated with loss come to evoke loss expectancy, and reactivity to the loss itself (and reward omission) becomes blunted [86].

Reward-related dysregulation can also be interpreted in terms of altered decision-making rather than reward processing per se [87]: neural responses in GDs may indicate a distorted representation of costs and benefits, rather than gains and losses [67]. Experimentally, this entails a shift towards studying the evaluation/selection stage of decision-making, and recognition that choice options can vary on multiple dimensions, including magnitude, probability and delay. In SUD, impulsive decision-making is reliably revealed by the tendency to discount larger future rewards in favor of smaller immediate rewards [88]. A similar bias is observed in GDs who also tend to discount uncertain (i.e., low probability) options *less* than healthy individuals [89, 90]. That is, GDs prefer immediate and uncertain rewards.

Assessing these *delay* and *probability discounting* biases during neuroimaging, Miedl and colleagues [65] found that GDs showed stronger value representations in VS during delay discounting, coupled with weaker value representations in the same region during probabilistic discounting. The bias towards immediate rewards can be further enhanced by gambling cues that elicit cravings: when such images were presented in the background of delay discounting choices, discounting rates were elevated and these background cues distorted neural representations of delayed value in the midbrain and striatum [91]. The bias can be attenuated, at least behaviorally, by 'episodic tags' that highlight personal events (e.g., $35 in 45 days - vacation in Paris) at the future delays [92].

Maladaptive decisional processes have been widely studied using the IGT, a neuropsychological probe of ventromedial PFC function in which the participant chooses among 4 virtual card decks that vary in both the magnitude and probability of gains and losses. In behavioral studies, GDs displayed increased risky choice on the IGT [34, 93]. The neural correlates of this effect are unclear. One study reported increased prefrontal signal during risky choice in GD [94]. Another study compared SUD individuals with and without GD: the comorbid group showed reduced prefrontal signal overall compared to controls, but in non-comorbid GDs, this effect was attenuated relative to non-comorbid SUD individuals [95]. IGT results may be hard to interpret because risk-taking is overlaid on learning about the deck contingencies [96]. Using a risky choice task that is better suited to fMRI modelling, Gelskov et al. [67] observed increased activity in GDs during high-risk decisions, with caudate and dorsolateral PFC responding under both the most appetitive and most aversive bet conditions. Recent studies have also begun to characterize some further elements of decision-making, such as strategy adjustment in order to reach a 'quota' [97]. A notably large study of effort-based decision-making in GD ($n = 80$) also characterized individual differences in depression. Fauth-Buhler et al. [40] found no differences between GD and control groups in reward anticipation, but depression severity correlated positively with outcome processing in insula and dorsal striatum activity among those with GD.

Task-related functional connectivity

fMRI studies of GD have recently begun to incorporate connectivity analyses. Traditional task-related analysis using general linear models (GLM) test how activity in each voxel in the brain varies with task condition. Functional connectivity analysis, by contrast, defines a seed region and tests for brain regions where activity correlates (or anti-correlates) with activity in the seed, either throughout the time series or as a function of specific task conditions (termed gPPI) [98]. Models of addiction that describe disrupted prefrontal control over subcortical reward activity [99] may be tested more directly with functional connectivity analyses than the GLM contrast approach. In the cue reactivity study by Limbrick-Oldfield et al [84], GLM analyses did not identify any significant group differences in the striatum, but group differences in functional connectivity were observed between a VS seed and left insular cortex and superior frontal gyrus. Within the GD group, higher craving also correlated with reduced functional connectivity between VS and medial PFC. During delay discounting, striatal connectivity with amygdala was increased in GDs [100]. Other studies on task-related functional connectivity in GD have examined emotional inhibition [101], quota-based decision-making [97], and slot machine near-misses [102], generally pointing to disrupted fronto-striatal interactions and also within the PFC.

fMRI summary

fMRI studies of reward processing in GD have reliably identified dysregulation in core circuitry in VS, medial PFC and OFC, and affiliated regions like the insula and dorsolateral PFC, but the direction of these group differences (i.e. hypo- or hyper-reactivity) is mixed. It should be noted that similar inconsistencies exist in the SUD literature [103]. While fMRI is arguably the best suited of the imaging modalities for localizing reward-related activity in real time, these studies highlight the multi-faceted nature of reward processing as well as the need for improved tasks to operationalize the Positive Valence category. Analyses of functional connectivity are starting to provide insights beyond those of conventional GLM tests. Nevertheless, functional connectivity is an inherently correlational technique that does not establish causal relationships (termed 'effective connectivity'). Alternate means of analyzing fMRI data may help resolve some of these inconsistencies, such as the use of spatial Independent Components Analysis [104] to disambiguate task-related networks, as well as growing insights from resting-state fMRI [105–107].

Positron emission tomography (PET)

PET studies of neurotransmitter function provide a complementary technique to the MRI investigations of brain anatomy and task-related changes in BOLD signal. PET studies have chiefly focussed on DA as the prime mediator of reward signalling [108], with preliminary studies also using PET radioligands for the GABA, opioid and serotonin systems. Although medication trials and behavioral pharmacology implicate further neurotransmitters in GD including glutamate [109, 110] and noradrenaline [111],

this section focuses on PET due to its potential for integration with the MRI data at a regional level and to assist the interpretation of hypo- versus hyper- responsivity in fMRI experiments.

Dopamine

Among the most reliable PET findings in SUDs is a decrease in striatal binding of the DA $D_{2/3}$ receptor radioligand, [^{11}C]-raclopride, indicating lower availability of $D_{2/3}$ receptors relative to the healthy brain. This decrease is especially clear in stimulant and alcohol use disorders, but has also been reported in opiate, nicotine and cannabis use disorders [112]. Using the equivalent PET protocol in GD, four independent studies reported no significant differences in striatal $D_{2/3}$ receptor availability relative to healthy controls [37, 38, 113, 114]. This disparity between SUDs vs. GD may indicate that reduced striatal $D_{2/3}$ binding in SUDs reflects neuroadaptive consequences of chronic substance use. Indeed, that argument is further supported by longitudinal PET imaging in primates as a function of cocaine self-administration [115] as well as correlations with cumulative drug exposure (e.g., years of use) in human raclopride studies [116, 117]. By contrast, pre-addiction vulnerability is not associated with differences in $D_{2/3}$ receptor binding in subjects at high clinical risk for SUD versus low risk controls [118]. Nevertheless, trait impulsivity has been associated with lower $D_{2/3}$ binding (using the [18F]-fallypride ligand) in an animal model, and highly impulsive rats showed higher subsequent rates of cocaine self-administration [119]. $D_{2/3}$ levels in striatum (and midbrain) of healthy humans also correlate negatively with trait impulsivity [120, 121] and delay discounting [122], similar to findings in methamphetamine [123, 124] and cocaine abusers [125]. In two small studies in GD, lower striatal $D_{2/3}$ levels were correlated with mood-related impulsivity ('Urgency') [37] and sensation seeking scores [126]. Thus, as in the fMRI studies in GD (see Table 3), individual differences in $D_{2/3}$ receptor levels may relate to trait vulnerability factors and supersede any case-control differences.

The [11C]-raclopride ligand binds non-selectively to both DA D_2 and D_3 receptors. The D_3 receptor, which is prevalent in midbrain and limbic/ventral striatum, may be especially relevant to GD, given the tendency for DA agonists with high D_3 affinity (e.g. pramipexole) to induce gambling symptoms in patients with Parkinson's Disease [31]. A key role for D_3 is supported by animal studies in which a selective D_3 agonist (PD128907) dose-dependently promoted a biasing effect of sensory cues (lights, sounds) on risky choice on the rodent gambling task (rGT) [127]. Using the D_3-preferring radioligand [11C]-(+)-PHNO in GDs, no group differences were observed in midbrain or striatal D_3 binding, but gambling severity was positively correlated with PHNO binding in the D_3-rich midbrain [38]. Increased PHNO binding in D_3-rich brain regions was also observed in SUD, and was associated with high impulsivity and risky decision making [128]. In healthy participants, multi-modal PET with both PHNO and raclopride indicates correspondence between high trait impulsivity, high D_3 in SN, and low striatal D_2 levels [38].

Using the DA precursor radioligand [^{18}F]-fluorodopa, a recent study found increased DA synthesis in GD [129]. However, Majuri et al [130]. employed a combined single photon emission-PET design with this ligand, as well as assessing opioid receptor binding with the mu agonist [^{11}C]-carfentanil (see below), finding no difference in striatal DA synthesis between GDs and healthy controls, but a marked reduction in a small third group of cases with Binge Eating Disorder. These results demonstrate differences in reward-related neurotransmission between two (putative) behavioral addictions, with the further implication that drug-induced neurotoxicity may not fully account for differences in PET profiles between SUD and GD.

Dopamine release

Displacement designs can quantify DA release in response to challenge, which is typically administration of a stimulant drug, but could also be a cognitive challenge such as a gambling game. Boileau et al. [39] used amphetamine (0.4 mg/kg), a standard challenge for subcortical DA release, to assess reward system reactivity in GD. They found significantly greater PHNO displacement in dorsal striatum, as well as positive correlations with gambling severity in VS. This result contrasts sharply with evidence of *blunted* amphetamine-induced DA release in cocaine [131, 132], opiate and alcohol addiction [116, 133]. In GD, elevated baseline D_3 binding in substantia nigra predicted amphetamine-induced PHNO displacement in VS, and was also linked to gambling severity. The additional effect in dorsal striatum in GD may indicate DA hyper-reactivity in a region linked to habit-based responding [16]. A similar correlation between DA release (in VS) and gambling severity was also seen by Joutsa et al. [113] measuring DA release in response to a realistic slot machine game: Both low and high monetary rewards caused striatal raclopride displacement, and the binding change in VS to high rewards correlated with subjective 'high.' Although there were no group differences in raclopride displacement between GD and controls, the degree of displacement was correlated with GD symptom severity. In a related analysis [134], GDs with higher delay discounting levels (measured off-line) exhibited lower baseline raclopride binding in VS, and lower DA release in VS in response to high reward slot machine play. As a measure of impulsive choice, these data

are consistent with other evidence linking elevated trait impulsivity with low striatal $D_{2/3}$ receptor levels [135]. A series of studies (in overlapping cohorts) by Linnet and colleagues have triangulated the relationship between uncertainty, risky decision-making and DA release, measuring raclopride displacement in response to the IGT [114, 136, 137]. GDs with riskier decision-making (operationalized as losing more money on the IGT) displayed greater DA release in left VS relative to controls. Opposing relationships were seen between DA release and IGT performance in GDs vs. controls, such that DA release predicted risky choice in GD but more judicious choices in control [138]. Further relationships were described with self-reported excitement in GDs [114]. Overall, these displacement studies indicate a pattern of elevated DA release in GD, which is further associated with gambling severity, impulsivity and risky choice, and positive stimulatory effects of gambling.

Gamma-amino-butyric acid (GABA)

Using [11C]-Ro15-4513 as a radioligand for the GABA-A receptor, Mick et al. [139] detected elevated binding in GD in right hippocampus, a pattern that is opposite to other experiments in alcohol dependence [140]. In the GD group, higher GABA-A binding in the amygdala was correlated directly with mood-related impulsivity (Negative Urgency). Whether these binding differences indicate low or high GABA transmission is unclear; however, low transmission and compensatory receptor up-regulation would align with deficient inhibitory modulation of DA signaling in these limbic regions, with possible implications for medication development targeting the GABA-A receptor.

Endogenous opioids

The pleasurable properties of primary rewards and drugs of abuse are known to depend upon the endogenous opioid system [141, 142]. Specifically, the mu opioid receptor is the primary binding site for morphine and heroin, and plays an important role in drug-induced euphoria [143]. Mu opioid antagonists reduce the pleasurable effects of food and drugs in healthy individuals and those with SUDs [142, 144]. Mu opioid receptor levels and opioid release can be quantified using PET with the [11C]-carfentanil radioligand, through analogous methods to those described above for DA. In cocaine [145–147] and alcohol use disorder [148], elevated mu opioid receptor binding in frontal and temporal cortex predicted both craving and relapse (but see opposite findings [149]). In GD, several clinical trials of the opioid antagonists naltrexone and nalmefene indicate efficacy, including reduced craving [150, 151], suggesting that mu opioid receptors may play a role in gambling-induced pleasure [152]. Two recent studies have examined the opioid system in GD using [11C]-carfentanil. One found no difference in baseline carfentanil binding, but a positive correlation between caudate binding and mood-related impulsivity [139]. The other [130] showed reduced opioid receptor binding in anterior cingulate, although the effect was much less than the ~30% reduction seen in a second clinical group with Binge Eating Disorder.

Using a relatively high-dose amphetamine challenge (0.5 mg/kg), the Mick et al. [153] study also measured [11C]-carfentanil displacement in GD. Opioid release was significantly attenuated across multiple brain regions in GDs, who also showed blunted subjective euphoria and alertness to the amphetamine. The directionally opposite effects of amphetamine on DA vs. opioid release in the studies by Boileau et al. [39] and Mick et al. [153] could indicate an imbalance between incentive-motivational (DA) and hedonic-satiating (opioid) effects of the amphetamine challenge in GD. This mirror-image effect is also consistent with the idea that incentive salience [24] and reward deficiency are complementary, interactive aspects of GD, whereby sensitization mediates the ability of signals for reward (or negative reinforcement) to activate responses expected to rectify deficits in hedonic state [154].

Serotonin (5-hydroxytryptamine; 5-HT)

5-HT is widely implicated in impulsivity and mood, as well as the modulation of DA transmission, with considerable relevance to addictive disorders [155]. Altered 5-HT receptor availability can influence DA to bias approach or avoidance via disinhibition. More specifically, 5-HT1 receptors are implicated in anxiety and depression [156], with 5HT1A activation generally dampening anxiety, and 5-HT1B activation promoting aggression, especially when accompanied by low D_2levels in VS [157, 158]. Using the 5-HT1B radioligand, [(11)C]-P943, Potenza et al [159] found no differences in binding levels between GD and control groups, but once again symptom severity in GDs predicted higher binding in VS, putamen and anterior cingulate. Given the critical role of serotonin in learning from punishment, these alterations may contribute to risk-taking in severe GD. Elevated 5-HT1B in severe GD contrasts with evidence of lower [^{11}C]-P943 binding in cocaine abusers [160], which may thus reflect a chronic neuroadaptation with repeated stimulant exposure. A recent investigation of 5-HT transporter status in GD also found no significant difference from controls [161]. This is in line with comparable studies in SUD [162], which also indicate no marked

Table 4 Strength of evidence for neurophysiological differences between individuals with Gambling Disorder (GDs) and healthy controls (HCs), and comparison to patterns for individuals with Substance Use Disorder (SUDs)

Substrate	GD ↓	GD ↔ HC	GD ↑	SUD ↓	SUD ↔ HC	SUD ↑
DA DR_2	NR	6 studies [37, 38, 113, 114, 136, 137]	NR	11 studies listed in Review [108]	NR	NR
DA DR_3	NR	1 study [38]	NR	NR	1 study [183]	3 studies listed in Review [108]
DA synthesis	NR	1 study [130]	1 study [129]	3 studies [184–186]	2 studies [187, 188]	3 studies [189–191]
OPRM	NR	2 studies [130, 153]	NR	2 studies [192, 193]	NR	3 studies [145, 146, 194]
5HT1B	NR	1 study [159]	NR	1 study [160]	NR	1 study [195]
5HTT	NR	1 study [161]	NR	8 studies [163, 196–202]	2 studies [162, 203]	NR
GABA-A	NR	NR	1 study [139]	2 studies [140, 204]	2 studies [205, 206]	2 studies [207, 208]
DA release	NR	2 studies [113, 114]	1 study [39]	5 studies listed in Review [108]	NR	NR

↔ No significant difference from controls ↓ Decrease relative to controls.↑ Increase relative to controls

DA dopamine, *DR* dopamine receptor, *OPRM* opioid mu receptor, *5-HT1B* 5-hydroxytryptamine (serotonin) 1B receptor, *5HTT* 5-hydroxytryptamine (serotonin) transporter, *GABA-A* Gamma-Aminobutyric acid receptor A, *NR* none reported

abnormalities in 5-HT transporter binding, except in the case of ecstasy (MDMA) users [163].

PET summary

Table 4 summarizes the PET findings in GD. Multiple studies using DA D_2 and D_3 radioligands indicate no differences in binding between GD and control groups, a conclusion that is also indicated for the 5-HT1B receptor. One study found elevated GABA-A receptor binding of GDs, suggestive of possible disinhibition of DA. Using displacement designs in GD, provocative evidence is emerging for increased DA release, which was significant in one case-control study (using amphetamine challenge) and was detected in two further studies as a function of individual differences in gambling severity and impulsivity / risky choice. These results for DA imaging contrast pointedly from SUDs, wherein both baseline DA D2 receptor availability and DA release are typically reduced. For the mu opioid receptor that is targeted by some of the most promising medications for GD, there are mixed results for baseline binding and one study has found lower amphetamine-induced opioid release.

Conclusions and future directions

The emergence of GD as a syndrome whose clinical characteristics and vulnerability factors overlap closely with those of SUD, and which only arises after chronic exposure to the reinforcer, indicates that drugs may not be unique in their ability to induce addiction. Within this framework, addiction is essentially a learning (rather than a substance) disorder, which manifests as an inflexible bias to seek a specific class of reinforcers. To the extent that DA release serves as a teaching signal [164], each episode of drug use or gambling could strengthen the incentive salience of associated stimuli through the perpetual escalation of prediction error signalling and anticipatory vigilance [19, 22]. In this framework, the neural aberrations associated with drugs and gambling primarily reflect the administration parameter(s) that mediate the ability of the reinforcer to evoke DA release. In the case of drugs, supra-physiological DA release occasioned by rapid entry of concentrated doses into the brain appears to be the critical mechanism [165]. In the case of gambling, we argue that the uncertainty of the monetary outcomes is crucial. First, this uncertainty perpetuates anticipatory arousal between the placing of the bet and the outcome, with sustained reward expectancy errors when wins occur [19, 22]. These responses may be enhanced by the presence of intense sensory feedback [127], as an example of a structural characteristic that is

amplified in modern forms of gambling. Second, reward uncertainty opens the door for decision-making biases, which can evolve in GD into powerful cognitive distortions concerning the nature of randomness and the degree of control over winning outcomes [166]. This formulation is consistent with recent work discussing slot machine addictions as arising from the combination of 'machine design features' (e.g. near misses) and 'human design features' (e.g., our susceptibility to illusory control) [167].

In this context, it is notable that low doses of sugar or saccharine can also sensitize the brain DA system in animal models, when these rewards are administered under conditions of uncertainty [168–170]. Moreover, in the cases of both drugs and gambling, stress associated with the removal of these abnormal reward configurations (i.e., withdrawal) is an inherent counterpart that increases susceptibility of the DA system to sensitization [171]. This formulation suggests that common structural and functional plasticity may be the neural manifestation of a bias to seek a specific reinforcer in SUD and GD, whereas differences between SUD and GD may reflect the different mechanisms by which this bias is brought about: pharmacologically-induced supra-physiological DA release and compensatory deficits in SUD; perpetual anticipatory vigilance, reward expectancy errors and DA upregulation without gross morphological deficits in GD.

This review focused exclusively on neuroimaging in GD as a window into the behavioral addictions, but emergent findings in people with excessive consumption of (online) video gaming, pornography, and Binge Eating Disorder/obesity may help to define boundary conditions for 'behavioral addictions' and the mechanistic divisions from SUDs. We specifically encourage studies allowing direct comparisons between putative behavioral addictions and SUD groups [33, 44, 130]. In the neuroimaging studies of GD and SUD, the widespread use of money as the reinforcer creates some neglected conceptual problems. Although money has many advantages from an experimental design perspective (e.g. it is linear, and represents gains and losses in common terms), it remains unclear to what extent monetary wins really are the key driver of the addictive behavior in GD (as opposed to excitement, or gambling to escape). This issue is also relevant to SUDs given the fungible nature of money, as money can be exchanged for drugs and may therefore represent a 'special' case of second-order conditioning. Acknowledging the bias in fMRI toward reliable activation procedures like the MIDT, we encourage researchers to consider, and manipulate, the relatedness of the reinforcer to the disorder. We recognize that the features of GD are not solely explained by dysregulation of the Positive Valence System, and that other relevant RDoC systems (e.g., Cognitive Systems, Negative Valence) also merit attention [12, 28, 29]. GD is also a heterogeneous disorder: gender, co-morbidity, personality and genetic factors all influence its etiology and functional-behavioral profile [172–175].

From the present review, it is apparent that neuroimaging markers often carry stronger effects *within* groups with GD, particularly as a function of gambling severity and impulsivity, than in the more traditional case-control comparisons. The mechanistic significance of this disparity warrants further consideration and should shape future designs in research on GD. In addition, MRI and PET only provide correlational data as response outputs to particular exogenous stimuli (drugs or cognitive- perceptual challenge). Although prospective repeated measures assessment can suggest a causal or mediating role for particular patterns of neuropathology, direct manipulation of neural function is still required for firm causal inference. Transcranial magnetic stimulation (TMS) provides a means to accomplish this with reasonable spatial and temporal resolution [176], and may be fruitfully used to inhibit or enhance neural activity in GD.

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Compliance with ethical standards

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