CHAPTER FIVE

Imaging the Gambling Brain

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Abstract

Neuroimaging studies examining the neurobiological basis of gambling disorder (GD) have increased over the past decade. Functional magnetic resonance imaging studies during appetitive cue and reward processing tasks demonstrate altered functioning in frontostriatal brain areas, including the ventral striatum and the ventromedial prefrontal cortex. Findings suggest differences in how the anticipation and outcome of rewards are processed in individuals with GD. Future research requires larger sample sizes and should include appropriate clinical reference groups. Overall, studies to date highlight a common pathophysiology between substance-based addictions and GD, the latter offering a unique condition in which to examine nonchemical factors in addiction.

The first neuroimaging study in pathological gambling (PG) was conducted in 2003 (Potenza, Steinberg, et al., 2003), since that time, neurobiological findings have demonstrated significant overlap between substance-use disorders and disordered gambling, providing substantial evidence to reclassify the disorder with other addictions. In 2013, gambling disorder (GD), formerly termed pathological gambling (PG), became the first nonsubstance-based disorder in a new "Addictions" category in the DSM-5 (APA, 2013). Over the past decade, brain imaging studies in GD have grown to over 30 directly investigating neural responses in populations with GD.

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Neuroimaging studies in GD offer several unique and significant contributions to the greater addictions research field. Due to neurotoxic effects of drugs on the brain, any neural alterations in substance-based addictions can be difficult to interpret; as a "chemical-free" addiction, GD presents the prospect of examining addiction mechanisms in the brain without the confound of a drug present. Aside from the ability to disentangle contributor/consequence factors in addiction, GD neuroimaging studies provide information on decision-making processes, for example, how the brain processes probability, risk, reward, and losses. Understanding these processes has enormous implications for other research fields such as behavioral economics and even more broadly, on how people form preferences and make decisions.

1. CUE-REACTIVITY STUDIES

To date, most neuroimaging studies in GD focus on reward processing, particularly examining appetitive stimuli during cue exposure or as an individual wins various amounts of money. Examining neural responses as an individual views gambling stimuli provides information on attentional processes in GD and can offer insights into craving mechanisms for this disorder. Gambling cues, even if they are not specific to an individual's preferred gaming type, can produce cravings in a person with GD (Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005). Thus cue-reactivity investigations in GD provide some insight into attentional and motivational processing, including craving in this disorder.

The first functional magnetic resonance imaging (fMRI) study in a gambling population had individuals watching gambling videos depicting various gambling situations while in the scanner (Potenza, Steinberg, et al., 2003). Results showed reduced activity in the ventromedial prefrontal cortex (vmPFC) as GD individuals, relative to healthy controls (HCs), watched the gambling situations (Potenza, Steinberg, et al., 2003). The vmPFC, located on the front, inferior portion of the brain, is reciprocally connected to many other prefrontal areas as well as the striatum, thereby making it an important region of the reward network (Ongur & Price, 2000). In particular, this brain region signals the incentive value of a stimulus and rapidly updates its activity to signal the changing value of a reinforcer (Levy & Glimcher, 2012; Noel, Brevers, & Bechara, 2013). While this early fMRI study in GD only included 10 individuals with PG, it nonetheless was the first to demonstrate neural response patterns for gambling cues that are distinct from other emotional states. Shortly thereafter, Reuter and colleagues

(2005) had participants with GD perform a guessing task and also found diminished vmPFC and reduced striatal activity relative to a control group. Reduced activity in these areas was additionally related to gambling severity: those individuals with the most severe GD showed the least striatal and vmPFC activity (Reuter et al., 2005).

Since those initial fMRI studies in GD, multiple other studies have replicated or demonstrated similar blunted frontostriatal processing in this population during cue exposure or reward processing (Balodis et al., 2012; Choi et al., 2012; de Greck et al., 2010; de Ruiter et al., 2009; Tanabe et al., 2007). These blunted reward neurocircuitry responses are similar to that seen in substance-dependent populations (Allain, Minogianis, Roberts, & Samaha, 2015), but diverge from increased frontostriatal reactivity to disorder-related cues reported in obsessive–compulsive disorder (OCD) (Saxena & Rauch, 2000). As such, fMRI studies to date provide more neurofunctional similarities in GD with substance-use disorders, than with OCD. Additionally, relationships between frontostriatal activity and measures of gambling pathology have continued to appear in the neuroimaging literature, suggesting important links between the two (eg, Balodis et al., 2012; Choi et al., 2012; de Ruiter, Oosterlaan, Veltman, van den Brink, & Goudriaan, 2012).

Nevertheless, several fMRI studies in GD demonstrate increased cortical and subcortical gambling cue reactivity. During gambling videos, Crockford and colleagues (2005) reported that a GD group showed increased activity in the dorsal visual processing stream. Specifically, individuals with GD showed greater dorsolateral prefrontal cortex activity, including the precuneus and the parahippocampal areas (Crockford et al., 2005). These brain areas are often implicated in attention, memory, and goal planning (Duncan & Owen, 2000; Gazzaley & Nobre, 2012). This early fMRI study also tested whether a relationship might exist between neural responses and physiologic reactivity; however, the investigators reported no relationship between brain activation with either respiration or heart rate.

Another study examining cue reactivity by Goudriaan, de Ruiter, van den Brink, Oosterlaan, and Veltman (2010) also found increased cortical and subcortical activity relative in a group of problem and pathological gamblers. This study included two control groups: a HC group, but also a group of heavy smokers. With two comparison groups, results demonstrated that the GD group had heightened activity when viewing gambling images in occipital, parahippocampal, amygdalar, and ventrolateral PFC areas, relative to both the heavy smokers and the HC group. While activity in some of the

areas was linked to craving in the GD group, it should be noted that craving measures were not statistically significantly increased during cue exposure (Goudriaan et al., 2010). Nonetheless, this study demonstrates the ability of gambling stimuli to recruit brain areas involved in visual processing, attention, memory, and emotional processing.

One of the largest neuroimaging studies in GD was recently published, as well as one of the first specifically investigating gender differences. The study compared a GD group with a cocaine dependent (CD) and a HC group as they viewed gambling-related videos in the scanner (Kober et al., 2016). In a sample of 28 individuals with GD, investigators were able to identify differentiated neural responses in males vs females. Specifically, females with GD showed greater activity in posterior putamen/insular regions while viewing gambling-related stimuli—regions that have previously been linked to drug craving and gambling urges (Garavan, 2010; Goudriaan et al., 2010). Altogether these findings suggest important gender-related differences in motivational responses to gambling cues and that craving states may be generated differently across males and females (Kober et al., 2016). While gender differences are noted in prevalence, onset and gambling motivations, this is one of the first to directly examine sex-specific neural substrates.

2. PARSING OUT SPECIFIC COGNITIVE CONSTRUCTS IN GD

2.1 Anticipatory Processing

Technical developments and improved anatomical segmentation through neuroimaging together with conceptual refinements in GD have resulted in more specific examination of cognitive constructs. For example, several recent neuroimaging studies examine anticipatory processing in GD. Anticipation refers to the period of time immediately prior to an outcome and can comprise powerful expectancy effects. A better understanding of anticipatory processes has implications for shedding light on motivational processing, particularly those related to the construct of craving, a central addiction characteristic. In the brain, anticipatory reward processing recruits striatal neurocircuitry, whereas the receipt of reward activates more medial prefrontal cortical regions (Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001). Notably, craving also recruits striatal areas (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Knutson, Adams, et al., 2001) and relates to anticipatory processes.

One fMRI study examining anticipatory processing in a GD population found diminished frontostriatal activity relative to an HC group as they won and lost different amounts of money in the scanner (Balodis et al., 2012). Notably, activity in the ventral striatum during anticipation was inversely linked to impulsivity: the higher impulsivity score that a GD individual presented, the less activity in ventral areas of the striatum. These results show similarities to previous reports linking striatal activity with gambling severity (eg, Reuter et al., 2005). Moreover, these findings closely parallel reduced anticipatory processing in the striatum reported in an alcohol-dependent population (Beck et al., 2009) and in individuals with a family history of alcohol dependence (Andrews et al., 2011) using the same task to examine anticipatory processing. Additionally, all studies report similar inverse relationships between anticipatory striatal signaling and impulsivity. Altogether, this growing body of research suggests neurobiological similarities in the relationship between anticipatory ventral striatal signaling with the construct of impulsivity across substance-based, nonsubstance-based as well as those at risk for addiction.

Altered activity in GD has also been noted in more dorsal areas of the striatum. For example, van Holst and colleagues reported that individuals with GD demonstrate increased activity in this area when anticipating winning €5 vs €1 on a guessing paradigm (van Holst, Veltman, Buchel, van den Brink, & Goudriaan, 2012). More dorsal regions of the striatum often show increasing activity over the course of learning, as an activity becomes more habitual (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007; O'Doherty et al., 2004; Reading, Dunnett, & Robbins, 1991). Additionally, the dorsal striatum codes for prediction errors as well as action–outcome associations (Haruno et al., 2004; O'Doherty et al., 2004; Tricomi, Delgado, & Fiez, 2004). Thus, increased dorsal striatal activity in response to winning €5 vs €1 on a guessing paradigm might suggest *increased* sensitivity to the magnitude of reward in the GD group, and/or increased propensity to think that their actions directly influence the outcome. Further research is necessary to explore these possibilities.

2.2 Subjective Value

In addition to advances in anatomical segmentation of striatal areas, other studies are highlighting the complexity of accounting for subjective reward valuation. A study by Miedl, Peters, and Buchel (2012) examined how individuals chose between fixed immediate rewards or larger, delayed rewards.

The authors demonstrated how the ventral striatum and the vmPFC signaled the value of stimuli, additionally, however, the activation in these areas was modulated by the subjective value of the stimuli (Miedl et al., 2012). These findings demonstrate important individual difference effects on brain activity and highlight the difficulty in controlling for these factors across various paradigms and task-dependent effects as well as across diverse populations. Nevertheless, even when controlling for differences in subjective value, Miedl and colleagues still found that risky rewards produced reduced frontostriatal recruitment in the GD group relative to an HC group. Moreover, Miedl and colleagues also found an inverse relationship between frontostriatal activity during delayed rewards and problem-gambling severity. These results are once again consistent with other studies finding an inverse relationship between frontostriatal recruitment and measures of pathology (Balodis et al., 2012; Reuter et al., 2005) (Fig. 1).

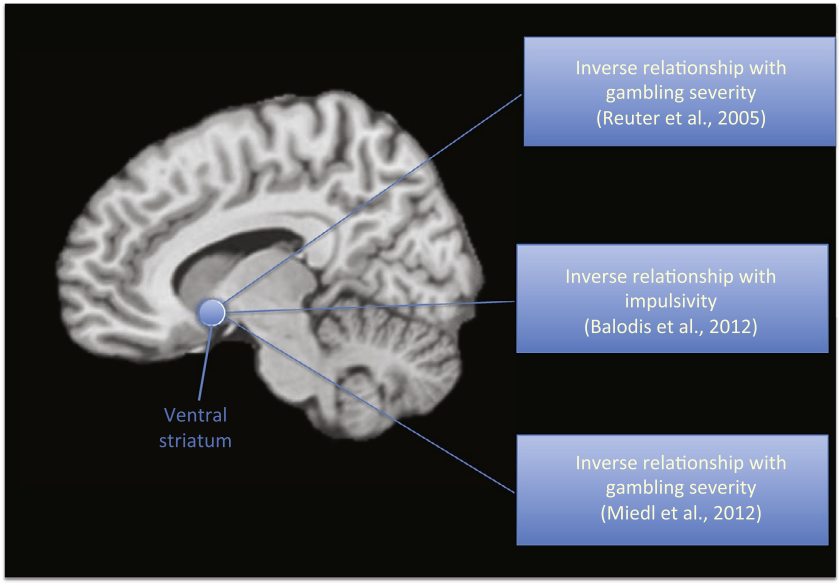

Fig. 1 Inverse relationship between striatal activity and measures of gambling pathology. Multiple neuroimaging studies demonstrate an inverse relationship between activity in frontostriatal areas and measures of gambling pathology, particularly in striatal areas. *Blue* (*white in the print version*) *circle* highlights the ventral striatum ($x = 9$).

2.3 Near Misses

"Near misses" are a unique feature of gambling that can have a profound effect on the individual. Several GD studies have examined the "near miss" phenomena, whereby a loss is perceived as almost winning. These near miss effects, while subjectively producing unpleasant feelings, nonetheless activate reward neurocircuitry and effectively increase the motivation to gamble (Chase & Clark, 2010; Clark et al., 2012; Worhunsky, Malison, Rogers, & Potenza, 2014). One recent neuroimaging study examining this effect compared a GD group with a HC as well as a CD group as they played a slot-machine task in the scanner (Worhunsky et al., 2014). Results showed that both the GD and the CD groups had amplified anticipatory responding in reward neurocircuitry to a near miss event. These findings can therefore provide a mechanistic idea of how near misses still stimulate reward neurocircuitry and generate cognitive distortions about control and winning thereby encouraging continued playing. In regular gamblers, near miss events produce increased activity in dopamine-rich areas, which further relates to gambling severity (Chase & Clark, 2010; Clark, Lawrence, Astley-Jones, & Gray, 2009).

Recently, neuroimaging studies examine not only brain areas activated by gambling stimuli but also how these areas communicate with each other. One neuroimaging study used functional connectivity to investigate near miss events across a population of regular and nonregular gamblers (van Holst, Chase, & Clark, 2014). The investigators reported stronger striatal–insula connections were related to greater illusions of control. These findings suggest that increased connections between reward circuitry and areas involved in interoceptive processing may lead to distorted beliefs about winning and ultimately promote loss-chasing in some individuals. Further research into understanding the neural mechanisms underlying cognitive distortions will be important.

2.4 Inhibitory Control Studies

To date, only a handful of imaging studies have examined inhibitory processing in GD. One early study of cognitive control had participants perform the Stroop task while undergoing fMRI (Potenza, Leung, et al., 2003). The Stroop task is a cognitive control task in which individuals name the color of a word, rather than read the word. This requires a person to inhibit the prepotent response of reading and effectively recruits inhibitory neurocircuitry including the anterior cingulate and dorsolateral prefrontal cortex

when the color of the word is incongruent with the word meaning (eg, the word "red" written in green ink). In a GD population, incongruent trials produce reduced vmPFC activity in a GD population relative to an HC group (Potenza, Leung, et al., 2003). Another task examining inhibition is the Stop Signal Task, which has the advantage of examining the neural substrates of error processing and response suppression once an action has been initiated. An elegant study by de Ruiter and colleagues found that during successful inhibition, relative to an HC group, GD individuals demonstrated reduced activity in dorsomedial prefrontal and anterior cingulate areas (de Ruiter et al., 2012). Additionally, activity in this latter area was inversely related to gambling severity, demonstrating that problem-gambling severity relates to recruitment of inhibitory neurocircuitry. Another well-designed feature of this study was the inclusion of a heavy smoker group who further demonstrated diminished processing in overlapping dorsomedial prefrontal and cingulate areas. Thus, heavy smokers and individuals with GD display hypoactivations in inhibitory neurocircuitry during inhibition, thereby providing additional support for similar neurobiological alterations across substance- and nonsubstance-based disorders.

3. POSITRON EMISSION TOMOGRAPHY STUDIES

A growing number of GD studies are also applying positron emission tomography (PET) scans to examine specific neurotransmitter systems potentially underlying dysregulated behavior. To date, most investigations have focused on dopamine, given its role in reward processing, substance dependence and the striatum as a key projection area for this neurotransmitter. Additionally, findings from a disorder characterized by reduced dopamine availability, Parkinson's Disease, provided some indications for dopamine's role in impulsive behaviors. Multiple studies now document the development of gambling problems and other impulse control problems, following dopamine replacement therapies in Parkinson's (Leeman & Potenza, 2011; Molina et al., 2000). Following administration of drugs that increase brain dopamine levels, some individuals with Parkinson's disease have developed problem behaviors, including gambling, sex, and shopping (Weintraub & Potenza, 2006; Weintraub et al., 2010). Nonetheless findings from PET imaging in GD have had complicated and mixed results. For example, one study examining dopamine changes as individuals performed the Iowa Gambling Task (IGT) did not find that all participants showed

dopamine increases in conjunction with the task (Linnet, Moller, Peterson, Gjedde, & Doudet, 2011). However, those individuals with GD who did show increased dopamine release were also those who reported greater excitement levels, although their performance was significantly poorer on the IGT. Thus the relationship between gambling excitement and dopamine release remains unclear, suggesting additional contributors. To date, several PET studies have not detected differences in the D2-like receptors when comparing GD with HC populations (Boileau et al., 2013; Joutsa et al., 2012), leading some to question the centrality of dopamine in GD (Potenza, 2013).

Following an amphetamine challenge, a recent PET study reported that individuals with GD had increased dopamine release in the striatum (Boileau et al., 2014). These findings are in contrast to PET studies in substance dependence, which report *reduced* dopamine release following drug challenges (Martinez et al., 2005).

Nonetheless, several PET studies describe relationships between dopamine availability and impulsivity or gambling-related measures (Boileau et al., 2014; Clark et al., 2012; Joutsa et al., 2012).

Altogether, the discrepant findings suggest that dopamine may differentially contribute to addiction symptoms in GD and/or may not play as central a role in this disorder (Potenza, 2013). Future studies including larger samples, as well as directly comparing clinical reference groups will be important in clarifying the role of this neurotransmitter in GD.

4. STRUCTURAL IMAGING

Recently, the first few structural imaging studies have emerged in GD, however, most do not find gray matter differences (Joutsa et al., 2012; Koehler et al., 2013; van Holst, de Ruiter, van den Brink, Veltman, & Goudriaan, 2012). One study found that a GD group had intermediary gray matter levels between an alcohol-dependent and an HC group, suggestive that the lower gray matter levels detected in alcohol dependence may represent a neurotoxic result of chronic alcohol use (van Holst, de Ruiter, et al., 2012). Nonetheless, another recent study controlling for comorbid conditions found reduced hippocampal and amygdalar relative to an HC group (Rahman, Xu, & Potenza, 2014). Some recent studies have detected white matter alterations in limbic and prefrontal regions that may suggest a first phase of neuropathology, prior to larger regional volume changes (Joutsa et al., 2012; Yip et al., 2013). More functional connectivity studies are necessary to evaluate these networks and their relationship with functional alterations.

5. CONCLUSIONS

Neuroimaging studies in GD are becoming more numerous and are contributing to our knowledge of the pathophysiology of addiction. These studies hold much potential in untangling some of the cause and consequence effects of addiction and probing aberrant learning mechanisms in the brain. However, until recently, most neuroimaging studies in GD have included very small samples; therefore, larger studies and replications are still necessary in order to move the field forward. Longitudinal studies and subgrouping will also be crucial in shedding light on the neuropsychology and neurobiology of GD.

Nonetheless, investigators are beginning to combine methodologies across neuroimaging, genetic, psychopharmacology, and cognitive fields. For example, one pilot study found that individuals with differences in a specific gene that breaks down dopamine in the prefrontal cortex responded better to a drug enhancing dopamine activity (Grant et al., 2013)—improvements were additionally related to increased frontal activity during an executive planning task (Grant et al., 2013). Thus, these studies are beginning to identify subgroups that might best respond to a specific treatment and can further pinpoint the mechanisms by which it may be working. Larger studies are still needed; nonetheless, these findings hold promise for more targeted interventions in the future. To date, neuroimaging studies demonstrate common pathophysiology between substance-based disorders and GD. Nonetheless these studies also highlight the heterogeneity of GD and the complexity of exploring how the brain makes decisions.

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