Behavioural Brain Research 275 (2014) 243–251

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Reward pathway dysfunction in gambling disorder: A meta-analysis of functional magnetic resonance imaging studies

Ya-jing Meng[a,b,1], Wei Deng[a,b,1], Hui-yao Wang[a], Wan-jun Guo[a,b,*], Tao Li[a,b,**], Chaw Lam[c], Xia Lin[d,e,f]

[a] Mental Health Center, West China Hospital, Sichuan University, PR China
[b] State Key Laboratory of Biotherapy, Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, PR China
[c] Department of Psychology, Illinois Institute of Technology, Chicago, IL, U.S.A
[d] Institute of post-disaster reconstruction, Sichuan University, Chengdu, China
[e] Department of Rehabilitation Sciences, The Hong Kong Polytechnic, Hong Kong, China
[f] Department of forensic medicine, North Sichuan Medical University, Nanchong, China

HIGHLIGHTS

- We selected 13 qualified voxel-wise whole brain fMRI studies of gambling disorder.
- GD showed hyperactivity in right lentiform nucleus and left middle occipital gyrus.
- The SOGS of GD was related to hyperactivity in right lentiform nucleus and left ACC.
- The result was also found in GD subgroups (regardless of excluding or not excluding any kind of substance use disorder).

ARTICLE INFO

Article history:
Received 5 July 2014
Received in revised form 25 August 2014
Accepted 30 August 2014
Available online 6 September 2014

Keywords:
Gambling disorder (GD)
Effect size signed differential mapping (ES-SDM)
Functional magnetic resonance imaging (FMRI)
The frontostriatal cortical pathway

ABSTRACT

Recent emerging functional magnetic resonance imaging (fMRI) studies have identified many brain regions in which gambling cues or rewards elicit activation and may shed light upon the ongoing disputes regarding the diagnostic and neuroscientific issues of gambling disorder (GD). However, no studies to date have systemically reviewed fMRI studies of GD to analyze the brain areas activated by gambling-related cues and examine whether these areas were differentially activated between cases and healthy controls (HC). This study reviewed 62 candidate articles and ultimately selected 13 qualified voxel-wise whole brain analysis studies to perform a comprehensive series of meta-analyses using the effect size-signed differential mapping approach. Compared with HC, GD patients showed significant activation in right lentiform nucleus and left middle occipital gyrus. The increased activities in the lentiform nucleus compared to HC were also found in both GD subgroups, regardless of excluding or not excluding any kind of substance use disorder. In addition, the South Oaks Gambling Screen scores were associated with hyperactivity in right lentiform nucleus and bilateral parahippocampus, but negatively related to right middle frontal gyrus. These results suggest dysfunction within the frontostriatal cortical pathway in GD, which could contribute to our understanding of the categories and definition of GD and provide evidence for the reclassification of GD as a behavioral addiction in the DSM-5.

* Corresponding author at: Mental Health Center & State Key Laboratory of Biotherapy, Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, PR China. Tel.: +86 28 85422629; fax: +86 28 85426118.
** Corresponding author at: Mental Health Center, West China Hospital, Sichuan University, Chengdu, Sichuan, PR China. Tel.: +86 28 85423561; fax: +86 28 85422632.
E-mail addresses: guowjcn@163.com (W.-j. Guo), xuntao26@hotmail.com (T. Li).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.bbr.2014.08.057
0166-4328/

Contents

1. Introduction

Gambling disorder (GD) is recognized and characterized by persistent and uncontrolled gambling leading to deleterious psychosocial consequences [1]. It is formally classified as the sole non-substance-related disorder in the "Substance-Related and Addictive Disorders" chapter of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [2], although it was termed "pathological gambling" in the "Impulse-Control Disorders Not Elsewhere Classified" chapter of the DSM-IV [3]. Epidemiological surveys have reported that GD has a prevalence of 0.5–3.0% [4–6] in adults and causes significant impairments in psychological and social functioning [7].

There are a number of similarities between GD and substance use disorders (SUDs), including genetic vulnerability [8], biomarkers [9], and poor cognitive performance on neurocognitive tasks [10–12], specifically with respect to impulsive choice and response tendencies and compulsive features. These findings from neuroimaging studies in GD suggest dysfunction involving similar brain regions, including the ventromedial prefrontal cortex (PFC) and striatum and similar neurotransmitter systems, including dopaminergic and serotonergic [13,14]. Therefore, recent studies have suggested that GD may be considered a behavioral addiction [15–19]. However, there are also some crucial differences between GD and SUD, such as toxic effects of exogenous substances on the brain and the expectation of gambling or drug use [20].

Brain imaging technologies have allowed neuroscientists to map out the neural landscape of GD in the human brain and start understanding how psychostimuli modify it. The reward deficiency hypothesis predicts that the susceptibility to addiction stems from an insensitive or ineffective dopaminergic system [21]. However, a contrasting model predicted that the addicted brain exists in a hyperdopaminergic state [22]. Some brain imaging studies found that dopamine (the key player in the "ventral frontostriatal reward circuit") increased in cases of GD [20] or a "double deficit" function of dopamine in GD [23,24]. Meanwhile, an alternative theoretical model of addiction that stressed the involvement of both the brain reward pathways (the ventral striatum) and the regulatory system (the PFC) has been raised based on recent evidence from functional magnetic resonance imaging (fMRI) studies of GD investigating reward processing, craving, decision-making, delay discounting, and other cognitive processes [25–27,14,15,28–30]. Considering these hypotheses, this model highlighted the features of GD that make it a valuable experimental model for the addiction field as well as the leverage that may be afforded by this illness for resolving the nature of the dysregulation in reinforcement processing in GD.

As with studies of drug addiction, these papers in GD have also isolated the striatum and the prefrontal lobe regions as lying at the core of this disrupted network [28]. However, different studies have included relatively small numbers of subjects with GD of varying severity, employed a variety of different cue or reward reactivity paradigms, and reported many different areas of cue-elicited activation [28], such as the dorsal and ventral striatum [31–33], PFC [10,12,34–36], middle occipital gyrus [30], insula [37], cuneus [38], and precuneus [34]. Although several qualitative reviews of neuroimaging studies of gambling cue or reward reactivity exist [20,39,40,28], no study to our knowledge has used a scientific statistical methodology such as meta-analysis to systemically review the fMRI studies of GD and systematically characterize the brain areas activated by cues across subject populations, cue-exposure paradigms, and imaging modalities. In the present study, we herein first surveyed the whole-brain functional neuroimaging investigations of GD using the effect size-signed differential mapping (ES-SDM) approach for quantitative meta-analysis to synthesize the findings from fMRI studies of GD. Secondarily, we sought to characterize the states and traits related to this activation by systematically reviewing correlations between activation and behaviors.

2. Method

2.1. Study collection and inclusion and exclusion criteria

Using PubMed (http://www.pubmed.org), Google Scholar (http://scholar.google.com), Embase (https://www.embase.com), and the Cochrane library (http://www.thecochranelibrary.com), we searched for English-language MRI studies of GD published between Jan 2000 and Dec 2013 using the keywords "gambling disorder" or "pathological gambling" or "problem gambling" in combination with a neuroimaging term (e.g. fMRI or neuroimaging). Abstracts of initially identified articles in English were first reviewed as the basis for selecting papers for full-text review. References cited in the selected articles were also reviewed.

These searches initially identified 62 candidate articles for possible inclusion. Studies that included a direct comparison between GD groups with at least one control group of healthy controls (HCs) or subjects without a diagnosis of GD were included in the meta-analysis. Other criteria included studies that reported whole-brain analysis of tasking-state fMRI scans and reported the coordinates of the activation areas of a voxel-wise whole-brain analysis in stereotactic coordinates using *t*, *Z*, or *P* values. Subjects with a diagnosis of anxiety and/or depression were not excluded because of their considerable comorbidity rates with gambling. Studies of GD that had