Review: Non-invasive Brain Stimulation in Behavioral Addictions: Insights from Direct Comparisons with Substance Use Disorders

Elena Gomis-Vicent, MSc [1], Volker Thoma, PhD [1], John J.D. Turner, PhD [1], Kevin P. Hill, MD, MHS [2] and Alvaro Pascual-Leone, MD, PhD [3,4]

[1] College of Applied Health and Communities, University of East London, London, United Kingdom
[2] Division of Addiction Psychiatry, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts
[3] Berenson-Allen Center for Noninvasive Brain Stimulation and Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[4] Institut Guttmann de Neurorehabilitació, Universitat Autonoma de Barcelona, Badalona, Spain

Running Head: Non-invasive Brain Stimulation in Addictions

- Corresponding author: Elena Gomis-Vicent, University of East London, Stratford Campus, Water lane, E15 4LZ, London, United Kingdom, +4402082234427, e.gomisvicent@uel.ac.uk
- Abstract: _250 words
- Narrative: _6383 words__
- Number of Tables: __4_
- Number of Figures: __1_
- Number of References: _95__

Abstract

Background

Treatment models developed for substance use disorders (SUDs) are often applied to behavioral addictions (BAs), even though the correspondence between these forms of addiction is unclear. This is also the case for non-invasive brain stimulation (NIBS) techniques being investigated as potential treatment interventions for SUDs and BAs.

Objective

To contribute to the development of more effective NIBS protocols for BAs.

Methods

Two literature searches using PubMed and Google Scholar were conducted identifying a total of 35 studies. The first search identified 25 studies examining the cognitive and neurophysiological overlap between BAs and SUDs. The second search yielded 10 studies examining the effects of NIBS in BAs.

Results

Impulsivity and cravings show behavioral and neurophysiologic overlaps between BAs and SUDs, however other outcomes, e.g. working-memory abilities or striatal connectivity, differ between BAs and SUDs. The most-employed NIBS target in BAs was dorsolateral prefrontal cortex (DLPFC), which was associated with a decrease in cravings, and less frequently with a reduction of addiction severity.

Discussion and Conclusions

Direct comparisons between BAs and SUDs revealed discrepancies between behavioral and neurophysiological outcomes, but overall, common and distinctive characteristics underlying each disorder. The lack of complete overlap between BAs and SUDs suggests that investigating the cognitive and neurophysiological features of BAs to create individual NIBS protocols that target risk-factors associated specifically with BAs, might be more effective than transferring protocols from SUDs to BAs.

Scientific Significance

Individualizing NIBS protocols to target specific risk-factors associated with each BA might help to improve treatment interventions for BAs.

Key words

Behavioral addictions, substance use disorders, non-invasive brain stimulation, transcranial electrical stimulation, transcranial magnetic stimulation.

INTRODUCTION

In addiction research, attention has been generally centered on the study of substance use disorders (SUDs) while behavioral addictions (BAs) have been relatively neglected. In fact, many BAs are even excluded from formal clinical diagnosis frameworks [1] even though, particularly linked to technological advances in recent years, the relevance and severity of BAs (e.g. online gambling, internet gaming, social-networking disorders) has become more evident. There is an increasingly

urgent need for preventive and therapeutic strategies for BAs [2], but this requires a deeper understanding of underlying neurobiological and cognitive processes. Many have argued that at a causal level, BAs are closely related to SUDs, and if so, one might be able to translate interventions proven to be of value in SUDs to patients with BAs. Nonetheless, the debate about the mechanistic overlap between BAs and SUDs remains, as does the argument of whether some BAs should be classified within the SUDs clinical category [3,4].

Gambling Disorder (GD) is the most widely studied of the BAs [5], and it was the first to be included in the category Substance-Related and Addictive Disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [6]. Internet Gaming Disorder (IGD) seems to be following GD in this direction, being currently included in the appendix of the DSM-5. The decision that supported the inclusion of GD in the DSM-5 was based on the similarities shared with SUDs, which included symptomatology, heritability, and neuro-circuitry correlates [7]. However, studies are showing not only common features, but also cognitive and physiological differences between BAs and SUDs [8,9]. Therefore, one aim of the present study was to systematically review mechanistic substrates of BAs and SUDs, and identify similarities and differences across neurobiological and cognitive domains to recognize potential risk-factors specifically associated with BAs and those shared with SUDs.

Specifically, we chose to focus on insights that can be gathered from NIBS studies because it is an emergent procedure with certain advantages over other already established addiction-related treatment interventions. Some interventions used traditionally to treat addictive behaviors include pharmacology [10,11] and therapy [12,13], however NIBS could potentially supersede previous approaches due to its capability to modulate decision-making cognitive processes [14], adjust

neurophysiological circuitry [15,16] and reduce addiction symptomatology [17] safely [18] with significantly fewer associated adverse events to those commonly related to pharmacological treatments [12,19].

The effects of NIBS have been increasingly investigated in SUDs [20,21,22,23] and to a lesser extent in BAs [24,25], in which studies generally focused in feasibility approaches that were frequently modelled according previous findings in SUDs. NIBS protocols could potentially be effective across SUDs and BAs if the targeted risk-factors are common in both types of disorders. However, if there are distinct behavioral or neurophysiologic underpinnings across SUDs and BAs, BAs-specific NIBS protocols would need to be developed to optimize their efficacy. Therefore, we hypothesized that investigating the degree of behavioral and neurophysiological overlap between BAs and SUDs will help establish more effective NIBS protocols for BAs.

Approaches to study behavioral addictions

The investigation of the particular mechanisms that underlie BAs can be approached from different perspectives. One common approach, frequently used in previous reviews and meta-analyses, is to perform indirect comparisons between BAs and SUDs contrasting studies that employed similar methodologies and outcome measures but examined both types of addiction separately [7,26]. Another approach consists of creating direct comparisons in research that included both BAs and SUDs in the same original study [27–29]. Direct comparisons between BAs and SUDs should provide stronger evidence about behavioral and neurobiological similarities and differences between both disorders and help to develop treatment strategies [30,31]. BAs could also be explored from another angle: as a separate entity, beyond its evaluation against, or within the context of SUDs [32]. This approach has not been widely used yet, but could reveal unique characteristics of BAs which could

better support the clinical recognition of BAs, and consequently help to develop specific clinical approaches where diagnosis and treatment protocols are constructed from the particular assessment of the condition´s unique characteristics and severity, rather than according to the overlap with SUDs [33].

Methodologies to study behavioral addictions: non-invasive brain stimulation

The two most commonly used forms of NIBS to date are: transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). Transcranial magnetic stimulation (TMS) is a NIBS technique that produces electrical pulses via electromagnetic induction. Single pulses are able to generate action potentials by depolarizing the neuronal membrane whereas repetitive pulses (rTMS) can modify cortical excitability [34]. The effects of TMS in the brain are usually assessed behaviorally by measuring cognitive task performance and physiologically using measures of cortical excitability such as motor evoked potentials (MEPs) [35]. tDCS is the most frequently used form of transcranial electric stimulation (tES). This technique produces an electric current that exerts a purely neuromodulatory effect, depending on polarity depolarizing or hyperpolarizing neurons, and thus increasing or decreasing cortical excitability, respectively [36]. The effects of tDCS in the brain are frequently assessed behaviorally by measuring cognitive task performance, and also physiologically measuring neuronal activity with brain imaging techniques such as electroencephalography (EEG), or measuring brain metabolite levels with magnetic resonance spectroscopy (MRS), among other methodologies.

NIBS has the potential to target specific brain areas, which allows the investigation of causal relations between brain activity and behavior through the manipulation of neuronal excitability. This capability might help improve the understanding of the physiological characteristics

underlying typical and atypical brain functioning, so NIBS could be used to identify potential biomarkers of specific disorders, such as BAs, but also to therapeutically restore dysfunctional brain networks. Nevertheless, the specific NIBS protocols that might be able to tackle particular symptoms in different addictive disorders are not established yet. Further research is necessary to better understand the physiological mechanisms of NIBS on brain circuitry and related induced behavior modulation effects.

Investigating the characteristics of behavioral addictions: evidence to create non-invasive brain stimulation protocols

Given that numerous studies comparing BAs and SUDs indirectly have already been published [1,7,31,37,38], this review will focus on studies that have produced direct comparisons between BAs and SUDs, and studies that investigated BAs independently of SUDs employing NIBS. Previous reviews investigated research findings from studies that applied NIBS to: SUDs [20,39–41], SUDs and food addiction (FA) [42,43], SUDs, FA and BAs [22,44], SUDs and BAs [23] and BAs including FA [45]. Sauvaget et al [45] conducted a systematic review in 2015 about the effects of tDCS in BAs and FA, but was only able to identify studies in FA, none in BAs. To our knowledge, there are not literature reviews yet exploring studies applying NIBS exclusively to BAs.

The decision to exclude food addiction (FA) from our search was based on the consideration that the concept and classification of FA is still under debate [46,47]. Previous research proposed positioning FA closer to BAs than to SUDs, based on relatively stronger indications of the existence of an addictive eating behavior underlying the disorder and the absence of agreement about an addictive substance-related effect [48]. However, there is not enough data supporting FA as purely a compulsion for eating in the absence of some form of substance-related influence, and it

has been well-documented that certain food ingredients seem to be more addictive than others [49–51], which implies that an addictive substance is involved in FA. Accordingly, recent research pursuing a clarification of the nature of FA [52] suggested that FA-related symptoms fit more appropriately with SUDs than with BAs [53,54]. For these reasons, in this review we did not merge FA and BAs to preserve our intention to collect findings on the investigation of NIBS in addictive behaviors that are not substance-related.

METHODOLOGY

Original studies published in English were identified in Web PubMed and Google Scholar. A manual search was used by one of the authors (EGV) to identify additional relevant research for example referenced in previously identified publications. Two different searches were conducted:

1. Research conducting direct comparisons between BAs and SUDs was identified by searching for the following key terms: “behavioral addiction” OR “gambling” OR “internet” OR “gaming” OR “social networking” OR “sex” OR “shopping” OR “buying” AND “substance” OR “dependence” OR “alcohol” OR “drink” OR “smoking” OR “tobacco” OR “cocaine” OR “heroin” OR “cannabis” OR “marijuana” OR “methamphetamine” OR “ecstasy”. Inclusion criteria involved full text articles in humans published from 2009-2019 using behavioral and/or neurophysiological measures in clinical groups to compare directly in the same study any of the BAs and SUDs listed above.

2. Research applying NIBS techniques in BAs was identified by searching for the following key terms: “non-invasive brain stimulation” OR “transcranial stimulation” OR “brain stimulation” OR “transcranial magnetic stimulation” OR “TMS” OR “rTMS” OR “electrical stimulation” OR “tDCS” OR “tACS” OR “tRNS” AND “behavioral addiction” OR “gambling” OR “internet” OR “gaming” OR “social networking” OR “sex” OR “shopping” OR “buying”. Inclusion criteria involved full text articles in humans that have employed NIBS in population affected by BAs.

Selection

Studies were first screened for title coincidences with key terms. To be considered for the review, both categories needed to be present in the title in search #1: BAs and SUDs. Secondly, abstracts were reviewed to confirm inclusion criteria, and finally the full article was reviewed. Exclusion criteria for search #1 included studies in which the main focus was to investigate the co-occurrence of BAs and SUDs, studies that included participant groups that were not BAs or SUDs, studies that only included self-report measures and review studies. Exclusion criteria for search #2 included studies in non-clinical population and review studies. A schematic view of the selection procedure is presented in Figure 1. The studies that met the inclusion criteria for search #1 were reviewed to identify overlapping or distinctive features between the pertinent BAs and SUDs investigated. These findings were grouped under similarities or differences and sub-grouped according to the type of data reported in behavioral or neurophysiological domains. The studies protocols and results were summarized in Table 1. Furthermore, these studies were divided in three categories depending on whether the authors reported only similarities, only differences or similarities and differences between the BAs and SUDs in the behavioral or neurophysiological

domains and are displayed in Table 2. The studies that met the inclusion criteria for search #2 were reviewed and the protocols and results were summarized and grouped according to the NIBS technique employed to investigate BAs: TMS studies are exposed in Table 3 and tDCS studies in Table 4.

RESULTS

After the selection process, 25 studies met the inclusion criteria in search #1. These studies focused on gambling and internet use disorder as BAs, and included cocaine, alcohol and tobacco addictions as SUDs. In search #2 we identified 10 studies that met the inclusion criteria including 9 studies on GD and 1 on IGD. These results are summarized in Tables 1-4.

Direct comparisons between behavioral addictions and substance use disorders

Traditionally, treatment models developed from SUDs research have been applied to BAs, however it is important to investigate whether the similarities and differences between both types of addiction systematically support the transfer of treatment methodologies and protocols between SUDs and BAs [31]. Different neurophysiological and cognitive mechanisms underlying BAs and SUDs would indicate the need to create specific condition-related treatment approaches, whereas common findings would indicate the existence of overlapping addiction-related risk-factors, and therefore BAs and SUDs could potentially share treatment protocols [26]. In order to provide a general overview of the literature findings in this review, a summary of the number of studies that reported to find only similarities, only differences or both similarities and differences between BAs and SUDs direct comparisons in the behavioral and neurophysiological domains is presented in Table 2.

Similarities between behavioral addictions and substance use disorders

Behavioral findings

The most prominent common behavioral result observed across studies directly comparing BAs and SUDs is increased impulsivity levels compared to healthy controls (HC). Higher impulsivity relative to HC has been reported by Lawrence et al [55] and Romanczuk-Seiferth et al [56] when investigating gambling disorder (GD) and alcohol use disorder (AUD); by Albein-Urios et al [57], Contreras-Rodriguez et al [29] and Yip et al [58] in cocaine use disorder (CUD) and GD; and by Son et al [28], Choi et al [59], Park et al [60] and Yoon et al [61] in internet gaming disorder (IGD) and AUD . Decreased Stroop-response inhibition abilities were identified in CUD and GD compared to HC [57], although de Ruiter et al [62] found similar inhibitory abilities between GD, smokers and HC. Goudriaan et al [63] found no differences in cue reactivity performance between GD, smokers and HC, neither Worhunsky et al [64] in slot-machine performance between GD, CUD and HC. Higher risk-taking behavior has also been associated with GD and AUD relative to HC [55]. Moreover, Kober et al [65] compared cravings between CUD and GD revealing that an increase of craving specifically matching the triggering stimulus, as well as a gender interaction, were present in both types of addiction. Verdejo-Garcia et al [66] and Torres et al [67] showed that CUD, GD and HC performance did not differ in specific measures of cognitive flexibility such as percentage of correct responses [66], or specific blocks of decision making [67] using a probabilistic reversal learning task. In addition, Vanes et al [68] showed that contingency learning capacity did not differ between GD and AUD, nor behavioural measures of reward processing in a monetary incentive task [56]. Other behavioral measures showing strong similarities between BAs and SUDs and contrasting with HC were neuroticism, agreeableness and conscientiousness [8], and loss aversion according to

Genauck et al [69], while de Ruiter et al [70] showed similar levels of planning abilities across smokers, GD and HC.

Neurophysiological findings

Direct comparisons between CUD and GD individuals revealed a number of neurophysiological similarities in relation to HC: Yip et al [58] found that impulsivity traits correlated negatively with grey matter structural alterations in bilateral insula, amygdala, hippocampal complex and parahippocampal gyri. Goudriaan et al [63] found no differences in brain activation during non-addiction related cues between smokers, GD and HC. Kober et al [65] showed that increased activity in dorsomedial prefrontal cortex (dmPFC) and dorsal anterior cingulate cortex (dACC) was present in both types of addiction when cravings were induced and Ren et al [71] showed that stronger brain activation matching the addiction-related triggering cues was present in GD and CUD, and that both groups contrasted with HC in relation to non-addiction related cues. Furthermore, Contreras-Rodríguez et al [29] found increased local connectivity in the orbitofrontal cortex (OFC) and amygdala, between OFC and dmPFC and striatum and between amygdala and insula as well as similar increased anticorrelation between amygdala and cerebellum overlapped between CUD and GD and contrasted with HC. Yip et al [72] showed that reduced secondary fiber orientation in the reward processing-related striatal and parietal-occipital regions was also a common characteristic of both CUD and GD. Worhunsky et al [9,64] also investigated these two populations which showed similar activity in the right-lateralised fronto-parietal network with higher engagement in coordinated systems of sustain control [9], increased activity in ventral striatum, insula and medial prefrontal cortex (mPFC) during reward anticipation, and distinct medial frontal or striatal responses following near-miss outcomes compared with HC [64]. Romanczuk-Seiferth et al [56] showed that successful loss avoidance was associated with reduced activity in ventral striatum in

AUD and GD compared with HC, and also to reduced mPFC activity in GD compared with HC. Verdejo-Garcia et al [66] revealed that cognitive shifting was associated with a decreased activation of right vlPFC in CUD and GD compared with HC. In addition, electroencephalography (EEG) outcomes for response to feedback during reversal learning did not differ between CUD and GD or HC according to Torres et al [67]. GD was also compared directly with smokers and HC by de Ruiter et al [62,70] showing that GD and smokers presented decreased activation in anterior cingulate cortex (ACC) during failed inhibition [62] and similar hypoactivation of dmPFC during inhibitory control compared to HC [70,62]. The studies by Han et al [27], Yoon et al [61], Kim et al [73] and Ge et al [74] investigated IGD and showed that cortical volume did not differ between IGD and AUD [61], and that IGD and AUD individuals showed increased functional connectivity between DLPFC, cingulate gyrus, and cerebellum and decreased functional connectivity between the DLPFC and the OFC [27] as well as increased regional homogeneity (ReHO) in posterior cingulate cortex (PCC) compared to HC [73]. IGD and nicotine dependent (ND) individuals shared decreased resting state functional connectivity (rsFC) in the right insula and left inferior frontal gyrus (IFG) with the DLPFC compared to HC, suggesting that both BAs and SUDs might have similar neural inhibitory mechanisms regulating craving and impulsivity [74].

Differences between behavioral addictions and substance use disorders

Behavioral findings

A direct comparison between GD, AUD and HC by Choi et al [59] showed that compulsivity measures were higher in GD compared with AUD, IGD and HC, whereas impulsivity was lower in GD compared with AUD and IGD, and also in smokers compared with IGD [74]. Goudriaan et al [63] found that subjective cravings were higher after a cue-reactivity task in GD compared with smokers. In addition, Lawrence et al [55] revealed that individuals with AUD showed working-

memory deficits and slower decision-making compared to GD and HC groups. Severe response perseveration had also been found in GD individuals compared with smokers by de Ruiter et al [70]; by Verdejo-Garcia et al [66] in CUD compared with GD and HC, showing that perseveration error rate was positively correlated with lifetime use, but in contrast, this correlation was negative in GD; and by Torres et al [67] in CUD compared with GD in specific decision-making outcomes. Vanes et al [68] showed that GD were faster in discrimination learning compared with AUD. Contreras-Rodriguez et al [29] found that the impulsivity-related trait of negative urgency was higher in CUD when compared to GD and HC. Furthermore, Yoon et al [61] found working-memory impairments in AUD compared with IGD and Albein-Urios et al [57] showed that decreased working-memory abilities were characteristic of CUD compared with GD, suggesting that working-memory deficits could be a possible effect of stimulant-induced neurotoxicity.

Neurophysiological findings

Direct comparisons between CUD and GD against HC revealed reduced insula and IFG as well as decreased grey matter volumes (GMVs) in ACC, OFC, medial frontal cortex and DLPFC, but only in CUD group compared to both GD and HC; with no differences in GMV between GD and HC, and no indication of shared GM structure between GD and CUD in the study by Yip et al [58]. CUD showed also higher global connectivity in areas of the ventral corticolimbic system, including the OFC, striatum, amygdala and thalamus, however no brain region showed increased global connectivity in GD compared to CUD or HC. Increased connectivity in the vmPFC was associated with higher impulsivity measures of negative urgency in CUD relative to GD. Addiction severity in CUD was associated with higher connectivity in striatum-thalamic-limbic areas and stronger anticorrelations of limbic-cerebellar areas, whereas there were no significant correlations between connectivity alterations and gambling severity in GD according to Contreras-Rodriguez et al [29].

Torres et al [67] revealed that reversal learning deficits were associated with abnormal activity in prefrontal and orbitofrontal areas in GD compared with CUD. Furthermore, Verdejo-Garcia et al [66] showed that the number of perseverative errors were correlated negatively with medial frontal gyrus activation in CUD but positively in GD. In addition, cognitive shifting was associated with reduced activation in the right dlPFC in CUD compared with GD and HC. Worhunsky et al [9,64] showed that GD presented a greater engagement of medial frontal cognitive-integration network and higher striato-amygdala engagement during decisions to quit chasing relative to continuing chasing losses. Using a simulated slot-machine game, CUD showed abnormal engagement of the striato-amygdala motivational network when losing compared to HC and during decision-making compared to GD [9]. GD showed higher striatal activity during anticipation of winning whereas CUD had greater deactivation during anticipation of losing outcomes, which indicated that GD presented higher positive possible-reward anticipation and CUD more negative certain-loss [64]. Genauck et al [69] compared GD with AUD individuals, with the latter showing altered loss-related activity in lateral prefrontal regions compared to altered amygdala-prefrontal functional connectivity in GD. AUD also presented reduced ventral striatal response during gain anticipation compared to HC, however there were no differences between GD and HC. In addition, loss anticipation was associated with a reduced activity in ventral striatum in AUD relative to HC, and with a higher activation of posterior striatum in GD compared to AUD and HC according to Romanczuk-Seiferth et al [56]. Van Holst et al [75] revealed that GMV were reduced in the left superior frontal cortex, left precentral cortex, right insula, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex in AUD compared to GD and HC. Compared against a sample of smokers there is also evidence by de Ruiter et al [70] that indicates a decreased activation in right ventrolateral PFC (rVLPFC) to reward and punishment in GD, whereas a decrease in

activation of rVLPFC was associated only with punishment in these smokers. Moreover, activity in DLPFC, posterior parietal cortex and hyperresponsiveness to monetary gains was increased in cigarette smokers compared to GD and HC. Goudriaan et al [63] found that cravings correlated positively with brain activation in left ventrolateral prefrontal cortex and left insula in GD, however comparing smokers with GD and HC, there were no differences in brain activity induced by smoking cues. Kober et al [65] showed specific differences in cues-related brain activity in CUD, with greater activation in occipital, temporal, frontal and hippocampal regions compared with GD and HC. Furthermore, Ren et al [71] revealed that activity in the insula, anterior cingulate cortex and prefrontal cortex could be associated with urge for cocaine, whereas activity in posterior and anterior cingulate cortex could be associated with gambling urges. According to Ge et al [74] internet gaming disorder (IGD) showed increased resting state functional connectivity (rsFC) in the left inferior temporal gyrus, right inferior orbitofrontal (OF) gyrus and decreased rsFC in in right middle occipital gyrus, supramarginal gyrus, and cuneus with DLPFC compared to smokers. IGD has been directly compared with AUD by Han et al [27] showing that AUD presented positive functional connectivity between DLPFC and temporal lobe and striatal areas, while IGD´s functional connectivity was negative for these areas. Yoon et al [61] showed that functional connectivity between left vmPFC and hippocampus/amygdala was stronger in IGD compared with AUD. Moreover, addiction severity correlated positively with larger hippocampus/amygdala volume in IGD compared with HC, and impaired working-memory correlated with smaller cerebellar function in AUD compared with HC. Kim et al [73] showed that reduced regional homogeneity (ReHo) in the superior temporal gyrus (STG) was specific of IGD and decreased ReHo in the ACC in AUD. Internet addiction severity was positively correlated with ReHo in the medial frontal cortex, precuneus posterior cingulate cortex (PCC), and left inferior temporal cortex

(ITC) in IGD. Impulsivity scores were negatively correlated with the left ITC in IGD. Electroencephalography (EEG) resting state results revealed different band patterns between IGD and AUD, in particular Son et al [28] showed lower beta power in IGD compared to AUD and HC, and higher absolute delta power in AUD compared to IGD and HC. Furthermore, Park et al [60] identified that IGD showed greater gamma coherence compared with AUD and HC, whereas AUD showed increased theta band compared with HC. These results suggested that different EEG neural connectivity could potentially be used as biological markers for each type of disorder.

Non-invasive brain stimulation in behavioral addictions

Two NIBS techniques have been applied to BAs: rTMS and tDCS. Studies employing rTMS in GD (see Table 3) [76,77,17,78,24,79] targeted the left primary motor cortex (Chowdhury et al [78]) and found a significant negative correlation between short-interval cortical inhibition (SICI - indicative of GABAergic activity) and stop signal task reaction time (SSRT), but no correlation between intra cortical facilitation (ICF - indicative of glutamatergic activity) and SSRT. As such, poor inhibitory control has been linked to weak GABAergic activity. At risk gamblers showed high impulsivity but did not differ on SSRT or SICI/ICF from HC [78]. Left dorsolateral prefrontal cortex (lDLPFC) rTMS applied with an H-coil, which induces currents that reach deeper into the brain, was investigated by Rosenberg et al [76] as a possible treatment for GD. They showed that the stimulation was initially associated with improvements in self-report measures including addiction severity and cravings, however gambling behaviors continued. Gay et al [24] targeted also lDLPFC with a conventional 8-shaped coil inducing current primarily in the cortex, which significantly decreased cue-induced craving compared to sham. Moreover, a recent case report by Pettorruso et al [79] showed that high frequency rTMS over lDPFC was associated with a decrease in dopamine transporter (DAT) availability in striatal regions and a cessation of gambling cravings and

gambling behavior. Sauvaget et al [17] showed that right DLPFC (rDLPFC) stimulation led to a significant decrease in gambling urge in both real stimulation and sham. Zack et al [77] showed that rTMS targeting mPFC reduced post-game increases in desire to gamble and cTBS on rDLPFC reduced amphetamine-like effects, decreased diastolic blood pressure and decreased symptoms of behavioral addiction but not impulsive choice.

Studies applying tDCS (see Table 4) [80,81,82,25] in GD and using a montage designed to target anodal rDLPFC (Soyata et al [80]) found that stimulation enhanced decision making and cognitive flexibility, and in addition Dickler et al [81] reported that active stimulation likely increases GABA levels compared to sham, whilst also showing positive correlations between metabolite levels in stimulation and risk-taking, impulsivity and craving levels. Martinotti et al [82] revealed that tDCS with a montage designed to target bilateral DLPFC was associated with significantly improved psychiatric symptomatology, gambling severity and craving levels as well as with a stop in gambling behaviors that lasted for up to 6 months after the intervention in a case study. tDCS has also been used to investigate online gaming by Lee et al [25], and results showed that a lDLPFC stimulation montage was associated with increases in self-control that correlated with decreases in addiction severity, time spent on games and changes in regional cerebral glucose metabolism in the DLPFC.

DISCUSSION

In this review, we examined results from studies that directly compared BAs and SUDs and studies that applied NIBS in BAs with the aim to contribute to the development of NIBS protocols for BAs. In our review, 22 out of 25 studies comparing directly BAs and SUDs found both similarities and differences between the disorders. Investigating the overlap between BAs and SUDs might

help improve the understanding of the unique characteristics of BAs and thus inform the development of treatment protocols specific for each disorder.

Not surprisingly, we found common behavioral and neurophysiologic features across BAs and SUDs, most notably impulsivity traits and brain structural and functional alterations affecting bilateral insula, amygdala, hippocampi and parahippocampal gyri; as well as dorsomedial prefrontal cortex (dmPFC) and dorsal anterior cingulate cortex (dACC) specifically during craving. On the other hand, we also found differences between BAs and SUDs, notably BAs specifically showed different patterns of striatal activity, in particular, greater striatal activation was linked to BAs during positive reward anticipation, however, during negative loss anticipation in SUDs. Moreover, striatal-amygdala interactions were greater during decisions to quit chasing losses in BAs but linked to losses in SUDs. BAs showed also lower activation of right ventrolateral prefrontal cortex (rVLPFC) during reward and punishment, and particularly, left (lVLPFC) activation correlated with cravings in BAs, however in SUDs lower activity of rVLPFC was linked only to punishment and did not correlate with cravings. Furthermore, altered amygdala-prefrontal functional connectivity was observed in BAs, with negative functional connectivity between DLPFC, temporal lobe and striatal areas, whilst in SUDs functional connectivity was positive in these areas. In addition, BAs showed lower levels of the impulsivity trait of negative urgency compared to SUDs. Together, these results suggest that the altered reward network in behavioral addicted populations might be linked especially to higher sensitivity to positive reinforcement. However, most of the studies reviewed comparing BAs and SUDs focused in GD, and additional studies considering other BAs will help to better understand the specific neurophysiological mechanisms underlying each disorder.

A closer examination of the similarities and differences found between BAs and SUDs revealed that in our results there was certain variability when splitting findings by behavioral and neurophysiological data (see Table 2): a greater number of studies reported finding similarities rather than differences between BAs and SUDs based on behavioral data (10 studies found similarities and differences, 11 studies reported only similarities and 1 reported only differences between BAs and SUDs). However, neurophysiological evidence showed that across studies numerous differences and similarities existed between different types of BAs and SUDs (15 studies found both similarities and differences, 2 studies reported only similarities and 4 studies reported only differences between BAs and SUDs). The 4 studies that reported only differences between BAs and SUDs in the neurophysiological domain compared GD or IGD against AUD, and the other study that reported only differences in the behavioral domain compared GD with smokers. This might suggest that these SUDs, particularly AUD, present more distinctive physiological characteristics when compared to BAs than other SUDs such as CUD. Furthermore, from the 18 studies that used both behavioral and neurophysiological outcome measures, the findings were consistent between both behavioral and neurophysiological domains in 8 studies (6 studies reported similarities and differences in both domains and 2 studies found only similarities in both domains). In contrast, there were discrepancies between the domains in 10 studies (7 studies reported similarities and differences between BAs and SUDs in the neurophysiological domain, however from those, 6 studies found only similarities, and 1 study only differences in the behavioral domain. Also, 3 studies reported only differences in the neurophysiological domain and only similarities in the behavioral domain). This indicates that the use of both types of outcome measures might help to detect possible markers associated with each type of addiction that could

remain uncovered when using only behavioral measures. Nonetheless, there are many factors in the protocols that should be considered, such as outcomes of interest and variables used to establish stronger conclusions about the findings associated with each type of addiction.

We summarized protocols and results from 10 studies using NIBS to investigate BAs. NIBS techniques included 6 studies using rTMS, and 4 tDCS; and for the BAs types assessed 9 studies were on GD and 1 on IGD. The most common stimulation target was the DLPFC, but the laterality varied across studies. Results showed neurophysiological changes in GABA levels, glucose metabolism, dopamine transporter availability and also addiction severity and behavioral modulation. In particular, cravings were successfully reduced across different studies, which aligns with NIBS findings in SUDs [20]. The correspondence between results revealing a decrease in cravings in studies that applied NIBS to both BAs and SUDs is congruent with the overlap in cognitive and neurophysiological features involving cravings outcomes between CUD and GD reported by Kober et al [65] and Ren et al [71], however the other study that focused in comparing cravings between BAs and SUDs by Gourdiaan et al [63] found also different craving related brain activation patterns between smokers and GD. Additional research investigating specific BAs features, such as cravings – which constitutes an important target in treatment interventions, will help to custom treatment protocols to each type of addiction. A reduction of cravings was reported in several studies using different TMS and tDCS protocols in BAs, however behavioral modulation effects were less frequent. The study by Rosenberg et al [76] in 2013 was the first to investigate the effects of TMS as a possible intervention for GD, and with that aim they applied 15 stimulation sessions, and although measures including cravings and addiction severity initially improved, they found no behavior changes. The other three studies that applied a higher number of stimulation sessions, found not only a decrease of cravings, but also a reduction of addiction severity and time

spent on games (Lee et al 2018 [25] applied 12 tDCS sessions in IGD) and even a cease of addictive behaviors (Martinotti et al 2018 [82] applied 38 tDCS sessions in GD and Pettorruso et al 2019 [79] applied 20 rTMS sessions in GD). These findings suggest that increasing the number of stimulation sessions might be a factor that could help to strengthen the effects of NIBS over the underlying mechanism regulating addictive behaviors, and therefore improve NIBS effectiveness as a treatment intervention for BAs. The DLPFC was the most employed targeted area, however investigating the effects of NIBS in additional brain areas involved in the reward system, such as mPFC, and examining brain resting state and connectivity networks activation might provide new information about the potential effects of NIBS as an effective promising treatment intervention for BAs. Moreover, employing reward/loss tasks addiction-specific that measure brain activation during anticipation, decision-making and reward/loss outcome is fundamental to effectively capture in more realistic scenarios the particular characteristics underlying each addictive behavior. As reviewed here, NIBS techniques are beginning to be explored in BAs and show some promising results. However, given our findings, neuromodulation protocols ought to consider the similarities as well as the differences between BAs and SUDs in order to be optimized to be most effective in BAs. In the following sections we offer some considerations that seem important to consider in such efforts.

Comorbidities

Comorbidity between BAs and SUDs and between addictions more broadly and other psychiatric disorders is high [83,84]. However, treatment protocols have not always been adapted to target specific comorbidities. The assessment of the interaction between comorbidities and between different types of treatments should be addressed to develop compatible protocols to treat diverse individual situations effectively [85]. In the field of NIBS, research has started to consider comorbid disorders

such as addiction and major depressive disorder, to examine the feasibility of the procedures [86] and to investigate the application of different protocols in the same person to target different symptoms: for example, tDCS stimulation over the left DLPFC to target cravings and over the right DLPFC to target emotional impulses [82]. More research is clearly needed to understand the interactive effects of several NIBS protocols applied to each specific disorder, and interactions between NIBS and other commonly used treatments such as pharmacology or psychotherapy.

Non-invasive brain stimulation methodologies

The biological differences that exist between individuals constitute a major factor that increases the variability of NIBS effects across studies, and its consideration represents a challenge in the development of new technologies designed to specifically modulate the selected brain targets with a particular purpose. Beyond considering individual differences, understanding the interactive effects of the electric field with different types of neurons and different types of tissues in the brain will help to identify which is the location where the electric current is highest during stimulation [87], and therefore will help optimize TMS coil positioning or tES electrode montages to optimally engage the desired stimulation target. To this end, computational models that provide biophysical metrics to be compared with behavioral and physiological outcomes, can be extremely valuable and could increase the efficacy and reproducibility of the results [88]. Future NIBS studies will benefit from including neuronavigation and modelling approaches to document brain target engagement and improve stimulation accuracy. In addition, by including not only behavioral outcomes but also neurophysiological measures such as EEG or magnetic resonance imaging (MRI), future NIBS studies can measure the physiological effects of NIBS in the selected brain target and relate these to the behavioral consequences of the intervention – thus providing true causal insights between brain activity and behavior. Most NIBS studies conducted to date focused

on proof-of-concept approaches with small samples sizes and lack of strong control conditions. Larger sample size studies, including randomized double blind sham conditions, are needed to truly explore the utility of NIBS in BAs.

Could non-invasive brain stimulation interventions cause addiction?

The dopamine replacement therapy treatment prescribed to Parkinson´s disease (PD) patients has been associated with the development of addictions [89]. This adverse effect of the medication underlines the biological component of addiction and also highlights how medical treatments that interact with the underlying neurophysiology, notably brain reward systems, may potentiate vulnerability to addiction. Pharmacological treatments are evaluated for possible adverse effects and behavioral change consequences, and research investigating the development of other interventions such as NIBS should also consider such factors. Previous studies have demonstrated the neurophysiological effects of NIBS [36,90,91] and its potential to modulate neural activity in dysfunctional brain networks [92], induce the release of endogenous dopamine [93] and to impact upon behavioral outcomes [94]. Neuromodulation techniques are brain state dependent and their effects can change due to pharmacological interactions [95]. Potential clinical procedures utilizing NIBS are still being developed and it is essential to be cautious and to carefully assess each trial protocol taking into account comorbid disorders, treatment combination interactions and the neurophysiological effects that might lead to specific behavioral modulation. As with other treatments which affect factors associated with addiction (e.g. dopamine, reward processing, impulsivity/decision making), NIBS based treatment and research needs to remain mindful of potentially negative consequences for the patients and study participants.

To summarize, further research employing modelling approaches to improve stimulation accuracy, that include behavioral and neurophysiological measurements, combining NIBS with neuroimaging techniques, include double-blind randomized sham conditions, and consider comorbid disorders, other treatment interactions and long-term effects, will contribute with the development of more precise treatment NIBS protocols. Furthermore, within BAs and SUDs, the development of individual protocols for each type of BAs and each type of SUDs will be more beneficial to successfully improve addiction treatment outcomes. In conclusion, it is important to acknowledge both the similarities and differences highlighted in BAs and SUDs research, so that whilst BAs cannot be effectively managed using simple mapping of SUDs findings to BAs, there are likely to be aspects of overlap that are worth further exploration – and that understandings of BAs and SUDs, and of NIBS based and other treatments in both fields, are likely to provide a rich dialogue from which individualized recovery and management can emerge.

Acknowledgements

This work was supported by GambleAware, Registered in London, England No 4384279, Charity No 1093910, operating grant N101706 to E.G.V.

Declarations of interest:

A.P.L. serves on the scientific advisory boards for Starlab Neuroscience, Neuroelectrics, Neosync, NovaVision, and Cognito; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. The other authors declare no competing interests.

REFERENCES

1. Grant JE, Potenza MN, Weinstein A, Gorelick DA. An Introduction to Behavioral Addictions. *Am J Drug Alcohol Abuse*. 2010;36(5):233-241. doi:110.3109/00952990.2010.491884

2. Gainsbury SM. Online Gambling Addiction : the Relationship Between Internet Gambling and Disordered Gambling. *Curr Addict Rep*. 2015;2:185-193. doi:10.1007/s40429-015-0057-8

3. Potenza MN. Should addictive disorders include non-substance- related conditions? *Addiction*. 2006;101:142-151.

4. M. Fauth-Bühlera, K. Manna and MNP. Pathological gambling: a review of the neurobiological evidence relevant for its classification as an addictive disorder. *Addict Biol*. 2017;22(4):885–897. doi:10.1017/adb.12378

5. Petry NM. Should the scope of addictive behaviors be broaderned to include pathological gambling. *Addiction*. 2006;101(1):152-160.

6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edit. Alrington, VA; 2013.

7. Clark L. Disordered gambling: The evolving concept of behavioral addiction. *Ann N Y Acad Sci*. 2014;1237(Addiction Reviews):46-61. doi:10.1111/nyas.12558

8. Zilberman N, Yadid G, Efrati Y, Neumark Y, Rassovsky Y. Personality profiles of substance and behavioral addictions. *Addict Behav*. 2018;82:174-181. doi:10.1016/j.addbeh.2018.03.007

9. Worhunsky PD, Potenza MN, Rogers RD. Alterations in functional brain networks associated with loss-chasing in gambling disorder and cocaine-use disorder. *Drug Alcohol Depend*. 2017;178:363-371. doi:10.1016/j.drugalcdep.2017.05.025

10. Heilig M, Goldman D, Berrettini W, O'Brien CP. Pharmacogenetic approaches to the treatment of alcohol addiction. *Nat Rev Neurosci*. 2011;12(11):670-684. doi:10.1038/nrn3110

11. Wimk van den Brink. Evidence-Based Pharmacological Treatment of Substance Use Disorders and Pathological Gambling. *Curr Drug Abuse Rev*. 2012;5:3-31. doi:10.2174/1874473711205010003

12. Yip SW, Potenza MN. Treatment of Gambling Disorders. *Curr Treat Options Psychiatry*. 2014;1(2):189-203. doi:10.1007/s40501-014-0014-5

13. Du YS, Jiang W, Vance A. Longer term effect of randomized, controlled group cognitive behavioural therapy for Internet addiction in adolescent students in Shanghai. *Aust N Z J Psychiatry*. 2010;44(2):129-134. doi:10.3109/00048670903282725

14. Ouellet J, McGirr A, Van den Eynde F, Jollant F, Lepage M, Berlim MT. Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): A randomized and sham-controlled exploratory study. *J Psychiatr Res*. 2015;69:27-34. doi:10.1016/j.jpsychires.2015.07.018

15. Clark VP, Coffman BA, Trumbo MC, Gasparovic C. Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: A1H magnetic resonance spectroscopy study. *Neurosci Lett*. 2011;500(1):67-71. doi:10.1016/j.neulet.2011.05.244

16. Hone-Blanchet A, Edden RA, Fecteau S. Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites. *Biol Psychiatry*. 2016;80(6):432-438. doi:10.1016/j.biopsych.2015.11.008

17. Sauvaget A, Bulteau S, Guilleux A, et al. Both active and sham low-frequency rTMS single sessions over the right DLPFC decrease cue-induced cravings among pathological gamblers seeking treatment: A randomized, double-blind, sham-controlled crossover trial. *J Behav Addict*. 2018:126-136. doi:10.1556/2006.7.2018.14

18. Bikson M, Grossman P, Thomas C, et al. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimul*. 2016;9(5):641-661. doi:10.1016/j.brs.2016.06.004

19. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med*. 2015;9(5):358-367. doi:10.1097/ADM.0000000000000166

20. Coles AS, Kozak K, George TP. A review of brain stimulation methods to treat substance use disorders. *Am J Addict*. 2018;27(2):71-91. doi:10.1111/ajad.12674

21. Rachid F. Neurostimulation techniques in the treatment of cocaine dependence: A review of the literature. *Addict Behav*. 2018;76:145-155. doi:10.1016/j.addbeh.2017.08.004

22. Schluter RS, Daams JG, van Holst RJ, Goudriaan AE. Effects of Non-invasive Neuromodulation on Executive and Other Cognitive Functions in Addictive Disorders: A Systematic Review. *Front Neurosci*. 2018;12(September). doi:10.3389/fnins.2018.00642

23. Trojak B, Sauvaget A, Fecteau S, et al. Outcome of Non-Invasive Brain Stimulation in

Substance Use Disorders: A Review of Randomized Sham-Controlled Clinical Trials. *J Neuropsychiatry Clin Neurosci*. 2017;29(2):105-118. doi:10.1176/appi.neuropsych.16080147

24. Gay A, Boutet C, Sigaud T, et al. A single session of repetitive transcranial magnetic stimulation of the prefrontal cortex reduces cue-induced craving in patients with gambling disorder. *Eur Psychiatry*. 2017;41:68-74. doi:10.1016/j.eurpsy.2016.11.001

25. Lee SH, Im JJ, Oh JK, et al. Transcranial direct current stimulation for online gamers: A prospective single-arm feasibility study. *J Behav Addict*. 2018;7(4):1166-1170. doi:10.1556/2006.7.2018.107

26. Leeman RF, Potenza MN. Similarities and differences between pathological gambling and substance use disorders: A focus on impulsivity and compulsivity. *Psychopharmacology (Berl)*. 2012;219(2):469-490. doi:10.1007/s00213-011-2550-7

27. Han JW, Han DH, Bolo N, Kim BA, Kim BN, Renshaw PF. Differences in functional connectivity between alcohol dependence and internet gaming disorder. *Addict Behav*. 2015;41:12-19. doi:10.1016/j.addbeh.2014.09.006

28. Son KL, Choi JS, Lee J, et al. Neurophysiological features of Internet gaming disorder and alcohol use disorder: A resting-state EEG study. *Transl Psychiatry*. 2015;5:e628. doi:10.1038/tp.2015.124

29. Contreras-Rodríguez O, Albein-Urios N, Vilar-López R, et al. Increased corticolimbic connectivity in cocaine dependence versus pathological gambling is associated with drug severity and emotion-related impulsivity. *Addict Biol*. 2016;21(3):709-718. doi:10.1111/adb.12242

30. Potenza MN. The neurobiology of pathological gambling and drug addiction: An overview and new findings. In: *Philosophical Transactions of the Royal Society B: Biological Sciences*. Vol 363. ; 2008:3181-3189. doi:10.1098/rstb.2008.0100

31. Potenza MN. Clinical neuropsychiatric considerations regarding nonsubstance or behavioral addictions. *Dialogues Clin Neurosci*. 2017;19(3):281-291.

32. Park M, Choi J-S, Park SM, et al. Dysfunctional information processing during an auditory event-related potential task in individuals with Internet gaming disorder. *Transl Psychiatry*. 2016;6:e721. doi:10.1038/tp.2015.215

33. Yuan K, Yu D, Cai C, et al. Frontostriatal circuits, resting state functional connectivity and cognitive control in internet gaming disorder. *Addict Biol*. 2017;22(3):813-822. doi:10.1111/adb.12348

34. Kobayashi M, Pascual-leone A. Reviews Transcranial magnetic stimulation in neurology. *LANCET Neurol*. 2003;2:145-156.

35. Buss S, Fried PJ, Pascual-Leone A. Therapeutic Noninvasive Brain Stimulation in Alzheimer's Disease and Related Dementias. *Curr Opin Neurol*. 2019. doi:10.1097/WCO.0000000000000669

36. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527(3):633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

37. Potenza MN. Should addictive disorders include non-substance-related conditions? *Addiction*. 2006;101(SUPPL. 1):142-151. doi:10.1111/j.1360-0443.2006.01591

38. Leeman R, Potenza MN. Targeted Review of the Neurobiology and Genetics of Behavioral Addictions: An Emerging Area of Research. *Can J Psychiatry*. 2013;58(5):260-273.

39. Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. *Neurosci Biobehav Rev*. 2010;34:559-574. doi:10.1016/j.neubiorev.2009.11.006

40. Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. *Ann N Y Acad Sci*. 2014;1327(1):79-93. doi:10.1111/nyas.12479

41. Spagnolo PA, Goldman D. Neuromodulation interventions for addictive disorders: Challenges, promise, and roadmap for future research. *Brain*. 2017;140(5):1183-1203. doi:10.1093/brain/aww284

42. Jansen JM, Daams JG, Koeter MWJ, Veltman DJ, Van Den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: A meta-analysis. *Neurosci Biobehav Rev*. 2013;37(10):2472-2480. doi:10.1016/j.neubiorev.2013.07.009

43. Grall-Bronnec M, Sauvaget A. The use of repetitive transcranial magnetic stimulation for modulating craving and addictive behaviours: A critical literature review of efficacy, technical and methodological considerations. *Neurosci Biobehav Rev*. 2014;47:592-613. doi:10.1016/j.neubiorev.2014.10.013

44. Naish KR, Vedelago L, MacKillop J, Amlung M. Effects of neuromodulation on cognitive performance in individuals exhibiting addictive behaviour: A systematic review protocol. *Syst Rev*. 2018;7(1):90. doi:10.1186/s13643-018-0749-y

45. Sauvaget A, Trojak B, Bulteau S, et al. Transcranial direct current stimulation (tDCS) in

behavioral and food addiction: A systematic review of efficacy, technical, and methodological issues. *Front Neurosci*. 2015;9:349. doi:10.3389/fnins.2015.00349

46. Finlayson G. Food addiction and obesity : unnecessary medicalization of hedonic overeating. *Nat Rev Endocrinol*. 2017;13:493-498. doi:10.1038/nrendo.2017.61

47. Ziauddeen H, Fletcher PC. Is food addiction a valid and useful concept? *Obes Rev*. 2013;14(1):19-28. doi:10.1111/j.1467-789X.2012.01046.x

48. Hebebranda J, Albayraka Ö, Adanb R, et al. 'Eating addiction', rather than 'food addiction', better captures addictive-like eating behavior. *Neurosci Biobehav Rev*. 2014;47:295-306. doi:10.1016/j.neubiorev.2014.08.016

49. Gearhardt AN, Grilo CM, Dileone RJ, Brownell KD, Potenza MN. Can Food be Addictive? Public Health and Policy Implications. 2011;106(7):1208-1212. doi:10.1111/j.1360-0443.2010.03301.x.

50. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS One*. 2015;10(2):1-18. doi:10.1371/journal.pone.0117959

51. Moran A, Musicus A, Soo J, Gearhardt AN, Gollust SE, Roberto CA. Believing that certain foods are addictive is associated with support for obesity-related public policies. *Prev Med (Baltim)*. 2016;90:39-46. doi:10.1016/j.ypmed.2016.06.018

52. Hone-Blanchet A, Fecteau S. Overlap of food addiction and substance use disorders definitions: Analysis of animal and human studies. *Neuropharmacology*. 2014;85:81-90. doi:10.1016/j.neuropharm.2014.05.019

53. Gordon EL, Ariel-Donges AH, Bauman V, Merlo LJ. What is the evidence for "food addiction?" A systematic review. *Nutrients*. 2018;10(4):1-30. doi:10.3390/nu10040477

54. Schulte EM, Potenza MN, Gearhardt AN. A commentary on the "eating addiction" versus "food addiction" perspectives on addictive-like food consumption. *Appetite*. 2017;115:9-15. doi:10.1016/j.appet.2016.10.033

55. Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. Problem gamblers share deficits in impulsive decision-making with alcohol-dependent individuals. *Addiction*. 2009;104(6):1006-1015. doi:10.1111/j.1360-0443.2009.02533.x

56. Romanczuk-Seiferth N, Koehler S, Dreesen C, Wüstenberg T, Heinz A. Pathological gambling and alcohol dependence: neural disturbances in reward and loss avoidance processing. *Addict Biol*. 2015;20(3):557-569. doi:10.1111/adb.12144

57. Albein-Urios N, Martinez-González JM, Lozano Ó, Clark L, Verdejo-García A. Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: implications for cocaine-induced neurotoxicity. *Drug Alcohol Depend*. 2012;126(1-2):1-6.

58. Yip SW, Worhunsky PD, Xu J, et al. Gray-matter relationships to diagnostic and transdiagnostic features of drug and behavioral addictions. *Addict Biol*. 2018;23(1):394-402. doi:10.1111/adb.12492

59. Choi S-W, Kim H, Kim G-Y, et al. Similarities and differences among Internet gaming disorder, gambling disorder and alcohol use disorder: A focus on impulsivity and compulsivity. *J Behav Addict*. 2014;3(4):246-253. doi:10.1556/jba.3.2014.4.6

60. Park SM, Lee JY, Kim YJ, et al. Neural connectivity in Internet gaming disorder and alcohol use disorder: A resting-state EEG coherence study. *Sci Rep*. 2017;7(1):1-12. doi:10.1038/s41598-017-01419-7

61. Yoon EJ, Choi JS, Kim H, et al. Altered hippocampal volume and functional connectivity in males with Internet gaming disorder comparing to those with alcohol use disorder. *Sci Rep*. 2017;7(1):1-12. doi:10.1038/s41598-017-06057-7

62. De Ruiter MB, Oosterlaan J, Veltman DJ, Van Den Brink W, Goudriaan AE. Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug Alcohol Depend*. 2012;121(1-2):81-89. doi:10.1016/j.drugalcdep.2011.08.010

63. Goudriaan AE, De Ruiter MB, Van Den Brink W, Oosterlaan J, Veltman DJ. Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: An fMRI study. *Addict Biol*. 2010;15(4):491-503. doi:10.1111/j.1369-1600.2010.00242.x

64. Worhunsky PD, Malison RT, Rogers RD, Potenza MN. Altered neural correlates of reward and loss processing during simulated slot-machine fMRI in pathological gambling and cocaine dependence. *Drug Alcohol Depend*. 2014;145:77-86. doi:10.1016/j.drugalcdep.2014.09.013

65. Kober H, Lacadie CM, Wexler BE, Malison RT, Sinha R, Potenza MN. Brain Activity during Cocaine Craving and Gambling Urges: An fMRI Study. *Neuropsychopharmacology*. 2016;41(2):628-637. doi:10.1038/npp.2015.193

66. Verdejo-garcia A, Clark L, Verdejo-roma J, et al. Neural substrates of cognitive flexibility

in cocaine and gambling addictions. *Br J psychiatry*. 2015;207:158-164. doi:10.1192/bjp.bp.114.152223

67. Torres A, Catena A, Cándido A, Maldonado A, Megías A, Perales JC. Cocaine dependent individuals and gamblers present different associative learning anomalies in feedback-driven decision making: A behavioral and ERP study. *Front Psychol*. 2013;4(MAR):1-14. doi:10.3389/fpsyg.2013.00122

68. Vanes LD, van Holst RJ, Jansen JM, van den Brink W, Oosterlaan J, Goudriaan AE. Contingency learning in alcohol dependence and pathological gambling: Learning and unlearning reward contingencies. *Alcohol Clin Exp Res*. 2014;38(6):1602-1610. doi:10.1111/acer.12393

69. Genauck A, Quester S, Wüstenberg T, Mörsen C, Heinz A, Romanczuk-Seiferth N. Reduced loss aversion in pathological gambling and alcohol dependence is associated with differential alterations in amygdala and prefrontal functioning. *Sci Rep*. 2017;7(1):16306. doi:10.1038/s41598-017-16433-y

70. Ruiter MB de, Veltman DJ, Goudriaan AE, Oosterlaan J, Sjoerds2 Z, Brink W van den. Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. *Neuropsychopharmacology*. 2009;34:1027-1038. doi:10.1038/npp.2008.175

71. Ren Y, Fang J, Lv J, et al. Assessing the Effects of Cocaine Dependence and Pathological Gambling Using Group-wise Sparse Representation of Natural Stimulus FMRI Data. *Brain Imaging Behav*. 2017;11(4):1179–1191. doi:10.1007/s11682-016-9596-4

72. Sarah W. Yip, Kristen P. Morie, Jiansong Xu, MD, R. Todd Constable, Robert T.

Malison, Kathleen M. Carroll and Marc N. Potenza M. Shared microstructural features of behavioral and substance addictions revealed in areas of crossing fibers. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;2(2):188–195. doi:10.1017/S0950268814002131

73. Kim H, Kim YK, Gwak AR, et al. Resting-state regional homogeneity as a biological marker for patients with Internet gaming disorder: A comparison with patients with alcohol use disorder and healthy controls. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2015;60:104-111. doi:10.1016/j.pnpbp.2015.02.004

74. Ge X, Sun Y, Han X, et al. Difference in the functional connectivity of the dorsolateral prefrontal cortex between smokers with nicotine dependence and individuals with internet gaming disorder. *BMC Neurosci*. 2017;18(1):54. doi:10.1186/s12868-017-0375-y

75. van Holst RJ, de Ruiter MB, van den Brink W, Veltman DJ, Goudriaan AE. A voxel-based morphometry study comparing problem gamblers, alcohol abusers, and healthy controls. *Drug Alcohol Depend*. 2012;124(1-2):142-148. doi:10.1016/j.drugalcdep.2011.12.025

76. Rosenberg O, Klein LD, Dannon PN. Deep transcranial magnetic stimulation for the treatment of pathological gambling. *Psychiatry Res*. 2013;206:111-113. doi:10.1016/j.psychres.2012.09.045

77. Zack M, Cho SS, Parlee J, et al. Effects of High Frequency Repeated Transcranial Magnetic Stimulation and Continuous Theta Burst Stimulation on Gambling Reinforcement, Delay Discounting, and Stroop Interference in Men with Pathological Gambling. *Brain Stimul*. 2016;9(6):867-875. doi:10.1016/j.brs.2016.06.003

78. Chowdhury NS, Livesey EJ, Blaszczynski A, Harris JA. Variations in response control

within at-risk gamblers and non-gambling controls explained by GABAergic inhibition in the motor cortex. *Cortex*. 2018;103:153-163. doi:10.1016/j.cortex.2018.03.004

79. Pettorruso M, Di Giuda D, Martinotti G, et al. Dopaminergic and clinical correlates of high-frequency repetitive transcranial magnetic stimulation in gambling addiction: a SPECT case study. *Addict Behav*. 2019;93(October 2018):246-249. doi:10.1016/j.addbeh.2019.02.013

80. Soyata AZ, Aksu S, Woods AJ, İşçen P, Saçar KT, Karamürsel S. Effect of transcranial direct current stimulation on decision making and cognitive flexibility in gambling disorder. *Eur Arch Psychiatry Clin Neurosci*. 2018:1-10. doi:10.1007/s00406-018-0948-5

81. Dickler M, Lenglos C, Renauld E, et al. Online effects of transcranial direct current stimulation on prefrontal metabolites in gambling disorder. *Neuropharmacology*. 2018;131:51-57. doi:10.1016/j.neuropharm.2017.12.002

82. Martinotti G, Chillemi E, Lupi M, Risio L De, Pettorruso M, Giannantonio M Di. Gambling disorder and bilateral transcranial direct current stimulation: A case report. *J Behav Addict*. 2018;7(3):834-837. doi:10.1556/2006.7.2018.85

83. Krawczyka N, Federa KA, Salonera B, Cruma RM, Kealhoferb M, Mojtabai R. The association of psychiatric comorbidity with treatment completion among clients admitted to substance use treatment programs in a U.S. national sample. *Drug Alcohol Depend*. 2017;1:175: 157–163. doi:10.1016/j.compmedimag.2015.12.001

84. Konkolÿ Thege B, Hodgins DC, Wild TC. Co-occurring substance-related and behavioral addiction problems: A person-centered, lay epidemiology approach. *J Behav Addict*. 2016;5(4):614-622. doi:10.1556/2006.5.2016.079

85. Dowling NA, Merkouris SS, Lorains FK. Interventions for comorbid problem gambling and psychiatric disorders: Advancing a developing field of research. *Addict Behav*. 2016;58:21-30. doi:10.1016/j.addbeh.2016.02.012

86. Dunlop K, Hanlon CA, Downar J. Noninvasive brain stimulation treatments for addiction and major depression. *Ann N Y Acad Sci*. 2017;1394(1):31-54. doi:10.1111/nyas.12985

87. Ruffini G, Wendling F, Merlet I, et al. Transcranial Current Brain Stimulation (tCS): Models and Technologies. *Trans NEURAL Syst Rehabil Eng*. 2013;21(3):333-345.

88. Miranda PC, Callejón-leblic MA, Salvador R, Ruffini G. ScienceDirect Realistic modeling of transcranial current stimulation : The electric field in the brain. *Curr Opin Biomed Eng*. 2018;8:20-27. doi:10.1016/j.cobme.2018.09.002

89. Antonini A, Cilia R. Behavioural Adverse Effects of Dopaminergic Treatments in Parkinson's Disease Incidence, Neurobiological Basis, Management and Prevention. *Drug Saf*. 2009;32(6):475-488.

90. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*. 1998;15(4):333-343.

91. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat Neurosci*. 2013;16(7):838–844. doi:10.2144/000114329

92. Fregni F, Pascual-Leone A. Technology Insight: Noninvasive brain stimulation in neurology - Perspectives on the therapeutic potential of rTMS and tDCS. *Nat Clin Pract*

Neurol. 2007;3(7):383-393. doi:10.1038/ncpneuro0530

93. Strafella AP, Toma´s P, Barrett J, Dagher A. Repetitive Transcranial Magnetic Stimulation of the Human Prefrontal Cortex Induces Dopamine Release in the Caudate Nucleus. *J Neurosci*. 2001;21(RC157):1-4. doi:]

94. Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing Risk-Taking Behavior by Modulating Activity in the Prefrontal Cortex: A Direct Current Stimulation Study. *J Neurosci*. 2007;27(46):12500 –12505. doi:10.1523/JNEUROSCI.3283-07.2007

95. Brittain J-S, Cagnan H. Recent Trends in the Use of Electrical Neuromodulation in Parkinson's Disease. *Curr Behav Neurosci Reports*. 2018;5(2):170-178. doi:10.1007/s40473-018-0154-9

TABLE 1

Summary of cognitive and neurophysiological findings in studies that directly compared behavioral addictions (BAs) and substance use disorders (SUDs).

Author	Sample	Outcomes of interest	Measures	Results
Albein-Urios et al. 2012 [57]	23 GD 29 CUD 20 HC	Cognitive performance, trait impulsivity, addiction severity, delay discounting, inhibition, working memory performance	UPPS-P trait impulsivity, Kirby delay discounting questionnaire, N-back task, Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (CWIT), Structured clinical interview (SCID-CV) diagnostic and statistical manual (DSM-IV)	CUD reported increased Negative Urgency and decreased working memory compared to GD. Delay- discounting rates were higher in GD. Positive Urgency and poorer Stroop inhibition was found in CUD and GD compared to HC. Cocaine use was negatively correlated with working memory and response inhibition performance.
Contreras-Rodriguez et al. 2016 [29]	19 GD 20 CUD 21 HC	Resting state functional connectivity, addiction severity, impulsivity	Magnetic resonance imaging (MRI), Interview for research in addictive behavior, UPPS-P impulsivity, Structured clinical interview (SCID-CV) diagnostic and statistical manual (DSM-IV-TR)	CUD showed greater global connectivity in ventral corticoestriatal network involving the orbitofrontal cortex, caudate, thalamus and amygdala compared with GD. CUD showed also increased connectivity between the orbitofrontal and subgenual cingulate cortices and between caudate and lateral prefrontal cortex compared with GD. Results showed overlapping connectivity changes between the orbitofrontal and dorsomedial prefrontal cortices and between amygdala and insula in CUD and GD compared to HC.
Choi et al. 2014 [59]	15 GD 15 AUD 15 HC	Impulsivity and compulsivity, addiction severity	Young's Internet Addiction Test (IAT), Structured clinical interview diagnostic and statistical manual (DSM-V, DSM-IV SCID), Problem Gambling Severity Index (PGSI), Barratt Impulsiveness Scale version 11 (BIS-11), Stop-signal task (SST), Intra–extra dimensional set shift, Trail Making Test	Impulsivity was higher in IGD and AUD compared to GD and HC. Compulsivity measures were higher in GD compared to IGD and HC. IGD and AUD showed decreased rate of successful stops in the stop signal task compared to HC.
Ge et al. 2017 [74]	27 IGD 29 Smokers 33 HC	Resting state functional connectivity of DLPFC, addiction severity, impulsivity	Magnetic resonance imaging (MRI), Structural Clinical Interview for diagnostic and statistical manual (DSM-IV), Diagnostic questionnaire for internet addiction (YDQ), Chinese Internet Addiction Scale (CIAS), Barratt Impulsivity Scale (BIS-11), Fagerström test of nicotine dependence (FTND)	IGD and smokers showed decreased rsFC with DLPFC in the right insula and left inferior frontal gyrus compared to HC. IGD had increased rsFC compared to smokers in the left inferior temporal gyrus, right inferior OF gyrus and decreased rsFC in right middle occipital gyrus, supramarginal gyrus, and cuneus with DLPFC, attributed to visual and auditory stimulation in gaming.

TABLE 1 (continued)

Author	Sample	Outcomes of interest	Measures	Results
Genauck et al. 2017 [69]	19 GD 15 AUD 17 HC	Loss aversion neural correlates, addiction severity, cognitive distortions	Functional magnetic resonance imaging (fMRI), Loss aversion task, German short questionnaire for gambling behavior (KFG), Structured Clinical Interview for diagnostic and statistical manual (DSM-IV) Axis I Disorders (SCID-I), Yale Brown Obsessive Compulsive Scale adapted for GD (PG-YBOCS), Gambling Symptom Assessment Scale (G-SAS), Alcohol Dependence Scale (ADS), Obsessive Compulsive Drinking Scale (OCDS), Gamblers' Beliefs Questionnaire (GBQ)	GD and AUD showed reduced loss aversion. AUD showed altered loss-related modulation of activity in lateral prefrontal regions. GD showed altered amygdala-prefrontal functional connectivity.
Goudriaan et al. 2010 [63]	17 GD 18 Smokers 17 HC	Cue reactivity neural correlates, addiction severity, cravings	Functional magnetic resonance imaging (fMRI), gambling, smoking-related and neutral pictures, cue reactivity task, probabilistic reversal learning task, planning task, Stop Signal Task, Diagnostic and statistical manual (DSMIV-TR), South Oaks Gambling Screen (SOGS), Fagerström Test for Nicotine Dependence (FTND), urges questionnaires	GD showed higher brain activation compared to smokers and HC when viewing gambling pictures in visual processing and emotion-motivation brain areas. GD´s craving correlated positively with brain activation in left ventrolateral prefrontal cortex and left insula. However, no significant differences in brain activity induced by smoking cues were found comparing smokers with GD and HC. Higher Nicotine Dependence scores in smokers was associated with increased activity in ventromedial prefrontal cortex, rostral anterior cingulate cortex, insula and middle/superior temporal gyrus when watching smoking pictures compared to smokers subgroup with lower scores.
Han et al. 2015 [27]	15 IGD 16 AUD	Functional connectivity, addiction severity	Magnetic resonance imaging (MRI), Diagnostic and statistical manual (DSM-V), Young Internet Addiction Scale (YIAS), Michigan alcohol screening test (MAST), Korean Alcohol Urge Questionnaire (AUQ-K)	Results showed that AUD and IGD had positive functional connectivity between DLPFC, cingulate and cerebellum and negative functional connectivity between DLPFC and OFC. AUD showed positive functional connectivity between DLPFC and temporal lobe and striatal areas while IGD´s functional connectivity was negative for these areas.

TABLE 1 (continued)

Author	Sample	Outcomes of interest	Measures	Results
Kim et al. 2015 [73]	16 IGD 14 AUD 15 HC	Resting state, local connectivity, clinical status, impulsivity	Functional magnetic resonance imaging (fMRI) - regional homogeneity (ReHo) measures, Young's Internet addiction test (IAT), Structured Clinical Interview for diagnostic and statistical manual (DSM-IV SCID), Korean version of Alcohol Use Disorder Identification Test (AUDIT-K), Barratt Impulsiveness Scale version 11 (BIS-11)	Results showed increased ReHo in the posterior cingulate cortex (PCC) in IGD and AUD and decreased ReHo in the right superior temporal gyrus (STG) in IGD compared with AUD and HC. There was a decreased ReHo in the anterior cingulate cortex in AUD. Internet addiction severity was positively correlated with ReHo in the medial frontal cortex, precuneus/PCC, and left inferior temporal cortex (ITC) in IGD. Impulsivity scores were negatively correlated with the left ITC in IGD.
Kober et al. 2016 [65]	28 GD 30 CUD 45 HC	Neural correlates of craving, addiction severity	Functional magnetic resonance imaging (fMRI), South Oaks Gambling Screen (SOGS), Fagerström Test for Nicotine Dependence (FTND), Urges/craving rating (scale 1-10), Structured clinical interview for GD (SCI-PG), Diagnostic and statistical manual (DSM-VI), Craving-inducing videos	CUD and GD reported strong cravings to cocaine and gambling videos respectively. Neuroimaging data showed the activation of the anterior cingulate cortex/ventromedial prefrontal cortex (mPFC) during cocaine videos in CUD, dorsal mPFC region during cocaine videos in CUD, gambling videos in GD, and sad videos in HC. There was also a gender interaction that distinguished men and women cravings-related neural correlates.
Lawrence et al. 2009 [55]	21 GD 21 AUD 21 HC	Decision-making, impulsivity and working memory	South Oaks Gambling Screen (SOGS), Diagnostic and statistical manual (DSM-IV-TR), Drug Abuse Screening Test (DAST-10), Severity of Alcohol Dependence Questionnaire (SADQ), Alcohol Use Disorders Identification Test (AUDIT-C), Cambridge Gambling Task (CGT), Information Sampling Task (IST), Spatial Working Memory, Digit Span	Results showed risky decision-making and cognitive impulsivity deficits in GD and AUD compared to HC. Working memory deficits and slower reaction time were found in AUD.

TABLE 1 (continued)

Author	Sample	Outcomes of interest	Measures	Results
Park et al. 2017 [60]	30 IGD 30 AUD 32 HC	Neural connectivity, level of phasic synchronization, addiction severity, impulsivity	Electroencephalography (EEG) intra and inter hemispheric coherence values, Diagnostic and statistical manual (DSM-V), Barratt Impulsivity Scale-11 (BIS-11), Internet Addiction Test (IAT), Alcohol Use Disorders Identification Test (AUDIT)	IGD showed increased intrahemispheric gamma (30-40Hz) coherence compared with AUD and HC. Right fronto-cetral gamma coherence predicted scores of the internet addiction test. AUD showed increased intrahemispheric theta (4-8Hz) coherence compared with HC.
Ren et al. 2017 [71]	15 GD 14 CUD 15 HC	Neural responses to naturalistic stimuli, addiction severity	Functional magnetic resonance imaging (fMRI), Structural Clinical Interview for diagnostic and statistical manual (DSM-IV, SCID), South Oaks Gambling Screen (SOGS), Video stimuli	Group-wise sparse coding and representation strategy detected similar activation patterns and different brain networks affected in GD and CUD.
Romanczuk-Seiferth et al. 2015 [56]	18 GD 15 AUD 17 HC	Neural correlates of reward processing, addiction severity, impulsivity	Functional magnetic resonance imaging (fMRI), Monetary Incentive Delay task, German short questionnaire for GD (KFG), ICD-10, Diagnostic and statistical manual (DSM-IV), Gambling Symptom Assessment Scale (G-SAS), Yale Brown Obsessive Compulsive Scale for GD (PG-YBOCS), Barratt Impulsivity Scale (BIS-10)	GD showed increased activity in right ventral striatum during loss anticipation compared to AUD, and decreased activation in the right ventral striatum and right mPFC during loss avoidance, which was associated inversely with severity of GD, compared to HC.
Ruiter et al. 2009 [70]	19 GD 19 Smokers 19 HC	Response perseveration, reward and/or punishment sensitivity, executive functions neural correlates, addiction severity	Functional magnetic resonance imaging (fMRI), Probabilistic reversal-learning task, Tower of London, Diagnostic and statistical manual (DSM-IV) Diagnostic Interview Schedule (DIS), South Oaks Gambling Screen (SOGS), Fagerström interview	GD showed severe response perseveration and diminished reward and punishment sensitivity associated with reduced activation of rvmPFC during monetary gains and losses compared to smokers, who showed hyperresponsiveness of the insular cortex to monetary gain compared to both healthy controls and GD. Planning and activation of dorsal frontostriatal circuit was intact in GD and smokers.

TABLE 1 (continued)

Author	Sample	Outcomes of interest	Measures	Results
Ruiter et al. 2012 [62]	17 GD 18 Smokers 17 HC	Response inhibition neural correlates, addiction severity	Functional magnetic resonance imaging (fMRI), Diagnostic Interview Schedule (DSM-VI), Stop Signal Task (SST), South Oaks Gambling Screen (SOGS), Fagerström scores	Behavioral performance on the SST was similar across all groups. GD and smokers showed hyporesponsiveness of DLPFC compared to HC.
Son et al. 2015 [28]	34 IGD 17 AUD 25 HC	Resting state, absolute and relative power, addiction severity, impulsivity	Quantitative electroencephalography (qEEG), Diagnostic and statistical manual (DSM-V), Young's Internet Addiction Scale (YIAS), Alcohol Use Disorder Identification Test-Korea (AUDIT- K), Barratt Impulsiveness Scale version 11 (BIS-11)	IGD had lower absolute beta power than AUD and HC. AUD had higher absolute delta power than ID and HC.
Torres et al. 2013 [67]	21 GD 20 CUD 23 HC	Associative learning and electroencephalographic response to feedback, addiction severity, impulsivity	Electroencephalography (EEG), Structural Clinical Interview for diagnostic and statistical manual (DSM-IV SCID), Interview for Research on Addictive Behavior (IRAB), UPPS impulsivity scale, Probabilistic reversal learning task (PRLT), Go/no-go inhibition task	GD and CUD showed different learning curves in a probabilistic reversal learning task. GD relative to HC showed reduced electroencephalographic response to feedback (Feedback Related Negativity, FRN), however FRN did not differ between CUD and GD or HC. Cortical activity in regions of interest differed between GD and CUD.
Van Holst et al. 2012 [75]	40 GD 36 AUD 54 HC	Grey-matter volumes, addiction severity	Whole-brain voxel-based morphometry, South Oaks Gambling Screen (SOGS), Diagnostic Interview Schedule (DSM-IV-TR), Dutch version of the Clinical International Diagnostic Inventory (CIDI), Alcohol Use Disorders Identification Test (AUDIT)	AUD presented smaller grey matter volumes in left superior frontal cortex, left precentral cortex, right insula, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex compared to GD and HC. There were no GMV differences between GD and HC.
Vanes et al. 2014 [68]	28 GD 33 AUD 18 HC	Discrimination, reversal and extinction learning, addiction severity, impulsivity	Structural Clinical Interview for diagnostic and statistical manual (DSM-IV SCID, DSM-IV-TR), South Oaks Gambling Screen (SOGS), Alcohol Use Disorders Identification Test (AUDIT), Barratt Impulsivity Scale (BIS-11), Deterministic discrimination learning task	Discrimination learning, reversal learning and extinction learning scores did not differ between GD, AUD and HC. Speed of learning was faster in GD compared with AUD, and both GD and AUD learnt slower than HC in reversal and extinction learning.

TABLE 1 (continued)

Author	Sample	Outcomes of interest	Measures	Results
Verdejo-Garcia et al. 2015 [66]	18 GD 18 CUD 18 HC	Neural mechanisms of cognitive flexibility	Functional magnetic resonance imaging, Genetic testing, Probabilistic reversal learning task, Diagnostic and statistical manual (DSM-IV) clinician Version (SCID-I-CV), International Personality Disorders Examination (IPDE)	Both GD and CUD showed reduced ventrolateral prefrontal cortex (PFC) activation during reversal shifting. CUD showed increased dorsomedial PFC activation compared to GD during perseveration, and decreased dorsolateral PFC activation compared to GD and HC during shifting. DRD2/ANKK Taq1A1+ genotype seem to be linked in CUD with shifting-related ventrolateral PFC signal.
Worhunsky et al. 2014 [64]	24 GD 24 CUD 24HC	Contextual reward-processing neural correlates, slot machine performance	Functional magnetic resonance imaging (fMRI) – slot machine task, Diagnoses using semi-structured clinical interviews (DSM-IV SCID)	GD and CUD showed increased anticipatory activity in mesolimbic and ventrocortical regions compared to HC. GD had higher positive possible-reward anticipation whereas CUD showed more negative certain-loss anticipation. Both groups differed from HC in the level of medial frontal or striatal responses following near-miss outcomes.
Worhunsky et al. 2017 [9]	25 GD 18 CUD 27 HC	Chasing losses neuro correlates	Functional magnetic resonance imaging (fMRI), loss-chase task, Diagnostic and statistical manual (DSM-IV) semi-structured clinical interviews (SCID)	GD showed greater engagement of medial frontal processing networks compared with CUD and HC in choices to quit chasing losses. CUD had altered striato-amygdala motivational network when losing compared to HC and during decision-making compared to GD. Findings showed greater coordinated activity between executive control network in both GD and CUD relative to HC.
Yip et al. 2017 [72]	38 GD 38 CUD 38 HC	White-matter microstructural features, impulsivity	Diffusion-weighted magnetic resonance imaging (dMRI), Diagnostic and statistical manual (DSM-IV) structured clinical interview (SCI) and (SCID), Barratt Impulsiveness Scale (BIS-11)	Results showed reduced anisotropy of secondary fiber orientations within the left internal capsule, corona radiata, forceps major and posterior thalamic radiation in GD and CUD compared to HC and no differences between GD and CUD.

TABLE 1 (continued)

Author	Sample	Outcomes of interest	Measures	Results
Yip et al. 2018 [58]	35 GD 37 CUD 37 HC	Neural structures alterations linked to addictions subtypes and trait impulsivity	Magnetic resonance imaging (MRI), Diagnostic and statistical manual (DSM-V), Barratt Impulsiveness Scale (BIS-11)	Decreased GMV in dorsal anterior cingulate and ventromedial prefrontal cortex was associated to CUD only. Results showed a negative association between impulsivity and insula-amygdala-hippocampus GMVs in all groups. The anatomical overlap between regions identified as differentiating diagnostic groups and regions covarying with impulsivity was minor.
Yoon et al 2017 [61]	19 IGD 20 AUD 25 HC	Morphological and functional mechanisms and neurocognitive function, addiction severity, impulsivity	Functional magnetic resonance imaging (fMRI), Diagnostic and statistical manual (DSM-IV), Internet Addiction Test (IAT), Alcohol Use Disorder Identification Test (AUDIT-K), Barratt Impulsivity Scale (BIS-11), Intra-Extra Dimensional Set Shift test, Stockings of Cambridge test, Spatial Span (SSP)	IGD showed greater hippocampus/amygdala and precuneus volume than HC, which correlated positively with severity of IGD. Stronger functional connectivity in the left vmPFC with hippocampus/amygdala cluster was found in IGD compared with AUD. Smaller cerebellar volume and thinner medial frontal cortex was shown in AUD compared with HC, and this correlated with impaired working memory abilities and addiction duration in AUD.

SUD, substance use disorder; BA, behavioral addiction; HC, healthy control; CUD, cocaine dependence; GD, gambling disorder; IGD, internet gaming disorder; AUD, alcohol dependence disorder; UPPS, urgency premeditation perseverance sensation seeking; DSM, diagnostic and statistical manual of mental disorders; SCID, structured clinical interview; YDQ, diagnostic questionnaire for internet addiction; CIAS, Chinese internet addiction scale; BIS-11, Barrat impulsivity scale; FTND, Fagerström test of nicotine dependence; D-KEFS, Delis-Kaplan Executive Function System; CWIT, Color-Word Interference; KFG, German short questionnaire for gambling behavior; PG-YBOCS, Yale Brown obsessive compulsive scale adapted for GD; G-SAS, gambling symptom assessment Scale; ADS, alcohol dependence scale; OCDS, obsessive compulsive drinking scale; GBQ, gamblers' beliefs questionnaire; YIAS, young internet addiction scale; MAST, Michigan alcohol screening test; AUQ-K, Korean alcohol urge questionnaire; IAT, Young's Internet addiction test; AUDIT-K, Korean version of alcohol use disorder identification test; SOGS, south oaks gambling screen; DAST, drug abuse screening test; SADQ, severity of alcohol dependence questionnaire; CGT, Cambridge gambling task; IST, information sampling task; CIDI, clinical international diagnostic inventory; GMV, grey matter volume; WM, working memory; EF, executive functions; mPFC, medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; PCC, posterior cingulate cortex; ITC, inferior temporal cortex; rsFC, resting state functional connectivity; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imagining; dMRI, diffusion-weighted magnetic resonance imaging; ReHo, regional homogeneity; IPDE, Personality Disorders Examination; IRAB, Interview for Research on Addictive Behavior.

TABLE 2

Summary of studies that reported behavioral and neurophysiological similarities, differences or similarities and differences between behavioral addictions (BAs) and substance use disorders (SUDs) direct comparisons.

Data	Similarities and differences (author: outcomes of interest/ addictions)	Only similarities (author: outcome of interest/ addictions)	Only differences (author: outcome of interest/ addictions)
Behavioral	· Albein-Urios et al. 2012 [57]: Cognitive performance, trait impulsivity, addiction severity, delay discounting, inhibition, working memory performance/ GD, CUD. · Contreras-Rodríguez et al. 2016 [29]: Resting state functional connectivity, addiction severity, impulsivity/ GD, CUD. · Choi et al. 2014 [59]: Impulsivity and compulsivity, addiction severity/ GD, IGD, AUD. · Goudriaan et al. 2010 [63]: Cue reactivity neural correlates, addiction severity, cravings/ GD, Smokers. · Lawrence et al. 2009 [55]: Decision-making, impulsivity, working memory/ GD, AUD. · Ruiter et al. 2009 [70]: Response perseveration, reward and/or punishment sensitivity, EF neural correlates, addiction severity/ GD, Smokers.	· Genauck et al. 2017 69: Loss aversion neural correlates, addiction severity, cognitive distortions/ GD, AUD. · Kim et al. 2015 [73]: Resting state, local connectivity, clinical status, depressive and anxiety symptoms, impulsivity/ IGD, AUD. · Kober et al. 2016 [65]: Neural correlates of craving, addiction severity/ GD, CUD. · Park et al. 2017 [60]: Neural connectivity and phasic synchronization, addiction severity, impulsivity/ IGD, AUD. · Romanczuk-Seiferth et al. 2015 [56]: Neural correlates of reward processing, addiction severity, impulsivity / GD, AUD. · Ruiter et al. 2012 [62]: Response inhibition neural correlates, addiction severity/ GD, Smokers.	· Ge et al. 2017 [74]: Resting state functional connectivity of DLPFC, addiction severity, impulsivity/ IGD, Smokers.

TABLE 2 (continued)

Data	Similarities and differences (author: outcomes of interest/ addictions)	Only similarities (author: outcome of interest/ addictions)	Only differences (author: outcome of interest/ addictions)
Behavioral	· Torres et al. 2013 [67]: Associative learning and electroencephalographic response to feedback, addiction severity, impulsivity/ GD, CUD. · Vanes et al. 2014 [68]: Discrimination, reversal and extinction learning, addiction severity, depression, impulsivity/ GD, AUD. · Verdejo-Garcia et al. [66]: Neural mechanisms of cognitive flexibility/ GD, CUD. · Yoon et al. [61]: Morphological and functional mechanisms and neurocognitive function, addiction severity/ IGD, AUD.	· Son et al. 2015 [28]: Resting state, absolute and relative power, addiction severity, impulsivity/ IGD, AUD. · Worhunsky et al. 2014 [64]: Contextual reward-processing neural correlates, slot machine performance/ GD, CUD. · Worhunsky et al. 2017 [9]: Chasing losses neurocorrelates/ GD, CUD. · Yip et al. 2017 [72]: White-matter microstructural features, impulsivity/ GD, CUD. · Yip et al. 2018 [58]: Neural structures alterations linked to addictions subtypes and trait impulsivity/ GD, CUD.	
Neurophysiological	· Contreras-Rodríguez et al. 2016 [29]: Resting state functional connectivity, addiction severity, impulsivity/ GD, CUD. · Goudriaan et al. 2010 [63]: Cue reactivity neural correlates, addiction severity, cravings/ GD, Smokers.	· Ruiter et al. 2012 [62]: Response inhibition neural correlates, addiction severity/ GD, Smokers. · Yip et al. 2017 [72]: White-matter microstructural features, impulsivity/ GD, CUD.	· Genauck et al. 2017 [69]: Loss aversion neural correlates, addiction severity, cognitive distortions/ GD, AUD. · Park et al. 2017 [60]: Neural connectivity and phasic synchronization, addiction severity, impulsivity/ IGD, AUD.

TABLE 2 (continued)

Data	Similarities and differences (author: outcomes of interest/ addictions)	Only similarities (author: outcome of interest/ addictions)	Only differences (author: outcome of interest/ addictions)
Neurophysiological	· Han et al. 2015 [27]: Functional connectivity, addiction severity/ IGD, AUD. · Kim et al. 2015 [73]: Resting state, local connectivity, clinical status, depressive and anxiety symptoms, impulsivity/ IGD, AUD. · Kober et al. 2016 [65]: Neural correlates of craving, addiction severity/ GD, CUD. · Ge et al. 2017 [74]: Resting state functional connectivity of DLPFC, addiction severity, impulsivity/ IGD, Smokers. · Ren et al. [71]: Neural responses to naturalistic stimuli, addiction severity/ GD, CUD. · Romanczuk-Seiferth et al. 2015 [56]: Neural correlates of reward processing, addiction severity, impulsivity / GD, AUD.		· Son et al. 2015 [28]: Resting state, absolute and relative power, addiction severity, impulsivity/ IGD, AUD. · Van Holst et al. 2012 [75]: Grey-matter volumes, addiction severity/ GD, AUD.

TABLE 2 (continued)

Data	Similarities and differences (author: outcomes of interest/ addictions)	Only similarities (author: outcome of interest/ addictions)	Only differences (author: outcome of interest/ addictions)
Neurophysiological	· Ruiter et al. 2009 [70]: Response perseveration, reward and/or punishment sensitivity, EF neural correlates, addiction severity/ GD, Smokers. · Torres et al. 2013 [67]: Associative learning and electroencephalographic response to feedback, addiction severity, impulsivity/ GD, CUD. · Verdejo-Garcia et al. [66]: Neural mechanisms of cognitive flexibility/ GD, CUD. · Worhunsky et al. 2014 [64]: Contextual reward-processing neural correlates, slot machine performance/ GD, CUD. · Worhunsky et al. 2017 [9]: Chasing losses neurocorrelates/ GD, CUD. · Yip et al. 2018 [58]: Neural structures alterations linked to addictions subtypes and trait impulsivity/ GD, CUD. · Yoon et al. [61]: Morphological and functional mechanisms and neurocognitive function, addiction severity/ IGD, AUD.		

SUD, substance use disorder; BA, behavioral addiction; GD, gambling disorder; IGD, internet gaming disorder; CUD; cocaine use disorder; AUD, alcohol dependence disorder; DLPFC, dorsolateral prefrontal cortex; EF, executive functions.

TABLE 3

Summary of stimulation parameters in transcranial magnetic stimulation (TMS) studies among behavioral-addicted populations.

Author	BA	Brain target	TMS protocol	# Sessions and participants	Aim: outcomes of interest (measures)	Results
Chowdhury et al. 2018 [78]	GD	Left Motor Cortex (M1)	Motor evoked potential (MEP)	1 session N=40 (20 at risk gamblers, 20 HC)	Association of modulatory mechanisms in M1 with inhibitory control: GABAergic activity (SICI at rest with EMG); Glutamatergic activity (ICF at rest with EMG); Inhibition (SST); Impulsivity (BIS); Gambling severity (PGSI); Severity of alcohol-related harm ; Severity of AUD (AUDIT-C), Severity of SUDs (DAST-10); Severity of ADHD (ASRS)	Results showed a negative correlation between SICI and SSRT but no correlation between ICF and SSRT indicating that reduced inhibitory control was associated to weak GABAergic activity. When controlling for ADHD symptom severity and SUDs effects, at risk gamblers showed high self-reported impulsivity but SSRT and SICI/ICF measures were similar to HC.
Gay et al. 2017 [24]	GD	Left DLPFC	rTMS 10 Hz, 3008 pulses	2 sessions (one week apart) N=22 Crossover design (active and sham)	High frequency rTMS effects on craving: DLPFC location determination (MRI); Gambling behavior (PG-YBOCS); Craving (VAS)	Cue-induced craving was decreased with active rTMS compared to sham but there were no effects on gambling behavior.

TABLE 3 (continued)

Author	BA	Brain target	TMS protocol	# Sessions and participants	Aim: outcomes of interest (measures)	Results
Pettorruso et al. 2019 [79]	GD	Left DLPFC	rTMS 15 Hz, 2400 pulses	20 sessions (twice a day, 5 days/week) N=1	High frequency rTMS effects on dopaminergic transporter (DAT) availability: DAT availability (SPECT), Gambling disorder diagnosis (DSM-V); Gambling severity (G-SAS, PG-YBOCS)	Over a six months follow up gambling behavior stopped with no relapse, there was absence of gambling cravings and GD symptoms and there was a decrease in DAT availability in striatal regions.
Rosenberg et al. 2013 [76]	GD	Left DLPFC	rTMS 1 Hz	15 sessions (daily) N=5	TMS effects on pathological gambling: Depression (HDRS); Anxiety (HARS); Obsessions (Y-BOCS); Gambling severity (SOGS, DAGS); Cravings (VAS); Clinical global impressions (CGI-I); Social adjustment (SAS)	rTMS was associated with initial improvements in scale ratings however gambling behaviors continued after the TMS intervention.
Sauvaget et al. 2018 [17]	GD	Right DLPFC	rTMS 1 Hz, 360 pulses	2 sessions (one week apart) N=30 Crossover design (active and sham)	Low frequency rTMS effects on craving: Cravings (VAS, GACS); Problem gambling severity (DSMIV); Gambling related cognitive biases (GRCS); Questionnaire about type of game and mode: online or offline; Clinical characteristics (MINI); Physiological measures (heart rate and blood pressure); Tolerability (follow up call)	rTMS was associated with a decrease in gambling urge in both real stimulation and sham conditions however when controlling cue-induced craving levels, there were no effects on craving for active rTMS. In general the effects of rTMS were well-tolerated.

TABLE 3 (continued)

Author	BA	Brain target	TMS protocol	# Sessions and participants	Aim: outcomes of interest (measures)	Results
Zack et al 2016 [77]	GD	mPFC; and Right DLPFC	rTMS 10 Hz, 450 pulses and cTBS 50Hz, 900 pulses	3 sessions (one week apart) N=9 Crossover design (rTMS, cTBS and sham)	High frequency rTMS effects on gambling reinforcement: Impulsive choice (DDT); Attentional control (Stroop); Blood pressure (wrist-cuff monitor); Subjective behavioral activation (vigor scale); Risky decision-making and speed of play (slot machine); Desire to gamble (VAS); Mood (POMS); Psychostimulant-like sensations (ARCI); brain target localization (MRI); Screen for Gambling Problems (NODS); Depressive symptoms (BDI); Alcohol dependence (ADS); Drug abuse (DAST); Nicotine dependence (FTND); Impulsivity (EIS); Self-reported measures validity (NEO- FFI)	Desire to gamble was reduced with rTMS. cTBS reduced amphetamine-like effects and diastolic blood pressure. Treatment was associated with a reduction of behavioral activation and both rTMS and cTBS increased Stroop interference.

TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; cTBS, continuous theta burst stimulation; BA, behavioral addiction; GD, gambling disorder; HC, healthy control; PGSI, problem gambling severity index; NODS, national opinion diagnostic screen; AUDIT-C, alcohol use disorder identification test; DAST-10, drugs abuse screening test; FTND, Fagerström test for Nicotine dependence; EIS, Eysenck impulsivity scale; NEO- FFI, neuroticism extraversion openness five factor inventory; ASRS, adult attention deficit hyperactivity disorder self-report scale; PG-YBOCS, Yale-Brown obsessive compulsive scale for GD; VAS, visual analogue scale; GACS, gambling craving scale; GRCS, gambling related cognitions scale; ; SOGS, south oaks gambling screen; Hamilton anxiety scale (HARS);HDRS, Hamilton depression rating scale; DAGS, Dannon and Ainhold gambling scale; CGI-I, clinical global impressions; SAS, social adjustment scale; MINI, mini international neuropsychiatric interview; POMS, profile of mood states; BDI, Beck depression inventory; ARCI, addiction research center inventory; DDT, delay discounting task; SST, stop signal task; SSRT, stop signal task reaction time; BIS, Barratt impulsivity scale; SICI, short interval cortical inhibition; ICF, intra cortical facilitation; EMG, electromyography; MRI, magnetic resonance imaging; MEP, motor evoked potential; DLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; Hz, hertz.

TABLE 4

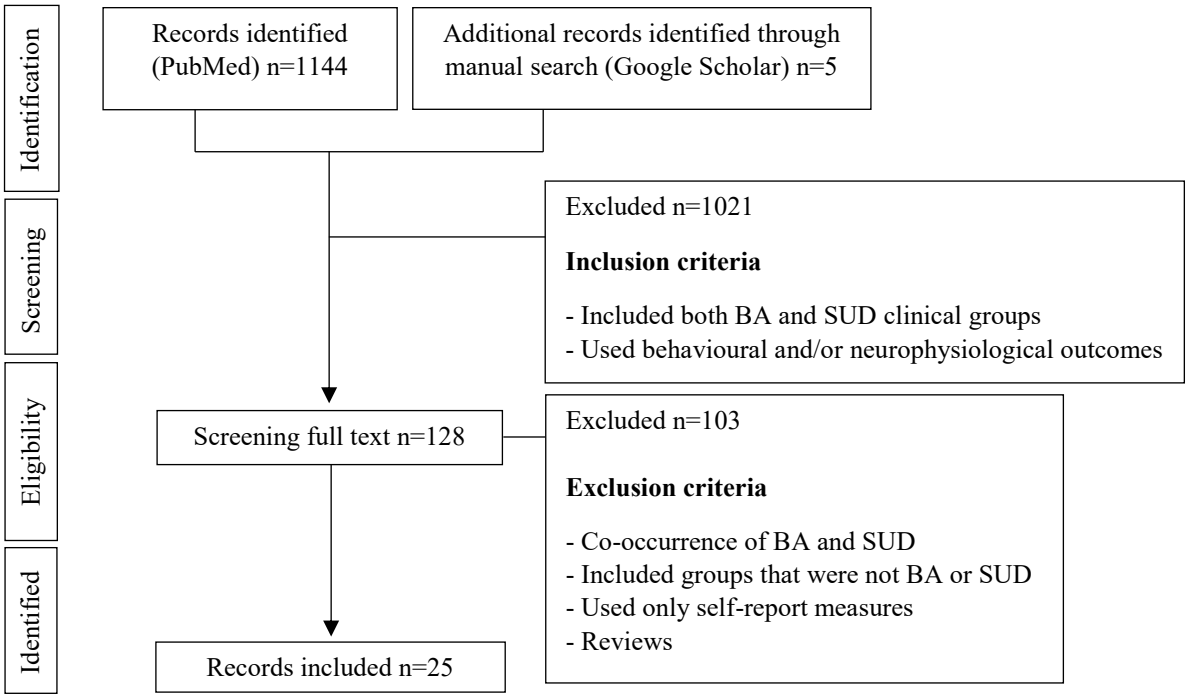
Summary of stimulation parameters in transcranial direct current stimulation (tDCS) studies applied to behavioral-addicted populations.

Author	BA	Brain target	tDCS Protocol	# Sessions and participants	Aim: outcomes of interest (measures)	Results
Dickler et al. 2018 [81]	GD	DLPFC	Anode right DLPFC, cathode left DLPFC; 1mA; 30min; Crossover design (active and sham)	2 sessions separated by 7 days N=16	tDCS effects on Metabolites: Metabolites level (MRS); Risk taking (BART); Impulsivity (BIS); Craving (GACS)	Active tDCS stimulation elevated GABA levels compared to sham. There were no stimulation effects on prefrontal glutamate + glutamine and N-actetyl Aspartate or in striatal metabolite levels. There were positive correlations between metabolite levels in active stimulation related to sham, and risk-taking, impulsivity and craving levels.
Lee et al. 2018 [25]	Online Gaming	DLPFC	Anodal left DLPFC, cathode right DLPFC; 2 mA; 30 min; Non-controlled design	12 sessions (3 times per week for 4 weeks) N= 15	Feasibility and tolerability of tDCS over DLPFC: Glucose metabolism (8F-fluoro-2-deoxyglucose positron emission tomography); Internet Addiction (IAT); Self Control (BSCS); Depressive symptoms (BDI-II)	Time spent on games, scores of IAT and BDI-II decreased and BSCS score increased after tDCS. Self-control increases were associated with decreases in addiction severity and time spent on games. Moreover, abnormal asymmetry of regional cerebral glucose metabolism in the DLPFC improved.

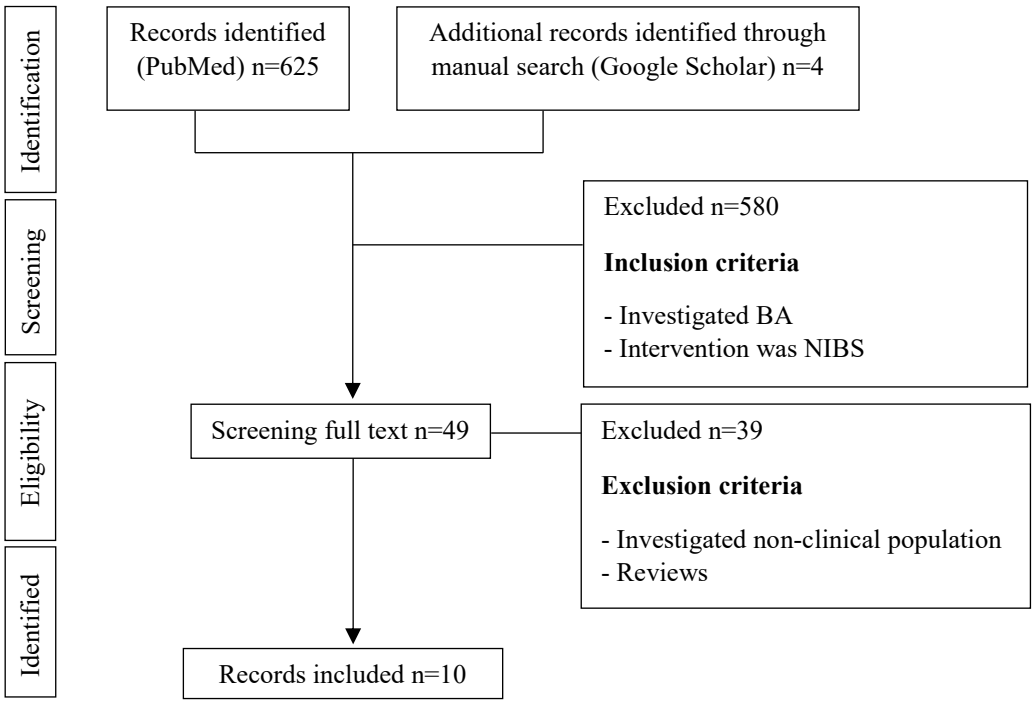
TABLE 4 (continued)

Author	BA	Brain target	tDCS Protocol	# Sessions and participants	Aim: outcomes of interest (measures)	Results
Martinotti et al. 2018 [82]	GD	Bilateral DLPFC	Anodal right DLPFC, cathode left DLPFC; and Anode left DLPFC, Cathode right DLPFC; Case report (non-controlled design)	38 sessions (twice a day for 10 days – once a week for 3 months – once every 2 weeks for 3 months) N=1	tDCS effects on GD: Gambling severity (SOGS); Psychopathological burden (Brief Psychiatric Rating Scale); Depression (HDRS); Impulsivity (BIS); Craving (VAS); Obsessive-compulsive symptoms (PG-YBOCS); Gambling symptoms (GSAS)	After 10 days of treatment psychiatric symptomatology improved, as did gambling severity and craving levels. Gambling behaviors ceased. After 3 and 6 months of treatment further improvement on overall psychopathological symptoms, continued absence of craving, improved addictive behavior and comorbid SUD symptomatology.
Soyata et al. 2018 [80]	GD	DLPFC	Anode right DLPFC, Cathode left DLPFC; 2mA; 20 min; Parallel design (active or sham)	3 sessions (every other day) N=20 (10 active, 10 sham)	tDCS effects on decision making and cognitive flexibility: Decision making (IGT); Cognitive flexibility (WCST)	tDCS enhanced decision making and cognitive flexibility in gambling disorder.

tDCS, transcranial direct current stimulation; BA, behavioral addiction; GD, gambling disorder; HC, healthy control; BART, balloon analogue risk taking task; BIS, Beck Depression Inventory; GACS, gambling craving scale; IAT, internet addiction test, BSCS, brief self-control scale; SOGS, south oaks gambling screen; BPRS, Brief Psychiatric Rating Scale; HDRS, Hamilton depression rating scale; VAS, visual analogue scale; PG-YBOCS, Yale-Brown obsessive compulsive scale for GD; GSAS, gambling symptom assessment scale; IGT, Iowa Gambling Task; WCST, Wisconsin Card Sorting Task; MRS, magnetic resonance spectroscopy.



(a) Search #1: research conducting direct comparisons between BAs and SUDs.



(b) Search #2: research applying NIBS techniques in BAs.

FIGURE 1.

Schematic view of the selection procedure in (a) search #1: research conducting direct comparisons between behavioural addictions (BAs) and substance use disorders (SUDs) and (b) search #2: research applying non-invasive brain stimulation (NIBS) techniques in behavioural addictions (BAs).