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**Behavioural Addiction - a rising tide?**

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## **Abstract**

The term 'addiction' was traditionally used in relation to centrally active substances, such as cocaine, alcohol, or nicotine. Addiction is not a unitary construct but rather incorporates a number of features, such as repetitive engagement in behaviours that are rewarding (at least initially), , loss of control (spiraling engagement over time), persistence despite untoward functional consequences, and physical dependence (evidenced by withdrawal symptoms when intake of the substance diminishes). It has been suggested that certain psychiatric disorders characterized by maladaptive, repetitive behaviours share parallels with substance addiction and therefore represent 'behavioural addictions'. This perspective has influenced the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which now has a category 'Substance Related and Addictive Disorders', including gambling disorder. Could other disorders characterised by repetitive behaviours, besides gambling disorder, also be considered 'addictions'? Potential examples include kleptomania, compulsive sexual behaviour, 'Internet addiction', trichotillomania (hair pulling disorder), and skin-picking disorder. This paper seeks to define what is meant by 'behavioural addiction', and critically considers the evidence for and against this conceptualisation in respect of the above conditions, from perspectives of aetiology, phenomenology, co-morbidity, neurobiology, and treatment. Research in this area has important implications for future diagnostic classification systems, neurobiological models, and novel treatment directions.

Key words: addiction, compulsivity, impulsivity, cognition, imaging

## **Introduction**

The term ‘addiction’ was traditionally used in relation to specific psychoactive substances, such as cocaine, alcohol, or nicotine. Substances with addictive properties exert to some extent common effects on the brain’s reward pathways, notably the ventral striatum, implicating the dopaminergic and opioid systems (Everitt and Robbins 2005; Dalley et al. 2007; Everitt and Robbins 2013). Core aspects of addiction, according to the Diagnostic and Statistical Manual Version 5 (DSM-5) (American Psychiatric Association 2013), include impaired control (e.g. craving increasingly large quantities, unsuccessful attempts to reduce intake), impairment (e.g. narrowing of interests, neglect of other areas of life), risky use (persisting intake despite awareness of damaging psychological or physiological effects), and pharmacological criteria (tolerance, withdrawal).

Certain psychiatric syndromes characterised by repetitive habits share considerable phenomenological parallels with substance addiction, and have thus been argued to represent candidate ‘behavioural addictions’ (Goodman 1993; Potenza 2001; Grant et al. 2006a; Petry et al. 2013; Petry et al. 2014). Studying behavioural addictions, such as gambling disorder, could serve as a model to investigate the underlying neural mechanisms related to addictive behaviours without the confounding influences of drugs of abuse. While different accounts of behavioural addictions have included different disorders, for the purposes of this paper we focus on gambling disorder, kleptomania (compulsive stealing), internet addiction, trichotillomania (hair pulling disorder), and excoriation disorder (skin-picking disorder). Far from being rare disorders only of theoretical interest, these conditions are relatively common, with lifetime prevalence rates for each estimated at 0.5-3% (Christenson et al. 1991b; Bohne et al. 2002; Odlaug and Grant 2010; Odlaug et al. 2013). Collectively, these conditions subtend a considerable burden of suffering to affected individuals and their families (Grant et al. 2013c).

The behavioural addiction model is tempting at face value: individuals with pathological types of various behaviors (gambling, excess grooming, stealing, setting fires, excess use of the internet) do share remarkable phenomenological parallels to people with addictive substances – including impaired control, functional impairment, and persisting engagement in the behavior despite negative consequences. Do these behavioural addictions also share parallels in terms of the DSM-5 physiological criteria, namely tolerance, and withdrawal? Evidence arguably abounds for gambling disorder involving these features, hence its inclusion in the new DSM-5 category of ‘Substance-Related and Addictive Disorders’ (American Psychiatric Association 2013). In contrast, trichotillomania (hair-pulling disorder) and skin-picking disorder are now classified within ‘Obsessive-Compulsive and Related Disorders’, while kleptomania is classified within ‘Disruptive, Impulse-Control, and Conduct Disorders’. DSM-5 does not include ‘Internet addiction’ in its main section but rather lists ‘internet gaming disorder’ as a condition requiring further study, acknowledging that this entity is also referred to variably as internet addiction, internet use disorder, or gaming addiction.

Psychiatric classification systems have traditionally relied on expert consensus, focusing mainly on the overt symptoms (phenomenology) and comorbid overlap between disorders, albeit DSM-5 made some efforts to focus also on other

validators. However, recent initiatives such as the National Institute of Mental Health's Research Domain Criteria (RDoC) and European Commission's ROAMER initiative emphasise the importance of expanding upon the traditional perspective, to incorporate additional intermediate neurobiological markers (Insel et al. 2010; Cuthbert and Insel 2013). As noted above, putative behavioural addictions are disparately classified in DSM-5, with only gambling disorder being recognized as a type of 'addiction'. Thus, it is timely to review the evidence supporting the conceptualization of the above disorders as behavioural addictions from a translational perspective. This paper focuses on cross-cutting issues between these disorders with an emphasis on comorbidity, neurobiology, and treatment. By drawing together these strands of evidence, we highlight the strengths and weaknesses of this model, future research directions, and important treatment implications.

### **Comorbidity**

Substance use disorders (SUDs) and the candidate behavioural addictions (i.e. gambling disorder, Internet addiction, trichotillomania and skin-picking disorder, and kleptomania resemble each other in many aspects, including comorbidity patterns. This section focuses on existing data on the construct of behavioural addiction from the perspective of comorbidity. Specifically, the focus will be on comorbidity in SUDs, in behavioural addictions, and comorbidity between SUDs and these behavioural addictions.

There are extensive data attesting to the strong association of SUDs with a broad range of psychiatric disorders including major depressive disorder (MDD), bipolar disorder, anxiety and related disorders such as social anxiety disorder (SAD) and posttraumatic stress disorder (PTSD), and conduct disorder/antisocial personality traits (e.g. Merikangas et al. 1998). Attention deficit / hyperactivity disorder (ADHD) is also commonly reported by individuals with SUD (Szobot et al. 2007), and some studies have indicated that the link between SUDs and ADHD is usually through conduct disorder or antisocial personality disorder (Disney et al. 1999; Elkins et al. 2007; Serra-Pinheiro et al. 2013).

Clinical and epidemiological research suggests that, similarly, behavioural addictions are also associated with a range of psychiatric disorders. Most prevalent seems to be mood disorders including bipolar disorder, anxiety disorders, ADHD and SUDs. A systematic review and meta-analysis of population surveys between 1998 and 2010 on comorbidity in individuals with problematic gambling also suggested high rates of comorbidity, with the highest mean prevalence for nicotine dependence, followed by a SUD, any type of mood disorder and any type of anxiety disorder (Lorains et al. 2011). The St. Louis Epidemiologic Catchment Area (ECA) study, for example, found that individuals with gambling disorder (both syndromal and subsyndromal) were more likely than those without to have mood disorders, SUDs (particularly relating to alcohol use) and psychotic disorders (Cunningham-Williams et al. 1998). More recently, data from the National Epidemiologic Survey of Alcohol and Related Conditions showed that individuals with gambling disorder also present with any mood disorder, bipolar disorder, anxiety disorders such as generalized anxiety disorder (GAD) and PTSD, any SUD, and alcohol use disorders (Petry et al. 2005). Data from the US National Comorbidity Survey Replication (NCS-R) suggested that onset and persistence of gambling disorder were predicted by a variety of prior DSM-

IV mood, anxiety, impulse-control and SUDs, and that gambling disorder also predicted the subsequent onset of GAD, PTSD and substance dependence (Kessler et al. 2008). There also have been reports of a close relationship between gambling disorder and ADHD (Rugle and Melamed 1993; Grall-Bronnec et al. 2011) and between gambling disorder and OCD (Frost et al. 2001; Scherrer et al., 2015). However, there is some evidence militating against a strong relationship between gambling disorder and OCD. In a community sample, gambling disorder symptoms correlated negatively rather than positively with obsessive-compulsive symptoms (Petrucelli et al. 2014).

Data on comorbidity in individuals with internet addiction shows similar associations: A review of 20 studies that investigated the association between internet addiction and psychiatric disorders found high comorbidity with depression, anxiety, obsessive-compulsive symptomatology and ADHD (Carli et al. 2013). In a meta-analysis, internet addiction was associated with increased rates of alcohol abuse (odds ratio ~3.1 versus controls), ADHD (~2.9), depression (~2.8), and anxiety (~2.7) (Ho et al. 2014).

Similarly, in clinical samples of patients with trichotillomania, high rates of comorbid mood and anxiety disorders have been reported (Swedo and Leonard 1992; Diefenbach et al. 2002; Lochner et al. 2002). Comorbidity with OCD and with other body-focused repetitive behaviour disorders is also common in individuals with trichotillomania (Christenson et al. 1991a; Woods et al. 2006). Although trichotillomania generally shows low rates of comorbidity with DSM-IV impulse-control disorders (ICDs) such as intermittent explosive disorder (McElroy et al. 1998; Grant and Kim 2003; Grant et al. 2005), there are data that indicate that lifetime rates of trichotillomania may be elevated in some ICDs, such as compulsive sexual behaviour (Black et al. 1997) and kleptomania (McElroy et al. 1991a; McElroy et al. 1991b). Paediatric samples with trichotillomania have similar comorbidity patterns but there are studies to suggest higher rates of comorbid social anxiety disorder (SAD), oppositional defiant disorder (Tolin et al. 2007; Franklin et al. 2008) and tics (Walther et al. 2014) than in adults.

A growing literature has documented a high degree of psychiatric comorbidity in skin-picking disorder, particularly with mood and anxiety disorders (Grant and Odlaug 2009). Comorbidity rates in skin-picking disorder for MDD range between 12.5-48% and between 8-23% for the anxiety disorders (Arnold et al. 1998; Wilhelm et al. 1999; Lochner et al. 2002; Grant et al. 2007b; Keuthen et al. 2007). Co-occurring OCD is also much more prevalent in skin-picking disorder (6%–52%) than in the community (1%–3%) (Arnold et al. 1998; Calikusu et al. 2003; Tucker et al. 2011), and other body-focused repetitive behaviour disorders also commonly co-occur. As with the other behavioural addictions in general, the high rates of co-occurrence work in both directions: for example, the reported rates of skin-picking disorder in individuals with OCD range between 8.9% and 24.0% (Cullen et al. 2001; Grant et al. 2006c), which are also markedly higher than community rates (1.4%–5.4%) (Hayes et al. 2009; Keuthen et al. 2010). Skin-picking disorder and body dysmorphic disorder (BDD) also often co-occur (Arnold et al. 1998; Phillips 2005; Grant et al. 2006d).

Clinical and epidemiological data indicate that SUDs and behavioural addictions frequently co-occur (Grant et al. 2006a; Lobo and Kennedy 2009). There are epidemiological data that strongly support a relationship between SUDs and gambling disorder; high rates of co-occurrence between these conditions have been found (Cunningham-Williams et al. 1998; Petry et al. 2005). A 3.8-fold increased risk for comorbid alcohol use disorder in particular was found in participants with gambling disorder in another epidemiological survey (Bland et al. 1993). The St. Louis ECA study similarly observed highest odds ratios between alcohol use disorders, antisocial personality disorder and gambling disorder. Again, the high rates of co-occurrence work in both directions: individuals with substance dependence may also have a 2.9 times higher risk of having moderate to high severity gambling problems (el-Guebaly et al. 2012). Individuals with Internet addiction across the globe also commonly report SUDs, with most research focusing on internet gaming disorder. For example, Internet addiction was significantly associated with cannabis use in a Finnish study (Korkeila et al. 2010), with substance use among Greek adolescents (Siomos et al. 2012), and with excessive or harmful alcohol use (odds ratio of 1.84) in a study of 2453 Taiwanese college students (Yen et al. 2009). For some individuals, however, it may be that compulsive internet use could protect against substance misuse, by providing a distraction or different outlet for repetitive behaviours. A study of DSM-IV impulse control disorders (including trichotillomania) also found increased comorbidity between nicotine dependence and trichotillomania (Lejoyeux et al. 2006). SUDs also often co-occur with skin-picking disorder (14-36%) (Arnold et al. 1998; Lochner et al. 2002).

There also is extensive evidence for overlapping comorbidity amongst the behavioural addictions themselves. For example, problem gambling has been found to co-occur with Internet addiction and substance use, i.e. alcohol use disorder in particular (Tozzi et al. 2013). Comorbidity between trichotillomania and skin-picking disorder is also common (Christenson et al. 1991a; Lochner et al. 2002; Odlaug and Grant 2008a; Odlaug and Grant 2008b). The majority of individuals with trichotillomania also report the presence of other grooming disorders (also called body focused repetitive behaviours [BFRBs]) such as skin-picking and nail-biting (McElroy et al. 1998; Christenson and Mansueto 1999; Stein et al. 2008; Snorrason et al. 2012a; Snorrason et al. 2012b). Trichotillomania has also been reported to be the most common current and lifetime comorbid disorder in clinically significant skin-picking (Arnold et al. 1998; Lochner et al. 2002; Odlaug and Grant 2008b; Odlaug and Grant 2008a). The lifetime prevalence of trichotillomania in skin-picking disorder is high (38.3% in one study) (Christenson and Mansueto 1999) compared to the rate of trichotillomania in the general population (0.6%–3.9%).

In summary, SUDs and behavioural addictions often co-occur, and have overlapping comorbidity with one another, and disorders such as the mood and anxiety disorders, OCD and ADHD. Comorbidity between SUDs and gambling disorder, and between trichotillomania and skin-picking disorder have consistently been reported over the years, suggesting that these relationships may be particularly strong.

In addition, data from family and twin studies have suggested a strong link between SUDs and some of the behavioural addictions (i.e. gambling disorder), between some of the behavioural addictions themselves (i.e. trichotillomania and skin-picking

disorder), and between many of these substance and behavioural addictions and OCD. For example, a recent family study showed that relatives (with problematic gambling themselves) of individuals with gambling disorder had higher comorbidity rates or a number of conditions including any SUD compared to control relatives (Black et al. 2014). Although family data on the behavioural addictions are limited, a possible family relation has been suggested between trichotillomania and skin-picking disorder. In one study, almost 8% of probands with skin-picking disorder (a sample size of  $n=718$ ) reported a family history of trichotillomania diagnosis (Snorrason et al. 2012b), a rate much higher than reported in samples of relatives of individuals in the general population (0%). Although some have argued that trichotillomania and skin-picking disorder may have a stronger association with each other than with OCD (Phillips et al. 2010), there also have been many reports of a significant link between some of these behavioural addictions (especially trichotillomania) and OCD. For example, in a family study of OCD patients that investigated the relationship of this condition with others – including behavioural addictions such as gambling disorder, trichotillomania and skin-picking disorder – it was found that any of these behavioural addictions occurred more frequently in first degree relatives of individuals with OCD, irrespective of whether or not cases also had the same diagnosis (Bienvenu et al. 2000). The association may be strongest for trichotillomania; a family study investigating the familial aggregation of trichotillomania and co-transmission of OCD and skin-picking disorder suggested that relatives of individuals with trichotillomania had higher recurrence risk estimates for both trichotillomania and OCD (but not skin-picking disorder) compared to control relatives (Keuthen et al. 2014). Based on these results, it was argued that there may be a familial subtype of trichotillomania related to OCD. The strong association between trichotillomania and OCD is also supported by three earlier studies that reported higher prevalence of OCD in first-degree relatives of patients with trichotillomania (compared to the general population) either via collection of family history or direct interviewing of relatives (Lenane et al. 1992; Schlosser et al. 1994; King et al. 1995). More recently, elevated grooming disorders including trichotillomania alone was also reported in OCD probands and their relatives compared to controls (Bienvenu et al. 2012).

Combined, these comorbidity and family history findings suggest that SUDs and some of the candidate behavioural addictions (e.g. gambling disorder) may share a common pathophysiology (Grant et al. 2010b). That said, data on associated comorbidity requires further work to make claims about causality. SUDs and behavioural addictions may interact and so perpetuate one another (Petry et al. 2005). For example, mood disorders and SUDs may develop as a consequence of gambling disorder, while disorders such as SAD and PTSD may share a common familial etiology with gambling disorder (Black et al. 2014). Recognition of the significant overlap between SUDs and some of the behavioural addictions in terms of comorbidity may have implications for future diagnostic classification systems, neurobiological models, and novel treatment directions.

## **Neurobiology**

In SUDs, the excessive intake of drugs has been suggested to induce a cascade of psychological, social and neurobiological disruptions. On the neurobiological level, drugs directly or indirectly increase dopamine levels in the neural ‘reward system’. In

addition, drug intoxication is associated with strong reinforcement effects, which induce reinforcement learning and heighten salience attribution to the drugs of abuse (Wise 2004). Continued drug use is associated with changes in neurotransmitter systems. The most well-known changes are reductions in dopamine (DA) D2/D3 receptors and dopamine transporter availability in the striatum measured by PET and SPECT imaging respectively (Volkow et al. 2009; Hou et al. 2014). Hence, diminished DA function is considered to be a hallmark of drug use disorders.

Another consequence of continued drug use is that the salience of drug-related stimuli increases at the expense of salience of other reinforcers (Kalivas and Volkow 2005). Evidence of this 'hijacking' of the reward system has been provided by fMRI studies showing diminished BOLD responses in the mesolimbic system, including the striatum, insula and ventromedial prefrontal cortex (VMPFC). Drug cues, on the other hand, elicit enhanced BOLD responses in these areas (Jasinska et al. 2014).

Besides the adaptations in the reward system and diminished functioning of cognitive control systems as a consequence of repeated drug exposure (Feil et al. 2010; George and Koob 2010; Goldstein and Volkow 2011), changes in the mesolimbic-prefrontal dopaminergic pathways have been found that show a transition from prefrontal cortical to dorsal striatal control over drug seeking and drug taking behaviours, as well as a progression from ventral to more dorsal parts of the striatum (Everitt and Robbins 2013). All the above processes are thought to contribute to 'compulsive use' or an inability to inhibit the drive to seek and consume drugs in substance dependence.

### *Neurobiology of disordered gambling*

Research into the neural mechanisms underlying disordered gambling has grown substantially in the last decade. Here we will give a concise overview of the recent and main findings in disordered gamblers. For detailed reviews regarding disordered gambling see (van Holst et al. 2010; Romer Thomsen et al. 2014).

An important hallmark of drug abuse disorders is the consistent finding of lower dopamine D2/D3 receptor binding and diminished DA release when the reward system is challenged with amphetamine (e.g. Martinez et al. 2007; Lee et al. 2009). Currently, no significant differences in baseline DA binding in pathological gamblers compared to HCs seem to be present but studies indicate positive correlations between DA binding and gambling severity and impulsivity (Linnet et al. 2010; Clark et al. 2012; Joutsa et al. 2012; Boileau et al. 2013). In addition, in a PET study measuring DA activity during the Iowa Gambling Task it was found that DA release in pathological gamblers was related to excitement (Linnet et al. 2011) and poor performance (Linnet et al. 2010). Overall these results do suggest a role for abnormal DA binding in PG but not to the same extent as that found in drug addiction (Clark and Limbrick-Oldfield 2013). In addition, instead of the diminished DA release in response to amphetamine challenges in substance use disorder studies, a recent PET study using the [11C] PHNO DA (D3) receptor ligand showed that an amphetamine challenge *increased* DA release in the dorsal striatum in disordered gamblers compared to healthy controls (Boileau et al. 2014). Hence, the DA system in disordered gambling could be differently affected than in the case of substance use disorders.

The most recent neuroimaging studies on disordered gambling have provided a mix of results concerning reward and loss anticipation and outcome processing. Studies have found diminished, normal or even increased BOLD responses in disordered



gamblers using a variety of fMRI tasks. For example, disordered gamblers showed attenuated ventral striatal responses during reward anticipation as well as in response to monetary wins (Balodis et al. 2012; Choi et al. 2012). A recent study found no abnormal processing in reward anticipation but higher ventral striatum activity during loss anticipation (Romanczuk-Seiferth et al. 2014). In addition, loss avoidance was associated with lower activity in ventral striatum and MPFC in gamblers compared to controls. In another fMRI study where subjects could make button presses to maximize their wins, no abnormal brain responses in gamblers were found (Fauth-Bühler et al. 2014). On the other hand, using a probabilistic guessing game to model anticipatory processing, gamblers showed greater dorsal striatum activity during anticipation of large rewards compared to small rewards (van Holst et al. 2012b). Similarly, in a task where subjective values for rewards were taken into account, a higher striatal response was found in gamblers compared to controls (Miedl et al. 2012). Finally, providing a more nuanced picture of reward processing in gamblers, Sescousse et al. used a modified monetary incentive delay task to test the sensitivity toward monetary and erotic rewards and found a relatively lower striatal activity when viewing erotic pictures versus monetary wins in gamblers compared to controls (Sescousse et al. 2013a). The authors suggest that in disordered gambling a differential sensitivity to monetary versus non-monetary rewards exists, which may create a bias towards monetary rewards, potentially promoting addictive gambling behaviour.

In order to explain these divergent findings it has also been suggested that under most conditions problem gamblers are characterized by a hypo-responsive reward circuitry. However, highly salient cues could lead to enhanced attention that can enable normal to even enhanced levels of striatal activation (Leyton and Vezina 2012; van Holst et al. 2012c). In line with this postulation is the finding from a study showing that salient gambling cues increased striatal activity during impulsive choices (i.e. delay discounting) in gamblers more than less salient gambling cues did (Miedl et al. 2014). In addition, fMRI studies investigating cue reactivity responses towards gambling cues in problematic gamblers have shown enhanced BOLD responses in the mesolimbic prefrontal regions (Goudriaan et al. 2010; Meng et al. 2014b), quite similar as findings in subjects with substance use disorders. The important message from these fMRI studies is that naturalistic gambling cues critically influence the behavioural and fMRI results in disordered gambling studies.

There is less consistent evidence for diminished cognitive control functions in disordered gambling, compared to the evidence in drug abuse disorders. Neuropsychological testing in subjects with either alcohol dependence or disordered gambling have shown that both disorders are associated with less advantageous decision making abilities and higher impulsive choice behaviour than people without addictive disorders (Goudriaan et al. 2006). However, dissimilar from subjects with substance use disorders, subjects with disordered gambling do not always have working memory problems (Yan et al. 2014), although response inhibition and cognitive flexibility problems seem to be present in more severe forms of pathological gambling (Goudriaan et al. 2006; Odlaug et al. 2011).

Neuroimaging studies have provided a subtler message, suggesting the existence of compensatory mechanisms in subjects with disordered gambling that can help them overcome sub-optimal cognitive functioning. For example, a stop signal fMRI task yielded no differences in behavioural performance between problem gamblers, heavy smokers and controls, but both groups showed hypo-responsiveness of the

dorsal medial prefrontal cortex compared to healthy controls (de Ruiter et al. 2012). A Tower of London task measuring working memory and cognitive planning abilities also revealed no cognitive impairments or abnormal brain responses in problem gamblers (de Ruiter et al. 2009). Similarly, no behavioural differences were found on a Go-NoGo task between problem gamblers and controls, whereas problem gamblers did show enhanced activity in the dorsal medial prefrontal cortex and inferior frontal cortex (van Holst et al. 2012a). However, in the context of contingency learning, slower reversal and extinction learning has been found, indicating less flexibility in reward related learning (de Ruiter et al. 2009; Vanes et al. 2014).

#### *Neurobiology of trichotillomania and skin-picking disorder*

In comparison to research into gambling disorder, relatively little research has studied neurobiological underpinnings of grooming disorders, and there is less evidence that these conditions are associated with primary problems in reward processing. For detailed review of the neurobiology of trichotillomania see (Chamberlain et al. 2009). There are a handful of structural and functional neuroimaging studies (radioligand studies are lacking), and some cognitive studies.

In terms of brain structure, increased grey matter density of the striatum (caudate/putamen), left amygdalo-hippocampal formation, bilateral anterior cingulate cortices, and right frontal lobe has been observed in patients with trichotillomania compared to controls (Chamberlain et al. 2008). These findings were complemented by reduced white matter connectivity of tracts inter-linking these neural nodes in one study (Chamberlain et al. 2010b), while another study did not identify white matter tract abnormalities in patients versus controls (Roos et al. 2013). Using permutation cluster analysis and automated techniques for quantification of grey matter morphology, patients with trichotillomania and their asymptomatic first-degree relatives showed excess cortical thickness compared to controls in right frontal lobe and other select regions (Odlaug et al. 2014), suggesting that these morphological abnormalities may represent a vulnerability or 'trait' marker. Another study reported that patients with trichotillomania had reduced thickness of right parahippocampal gyrus compared to a pooled control group that included patients with skin-picking disorder and healthy individuals (Roos et al. 2014).

Using an implicit sequence learning task, patients with trichotillomania did not differ significantly from controls in terms of brain activation in regions of interest (Rauch et al. 2007). When a reward processing task was utilized in a separate study, patients with trichotillomania showed dampened neural responses in the nucleus accumbens for reward anticipation, but relative over-activity for gain and loss outcomes (White et al. 2013). Furthermore, trichotillomania was associated with functional dysconnectivity between anterior cingulate cortex and the nucleus accumbens, in the resting state. These preliminary findings implicate reward dysfunction in trichotillomania.

For skin-picking disorder, one study identified excess volume of the ventral striatum, reduced cortical thickness in the right frontal lobe, and excess thickness of the cuneus bilaterally, as compared to controls (Roos et al. 2014). In a separate study, skin-picking disorder was associated with reduced integrity of white matter tracts bilaterally (Grant et al. 2013a) in regions remarkably akin to those previously observed to be abnormal in trichotillomania (Chamberlain et al. 2010a).

Cognitive deficits have been reported in some but not all studies of trichotillomania (Chamberlain et al. 2009). Much of this limited research has focused on inhibitory

control, given the repetitive motoric nature of grooming disorders. Stop-signal impairment, indicative of motor impulsivity, has been observed in patients with trichotillomania and in their clinically asymptomatic first-degree relatives, suggesting a trait marker (Chamberlain et al. 2006; Odlaug et al. 2014); as well as in patients with skin-picking disorder (all versus healthy controls) (Odlaug et al. 2010; Grant et al. 2011). Further research is needed to explore this and other cognitive domains in grooming disorders.

### *Neurobiology of kleptomania*

The neural correlates of kleptomania (compulsive shoplifting) have barely been studied, despite the condition being recognized in the medical and legal literature for centuries. This lack of scientific scrutiny may reflect the perceived rareness of the condition, difficulty obtaining funding for this topic, and recruitment difficulties.

In a pilot study, presented to date in conference proceedings only, kleptomania was associated with reduced platelet serotonin transporter levels as compared to controls (Marazziti et al. 2000). In a relatively small neuroimaging study, kleptomania was associated with significantly reduced fractal anisotropy (suggestive of disorganized and/or damaged white matter tracts) in frontal brain regions compared to controls (Grant et al. 2006b). To the knowledge of the authors, no other neuroimaging studies of kleptomania exist.

One study has explored aspects of cognitive functioning in people with kleptomania, but did not include a control group and so performance was compared to normative data (Grant et al. 2007c). Using pen/paper tasks, it was found that the mean cognitive scores for the kleptomania group were within 0.5 standard deviations of the normative standard for age. However, in secondary analysis, worse symptom severity was correlated significantly with greater impairment in Wisconsin Card Sorting Test global performance. More recently, a study examined cognitive functioning in people with shoplifting (having shoplifted at least once in the preceding year) compared to controls, using computerized neurocognitive paradigms. The shoplifters gambled significantly more points on the Cambridge Gamble Task, and showed deficits on the hardest difficulty level of a Spatial Working Memory task (Grant et al. 2012a). Other cognitive domains were intact. Shoplifters also scored higher on questionnaire-based scores relating to impulsivity (Barratt Impulsiveness Scale). Interestingly, elevated Barratt impulsivity scores have also been documented in a kleptomania sample previously (Bayle et al. 2003).

### *Neurobiology of compulsive sexual behaviour*

There are few neuroimaging and neuropsychological investigations of compulsive sexual behaviour to date. This may be for similar reasons to kleptomania, with the additional problem that a widely accepted definition for the disorder is lacking. Criteria for hypersexual disorder were proposed for DSM-5 but the disorder was not included therein.

In a pilot study, people with compulsive sexual behaviour showed lower white matter diffusivity in superior frontal brain regions compared to controls, coupled with impulsive behavioural performance on a go/no-go paradigm (Miner et al. 2009).

In healthy volunteers, it is reasonably well established that viewing of erotic stimuli activates distributed neural circuitry including the ventromedial prefrontal cortex, nucleus accumbens, amygdala, insula, and thalamus; findings redolent of those for exposure to monetary and food-related rewards (Sescousse et al. 2013b). Hours

spent viewing pornography per week was found to correlate negatively with grey matter volume in the right caudate, with fMRI activity during sex-related cues in the left putamen, and with functional connectivity between right caudate and left dorsolateral prefrontal cortex (Kuhn and Gallinat 2014).

Using fMRI, people with compulsive sexual behaviour, compared to controls, showed enhanced neural responses to erotic videos in the dorsal anterior cingulate cortex, nucleus accumbens, and amygdala (Voon et al. 2014a). Processing bias for sex-related visual stimuli has been found in a separate study using a dot-probe attentional task, in people with compulsive sexual behaviour compared to controls (Mechelmans et al. 2014).

Dopamine appears to play a key role in various aspects of reward, including in relation to sexual stimuli. In frontotemporal dementia, a disorder associated with reduced presynaptic dopamine receptors in the striatum (and elsewhere), hypersexuality was associated with relative atrophy of right ventral putamen and pallidum (Perry et al. 2014). Pro-dopaminergic medication has been linked with sexual behaviour in Parkinson's Disease (Vilas et al. 2012; Poletti et al. 2013). In patients with Parkinson's Disease, increased sexual desire correlated with enhanced activation in the nucleus accumbens, cingulate cortex, and orbitofrontal cortex (Politis et al. 2013). In healthy controls, dopamine agonism with l-dopa enhanced nucleus accumbens and anterior cingulate activation in response to subliminal sexual stimuli (Oei et al. 2012), also consistent with a role for dopamine in processing of sexual stimuli, and – by implication – possibly compulsive sexual behaviour.

Apart from the focus on attentional biases, other aspects of cognitive functioning in people with compulsive sexual behaviour have received little attention.

### *Neurobiology of internet addiction*

Compulsive internet use, or internet addiction, is likely to be heterogenous. Some argue that in fact the internet is merely a 'route' or 'throughway' that facilitates another type of behavioural addiction, such as compulsive online pornography viewing (which may have direct parallels with compulsive sexual behaviour, considered above), compulsive online shopping, or internet gaming disorder. There is a burgeoning neuroimaging and neurocognitive literature relating to internet addiction, much of which has arisen from Asia, where perhaps this issue has received more attention.

Structurally, internet gaming addiction has been linked with reduced grey matter density in inferior frontal gyrus, cingulate, insula, precuneus, and hippocampus; along with lower white matter density in related regions (Lin et al. 2015). In a meta-analysis of ten voxel-wise whole-brain fMRI studies, using a variety of cognitive challenge paradigms (mainly focusing on aspects of inhibitory control and flexible responding), internet gaming disorder was associated with excess activation, compared to controls, in the bilateral medial frontal gyrus, left cingulate gyrus, left medial temporal gyrus, and fusiform gyrus (Meng et al. 2014a). In a relatively small resting state fMRI study, internet addiction was associated with reduced functional connectivity versus controls across distributed neural circuitry, particularly implicating the bilateral dorsal striatum (putamen), and connections between cortical and subcortical regions (Hong et al. 2013). Another resting state fMRI study, this time in a larger sample of adolescents with internet gaming addiction versus controls, found increased functional connectivity in the bilateral cerebellum and middle temporal

gyrus; and reduced connectivity involving the bilateral inferior parietal lobule and right inferior temporal gyrus (Ding et al. 2013).

Some cognitive deficits have been described in internet addiction, for example in relation to aspects of mental flexibility and inhibitory control (Zhou et al. 2012; Ko et al. 2014). However, a recent meta-analysis reported inhibitory deficits in SUDs and pathological gambling, but contradictory evidence for the existence of such deficits in internet addiction (Smith et al. 2014). In particular, internet addicts showed medium deficits on some go/no-go variants but no difference to controls on the stop-signal task.

### *Parkinson's Disease and Medications: broader implications for neurobiology of behavioural addictions*

In some cases, behavioural addictions may be induced by dopaminergic agents used in the treatment of Parkinson's Disease, restless leg syndrome, and/or hyperprolactinaemia. In a retrospective analysis of adverse event reports (FDA database), the dopamine agonists pramipexole and ropinirole, which have preferential affinity for dopamine D3 receptors, were most strongly associated with impulse control disorders (Moore et al. 2014). Various approaches have been used to study the neurobiological underpinnings of impulse control disorders in Parkinson's Disease, including radiotracers, drug manipulations, and neuropsychological tasks (for excellent review see Napier et al. 2015). For example, in a radioligand imaging study in patients with Parkinson's Disease, patients with concurrent impulse control disorders showed significantly lower binding of striatal dopamine receptors (Voon et al. 2014b). In all, behavioural addictions in patients with Parkinson's Disease appear to be linked with dysregulation of striatal dopamine pathways, supporting involvement of reward circuitry in the manifestation of these disorders more widely. However, it is important to note that effects of dopaminergic drugs on behaviour and occurrence of behavioural addictions is likely to be contingent on baseline function of the dopamine system.

## **Treatment**

Understanding a range of impulsive disorders as 'behavioural addictions' has arguably resulted in new treatment directions. These putative behavioural addictions in fact often, but not always, respond positively to the same psychosocial and pharmacological treatments used for substance addictions. The self-help approaches based on the 12-step model, motivational interviewing, and cognitive behavioural therapies commonly used to treat SUDs have been successfully used to treat gambling disorder, compulsive sexual behavior and kleptomania (Garcia and Thibaut 2010; Grant et al. 2012b; Lourenco Leite et al. 2014; Rash and Petry 2014). Psychosocial interventions for both behavioural addictions and SUDs often rely on a relapse prevention model that encourages abstinence by identifying and coping with high-risk triggers for use and modifying lifestyle to reinforce healthier behaviours.

There are no medications currently approved in any jurisdiction for the treatment of behavioural addictions, but some medications that have shown promise in treating SUDs have also shown promise in treating behavioural addictions.

Opioid antagonists (e.g., naltrexone, nalmefene), well researched for the treatment of alcohol and opiate use disorders, have shown efficacy in controlled clinical trials (three positive) for gambling disorder and (one positive trial) for kleptomania (Grant et al. 2009a; van den Brink 2012). These medications have also demonstrated efficacy in uncontrolled studies or in case reports for the treatment of compulsive sexual behaviour (Raymond et al. 2010), and in subtypes of individuals with trichotillomania (i.e. those with family histories of alcoholism) (Grant et al. 2014b). These findings suggest that the opioid system may play a similar role in behavioural addictions as it does in SUDs, possibly through modulation of the dopaminergic mesolimbic pathway.

Medications that modulate glutamatergic activity have also been used to treat both behavioural addictions and SUDs. Glutamate may play an important role in impulsivity, craving, attentional bias, and relapse. N-acetyl cysteine, an amino acid that restores extracellular glutamate concentration in the nucleus accumbens has demonstrated efficacy in reducing the reward-seeking behaviour in individuals with a range of substance addictions, including nicotine dependence and marijuana addiction (Asevedo et al. 2014). N-acetyl cysteine has also demonstrated promise in the treatment of behavioural addictions such as gambling disorder and trichotillomania (Grant et al. 2007a; Odlaug and Grant 2007; Grant et al. 2009b).

Another pharmacological agent with glutamatergic effects is memantine, a medication that has also demonstrated early promise in treating substance use disorders and behavioural addictions. Memantine is a noncompetitive antagonist at the NMDA receptor and is used primarily for the treatment of cognitive decline in Alzheimer's disease. In addition to its antagonist actions at NMDA receptors, memantine also blocks the serotonin type 3 receptor (5-HT<sub>3</sub>) as well as nicotinic acetylcholine receptors. Memantine has been reported to be superior to placebo in attenuating on-going drinking and/or craving for alcohol in alcoholic subjects, despite a larger placebo-controlled study indicating it did not reduce on-going drinking behaviour in alcohol-dependent patients (Olive et al. 2012). Memantine has been reported to decrease the subjective effects of cigarette smoking and intravenous heroin as well (Olive et al. 2012). In uncontrolled clinical trials, memantine has demonstrated promise in reducing the pathological behaviours of gambling and stealing (Grant et al. 2010a; Grant et al. 2012c; Grant et al. 2013b). Amantadine is used for Parkinson's Disease and acts in part as an NMDA receptor weak antagonist. Amantadine has been found to reduce gambling problems in patients with Parkinson's Disease (Thomas et al. 2010) and also was associated with reductions in symptom severity in a case report of a patient with gambling disorder (Pettorruso et al. 2012).

Topiramate, like other anticonvulsants including gabapentin and lamotrigine, has multiple mechanisms of action, including inhibition of presynaptic voltage-gated Na<sup>+</sup> and Ca<sup>2+</sup> channels which in turn inhibit the release of neurotransmitters such as glutamate. Topiramate has shown promise in controlled clinical trials for SUDs, particularly alcoholism and cocaine addiction (Olive et al. 2012; Johnson et al. 2013;

Kranzler et al. 2014). With regards to behavioural addictions, small uncontrolled studies and case reports suggest that topiramate may also be of potential use in the treatment of gambling disorder, kleptomania, skin-picking, trichotillomania, and compulsive sexual behaviour (Khazaal and Zullino 2006; Lochner et al. 2006; Roncero et al. 2009). Pilot data suggest that other anticonvulsants, such as gabapentin, pregabalin, and oxcarbazepine, show promise in treating alcohol addiction and/or gambling disorder, and therefore may merit clinical scrutiny in other behavioural addictions (Martinotti et al. 2007; Pettorruso et al. 2014). Collectively, the available studies suggest that glutamatergic modulation of dopaminergic tone in the nucleus accumbens, and possibly the prefrontal cortex, may be the mechanisms common to behavioural addiction and substance use disorders.

Brain stimulation, such as with transcranial magnetic stimulation (TMS), has been used with success to explore the basis of substance addictions in animal models and in humans (Feil and Zangen 2010; Fraser and Rosen 2012). There have been some promising findings in brain stimulation treatment trials in patients with nicotine addiction and cocaine use disorder (Gorelick et al. 2014). While experimental at this stage, it would be valuable to explore TMS and related techniques in the context of behavioural addictions in future, both as a means of probing the underlying neural substrates, and potentially as novel treatment approach.

## **Conclusions**

This paper has surveyed comorbid, neurobiological, and treatment overlap across several putative behavioural addictions, as contrasted with substance addiction. Can the notion of behavioural addiction be supported? Phenomenologically, behaviourally addicted individuals frequently exhibit impaired control (e.g. craving, unsuccessful attempts to reduce the behavior), impairment (e.g. narrowing of interests, neglect of other areas of life), and risky use (persisting intake despite awareness of damaging psychological effects). Whether these behaviors also meet physiological criteria relating to addiction (tolerance, withdrawal) is more debatable, but there is good evidence for these variables playing a role at least for gambling disorder. From the perspective of comorbidity, there is evidence for overlap across substance and behavioural addictions. For several behavioural addictions, it remains unclear whether this overlap with substance addictions, and with other behavioural addictions, is particularly strong, as compared to overlap with other psychiatric disorders, notably mood/anxiety disorders, OCD, and ADHD. The strongest evidence for a special comorbid relationship between addictive disorders at present is for a link between (i) substance addiction and gambling disorder; and (ii) between trichotillomania and skin-picking disorder. Indeed, there is evidence to support shared heritable contributions across gambling disorder and substance dependence (Slutske et al. 2000). For internet addiction, it is an open question whether this represents a discrete, tangible entity, or rather represents a conduit for other more concrete manifestations of addiction (such as compulsive pornography use [sexual behavior], or gaming use).

Neurobiological evidence that can inform the debate about behavioural addictions includes structural brain imaging, objective cognitive assessment, and functional brain imaging (during the resting state, cognitive challenge, and/or symptom challenge). There appear to be overlapping neurobiological features between

substance use disorders and behavioural addictions: the strongest evidence to date is for an overlap between SUDs and gambling disorder, but this may simply reflect the relative lack of research into other putative behavioural addictions considered. Across behavioural addictions, the most consistently implicated neural regions include the ventral striatum (nucleus accumbens), dorsal striatum (caudate/putamen), the cingulate cortices, and frontal cortices. It should be noted that while evidence bounds for reward circuitry dysfunction in gambling disorder, evidence for this in trichotillomania is preliminary (single study), and is lacking completely for skin picking disorder so far. From a cognitive perspective, inhibitory dyscontrol has been a main focus, with evidence of impairment across the behavioural addictions, albeit not consistently, and to an extent contingent on the nature of the task being utilised. Clearly behavioural addiction is not 'one thing': to tease apart commonalities and differences in the neural underpinnings of these conditions will require large scale international research efforts. Some of the neural and cognitive abnormalities in behavioural addictions may represent 'vulnerability' or 'trait' markers rather than being directly affiliated with symptoms. To clarify this issue, a paradigm shift is required to also consider whether markers exist in asymptomatic individuals who are at increased genetic risk of developing the given disorder (first-degree relatives).

It should be noted as a limitation that this review focused selectively on particular candidate behavioural addictions. There are multiple other behaviors that may also be considered within the behavioural addiction model, and by no means do we intend to discount them. Key examples include exercise addiction (Berczik et al. 2012), work addiction (Elowe 2010), compulsive buying/shopping (Muller et al. 2015), and food addiction (e.g. as conceptualised in binge-eating disorder) (Ziauddeen and Fletcher 2013). Vital areas for future research will be to establish the validity of these other entities within the behavioural addiction framework, and also to consider whether common psychological and pharmacological treatments can be utilised across these entities.

The heuristic construct of 'behavioural addiction' has proven fruitful in psychiatry even thus far, informing the inclusion of gambling disorder alongside substance addictions in DSM-5, and leading to treatments initially developed for substance addictions being trialed in behavioural addictions: this has already contributed to several promising treatments being identified for previously neglected disorders, such as n-acetyl cysteine for trichotillomania. We hope that research in this area will further flourish and inform subsequent revisions to diagnostic and classification systems, and novel treatment directions. Whether or not future nosological systems should include a category of 'behavioural addictions', which would implicitly reject other models, remains open to debate. Focusing on behavioural addiction *per se* may neglect other common aspects of these conditions. Other more comprehensive models may be useful, such as the idea of 'body-focused repetitive behaviour disorders' (Stein et al. 2006), which considers not only behavioural addiction, but also affect dysregulation, and cognitive dyscontrol (impulsivity). In a recent review of the evidence, the ICD-11 working group on OC and Related Disorders recommended that a grouping of impulse control disorders be retained, defined by repeated failure to resist impulses/drives/urges, despite deleterious longer term consequences (Grant et al. 2014a).



### Key questions for future research:

- Are behavioural addictions similar to substance addition in all phenomenological aspects, including tolerance and withdrawal? If withdrawal does exist, over what time course? Are all behaviours in these disorders initially 'rewarding'?
- While there are some genetic studies for gambling disorder, similar studies for most other candidate behavioural addictions are severely lacking. Are the behavioural addictions heritable, and if so, what genetic factors are implicated?
- To what extent are neural and cognitive findings in behavioural addictions replicable across studies, and do they reflect trait or state markers?
- If there are common underpinnings across behavioural and substance addictions, why do some disorders share stronger comorbid overlap (*viz* substance addiction and gambling disorder; trichotillomania and skin-picking disorder); and what are the mediating etiological factors?
- How best should behavioural addictions be treated? Can an evidence base for treating less well studied behavioural addictions (e.g. internet addiction) be established? If a novel psychological or pharmacological intervention (e.g. glutamate modulator) works for one behavioural addiction, does it work for others?
- Is the behavioural addiction model oversimplistic? Would a more comprehensive model, such as one that emphasised not just addiction but also affect dysregulation and lack of top-down control (i.e. impulsivity/compulsivity), better capture the underlying pathology?

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