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Impulsive and Compulsive Behaviours in Parkinson's disease

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Abstract

Impulsive compulsive behaviours (ICBs) in Parkinson's disease (PD) are a common and devastating side effect of dopamine replacement therapy. In this review we describe the phenomenology, prevalence and risk factors of these patients. Results of behavioural studies assessing the neuropsychological profile emphasize that the ICBs, which are behavioural addictions, are not hedonically motivated. Rather, other factors such as the inability to cope with uncertainty may be triggering ICBs. New insights from functional imaging studies, strengthening the incentive salience hypothesis are discussed and therapeutic guidelines for the management of ICBs in PD are given.

Introduction

Parkinson's disease (PD), described by James Parkinson in 1817 (Parkinson 1817), is the second most common neurodegenerative disorder after Alzheimer's disease (de Lau and Breteler 2006) and is characterized by dopaminergic cell loss in the substantia nigra (Kish, Shannak et al. 1988; Fearnley and Lees 1991). The median age of disease onset is 60 years and the incidence increases with age and affects about 1% of people over 60 and 2–3% over 65. The cardinal features of PD, bradykinesia, tremor, rigidity and postural instability, only emerge when more than 30% of the dopaminergic neurons in the ventrolateral tier of the pars compacta have been destroyed (Cheng, Ulane et al. 2010).

L-dopa still remains the most efficacious treatment for PD, despite being introduced in the late 1960s (Lees, Hardy et al. 2009). Non ergoline dopamine agonists such as pramipexole, ropinirole and rotigotine are other albeit less effective drugs targeting mainly the dopamine D2 and D3 receptors. Dopamine agonists have been claimed to be particularly useful in younger onset PD patients because when used as monotherapy they induce less often problematic dyskinesias. However, increasing reports of devastating behavioural side effects directly triggered by dopamine agonists have limited its use, which have been clinically defined as impulsive compulsive behaviors (ICBs). These addictive behaviours include

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gambling addiction, compulsive sexual behaviour and shopping and the inappropriate, excessive use of dopaminergic medication (dopamine dysregulation syndrome, DDS). Dopamine agonists can cause neuroplastic changes in susceptible individuals with increased dopamine release in the ventral striatum to reward related cues (Steeves, Miyasaki et al. 2009; O'Sullivan, Wu et al. 2011), causing sensitization of the ventral striatum (O'Sullivan, Wu et al. 2011). This higher mesolimbic dopamine levels are thought be a key mechanism in driving these aberrant behaviours.

Before discussing ICBs associated with PD, it is important to acknowledge that impulsivity and compulsivity have been defined in various ways. Furthermore, the behavioural tasks that are useful as measures of impulsivity and compulsivity, and the neural circuits that underlie these behaviors, are the subject of on-going research. Impulsivity as a construct has been defined and studied on at least three levels. At the descriptive level, it has been described as "a behaviour that is performed with little or inadequate forethought" (Evenden 1999). Such behaviours are often characterized by a failure to "resist an impulse". At a more quantitative level, self-rating questionnaires have also been used to measure impulsivity. They contain questions such as, "I say things without thinking" (Patton, Stanford et al. 1995), and the answers to these questions are thought to quantify whether one in fact acts accordingly. The use of self-report questionnaires is still prevalent, although some caution is needed in interpreting their results. For example, a patient with addictive behaviours may give less attention to the questionnaire and may have poor insight into their own predilections (Verdejo-Garcia, Lawrence et al. 2008).

Computerized tests that directly measure behavioural responses have been developed more recently (Verdejo-Garcia, Lawrence et al. 2008), as a more quantitative tool for assessing impulsivity. This approach has been motivated by the fact that behavioral tasks are better suited to isolating the contribution of specific neural circuits to behaviour. Further, the behavioural tasks can be used in preclinical studies in animal models and functional imaging experiments in human subjects.

At least three aspects of impulsivity have been assessed so far using computerized tests. (1) Impulsive action. These tasks include the stop signal reaction time task; go, no-go tasks and related tasks that measure the participant's ability to stop an automatic response ('action restraint'). (2) Temporal discounting. Temporal discounting tasks measure preferences for smaller immediate rewards over larger delayed rewards. These tasks are either administered as pencil and paper questionnaires that ask hypothetical questions or as computer based tasks that deliver money over short intervals on the order of 10s of seconds. The questionnaires contain questions such as, "Would you prefer $5 today, or $20 in 6 months?" (3) Cognitive impulsivity. Tasks that measure cognitive impulsivity include decision making under risky conditions and reflection impulsivity, which is defined as the ability to gather and evaluate more information before making a choice (Evenden 1999; Verdejo-Garcia, Lawrence et al. 2008). The relationship between these three domains at the behavioral or neural circuit levels, if there is one, is still unclear.

Compulsivity as a construct is related to, but in some aspects distinct from impulsivity (Dalley, Everitt et al. 2011; Robbins, Gillan et al. 2012). While impulsivity, at a descriptive

level, focusses more on actions which are not well planned, compulsivity is better characterized as persistent non-goal orientated behaviour, often leading to untoward outcomes. There is, however, a clear overlap between impulsivity and compulsivity (Robbins, Gillan et al. 2012) making it difficult clinically to label a behavioural addiction seen in PD as purely impulsive or compulsive. For example, PD patients with gambling addictions prefer playing slot machines or buying scratch cards (Gallagher, O'Sullivan et al. 2007; Djamshidian, Cardoso et al. 2011). Both of these games require stereotyped repetitive movements, which would be consistent with compulsivity. However, gambling is also risky, and therefore these games also fall into the category of cognitive impulsivity.

Hence for this review we describe addictive behaviours in PD as impulsive and compulsive behaviours (ICBs) as opposed to impulse control disorders (ICDs), emphasizing that both components can coexist at the same time. It is also important to point out that neither impulsivity nor compulsivity is necessarily maladaptive. Studies performed under time pressure have shown better task performance in high trait-impulsive volunteers compared to those with low trait-impulsivity. This has led to the terms “functional” and “dysfunctional” impulsivity (Dickman 1990). These traits become maladaptive when they interfere with daily life sufficiently to lead to substantial distress and dysfunction.

Phenomenology and epidemiology of ICBs

ICBs in PD occur in at least 14% of treated patients (Weintraub, Koester et al. 2010). Cross cultural differences in these estimates exist with a much lower prevalence in China and Korea (Fan, Ding et al. 2009; Lee, Kim et al. 2009) and much higher prevalence, up to 35%, in Finland (Joutsa, Martikainen et al. 2012). ICBs commonly co-occur in the same patient, with one published study reporting 28% of respondents with ICBs exhibiting more than one aberrant behaviour (Weintraub, Koester et al. 2010). It is likely that a large proportion of PD-related ICBs are undiagnosed in routine clinical settings where the symptoms are not specifically looked for. Patients and their families often do not spontaneously disclose ICBs (Avila, Cardona et al. 2011), probably for a number of reasons including embarrassment and lack of insight. Furthermore, patients and their families may think that these behaviours are unrelated to PD and therefore irrelevant to their treating physicians. While face-to-face interviews with a healthcare professional are still the accepted “gold standard” for identification and grading of ICB severity, validated patient-completed and carer-completed questionnaires may be an important screening tool to allow these sensitive conversations to occur (Weintraub, Hoops et al. 2009).

Gambling addiction

Pathological gambling is defined as inappropriate, persistent, and maladaptive gaming behaviour. According to the new diagnostic criteria pathological gambling has been reclassified and falls now into the category of “Addiction and Related Disorders”. (Table 1). In a large population survey of 43,093 healthy US respondents, the lifetime prevalence of gambling addiction was estimated at 0.42% (Petry, Stinson et al. 2005). The lifetime prevalence of gambling addictions in patients with PD has been reported to be between 3.4% and 8%. Social and cultural differences in addition to easier access to gambling venues may explain why prevalence rates of pathological gambling in PD are higher in the US (5.5%)

compared to Canada (3.6%) (Weintraub, Koester et al. 2010). Further, the prevalence of pathological gambling in PD is lower in Korea and China where estimates range between 0.32% and 1.3% (Fan, Ding et al. 2009; Lee, Kim et al. 2009). Preferred gambling activities include slot machines, lottery/scratch cards and internet gambling, suggesting a predilection for activities which are repetitive, require little higher cortical processing and have high reward uncertainty (Gallagher, O'Sullivan et al. 2007). Further, in these types of gambling "near misses" are frequently seen, and losses can be instantly chased, which likely contributes to the highly addictive potential of these activities. Vulnerable patients also think that they are "in control" in gambles where the probability of winning is at chance level (Langer 1975) and PD patients sometimes develop complex ritualistic behaviours such as lucky charms prior to gambling (Djamshidian, Cardoso et al. 2011).

Compulsive sexual behaviour

All ICBs are likely underdiagnosed in PD, as patients and their families often do not report them in the earlier stages because of embarrassment or lack of insight (Singh, Kandimala et al. 2007). This is particularly true for compulsive sexual behavior. The largest study so far reports a prevalence rate of 3.5% (Weintraub, Koester et al. 2010). Related behaviours including zoophilia and paraphilia have also been described (Raina, Cersosimo et al. 2012; Solla, Cannas et al. 2012). Proposed criteria are shown in Table 2.

Punding

Punding is defined as stereotyped and repetitive non-goal orientated behaviour. It was first described in the 1970s in amphetamine and cocaine addicts in Denmark and California (Rylander 1972) and in 1994 in PD patients treated with L-dopa (Friedman 1994). Excessive hobbyism centered on specific activities including fishing, internet use, driving or walkabouts are commonly observed (Giovannoni, O'Sullivan et al. 2000; Fasano, Ricciardi et al. 2011). Patients often describe their activity as soothing and calming and get irritable when limited in their behaviour (Evans, Katzenschlager et al. 2004). The prevalence rate for punding varies widely from 1.4 % to 14%. In contrast to the previously described addictive behaviours, patients with punding demonstrate more compulsive symptoms and their stereotypies are idiosyncratic, depending on individual life histories (Evans, Katzenschlager et al. 2004). For example, men tend to manipulate more often with technical equipment, such as car engines or watches whereas women prefer sorting and cleaning. As punding behaviours often correlate with pre-morbid occupations or hobbies (Evans, Katzenschlager et al. 2004), it can sometimes be difficult to determine whether the behaviour is new. In these instances, enquiring whether the behaviour interferes with sleep or the person's ability to complete necessary daily tasks may be of most relevance. Proposed criteria are shown in Table 3.

Dopamine dysregulation syndrome (DDS)

DDS is characterised by an addictive or compulsive overuse of dopamine replacement therapies. Patients with DDS take larger amounts of their dopaminergic medication than are necessary to adequately control their motor symptoms in order to avoid "off" periods. The excessive use often leads to adverse consequences such as dyskinesia, which is accompanied by dysphoria and anxiety. Punding is frequently comorbid in this cohort (Evans, Lawrence

et al. 2005). DDS is more commonly associated with L-dopa use (Evans, Lawrence et al. 2005). Therefore, DDS may be seen more frequently in the future because of the more cautious use of dopamine agonists and consequently the more frequent use of L-dopa. Further, PD patients with dopamine agonist withdrawal syndrome are at particular risk of developing DDS in an attempt to alleviate motor deficits (Rabinak and Nirenberg 2010). Estimates for DDS in PD range from 0.6% to 4% (Giovannoni, O'Sullivan et al. 2000; Weintraub, Hoops et al. 2009). Criteria for diagnosis are given in Table 4.

Compulsive shopping

Compulsive shopping has been reported to occur in about 4% of the US-population (Weintraub, Koester et al. 2010). Criteria are given in table 5.

Other impulsive or compulsive behaviours

Reckless generosity (O'Sullivan, Evans et al. 2010), excessive hoarding (O'Sullivan, Djamshidian et al. 2010), drug addiction (Friedman and Chang 2013) and compulsive smoking (Bienfait, Menza et al. 2010), are other less frequently reported ICBs in PD. Binge eating occurs in about 4% of PD patients in the US (Weintraub, Koester et al. 2010) and although clinically it is relatively rare, a large proportion of PD patients develop sub-clinical craving for sweets.

Risk factors for ICBs in PD

Medications

Dopamine replacement therapy is the greatest risk factor for developing addictive behaviours in PD. While nearly all forms of dopamine replacement therapy have been associated with ICBs, including Levodopa and monoamine-oxidase inhibitors (O'Sullivan, Evans et al. 2009; Vitale, Santangelo et al. 2013), dopamine agonists are particularly strongly implicated. Dopamine agonist treatment in PD was associated with a 2- to 3.5-fold increased odds of having an ICB, and this association represents a drug class relationship across ICBs (Weintraub, Koester et al. 2010). Higher doses of dopamine agonists have been also linked with a higher incidence of ICBs in PD (Hassan, Bower et al. 2011) and dopamine agonists in combination with L-dopa have been identified as a risk factor for pathological gambling in PD (Voon, Thomsen et al. 2007). Doses of dopamine agonist, when calculated as a “Levodopa equivalent dose” of over 160 mg per day, have correlated with the incidence of new onset ICBs at follow up after 15 months (Joutsa, Martikainen et al. 2012). Although dopamine agonists can cause punding behaviour in rare instances (McKeon, Josephs et al. 2007) punding is more commonly associated with L-dopa use. Similarly, L-dopa therapy is the greatest risk factor for developing DDS (Evans, Lawrence et al. 2005).

PD itself is not associated with an increased risk for developing ICBs. Two recent studies demonstrated no differences in impulsive tendencies in de novo PD patients compared to matched controls, strengthening further the hypothesis that dopaminergic therapy is responsible for triggering these behaviours (Antonini, Siri et al. 2011; Weintraub, Papay et al. 2013). Furthermore, dopamine agonist use is associated with the development of ICBs in

non-PD conditions, such as in progressive supranuclear palsy (O'Sullivan, Djamshidian et al. 2010) and restless legs syndrome (Cornelius, Tippmann-Peikert et al. 2010), despite the use of lower doses in these conditions compared with PD.

Pharmacological differences between dopamine agonists and L-dopa

Different receptor affinity and binding kinetics may be responsible for the increased prevalence of addictive behaviours with dopamine agonist treatment compared to L-dopa monotherapy. Ropinirole, rotigotine and pramipexole bind to dopamine D_3 receptors 100 fold more strongly than D_2 receptors and have no affinity for the D_1 dopamine receptor (Gerlach, Double et al. 2003; Jenner 2005). Conversely, dopamine, the concentration of which is increased by L-dopa, has a higher affinity for dopamine D_1 and D_2 receptors than D_3 receptors (Ahlskog 2011). Dopamine D_3 receptors are enriched in the limbic system (Sokoloff, Giros et al. 1990; Gurevich and Joyce 1999) and this, therefore, may explain the increased incidence of ICBs seen in PD patients treated with dopamine agonists (Ahlskog 2011).

Furthermore, dopamine stimulates dopamine receptors phasically, before it is broken down by enzymes or transported into the axons by the dopamine transporter. In contrast to this, dopamine agonists stimulate these receptors tonically. This may have consequences on decision making. In non-impulsive PD patients dopamine agonists have been associated with increased risk taking behaviour and it has been suggested that tonic agonism causes an insensitivity to dopamine dips, which are supposed to signal a reward which is smaller than what was expected (so called negative reward prediction error) (van Eimeren, Ballanger et al. 2009). However, this hypothesis is contentious and as we review below, direct estimates of the effect of dopamine agonists on reward prediction error have not strongly supported this.

Additional risk factors: clinical features and personality traits

Patients that have disease onset at an earlier age have an elevated risk for developing ICBs (Weintraub, Koester et al. 2010). Although younger patients are more likely to be treated with a dopamine agonist, the age effect remains significant after controlling for dopamine agonist exposure (Weintraub, Koester et al. 2010). Recent work has suggested that PD patients characterized with postural instability and gait difficulties (PIGD) rather than tremor have increased motor impulsivity (Wylie, van den Wildenberg et al. 2012). However, it is currently unknown whether PD motor phenotypes are more associated with ICBs.

Alcohol abuse or illicit drug addiction, smoking and high novelty seeking personality traits have been also regarded as risk factors for developing ICBs in PD, especially in those with DDS (Evans and Lees 2004; O'Sullivan, Evans et al. 2009; Weintraub, Koester et al. 2010; Voon, Mehta et al. 2011). This suggests a common underlying pathophysiology shared by drug abusers and those with behavioural addictions (Volkow, Wang et al. 2008). The novelty-seeking trait commonly described in PD patients with ICBs is contrary to a previously described (albeit controversial) pre-morbid “parkinsonian personality” (Poletti and Bonuccelli 2012). These so-called “typical” non-ICB PD patients scored higher on ratings of premorbid personality traits such as harm avoidance and were less novelty seeking

(Menza, Golbe et al. 1993; Menza 2000). They are also less likely to have smoked or consumed caffeinated beverages than the background population (Evans, Lawrence et al. 2006). Perhaps related to novelty-seeking is artistic creativity, which has been suggested as an independent risk factor for ICBs in some (Schwingenschuh, Katschnig et al. 2010), but not all studies (Canesi, Rusconi et al. 2012).

Depression and anxiety is more frequently seen in PD patients with ICBs (Evans, Lawrence et al. 2005; Voon, Sohr et al. 2011), although it is difficult to establish the temporal cause-effect relationship between ICBs and other psychiatric comorbidities. In addition, young-onset PD patients, who are more likely to develop ICBs, are significantly more likely to have co-morbid depression, substance abuse/dependence, personality/impulse control disorders, and psychosocial dysfunction relative to 3.5 million disabled Americans, aged 30–54 adjusting for race, age, and sex (Willis, Schootman et al. 2013). Some authors have suggested that the development of ICBs may reflect a coping mechanism following a diagnosis of PD (Delaney, Leroi et al. 2012). Young onset PD patients may also feel more embarrassed by their disease and withdraw socially in favour of introverted activities such as watching TV, online gambling or shopping (Delaney, Leroi et al. 2012). In line with this, quality of life has been shown to be significantly reduced in PD patients with ICBs compared to the non-impulsive group (Leroi, Ahearn et al. 2011). Alexithymia has been associated with impulsivity in newly-diagnosed, drug-naive patients with Parkinson's disease, leading authors to suggest that this may represent a risk factor for the development of impulse-control disorders (Poletti, Frosini et al. 2012).

Dyskinesias have also been associated with the development of punding, independent of increased amounts of dopamine replacement therapy (Silveira-Moriyama, Evans et al. 2006). Dyskinesias and motor fluctuations have also been related to hypersexuality and compulsive shopping but not in patients with pathological gambling (Mestre, Strafella et al. 2013). Shared features between punding and dyskinesias such as an association with young age, high levodopa dose, and improvement seen with STN DBS has led authors to consider whether behavioural and motor disorders in PD part of the same continuum (Voon, Fernagut et al. 2009).

Genetics in PD patients with ICBs

A role for genetic factors in PD patients with ICBs is suggested by the increased likelihood of a family history of gambling problems among patients with ICBs (Weintraub, Koester et al. 2010) and of alcohol use disorders in PD pathological gamblers (Voon, Thomsen et al. 2007). Studies in non PD patients have shown associations between various aspects of impulsivity and dopaminergic (DAT1, COMT, MAOA, DRD2-family genes), serotonergic (serotonin transporter gene, TPH2) and glutamatergic (NMDA receptors) genes (Cormier, Muellner et al. 2013). In PD patients with ICBs, negative results have been seen in studies with relatively small sample sizes. Specifically, genetic polymorphisms of the dopaminergic system including variants of the DRD2 Taq1A, COMT Val(158)Met and DAT1 genes have not shown an association with ICBs in PD patients (Vallelunga, Flaibani et al. 2012). A possible contribution of genetic variation in the serotonergic 2A receptor gene (HTR2A) to the susceptibility to impulse control and repetitive behaviors in Parkinson's disease has been

shown in one Korean study, although the effects were marginal (Lee, Jeon et al. 2012). Future large studies with well-phenotyped ICBs are required to determine the importance of genetic factors in the development of ICBs.

Neural mechanisms underlying ICBs in PD

Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have been done to examine the neural substrates that might be affected in ICBs. PET studies examine changes in neurotransmitter systems, whereas fMRI studies examine activation in neural circuits that putatively underlie behavioural addictions.

PET studies have shown that PD patients with DDS have enhanced L-dopa-induced ventral striatal dopamine release compared to non-impulsive PD patients (Evans, Pavese et al. 2006). This result closely mirrors previous work showing increased ventral striatal dopamine release in cocaine addicts in response to methylphenidate (Volkow, Wang et al. 1997). Two other PET studies also demonstrated higher ventral striatal dopamine release in PD patients with ICBs compared to PD patients without ICBs. One PET study showed higher dopamine release in PD patients with pathological gambling during gambling (Steeves, Miyasaki et al. 2009), and another study found that PD patients with a variety of different ICBs had greater ventral striatal dopamine release following heterogeneous reward-related cues after L-dopa therapy (O'Sullivan, Wu et al. 2011).

Overall, the PET studies have demonstrated a “global sensitization” within the ventral striatum to appetitive stimuli in vulnerable individuals. These studies are consistent with reward/addiction theories which suggest that dopamine motivates the pursuit of rewards by attributing incentive salience to reward-related stimuli. The dopamine triggers craving or wanting of the drug or behavior (Berridge 2007). In ICBs and other addictions, reward cues or dopamine itself may be attributed with pathological incentive salience (Robinson and Berridge 2008) and excessively “wanted” in the absence of differences in hedonic response (“liking”) to the reward-related images or dopamine replacement therapies themselves (Evans, Pavese et al. 2006; O'Sullivan, Wu et al. 2011). This global sensitization or “reward-spillover” reflects the frequent clinical observation of more than one ICB co-occurring in an individual patient (Weintraub, Koester et al. 2010).

Single-photon emission computed tomography (SPECT) in PD patients with pathological gambling has also shown increased brain perfusion in multiple regions, such as the orbitofrontal cortex, the hippocampus, the amygdala, the insula, and the ventral pallidum. This might reflect overstimulation of an intact mesolimbic dopamine system due to dopaminergic medication (Cilia, Siri et al. 2008). More recently, the importance of extrastriatal dopaminergic systems has been suggested by PET imaging of D2 receptor binding showing reduced dopaminergic tone in the anterior cingulate cortex (Ray, Miyasaki et al. 2012), with another PET study showing higher fluorodopa uptake in the medial orbitofrontal cortex, compared to control PD patients, but no differences in the striatum (Joutsa, Martikainen et al. 2012).

Functional imaging studies have also strengthened the links between the ICBs seen in PD and addiction in general, demonstrating abnormalities of neural circuits involving the ventral

striatum, the cingulate gyrus and the orbitofrontal cortex (Dagher and Robbins 2009; Koob and Volkow 2010). For example fMRI studies in PD patients with ICBs showed an increase in ventral striatal activity following reward after dopamine agonist medication (Frosini, Pesaresi et al. 2010; Voon, Pessiglione et al. 2010). Other studies have shown a significant correlation of sexual desire with enhanced activation in the ventral striatum, the anterior cingulate and the orbitofrontal cortex in PD patients with addictive behavours but not in a control patient group (Politis, Loane et al. 2013). In this study, PD patients with hypersexuality reported increased sexual desire after exposure to sexual cues. Consistent with the incentive salience hypothesis, this increased desire did not correlate with "liking" scores.

Using surgically implanted subthalamic electrodes, local field potentials of PD patients who underwent deep brain stimulation (DBS) of the subthalamic nucleus were recorded to assess differences between PD patients with ICBs, non-impulsive PD patients with dyskinesias and PD patients with neither ICBs nor dyskinesias (Rodriguez-Oroz, Lopez-Azcarate et al. 2010). Results showed no difference between these groups when they were off their dopamine medication. However, in the on medication state PD patients with ICBs and PD patients with dyskinesias showed significant changes in the theta-alpha (4–10 Hz) band. While for the ICB group this frequency was generated in the ventral subthalamic area and was coherent with frontal premotor activity, in the PD group with dyskinesias the frequency derived from the dorsal subthalamic area was coherent with cortical motor activity (Rodriguez-Oroz, Lopez-Azcarate et al. 2010). Thus, the subthalamic nucleus may play an important role in generating impulsive and compulsive behaviours. Amongst several projections the ones to associative limbic areas regardless of the type of addiction strengthen further the link between dyskinesias and ICBs.

Another hypothesis that predicts the development of ICBs follows from the study of habit learning. Within this framework, during repetitive behaviours, the outcome and thus the reward related to an action becomes less important and the patient's behaviour shifts from "goal directed" to "stimulus-response". Stimulus-response behaviours are behaviours in which the stimulus (and not an outcome) drives an action. The transition from goal directed to habitual actions is thought to underlie habit formation in addictive behaviours. In contrast to goal directed behaviour, where actions have to be reassessed and learning is necessary, habit-responses are automatic and are processed via the dorsolateral striatum (Voon, Fernagut et al. 2009; Muresanu, Stan et al. 2012). The development of automatic habit responses may be implicated in the more compulsive, non-strategic types of gambling preferred in PD pathological gamblers, as well as behaviours such as DDS, punding and excessive hoarding which has been correlated with obsessive-compulsive symptoms (O'Sullivan, Djamshidian et al. 2010).

Non-dopaminergic mechanisms in PD ICBs

Apart from dopaminergic pathways, some studies have shown that cortisol might contribute to addiction and impulsivity (Lovallo 2006). In non-PD pathological gamblers, increased salivary cortisol levels have been positively correlated with risk taking (Meyer, Hauffa et al. 2000) and were elevated during gambling (Franco, Paris et al. 2009). Similarly, cortisol has

been shown to be crucial for maintenance of illicit drug abuse (Goeders 2002). Consistent with this, studies have found an acute rise of salivary cortisol levels during gambling only in PD patients with ICBs, which strengthens the link between the hypothalamic-pituitary-axis and addiction (Djamshidian, O'Sullivan et al. 2011).

Other non-dopaminergic mechanisms potentially implicated in the development of ICBs may include the serotonergic system (Lee, Jeon et al. 2012). Serotonin has widespread projections to brain areas important in regulating impulsivity, such as the ventral striatum, the amygdala and the prefrontal cortex and has been found to be critical for action restraint in animal models (Dalley and Roiser 2012). Glutamate may also play a role. Imbalance of extracellular glutamate levels with increased synaptic levels during drug seeking has been described and regulation of this imbalance can improve various addictive behaviours such as smoking or drug craving in humans (Kalivas 2009). Human imaging studies have shown that increased glutamate levels in the anterior cingulate correlate with increased impulsivity (Hoerst, Weber-Fahr et al. 2010) and higher glutamate levels were also found in the cerebrospinal fluid of patients with obsessive compulsive disorders (Chakrabarty, Bhattacharyya et al. 2005; Grant, Odlaug et al. 2009), as well as dyskinesias in humans and animals (Sgambato-Faure and Cenci 2012). The efficacy of amantadine (with glutamate antagonist properties) in reducing ICBs in PD is, however, unclear with one small study showing improvement (Thomas, Bonanni et al. 2010) but others worsening of addictive behaviours (Weintraub, Sohr et al. 2010; Lee, Kim et al. 2011).

Neuropsychological tests

Tests in PD patients without ICBs

Neuropsychological testing in PD patients with and without ICBs has been driven by theories of dopamine function, as well as the hypothesis that ICBs are addictions that may be triggered by underlying impulsive or compulsive tendencies. Therefore, tasks have focused on measures of learning, which is presumably driven by phasic dopamine, as well as behavioural correlates of impulsivity and compulsivity. The learning tasks in patients with PD often ask the subjects to discern, by trial and error, which of two (or more) stimuli is more often being rewarded. Therefore, in each trial the subject is presented with two stimuli and asked to choose one. Usually one of the stimuli is rewarded at a higher rate than the other, for example an 80% reward rate for the “good” stimulus and a 20% reward rate for the “bad” stimulus. After choosing the stimulus they are told whether or not they received a reward. The subject’s task is to select the stimulus that is being rewarded most often, as many times as possible. In the reversal learning version of this task, after the subject has correctly acquired the reward association, measured by a consistent choice of the good stimulus, the reward mapping is reversed and the subject must learn to select the previously bad stimulus.

In PD patients without ICBs several studied have assessed the effects of dopamine medication on learning behaviour. The effect of medication is usually tested by examining the performance of patients off and on their dopamine replacement medication. In most studies both L-dopa and dopamine agonists are either provided as usual (“on” medication) or withdrawn overnight (“off” medication) before testing. In PD patients without ICBs, Cools

and colleagues have shown that dopamine medication can positively or negatively affect task performance, depending on the task. While dopaminergic medication improved task switching behaviour in the on relative to the off state, the same medication impaired reversal learning (Cools, Barker et al. 2001). This apparently paradoxical effect of dopamine on behaviour has been explained by the fact that task switching and reversal learning likely rely on distinct frontal-striatal networks, and dopamine is differentially depleted in these networks. Specifically, task switching relies on networks connecting the dorsolateral prefrontal cortex to the dorsal striatum. In contrast, reversal learning depends on orbitofrontal cortex and the ventral striatum. The dopamine innervation of the ventral striatum is relatively intact in early stage PD patients, whereas dopamine is relatively depleted in the dorsal striatum (Kish, Shannak et al. 1988; Cools, Barker et al. 2001). Effective dopamine replacement in the dorsal striatum designed to reverse bradykinesia might, therefore overstimulate the relatively intact ventral striatum and lead to undesirable cognitive changes in vulnerable individuals. This has been referred to as the ‘cognitive overdose hypothesis’ (Gotham, Brown et al. 1988).

Dopaminergic medication state also has an effect on the way positive and negative feedback are integrated in learning behaviour. Frank and colleagues have shown that non-impulsive PD patients “off” medication were more sensitive to negative feedback (learning from not receiving a reward to not choose a particular stimulus) and had impaired learning from positive feedback (learning from receiving a reward to choose a particular stimulus), whereas patients on medication were more sensitive to positive feedback and had impaired learning from negative feedback (Frank, Seeberger et al. 2004). This original study, however, did not examine performance during the acquisition of reward associations; they examined performance on transfer of learned reward associations to novel stimulus combinations following training. A recent study re-examined these effects and specifically reported results during learning, as well as during transfer (Shiner, Seymour et al. 2012). They found that during acquisition non-impulsive PD patients learned equally well in their “on” and “off” state to discern which of the two stimulus pairs was more likely to be rewarded. However during the performance or transfer phase when novel stimulus pairs were introduced and no feedback was given PD patients “on” medication were significantly better in selecting the correct image compared to those who were “off” medication. This suggests that acute changes in medication do not impact learning. Rather, medication impacts transfer of learned knowledge to novel contexts.

Consistent with an effect of medication on learning reward associations, it has recently been reported that never-medicated PD patients who were given pramipexole or ropinirole and who were followed up for 12 weeks showed differences in learning behaviour at follow up (Bodi, Keri et al. 2009). At baseline, untreated patients had intact learning from negative feedback but impaired reward learning. An opposite learning profile was found after 12 weeks of dopamine agonist therapy, with significant impairment in avoidance of negative outcomes compared to controls but normal reward seeking behaviour.

Tests in PD patients with ICBs

Research in PD patients with ICBs has examined learning, as well as examining a number of tasks thought to assess risk preference, novelty seeking, and several other putative behavioural correlates of impulsive/compulsive tendencies. One early hypothesis for why PD patients develop ICBs was that they overvalue positive feedback, and undervalue negative feedback. This would be consistent with the findings that PD patients without ICBs, on medication, are better at selecting positively rewarded stimuli than negatively rewarded stimuli, following learning (Frank, Seeberger et al. 2004; Shiner, Seymour et al. 2012). Patients that go on to develop ICBs would simply have an exaggerated tendency to overvalue positive feedback. Thus, an addiction to gambling could develop because of a few wins that were over-valued, combined with insensitivity to the losses or negative outcomes. However, studies have shown that PD patients with ICBs in their “on” state are not impaired at learning relative to healthy volunteers (Djamshidian, Jha et al. 2010; Housden, O'Sullivan et al. 2010; Voon, Pessiglione et al. 2010; Djamshidian, O'Sullivan et al. 2012), suggesting that differential response to reward is not the underlying mechanism of ICBs seen in PD. Two studies have in fact shown that PD patients with ICBs respond more to negative feedback on medication and less to positive feedback, whereas this profile is reversed off medication (Djamshidian, Jha et al. 2010; Djamshidian, O'Sullivan et al. 2012). This is the opposite of what has been shown in PD patients without ICBs.

Another possible explanation for the development of ICBs would be a preference for risk. Within a behavioural economics framework risk is defined as an over-preference for large rewards. In other words, if one is risk prone, one values a reward which is twice as large more than twice as much. This can be dissociated from preferential learning from positive feedback, as is studied in the learning paradigms, because risk can be studied outside the context of learning. For example, one can simply present two gambles to a subject and ask them which they prefer. A standard paradigm would present a choice between: (1) £5 for sure or (2) a 5% chance of £20 and a 95% chance of £0. On average, gamble 2 is worth less than gamble 1. Therefore, if one chooses gamble 2, one is defined as risk prone. Studies examining risk using this behavioural economics framework have found a significant increase in risk taking behaviour in the “on” compared to the “off” state in all PD patients, independent of whether they had an ICB. However, a subgroup of PD patients with pathological gambling was more risk prone (Djamshidian, Jha et al. 2010). Thus, dopamine medication and an addiction to gambling led to riskier behaviour, but there was no group effect in ICBs relative to PD patients without an ICB.

The Iowa gambling task (IGT) has also been used to assess risk in patient groups. However, the Iowa gambling task confounds learning and risk, and therefore it cannot be clearly interpreted as a measure of either. In the IGT participants decide from which of four decks of cards they want to draw. Two decks offer high rewards early in the drawing sequence but also high losses later. They are ultimately disadvantageous. The other two decks are associated with smaller early rewards but also fewer losses. These decks are advantageous (Bechara, Damasio et al. 1994). PD patients with pathological gambling performed poorer on this task and more often chose the disadvantageous decks (Rossi, Gerschcovich et al.

2010). Whether this was due to differences in risk preference, or differences in learning, however, is not clear.

ICBs are often thought to arise because of excessive drive, or reduced inhibitory control. Furthermore, dopamine and the basal ganglia are often thought to underlie drive, and prefrontal cortex is often thought to underlie inhibitory control. Thus, dysfunction in frontal striatal networks is implicated in impulsive behaviors. There is relatively little direct evidence for this hypothesis. However, several studies have been motivated by this framework. Often, response inhibition tasks are used to study this. On the Stroop task, which is a response inhibition task in which participants need to say the ink colour of a word, but suppress the word identity, no differences were found between PD patients with or without ICBs (Rossi, Gerschcovich et al. 2010; Djamshidian, O'Sullivan et al. 2011). Further, in their “off” medication state both PD groups performed significantly worse than healthy volunteers. However, in their “on” medication state task performance improved in both groups, resulting in no differences between the patients and healthy controls (Djamshidian, O'Sullivan et al. 2011). Performance on the “Simon task” has also been examined. In this task subjects are required to make a quick response to a left or right button which matches the colour of a cue. The cue can appear either on the left or the right of the screen. If the cue appears on the same side as the button which matches the colour of the cue, it is a congruent trial, and if the cue appears on the opposite side it is an incongruent trial. Similar to the results in the Stroop task, there were no group differences between PD patients with and without ICBs. In fact patients with ICBs made less impulsive errors than the non-ICB PD group (Wylie, Claassen et al. 2012).

Another measure of frontal function is working memory. Studies have shown that working memory, particularly when mental manipulation of information was required, was significantly impaired in PD patients with ICBs compared to control PD patients and healthy volunteers, regardless of their dopaminergic state (Djamshidian, Jha et al. 2010). However, in another study using geometric shapes instead of numbers, PD patients with ICBs did not have working memory impairments, though they remembered task irrelevant information significantly better than non-impulsive PD patients “off” and “on” medication, suggesting that the ability to suppress distractors may protect control patients from developing an ICB (Djamshidian, O'Sullivan et al. 2012). Other studies have shown no impairment on the frontal assessment battery (FAB) scores in PD patients with pathological gambling compared to those without ICBs (Voon, Thomsen et al. 2007; Siri, Cilia et al. 2010). Thus, frontal deficits have not been consistently shown for patients with ICBs.

Several tasks other than learning have often been associated with impulsive tendencies. Specifically, novelty preference, temporal discounting, and information sampling (reflection impulsivity) have been suggested as measures of impulsivity(Verdejo-Garcia, Lawrence et al. 2008). All of these tasks have been examined in PD patients with ICBs. Novelty seeking has been examined using a three-armed bandit task in which participants were given three black and white landscape pictures. Each picture had an associated reward probability and the participants had to learn by trial and error which pictures most often were rewarded when chosen. On a subset of trials, one of the pictures that the subjects had been choosing in previous trials was replaced with a novel choice option. The question then is, how often do

subjects choose the novel option? Consistent with previous literature demonstrating increased novelty seeking personality traits in PD patients with DDS and pathological gambling (Evans, Lawrence et al. 2005; Voon, Thomsen et al. 2007), PD patients with a variety of different ICBs were more prone to select novel options compared to matched PD patients without behavioural addictions (Djamshidian, O'Sullivan et al. 2011). Dopaminergic medication, however, had no effect on novelty seeking behaviour. Imaging studies in healthy controls using this task have demonstrated that novelty preference is driven by ventral striatal activation (Wittmann, Daw et al. 2008). Thus, this effect may be driven by increased engagement of the ventral striatum in the PD patients with ICBs.

Temporal discounting, the preference for a smaller immediate reward over a larger delayed reward, has also been shown to differentiate reliably PD patients with and without ICBs. In one study participants were presented with a set of 27 choices between smaller, immediate rewards, and larger, delayed reward (Kirby, Petry et al. 1999). For example: ‘Would you prefer £54 today, or £55 in 117 days?’ or ‘Would you prefer £55 today, or £75 in 61 days?’ PD patients with ICBs showed increased temporal discounting, preferring smaller immediate over larger delayed rewards (Housden, O'Sullivan et al. 2010; Voon, Reynolds et al. 2010).

Reflection impulsivity, or information sampling, has also been examined in PD patients with ICBs. The ‘beads task’ has been used to measure reflection impulsivity (Evenden 1999; Clark, Robbins et al. 2006). This task is related to the matching familiar figures task (Kagan 1966) in which participants need to compare a target picture to a set of other pictures, and find the picture in the set that matches. Another task that is related to the beads task is, the “box opening task” (Clark, Robbins et al. 2006) which has been shown to distinguish current and former substance abusers from control subjects (Clark, Robbins et al. 2006). In the beads task participants are asked to predict from which of two cups coloured beads are being drawn. One of the cups contains, for example, 80% blue beads and 20% green beads; whereas the other cup contained 80% green beads and 20% blue beads. Subjects are rewarded for correctly guessing which cup is being drawn from, penalized for guessing the wrong cup, and charged for each bead they draw. Within this task there is an optimum number of beads to draw to maximize rewards (Furl and Averbeck 2011). In general, however, we were interested in the relative number of beads drawn by the different groups.

PD patients with and without ICBs were compared to two groups with addictions neither of which had PD (Figure 2). The non-PD addicts were pathological gamblers and illicit substance abusers on opioid replacement therapy (Djamshidian, O'Sullivan et al. 2012). Results demonstrated that all patient groups “jumped to conclusions”, drawing significantly fewer beads than healthy controls before guessing a cup. PD patients with ICBs resembled illicit substance abusers, and these two groups drew the fewest beads overall. Interestingly, PD patients without ICBs, who were treated with a dopamine agonist, drew significantly fewer beads than PD patients on L-dopa monotherapy. In fact, the PD group treated with dopamine agonists performed similarly to pathological gamblers. All patients also made more irrational decisions, e.g. selecting the cup that was less likely to be correct given the evidence, than matched healthy volunteers. Anecdotally, many PD patients treated with a dopamine agonist reported that they could “feel the right choice”, which is consistent with previous studies reporting higher schizotypy scores in PD, especially those who have ICBs

(Housden, O'Sullivan et al. 2010). Predictive analysis using the behaviour in the beads task allowed us to correctly identify ICB patients with a sensitivity of 96% (Djamshidian, O'Sullivan et al. 2012).

A follow up study has demonstrated that dopamine agonist therapy was responsible for "jumping to conclusions" behaviour in PD patients without ICBs (Djamshidian, O'Sullivan et al. 2013). Specifically, this study compared patients on L-dopa monotherapy, to patients treated with L-dopa in combination with a dopamine agonist, as well as patients that did and did not have deep brain stimulation (DBS) of the subthalamic nucleus. PD patients on an agonist, whether or not they had DBS drew fewer beads. DBS, however, had no effect on drawing behaviour. In line with this, previous studies have demonstrated increased temporal discounting in non-ICB PD patients treated with a dopamine agonist (Milenkova, Mohammadi et al. 2011) and tendencies for impulsivity on self-rating questionnaires (Papay, Mamikonyan et al. 2011).

A unifying theory of ICBs

Do the results outlined above support any specific hypotheses for the behavioural tendency that underlies ICBs? Three tasks have shown relatively robust differences between PD patients with and without ICBs. Specifically, temporal discounting, novelty preference and information sampling all showed relatively robust group effects. This raises the question of whether these three tasks can be accounted for by a single underlying mechanism. We have recently been exploring this possibility using a modelling framework known as Markov Decision Processes (MDPs) (Averbeck, Djamshidian et al. 2013). This framework is related to the reinforcement learning framework that is used to study many of the learning tasks described above (Djamshidian, Jha et al. 2010; Voon, Pessiglione et al. 2010). However, MDPs allow one to explicitly model the effects that current actions can have on future rewards. This is critical because many of the features of the behavioural addictions suggest that the subjects are not explicitly considering the impact of their choices on their ability to obtain reward in the future. Rather they are over-emphasizing the immediate rewards. Further, this same signature can unify novelty seeking, temporal discounting and information sampling.

Using the MDP framework we found that we could account for performance in all three tasks by assuming that subjects with ICBs behaved as if they had increased uncertainty about their ability to take actions in the future that would lead to rewards. In temporal discounting this arises because the choice of a delayed reward entails the need to collect a reward in the future. If one believes that any reward delayed further into the future becomes more uncertain, then one will less often select this reward. In the beads task, if one believes that sampling additional information will not actually improve one's ability to make better decision in the future, then one will not sample additional beads. Note that in general PD patients with ICBs learn as well as patients without ICBs (Djamshidian, Jha et al. 2010; Housden, O'Sullivan et al. 2010; Voon, Pessiglione et al. 2010; Djamshidian, O'Sullivan et al. 2012). Therefore, information accumulation is not impaired in these patients. Rather, they do not believe that gathering additional information will improve their future decisions. Finally, the choice of novel options in the novelty seeking tasks suggests that the

participants overestimate the value of their prior beliefs about rewards, and rely less on the evidence provided in the task about which choices would be better. In other words, they do not trust evidence provided in the task about which stimuli are better, as much as they trust their internal beliefs. This might also be related to the irrational decisions in the beads task, shown by the patient groups as these are choices of an urn less likely given the beads the subjects have drawn. Thus, these results can be summarized by the hypothesis that PD patients with behavioural addictions make choices as if they cannot use information to generate useful beliefs about actions that will result in future rewards. This may in fact be a relatively consistent tendency in many groups that display impulsive behaviours or behavioural addictions.

The treatment of PD patients with ICBs

General recommendation

All PD patients and their families should be advised about the potential risk of developing behavioural addictions after dopamine replacement therapy has been initiated, especially when a dopamine agonist is to be started. Although many patients develop these behavioural complications in the first year of treatment, long term vigilance is required as ICBs can occur even after more than 10 years of treatment with a dopamine agonist. Careful monitoring is required in patients that are young at disease onset, who have a personal or family history of addictive behaviour or a risk and novelty seeking personality profile (Singh, Kandimala et al. 2007; Voon, Thomsen et al. 2007; Weintraub, Koester et al. 2010). In these patients L-dopa monotherapy rather than a dopamine agonist should be considered as the initial therapy. Various myths, such as L-dopa being toxic or losing its efficacy over time have led to an “L-dopa phobia” amongst PD patients. These speculations have never been proven in human studies. In fact, L-dopa should be considered in all stages of PD, emphasizing disease status, quality of life (Vlaar, Hovestadt et al. 2011), patient preference, age, and severity of motor disability. If a dopamine agonist has been prescribed low doses should be used initially to minimize the risk of behavioural side effects (Hassan, Bower et al. 2011).

An ICB usually does not start abruptly and subtle behavioural changes such as increased irritability when an immediate goal cannot be achieved, a “sweet tooth” or increased spending might be harbingers. Patients and their partners should watch out for disturbed sleep at night, as insomnia is frequently observed in PD patients with ICBs (O'Sullivan, Loane et al. 2010). Further, an ICB may be tolerated or not recognized as a problem, depending on the financial situation and the social environment (Cormier, Muellner et al. 2013).

Specific treatment

If an ICB has been reported, dopamine agonists should be slowly reduced and eventually stopped if no improvement occurs with dose reduction (Evans, Strafella et al. 2009). It has been shown in a long-term follow up study that PD patients who had pathological gambling lost their gambling urges after withdrawal of dopamine agonists (Macphee, Copeland et al. 2009). In patients with DDS all treating physicians should be informed to prevent the

writing of extra prescriptions demanded by the patients. Further, access to credit cards, internet and money should be restricted. Cognitive behavioural therapy may be useful in some patients (Okai, Askey-Jones et al. 2013), although long term follow up studies are pending. Depression, which is recognized as a risk factor for developing these behaviours, should be treated with either a tricyclic antidepressant such as nortriptyline (Seppi, Weintraub et al. 2011) or selective serotonin reuptake inhibitors (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) (Richard, McDermott et al. 2012). Sleep problems are a key feature of ICBs in PD and should be treated accordingly (O'Sullivan, Loane et al. 2010). Carers and partners may also need support as they report significantly greater burden than spouses of non-impulsive patients (Leroi, Harbishettar et al. 2012).

Reduction of dopamine agonists can be challenging since often the patients' insight into these behaviours is low. During reduction, withdrawal symptoms such as anxiety, irritability and the subjective feeling of being "off" are frequently reported (Rabinak and Nirenberg 2010). In some of these cases hospital admission, and a multidisciplinary approach including a psychiatrist, may be required. Most patients with dopamine agonist withdrawal symptoms improve after 6 months. However, in some it can take up to 1 year for the withdrawal symptoms to improve and around 15% of patients are unable to tolerate the reduction of the dopamine agonist because of side effects (Pondal, Marras et al. 2013). One study has shown that an increase in L-dopa to alleviate motor deficits was not efficacious (Pondal, Marras et al. 2013). Further, this can lead to DDS in some patients (Rabinak and Nirenberg 2010). Usually it takes several weeks and occasionally up to few months after dopamine agonists have been withdrawn for the behavioural addictions to significantly improve.

Patients with pathological gambling should seek advice from Gamblers Anonymous or if available should be referred to a specialist gambling clinic. Compulsive sexual behaviour is more often problematic in men than women and in those who continue to have hypersexuality despite stopping dopamine agonists, some have suggested that the anti-androgen cyproterone, which involves endocrinological monitoring, may be beneficial in some cases (Evans, Katzenschlager et al. 2004). The use of neuroleptic treatment is still controversial in PD patients with ICBs (Sevincok, Akoglu et al. 2007; McElroy, Nelson et al. 2008). If necessary clozapine should be initiated as other antipsychotics can lead to worsening of extrapyramidal symptoms, although regular blood tests are also required with clozapine.

Functional surgery in PD patients with ICB

Conflicting results have been published on the effect of DBS of the subthalamic nucleus (STN) in PD patients with ICBs. Larger studies have shown that functional surgery does not cause ICBs in PD, and might even have beneficial effects because DBS allows for the reduction of dopaminergic medication (Ardouin, Voon et al. 2006; Lhommee, Klinger et al. 2012). Others, however, have reported an increased frequency of ICBs in PD directly triggered by DBS (Lu, Bharmal et al. 2006; Halbig, Tse et al. 2009; Zahodne, Susatia et al. 2011; Moum, Price et al. 2012). One small study compared the effects of internal globus pallidus stimulation (GPi) versus STN-DBS on ICBs in PD. Both stimulation targets failed to improve DDS and functional surgery improved ICBs only in 2/7 patients. In contrast, new

onset addictive behaviours were observed in 17 patients (Moum, Price et al. 2012). Despite these results stimulation of the STN compared to GPi stimulation may be more promising in improving addictive behaviours in PD, since it allows a greater reduction in dopaminergic therapy (Mestre, Strafella et al. 2013). Reduction of dopamine agonist therapy and physician vigilance has been associated with a good prognostic outcome in PD patients after functional surgery (Lim, O'Sullivan et al. 2009; Lhommee, Klinger et al. 2012). It is important to consider that the subthalamic nucleus is small with a volume of about 240mm^3 (Hardman, Henderson et al. 2002) and functional surgery is likely to cause a current spread of 113mm^3 volume (Saint-Cyr, Hoque et al. 2002). Therefore conflicting results might depend on whether the spread of stimulation affects the ventral STN, or not. Stimulation of the ventral subthalamic nucleus should be avoided as this part projects to limbic areas (Broen, Duits et al. 2011) and is involved in aberrant neuronal circuits in PD patients with ICBs (Rodriguez-Oroz, Lopez-Azcarate et al. 2010).

Various neuropsychological tests have reported impulsive choice (Frank, Samanta et al. 2007) and loss-chasing behaviour after STN-DBS (Rogers, Wielenberg et al. 2011). However, these patients were treated in addition with dopamine agonists and thus it is not clear whether STN-DBS or dopamine agonists were responsible for impaired decision making in these studies. Conversely, our group has recently shown that those PD patients treated with STN-DBS, in whom dopamine agonist could be successfully weaned off, no evidence for impairment in information sampling compared to healthy controls was found (Djamshidian, O'Sullivan et al. 2013).

Potential new treatment options

Smaller studies have reported beneficial effects using zonisaminde, topiramate and memantine in improving behavioural addictions seen in PD (Grant, Chamberlain et al. ; Bermejo 2008; Bermejo, Ruiz-Huete et al. 2010). In patients with DDS valproic acid has been shown to be useful without worsening of parkinsonism (Sriram, Ward et al. 2013). Naltrexone, an opioid antagonist, has been suggested to improve pathological gambling in PD patients, where reduction of dopamine agonists was not possible because of dopamine agonist withdrawal syndromes (Bosco, Plastino et al. 2012). An open label study using the N-methyl d-aspartate (NMDA) amantadine reported reduction in gambling urges in PD (Thomas, Bonanni et al. 2010), but these results could not be confirmed in two other studies, which have actually shown that amantadine is associated with ICBs in PD (Weintraub, Sohr et al. 2010; Lee, Kim et al. 2011). Finasteride, an alpha reductase inhibitor used for treating prostate hypertrophy, has been also shown to improve gambling behaviour in two PD patients (Bortolato, Cannas et al. 2012).

However, in the non PD population placebo responses are seen in up to 59% of subjects (Blanco, Petkova et al. 2002) and therefore larger studies are needed to confirm these results. A large randomized placebo controlled prospective trial examining the effects of naltrexone has recently finished and first results are expected by the end of this year (ClinicalTrials.gov identifier: NCT01052831). Prospective trials examining the effects of nicotine (ClinicalTrials.gov identifier: NCT01216904) are currently underway.

Outcomes of ICBs in PD

In general, the earlier that an ICB can be identified, the better the prognosis for the patient. Because the interval between developing an ICB from the commencement of DA therapy is highly variable, with one study showing a median of 23 months (range of 3.0 to 114.0 months) (Bastiaens, Dorfman et al. 2013), there is a need for on-going clinician vigilance. In a 29-month follow-up study of 18 PD patients with ICBs, 12 had discontinued or decreased DA treatment and all had full or partial remission of ICB by self-report. Ten (83.3%) no longer met diagnostic criteria for an ICB (Mamikonyan, Siderowf et al. 2008). Similar results were found in another long term follow-up study of 43 months. In this study behavioural side effects persisted in one third of the patients, who were treated with high doses of dopamine agonists, suggesting that these ICBs may be irreversible in patients with high dose dopamine agonist therapy (Sohtaoglu, Demiray et al. 2010).

Although reducing dopamine agonists is often beneficial in alleviating the ICBs, PET studies and behavioural testing have demonstrated increased impulsivity in patients previously diagnosed with ICBs, even after dopamine agonist medication has been stopped (O'Sullivan, Wu et al. 2011; Djamshidian, O'Sullivan et al. 2012). This suggests that irreversible changes have occurred in wide areas of the brain in these patients.

Future work

Functional imaging studies focussing on dopamine and other neurotransmitters, such as glutamate and serotonin in PD with ICBs will further understanding of the underlying mechanisms of these undesired side effects. Prospective long term follow up studies in drug naïve PD patients treated with either dopamine agonist monotherapy or L-dopa alone ideally combined with functional imaging are pending. In addition, genome wide association studies (GWAS) in PD patients with ICBs may identify genetic risk factors and ultimately allow clinicians to screen PD patients and adjust individual dopaminergic therapy accordingly. Because patients with PD require dopamine replacement therapies, their associated addictive behaviours are often extremely difficult to treat, with prevention of the developing behaviours the main treatment strategy currently available. There is a clear unmet need for large randomised controlled trials on potential ICBs treatment, which will hopefully be addressed in the near future.

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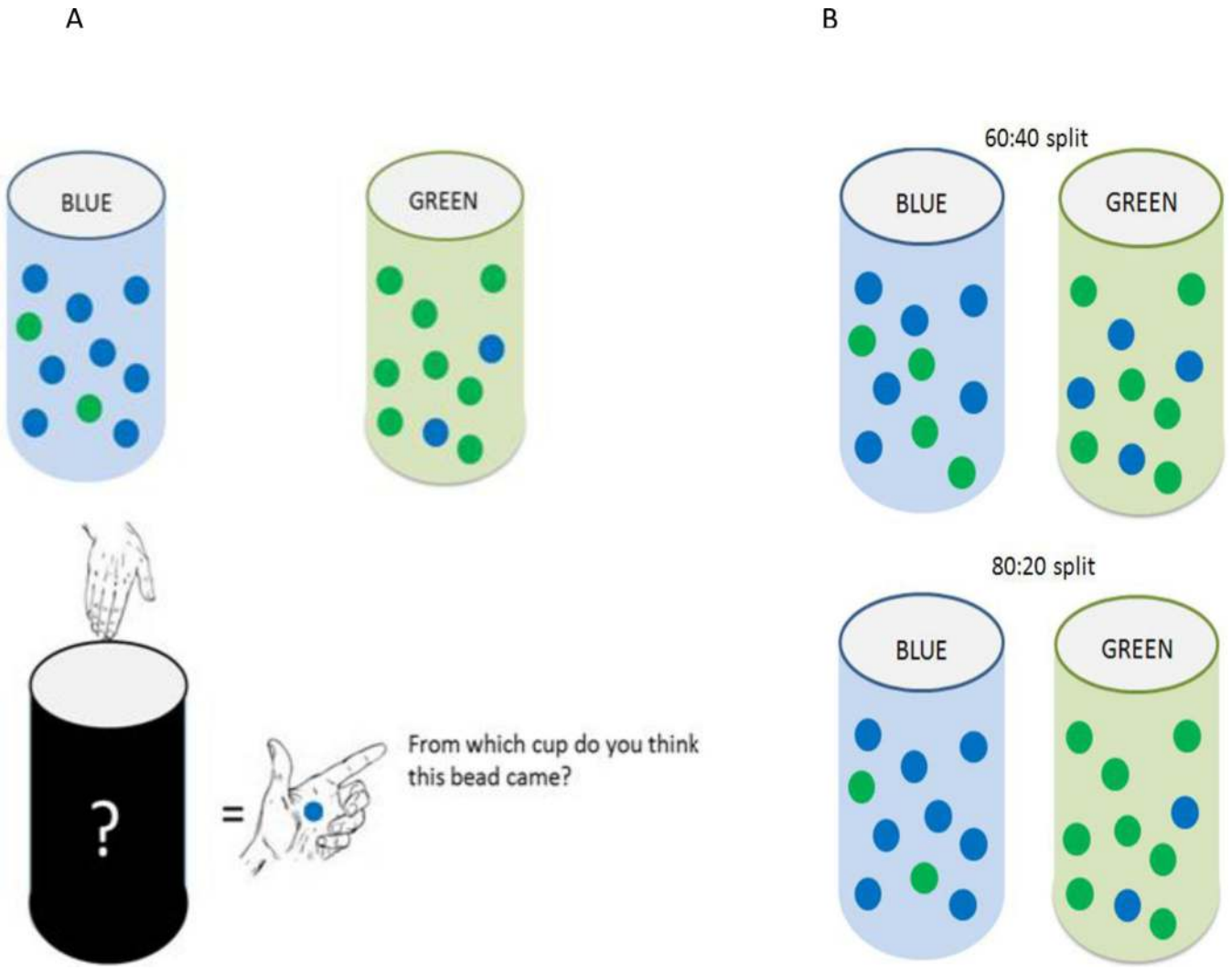

Figure 1.

A: Two cups were presented with the blue cup containing more blue than green beads and the green cup more green than blue beads. One bead was drawn and showed to the participant. They could either ask for up to 10 additional draws before deciding or immediately guess the cup, from which they thought the bead was drawn.

B: Two different ratios were used. One 60/40 ratio (above) and one 80/20 split (below).

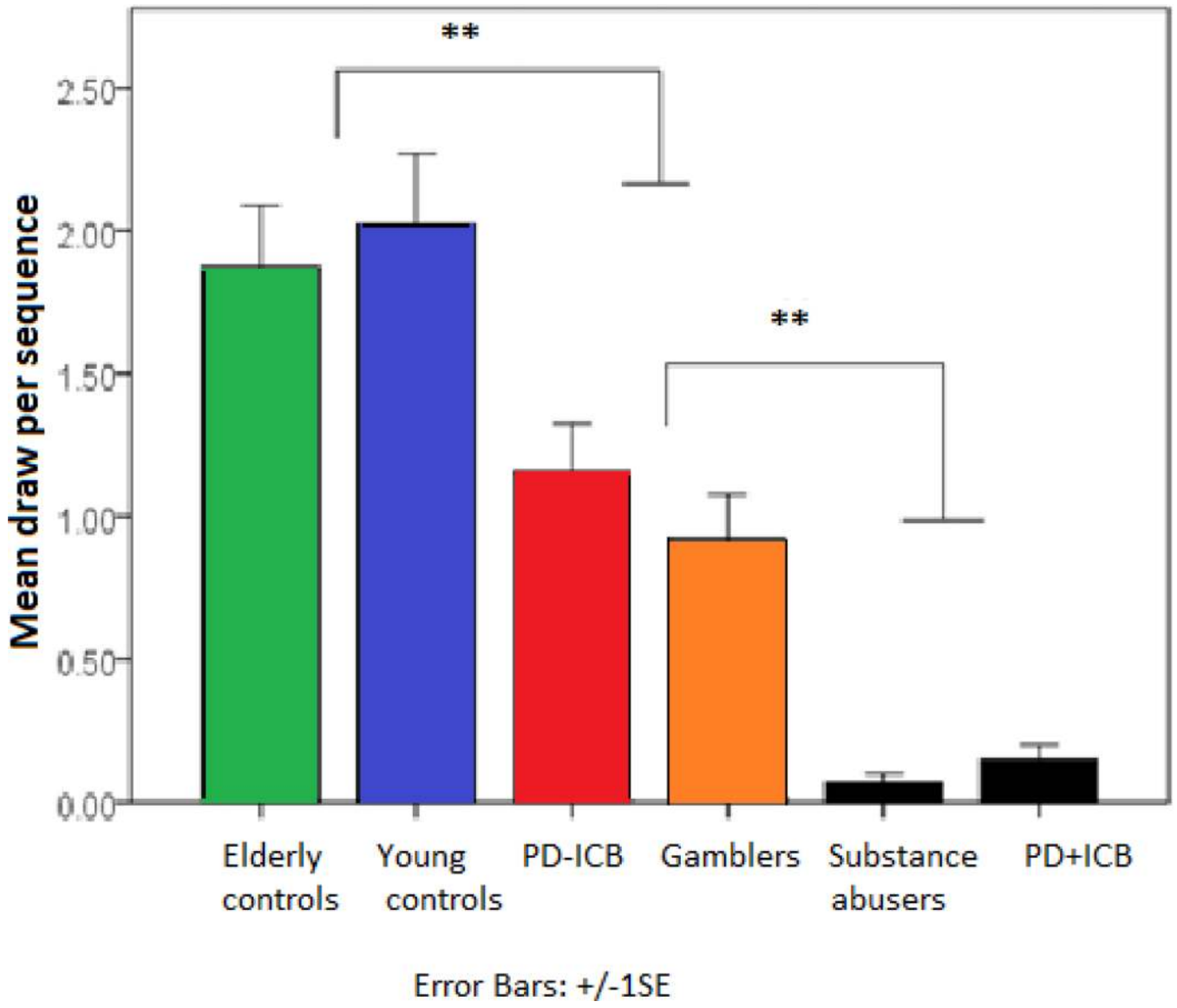

Figure 2.

Results of the beads task demonstrate 3 distinct groups with both control groups drawing significantly more beads than all patients. PD patients without ICBs (PD-ICBs) resembled pathological gamblers, whereas PD patients with ICBs (PD+ICBs) performed similarly to substance abusers. One bead is always shown at the start of the task, so total beads seen are mean draws plus one. Significant differences ($p<0.001$) are labelled with "**".

Table 1

Diagnostic criteria of pathological gambling from DSM-V.

A. Persistent and recurrent maladaptive gambling behaviour as indicated by four (or more) of the following:

- is preoccupied with gambling (e.g. preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)
- needs to gamble with increasing amounts of money in order to achieve the desired excitement
- has repeated unsuccessful efforts to control, cut back, or stop gambling
- is restless or irritable when attempting to cut down or stop gambling
- gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g. feelings of helplessness, guilt, anxiety, depression)
- chases losses
- lies to family members, therapist, or others to conceal the extent of involvement with gambling
- has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling
- relies on others to provide money to relieve a desperate financial situation caused by gambling
- symptoms are present during a 12 months period

B. The gambling behaviour is not better accounted for by a Manic Episode.

Table 2

Proposed criteria for compulsive sexual behaviour (Voon, Hassan et al. 2006).

Proposed criteria for pathological hypersexuality in PD
A. The sexual thoughts or behaviours are excessive or an atypical change from baseline marked by ≥1 of the following: • Maladaptive preoccupation with sexual thoughts • Inappropriately or excessively requesting sex from partner • Habitual promiscuity • Compulsive masturbation • Using telephone sex lines or viewing pornography • Paraphilias
B. The behaviour must be persistent for ≥1 month
C. The behaviour causes ≥1 of the following: • Marked distress • Attempts to control thought or behaviour are unsuccessful or result in marked anxiety or distress • Are time consuming • Interfere significantly with social or occupational functioning
D. Not occurring exclusively during (hypo)manic periods
E. If all criteria except C is fulfilled the disorder is subsyndromal

Table 3

Suggested screening questionnaire for punding adapted from (O'Sullivan, Evans et al. 2007).

Do you have any hobbies or pastimes or activities you do repeatedly?
Does your hobby interfere with sleep?
Does your hobby interfere with your ability to complete necessary daily tasks?
When did you become interested in your hobby (years)?
How do you feel when you are doing your hobby?
How many hours per day do you spend on your hobby?
Do you have difficulties in finishing your hobby projects?
How do you feel if you are interrupted when you are engaged with your hobby (ie, do you ever get angry or upset)?
Do you make a mess when you are pursuing your pastimes or hobbies?
Are you interested in your hobby only when “on”?
How many hours per day do you spend on the following?
• cleaning/tidying
• gardening or home improvements
• collecting things
• repairing/dismantling, eg, computers, television, radio (if yes, were you able to put them back together?)
• sorting, eg, papers, through drawers/handbag
• on the computer
• on the internet

Table 4

Diagnostic criteria for DDS (Giovannoni, O'Sullivan et al. 2000).

Diagnostic criteria for DDS
• Parkinson's disease with documented L-dopa responsiveness • Need for increasing doses of dopamine replacement therapy (DRT) in excess of those normally required to relieve parkinsonian symptoms and signs • Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being "on", drug hoarding, drug seeking behaviour, unwillingness to reduce DRT, absence of painful dystonias • Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence of work, loss of job, legal difficulties, arguments or difficulties with family • Development of hypomanic, manic or cyclothymic affective syndrome in relation to DRT • Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the level of DRT • Duration of disturbance for at least 6 months

Table 5

Diagnostic criteria for compulsive shopping (McElroy, Keck et al. 1994).

Diagnostic criteria for compulsive shopping
• Maladaptive preoccupation with buying or shopping that is manifested as impulses or behaviours that **1.** Are experienced as irresistible, intrusive and/or senseless **2.** Result in frequent buying of more than can be afforded, items that are not needed, or longer period of time than intended • Cause marked distress, are time consuming, significantly interfere with social and occupational functioning, or result in financial problems • Not occurring exclusive during (hypo)manic episodes