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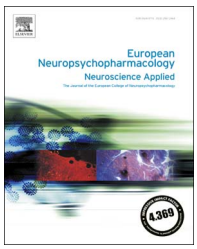

REVIEW

Neurocognitive correlates of medication-induced addictive behaviours in Parkinson's disease: A systematic review

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Abstract
Dopaminergic medication can induce severe addictive behaviours (e.g., pathological gambling) in susceptible Parkinson's disease (PD) patients. It is still unknown which particular neurocognitive processes become exacerbated or dysfunctional in PD patients with addictive behaviours. We sought to systematically review the relevant literature to identity potential neurocognitive correlates of medication-induced addictive behaviours in PD. We framed our review around neurocognitive processes central to four dominant accounts of substance addiction: 'aberrant learning', 'incentive sensitization', 'impulsivity to compulsivity' and 'impaired response inhibition and salience attribution'. Searches of the PubMed and Scopus databases were completed on June 23, 2017. To be included, studies were required to involve: (a) medicated PD patients, without a history of deep brain stimulation, with and without addictive behaviours; (b) a reward-related or decision-making task; and (c) statistical comparison of addictive and non-addictive groups' 'on' medication performance on the task(s). Studies were summarised

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qualitatively with statistically significant ($p < .05$) group differences and effect sizes (Cohen's *d*) highlighted. 35 studies were included. Findings showed that the extant literature is highly heterogeneous. The domains of reward and punishment learning, reflection impulsivity and disadvantageous decision-making exemplify this. More homogeneity exists in domains in which (a) neurocognitive dysfunction is not apparent (motor control, cognitive/attentional flexibility and cognitive control) or (b) typical neurocognitive processes appear exacerbated by medication (reward motivation and choice impulsivity). Future large-scale neurocognitive studies are still required to develop our scientific understanding of addictive behaviours in PD and aid their clinical treatment and prediction.

1. Introduction

It is widely recognised that routine administration of dopaminergic medication can cause behavioural changes in susceptible patients with Parkinson's disease (PD) (Weintraub et al., 2015). Behavioral changes can present in subsyndromal forms (e.g., purchasing additional items online), to extremely severe, often-devastating forms (e.g., the case of a hypersexual patient convicted for soliciting sex from a minor; cases of gambling losses over $100,000) (Bartlett et al., 2013; Stenberg, 2016). These more severe instances were initially labelled 'impulse control disorders', following the *DSM-IV* nomenclature (Weintraub et al., 2010), but now are also referred to as 'impulsive-compulsive behaviours', 'behavioural addictions' or 'addictive behaviours' (Averbeck et al., 2014; Witjas et al., 2012).

A study of over 3000 people with PD found 13.6% had an addictive behaviour (Weintraub et al., 2010), the most common being compulsive shopping (5.7%), pathological gambling (5%), binge eating (4.3%) and hypersexuality (3.5%). These addictive behaviours are strongly associated with dopamine agonists (e.g., pramipexole) (Weintraub et al., 2010), although no dose-dependent relationship has been established (Ambermoon et al., 2010). Addiction-like abuse of medication (or 'dopamine dysregulation syndrome' (DDS)) occurs in 2% of patients, while 7% of patients display prolonged, repetitive, stereotyped behaviors (or 'punding') (Averbeck et al., 2014). These dysfunctions are associated more with levodopa use than dopamine agonists (Evans et al., 2005). It is worth noting that these figures are potentially underestimated: there is sometimes lack of clinical screening for addictive behaviours; afflicted patients show impaired insight, guilt and denial (Averbeck et al., 2014; Goerlich-Dobre et al., 2014); there is documented underreporting of addictive behaviours in patients without caregivers (Baumann-Vogel et al., 2015); and there are discrepancies in patient-caregiver addictive behaviour ratings (Ricciardi et al., 2016).

Despite a strong (epidemiologically) causal link between dopaminergic medication administration and addictive behaviours in PD (Ambermoon et al., 2011), it is not clear which neurocognitive processes become exacerbated or dysfunctional in patients with addictive behaviours. Drawing on theories of substance addiction, medication administration could gradually enhance reward learning and impair punishment learning in vulnerable patients (Everitt and Robbins, 2016); enhance the incentive salience of reward cues and motivate their pursuit (Robinson and Berridge, 2008); lead to reduced subjective valuation of long-term rewards and reduced cognitive flexibility (Fineberg et al., 2014); and/or impair impulse inhibition (Goldstein and Volkow, 2011). Numerous individual studies have attempted to assess the impact of medication on a wide range of neurocognitive domains with varying and conflicting results. The neurocognitive correlates of addictive behaviours in PD are thus still unclear (cf. Averbeck et al., 2014).

There has been no attempt to comprehensively review the relevant literature to identity potential neurocognitive correlates of medication-induced addictive behaviours in PD (cf. Santangelo et al., 2017). We reviewed studies assessing neurocognitive processes central to the four following dominant accounts of substance addiction: 'aberrant learning', where over-learned habits come to underpin addictive behaviours (Everitt and Robbins, 2016); 'incentive-sensitization', where excessive incentive salience is attributed to drugs and associated stimuli, driving addictive craving and relapse (Robinson and Berridge, 2008); 'impulsivity to compulsivity', where prolonged, excessive and impulsive substance use eventually leads to compulsive behaviour in vulnerable individuals (Fineberg et al., 2014); and 'impaired response inhibition and salience attribution (iRISA)', where, in addition to drug-induced subcortical neuroadaptations affecting reward processing, drug-induced cortical neuroadaptations impair valuation and control processes (Goldstein and Volkow, 2011). These specific processes and the tasks with which they have been measured in the reviewed literature are outlined in Supplementary materials. We qualitatively summarise findings, before identifying the domains in which further work is required.

2. Experimental procedures

This (unregistered) systematic review followed the PICOS methodology embedded within the PRISMA framework (Liberati et al., 2009). Studies were included if they included: (a) medicated PD patients, without a history of deep brain stimulation (given the significant uncertainty about the role of DBS in independently inducing or ameliorating impulsive behaviour in PD patients), with (*population*) and without (*comparator*) addictive behaviours; (b) reward-related and decision-making tasks that measure the neurocognitive processes outlined in Supplementary materials (*interventions/indices*); and (c) statistical comparison of addictive and non-addictive groups' 'on' medication performance on the tasks (*outcomes*; *study design*). Within-group 'on' and 'off' comparisons were not performed as (a) they are not central to the

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