CHAPTER

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Role of dopamine and clinical heterogeneity in cognitive dysfunction in Parkinson's disease

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Abstract

Parkinson's disease (PD) is commonly treated with dopaminergic medication, which enhances some, while impairing other cognitive functions. It can even contribute to impulse control disorder and addiction. We describe the history of research supporting the dopamine overdose hypothesis, which accounts for the large within-patient variability in dopaminergic medication effects across different tasks by referring to the spatially non-uniform pattern of dopamine depletion in dorsal versus ventral striatum. However, there is tremendous variability in dopaminergic medication effects not just within patients across distinct tasks, but also across different patients. In the second part of this chapter we review recent studies addressing the large individual variability in the negative side effects of dopaminergic medication on functions that implicate dopamine, such as value-based learning and choice. These studies begin to unravel the mechanisms of dopamine overdosing, thus revising the strict version of the overdose hypothesis. For example, the work shows that the canonical boosting of reward-versus punishment-based choice by medication is greater in patients with depression and a non-tremor phenotype, which both implicate, among other pathology, more rather than less severe dysregulation of the mesolimbic dopamine system. Future longitudinal cohort studies are needed to identify how to optimally combine different clinical, personality, cognitive, neural, genetic and molecular predictors of detrimental medication effects in order to account for as much of the relevant variability as possible. This will provide a useful tool for precision neurology, allowing individual and contextual tailoring of (the dose of) dopaminergic medication in order to maximize its cognitive benefits, yet minimize its side effects.

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Keywords

Dopaminergic medication, Side effects, Parkinson's disease, Cognitive dysfunction, Heterogeneity, Reinforcement learning, Decision making, Gambling, Impulse control disorder, Depression, Striatum, Overdose hypothesis, Prefrontal cortex, Tremor phenotype

1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, and its prevalence is rapidly increasing, taking the shape of a pandemic (Dorsey et al., 2018). It is a progressive condition, hallmarked primarily by damage to the dopaminergic neurons of the substantia nigra (SN), and αSynuclein (αSyn) containing inclusion bodies (Lewy pathology; LP) in the surviving neurons. This results clinically in a set of easily recognizable motor symptoms such as tremor, rigidity and bradykinesia. However, the Parkinson's syndrome also includes a wide range of non-motor features, including cognitive decline, depression, anxiety, pain, disturbed sleep and autonomic dysfunction. Additional neuropathological features may include vascular disease (as a comorbid occurrence), neurofibrillary tangles and amyloid plaques also commonly seen in other forms of dementia as well as changes in the noradrenergic, serotoninergic and cholinergic systems, by causing degeneration respectively of the locus coeruleus (Cash et al., 1987; Chan-Palay and Asan, 1989; Zarow et al., 2003), dorsal raphé nuclei (Brooks and Piccini, 2006; Isaias et al., 2011; Pasquini et al., 2018; Qamhawi et al., 2015; Scatton et al., 1983) and cholinergic brainstem nuclei, particularly the basal nucleus of Meynert (Jellinger, 1991) (Fig. 1). In addition to an increased risk for dementia and depression (Brown and Marsden, 1984), PD patients are now well recognized to exhibit more or less subtle cognitive problems, even in the earliest non-demented and non-depressed disease stages. The importance of unraveling the mechanisms of these cognitive problems and their therapeutic remediation is well recognized, as they considerably impact quality of life (Khoo et al., 2013; Lawson et al., 2014; Schrag et al., 2000, 2006). Indeed for many of the individuals affected by PD, the cognitive symptoms belong to the most debilitating components of the Parkinson's syndrome.

2 Deficient functions associated with fronto-striatal circuitry

Extensive and influential programs of neuropsychological studies in PD have been undertaken to address the mechanisms of cognitive dysfunction in PD. The starting point of much of this work has been the severe loss of dopamine cells in the substantia nigra, and the ensuing dopamine depletion in the striatum, leading indirectly to abnormal functioning of the prefrontal cortex through aberrant outflow from the striatum via the established thalamo-striato-frontal circuitry (Alexander et al., 1986; Nagano-Saito et al., 2008; Owen et al., 1998). Indeed, many of the motor symptoms and some of the cognitive deficits are commonly alleviated by replenishment of striatal dopamine through the oral administration of the dopamine precursor

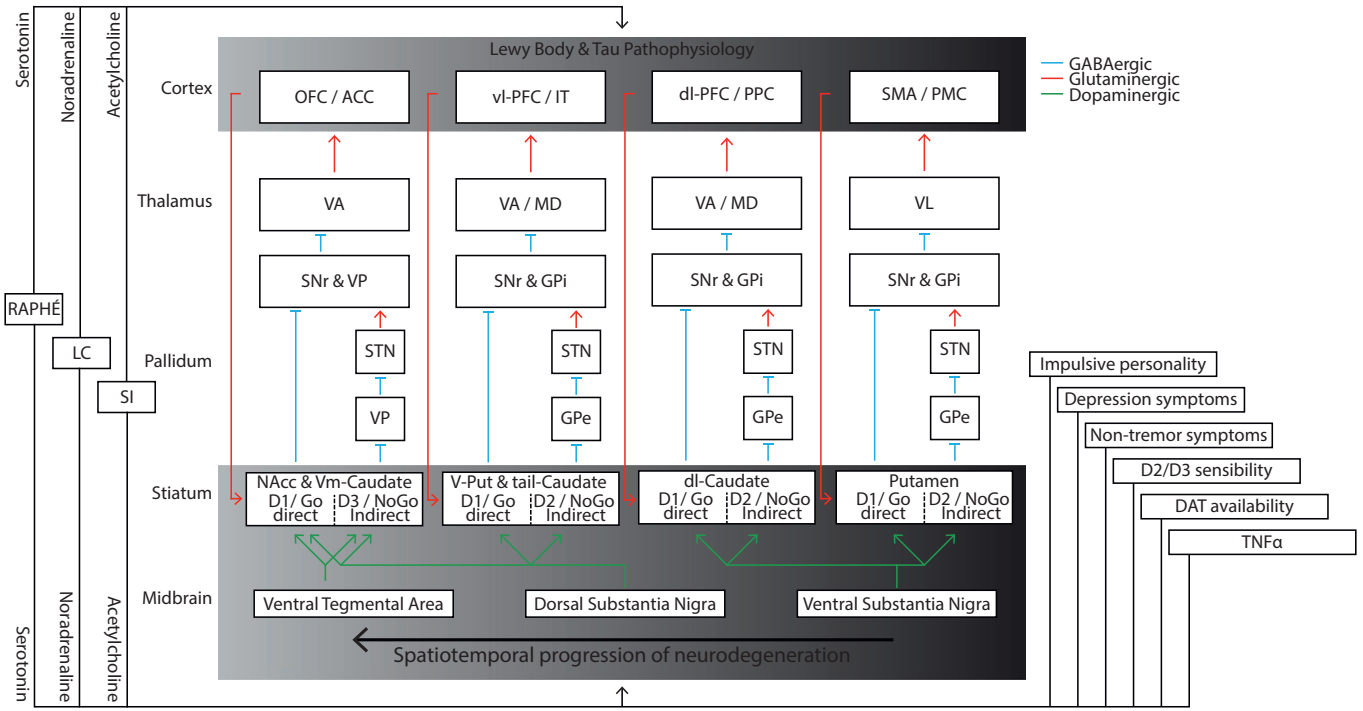

FIG. 1

Schematic representation of the spatiotemporal progression of degeneration affecting distinct cortico-basal-ganglia-thalamo-cortical loops in PD. Dopaminergic cell loss starts in the ventral tier and progresses to the dorsal tier of the substantia nigra and eventually to the ventral tegmental area (indicated by the black to white gradient). The projections from the most affected ventral SNc lead to the dorsal parts of the striatum which in turn connects to the cortical motor areas. The relatively intact dorsal SNc and ventral tegmental area project to the ventral striatum, which projects to the OFC & ventral PFC. Aberrant dopamine signaling from the midbrain is not uniform between patients and is influenced by symptom phenotype, inflammatory and genetic factors. Figure is inspired by Cools (2006). *Abbreviations:* VTA, ventral tegmental area; RAPHE, dorsal and medial raphé nuclei; LC, locus coeruleus SI, substantia innominata; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; vl-PFC, ventrolateral PFC; IT, inferotemporal cortex; dl-PFC, dorsolateral PFC; PPC, posterior parietal cortex; SMA, supplementary motor area; PMC, premotor cortex; MD, dorsomedial nucleus of thalamus; VA, ventral anterior thalamus; VL, ventrolateral thalamus; SNr, substantia nigra, pars reticulata; GPi, internal globus pallidus; STN, subthalamic nucleus; VP, ventral pallidum; GPe, external globus pallidus; NAcc, nucleus accumbens; Vm-Caudate, ventromedial -caudate V-Put, ventral-putamen; dl-Caudate, dorsolateral-Caudate; TNFa, tumor necrosis factor alpha.

L-DOPA or synthetic dopamine receptor agonists (Hornykiewicz, 1974). Many (but certainly not all, see below) of the cognitive deficits seen in mild PD patients resemble those observed in patients with dorsolateral frontal lobe damage (Brown and Marsden, 1988a; Dubois et al., 1994; Owen et al., 1995), and contrast with those seen in patients with medial temporal lobe damage, such as long-term memory impairments (Knowlton et al., 1996; Owen et al., 1992; Sahakian et al., 1988). Thus there is extensive evidence for deficits on tasks requiring so-called executive control, often associated with dorsolateral fronto-parieto-striatal circuitry (Brown and Marsden, 1988a; Cooper et al., 1991; Dubois and Pillon, 1996; Lees and Smith, 1983; Owen et al., 1992, 1993; Partiot et al., 1996; Taylor and Saint-Cyr, 1995; Taylor et al., 1986). Such deficits include highly selective impairments in spatial working memory, Tower of London planning (Bowen et al., 1975; Cools et al., 1984, 2001a,b, 2002, 2003; Cooper et al., 1992; Fournet et al., 1996; Gotham et al., 1988; Lange et al., 1992; Lees and Smith, 1983; Owen et al., 1992, 1995; Taylor et al., 1986), feedback-based, goal-directed and model-based learning (de Wit et al., 2012; Schonberg et al., 2010; Sharp et al., 2016; Shohamy et al., 2004), interval timing (Malapani et al., 1998; Singh et al., 2021) as well as attentional set-shifting (Beatty and Monson, 1990; Bowen et al., 1975; Brown and Marsden, 1988b; Caltagirone et al., 1989; Canavan et al., 1989; Cools et al., 1984, 2001a,b, 2003; Cooper et al., 1991; Dimitrov et al., 1999; Downes et al., 1989; Gauntlett-Gilbert et al., 1999; Inzelberg et al., 2001; Lees and Smith, 1983; Owen et al., 1992, 1993; Paolo et al., 1995; Taylor et al., 1986; van Spaendonck et al., 1995) and task-set switching (Cools et al., 2001a,b, 2003; Hayes et al., 1998; Meiran et al., 2004; Pollux, 2004; Pollux and Robertson, 2002; Woodward et al., 2002). The selectivity of these deficits (Cools et al., 2003; Kehagia et al., 2013) indicates that they cannot be accounted for by global, nonspecific effects on motor symptoms or arousal. These frontal-like deficits might reflect mesocortical dopamine depletion (Alberico et al., 2015; Javoy-Agid and Agid, 1980; Narayanan et al., 2013). However, although they resemble those seen in patients with frontal lobe lesions, they are certainly not identical (Cools et al., 2010; Owen et al., 1993). In fact there is also some evidence for enhanced frontal function, surfacing as enhanced distractor-resistance of working memory, in early PD patients (Cools et al., 2010; Fallon et al., 2019; Moustafa et al., 2008). Such enhanced distractor resistance might well reflect compensatory upregulated dopamine synthesis capacity in the prefrontal cortex (Kaasinen et al., 2001; Rakshi et al., 1999), in line with a reciprocal relationship between frontal and striatal dopamine as shown in rats and monkeys (Pycock et al., 1980; Roberts et al., 1994). Thus, PD seems to confer either cognitive deficits or benefits, depending on the precise task demands under study.

3 Role of dopamine in fronto-striatal dysfunction

A key role for brain dopamine in many of these deficits was firmly established by a series of controlled medication withdrawal studies, which manipulated brain dopamine over short periods by withdrawing the normal regimen of dopamine

replacement drugs (i.e., levodopa). This is doable because the half-life of these drugs is relatively short, even though a complete washout requires a withdrawal of more than 4 weeks due to the long-duration response of levodopa (Cilia et al., 2020). Effects can be easily monitored by comparing performance of patients when they were tested ON and/or OFF their dopaminergic medication, and validated by observing deterioration in the motor status of the patient. For example, the task-set switching deficit was repeatedly shown to be ameliorated in patients ON vs OFF medication (Cools et al., 2002, 2003; Hayes et al., 1998). In addition, dopaminergic medication has consistently been found to alleviate deficits on tasks requiring the flexible reorganization of information, for example in working memory (Costa et al., 2003; Fournet et al., 2000; Gilbert et al., 2005; Lange et al., 1992; Lewis et al., 2003, 2005; Malapani et al., 1994; Mollion et al., 2003), or long-term memory (Buytenhuijs et al., 1994; Gabrieli et al., 1996; Lewis et al., 2003; Morris et al., 1988; Owen et al., 1992, 1995; Pillon et al., 1998; Stebbins et al., 1999). The functional specificity of such dopamine effects on executive components of working memory is demonstrated by studies showing a lack of dopaminergic medication on classic measures of working memory span or storage (Bradley et al., 1989; Cooper et al., 1991; Dalrymple-Alford et al., 1994; Ketcham et al., 2003). Next pharmacological neuroimaging studies have demonstrated that these beneficial effects of dopaminergic medication are accompanied by increased neural signaling (efficiency) in dorsolateral fronto-striatal circuitry. This was the case for task-set switching, where medication-related improvements in tasks-switching (decreased switch costs) were associated, on an individual basis, with medication-related increases in switch-related BOLD signal (switch-repeat) in the dorsomedial striatum (Aarts et al., 2014). Moreover, in the domain of spatial working memory and planning, analogous findings have been reported across multiple pharmacological neuroimaging studies (Cools et al., 2002; Mattay et al., 2002). For example, levodopa medication was shown to normalize blood flow in the dorsolateral prefrontal cortex of PD patients during the Tower of London planning task and a related test of spatial working memory in a manner that was proportional to the degree that the medication improves task performance (Cools et al., 2002). These early findings from small sample studies already suggested that there is large individual variability in the degree to which patients are sensitive to the beneficial effects of dopaminergic medication. Before returning to this issue of individual heterogeneity below, we first review the evolution of evidence for, and accounts of the remarkable side effects of dopaminergic medication in PD.

4 Detrimental effects of dopaminergic medication on fronto-striatal function

The observation that the dopaminergic medication regimes used to treat the motor symptoms of PD not only remediate but in fact also contribute to cognitive dysfunction has attracted a lot of attention in the past decade or two. This surge in interest was

in part driven by the clinical observation that a considerable proportion of PD patients develop severely disabling side effects as a consequence of this medication in the form of impulse control disorder (ICD), or even of psychosis and addiction (Dagher and Robbins, 2009; Driver-Dunckley et al., 2003; Lawrence et al., 2003; Pontone et al., 2006; Voon and Fox, 2007; Voon et al., 2017; Weintraub et al., 2006). Medication-related ICDs include gambling addiction, binge eating disorder, compulsive hobbying (punding), compulsive sexual behavior, and compulsive shopping, and occur in about 17% of PD patients on dopamine agonists (Voon et al., 2017). Which cognitive mechanisms account for these negative effects of medication? To address this question, a number of alternative hypotheses have been raised. Here we discuss three of these: the dopamine denervation hypothesis, the double hit hypothesis and the dopamine overdose hypothesis.

5 The dopamine denervation hypothesis

The first "dopamine denervation" hypothesis states that the cognitive impairing effects of levodopa depend on the progression of dopamine cell loss and deficiency of compensatory mechanisms, so that beneficial medication effects are seen more readily in earlier stage patients, in whom cell loss is relatively minor. Patients with a greater fluctuating response to levodopa with relatively severe dopamine loss would exhibit greater vulnerability to levodopa-related cognitive impairment, for example because of reduced storage, reuptake and/or regulated release mechanisms, and/or super-sensitivity of striatal neurons to dopamine receptor stimulation (Bédard et al., 1992; Gerfen, 2003; Kostrzewa et al., 2005), relative to stable responders. This hypothesis is supported by findings from, for example, Kulisevsky and colleagues (Kulisevsky, 2000; Kulisevsky et al., 1996), who observed that levodopa improved cognitive task performance in never-medicated patients (Kulisevsky et al., 1998), left unchanged performance in patients with a stable levodopa response and impaired performance in patients with fluctuating, "wearing-off" motor responses to the drug. This dopamine denervation hypothesis concurs with evidence from microdialysis studies with rodents showing greater levodopa-related increases in extracellular dopamine in the dopamine-depleted striatum than the dopamine-intact striatum (Abercrombie et al., 1990; Carey et al., 1995; Miller and Abercrombie, 1999). The proposal is somewhat reminiscent of the "reward deficiency" hypothesis of addiction, according to which reduced mesolimbic dopamine function predisposes individuals to addiction (Blum et al., 2000; Drew et al., 2020). Relevant in this context might be our finding that the impact of a reward incentive on cognitive control was associated with dopamine cell loss in PD, as measured with DAT SPECT imaging (Aarts et al., 2012). Specifically we showed that PD patients with greater dopamine cell loss in the most severely affected dorsolateral putamen exhibited greater reward-related speeding, yet also greater reward-related error rates on switch versus nonswitch trials of a rewarded task-switching paradigm (Aarts et al., 2012), an effect potentially related to paradoxical kinesia. However, this enhanced impact of reward on task-switching

was not exacerbated, but rather reduced to normal by dopaminergic medication. The question whether the medication-related cognitive deficit can be attributed to cell loss has not yet been answered, in part because the fluctuating patients in the prior studies (Kulisevsky et al., 1996) received higher levodopa doses than the stable patients and plasma levodopa levels peaked earlier in fluctuating than stable responders. Thus, the deficit in fluctuating versus stable patients might reflect higher (and/or earlier) peaks in dopamine stimulation rather than greater dopamine depletion.

6 The double hit hypothesis

The double hit hypothesis is strongly related to the denervation hypothesis and states that dopaminergic medication has detrimental cognitive deficits only in patients who also exhibit additional serotonergic, noradrenergic and/or cholinergic deficiency (Marín-Lahoz et al., 2019). Indeed non-dopaminergic forms of pathology, including noradrenergic, serotonergic and cholinergic deafferentation of the cortex and cortical Lewy bodies may play a significant role in some of the cognitive deficits (see below). Levodopa affects all catecholamines including noradrenaline, which may also alter cognitive functioning (Arnsten, 1998; Coull, 1994). In addition, levodopa reduces the serotonin (5-HT) concentration in the brain (Bartholini et al., 1968; Everett and Borcherding, 1970; Kostrzewa et al., 2005). Thus, levodopa may well impair certain cognitive functions via alternative non-dopaminergic mechanisms such as reduction of serotonin transmission. Having said that, we also know that the effects of serotonin depletion and dopaminergic medication in PD on relevant tasks are qualitatively different. For example, while dopaminergic medication in PD impairs learning from punishment (Cools et al., 2006), decreases in serotonin with acute tryptophan depletion in fact increases punishment learning (Cools et al., 2008; Robinson et al., 2012).

7 The dopamine overdose hypothesis

The dopamine overdose hypothesis was put forward originally by Gotham et al. (1986), Gotham et al. (1988); see also Poewe et al. (1991), and extended by Swainson et al. (2000) and Cools et al. (2001a, 2003), Rowe et al. (2008). Gotham et al. (1986) observed beneficial effects of medication on verbal fluency, but a strong negative correlation between levodopa dose and performance on a conditional associative learning task: the higher the dose, the more learning errors were made. This dopamine over-dose hypothesis was consistent with accumulating evidence from work with experimental animals (Arnsten, 1998) demonstrating an inverted-U shaped relationship between dopamine and cognition, and raised the possibility that extant variability in the effects of dopaminergic medication could be resolved to some extent by taking into account the functional and neural heterogeneity of complex cognitive function. However, at the time, there was no strong

prior evidence that the tasks used in these studies implicate circuits that are differentially depleted in PD.

The next set of studied resolved this issue by leveraging the key observation that PD is associated with a spatiotemporal progression of dopamine depletion within the striatum: Most severe in PD is the dopamine cell loss in the ventrolateral tier of the substantia nigra pars compacta, which projects primarily to the dorsal striatum (i.e., the dorsolateral putamen and the dorsal parts of the caudate nucleus) (Aarts et al., 2012; Bernheimer et al., 1973; Dauer and Przedborski, 2003; Kish et al., 1988). Much less affected are neurons in the dorsal tier of the substantia nigra and the ventral tegmental area (VTA), which project to the ventral striatum (i.e., the ventral putamen, the ventral caudate nucleus and the nucleus accumbens) and the prefrontal cortex. What followed is the specific prediction that in early PD dopaminergic medication may improve certain cognitive functions that are associated with the severely depleted dorsal striatum, while at the same time impairing (by "overdosing") other cognitive functions, associated with the relatively intact ventral striatum (Cools et al., 2001a; Swainson et al., 2000). We tested this hypothesis by examining the effects of controlled medication withdrawal on two tasks reliably associated with dissociable striatal areas (Cools et al., 2001a): a task-switching paradigm implicating the severely depleted dorsolateral frontostriatal circuitry (Brass et al., 2003; Meyer et al., 1998; Sohn et al., 2000) and a probabilistic reversal learning task implicating the relatively unaffected ventral striatum and orbitofrontal cortex. The results revealed a double dissociation and were in line with this overdose model (Cools et al., 2001a, 2006), with beneficial effects on task-switching, but detrimental effects on reversal learning. This pattern indicates that dopaminergic medication effects on cognition are task-specific and depend on the neural substrates of the tasks. Notably the findings contrasted with predictions from the dopamine-denervation model, according to which we should have seen greater medication-induced impairment on task-switching associated with the severely depleted dorsal striatum than on reversal learning associated with the relatively intact ventral striatum.

Further support for the overdose hypothesis came from a subsequent controlled medication withdrawal study, which again revealed a double dissociation (Cools et al., 2003). This within-patient study not only provided convergent evidence for a medication-induced enhancement of task-switching, but also demonstrated a medication-related increase in impulsive betting on the Cambridge Gambling task, known to implicate brain regions such the orbitofrontal cortex that are more strongly connected with the intact ventral than the depleted dorsal striatum (Cools et al., 2003; Rogers et al., 1999). The latter effect might have reflected enhanced delay aversion, and was argued to contribute to medication-related gambling addiction. A variety of independent labs have substantiated that dopaminergic medication can have detrimental effects on cognitive functions putatively implicating ventral limbic frontostriatal circuitry (Czernecki et al., 2002; Jahanshahi et al., 2010). The proposal that the negative effects of medication reflect modulation of relatively intact brain regions in early PD was supported by pharmacological fMRI work. In this work, PD patients were scanned during the performance of an fMRI-compatible version of the

probabilistic reversal learning task that was previously observed to be impaired by medication. Dopaminergic medication indeed altered reversal-related signal specifically in the relatively intact ventral striatum, while leaving signal in the dorsal striatum and in the frontal cortex unaltered (Cools et al., 2007). Other fMRI studies provided generally convergent results with medication-related cognitive improvements in PD being associated with modulation of the dorsal striatum, but medication-related impairments being associated with modulation of the ventral striatum (Aarts et al., 2014; MacDonald et al., 2011). Together this pharmacological neuroimaging evidence is in favor of the dopamine overdose hypothesis, and in contrast with the denervation hypothesis, according to which the detrimental effects should have been mediated by changes in the more severely affected regions of the striatum.

The dopamine denervation and overdose models also make contrasting predictions with regard to disease severity and the associated progression of cell loss. The denervation hypothesis predicts disproportionate medication-induced impairment in clinically severely affected patients, while, by contrast, the overdose model predicts greater drug-induced deficit in mildly affected patients. In line with the overdose, but not the denervation model, a variety of studies have suggested that medication-related cognitive impairment is reduced when dopamine depletion progresses also to previously less affected cortico-limbic regions due to higher disease severity (Foltynie et al., 2004; Hughes et al., 2010, 2013; Meder et al., 2019; Rowe et al., 2008; Williams-Gray et al., 2009). For example, Hughes et al. (2010, 2013) have shown that dopaminergic medication increased perseveration on an action selection task in clinically mildly affected patients, but reduced it in more severely affected patients, and these effects were accompanied by neural activity changes in the caudate nucleus and connected ventrolateral PFC. Furthermore, dopaminergic medication dose and the MET-allele of the well-known COMT polymorphism contributed to impairment on Tower of London planning in early PD patients, putatively reflecting detrimental overdosing of intact prefrontal dopamine levels. This contrasted with the finding that the COMT MET-allele was associated with enhanced performance on the same task in more severely affected PD patients (Williams-Gray et al., 2009). This evidence regarding disease severity is in favor of the overdose hypothesis, although stronger evidence should come from future longitudinal studies that test within-patient medication effects in both the early and late disease stage.

8 Mechanisms of impaired learning and choice with excessive dopamine stimulation

A detailed mechanistic account of the detrimental effects of medication on learning in terms of changes in striatal dopamine signaling was provided by Frank (2005) and Frank et al. (2004). This model built on the observation that rewards and punishments elicit phasic dopamine bursts versus dips, respectively, subsequently modifying

synaptic plasticity in D1 neurons of the direct Go pathway versus D2 neurons of the indirect NoGo pathway of the basal ganglia. The consequence of this modulation of direct and indirect pathway neurons is the facilitation versus suppression of cortical activity associated with the current response. In the model, PD biases patients away from "go" learning from rewards, towards "nogo" learning from punishment. An overdose of dopaminergic medication has the opposite effect, biasing patients towards reward-based "go" response and away from punishment-based "nogo" learning. Model-based simulations demonstrated that this shift can account for the medication-induced reversal learning deficit we had observed earlier (Cools et al., 2001a; Frank, 2005). A series of subsequent empirical medication withdrawal studies in PD patients substantiated key predictions from this model, showing better reward-based learning (Rutledge et al., 2009) but impaired punishment-based (reversal) learning in PD patients ON vs OFF their medication (Bodi et al., 2009; Frank et al., 2004, 2007; Graef et al., 2010; McCoy et al., 2019; Moustafa et al., 2008). The model also provided an account of the medication-related attenuation of BOLD signal in the ventral striatum that we had previously seen to occur at the time of the punishment events that signaled contingency reversal (Cools et al., 2007): These medication-related increases in dopamine might have occluded the phasic dopamine dips that were required to elicit the disinhibition, via action on D2 receptors, of NoGo pathway activity and/or plasticity necessary for punishment-based reversal learning. A more recent pharmacological fMRI study of reinforcement learning with PD patients substantiated this finding, demonstrating that dopaminergic medication in PD reduces negative (but not positive) outcome learning rates, as well as prediction error related BOLD signals (McCoy et al., 2019). Evidence from parallel work with experimental rodents that combined pharmacology with chemogenetics, fiber photometry and electrophysiological recordings from the VTA provided more direct evidence for this account: Reversal learning was impaired by administration of dopaminergic drugs (i.e., cocaine and d-amphetamine) as well as by chemogenetic activation of ascending dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens, which induced insensitivity to loss. Critically these dopaminergic manipulations also attenuated dopaminergic negative reward prediction error signals in the nucleus accumbens, measured with in vivo fiber photometry, but not in the VTA measured electrophysiologically (Verharen et al., 2018). The authors concluded that as baseline dopamine tone is increased, the signaling threshold in the nucleus accumbens that allows for the incorporation of negative reward prediction errors into adaptive behavior cannot be reached during reward omission or punishment.

To assess whether the negative effect of medication on reversal learning in PD indeed reflects reduced impact of punishment prediction errors and not of reward prediction errors, we designed a novel reversal task that required reward and punishment predictions (a valenced weather prediction-like task) (Cools et al., 2006). In this task, patients had to learn to press one of two buttons in order to predict whether a stimulus was followed by a reward or punishment. The deterministic stimulus-outcome contingencies reversed unexpectedly, so that reversals were signaled to

patients by either an unexpected reward or an unexpected punishment. The pattern of effects of dopaminergic medication in PD paralleled that observed by Frank et al. (2004): Medication impaired reversal learning based on punishment, but improved reversal learning based on reward. Notably, this result also demonstrated that dopamine-related biases away from punishment towards reward learning surfaces irrespective of the requirement to make a Go or Nogo response. Indeed response (shifting, activation and inhibition) requirements were well matched between the reward and punishment reversal conditions.

This selective set of findings concurs with accumulating evidence from work with healthy volunteers demonstrating that dopamine-induced increases in reward versus punishment prediction-error related striatal BOLD signaling are associated with a bias towards better reward versus punishment learning (Chowdhury, 2013; Pessiglione et al., 2006). However, there is also confusing evidence from other neuroimaging studies. Some have observed that dopaminergic medication in PD actually reduced reward prediction error signals in the ventral striatum (Schmidt et al., 2014; van Eimeren et al., 2009), suggesting that increases in dopamine transmission with levodopa and/or agonist medication can distort the phasic increases in dopamine release elicited by reward prediction errors, known to be essential for learning. This alternative account is reminiscent of a different line of theoretical and empirical work that has focused on dopamine's effects on behavioral activation and vigor rather than learning (Niv et al., 2007). Such invigorating effects have been attributed to levodopa-related increases in tonic dopamine transmission, which might impact a long-run average reward rate (Beierholm et al., 2013). The effect of increasing average reward rate might be multifold, but is most commonly associated with changes in the expression of learnt value on choice rather than with changes in learning itself (Box 1). It is possible that the existing discrepancy in dopamine's effects on reward- and punishment-related BOLD signals in the striatum (reviewed also in Cools et al., 2007) reflects differences in the computational requirements for learning versus choice of the task under study. To resolve this discrepancy, we need to combine pharmacological imaging work with paradigms that are amenable to sophisticated computational modeling to unravel the latent learning vs choice computations that can then be linked with meaningful BOLD signals (McCoy et al., 2019; van Nuland et al., 2020).

BOX 1 Do effects of dopaminergic medication reflect changes in value-based learning or changes in the expression of value on choice?

While dopamine-related changes in reward prediction error signaling can account for changes in learning, changes in the long-run, average reward rate can account for other well-known effects of dopaminergic medication. These other effects include increases in behavioral activation (Niv et al., 2007), risk taking (e.g., by raising the baseline reference point against which phasic reward prediction errors are compared, making gains look more like losses (Cools et al., 2011)), an undermining of model-based deliberative control by increasing the cost of time (Boureau et al., 2015; Froböse and Cools, 2018) as well as perseveration after contingency reversals, which can be conceptualized as a cumulative reinforcement-based reduction of the learning rate, i.e. surfacing as a stamping in of previously reinforced habits (den Ouden et al., 2013).

Continued

BOX 1—cont'd

Driven by discussions regarding dopamine's role in learning vs incentive salience and choice (Berridge, 2007; Niv et al., 2007; Robbins and Everitt, 2007), a number of medication withdrawal studies in PD have addressed the question whether the asymmetric effects of dopaminergic medication on reward and punishment learning in PD might in fact reflect changes in the expression of already learnt behaviors on choice (Shiner et al., 2012; Smittenaar et al., 2012). Indeed, learning and choice are often confounded in reinforcement learning paradigms, in which learning ability derives from optimal value-based choice. In one study, we have circumvented this confound by assigning value to the outcome of a choice option by instruction, obviating the need to learn from unexpected reward or punishment. Even in this context that minimized learning demands, we found that medication in PD biased patients to select reward- over punishment-associated options (Smittenaar et al., 2012), thus demonstrating that dopaminergic medication can alter the impact of benefits vs costs of options on action per se without impacting plasticity. Such effects on the expression of learnt value on choice was indeed explicitly incorporated in an algorithmic version of the Go/Nogo model of the basal ganglia, the anatomical and physiological architecture of which is perfectly suited not only to allow dopamine-dependent modulation of synaptic plasticity but also of the selective gating of activated cortical actions (Collins and Frank, 2014). More recent medication withdrawal studies in PD have confirmed that dopaminergic medication in PD can impact cost/benefit-based decision making outside of learning contexts, in the domain of cognitive effort (McGuigan et al., 2019), physical effort (Le Heron et al., 2018; Skvortsova et al., 2017), risk (Brand et al., 2004; Cools et al., 2003; Euteneuer et al., 2009; Onge et al., 2010; Rutledge et al., 2015; St Onge and Floresco, 2009) and/or delay costs, putatively by increasing sensitivity to the benefits (Manohar et al., 2015) and decreasing the sensitivity to the costs of the choice options (Westbrook et al., 2020). Effects of dopaminergic medication on both value-based learning as well as the expression of already learnt value on choice may contribute to the impulsive and compulsive behaviors observed in a subset of patients, particularly when aberrant reward-related learning is combined with hypothetical under-expression of punishment-related processing or "myopia for future (losses)" (Bechara and Damasio, 2002; Frank et al., 2004; Voon et al., 2010, 2011a).

9 From accounts of within-patient variability to between-patient variability in dopamine drug effects

In sum, the dopamine overdose hypothesis has inspired at least two decades of computational and mechanistic work aimed at unraveling the mechanisms underlying the detrimental side effects of dopaminergic medication. These studies have greatly advanced our understanding of the functions of dopamine in the human striatum. Having said that, it is also clear from extensive pathological research (Agid et al., 1987; Gibb et al., 1989; Paulus and Jellinger, 1991), as expressed in influential proposals (Borghammer and Van Den Berge, 2019; Braak et al., 2003; Dagher and Zeighami, 2018; Fereshtehnejad et al., 2017; Foffani and Obeso, 2018; Markello et al., 2021), that different PD patients exhibit abnormalities in different systems, including cortex, the ascending noradrenergic, serotonergic and cholinergic pathways as well as peripheral systems in the gut (Doppler et al., 2021), that correlate with cognitive dysfunction (Prasuhn et al., 2021; van der Zee et al., 2021). Thus, the classic notion of PD as a model of fronto-striatal dopamine depletion has become outdated, not least also since the advent of large, often longitudinal

cohort studies that have begun to allow the systematic unraveling of large neural, neurochemical, genetic and clinical heterogeneity in PD (Robbins and Cools, 2014). Indeed, it is now evident that there is tremendous variability in the pattern of cognitive deficits and in the effects of the different treatment strategies not just across different tasks within the same patients, but also most critically across different patients (Bloem et al., 2021). This heterogeneity certainly does not just reflect the fact that the optimal level of dopamine stimulation is different for different cognitive functions (Cools and Robbins, 2004; Fallon et al., 2015), but also the large individual variability in underlying pathology. For example, the commonly observed deficits in response inhibition, measured with the stop-signal reaction time task are now well established to be more amenable to noradrenergic than dopaminergic medication (Borchert et al., 2016; Kehagia et al., 2014; Meder et al., 2019; Rae et al., 2016; Ye et al., 2015), in a manner that depends on the integrity of the locus coeruleus (O'Callaghan et al., 2021). As such these deficits are much more likely to reflect neurodegeneration of the noradrenergic neurons in the LC (Braak et al., 2003; Hawkes et al., 2010). Furthermore, degeneration of the cholinergic neurons has been associated with the type of cognitive deficits more commonly associated with cortical dementia. Influential in this regard have been insights from the Cambridgeshire Parkinson's Incidence from GP to Neurologist' (CamPaIGN) study (Foltynie et al., 2004), which has identified a number of subgroups of patients: with or without fronto-striatal deficits (such as impairment on the Tower of London task), with or without temporal lobe dysfunction (such as visual pattern recognition memory deficits) and with or without the more marked cognitive impairment associated with clinical cortical dementia (as indicated by low scores on the Mini Mental State Exam). In line with this large heterogeneity in pathology, certainly not all patients exhibit beneficial effects of dopaminergic medication, and only a proportion of patients suffer negative side effects or develop impulse control disorder as a consequence of their medication regime. While almost all patients eventually receive dopaminergic medication, impulse control disorder (ICD) occurs only in a subset (∼10%–15%) (Weintraub et al., 2010). Such observations inspired the dual syndrome hypothesis (Kehagia et al., 2010, 2013), according to which two broad syndromes can be distinguished: (i) A profile of neuropsychological deficit in non-demented PD patients with "mild cognitive impairment" (MCI) and a tremor-dominant phenotype. These patients perform more poorly on tests of planning, working memory and executive function reflecting fronto-striatal dysfunction. These fronto-striatal deficits are amenable to dopaminergic medication, but susceptible to overdosing effects. They are modulated by the COMT polymorphism and disease severity. (ii) An akinetic subgroup with pronounced gait disturbance demonstrating early deficits in visuospatial function and semantic fluency indicative of posterior cortical and temporal lobe dysfunction, who exhibit rapid cognitive decline to dementia and in whom cholinergic treatment may offer some clinical benefit (Emre et al., 2004).

In the remainder of this chapter we address specifically the individual variability in the negative effects of dopaminergic medication on functions that are well-established to be sensitive to dopamine, such as reinforcement learning and value-based decision making. While the contrasting effects of dopaminergic medication

in PD on reward versus punishment learning have become almost canonical due to their cross-lab replication (Bodi et al., 2009; Cools et al., 2006; Frank et al., 2004; McCoy et al., 2019; Palminteri et al., 2009), there have also been notable failures to replicate these asymmetric effects on reward and punishment learning (Coulthard et al., 2012; Grogan et al., 2017; Shiner et al., 2012; Timmer et al., 2017). We argue here that these studies might well have failed to detect such effects, because they did not take into account key individual variability, when collapsing data across all patients. This large individual variability poses not only a major problem for medication studies aimed at isolating the role of dopamine in human cognition, but also for neurology and psychiatry: How to identify which patients will benefit from which treatments and who will suffer the greatest side effects?

There are likely many clinical, cognitive, genetic, neural and molecular factors that mediate the individual differences in detrimental medication effects on learning and choice. In recent work, we have studied the value of taking into account two such factors and it is these factors that we will focus on in the next part of the chapter: (i) comorbid psychiatric disorders that implicate, among other things, mesolimbic dopamine abnormality, such as depression (Joutsa et al., 2012; Voon et al., 2011b); and (ii) tremor phenotype, which implicates disproportionate neurodegeneration in the midbrain and dopamine depletion in the striatum (Hirsch et al., 1992; Jellinger, 2012). As will become clear below, doing so has also informed our understanding of the mechanisms by which medication elicits cognitive impairment.

10 Dopaminergic medication effects on risky choice depend on depression history

While the mechanisms underlying depression in Parkinson's disease are complex and multifactorial, nuclear imaging studies have consistently revealed lower striatal dopamine transporter binding, specifically in ventral striatal regions, in depressed compared with non-depressed PD patients (Remy et al., 2005; Vriend et al., 2014; Weintraub et al., 2005). Moreover, depressive symptoms in PD occur more frequently when dopaminergic medication effects wear OFF and can be ameliorated (to some degree) by dopaminergic medication (Barone, 2010; Maricle et al., 1998), generally in line with theories that link depression with dopamine (Pizzagalli, 2014). In addition, ventral striatal dopamine dysfunction is strongly implicated in reward-related motivational and learning abnormalities observed in depression (Admon et al., 2017; Eshel and Roiser, 2010; Pizzagalli, 2014). Therefore, according to the overdose hypothesis, PD patients with concurrent depression might be expected to be less likely to experience overdosing effects of dopaminergic medication. We have addressed this hypothesis in a series of controlled withdrawal experiments.

In one of these experiments (Timmer et al., 2018), we focused on risky choice (gambling behavior) and took into account a history of depressive episodes that occurred up to 5 years prior to diagnosis. A well-established gambling paradigm was employed. Based on evidence that depression in PD is accompanied by

disproportionately reduced ventral striatal dopamine levels (Remy et al., 2005; Vriend et al., 2014; Weintraub et al., 2005), we hypothesized that dopamine-induced increases in risky choice are greater in PD patients without a depression history than in PD patients with such a history. However, based on clinical observations that ICDs including gambling addiction are often comorbid with depression (Joutsa et al., 2012; Voon et al., 2011b), we also considered that alternative possibility that, by contrast, dopamine-induced increases in risky choice might be greater in PD patients with than without a history of depression. In addition, the study allowed us to unravel the computational mechanisms contributing to drug-induced increases in risky choice. To this end, we employed a computational modeling approach based on prospect theory, one of the more successful accounts of decision making under risk (Kai-Ineman and Tversky, 1979; Tversky, 1984). The mechanistic hypothesis was inspired by the theoretical and empirical work described above, indicating that excessive striatal dopamine stimulation by dopaminergic medication in PD can alter task performance by boosting the relative weighting of reward versus punishment on learning and choice (Collins and Frank, 2014; Cools et al., 2006; Frank et al., 2004; Shiner et al., 2012; Smittenaar et al., 2012; van der Schaaf et al., 2014). Specifically, we reasoned that dopaminergic medication might increase risky choice by attenuating loss aversion, which reflects our tendency to weigh losses more than equally sized gains. The results were partly consistent with this latter prediction, in the sense that dopaminergic medication reduced loss aversion. However, it did so to a greater extent in PD patients with a depression (history) than in non-depressed PD patients. Correlation analyses revealed that dopamine-induced decreases in loss aversion were related to current depression severity and to effects of dopaminergic medication on depressive symptoms. Patients with the highest current depression scores and the greatest beneficial effect of dopaminergic medication on depression scores also exhibited the greatest dopamine-induced decreases in loss aversion. This finding concurs with clinical evidence indicating that PD patients with more severe depressive symptoms are at increased risk for having ICD (Evans et al., 2005; Joutsa et al., 2012; Marín-Lahoz et al., 2019; Voon and Fox, 2007), although a strong link between (dopamine-induced decreases in) loss aversion and ICD is yet to be established (Giorgetta et al., 2014; Voon et al., 2011a). The finding raises the hypothesis, to be addressed in future studies, that dopamine-related reductions in loss aversion might underlie previously observed comorbidity between depression and medication-related side effects in PD, such as ICDs. The result also suggests that the dopamine overdose hypothesis might need to be revised, by recognizing that detrimental medication effects on choice behavior do not surface most readily in patients with the most intact mesolimbic dopamine system, but rather in patients who exhibit (perhaps genetically determined) mesolimbic dopamine abnormalities. Given that depression in PD is accompanied by decreased striatal DAT (Rektorova et al., 2008; Remy et al., 2005; Vriend et al., 2014; Weintraub et al., 2005) and decreased D2/D3 receptor availability (Boileau et al., 2009), these may include deficiency in autoregulatory mechanisms that render the ventral striatal dopamine levels overly dynamic, such as the dopamine D2/D3 auto-receptor and the presynaptic dopamine transporter (DAT). They may also include a vulnerable serotonin system.

This hypothesis is supported by the observation that depression, ICDs and behavioral addiction are often accompanied by levodopa-induced dyskinesias (Voon et al., 2009, 2017) (i.e., involuntary movements observed in 80% of the more severely affected patients (Voon et al., 2017)), which are commonly ascribed to progressive failure of cellular re-uptake and recycling of striatal dopamine, leading to fluctuating dopamine levels (Meder et al., 2019), and/or serotonin depletion due to levodopa-to-dopamine conversion in serotonin neurons (Espay et al., 2018). Evidence from PET and SPECT studies demonstrates that patients who are at risk of ICDs or depression exhibit reduced negative feedback control over dopamine release in the striatum (Ray et al., 2012), and reduced dopamine transporter (DAT) availability in the ventral striatum, suggesting reduced dopamine clearance from the synaptic cleft (Cilia et al., 2010; Smith et al., 2016; Voon et al., 2010; Vriend et al., 2014). Hypersensitivity of the ventral striatum to medication or gambling task exposure has been demonstrated in PD patients with ICDs and/or compulsive drug use (Evans et al., 2006; O'Sullivan et al., 2011; Steeves et al., 2009; Claassen et al., 2017). ICD severity is associated with reduced D2/3 receptor availability in the ventral striatum (Payer et al., 2015), again perhaps reflecting reduced autoregulatory capacity. Together this work implicates dysregulation of the ventral mesolimbic dopamine system in both ICD and depression. Such deficient autoregulation of dopamine transmission in the ventral striatum might reflect genetic variation associated with predisposing personality characteristics such as trait impulsivity and novelty seeking (Dagher and Robbins, 2009). Indeed [^{11}C]-raclopride PET imaging has shown that healthy volunteers with higher trait impulsivity scores exhibit lower D2 receptor availability in the dopaminergic midbrain, but enhanced dopamine release in the ventral striatum (Buckholtz et al., 2010; Dalley et al., 2007), again consistent with deficient autoregulation and an unstable, likely hyperdynamic mesolimbic dopamine system. The observation of comorbidity and shared individual susceptibility to medication-related addiction and ICDs, depression and levodopa-induced dyskinesias suggests that medication-related cognitive impairment on learning and choice tasks might also follow from an unstable, hyperdynamic rather than simply an intact mesolimbic dopamine system. These observations substantiate the suggestion that the strict version of the overdose hypothesis, which states that medication elicits the greatest impairments when modulating the most intact brain regions might need to be revised.

It should be noted that in the risky choice study described above, non-depressed PD patients also exhibited an effect of dopaminergic medication. Specifically, as was shown previously in healthy volunteers (Rigoli et al., 2016; Rutledge et al., 2015), dopaminergic medication enhanced the computational value-independent gambling bias parameter, reflecting a boosting of nonspecific attraction to gambling perhaps due to an exploration bonus associated with surprising outcomes that potentiates information, sensation- and novelty seeking (Dagher and Robbins, 2009; Norbury et al., 2013). However, this effect did not represent a medication-induced impairment, but rather a restoration of an abnormally low gambling bias for non-depressed PD patients OFF their medication, compared with gambling bias seen in healthy controls.

The study thus illustrated the power of a computational model-based approach to analyzing behavioral data, particularly given that no medication effects were observed on raw behavioral outcome measure of the proportion of accepted gambles. In other words, we would have failed to reveal any of the effects on risky choice processes, if we had not taken into account the prior theoretical insight that the proportion of accepted gambles on tasks such as the one used here is a function of multiple parameters. Here this proportion of accepted gambles was a function of both a value-independent gambling bias and loss aversion, which, in this case, were both modulated by medication but in different groups and in different directions.

11 Dopaminergic medication effects on reversal learning depend on depression

In another recent study (Timmer et al., BioRxiv; original data presented here), we revisited the cognitive construct that we had originally found to be so vulnerable to dopaminergic medication in mild PD patients: reversal learning. As in the risky choice study, described above, we asked whether the detrimental effects of dopaminergic medication in PD on reversal learning, which we had previously found to reflect modulation of the ventral striatum, might depend on depression status. Again, the starting point of this study was the dopamine overdose hypothesis, according to which the detrimental effects of dopaminergic medication on reversal learning in PD would be restricted to patients with intact levels of ventral striatal dopamine, not extending to patients with deficient dopamine transmission in the ventral striatum (Cools et al., 2006). To test this, we leveraged an available dataset from a large sample PD study (the ParkFit study (van Nimwegen et al., 2010)) that allowed us to investigate the association between dopaminergic medication dose and reversal learning impairment in 569 PD patients with various degrees of depressive symptoms (data obtained from the baseline, pre-intervention session), quantified using the depression score of the Hospital Anxiety and Depression Scale (HADSd). The task employed was the well-established CANTAB intradimensional/extradimensional set-shifting paradigm (ID/ED) (Downes et al., 1989) and the average number of errors on the four reversal stages (2, 5, 7 and 9) was used as a measure of reversal learning performance. In all analyses we controlled for age, MMSE and scores on the UPDRS part-III. Critically, the (partial) correlation between levodopa equivalent dose (LED) and reversal errors was highly significant ($r_{(564)} = 0.124$, $P = 0.003$), indicating that higher dopaminergic medication dose was significantly associated with more reversal errors, consistent with an overdose effect. Conversely, the (partial) correlation between levodopa dose and extra-dimensional set-shifting errors, which had previously been shown to implicate the dorsolateral prefrontal cortex (Dias et al., 1996) was not significant ($r_{(564)} = 0.041$, $P = 0.32$). Moreover, the (partial) correlation of medication dose with reversal errors was significantly stronger than that with EDS errors (Fisher test $z = 2.09$, $P = 0.037$). Mediation analyses revealed not only a significant direct effect of dopaminergic medication dose on reversal errors

(B = 0.002, 95%CI = 0.001–0.003) (Fig. 2A), but also a significant positive effect of dopaminergic medication dose on depression scores (B = 0.001, 95%CI = 0.001–0.002) and of depression scores on reversal errors (B = 0.215, 95% CI = 0.086–0.344). Most critically, bias-corrected bootstrapped 95% confidence intervals of the indirect path (e.g., mediation effect) revealed that the correlation between dopaminergic medication dose and reversal learning was mediated by current depression severity (B = 0.0003, bias-corrected 95%CI = 0.001–0.006) (Fig. 2B). Current depression severity explained 17% of the total effect of dopaminergic medication dose on reversal learning.

These data demonstrate that, consistent with the overdose hypothesis, higher amounts of dopaminergic medication were associated with greater impairments in reversal learning. Critically, and in contrast to our original hypothesis, mediation analyses revealed that this association is greatest in patients who exhibit the highest depression scores. The obvious caveat of this large sample study is that it did not involve controlled manipulation of the medication state. As in any other study in which patients are tested only on their medication (Swainson et al., 2000), any association between medication dose and task impairment might also reflect disease severity, which often covaries with medication dose. Indeed, there was also a significant correlation between disease duration and reversal learning impairment. However, in all our analyses we carefully controlled for this. As such, the finding that the

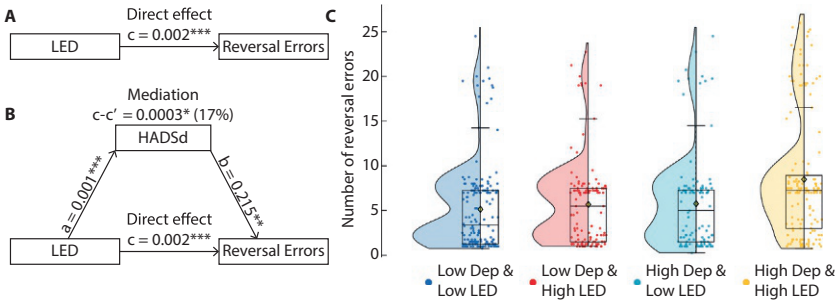

FIG. 2

Influence of current depression severity (HADS depression scale) and medication status on reversal errors. (A) The direct effect of dopaminergic medication dose (LED) on the number of reversal errors, as calculated by mediation analysis. (B) The mediation effect of the current depression severity (HADS depression subscale) on the effect of dopaminergic medication on reversal errors. c-c′ represent is the indirect mediating effect (% mediation). c-c′ represents the indirect (mediating) effect (with % mediation). c′ represents the direct effect of dopaminergic medication dose on reversal errors when adjusting for the indirect (mediating) effect of depression severity. (C) Raincloud plot of the number of reversal errors for each subgroup. Subgroups were determined based on a median split for their medication dose (LED) and depression status (HADS depression subscale). Means are depicted as yellow diamonds, medians as the center line in the boxplot. $*P<0.05$, $**P<0.01$, $***P<0.001$.

association with reversal learning is greater than that with attentional set-shifting cannot be accounted for by disease severity. A medication account of the disproportionate association is more plausible.

Of course, reversal learning and depression are also well known to implicate other major neuromodulators than dopamine, such as serotonin (Cools et al., 2011). We cannot rule out completely the possibility that the effects of interest of dopaminergic medication on reversal learning reflect use of serotonergic antidepressants in the patients with the higher depression ratings. Data regarding the use of antidepressant medication were not available. However, we argue it is unlikely that the effect of interest (the mediating effect of depression on the link between dopaminergic medication and reversal learning) reflects use of serotonergic drugs because of the following reasons. First, the non-dopaminergic drugs that were most likely used by the patients with high depression ratings are selective serotonin reuptake inhibitors (SSRIs). Chronic (although not necessarily acute (Chamberlain et al., 2006)) administration of such SSRIs is generally thought to increase serotonin transmission, which has been associated with improvement rather than impairment of reversal learning (Bari et al., 2010; Furr et al., 2012; Scholl et al., 2017) (for review see (Izquierdo et al., 2017)). As such, the possibly increased chronic use of SSRIs by our patients with high depression ratings is unlikely to mediate a positive correlation between dopaminergic medication and reversal learning errors. Second, on a related note, although serotonin has been argued previously to mediate detrimental effects of dopaminergic medication in Parkinson's disease (De Deurwaerdère and Di Giovanni, 2017; Everett and Borcherding, 1970; Miguelez et al., 2014, 2016), this effect would be in the opposite direction, with dopaminergic medication impairing cognitive function via decreasing (rather than increasing) serotonin. As such, any serotonin-increasing effect of any SSRIs would therefore counteract the observed negative link between dopaminergic medication dose and reversal learning. This observation does raise the question whether the pattern of effects reflects a 'double hit', so that depressed patients, who likely exhibit pre-existing serotonergic deficiency, suffer the greatest medication-related impairments in reversal learning, because of greater decreases in serotonin by dopaminergic medication (Proulx et al., 2014; Shabel et al., 2012; Sourani et al., 2012). While it is true that, at least superficially, the effects of dopaminergic medication can resemble those of serotonin depletion, there are also key qualitative differences between the effects of medication and serotonin depletion (Cools et al., 2011). For example, while dopaminergic medication in PD impairs punishment-based reversal learning (Cools et al., 2006), decreasing serotonin through dietary tryptophan depletion actually enhances punishment prediction (Cools et al., 2008; Robinson et al., 2012). We think an account in terms of greater use of noradrenergic drugs (e.g., to counteract depression) is also unlikely, given previous studies showing that noradrenergic drugs, like atomoxetine, did not alter reversal learning (Chamberlain et al., 2006). Nevertheless, the failure to obtain data regarding non-dopaminergic medication is a shortcoming of the study and future work should address the role of, for example, antidepressants and/or double-hit by non-dopaminergic abnormality in the negative association between dopaminergic medication and cognitive impairment.

The two studies by Timmer et al. on risky choice and reversal learning significantly extend previous literature by suggesting that the detrimental effects of dopaminergic medication on learning and choice are more severe in patients with higher depression scores, and raise the possibility that ventral striatal dopamine dysfunction (i.e., those who suffer from depression) predisposes rather than protects against the detrimental effects of dopaminergic medication on reversal learning.

The observation that the mediating effect of depression remained significant after controlling for disease severity (among other variables), suggests that presynaptic dopamine dysfunction in the ventral striatum, associated with depression, might be more relevant for explaining medication-induced cognitive impairments than is presynaptic dopamine dysfunction in dorsal striatum, associated with PD severity. Future research is warranted to elucidate the mechanisms underlying disproportionate medication-induced learning impairment in depressed versus non-depressed PD patients. However, the results have obvious implications for clinical practice, warranting stricter monitoring of cognitive side effects during dopaminergic treatment in PD patients with concurrent depression.

12 Dopaminergic medication effects on learning and choice depend on motor phenotype

Cognitive dysfunction in PD varies not only with variability in psychiatric comorbidity such as depression and ICDs, but also with variability in motor symptoms, in particular with regard to the presence or absence of a tremor phenotype (Helmich et al., 2012; Marras and Lang, 2013) This might reflect the spatial distribution of neurodegeneration in the midbrain and dopamine depletion in the striatum (Hirsch et al., 1992; Jellinger, 2012). Compared with tremor-dominant PD patients, non-tremor patients exhibit a variety of neurochemical alterations, predominantly in the dopaminergic system. Specifically, dopamine cell loss has been demonstrated to be more severe in non-tremor patients than in tremor-dominant patients, in both postmortem and nuclear imaging studies (Helmich et al., 2011; Rossi et al., 2010; Spiegel et al., 2007). Furthermore, non-tremor patients have more extensive substantia nigra degeneration (Jellinger, 2012; Paulus and Jellinger, 1991), which contains the majority of mesencephalic dopaminergic neurons (76% in non-human primates (François et al., 1999)). In contrast, tremor-dominant patients have more extensive retro-rubral area degeneration (Hirsch et al., 1992), which in non-human primates, contains only 10% of mesencephalic dopaminergic neurons (and the remaining 14% in the ventral tegmental area) (François et al., 1999). Given that tremor-dominant and non-tremor PD patients have different dopaminergic phenotypes, we hypothesized that the effects of dopaminergic medication on reinforcement learning and choice differ between tremor-dominant and non-tremor patients (van Nuland et al., 2020). Following the line of argument in the current chapter, if detrimental effects of dopaminergic medication surface primarily in patients with the most intact dopamine system, then we should observe these primarily in patients with a tremor phenotype. Patients were tested both ON and OFF dopaminergic medication on a

probabilistic instrumental learning task, requiring patients to make Go or Nogo responses based on reward or punishment. In line with the general pattern of dopamine-related bias towards rewards and away from punishments in prior studies (Cools et al., 2006; Frank et al., 2004), results revealed that dopaminergic medication boosted reward- versus punishment-based choice beyond that in healthy controls. However it did so only in non-tremor patients who exhibit greater dopamine depletion. As was the case in a prior levodopa study with healthy volunteers (Guitart-Masip et al., 2014), the boosting of reward-based choice on this task was particularly prominent on trials requiring a NoGo response, possibly because Go-to-win trials were at ceiling, leaving little room for further modulation. Regardless of the precise computational and neurochemical mechanisms underlying the differential medication effects as a function of motor phenotype, this finding establishes differential sensitivity of value-based learning and choice to medication effects in tremor vs non-tremor Parkinson patients, and highlights the importance of considering motor phenotype in future work.

13 Conclusion

In the first part of this chapter, we have described the history of research that led to and substantiated the dopamine overdose hypothesis, which accounts for the contrasting beneficial versus detrimental effects of dopaminergic medication on distinct cognitive functions in people with PD. The evidence favors this overdose account over an alternative non-specific denervation account, because the observed medication effects are task-specific and correspond with the spatiotemporal progression of dopamine depletion from dorsal to more ventral frontostriatal circuitry. This dopamine overdose hypothesis has inspired at least two decades of computational and mechanistic work aimed at unraveling the mechanisms underlying the detrimental side effects of dopaminergic medication. Given that the early work focused in particular on the vulnerability to dopaminergic medication of reversal and reinforcement learning, the program also contributed to substantiating the empirical foundations of the pervasive reinforcement learning hypothesis of dopamine according to which dopamine boosts learning from reward, while impairing learning from punishment. In addition, it has motivated the development of neurobiologically realistic models of how the cell-specific anatomical and receptor architecture of the striatum can account for dopamine's effects on reinforcement learning. Furthermore, the work has also played a key role in revising this hypothesis to clarify that dopamine's role is certainly not restricted to reinforcement learning, but extends to value-based choice, evident already from early behavioral neuroscience studies on incentive salience and behavioral activation and in later computational accounts of basal ganglia dopamine. Thus, the study of dopaminergic medication effects in PD has greatly advanced our understanding of the functions of dopamine in the human striatum.

Nevertheless, the classic notion of PD as a model of fronto-striatal dopamine depletion has become outdated, and it is now evident that there is huge variability across patients in the pattern of cognitive deficits and the sensitivity of those deficits to dopaminergic medication. Certainly not all patients exhibit beneficial effects of

dopaminergic medication, and only a proportion of patients suffer negative side effects or develop impulse control disorder as a consequence of their medication regime. In the second part of this chapter we review recent studies and present an original dataset addressing specifically the large individual variability in the negative effects of dopaminergic medication on functions that are well-established to be sensitive to dopamine, such as reinforcement learning and value-based decision making. Specifically, we have focused on depression history and non-tremor phenotype, which have both been shown to be associated, among other pathology, with deficient dopamine regulation. The studies suggest that it is time to revise the strict version of the dopamine overdose hypothesis, which states that the greatest medication-induced impairment should be seen on tasks recruiting brain regions that are intact. By contrast, results suggest that the typical medication-related increase in the impact of reward versus punishment is greater in patients with putatively more unstable mesocorticolimbic circuitry, such as those suffering from depression, than in less affected PD patients. This is not surprising given that depression is recognized to be a risk factor for ICDs in PD. Future large, longitudinal cohort studies, building on the Parkinson's progression markers initiative (Marek et al., 2018), the Personalized Parkinson Project (Bloem et al., 2019) and the CAMPAIGN study (Foltynie et al., 2004) which allow the systematic unraveling the neural, neurochemical, molecular and genetic factors that contribute to the large clinical heterogeneity in PD will be necessary to predict which patients will benefit and who will suffer those disabling side effects of dopaminergic medication, such as ICD and addiction. A suitable prediction model of such side effects likely comprises an optimal combination of multiple parameters, including depression history, non-tremor motor phenotype, premorbid personality traits like impulsivity and a novelty seeking, and genetic variation in molecules that affect the autoregulation of dopamine transmission (presynaptic D2/3 receptor sensitivity, DAT density) (Fig. **1**). Also promising in this regard are markers of neuroinflammation, given that pro-inflammatory molecules, likely produced by microglial cells, can accelerate dopaminergic cell death (Hirsch and Hunot, 2009) and have been implicated in reinforcement learning and value-based choice (Felger and Treadway, 2017). Finally, the disproportionate sensitivity of PD patients with ICDs and addictions to the acute effects of medication withdrawal on reinforcement learning and choice (Cilia and van Eimeren, 2011; Drew et al., 2020; Meder et al., 2019; Voon et al., 2010, 2011a), suggest that the value of a prediction model for anticipating severe psychiatric abnormality elicited by medication might be greatly enhanced by also including medication-related effects on learning and choice and associated neural activity.

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Conflict of interest

R.C. is a consultant for Roche Ltd, but receives no royalties.

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