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The role of dopamine in the brain - lessons learned from Parkinson's disease

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ABSTRACT

Parkinson's disease causes a characteristic combination of motor symptoms due to progressive neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta. The core impairment of dopaminergic neurotransmission has motivated the use of functional magnetic resonance imaging (fMRI) in patients with Parkinson's disease to elucidate the role of dopamine in motor control and cognition in humans. Here we review the main insights from functional brain imaging in Parkinson's disease. Task-related fMRI revealed many disease-related alterations in brain activation patterns. However, the interpretation of these findings is complicated by the fact that task-dependent activity is influenced by complex interactions between the amount of dopaminergic neurodegeneration in the task-relevant nuclei, the state of medication, genetic factors and performance. Despite these ambiguities, fMRI studies in Parkinson's disease demonstrated a central role of dopamine in the generation of movement vigour (bradykinesia) and the control of excessive movements (dyskinesia), involving changes of both activity and connectivity of the putamen, premotor and motor regions, and right inferior frontal gyrus (rIFG). The fMRI studies addressing cognitive flexibility provided convergent evidence for a non-linear, U-shaped, relationship between dopamine levels and performance. The amount of neurodegeneration in the task-relevant dopaminergic nuclei and pharmacological dopamine replacement can therefore move performance either away or towards the task-specific optimum. Dopamine levels also strongly affect processing of reward and punishment for optimal learning. However, further studies are needed for a detailed understanding of the mechanisms underlying these effects.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which causes a characteristic combination of motor symptoms, comprising slowness of movement (bradykinesia), increased muscle tone (rigidity), shaking (tremor), and impaired postural control. The neuropathological hallmark of PD is the presence of alpha-synuclein inclusions called Lewy-bodies in neurons, associated with progressive loss of dopaminergic neurons in the substantia nigra pars compacta (Kalia and Lang, 2015). Despite early, prevalent and disabling non-motor features, PD has for many years mainly been viewed as a movement disorder. Accordingly, pathophysiological models of PD have mainly focussed on neurodegeneration of dopaminergic neurons in the ventral tier of the substantia nigra (SN) and its projections to the dorsal ('motor') striatum (Fearnley and Lees, 1991; Jellinger, 1999). Dopamine replacement therapy effectively alleviates many of the motor symptoms of PD, especially during the first years after clinical disease onset. This qualifies PD as a valuable disease model for understanding the motor dopaminergic system in the healthy brain by mapping changes in neural activity between unmedicated patients in a dopamine-depleted state and medicated patients with restored dopamine levels and healthy controls. Yet, an exclusive focus on the motor

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domain and its dopaminergic neurotransmission would overlook several important aspects of PD. First, the dopaminergic system is not uniformly affected by neurodegeneration, dopaminergic neurons in the ventral tegmental area (VTA) are less affected by neurodegeneration (Alberico et al., 2015). In addition, neurodegeneration also affects other neuromodulatory systems including noradrenergic (NA), cholinergic and serotonergic neurotransmitter system (Braak et al., 2003; Hawkes et al., 2010) with which dopamine can interact. This multi-system involvement explains why PD patients frequently suffer from several disabling 'non-motor' symptoms that oftentimes are changed in intensity, but not effectively treated, by dopaminergic medication (Schapira et al., 2017).

PD was among the first clinical applications of functional neuroimaging, from the 1980's onwards (Rowe and Siebner, 2012). Well-designed imaging studies in PD provided valuable insights, not only into the disease, but also into the functioning of dopaminergic systems relevant to the healthy brain.

One way to capture dopamine-related changes in brain function, is to test patients in two dopamine states; once after dopamine withdrawal with relatively low levels of dopamine in a pragmatic OFF-medication state and once after dopamine intake with relatively high levels of dopamine in an ON-medication state. The differences in the patient's behaviour and neural activation between the ON- and OFF-medication state, considered together with the behaviour and activation patterns of healthy control participants, is then used to infer the functional effects of dopamine in the human brain.

Another useful approach is to include PD patients who developed an unwanted effect of dopamine replacement, such as involuntary 'dyskinesia' movements or impulse control disorders (ICD), reflecting deleterious side effects of dopamine replacement therapy. Comparing how dopamine alters behaviour and neural activation in patients who develop side effects versus patients who do not, provides a better understanding of dopamine-mediated mechanisms of behaviour. For instance, dopamine induced dyskinesia can be conceptualized as aberrant modulation of movement vigour while the emergence of ICDs can be seen as dysfunctional computation of reward prediction errors. Thus, these studies are not only informative on mechanisms mediating side effects of dopamine in PD, but also elucidate the role of dopamine in cognition and behaviour. For an overview over the literature applying different combinations of these approaches, see Table 1.

Another neuroimaging strategy is to relate inter-individual differences in behaviour and neural activity to inter-individual differences in dopamine deficiency. The latter can for example be assessed by single-photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging markers of neurodegeneration (e.g. Aarts et al., 2012) or quantification of dopamine-related motor symptoms (e.g. Rowe et al., 2008). Rather than comparing patients with healthy controls, this approach exploits the strong heterogeneity of dopamine deficiency in patients with PD.

Other neuroimaging modalities have also contributed substantially to our understanding and diagnosis of PD, for example structural MRI using diffusion MRI, MRI sequences sensitive to local iron or neuromelanin concentrations, or volume based morphometry (Lehericy et al., 2017). Other neuroimaging studies have explored the impact of genetic factors in PD (Robbins et al., 2016). For example, polymorphism of the catechol-o-methyltransferase (COMT) gene that metabolises dopamine in the frontal cortex leads to differences in the activity of executive cognition systems in PD and in health and can explain some of the heterogeneity of effects among patients (Nombela et al., 2014b).

Finally, there exists a large body of literature on resting-state neuroimaging having established consistent changes in PD related to motor and cognitive dysfunction (e.g. Eidelberg, 2009; Kim et al., 2017; Spetsieris et al., 2015; Tahmasian et al., 2015; Tang et al., 2010; Vo et al., 2017; Zhuang et al., 2018). However, given the absence of a direct relation to behaviour in these studies, we will only refer to this literature where it is relevant with respect to the functional neuroimaging studies discussed.

It should also be noted that dopaminergic challenges in healthy subjects can further elucidate the role of this neurotransmitter in the healthy brain (e.g. Beierholm et al., 2013; Fiore et al., 2018; Rigoli et al., 2016). Yet, the focus of this review is on the contribution of PD research to our understanding of the diseased and the healthy brain and studies on healthy participants will not be discussed.

In the following sections, we illustrate the value of functional brain imaging studies of motor and non-motor functions in PD. We focus on functional neuroimaging studies that have contributed to our understanding of physiological and pathological functions of dopamine and only include important structural and genetic imaging studies where they complement the functional data. Furthermore, the non-motor symptoms of PD span many domains, such as sleep, mood, autonomic function, sensory processing or pain. Here, we focus on cognitive symptoms that are typically modulated by dopamine. The selected studies are summarized in Table 1.

2. Motor control in Parkinson's disease

2.1. Slowness of movement

Bradykinesia is a clinical hallmark of PD and comprises the slowing of movement initiation as well as a progressive reduction in speed and amplitude during repetitive actions (Hughes et al., 1992). Bradykinesia has been attributed to an impaired ability to optimally modulate movement vigour, resulting in a failure to sufficiently "charge" movement speed, amplitude and frequency during motor execution (Hallett and Khoshbin, 1980). A lack of vigour is also relevant to akinesia which is another prominent motor symptom of PD and refers to poverty or absence of movements (Hallett and Khoshbin, 1980; Massano and Bhatia, 2012; Turner et al., 2003). Some authors differentiate hypokinesia from bradykinesia with the former describing a decrease in amplitude (e.g. micrographia) and the latter a reduction in the speed of movements (Berardelli et al., 2001). However, in most studies the terms hypo- and bradykinesia are used interchangeably. A prominent theory interprets bradykinesia and akinesia as an impaired ability to assign appropriate kinematics to selected actions, putatively due to an abnormal computation of vigour costs (Baraduc et al., 2013; Bouc et al., 2016; Mazzoni et al., 2007; Niv et al., 2007; Panigrahi et al., 2015).

Bradykinesia is the core parkinsonian symptom that most closely correlates with dopamine deficiency (Bernheimer et al., 1973; Vingerhoets et al., 1997). Furthermore, bradykinesia responds well to dopamine replacement therapy (Birkmayer and Hornykiewicz, 1961; Cotzias et al., 1969; Hauser, 2009), corroborating the notion that dopamine plays an important role in modulating movement vigour. Precise modulation of movement vigour is central to skilful movements (Dudman and Krakauer, 2016). Hence, a better understanding of how changes in dopamine neurotransmission impact on motor circuits controlling movement kinematics is not only relevant for PD research, but for motor neuroscience in general.

Herz et al. (2014b) aimed to quantify the results of previously conducted fMRI and H_2O-PET studies in PD using an activation likelihood estimation meta-analysis approach (Fig. 1). Consistent differences were primarily found in caudal ("motor") putamen where patients with PD showed less movement-related activation than healthy controls and where dopamine replacement increased task-related motor activation. Furthermore, studies that included more severely affected PD patients, with presumably lower levels of striatal dopamine, were more likely to show a decrease in putaminal activation during motor tasks. At the cortical level, neuroimaging results were less consistent. Motor activation of inferior parietal cortex, superior parietal lobule, primary motor cortex (M1) and

Table 1
Selected publications studying patients with PD during motor paradigms, paradigms related to cognitive and behavioural control, paradigms related to reward and punishment, resting state and on structural changes.

Authors	Year	Participants (disease severity)	Medication state	Paradigm	Main findings in patients with Parkinson's disease
Activation during motor tasks					
Buhmann et al.	2003	8 (drug-naïve, H&Y 1–1.5)	OFF/ON	Simple paced finger opposition task	Decreased activity in SMA and M1 in the OFF state. L-Dopa increases activity in SMA and M1
Cerasa et al.	2012	10 LID (UPDRS total 18), 10 non-LID (UPDRS total 15)	OFF	Simple internally and externally paced finger tapping	LID patients with higher activity in preSMA and rIFG compared to non-LID patients. preSMA activity correlated positively, rIFG negatively with LID severity.
Cerasa, Donzuso et al.	2015	12 LID (29.8), 12 non-LID (25.7)	OFF/OFF to ON	Stop-signal task	Levodopa-induced increase in SMA activity during errors of commission and decreased rIFG activity during successful inhibition compared to non-LID patients.
Herz et al.	2014	13 LID (32.5), 13 non-LID (32.9)	OFF/OFF to ON	GoNogo task	During NoGo trials, levodopa led to stronger activity increase in preSMA and putamen in LID patients, preSMA increase correlated with LID severity.
Herz et al.	2015	13 LID (32.5), 13 non-LID (32.9)	OFF/OFF to ON	GoNogo task	Levodopa-induced change in putamen to M1 connectivity in LID patients only. Levodopa-induced putamen to M1 and to preSMA connectivity change correlated with LID severity.
Kraft et al.	2009	12 (21.0)	OFF/ON	Simple uni- and bimanual power grip	Decreased activity in putamen in OFF state compared to healthy controls, no difference in ON state.
Spraker et al.	2010	14 (drug-naïve, UPDRS total 17.93)	OFF	Two simple grip-slip force tasks	Slow-paced task: decreased activity in putamen, GPe and thalamus. High-paced task: decreased activity in all BG nuclei, thalamus, M1 and SMA.
Turner et al.	2003	12 (41.4)	OFF	PET study Simple visuomanual joystick tracking task	Increase in velocity leads to increased putaminal activity only in patients.
Activation studies of cognitive and behavioural control					
Aarts et al.	2014	15 (ON 20.5, OFF 29.3)	OFF/ON	Task-switching with different reward levels	ON state reduced VS response to reward anticipation, stronger attenuation improved task performance more. Stronger DS increase ON improved task-switching.
Cools et al.	2007	14 (15.9)	OFF/ON	Probabilistic reversal learning task	VS response to errors preceding behavioural switch was reduced ON compared to OFF
Hughes et al.	2010	16 (18.9 ON, 31.3 OFF), 43 healthy controls	OFF/ON	Free choice vs. specified button presses	Patients showed more perseveration than controls, this was exacerbated ON, suggesting overdosing. Higher disease severity associated with decreased vlPFC and PM activity.
Hughes et al.	2013	17 (10.5 ON, 22.2 OFF), 18 healthy controls	OFF/ON	Free choice vs. specified button presses	Higher disease severity led to less perseveration ON compared to OFF and to higher caudate activity when repeating an action.
MacDonald et al.	2011	22 (ON 17.22, OFF 22.36), 22 healthy controls	OFF/ON	Simple selection task with congruent and incongruent stimuli	Patients OFF show less interference by incongruent cues, ON brings interference to level seen in controls. In controls, congruent stimuli elicit VS activity, incongruent DS.
Rae et al.	2016	19 (ON 25.87), 20 controls	ON DRT, OFF/ON atom.	GoNogo/stop-signal	OFF atom. longer SSRT, reduced stopping activity in rIFG, preSMA, putamen and STN. ON atom. restored rIFG-preSMA connectivity.
Rowe et al.	2008	19 (19.2 ON, 31.9 OFF), 19 controls	OFF/ON	Bimodality continuous performance task	Left vlPFC and mid-caudate activation with nonlinear U-shaped relationship to motor disease severity. L-Dopa shifted this U-shaped function, indicating differential neurodegeneration in distinct connections between cortex and BG.
Ye et al.	2015	21 (20.6 ON), 20 controls	ON DRT, OFF/ON atom.	GoNogo/stop-signal	OFF atom. longer SSRT, reduced stopping activity in rIFG and rIFG-striatum connectivity compared to controls.
Activation studies of reward, punishment and learning					
O'Sullivan et al.	2011	11 ICD (24.1 ON, 43.3 OFF) 7 non-ICD (22.0 ON, 37.4 OFF)	OFF/ON	PET study Passive viewing of reward-cues	Decreased D2/D3 binding (increased dopamine release) in VS to reward-related cues compared to neutral cues in ICD compared to non-ICD ON medication.
Politis et al.	2013	12 hypersexuality-ICD (23.1 ON, 40.2 OFF), 12 non-ICD (20.0 ON, 34.9 OFF)	OFF/ON	Passive viewing of reward-cues (including sexually themed) and neutral cues	No interaction between medication and ICD status, but increased activity in several brain regions, including VS, to sexual cues independent of medication.
Ray et al.	2012	7 ICD (21.00), 7 non-ICD (17.14)	ON	PET study Gambling task and control task	Decreased D2/D3 binding (increased dopamine release) in midbrain (approx. SN and VTA) in non-ICD patients in gambling task compared to control task. No such reduction in ICD patients.
Schmidt et al.	2014	21 (12.7 ON, 17.3 OFF, 17.3 OFF + placebo)	OFF/ON/ OFF + placebo	Reinforcement learning task	ON and placebo reduced reward prediction error signal in VS and increased vmPFC activity for value of rewarding options.
Shiner et al.	2012	13 (H&Y 1.69)	OFF/ON/ OFF + ON	Reinforcement learning task	In a 2-stage learning task, medication did not affect learning stage, but ON improved performance phase. In performance phase, vmPFC and VS increased activity with option value ON only.
Steeves et al.	2009	7 ICD (25.2), 7 non-ICD(20.2)	OFF	PET study Gambling task	Reduced D2/D3 binding (increased dopamine release) in VS in ICD patients during gambling compared to non-ICD.
van der Vegt et al.	2013	13 (drug-naïve, 25.6), 12 controls	OFF	Simple reward paradigm	Reduced increase in activity in striatum and VTA for increasing gamble-outcome value. Response to punishment reduced in ventral putamen and PFC.
van Eimeren et al.	2009	8 (L-Dopa 19.6, dopamine agonists 21.5, OFF 27.5)	OFF/ON/ON	Gambling task	ON L-Dopa and ON dopamine agonists both reduce VS response to reward compared to OFF. Only ON dopamine

(*continued on next page*)

Table 1 (*continued*)

Authors	Year	Participants (disease severity)	Medication state	Paradigm	Main findings in patients with Parkinson's disease
					agonists impaired OFC increase with reward prediction errors.
Voon et al.	2010	14 ICD (H&Y 1.99), 14 non-ICD (H&Y 2.35), 16 controls	OFF/ON	Probabilistic learning task	Dopamine agonists increase the rate of learning from gain outcomes in ICD and led to an increased prediction error in the VS. Additional differences between ICD and non-ICD for gains and losses in striatum.
Voon et al.	2011	14 ICD (H&Y 1.91), 14 non-ICD (H&Y 2.35)	OFF/ON	Risk-taking task	ICD patients with more risky choices and decreased activation in OFC and ACC. Enhanced sensitivity to risk along with decreased activation in the VS ON medication in ICD patients but not non-ICD.
Resting state					
Borchert	2016	33(ON 22.6), 76 controls	ON DRT, OFF/ ON atom.	Resting state	OFF atom. reduced rIFG connectivity with dorsal ACC, dlPFC and left IFG. ON atom. increased rIFG-dorsal ACC connectivity.
Cerasa, Koch et al.	2015	12 LID (29.4), 12 non-LID (26.4)	OFF/OFF to ON	Resting state	Levodopa-induced decreased IFG to M1 connectivity and increased IFG to putamen connectivity in LID compared to non-LID patients.
Esposito et al.	2013	20 drug-naïve (OFF 18.4, ON 10.7, placebo 19.8), 18 controls	OFF/ON/ placebo	Resting state	Levodopa-induced enhanced connectivity in SMA compared to placebo. Regional changes in SMA correlate with motor improvement.
Herz et al.	2016	12 LID (32.2), 12 non-LID (33.2)	OFF/OFF to ON	Resting state	Levodopa-induced change in preSMA/SMA to putamen connectivity correlated with LID severity. Levodopa-induced change in putamen-M1 connectivity classified LID and non-LID patients with high accuracy.
Structural imaging studies					
Aarts et al.	2012	23 (OFF 26.3), 15 healthy controls	OFF	DAT SPECT Task-switching with different reward levels	Patients with stronger neurodegeneration in DS impaired in task-switching and task-set maintenance.
Cerasa et al.	2011	36 LID (UPDRS total 20.0), 36 non-LID (UPDRS total 23.5)	OFF	–	LID patients showed higher bilateral IFG volume compared to non-LID patients.
Claassen et al.	2017	17 ICD (ON 15.5, OFF 25.8), 17 non-ICD (ON 23.7, OFF 32.9)	OFF/ON	Arterial spin labeling	Compared to non-ICD, dopamine agonists increased regional blood flow in VS in ICD patients, scaling with ICD severity.
Cilia et al.	2010	8 ICD (18.3), 21 non-ICD (20.2), 14 controls	ON	DAT SPECT	Reduced DAT in right VS in ICD compared to non-ICD patients.
Payer et al.	2015	11 ICD (33.1), 21 non-ICD (28.1)	ON	PET	Lower D2/D3 receptor density in VS in ICD patients, correlating with ICD severity.
Smith et al.	2016	320 non-ICD at baseline (21.2), 54 developed ICD	ON	DAT SPECT	Greater decrease in DAT availability in right caudate and mean striatum as risk-factors for ICD.
Voon et al.	2014	15 ICD (H&Y 3.0), 15 non-ICD (H&Y 3.0)	ON	DAT SPECT	Reduced DAT in right striatum in ICD compared to non-ICD patients.
Vriend et al.	2014	31 non-ICD at baseline (baseline: later developing ICD (n = 11) 26.3, non-ICD (n = 20) 19.2)	OFF	DAT SPECT	Reduced DAT availability in right VS, anterior DS and posterior putamen in ICD compared to non-ICD. DAT availability in right VS and anterior DS correlated negatively with ICD severity.

Studies are listed in alphabetical order in each section. Studies are fMRI studies if not otherwise mentioned. Disease severity in parentheses in third column is Unified Parkinson's Disease Rating Scale motor subscale score if not otherwise mentioned.

Abbreviations: *ACC* anterior cingulate cortex, *atom.* atomoxetine, *BG* basal ganglia, *CMA* cingulate motor area, *dlPFC* dorsolateral PFC, *DRT* dopamine replacement therapy, *DS* dorsal striatum, *GPe* globus pallidus external, *H&Y* Hoehn & Yahr stage, *ICD* impulse control disorder, *IFG* inferior frontal gyrus, *IPC* inferior parietal cortex, *LID* levodopa-induced dyskinesia, *M1* primary motor cortex, *MFC* middle frontal cortex, *MFG* middle frontal gyrus, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *PM* premotor cortex, *Pre-SMA* pre-supplementary motor area, *SMA* supplementary motor area, *SN* substantia nigra, *SPC* superior parietal cortex, *STN* subthalamic nucleus, *UPDRS* Unified Parkinson's Disease Rating Scale, *vlPFC* ventrolateral PFC, *VS* ventral striatum, *VTA* ventral tegmental area.

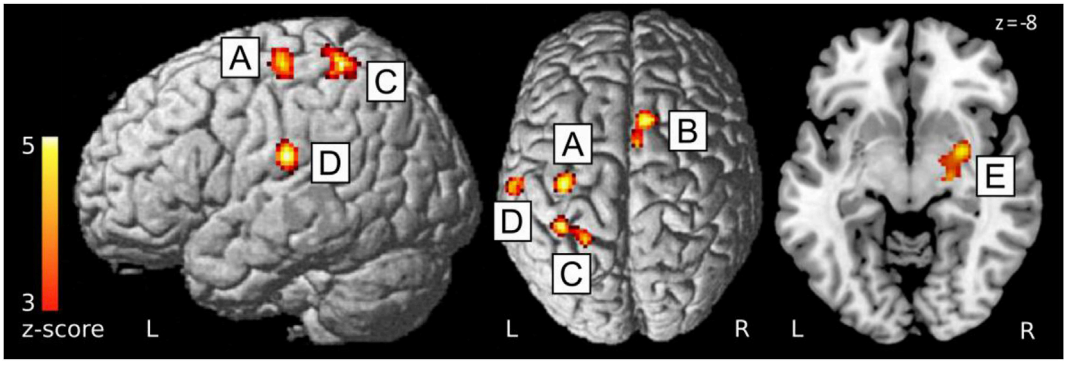

Fig. 1. Convergence of activation maxima for the comparison between PD patients off medication and healthy controls reported in previous functional neuroimaging studies during motor tasks. Activation differences were consistently observed in M1 (A), a cluster spanning preSMA and SMA (B), superior parietal lobule (C), inferior parietal cortex (D) and posterior putamen (E). Activation of posterior putamen was also consistently increased by dopaminergic medication and correlated with differences in PD severity across studies (not shown, see Herz et al., 2014b for more details).

pre-supplementary motor area (preSMA[1]) was different between PD patients and controls but did not significantly differ in PD patients on and off medication.

While activation differed from healthy controls, the direction of task-related activity changes varied across studies. Some studies showed increases in task-related motor activation, whereas other studies showed decreases relative to healthy controls. Why do changes in task-related cortical activation differ so strongly across studies? One reason could be that task performance varied between studies, influencing the observed activity patterns. Most studies tried to match performance in both groups by using relatively simple motor tasks (e.g. cued button presses or finger tapping). However, more subtle measures such as peak force, peak movement acceleration, smoothness or stability of movement trajectories might reveal differences. While such detailed neuroimaging studies of subtle behavioural differences in bradykinesia are still amiss, Buhmann et al. (2003) shed some light onto the neural mechanisms underlying bradykinesia by relating changes in neural activity to changes in clinically relevant behaviour. During fMRI acquisition patients and healthy controls performed a finger tapping task once off medication and then after intake of the dopamine precursor levodopa, while dopamine levels gradually increased. In the OFF-medication state, task-related activation of the hand area of M1 in the more affected hemisphere was decreased compared to the less affected hemisphere. In addition, motor activation of M1 and SMA was reduced relative to healthy controls. Levodopa intake increased motor activation of M1 and SMA in the most affected hemisphere compared to the OFF-medication state. The levodopa-induced activation of M1 correlated strongly with the individual improvement in movement performance. In a subgroup of patients this correlation was also found in caudal SMA. These results suggest that the dopamine-induced activation increase in M1 and SMA is directly related to improvement in bradykinesia. In that study, the field-of-view did not cover the basal ganglia, therefore levodopa-related changes in putaminal activity and its correlation with bradykinesia could not be evaluated. However, several neuroimaging studies have provided evidence that the putamen is related to movement vigour in PD. Spraker et al. (2010) demonstrated that putaminal activity is decreased in drug-naïve PD patients compared to healthy controls during a precision grip-force task. In line with this, Kraft et al. (2009) showed decreased putaminal activity during grip force production in PD patients off medication compared to healthy controls, which significantly increased after dopamine intake. Finally, a H_2O-PET study revealed a close relationship between increases in movement velocity and putaminal activity in PD patients during a visuo-manual tracking task (Turner et al., 2003). A resting-state fMRI study also suggested the SMA as a core target of dopaminergic medication in PD (Esposito et al., 2013).

Together, these results suggest that a cortico-subcortical network including SMA, M1 and putamen is closely related to modulations of movement vigour and that physiological function of this network seems to critically depend on dopamine.

2.2. Involuntary movements: dyskinesia

Even though bradykinesia is a core feature of PD, many patients come to exhibit a seemingly opposite behaviour with constant, purposeless movements making patients appear restless or fidgety (Edwards et al., 2008). This phenomenon is termed dyskinesia or levodopa-induced dyskinesia, since it is typically observed after levodopa intake (Nutt, 2008). Dyskinesia is one of the most frequently observed side effects of dopamine replacement occurring in ~40% of patients after 4–6 years of PD (Ahlskog and Muenter, 2001; Cilia et al., 2014). Most commonly, patients are dyskinetic when levodopa levels reach their peak ('peak-dose dyskinesia') and their dyskinesia gradually disappears when levodopa levels decrease. Affected patients may fluctuate between hypokinetic (bradykinesia) and hyperkinetic (dyskinesia) states. In terms of pathophysiology, the aberrant dyskinetic response to levodopa therapy is driven by the progressive failure of cellular re-uptake and recycling of striatal dopamine, leading to fluctuating dopamine levels (Cenci and Lundblad, 2006; Troiano et al., 2009). While bradykinesia indicates deficient vigour to move in a dopamine depleted state, dyskinesia might be related to an excessive enforcement of movement vigour in the dopamine repleted state (Hallett and Khoshbin, 1980; Ingvarsson et al., 1997; Wenzelburger et al., 2002).

Until recently there was a paucity of imaging studies in PD patients with dyskinesia, in part because patients' involuntary movements cause severe fMRI artefacts, affecting data quality. Another methodological problem is that the comparison of dyskinetic patients with non-dyskinetic patients may result in a stronger activation of motor areas due to the vigorous (but involuntary) movements of the dyskinetic patients in the scanner (Rascol, 1998; Brooks, 2000).

To circumvent these problems, new neuroimaging paradigms have compared patients who are prone to dyskinesia with patients unaffected by dyskinesia, in an off-medication state where neither is currently dyskinetic. The underlying assumption that PD patients affected by dyskinesia display abnormal functional brain patterns even in a non-dyskinesia state is supported by behavioural studies (e.g. Stevenson et al., 2014, 2011). Cerasa et al. (2012) found that patients with dyskinesia showed stronger activation in preSMA and decreased activation in the right inferior frontal gyrus (IFG) during self-initiated and externally triggered movements. Task-related activity in preSMA during both tasks correlated positively with dyskinesia severity. In contrast, IFG activity correlated negatively with dyskinesia severity. In a morphometric study, they found that IFG grey matter volume was significantly larger in dyskinetic versus non-dyskinetic patients (Cerasa et al., 2011).

These studies revealed abnormalities in dyskinetic patients, but not the role of dopamine. To address this question, Herz et al. (2014c) studied patients with and without dyskinesia after prolonged withdrawal of dopaminergic medication and immediately after levodopa intake. Patients performed a Go-NoGo task, until dyskinesia emerged. This pharmacodynamics fMRI approach traced the gradual change in neural activity, while dopamine levels increased but before the onset of dyskinesia. The change in neural activity immediately (<25 min) after levodopa intake was significantly stronger in the preSMA and the bilateral putamen in patients who *later* developed dyskinesia compared to patients who did not. This difference was specific to NoGo response inhibition trials. Furthermore, the activity change in preSMA was strongly correlated with the severity of dyskinesia that later emerged. The analysis of dopamine-induced changes in effective connectivity in the motor network (Herz et al., 2015) showed that an early change in connectivity from putamen to M1 was only observed in patients with dyskinesia. This change in connectivity from putamen to cortical areas was correlated with out-of-scanner dyskinesia severity.

Even in the resting state, the change in connectivity between pre-SMA/SMA and putamen after levodopa in dyskinetic patients correlated with the severity of emerging dyskinesia. The change in connectivity accurately predicted whether a patient would develop dyskinesia or not (Herz et al., 2016). Importantly, the link between resting-state connectivity and the manifestation of dyskinesia only emerged when considering the dopamine-induced change in connectivity. Neither connectivity estimates derived from the off-medication state alone nor from the on-medication state alone could distinguish between dyskinetic and non-dyskinetic patients. Cerasa et al. (2015b) found that resting-state connectivity decreased between IFG and M1 and increased between

[1] SMA and preSMA lie directly adjacent in the superior frontal gyrus in Brodman area (BA) 6 (Picard and Strick, 2001). SMA is mainly interconnected with other premotor and motor areas as well as the spinal cord (Muakkassa and Strick, 1979; Picard and Strick, 2001). Conversely, preSMA is interconnected with prefrontal areas (Nachev et al., 2008; Picard and Strick, 2001). Following Johansen-Berg et al. (2004) and Picard and Strick (2001), we assign activations located anterior to the vertical commissure anterior (VCA) line, i.e. anterior to y = 0, to the preSMA and activation posterior to VCA to the caudal SMA proper.

IFG and putamen in patients with dyskinesia, compared to patients without (Cerasa et al., 2015b). Dyskinesia severity correlated negatively with connectivity changes between IFG and M1, and positively with connectivity changes between IFG, the putamen and STN.

These studies link two cortico-subcortical networks to dopamine-induced involuntary dyskinesia movements: a prefrontal network comprising IFG and preSMA and a caudal motor network comprising M1 and SMA along with their striatal connections. The preSMA and IFG may be recruited in order to suppress emerging dyskinesia (Aron and Obeso, 2012; Cerasa et al., 2015c; Rothwell and Obeso, 2015), since they are critically involved in other aspects of motor inhibition (Aron et al., 2016; Rae et al., 2014; Ridderinkhof et al., 2011). The ability of the prefrontal network to suppress dyskinetic movements might explain some of the differences in dyskinesia severity. However, this interpretation remains speculative. Given the correlative nature of previous studies, it remains to be elucidated whether activation of prefrontal networks during dyskinesia constitutes a compensatory mechanism or might, in contrast, be involved in the generation of involuntary movements. These hypotheses could be tested by combining transcranial magnetic stimulation (TMS) to perturb cortical areas and mapping its effect on neural activity using fMRI. For example, TMS over SMA has beneficial - albeit moderate and short lasting - effects on dyskinesia (Brusa et al., 2006; Koch et al., 2005), but it remains unclear whether this is due to local suppression of SMA activity or modulation of interconnected neural areas (see e.g. Herz et al., 2014a; Obeso and Strafella, 2014).

A general shortcoming of many neuroimaging studies in dyskinesia is the prevalence of simple movement tasks and gross measures of behaviour. A notable exception is the assessment of behavioural inhibition using the stop-signal reaction time (SSRT) by Cerasa et al. (2015a). Patients with dyskinesia had higher activity in the SMA during commission errors and lower activity in right IFG during successful inhibition after dopamine intake, compared to patients without dyskinesia. Such 'behaviourally-driven' neuroimaging studies are particularly useful (Krakauer et al., 2017).

In summary, neuroimaging studies in PD assessing motor execution indicate that dopamine modulates pathways connecting M1 and SMA with the basal ganglia for the enforcement of motor vigour. It remains to be shown whether the activation of prefrontal networks is related to compensatory inhibitory mechanisms contributes to the generation of involuntary movements.

3. Non-motor symptoms in PD

Dopaminergic neurons in the VTA project mainly to ventral ('limbic') striatum. The antero-dorsal 'associative/cognitive' striatum receives input from both SN and VTA (Haber, 2003). Although VTA neurons are less affected by neurodegeneration (Kish et al., 1988), cognitive functions associated with the mesolimbic (VTA-striatum) and mesocortical (VTA-cortex) pathways are also impaired in PD (Robbins and Cools, 2014). This may reflect phasic dopamine release in ventral striatum that codes prediction error during learning (Schultz, 2017), and dopamine's contribution to risk assessment, effort evaluation and motivational drive (e.g. Christopoulos et al., 2009; Niv et al., 2007; Schultz, 2015). Therefore, PD and the impact of dopaminergic treatment have been used to investigate the effects of changing dopamine levels on this area of cognition. In this section, we discuss what has been learned from fMRI about the involvement of dopamine in cognitive flexibility, reward processing and learning mechanisms, both in PD as well as in the healthy brain. We also consider how other neurotransmitter systems e.g. alterations in noradrenergic neurotransmission contribute to cognitive deficits in PD and interact with dopamine.

3.1. Cognitive and behavioural flexibility

3.1.1. Switching between tasks and actions

Cognitive flexibility enables one to balance between maintaining behaviour that is overall advantageous in spite of occasional negative outcomes and switching behaviour when the rules of the environment have changed. Task performance can require shifts between cognitive strategies or the use of different response rules. A seminal study on cognitive flexibility in PD was conducted by Cools et al. (2007). The study was important because it tested an influential idea: that the relationship between the level of striatal dopaminergic innervation and optimal neural processing in the striatum is characterized by an inverted U-shaped Yerkes-Dodson function (Arnsten et al., 1994; Cools, 2006; Cools et al., 2001; Robbins, 2000). Assuming an inverted U-shaped relationship between dopamine levels and cognitive function, the prominent nigrostriatal neurodegeneration causes a leftwards shift on the inverse U-shaped curve away from the optimum for those cognitive or motor functions that are mediated by the SN-dorsal striatum pathway (Fig. 2). This leftward shift can be reversed by dopamine replacement therapy. At the same time, dopamine "replacement" leads to relative "dopamine overdosing" in the less-affected ventral VTA-striatal ('limbic') circuitry and anterior dorsal nigro-striatal ('associative/cognitive') circuitry. This relative excess in dopamine in the ON medication state would result in a rightward shift towards the descending part of the U-shaped curve, causing suboptimal circuit function with adverse effects on cognition (Cools, 2006; Cools et al., 2001, Fig. 2).

Cools et al. (2007) used a probabilistic reversal learning task which required patients on two days (ON and OFF medication) to choose between two abstract visual stimuli, receiving subsequent feedback about the correctness of their choice. One of the stimuli was the correct choice in most trials, while the other one most often was the incorrect choice. At several points throughout the experiment, this association was reversed without informing the participants about the reversal of outcome probabilities. There were no consistent dopaminergic effects on behaviour or regional activity in dorsal striatum. Yet dopamine replacement reduced the BOLD response in the ventral striatum to "final" reversal errors, i.e. errors which were followed by a switch in choice behaviour in the next trial. Neural activity evoked during these events reflects a multitude of processes, including neural processing of negative feedback, the decision to switch behaviour and the expectation of reward in the subsequent trial. While it is not clear which of these cognitive processes are mediated by the ventral striatum and modulated by medication, the results do suggest dopaminergic involvement of ventral (but here not dorsal) striatal areas in reversal-related behaviour (Cools et al., 2007).

Rowe et al. (2008) also examined different aspects of cognitive flexibility in a task where participants had to detect targets comprising combinations of spatial or verbal cues, with three consecutive correct detections leading to a reward. In short, the task involved set-shifting, between spatial and verbal domains to detect targets, and reward expectation. There was no direct effect of medication on task performance, but task-related activation of the right mid-caudate and left ventrolateral PFC (vlPFC) activity increased in proportion with task performance in a non-linear U-shaped manner depending on disease severity. The peak of this U-curve shifted dependent on the state of medication (OFF or ON). Similar shifts in the U-shaped relationship between disease severity and neural activity changes were found in the anterior cingulate cortex (ACC) for anticipating and receiving a reward. The results support the hypothesis that differences in the amount of dopaminergic neurodegeneration among dorsal and ventral basal ganglia circuits cause differential responses in these circuits to dopamine replacement. A medication-induced increase in dopamine levels shifts performance towards optimum in one of the circuits, but away from optimum in another circuit (Rowe et al., 2008). Interestingly, medial frontal responses to reward expectation were diminished in patients, but their response to actual (unexpected) reward was enhanced.

Aarts et al. (2014) investigated the involvement of the ventral and dorsal striatum pathways on reward expectation and task-switching. Patients were studied with fMRI in the ON and OFF medication state, while they had to respond to an arrow pointing left or right and the words "left" or "right" shown inside the arrow. The symbol and word stimulus

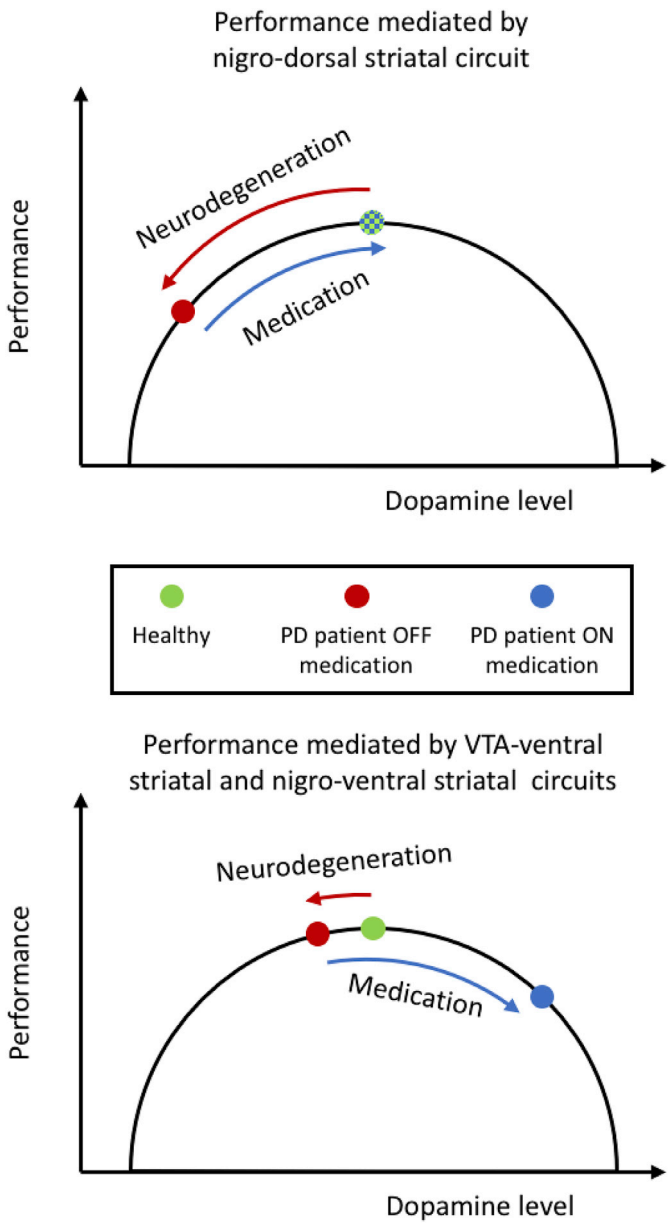

Fig. 2. "Overdosing theory" describing the restoration of optimal dopamine levels for performance of some tasks and overdosing for others. Depending on the degree of neurodegeneration, performance in different tasks is impaired to different degrees by the disease. Dopaminergic treatment can then restore dopamine levels to an optimum in the SN-posterior dorsal striatum pathway responsible for the motor symptoms, but leads to relative "overdosing" of the VTA-ventral striatum pathway showing less neurodegeneration, impairing performance. For simplicity, only two hypothetical midbrain-striatal pathways are depicted, but it should be noted that other networks (including cortical-subcortical networks) might be affected to different degrees and show different shapes of the inverse U-shaped curves (e.g. more flat, more peaked, or skewed). In some tightly controlled laboratory situations, the "normal" dopaminergic tone in the healthy brain might even result in performance positioned away from the curve's optimum, such that neurodegeneration or dopamine administration unexpectedly might improve performance (e.g. MacDonald et al., 2011).

could either be congruent or incongruent in terms of the indicated direction. Participants were cued in each trial to either indicate the arrow direction or the direction described by the word, requiring task-switching in 50% of trials. The study revealed a differential effect of dopaminergic medication on ventral and dorsal activity in the striatum depending on the cognitive process involved. Dopaminergic medication attenuated the response of ventral striatum to reward anticipation where stronger attenuation was associated with a higher benefit of reward anticipation on task performance in the ON compared to the OFF medication state. In the dorsal striatum, the more dopamine increased regional activity during task-switching, the more patients showed an improvement in task-switching performance in the ON medication state (location of peak activity changes was not reported). The effect of dopamine medication on task-related activity and its effects on task-switching behaviour fit well to the idea that dopamine medication can not only restore the motor symptoms of PD but also cognitive functions that are subserved by the anterior-dorsal striatum.

The same task was used in a separate group of PD patients in which the extent of striatal dopaminergic neurodegeneration was assessed with dopamine transporter (DAT) Single Photon Emission Computed Tomography (SPECT) (Aarts et al., 2012). Patients with stronger neurodegeneration in the posterior dorsal "motor" striatum performed worse in balancing between switching tasks and repeating the same task instructions (continuous behaviour in spite of distracting information), again highlighting the importance of the dorsal striatum for flexible action selection (Aarts et al., 2012).

While both studies by Cools et al. (2007) and Aarts et al. (2014) investigated task-switching, the former study found an effect in the ventral striatum, but the latter study in the dorsal striatum. In the study by Cools et al. (2007), the main analyses were based on the event-related responses to the final reversal error, reflecting a mixture of cognitive processes. In contrast, the experimental paradigm employed by Aarts et al. (2014) dissociated more rigorously reward anticipation from task-switching and thus may reflect more specifically activity related to switching.

Two additional studies investigated action selection, contrasting externally cued and freely chosen actions (Hughes et al., 2013, 2010). Depending on the specific experimental design, dopaminergic medication led to an increase or a decrease in perseveration (choosing to move the same finger as in the previous trial). The pattern of results suggested "overdosing" in less severely affected patients with less dopamine depletion, but a recovery of function in more severely affected patients. These behavioural patterns were associated with corresponding activity changes in bilateral body and tail of the caudate nucleus as well as right vlPFC (Hughes et al., 2013, 2010).

The role of dopamine in action selection may also be revealed by examination of the effects of COMT polymorphisms, which lead to chronic variations in frontal cortical dopamine and correspondingly to changes in activity in response planning (Fallon et al., 2013; Nombela et al., 2014b) and response selection (unpublished). But, these polymorphisms also influence brain structure in development and adulthood, including the same prefrontal cortical regions (Rowe et al., 2010), suggesting possible effects of dopamine on long-term cortical plasticity as well as acute neurotransmission.

In summary, these studies showed that delicate optima of dopamine levels are required for optimal cognitive and behavioural flexibility. They also suggest that dopamine exerts its effect on cognitive flexibility in the human brain through non-linear modulation of task-related neural activity in striatal (especially the anterior-dorsal striatum) as well as prefrontal cortical regions. The relationships between dopamine levels, regional task-related brain activity, and optimal cognitive function can be described by as inverse U-shaped curve. The optimal dopamine level (i.e. the peak of the inverse U-shape curve) depends on how much the various striato-thalamo-cortical circuits are affected by dopaminergic denervation and thus reflects the dorsoventral gradient of striatal neurodegeneration.

3.1.2. *Impulsivity and inhibitory control*

A critical aspect of cognitive and behavioural control is the ability to inhibit actions. While inhibition may facilitate task-switching (above), recent studies have indicated catecholaminergic moderation of different

aspects of inhibitory action control. This is typically achieved by using tasks with competing response options, either by simultaneously presenting cues that can be congruent or incongruent with regard to the associated action (e.g. Stroop task), by having some repeatedly cued prepotent response that has to be restrained on the occasion of another rarely cued response (e.g. GoNogo task) or by cancelling an action after it has been initiated (e.g. stop-signal task).

When patients with PD performed a complex task with congruent and incongruent target stimuli, response facilitation by congruent cues (i.e., a shortening of reaction times) was reduced in the ON compared to the OFF medication state (MacDonald et al., 2011). Yet the interference effect of incongruent cues (i.e. prolongation of reaction times) was enhanced by medication, revealing that dopamine replacement impaired performance in both trial types. Interestingly, the increase in interference by incongruent cues induced by dopamine medication brought patients' performance to a similar level of interference as seen in healthy controls, whereas patients off medication were performing better than healthy controls. The authors suggested that patients off medication were impaired in integrating the conflicting information in the incongruent task condition which in this specific task actually gives them an advantage in terms of reaction times. In a separate experiment, healthy controls performed the task inside the MRI-scanner, revealing ventral striatal activity associated with congruent trials and anterior dorsal striatal activity associated with incongruent trials. This is compatible with the hypothesis that the behavioural effects seen in the patient group are due to an overdosing of the ventral striatum (impaired facilitation) but the recovery of dorsal striatum function (MacDonald et al., 2011).

The type of inhibition required for cancellation of a task is distinct from inhibition of inappropriate response tendencies during action selection and commonly studied with a stop-signal task, in which a prepotent Go action has to be cancelled. Critically, the cancellation cue is given after the Go cue, and by varying the delay, one can chart the inhibitory response function or standardise performance in every participant (at say 50% successful stopping). Performance on such stop-signal tasks is not affected by dopamine treatment in drug naïve patients, or dopamine withdrawal (Nombela et al., 2014a; Obeso et al., 2011). However, the task and its associated neural systems, are affected by drugs with joint dopaminergic and noradrenergic effects such as methylphenidate. Moreover, the neurodegeneration of noradrenergic neurons in the locus coeruleus precedes dopaminergic neurodegeneration in the SN in PD (Braak et al., 2003; Hawkes et al., 2010). This has led to a recent focus on the noradrenergic role in inhibitory control (Borchert et al., 2016; Rae et al., 2016; Ye et al., 2015). Even though the focus of this article is on the dopaminergic system, these studies are relevant because they use PD as a model disease to provide insights into the importance of the noradrenaline system in inhibitory control in the healthy brain, and the interactions between noradrenergic and dopaminergic signalling.

In an fMRI study, PD patients performed a combined GoNogo/stop-signal task on the noradrenaline reuptake inhibitor atomoxetine (or placebo) while on their usual dopamine medication (Ye et al., 2015). On Placebo, patients had longer SSRT (poorer inhibitory control), lower activity related to successful stopping in the right IFG and weaker functional connectivity between the right IFG and striatum compared to healthy controls (Fig. 3a). Individual improvements in SSRT on atomoxetine were correlated with a stronger increases in right IFG activity, right IFG-striatum functional connectivity and greater structural frontostriatal connectivity (Fig. 3b and c; Ye et al., 2015). A second study used a similar experimental design in a separate group of participants (Rae et al., 2016). On placebo, patients again had longer SSRT and showed less activity for successful stopping in right IFG, but also preSMA, putamen and STN. Atomoxetine significantly increased striatal activity during successful stop trials. Furthermore, patients on placebo lacked connectivity between preSMA and IFG: this connection was restored by noradrenergic reuptake inhibition. The pre-SMA and IFG interacted synergistically in their influence on the STN, and the higher the atomoxetine blood-plasma levels the stronger this interaction (Fig. 3d and e; Rae et al., 2016). The medication-induced improvement in performance correlated with structural connectivity of the IFG. Despite the emphasis

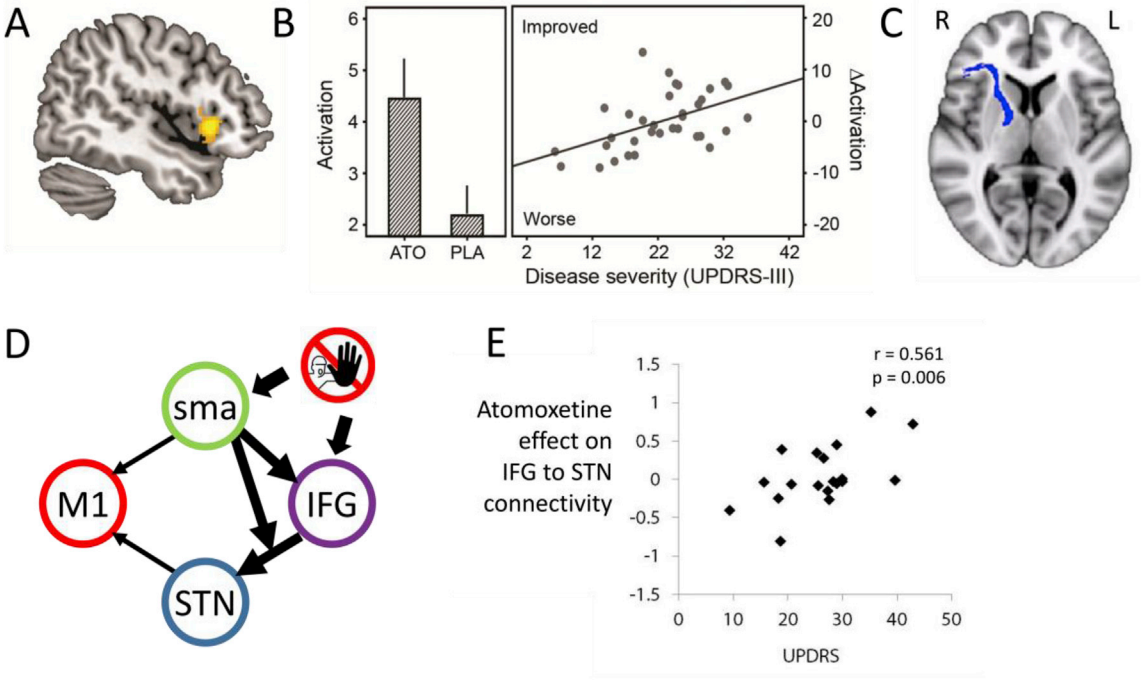

Fig. 3. Noradrenaline and inhibition. A. The inferior frontal gyrus (IFG) activation on successful stop-trials is reduced in PD, versus controls. B. Atomoxetine increases activation of IFG, versus placebo, but variability about the main effect of drug is driven by disease severity as measured by the UPDRS. C. The mean diffusivity of frontostriatal pathways (blue) correlates with the impulsivity (SSRT). D. Dynamic causal modelling of the interactions among IFG, SMA, motor cortex (M1) and subthalamic nucleus (STN) indicates synergistic interactions between the projections from SMA and IFG to the STN. E. Atomoxetine modulates the IFG to STN connectivity, in proportion to disease severity. Patients were on their usual dopaminergic medication at all times. From Rae et al. (2016) and Ye et al. (2015) with permission.

on noradrenaline, the behavioural response to atomoxetine could be predicted in part by the patients' levodopa dose equivalent (Ye et al., 2016), in keeping with an interaction between these two neurotransmitter systems. Similar effects of atomoxetine (versus placebo) on right IFG connectivity to medial prefrontal cortex have been observed in resting-state fMRI of patients with PD (Borchert et al., 2016).

Together, these results suggest an impairment in inhibitory control in PD patients even when they are on their dopamine medication: these impairments could be relieved by noradrenergic treatment in a subset of patients. Since the locus coeruleus undergoes marked and early degeneration in PD (Braak et al., 2003; Hawkes et al., 2010), these studies highlight the importance of noradrenergic projections from the locus coeruleus to prefrontal cortex and interactions with dopamine systems for the adequate inhibitory control of actions.

Complementing the work on the noradrenergic system, some neuroimaging studies showed a strong association between neurodegeneration in the cholinergic network and the severity of cognitive symptoms and the development of dementia in PD (Gratwicke et al., 2015; Gratwicke and Foltynie, 2018; Kehagia et al., 2013). Together, these studies reveal the importance of taking into account the degeneration of non-dopaminergic neurotransmitter systems. Future studies should therefore consider combined manipulation of several transmitters to scrutinize their combined effects on cognition.

In summary, the weight of evidence is for dopaminergic modulation of action evaluation (including reward) and selection (including task switching) but primarily non-dopaminergic modulation of response inhibition *per se*. The study by MacDonald et al. (2011) tentatively suggests an overdosing of ventral striatum (impairing facilitation) and a restoration of information integration in anterior dorsal striatum (increasing the incongruency effect) with dopamine medication. Consequently, these results suggest dopaminergic involvement in inhibition and conflict resolution in ventral and dorsal striatum in the healthy brain. However, this is only indirect evidence at best and shows the need for further studies directly investigating dopaminergic modulation of inhibitory control. Together, these studies corroborate the importance of optimal noradrenaline levels (likely mediated by the locus coeruleus) in a circuitry centred on right IFG and additionally pre-SMA, caudate and STN (Borchert et al., 2016; Rae et al., 2016; Ye et al., 2015).

3.2. Reward, punishment and learning

Dopamine neurons in the VTA are relatively spared in PD, but functionally relevant changes occur in this circuit as well, affecting its core functions in reward, prediction error coding and learning. We discuss imaging studies in PD investigating neural changes to reward and punishment and what these types of studies can reveal about the neural correlates of reinforcement learning in the diseased and healthy brain.

Van der Vegt et al. (2013) studied reward and punishment encoding in *de novo* PD patients who had just been diagnosed but not yet begun dopamine treatment. This provided the unique opportunity to investigate the effects of dopamine neuron degeneration before the system had adapted to long-term dopamine treatment. In a simple gambling paradigm, subjects chose one of two cards and received either high or low monetary reward or punishment with a fixed probability of 50%. Rewards and punishments occurred simply by chance, without learning card-reward associations. In healthy participants, there was a linear increase in BOLD activity with outcome value (from high losses, low losses, low wins to high wins) in a large network of brain regions, including ventral and dorsal putamen, caudate and VTA. Brain activity associated with winning was reduced in PD patients in dorsal putamen, caudate and VTA, amongst others. The functional response to punishments was also reduced in PD patients in the ventral putamen and prefrontal cortex (van der Vegt et al., 2013). In line with the neurodegeneration of the dopaminergic projections from VTA to ventral striatum (Alberico et al., 2015), these findings highlight that the encoding of reward and punishment is affected in PD and is already evident at the time of clinical diagnosis.

While much of the BOLD activity in the study by Van der Vegt et al. (2013) was most likely related to the processing of prediction errors, there was no learning involved in task performance. Prediction errors are, however, used in order to update one's estimation of the future likelihood of success and are often investigated in the context of reinforcement learning in tasks that allow learning from the outcome of one's actions in order to maximize reward and minimize punishment. An influential study by Frank et al. (2004) introduced the notion that reinforcement learning from prediction errors elicited by positive and negative outcomes is affected by dopamine depletion and dopamine replacement therapy in a predictable manner. Dopaminergic medication was proposed to increase D2 receptor inhibition in the indirect NoGo pathway and thus to lead to a decrease in learning from punishment. At the same time, medication-induced activation of D1 receptors in the direct pathway should facilitate learning from reward. In accordance with these predictions, in the dopamine depleted OFF state, patients tended to learn relatively more from punishment compared to reward. Dopamine medication then shifted that balance towards the opposite pattern where they learned more from reward compared to punishment. Some studies found results that at least partially supported this finding (Bódi et al., 2009; Maril et al., 2013; Palminteri et al., 2009; Rutledge et al., 2009; Schmidt et al., 2014), but most other studies have actually found dopamine medication to affect choice behaviour after learning, but not the learning itself (Coulthard et al., 2012; Grogan et al., 2017; Shiner et al., 2012; Smittenaar et al., 2012). This post-learning effect might be attributed to repeated dopamine release in VTA-hippocampal and VTA-striatum connections affecting longer-term memory (Bethus et al., 2010; Calabresi et al., 1997). Another study by Timmer et al. (2017) suggested that depression, a frequent non-motor symptom of PD (approximately 35%, Reijnders et al., 2008), may explain differences in reward learning, at least when learning from punishing stimuli. Crucially, one recent study (Grogan et al., 2017) carefully replicated the study by Frank et al. (2004) and failed to find any effects of disease or medication.

Only a few studies on learning from reward and punishment have acquired fMRI data. Shiner et al. (2012) found that dopaminergic medication only affected neural activity for choice during recall after the learning phase, but not for prediction errors during learning. During recall, ventromedial prefrontal cortex (vmPFC) and ventral striatum significantly increased their activity with the value of the chosen option ON, but not OFF dopaminergic medication (but note that the authors did not test those effects directly against each other). Similarly, Rowe et al. (2008) found less ACC activation with increasing disease severity suggestive of a failure of reward prediction (anticipation) rather than insensitivity to reward *per se*. In another study, medication and interestingly also placebo reduced reward prediction error responses in the ventral striatum and increased vmPFC activity for the value of rewarding options (Schmidt et al., 2014). At first sight, the decrease in prediction error activity in the ventral striatum in the ON state might seem surprising. However, given the complex compensatory response of dopamine receptors to changes in dopamine levels (Navntoft and Dreyer, 2016), it is unclear how a putative "overdosing" of ventral striatal dopamine levels affects the prediction error signal. Another study used a gambling task not involving learning (previous outcomes were not useful for predicting future outcomes), but still allowing the calculation of prediction errors (van Eimeren et al., 2009). They found that the response to rewarding outcomes was significantly reduced by levodopa and dopamine agonist treatment in the ventral striatum. Only three studies, including the two imaging studies by Shiner et al. (2012) and Schmidt et al. (2014), used reinforcement learning models to investigate changes in the learning rate. The learning rate is a central parameter assumed to govern adaptive reinforcement learning since it scales the extent to which a reward prediction error for the outcome of a given choice adjusts one's estimate of future success for that choice. Depending on the (in-)stability of the probabilities generating outcomes, one should adapt the learning rate in order to optimally learn from outcomes and

make the best possible predictions (Behrens et al., 2007; Meder et al., 2017; Nassar et al., 2010). Thus, it is an interesting question whether the disease itself or dopamine replacement therapy cause changes in adaptive scaling (i.e. the learning rate), potentially impairing optimal learning. Given that phasic increases in dopamine neuron firing code the magnitude of the prediction error (Schultz, 2017), it might be expected that dopaminergic medication would increase this prediction error magnitude. In the reinforcement learning model, this might be reflected in an increased learning rate parameter which scales the magnitude. While Shiner et al. (2012) did not find effects of medication on the learning rate, Rutledge et al. (2009) found the predicted increase in learning rate in the ON condition compared to OFF. Additionally, when modelling separate learning rates for rewarding and punishing outcomes, only the learning rate for rewarding outcomes was increased by medication. While being in line with the proposed hypotheses, the results do not show that the effect is actually due to an upscaling of prediction error magnitude by dopaminergic medication. Dopamine replacement is thought to increase baseline firing whereas the prediction error is coded by a phasic dopamine signal. An up-scaling of prediction error magnitude also does not conform with the reduced ventral striatum response to prediction errors under medication reported by Schmidt et al. (2014) and van Eimeren et al. (2009).

Interestingly, Schmidt et al. (2014) found that placebo medication significantly increased the learning rate compared to the OFF state. This study reported several behavioural and neural differences in the placebo condition compared to the OFF-medication state. The placebo effects further complicate the interpretation of changes in behaviour and neural activity resulting from manipulations of the dopaminergic state in PD. The expectation of dopaminergic treatment may lead to an endogenously mediated increase in dopamine levels comparable to actual medication.

In summary, despite rather clear theoretical predictions about the effects of dopaminergic neurodegeneration and medication on excitatory and inhibitory basal ganglia pathways for learning and a first study finding according behavioural results (Frank et al., 2004), subsequent behavioural and imaging data did not provide clear support (Coulthard et al., 2012; Grogan et al., 2017; Shiner et al., 2012; Smittenaar et al., 2012). If anything, due to unknown mechanisms, dopaminergic medication seems to lead to a reduction of prediction error coding in ventral striatum (Schmidt et al., 2014; van Eimeren et al., 2009). Tonic dopamine levels, especially in ventral striatum, have also been suggested to modulate the motivation to exert effort in order to obtain rewards (e.g. Collins and Frank, 2014; Niv et al., 2007; Walton et al., 2006). However, while some studies have found effects of PD and dopaminergic medication on effort taking (Chong et al., 2015; Le Heron et al., 2018), another group found tonic dopamine levels to affect reward- but not effort-learning (Skvortsova et al., 2017).

The findings also highlight the complex interplay of tonic dopamine levels changed by disease and medication on the one hand and the phasic signals involved in reinforcement learning on the other hand.

3.2.1. *Reward and punishment in PD patients with ICDs*

In recent years, impulse control disorders (ICD) have come into the focus of Parkinson-related research. There is a wide continuous spectrum of impulsive behaviours in PD (Nombela et al., 2014a), but a sub-group of approximately 15% of patients develop a severe ICD as a result of disease and dopamine replacement therapy (Weintraub et al., 2010). These ICDs include pathological gambling, compulsive shopping, binge eating or compulsive sexual behaviours (Schreiber et al., 2011). It has been suggested that PD patients developing ICDs are especially vulnerable to ventral striatal “overdosing” (Cilia and van Eimeren, 2011). The investigation of this sub-population of PD patients has provided further insights into the difference in optimal dopamine levels in different cortico-basal ganglia circuits.

PET and SPECT studies have generally support the hypothesis that PD-ICD patients show a stronger overdosing in ventral striatum due to medication. There is decreased dopamine transporter (DAT) availability in the ventral striatum of patients with ICDs, suggesting a reduced dopamine clearance from the synaptic cleft, amplifying the overdosing effect of dopaminergic medication (Cilia et al., 2010; Voon et al., 2014). Decreased DAT availability in different striatal regions are a risk factor for developing ICDs (Smith et al., 2016; Vriend et al., 2014). Measuring regional perfusion with arterial spin labelling, Claassen et al. (2017) found additional support for a hypersensitive mesocorticolimbic loop in patients with ICD. Compared to patients without ICD, the administration of dopamine agonists increased regional blood flow in ventral striatum, in proportion to ICD severity.

Lower D2/D3 receptor density in the ventral striatum correlates with ICD severity (Payer et al., 2015), which at first sight contradicts the overdosing hypothesis, but might reflect a compensatory response. Other ligand-based imaging studies have investigated task-related changes in dynamic dopamine receptor binding, showing a relatively increased dopamine release in ICD patients in the ventral striatum during gambling tasks or the presentation of reward-cues (O'Sullivan et al., 2011; Steeves et al., 2009) as well as diminished negative feedback control over dopamine release in the midbrain (Ray et al., 2012).

A few imaging studies studied PD patients with and without ICD, both ON and OFF dopaminergic medication, so as to test the hyper-sensitive ventral striatal dopamine system and its reactivity to dopaminergic medication. Voon and colleagues (Voon et al., 2011, 2010) acquired fMRI data while patients learned stimulus-outcome probabilities in three different conditions (loss *vs*. no loss, win *vs*. no win and neutral) or took low- or high-risk decisions in a loss- or a gain-context. These studies revealed complex effects of ICD pathology and dopaminergic medication state on brain activity related to different aspects of the tasks. For example, in the gain condition, ICD patients showed a stronger medication-induced increase in ventral, but also posterior dorsal striatal activity to positive prediction errors and gain prediction. Another key finding was that ICD patients showed a reduced striatal signal to reward omission, independent of medication (Voon et al., 2010), accompanied by a stronger medication-induced increase in learning rate. Also in the loss context, dopamine medication seemed to increase ventral and anterior striatal responsivity to the omission of loss events while decreasing the activity related to loss itself in ICD patients, again in line with the idea that increased dopaminergic tone in striatal regions impairs D2 mediated encoding of negative prediction errors (dips in DA) and D1 mediated positive prediction error signalling (phasic bursts) (Voon et al., 2010).

ICD patients display reduced ventral striatal response to risk while ON medication (Voon et al., 2011). This finding is at variance with the simple expectation of higher signal with higher DA levels, but it might be related to the problematic behaviour (e.g. gambling). ICD patients with hypersexual disorder displayed stronger activity to sexual cues in the ventral striatum, independently of medication state (Politis et al., 2013).

Together, these results suggest that increased dopaminergic activity in ventral striatal regions, possibly accompanied by decreased dopaminergic activity in the PFC (van Eimeren et al., 2009), may underlie the adverse effects of dopaminergic treatment on cognition and behaviour in ICD. Averbeck et al. (2013) have suggested that this pathology leads to an increased uncertainty about the utility of future actions, which is underlying many aspects of ICD behaviour, such as increased temporal discounting, reduced information sampling or increased novelty seeking.

Most neuroimaging studies accord with the hypothesis of an exaggerated “overdosing” response in ventral striatum in PD-ICD patients. In healthy individuals, there is an optimal balance of ventral striatal and prefrontal tonic and phasic DA release, securing an optimal striatal-prefrontal interplay when encoding the outcomes of actions as well as when planning future actions. PD causes an imbalance in this complex system which is further accentuated in patients with ICD by putative susceptibility traits as well as dopaminergic medication. Neuroimaging of PD patients with ICD provides additional insights into the function of the dopaminergic system in cognition and especially reward related

decisions. Future studies should take into account ICD subtypes, since different forms of ICD are related to distinct behavioural and neurobiological changes (Voon et al., 2017).

4. Discussion

The prominent nigrostriatal dopaminergic degeneration and routine dopaminergic medication make PD a valuable "disease model" to probe the functions of dopaminergic neurotransmission. Comparing the unmedicated state (dopamine depletion) with the medicated state (restored dopamine levels) allows inferences on the dopaminergic system's function in the healthy brain. Yet, there are many complexities of the disease that prevent a simple interpretation of functional changes in brain activity depending on the state of medication.

Nevertheless, key insights about the dopaminergic system in the healthy brain emerge. Firstly, changes in dopamine levels not only affect the striatum as a target area of dopaminergic neurons, but also cortical areas show consistent activation changes. Studies on bradykinetic PD patients suggest a crucial role for dopaminergic transmission in a cortico-subcortical network centred on SMA, M1 and putamen for the enforcement of movement vigour. In this same network, with additional involvement of areas related to inhibitory action control (preSMA and rIFG), dopamine dynamics also seem to be implicated in the development of involuntary, purposeless movements, while the exact contribution of prefrontal-basal ganglia networks to these involuntary movements remains to be elucidated.

Studies on cognitive flexibility indicate that the pattern of brain activity changes due to disease and dopamine medication depend on (i) the specific aspect of cognitive flexibility under investigation and (ii) type of task used in the experiment. Dopamine modulates many cortical and subcortical areas, including the anterior dorsal striatum. The diversity of activity changes, both regarding the anatomical location and the direction of the effects (activation and de-activation) point to the existence of different optima of dopamine levels for different kinds of cognitive tasks in different neural networks. The amount of neurodegeneration differs among ventral and dorsal nigrostriatal pathways, causing different magnitudes of dopamine depletion. This explains why dopamine replacement therapy results in restoration or overdosing of dopamine levels in dorsal and ventral striatal territories, leading to functional improvement or deterioration by moving towards or away from this optimal level along an inverse U-shaped curve. This interaction is additionally modulated by individual COMT variants, affecting prefrontal dopamine levels (Collins and Williams-Gray, 2016; Nombela et al., 2014b). Studies using noradrenergic manipulation in tasks on inhibitory control reveal that other neurotransmitters may be equally affected by neurodegeneration and point to an important role of noradrenalin for the response inhibition network with the right IFG as core node.

In addition, experiments on reward, punishment and learning clearly show a strong influence of dopamine on these aspects of cognition. These results can be difficult to interpret in the absence of sufficiently precise predictions about how changes in tonic dopamine levels due to nigrostriatal neurodegeneration and dopamine replacement therapy affect phasic firing patterns of dopaminergic neurons; and how this in turn affects receptor-specific striatal responses to dopamine release. The relatively spared VTA-ventral striatum pathways are overdosed by dopaminergic treatment, moving subjects away from optimal performance, especially in those with ICDs.

We do not propose a simplistic unified theory of dopamine function in the brain. There is evidence for the role of dopamine for adequate movement generation and reward prediction error processing, and in cognitive flexibility, but via different functional anatomical systems with differences in their optimal dopamine levels. In PD, there is no generalised optimal level of dopaminergic medication to meet all systems. Rather, different dopaminergic states optimise brain networks for motor and cognitive performance.

4.1. Moving forward

What are the lessons to be learned from existing functional neuroimaging studies that can guide the design of future fMRI studies in PD patients? First, a sufficient sample size is of paramount importance despite the practical difficulties of recruitment and study adherence in studies with multiple test days. The low sample sizes in many early studies, including some of those reviewed here, most likely accounts for most of the variability of results across studies, resulting in low power and reproducibility (Button et al., 2013). Second, to enable a better mechanistic interpretation, there is a clear need for well-designed experiments in which patients are tested both OFF and ON medication and preferably also compared against healthy controls to dissect different aspects of cognition, action selection and motor behaviour. Third, the cognitive process under investigation needs to be isolated from confounding variables, either via the experimental design (cognitive subtraction, but see e.g. Friston et al. (1996)) or by applying computational models that allow the investigation of otherwise hidden latent variables. Tracking the change in parameter values by medication or disease state can give deep insights into computational changes underlying a number of disease and medication related symptoms (Huys et al., 2016). Also, multivariate analysis approaches are highly sensitive methods that can provide insights that classical univariate analyses are unable to reveal (Lessov-Schlaggar et al., 2016).

Furthermore, future neuroimaging research should take into account the involvement of other neurotransmitters because neurodegeneration extends beyond the dopaminergic system. These include noradrenalin, serotonin and acetylcholine, and their effects both individually and in conjunction with dopamine.

Fourth, a better understanding of compensatory effects and the dynamics of dopaminergic medication is needed. Some studies find increased activation or connectivity in PD patients OFF medication, which could be interpreted as compensatory mechanisms or a loss of efficiency (e.g. Cerasa et al., 2015b; Mallol et al., 2007; Poston et al., 2016; Turner et al., 2003). Few studies use dopamine medication in drug-naïve patients, but this cannot be assumed to be equivalent to acute drug-withdrawal regimes in patients with long-term medical treatment (Navntoft and Dreyer, 2016; Payer et al., 2015). For example, one study compared non-medicated early PD patients just before treatment against the same patients after 12 weeks and against recently medicated PD patients, showing differential effects on learning from punishment or reward (Bódi et al., 2009). Another example for the importance of understanding longer-term dynamics of disease progression comes from studies suggesting a compensatory upregulation of prefrontal dopamine metabolism in early, but not late PD patients (Kaasinen et al., 2001; Rakshi et al., 1999).

Fifth, we would like to point out that functional neuroimaging of resting-state connectivity has identified a unique PD-related pattern of changes in pallidum, thalamus and premotor regions associated with motor symptoms as well as a PD-related cognitive pattern in medial prefrontal, parietal associative and cerebellar regions associated with cognitive dysfunction (Eidelberg, 2009; Tahmasian et al., 2015). The changes in resting-state connectivity related to PD and medication state involve brain regions outside the cortico-striatal pathways. This warrants an extended perspective on candidate regions (e.g. cerebellum or hippocampus) for future investigation (Tahmasian et al., 2015). Finally, there is a clear need for a better understanding of the effects of tonic dopamine level manipulations on the phasic firing patterns which are at the core of reinforcement learning, highlighting the importance of animal studies that allow for causal manipulations and measures of activity and transmitter concentrations with high spatial and temporal resolution. Valuable contributions to these efforts can also be expected from ultra high-field MR, allowing a more precise characterization of the individual degree of neurodegeneration in different brain nuclei and relating this to changes in activity depending on the state of medication and in comparison with healthy subjects (Lehericy et al., 2017).

Conflicts of interest

Hartwig R. Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark and as senior editor of NeuroImage from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany, and has received a research fund from Biogen-idec. James Rowe serves as Editor for Brain, and the Scientific Advisory Board for Asceneuron, with research grants from AZ-Medimmune unrelated to this work. The remaining authors have no conflicts of interest.

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