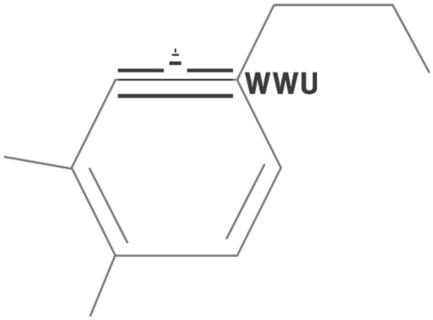

Ima Trempler

Neurocognitive Mechanisms of Flexibility and Stability of Prediction and their Impairment in Parkinson's Disease

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Neurocognitive Mechanisms of Flexibility and Stability of Prediction and their Impairment in Parkinson's Disease

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Summary

The ability to continually predict future states of the environment is not only a remarkable human capacity, but also an efficient principle of neural processing. In daily life, however, we usually need to adjust our behaviour to unexpected environmental changes (requiring flexibility) while at the same time sustaining the pursuit of our action goals despite distractions (requiring stability). In case of a violation of our current expectations, we must decide whether these *prediction errors* are relevant or irrelevant with respect to an adjustment of our predictions and our ongoing behaviour. According to recent physiological and computational models, dopamine plays a crucial role in balancing this interplay between flexibility and stability of prediction. Hence, motor as well as cognitive symptoms resulting from dopaminergic decline in idiopathic Parkinson's disease (PD) may trace back to deficits in these two fundamental mechanisms of coping with environmental challenges.

The present thesis aimed at studying the neurocognitive mechanisms that underly flexibility and stability of prediction as well as their potential impairment in PD. For this purpose, three studies were conducted, which involved behavioural measurements as well as functional and structural magnetic resonance imaging (MRI) of healthy subjects and PD patients. In all studies, participants were presented with a simple digit sequence that allowed to predict the forthcoming input. To assess flexible responses, the participants' task was to indicate directional changes within the sequence by button press. As these prediction errors implied the need to update the current prediction, they served as behaviourally *relevant* prediction errors revealing flexibility. In contrast, participants had to ignore digit omissions, as the reaction to these behaviourally *irrelevant* prediction errors required a stabilisation of the current prediction. Varying the probability of either type of prediction error over the experiment allowed us to measure learning from prediction errors, i.e., the adoption of flexible and stable states.

The first study assessed the neural networks of flexible and stable responses as well as of transitions between flexible and stable states in young healthy subjects using fMRI. Flexible responses to relevant and stable responses to irrelevant prediction errors were accompanied by activity in distinguishable neural networks. Successful response selection following the two types of prediction errors was associated with striatal activity. Substantia nigra activity was modulated by transitions between flexible and stabile states, depending on previous performance. Based on these results, the second study investigated deficient flexible and stable responses in PD patients compared with healthy controls and assessed variations in grey matter structure accompanying these deficits. The results revealed both inflexible and unstable responses to prediction errors in PD patients, which were associated with grey matter variations in specific brain regions (i.e., in the hippocampus and the inferior frontal gyrus). Finally, the third study focused on deficits of PD patients in probabilistic learning from prediction errors to adopt flexible or stable states. In healthy control subjects but not in PD patients, the probability of relevant and irrelevant unexpected events was associated with the participants' error rate in response to these events as well as with the blood-oxygen-level dependent (BOLD) amplitude in the respective brain areas targeted by the two previous studies.

The results of this thesis further clarify the role of dopamine in flexibility and stability of prediction and provide evidence for a corresponding impairment of predictive mechanisms in PD, possibly reflecting a core of motor and cognitive symptoms.

Zusammenfassung

Dass wir unablässig zukünftige Zustände und Geschehnisse in unserer Umgebung antizipieren, ist nicht nur eine bemerkenswerte menschliche Fähigkeit, sondern auch ein effizientes Prinzip neuronaler Verarbeitung. Zugleich müssen wir unser Verhalten jedoch auch unerwarteten relevanten Veränderungen anpassen, ohne unsere Ziele trotz zahlreicher irrelevanter Ablenkungen aus den Augen zu verlieren. Im Falle einer Verletzung unserer Erwartung müssen wir also entscheiden, ob diese sogenannten *Vorhersagefehler* relevant oder irrelevant hinsichtlich einer Anpassung unserer Erwartung wie auch unseres Verhaltens sind. Jüngeren physiologischen und komputationalen Modellen zufolge spielt der Neurotransmitter Dopamin eine entscheidende Rolle in diesem Wechselspiel von Flexibilität und Stabilität der Vorhersage. In diesem Sinne könnten sich sowohl motorische als auch kognitive Symptome des idiopathische Parkinson-Syndroms (IPS), das aus einer dopaminergen Unterversorgung resultiert, auf Defizite der Flexibilität und Stabilität der Vorhersage zurückführen lassen.

Ziel der vorliegenden Arbeit bestand in einer Untersuchung der neurokognitiven Mechanismen der Flexibilität und Stabilität der Vorhersage sowie deren möglicher Beeinträchtigung im Rahmen eines IPS. Drei Studien wurden durchgeführt, die behaviorale Messungen sowie funktionelle und strukturelle Magnetresonanztomographie (MRT) bei Gesunden und IPS-PatientInnen beinhalteten. In den Studien wurde den TeilnehmerInnen eine einfache Zahlensequenz präsentiert, welche die Vorhersage der aufeinanderfolgenden Zahlenstimuli ermöglichte. Um flexibles Antworten zu erfassen, wurden die TeilnehmerInnen instruiert, Richtungswechsel innerhalb der Sequenz per Tastendruck zu detektieren. Insofern diese Richtungswechsel ein Update der jeweils aktuellen Vorhersage beinhalteten, stellten sie *relevante* Vorhersagefehler dar. Im Gegensatz dazu sollten Auslassungen einzelner Zahlen innerhalb der Sequenz ignoriert werden, da diese *irrelevanten* Ereignisse eine Stabilisierung der aktuellen Vorhersage erforderten. Das Variieren der Wahrscheinlichkeiten für das Auftreten

relevanter und irrelevanter Vorhersagefehler über das Experiment hinweg erlaubte es zudem, flexible bzw. stabile Zustände der TeilnehmerInnen zu erfassen.

In der ersten Studie wurden mittels funktioneller MRT die neuronalen Netzwerke, die flexiblen und stabilen Antworten sowie Übergängen zwischen flexiblen und stabilen Zuständen zugrunde liegen, bei jungen gesunden ProbandInnen untersucht. Flexible bzw. stabile Antworten auf relevante bzw. irrelevante Vorhersagefehler gingen mit Aktivierungen in jeweils unterschiedlichen Netzwerken einher. Die erfolgreiche Antwortauswahl hing mit der Aktivität des Striatums zusammen. Darüber hinaus wurde die Aktivität der Substantia nigra von Übergängen zwischen flexibleren und stabileren Zuständen moduliert, die von der vorherigen Performanz abhingen. Basierend auf diesen Ergebnissen wurden in der zweiten Studie Beeinträchtigungen des flexiblen und stabilen Antwortens sowie damit zusammenhängende Veränderungen der Struktur spezifischer Hirnregionen bei IPS-PatientInnen im Vergleich zu gesunden ProbandInnen untersucht. Die Ergebnisse weisen auf ein unflexibles und instabiles Antwortverhalten im IPS hin, welches mit Unterschieden in der grauen Substanz spezifischer Hirnregionen (d.h. des Hippokampus und des inferioren frontalen Gyrus) in Zusammenhang steht. Schließlich wurden in der dritten Studie Defizite im probabilistischen Lernen bei IPS-PatientInnen erfasst. Bei gesunden ProbandInnen, nicht aber bei IPS-PatientInnen konnte ein Zusammenhang zwischen der Wahrscheinlichkeit von relevanten und irrelevanten Vorhersagefehlern sowie der Aktivierung spezifischer Gehirnregionen gefunden werden.

Die Ergebnisse dieser Arbeit vertiefen das Verständnis der Rolle von Dopamin im Wechselspiel von Flexibilität und Stabilität der Vorhersage. Zudem bieten sie Evidenz für eine entsprechende Beeinträchtigung prädiktiver Mechanismen im IPS, welche möglicherweise die Grundlage motorischer und kognitiver Symptome darstellt.

List of Original Publications

This thesis is based on the following original research articles:

Study I. Trempler, I., Schiffer, A. M., El-Sourani, N., Ahlheim, C., Fink, G. R., & Schubotz, R. I. (2017). Frontostriatal Contribution to the Interplay of Flexibility and Stability in Serial Prediction. *Journal of Cognitive Neuroscience, 29*(2), 298-309.

Study II. Trempler, I., Binder, E., El-Sourani, N., Schiffler, P., Tenberge, J.-G., Schiffer, A.-M., Fink, G. R., & Schubotz, R. I. (2018). Association of Grey Matter Changes with Stability and Flexibility of Prediction in Akinetic-Rigid Parkinson's Disease. *Brain Structure and Function, 223*(5), 2097-2111.

Study III. Trempler, I., Bürkner, P.-C., El-Sourani, N., Binder, E., Reker, P., Fink, G. R., & Schubotz, R. I. (2018). Dopaminergic Modulation of Surprise: fMRI Evidence for Deficient Flexible Adaptation of Prediction in Parkinson's Disease. *Manuscript submitted for publication.*

1. Theoretical and Empirical Background

Just a little over two centuries ago, in his essay *On the Marionette Theatre*, Heinrich von Kleist (1801) stated that in order to achieve the grace of a marionettes' dance, which "only glance the ground, like elves", we should have "either no consciousness or an infinite amount of it". Kleist's observation provides the starting point for contemporary questions regarding differences between human and artificial intelligence and highlights that, even if it is not consciousness, the control of our movements is closely linked to cognitive processes.

Traditionally, motor and cognitive functions have been studied in isolation. Research on *motor control* is concerned with processes by which humans produce intentional and coordinated movements. It is suggested that sensory information about the current state of the environment as well as of the body are integrated to predict the consequences of planned movements prior to their execution (Wolpert & Flanagan, 2001). Similarly, but on a more abstract level of description, *cognitive control* refers to the decision processes required to guide one's behaviour toward distant goals (E. Miller & Cohen, 2001; Botvinick, 2008). Studies on cognitive control deal with information prioritisation: the ability to select appropriate sensory information, while inhibiting irrelevant distraction (Posner & Snyder, 1975). Moreover, it is of interest how relevant contextual information is used and maintained to inform this decision and selection process (Koechlin, Ody, & Kouneiher, 2003).

Thus, rather than representing two separate functions, motor and cognitive control appear inherently linked or even mutually dependent: motor functions are required to translate one's higher-order goals into detailed action plans, whereas cognitive control processes account for the purposefulness of motor behaviour, especially when changing environmental demands trigger behavioural adjustments. In the following, I will therefore use the term *cognitive motor control* to refer to this intertwining of cognitive and motor functions.

The starting point of this thesis is that predictive processing, as a fundamental principle of brain function (Grush, 2004; Bubic, Cramon, & Schubotz, 2010; Colder, 2011), can provide a link between motor and cognitive control. While we use predictions to execute rapid accurate or corrective movements (Bays & Wolpert, 2006), the selection of actions depends on their anticipated outcomes (Hommel, Müsseler, Aschersleben, & Prinz, 2001). One of the most influential contemporary elaborations of this proposal is the framework of *predictive coding* (Clark, 2013). Although predictive coding claims to represent a unified theory of cortical processing in virtually any domain (i.e., from the perceptual to the social and emotional domain), in the following I will focus on those aspects that are important for an understanding of cognitive motor control.

1.1 Prediction Provides a Link between Motor and Cognitive Control

1.1.1 Predictive Coding and Active Inference

The classical view of neural processing is that sensory information from the environment propagates through bottom-up pathways from lower to higher cortical areas in a feedforward manner. In contrast, according to predictive coding, cognitive systems are not passively awaiting sensory input. Instead, they continuously predict the most probable sensory stimulation based on internal, so-called *generative models* (Clark, 2013). These predictive computations imply a preference for the processing of informative unpredicted input over predicted input, thereby rendering neural processing computationally and metabolically efficient (Rao & Ballard, 1999). The generation and optimisation of generative models is achieved through Bayesian inference about the causes of sensory input (Friston, 2003). Thus, generative models are probabilistic in their nature and informed by the statistical regularities of the environment. Moreover, predictive coding operates hierarchically: probabilistic predictive models are generated at superior cortical areas and communicated through feedback

connections to lower sensory areas (T. Lee & Mumford, 2003; Friston, 2005). What propagates from inferior to superior areas are only *prediction errors*, i.e., the residual differences between current sensory inputs and the predicted states (Clark, 2015). Prediction errors drive further processing by informing us of what is surprising and has yet to be explained. In this respect, the errors sharpen the predictions until they match the sensory signals - a process termed *prediction error minimisation* (Feldman & Friston, 2010). A distinction can be made between *signed* and *unsigned* prediction errors (den Ouden, Kok, & Lange, 2012): the signed prediction error refers to the value or valence of a stimulus, i.e., whether it is better or worse than expected. The unsigned prediction error signals the degree of *surprise* triggered by a stimulus, independent of its sign. It modulates the learning rate by increasing or decreasing the uncertainty of current predictions. Although in the present thesis, the term prediction error will primarily refer to unsigned prediction errors, their behavioural relevance (rather than their valence) will play a crucial role.

Predictions and prediction errors activate separate sub-populations of neurons in the brain, termed *representation units* and *error units*, respectively (Rao & Ballard, 1999; Summerfield & Egner, 2009). When there is a mismatch between predictions and the sensory input, error units produce a prediction error signal, which is then transferred to the next level of the hierarchy to update the generative model conveyed via representation units. Given statistical noise of the environment, prediction error minimisation is state- or context-dependent. This means that, in a given context, it should be clear that a deviation from the current prediction reflects a legitimate prediction error and not noise: “For example, it is important to know whether certain sensory inputs fail to match our prior expectations because they contain information that disproves our current hypothesis (e.g., we hear a dog but see a cat), or because the sensory inputs are simply too noisy (we hear a dog but see only mist). While the former should cause us to update our beliefs (a barking cat!), the latter should not.” (den Ouden et al.,

2012). That is why prediction errors are weighted with regard to their *precision,* i.e., the confidence with which a prediction error is allowed to revise the generative model (Friston, 2005). The higher the precision, the higher is the gain on prediction error units so that they have a greater influence on a potential revision of the generative model in representation units. The expected precision of a prediction error is part of the generative model itself: it entails a second-order prediction of the levels of noise or uncertainty and enables a flexible adaptation of a prediction error's actual precision to changing environmental contexts (Hohwy, 2014).

Crucially, behaviours and actions are suggested to be implemented through similar functional mechanisms to those of perception (Friston, 2003; 2010). According to the *active inference* framework, actions are explained in terms of inferences on the causes of proprioceptive sensations (Adams, Shipp, & Friston, 2013). The initiation of motor output serves prediction error minimisation by the active generation of those sensations that are predicted by corresponding proprioceptive predictions. Paralleling perceptual inference, this active mode of prediction error minimisation is hierarchically structured: areas higher in the hierarchy represent more abstract information (i.e., action goals) and inform predictions at lower levels, which represent more concrete information (i.e., kinematics) (Ondobaka & Bekkering, 2013). Because proprioceptive predictions are conceptually comparable to classical motor commands, active inference corresponds to what is commonly described as action or motor control (H. Brown, Friston, & Bestmann, 2011; Friston, 2010).

The notion of hierarchical predictive processing in the brain is complemented by a hierarchical structure in cortical architectures (e.g., Kanai, Komura, Shipp, & Friston, 2015; Kiebel, Daunizeau, & Friston, 2008). In the following section, I will describe the cortical network that plays a role in the hierarchical control of motor output.

1.1.2 Neural Implementations of Hierarchical Cognitive Motor Control

In the late nineteen-eighties, Rizzolatti, Riggio, Dascola, and Umiltá (1987) observed that the activity of neurons in the ventral premotor area F5 of the macaque monkey reflected the orientation of spatial attention even in the absence of any motor behaviour. The authors concluded that the same frontal-parietal circuits that determine motor output toward specific spatial locations are also responsible for spatial attention. Although their *Premotor Theory of Attention* is still controversially discussed (D. Smith & Schenk, 2012), their findings imply that the neural pattern of the motor system's response represents, alongside classical motor processes, functions that are classically conceptualised as rather cognitive functions.

The premotor system, including lateral premotor cortex (PM) and (pre-) supplementary motor area (SMA), acts as a crucial hub in neural implementations of cognitive-motor interactions. It is anatomically positioned between the dorsolateral prefrontal cortex (dlPFC) anteriorly and the primary motor cortex (M1) posteriorly. This position allows the premotor system to receive direct inputs from the dlPFC associated with abstract goal representations and from the posterior parietal cortex supporting, amongst other functions, sensorimotor transformation (Cui, 2014). The output of the premotor system is projected to M1 for movement execution. According to Schubotz (2007), the premotor system mediates the prediction of dynamically changing events by processing transitions between distinct stimuli, with lateral PM associated with externally guided and (pre-)SMA associated with internally guided prediction (Schubotz & Cramon, 2003, 2004). Accordingly, during motor control, premotor activation represents the processing of potential motor *sequences* (Schubotz, 2007). Under certain circumstances, these sequences are then translated into concrete motor commands (or proprioceptive predictions) descending from upper motor neurons in M1 to alpha motor neurons on the ventral horn of the spinal cord (Fadiga, Fogassi, Gallese, & Rizzolatti, 2000; Adams et al., 2013). However, the premotor system not only mediates sequential predictions

when we move but also when we attend to dynamic change in the environment (Schubotz, 2015). Thus, cognitive functions of the premotor system consist of the encoding of re-afferent changes including the prediction of action effects as well as of environmental changes (Schubotz, 2007). Indeed, brain imaging studies show that the premotor cortex is involved in the prediction and planning of events, which occur in short time frames of only a few seconds (Schubotz & Cramon, 2002, 2004).

Functions of prefrontal areas are typically subsumed under cognitive control processes, which points to a functional rostral-to-caudal gradient of cognitive motor control. Rather than dealing with regular sequences, the PFC appears to be concerned with the processing of single stimuli (Schubotz, 2015), for example during the detection of sequential violations (Bubic, Cramon, Jacobsen, Schröger, & Schubotz, 2009). The representations of these stimuli can exhibit different degrees of abstraction and evolve at different time scales, which in turn lead to functional hierarchical levels within the PFC itself (Kiebel et al., 2008). More anterior sites contribute to the processing of higher conceptual representations such as goals and abstract action plans, whereas more posterior areas process immediate behavioural or perceptual requirements and options (Jeon, 2014; Badre & Wagner, 2007; Koechlin et al., 2003). In addition to this *representational hierarchy*, Badre and Nee (2018) suggest that the dlPFC represents the top of the *control hierarchy*. It receives input from both caudal and rostral regions and, thus, forms a hub of converging information to control motor output. Explicitly referring to predictive coding, W. Alexander and J. Brown (2018) further proposed only recently the so-called *hierarchical error representation model.* According to this model, the medial PFC generates prediction error signals, whereas the lateral PFC represents those stimuli that precede prediction errors. Since prediction error signals associate with their preceding stimuli, the lateral PFC can elicit error predictions. These predictions descend to more inferior levels of the

predictive motor control hierarchy to reduce uncertainty regarding the outcome of a potential motor behaviour.

Cognitive motor control is not limited to cortical contributions. The basal ganglia play a key role in carrying out complex behaviour (cf. Yin, 2016; 2017). G. Alexander, DeLong, and Strick (1986) describe five separate loops, which link the basal ganglia via the thalamus to cortical premotor areas and prefrontal regions including the dlPFC, the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC). Working in parallel, these loops are assumed to support various cognitive and motor functions. Thereby, prefrontal and premotor areas project to the striatum, which is the main input structure of the basal ganglia. This top-down predictive input allows coordinated behaviour to be maintained and focused (see section 1.2.2). Concurrently, the striatum also processes bottom-up signals (i.e., prediction errors) that are gated to cortical regions via the thalamus to modify current predictions (Haber, 2016). Thus, by determining whether to act on a prediction error or not, different areas of the brain are constantly engaged in stabilising as well as adjusting predictions and behaviours according to current action plans in response to environmental changes. Both processes mirror a fundamental aspect of predictive processing, the trade-off between flexibility and stability.

1.1.3 The Flexibility-Stability Trade-Off in Response Selection

According to predictive coding, the only input that is newsworthy is the prediction error, the mismatch between predicted and actual states of the world and the body. Due to their inherent saliency, prediction errors - at least those of high precision - almost automatically capture our attention (den Ouden et al., 2012; Hohwy, 2012).[1] However, in everyday life

[1] According to Feldman and Friston (2010), visual attention is nothing but inferring or optimising the precision of sensory input. Correspondingly, H. Brown et al. (2011) suggest that motor attention consists in the optimisation of top-down predictions of proprioceptive sensations in the context of motor preparation. Finally, Pezzulo (2012) suggests that cognitive control refers to the optimisation of action goals generated in nested covert loops (aiming at proprioceptive prediction error minimisation) prior to the overt execution of the corresponding action.

unpredicted events can consist of more or less relevant information, dependent on our current goals and motivational priorities - be it the ringing of your telephone or the loud laughter from the party in the neighbour's flat while you are writing an article. Moreover, our processing resources are limited and not everything that has not been foreseen can be equally processed.

E. Miller and Cohen (2001) provided an influential theoretical foundation of top-down control exerted by the PFC, according to which we are able to voluntarily guide the processing of relevant as opposed to irrelevant stimuli. This top-down control allows the adjustment of one's behaviour in pursuit of current action goals by processing particular relevant information in a prioritised way (referred to as *cognitive flexibility*), while irrelevant distraction is inhibited (referred to as *cognitive stability*) (J. Duncan, 2001). Cognitive flexibility and stability are usually suggested to reflect specific operations of working memory representations. Working memory is defined as the "temporary retention of information that was just experienced or just retrieved from long-term memory but no longer exists in the external environment" (D'Esposito, 2007). Such representations of information can be held and stabilised through active maintenance but also manipulated and updated in response to environmental changes. They entail beliefs about environmental states that should be updated when things turn out to be different than expected.[2]

Crucially, cognitive flexibility and stability appear to reflect two functionally opposing processes relying on one common neural mechanism: a state of high flexibility renders working memory representations unstable and prone to distraction, whereas stabilisation could lead to inflexible and rigid behaviour although relevant information is available. In fact, studies support the notion that cognitive flexibility and stability in response to environmental changes oppose each other (e.g., Müller et al., 2007; Armbruster, Ueltzhöffer, Basten, & Fiebach, 2012).

[2] Although the relationship between working memory and predictive coding appears quite obvious here, it is noteworthy that the trade-off between flexibility and stability, i.e., the question of how the brain deals with input of differing relevance, has been investigated independently of the concept of prediction (but see Parr and Friston (2017), for a conceptualisation of working memory in the active inference framework).

Cognitive flexibility is typically measured by task switching or set-shifting paradigms, which require maintenance and updating of task rule representations, but also an inhibition of the previously active task set (Vandierendonck, Liefooghe, & Verbruggen, 2010). By contrast, delayed response tasks with distraction are used to measure cognitive stability requiring active maintenance, shielding and cognitive inhibition (Goschke & Dreisbach, 2008; Lavie, 2005). However, even though we might not be able to update and to stabilise current representations in working memory at the same time, we need to be both flexible and stable, "at least at the global level. Thus, while we should be flexible in response to task-relevant changes, we should be simultaneously stable as long as the changes are irrelevant" (Cools & D'Esposito, 2011). In this regard, flexibility and stability are substantiated as two separate mechanisms of information processing which nevertheless work together.

The neurotransmitter dopamine is supposed to play a key role in the interplay of flexibility and stability. As will be developed in the following sections, the dopamine system might support a potential bridge between classical concepts of working memory functions on the one hand and predictive processing on the other hand. This will provide a comprehensive picture of how the brain processes and learns from relevant prediction errors requiring a behavioural adaptation, while irrelevant prediction errors and corresponding motor reactions are inhibited.

1.2 The Role of Dopamine in Response Selection

1.2.1 The Dopamine System

Amongst adrenaline and noradrenaline, dopamine is one of the main catecholamine transmitters in the central nervous system transferring signals between the neuron cells. Dopamine is involved in the control of movement, cognition and emotion and plays a role in various neurological and psychiatric diseases such as Parkinson's disease, schizophrenia and

drug addiction. Dopamine-producing cells, of which there are about a million in the human brain (Schultz, 2016), are found in only a few areas in the human brain (Björklund & Dunnett, 2007). The main source of dopamine are the neurons of the dopaminergic midbrain, which consists of the substantia nigra and the ventral tegmental area. From here, the long axons of dopamine neurons project and transmit dopamine to many other brain regions creating dopaminergic pathways throughout the brain. The major pathways are the *nigrostriatal*, the *mesolimbic* and the *mesocortical* pathway. The nigrostriatal pathway connects the substantia nigra with the dorsal basal ganglia, that is, the nucleus caudatus, the putamen and the globus pallidus (Gerfen, 1992). As part of the motor loop (cf. section 1.2.2), this pathway plays a role in the initiation and coordination of movements (Bourdy et al., 2014). The mesolimbic and mesocortical pathways transmit dopamine from the ventral tegmental area to limbic and cortical regions, respectively. Target regions within the limbic system are, amongst others, the nucleus accumbens, the amygdala and the hippocampus, whereas the mesocortical pathway particularly innervates areas of the PFC. Due to the contribution of the mesolimbic and mesocortical pathways to motivational and cognitive control, respectively, they play a considerable role in learning and goal-directed behaviour (Seamans & Yang, 2004). Thus, dopamine modulates motor and cognitive control through extensive projections from midbrain nuclei to the basal ganglia and cortical areas (Fallon & R. Moore, 1978; Joel & Weiner, 2000).

Dopamine binds to specific G protein-coupled membrane receptors that detect dopamine outside the neuron and activate cellular responses. There are at least five subtypes of dopamine receptors, D1 - D5, which are differentiated based on their inhibitory and excitatory action as well as on their binding affinity to dopamine (P. Andersen et al., 1990). These receptors are divided into two major groups: the excitatory D1 receptors (D1, D5), and the inhibitory D2 receptors (D2, D3, D4) (Beaulieu & Gainetdinov, 2011; Vallone, Picetti, & Borrelli, 2000). D2 receptors have pre- and postsynaptic localisation, whereas D1 receptors are

only postsynaptically present. While postsynaptic receptors cause ionic channels on the postsynaptic membrane to either open or close, presynaptic autoreceptors regulate the activity of dopamine neurons by controlling the timing and amount of dopamine release in target regions (Ford, 2014). The distribution of D1 and D2 receptors is not homogenous throughout the brain. The highest densities of the D2 class dopamine receptors are found in the striatum (Camps, Cortés, Gueye, Probst, & Palacios, 1989), whereas there are four to seven times higher densities of the D1 than of the D2 receptors in the PFC, the hippocampus and the visual cortex (Hall et al., 1994).

Furthermore, there are two regulation mechanisms of dopamine release: phasic and tonic release (Grace, 1991). Phasic spike firing refers to short-term single dopamine cell activity usually in response to salient stimuli, whereas tonic release is caused by a constant low-frequency baseline spike activity driven by pacemaker-like membrane currents of dopamine neurons (Goto, Otani, & Grace, 2007). There is a reciprocal relationship between phasic and tonic dopamine release since tonic dopamine can inhibit phasic release by regulating presynaptic autoreceptors (Grace, 1991). According to Dreyer, Herrik, Berg, and Hounsgaard (2010), D2 receptors are more sensitive to changes in tonic dopamine levels, whereas D1 receptors are sensitive to phasic changes. Like the different dopamine receptor classes and their respective distribution within different brain regions, both mechanisms are suggested to have selective behavioural effects or functional consequences.

1.2.2 The Contribution of Dopamine to Cognitive Motor Control

Coordinated movements resulting from motor learning include the initiation and maintenance of motor action sequences. Here, the motor loop, which connects the putamen to the premotor system, plays a major role. As previously described, the premotor cortex is not only activated during performing but also during imagining, planning and observation of an

action (Decety et al., 1994; Jeannerod, 2001); it is involved in the prediction of movements based on their sequential structure (Schubotz, 2007). Accordingly, Graybiel (1998) suggests that dopamine action in the putamen mediates chunking of motor sequences by probabilistic weighting of transitions between serial cortical activation patterns. In this way, motor sequences are executed as single activity patterns instead of multiple serial computations, which reduces motor variability (Poldrack et al., 2005; Schneider, 2003; Wymbs, Bassett, Mucha, Porter, & Grafton, 2012).

Whether a cortical representation of a movement is selected to be executed or not depends primarily on the activation of the direct or indirect pathway of the basal ganglia, also termed “Go”- and “NoGo”-pathways, respectively (Frank, Seeberger, & O'Reilly, 2004) (see Figure 1). Medium spiny neurons (MSN) of the direct pathway express D1 dopamine receptors in the striatum. They send inhibitory projections directly to the output structures of the basal ganglia, that is, the globus pallidus internal segment and the substantia nigra pars reticulata (GPi/SNr). Inhibition of these nuclei leads to a disinhibition of the thalamus, thereby facilitating the excitation of cortical representations. In contrast, MSN of the indirect pathway expressing D2 receptors initially send inhibitory projections to the globus pallidus external segment causing a disinhibition of the subthalamic nucleus. Excitatory projections from the subthalamic nucleus to the GPi/SNr trigger the inhibition of the thalamus, thereby suppressing actions from being executed. Modulatory input of dopamine from the substantia nigra pars compacta to the striatum consists of an excitement of the direct pathway via D1 receptors and an inhibition of the indirect pathway via D2 receptors, which in both cases causes a disinhibition of the thalamic excitation of cortical areas.

Obviously, motor behaviour should accord with current action goals, whereas irrelevant information and unfocused behaviours should be supressed. Just as dopamine neurotransmission drives motor execution, dopamine has been shown to be involved in working

memory and cognitive control, in particular in the trade-off between flexibility and stability (Cohen, Braver, & J. Brown, 2002; Cools & D'Esposito, 2011; Mehta & Riedel, 2006). On the one hand, active maintenance during delayed response tasks has long been attributed to dopamine action in the PFC (Watanabe, Kodama, & Hikosaka, 1997). On the other hand, dopaminergic projections from the striatum to the PFC involving the direct and the indirect pathway are supposed to serve an input gating function allowing flexible updating of working

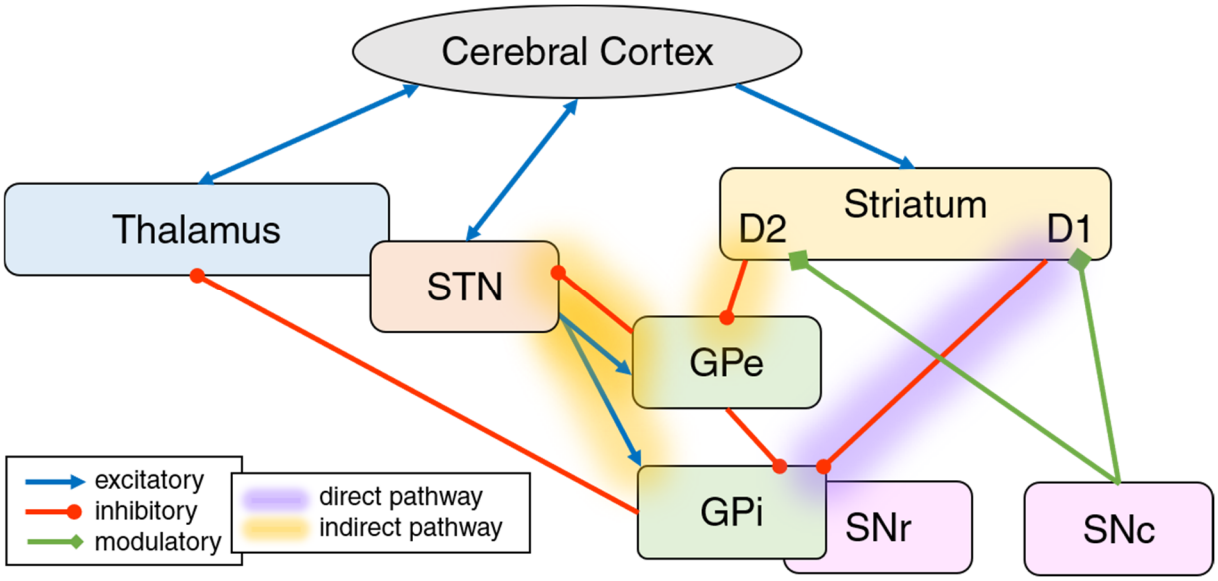

Figure 1. The direct and the indirect pathways of the basal ganglia. Neurons of the direct pathway expressing D1 receptors in the striatum inhibit GPi/SNr neurons, which in turn causes disinhibition of thalamus activity. Neurons of the indirect pathway expressing D2 receptors have an opposing effect: they inhibit the GPe, which leads to reduced inhibitory projections to the STN. As a result, the STN sends more excitatory signals to the GPi/SNr causing an increased inhibition of the thalamus. The net effect is thus the excitation or inhibition of the thalamus, which sends excitatory projections to the cortex. Dopamine from the SNc projecting to the striatum causes an excitation of the direct pathway via D1 receptors, and an inhibition of the indirect pathway via D2 receptors, thereby stimulating cortical representations. GPi: globus pallidus internal segment; GPe: globus pallidus external segment; SNr: substantia nigra pars reticulata; SNc: substantia nigra pars compacta; STN: subthalamic nucleus. Adapted from Frank et al. (2004).

memory representation when relevant information becomes available (Braver & Cohen, 1999; Hazy, Frank, & O'Reilly, 2006; van Schouwenburg, Aarts, & Cools, 2010). According to Cools and D'Esposito (2011), dopamine in the PFC contributes to the stabilisation of working memory representations, whereas dopamine in the striatum plays a role in the flexible updating of these

representations. Moreover, the authors suggest that the delicate trade-off between flexibility and stability depends on optimal baseline dopamine levels in frontostriatal circuits, which follow an inverted-U-shaped function. Both too high and too low levels of dopamine in the PFC and the striatum can impair stability and flexibility, respectively. Furthermore, according to the the *dual-state theory* of dopamine function put forward by Durstewitz and Seamans (2008), flexible and stable states depend on differential dopamine receptor functions. A D1-induced regime of network activity is characterized by a high energy barrier favouring active maintenance of working memory representations. In contrast, a D2-dominated state is susceptible to noise but also to spontaneous transitions between different states. It allows to flexibly switch between states or to update working memory representations in response to unpredicted relevant events. The varying receptor concentration throughout the brain, with highest concentrations of D1 and D2 receptors in the PFC and the striatum, respectively, thereby substantiate the suggested functional dichotomy between the PFC supporting stability and the striatum supporting flexibility (cf. section 1.2.1).

However, the question remains how relevant representations that are stored in the PFC can have an influence on behaviour. Analogous to input gating via frontostriatal loops, there is indirect evidence from computational models (Collins & Frank, 2013; Frank & Badre, 2012) and functional magnetic resonance imaging (fMRI) (Chatham, Frank, & Badre, 2014) for a corresponding output gating mechanism: relevant working memory representations maintained in the frontal cortex act as input to the dorsal striatum. According to Frank and O'Reilly (2006), cortical representations of planned motor actions trigger the activation of the direct pathway, whereas alternative actions trigger activation of the indirect pathway hindering them from being executed. Output gating is proposed to rely on the hierarchical structure of the PFC (see chapter 1.1.2): higher order regions identify the relevant representation according to the current goal and context and influence lower order regions, which, in turn, determine the correct output

(Chatham & Badre, 2015). Only recently, Vogelsang and D'Esposito (2018) suggested that a rostral-caudal gradient as observed in the PFC may also exist in the striatum reflected by the distribution of dopamine receptors: frontal and striatal regions with higher dopamine receptor density would influence regions with lower density. Hence, it appears that dopamine represents an important neuromodulator, not only during input gating (of prediction errors) but also during (predictively guided) output gating. Moreover, according to predictive coding, tonic dopamine is assumed to control the precision of unexpected input and, thus, impacts on learning and adaptation of predictions and corresponding behaviours. In the following, I will consider the question of how dopamine's role in the described gating mechanisms can be reconciled with its role in the framework of predictive coding.

1.2.4 Dopamine and Precision Weighting

The established view of dopamine function derived from reinforcement learning models is that phasic responses in midbrain dopaminergic neurons represent reward prediction errors, which transfer back to a cue that predicts their occurrence (Nasser, Calu, Schoenbaum, & Sharpe, 2017; Schultz, 1998). However, dopamine release seems to be triggered shortly after any salient, unpredicted external event, irrespective of whether it is rewarding or not (D'Esposito & Postle, 2015; Redgrave & Gurney, 2006; Schultz & A. Dickinson, 2000). In the framework of active inference, Friston et al. (2012) state that "dopaminergic discharges […] are an integral part of Bayes-optimal perception and sensorimotor integration: they respond to salient or precise cues that portend a predictable sequence of sensorimotor events that will be registered by specific proprioceptive and exteroceptive processing channels." The authors further argue that dopamine does not encode the predicted state or the prediction error itself, i.e., perceptual content, but the uncertainty about the state of the world by encoding the precision of sensory information. Given the distinction between the expected precision and the

actual precision of a prediction error (cf. section 1.1.1), the expected precision is suggested to be reported by tonic dopamine release, which, in turn, biases phasic dopamine release reflecting the degree of surprise conveyed by the actual prediction error. Thus, by modulating short-term synaptic plasticity, tonic dopamine determines the surprise of prediction errors and modulates the rate of learning regarding an adaptation of current predictions and behaviours (Beeler, Daw, Frazier, & Zhuang, 2010; Humphries, Khamassi, & Gurney, 2012). FMRI studies have demonstrated prediction error signals of different precision in the substantia nigra (D'Ardenne, McClure, Nystrom, & Cohen, 2008; Iglesias et al., 2013) as well as in regions targeted by its projections, such as the striatum (McClure, Berns, & Montague, 2003; Schiffer & Schubotz, 2011) and the dlPFC (D'Ardenne et al., 2012). Surprise-driven learning of statistical regularities of the environment has been found to depend on the hippocampus (Bornstein & Daw, 2012; Harrison, Duggins, & Friston, 2006; Strange, Duggins, Penny, Dolan, & Friston, 2005). The hippocampus is a target area for dopamine projections from the ventral tegmental area of the dopaminergic midbrain (Lisman & Grace, 2005). Furthermore, there is evidence that dopamine is co-released by the noradrenergic locus coeruleus into the hippocampus (Kempadoo, Mosharov, Choi, Sulzer, & Kandel, 2016). Thus, dopaminergic influence in the hippocampus might play a role in learning from prediction errors and in the encoding of uncertainty.

This view on the role of dopamine in encoding the precision of prediction errors appears to be compatible with its role in the flexibility-stability balance. Assuming that precision estimation implies inferring environmental volatility, i.e., the rate of change in the environment (Behrens, Woolrich, Walton, & Rushworth, 2007; Y. Yu, FitzGerald, & Friston, 2013), stable and flexible states might correspond to the demands of precise and uncertain predictions, with low and high weight on potential prediction errors, respectively (Y. Yu et al., 2013). The precision of sensory input, encoded by dopamine, is thus of importance in determining whether to revise or to stabilise current predictions. However, this conceptualisation of the flexibility-

stability trade-off does not account for the relevance of (more or less) precise input. If top-down control to prioritise information was nothing but the optimisation of the prediction errors' precision, then it would also be driven by a high expected precision of irrelevant sensory input (Ransom & Fazelpour, 2015). In the present thesis, flexible and stable states are therefore defined as states of anticipating either relevant or irrelevant input resulting in a high or low precision of the expected input, respectively.[3] Therefore, it is of interest how dopamine contributes to these states while also accounting for the relevance of the upcoming input.

Dopamine integrity is an important indicator of aging and involved in a wide range of neuropsychiatric diseases, such as Alzheimer's disease, schizophrenia, and Parkinson's disease (cf. Money & Stanwood, 2013; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). Therefore, it is of importance to translate results on the role of dopamine in flexibility and stability into the diagnostic assessment of these patients and their therapeutic treatment. With regard to prediction as a joint principle of motor and cognitive control, the current research is particularly concerned with Parkinson's disease, which - although predominantly regarded as a movement disorder - might be regarded as a disorder of predictive processing in general.

1.3 Parkinson's Disease: An Impairment of Predictive Processing?

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 1% of the population above the age of 60 (Tysnes & Storstein, 2017) and whose prevalence is expected to double from 4.6 million in 2005 to 9.3 million by 2030 (Dorsey et al., 2007). The main neuropathological characteristics are the formation of α-synuclein-containing

[3] It is not claimed that this thesis can provide a final answer of how exactly stable and flexible states can be conceptualised with a view to precision estimates. Of course, one can also define flexibility as the ability to adjust predictions to varying (and not necessarily to relevant) demands. It becomes clear that it is crucial to unambiguously define flexibility and stability when operationalising and drawing conclusions on the two functions.

Lewy bodies and a disruption of dopamine production in the substantia nigra pars compacta suggested to be caused by genetic as well environmental factors (Obeso et al., 2010). The clinical picture of PD is heterogeneous: although the cardinal symptoms resulting from dopamine deficiency are the motor symptoms bradykinesia, rigidity and resting tremor, non-motor symptoms such as sleep and mood disorders as well as cognitive deficits and dementia cause considerable problems for the patients. This leads to a gradual shift in the definition of the disease, from a classical movement disorder to a complex disorder affecting multiple cognitive domains (Yarnall et al., 2014).

Muslimovic, Post, Speelman, and Schmand (2005) reported that 24% of newly diagnosed PD patients showed impaired cognitive performance in a wide range of standardised neuropsychological tests. Moreover, up to 80% eventually develop mild cognitive impairment (MCI) and dementia (Aarsland, K. Andersen, Jan Larsen, Lolk, & Kragh-Sørensen, 2003; Buter et al., 2008). According to the dual-syndrome hypothesis put forward by Kehagia, Barker, and Robbins (2013), MCI and dementia reflect two different cognitive profiles of PD patients, with disruption of dopaminergic frontostriatal circuits on the one hand and temporoparietal alterations due to a decline in cholinergic function on the other hand. In the next section, I will take a closer look at MCI in PD patients resulting from dopaminergic decline.

1.3.1 Cognitive Profile Derived from Dopamine Decline

An evaluation of MCI in PD patients typically relies on the Parkinson's Disease Mild Cognitive Impairment criteria developed by the Movement Disorder Society (MDS PD-MCI). These criteria include the diagnosis of idiopathic PD as based on the UK PD Brain Bank Criteria, gradual cognitive decline reported by the patient or the clinician, and cognitive deficits on neuropsychological testing which do not significantly interfere with functional independence and cannot be traced back to dementia or other primary explanations (Litvan et

al., 2012). Neuropsychological testing includes five cognitive domains: attention and working memory, language, memory, and executive and visuospatial functions.

Regarding working memory dysfunctions, there is substantial evidence for inflexible updating in PD. Patients exhibit difficulties in set-shifting as assessed by discrimination learning tasks or task-switching paradigms (e.g., Cools, 2001b; B. Kopp, 2016; Lees & E. Smith, 1983), and their performance has been shown to be restored by administration of dopaminergic medication (Cools, 2001a; Costa et al., 2014). Concurrently, PD patients reveal decreased activation in the striatum during working memory tasks (Lewis, Dove, Robbins, Barker, & Owen, 2003; Monchi et al., 2004). Moreover, atrophy within this regions is particularly found in PD patients with MCI (Mak et al., 2015).

In contrast, findings on an impairment of cognitive stability in PD are inconsistent, probably due to operationalisation differences between the studies. Some studies reported deficits in working memory maintenance (e.g., Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; E.-Y. Lee et al., 2010; Possin, Filoteo, Song, & Salmon, 2008) and in the inhibition of irrelevant distractors or background noise (Castiello, Bonfiglioli, & Peppard, 2000; Machado, Devine, & Wyatt, 2009; Zhao, Chen, Zhang, Shen, & Gao, 2018). Other studies report even increased stability and distractor-resistance in PD (Cools, Miyakawa, Sheridan, & D'Esposito, 2010; Uitvlugt, Pleskac, & Ravizza, 2016). Intriguingly, different fMRI studies reported both decreased and enhanced activity in the PFC in PD patients compared to healthy controls (Lucas-Jiménez et al., 2015; but see Caminiti, Siri, Guidi, Antonini, & Daniela Perani, 2015; Cools et al., 2010). Moreover, increases in cortical thickness (Biundo et al., 2013) and an upregulation of dopamine metabolism (Kaasinen et al., 2001; Rakshi et al., 1999) in frontal regions have been reported. These findings speak in favour of compensatory (but not necessarily adaptive) mechanisms, at least in early stages of the disease. However, given the relationship between the two partly opposing functions, measures that are suggested to reflect stability could also reflect

an impaired flexible gating of irrelevant perceptual content. Thus, increased distractor-resistance could either be caused by compensatory upregulation of dopamine neurotransmission in the PFC (reflecting increased stability) or by impaired working memory gating of distracting stimuli in the striatum (reflecting impaired flexibility). From the perspective of predictive processing, the question arises whether patients are not only impaired in flexible responding to relevant prediction errors but also in stabilising predictive models following irrelevant unexpected perceptual input.

1.3.2 Serial Prediction and Prediction Error Signalling in Parkinson's Disease

Due to the predominant motor symptoms in PD, the most obvious impairment of predictive processing may be found in motor sequence learning. Indeed, several studies using the serial reaction time task (SRTT) report deficient learning of motor sequences in PD (Kemény, Demeter, Racsmány, Valálik, & Lukács, 2018; Siegert, Taylor, Weatherall, & Abernethy, 2006). During the SRTT, participants have to respond to the location of a target stimulus, which appears at one of four possible locations following a deterministic sequence (Nissen & Bullemer, 1987). However, deficits in PD patients could be based on difficulties in the initiation of a motor response and might, therefore, be independent from deficits in the generation of an internal model of the sequence. Nevertheless, there is evidence that PD patients show difficulties in (internally guided) serial prediction, which is supposed to reflect a joint principle of motor and cognitive control. The serial prediction task (SPT; Schubotz, 2004) consists of the prediction of stimulus sequences, independent of any motor behaviour. In an extended version of the task, stimuli are sometimes suspended, which requires the participants to rely on internal sequence representations. Behavioural as well as fMRI studies reveal difficulties during memory-driven but initially not during stimulus-driven serial prediction in early PD: corresponding to findings from motor control (Haslinger et al., 2001; Michely et al.,

2015; Samuel, 1997), these studies suggest a compensatory reliance on lateral PM during the external stimulation but not during memory-driven performance, which is rather accompanied by hypoactivity of the putamen and the SMA (Schönberger et al., 2013; Schönberger, Hagelweide, Pelzer, Fink, & Schubotz, 2015). However, as it has recently been shown, stimulus-driven prediction fails to be compensated in later stages of the disease (Hagelweide et al., 2018)

As already pointed out, sequence learning relies on probabilistic weighting of stimulus-stimulus transitions generating internal models of the sequence. Following from this, a further question is whether PD patients are impaired in probabilistic learning. Studies on probabilistic learning in PD revealed inconsistent results, which might be due to the different strategies with which corresponding tasks can be solved (Kemény et al., 2018; Speekenbrink, Lagnado, Wilkinson, Jahanshahi, & Shanks, 2010). Some studies suggest that PD patients are impaired in classifications tasks such as the Weather Prediction task, which require the prediction of the state of the weather based on a combination of cues (Knowlton, Squire, & Gluck, 1994; Shohamy, Myers, Onlaor, & Gluck, 2004). Moreover, studies provide evidence for a deficient processing of prediction errors in PD. For example, PD patients exhibit impaired reward prediction error signalling in the dorsolateral striatum (Schonberg et al., 2010). Moreover, Galea, Bestmann, Beigi, Jahanshahi, and Rothwell (2012) showed that during action reprogramming, i.e., switching from an expected to an unexpected response, PD patients' impaired responses to prediction errors increased in contexts of generally high compared to low predictable sequence occurrence. As the authors suggest, low dopamine levels may result in a low confidence about incoming sensory information and a high reliance on top-down predictions. This finding appears inconsistent with an impaired serial prediction in PD, which parallels the inconclusive results regarding a possible impairment of stability of working memory representations.

In summary, further evidence is required to clarify (1) the relationship between stability and flexibility in the specific scope of predictive processing, (2) how dopamine contributes to the balance between the two functions, and (3) whether PD patients are impaired in both flexible updating and stabilisation of prediction in response to prediction errors.

2. Research Questions

The studies composing the present thesis aimed to clarify the neurocognitive mechanisms of flexibility and stability of prediction. Specifically, functional and structural MRI experiments were conducted to investigate the relationship between the two functions, and to assess a putative contribution of dopamine to the flexibility-stability trade-off as well as a corresponding impairment in PD patients. In this context, a distinction was made between immediate flexible and stable *responses* to prediction errors and longer-term flexible and stable *states* depending on current environmental challenges.

Within three studies, I posed the following questions:

1. Which neural mechanisms mediate the selection of flexible and stable responses to prediction errors on the one hand, and transitions between flexible and stable predictive states on the other hand?
2. Do PD patients exhibit difficulties in flexible and stable responding to prediction errors and do potential deficits correspond with structural alterations in specific dopaminergic and cortical regions?
3. Are neural learning signals that lead to the adoption of flexible and stable states impaired in PD patients?

As a first step towards answering these questions, a task was established to assess flexibility and stability of prediction that healthy participants in the same age range as PD patients should be able to perform. In a first design of the task, participants were required to either detect or ignore relevant and irrelevant digit changes in a randomly generated five-digit sequence, respectively. As it turned out in a pilot study, the task was too difficult for the elderly participants: because the detection of changes required fast learning of the digit sequence, behavioural measures of stability and flexibility were confounded with the participants' general

working memory capacity (for results of a study using a similar paradigm in younger healthy participants, see Trempler, Kaltwasser, Fink, & Schubotz, 2018). Therefore, a modified version of the paradigm was developed: instead of the randomly five-digit sequence, participants were now presented with an overlearned digit sequence in either ascending (1 – 2 – 3 – 4) or descending (4 – 3 – 2 – 1) order. Directional changes (*switches*, hereafter) occurred at random ordinal positions within the initial sequence and had to be acknowledged by a button press. Switch detection served as a measure of flexibility. In addition, single digits were omitted occasionally at variable positions without a temporal gap (*drifts*, hereafter). Participants were instructed to ignore these omissions serving as a measure of stability. The proportion of switches and drifts changed across the experiment to investigate not only the participants' responses to these critical events, but also the adaptation to different environments requiring either an increased flexibility or an increased stability.

In **Study I**, I focused on the frontostriatal contribution to the interplay of stability and flexibility of prediction in young healthy participants using fMRI. I hypothesised that flexible and stable responses to relevant and irrelevant prediction errors, respectively, would recruit different neural cortical areas, yet both would activate the striatum, which mediates bottom-up gating of prediction errors. Moreover, I assessed the potential dopaminergic involvement in the adaptation to different environments depending on previous performance. Based on the findings of Study I, I conducted **Study II** on potential deficient flexible and stable responses to prediction errors in PD patients. I examined whether such deficits correlated with structural changes in those brain regions that were activated in response to prediction errors in Study I. Finally, in **Study III** I focused on deficits of PD patients in probabilistic learning from prediction errors to adopt flexible or stable states. The probability of relevant and irrelevant unexpected events should predict the participants' error rate, as well as the blood-oxygen-level dependent (BOLD) amplitude in those brain areas that were targeted by Study I and Study II.

3. Research Articles

3.1 Study I: Frontostriatal Contribution to the Interplay of Flexibility and Stability in Serial Prediction

Running title: Flexibility and Stability in Serial Prediction

Ima Trempler, Anne-Marike Schiffer, Nadiya El-Sourani, Christiane Ahlheim,
Gereon R. Fink, & Ricarda I. Schubotz (2018)

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Frontostriatal Contribution to the Interplay of Flexibility and Stability in Serial Prediction

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Abstract

■ Surprising events may be relevant or irrelevant for behavior, requiring either flexible adjustment or stabilization of our model of the world and according response strategies. Cognitive flexibility and stability in response to environmental demands have been described as separable cognitive states, associated with activity of striatal and lateral prefrontal regions, respectively. It so far remains unclear, however, whether these two states act in an antagonistic fashion and which neural mechanisms mediate the selection of respective responses, on the one hand, and a transition between these states, on the other. In this study, we tested whether the functional dichotomy between striatal and prefrontal activity applies for the separate functions of updating (in response to changes in the environment, i.e., switches) and shielding (in response to chance occurrences of events violating expectations, i.e., drifts) of current predictions. We measured brain activity using fMRI while 20 healthy participants performed a task that required to serially predict upcoming items. Switches between predictable sequences had to be indicated via button press while sequence omissions (drifts) had to be ignored. We further varied the probability of switches and drifts to assess the neural network supporting the transition between flexible and stable cognitive states as a function of recent performance history in response to environmental demands. Flexible switching between models was associated with activation in medial pFC (BA 9 and BA 10), whereas stable maintenance of the internal model corresponded to activation in the lateral pFC (BA 6 and inferior frontal gyrus). Our findings extend previous studies on the interplay of flexibility and stability, suggesting that different prefrontal regions are activated by different types of prediction errors, dependent on their behavioral requirements. Furthermore, we found that striatal activation in response to switches and drifts was modulated by participants' successful behavior toward these events, suggesting the striatum to be responsible for response selections following unpredicted stimuli. Finally, we observed that the dopaminergic midbrain modulates the transition between different cognitive states, thresholded by participants' individual performance history in response to temporal environmental demands. ■

INTRODUCTION

From changing our way to work when we learn about the opening of a new ring road to sticking to the usual route despite heavy traffic, we constantly rely on balancing between the adaptation of expectations to persistent changes and the maintenance of successful strategies despite temporary distraction.

In sensory processing, this interplay between flexibility and stability is explained by a fundamental characteristic of brain function: Perception is an inherently predictive process, which relies on the comparison between predicted and actual sensory input (for a review, see Clark, 2013). Predicted input contains little information beyond the confirmation of our internal model of the world and therefore receives little attention. Improbable input, in contrast, violates predictions and is informative as it may require flexible adaptation of the internal model.

However, violations of prediction could either signal the need for adapting to lasting changes of the environment, that is, switches, or be caused by temporary chance occurrences of uncommon events (drifts, hereafter). Experiencing violations of predictions may therefore either require flexible updating or stabilization of current predictions. This delicate balance in response selection has been suggested to depend on optimal dopamine (DA) levels in frontostriatal circuits: Whereas DA in the lateral pFC is essential for stabilizing working memory representations, DA in the striatum has been associated with flexible updating of working memory (for a review, see Cools & D'Esposito, 2011). However, the specific mechanisms and functional anatomy of stimulus selection and processing of relevant and irrelevant prediction errors to date remain poorly understood.

Recent work suggests that phasic DA release in the dopaminergic midbrain, that is, the substantia nigra (SN) and ventral tegmental area, is triggered in response to salient, unpredicted external stimuli independent of associated reward (Schiffer, Waszak, & Yeung, 2015; Redgrave & Gurney, 2006; Schultz & Dickinson, 2000) and thus constitutes a global teaching signal (D'Esposito & Postle,

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2015). In contrast, DA receptor activation in the striatum, one of the main target structures of SN and ventral tegmental area projections, has been linked to flexible updating of relevant information in working memory (e.g., D'Ardenne et al., 2012; Cools, Sheridan, Jacobs, & D'Esposito, 2007; Bilder, Volavka, Lachman, & Grace, 2004; Frank, Loughry, & O'Reilly, 2001). This has been described as a selective gating process (Chatham & Badre, 2015; Badre, 2012), in which input gating of the striatum ensures that behaviorally relevant information enters cortical working memory. The first questions of this study therefore is whether striatal activity relates exclusively to flexible updating driven by relevant changes or rather reflects the processing of unpredicted sensory information in general.

Beyond this moment-by-moment perspective, the volatility, that is, the rate of change in the environment, plays a role in regulating the interplay between flexible and stable states. Temporary extended increases in prediction errors indicate volatile environments and lead to a fast adjustment of internal predictions and behavior (Jiang, Beck, Heller, & Egner, 2015; Chumbley et al., 2014; Schiffer, Ahlheim, Wurm, & Schubotz, 2012; Friston, Daunizeau, & Kiebel, 2009; Behrens, Woolrich, Walton, & Rushworth, 2007). Recent studies provide evidence that longer timescale tonic DA modulates the extent to which prior action outcome biases phasic DA release and hence future action selection (Yu, FitzGerald, & Friston, 2013; Humphries, Khamassi, & Gurney, 2012; Beeler, Daw, Frazier, & Zhuang, 2010). This idea has been formalized in the dual-state theory of working memory, according to which representations in pFC are regulated by so-called attractor networks (Durstewitz & Seamans, 2008; Durstewitz, Seamans, & Sejnowski, 2000). These can assume either high- or low-energy barriers, corresponding to a shielding or a destabilization of current working memory representations, respectively. The adjustment of each of the two states relies on tonic DA release in the dopaminergic midbrain, driven by the interplay of previous event predictability and the history of behavioral outcomes. This leads to the hypothesis that the failure to flexibly adapt in volatile environments would lead to increased DA levels thereby promoting transition into a flexible cognitive state. Conversely, the failure to ignore drifts and to maintain stable responding in stable environments should be accompanied by decreased DA activity, thereby promoting transition into a more stable state. Whereas the first question of this study thus pertains to the immediate response to different types of prediction errors (i.e., flexible switching or stable maintenance), the second question is whether these responses are modulated by cognitive states pertaining to recent performance history resulting from different levels of volatility.

We employed fMRI while participants performed a task that required monitoring of a digit sequence for structure-violating items. Switches between predictable sequences had to be indicated via button press (cognitive flexibility), whereas sequence omissions (drifts) had to be ignored (cognitive stability). Switch and drift probabilities varied across the experiment. Implementing switches and drifts in the same design allowed us to use correlational analysis on the rate of correctly detected switches and ignored drifts to show that cognitive flexibility and stability are functionally independent (Cools & D'Esposito, 2011). This way, we could further test our hypothesis that model updating and stabilization as functionally independent processes would recruit different cortical regions: Model update and retrieval from episodic memory was expected to be reflected in activity of medial prefrontal areas and the hippocampus (Schlichting & Preston, 2015; Preston & Eichenbaum, 2013). In contrast, stabilization of prediction was hypothesized to be accompanied by premotor and lateral pFC activation (Cohen, Braver, & Brown, 2002; Miller & Cohen, 2001), whereby either dorsal or ventral activation would reflect the way a model content is stored in working memory, that is, spatially or verbally, respectively (Rottschy et al., 2012). With regard to the role of the striatum in immediate response selection, we hypothesized caudate activity in response to both switches and drifts (Schiffer et al., 2012). Crucially, we expected the degree of activation increase to be correlated with the ability to discriminate between both events, showing that the striatum is related to selecting correct responses toward different types of prediction errors (Chatham & Badre, 2015; Badre, 2012). Finally, to test the idea that the dopaminergic midbrain is involved in the transition between cognitive states (Humphries et al., 2012; Durstewitz & Seamans, 2008), we measured adaptation of flexible and stable states as determined by previous performance within time windows that were individually fitted by levels of volatility predicting participants' behavioral data.

METHODS

Participants

Twenty-two right-handed healthy participants (16 women; 23.26 ± 2.19 years old, range = 19–27 years) with normal or corrected-to-normal vision participated in the study. None of them reported a history of medical, neurological, or psychiatric disorders or substance abuse. The study protocol was conducted in accordance with ethical standards of the Declaration of Helsinki and approved by the local ethics committee of the University of Münster. Each participant submitted a signed informed consent notification and received reimbursement or course credits for their participation afterwards. For further assessment, participants were given the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995). Two participants were excluded (because of pressing the wrong response button and an incidental finding of brain abnormality). Thus, a total of 20 participants (15 women; 23.57 ± 2.60 years old, range = 19–27) were included in the analysis.

Task

Participants were presented with two different digit sequences, which allowed them to generate an internal model predicting forthcoming input (ascending model: 1–2–3–4, descending model: 4–3–2–1). Digits continuously followed one another and were presented on the screen for 900 msec, separated by an ISI of 100 msec (Figure 1). Sequences repeated constantly to enable the participants to predict the regular sequence. Occasionally, switches between the models, that is, directional changes, occurred at a random position within the current sequence. In addition, single digits were omitted sometimes at variable positions without experiencing a temporal gap (drifts, hereafter). Derived from signal detection theory measures, the participant's task was to indicate a switch from one model to the other by button press (switch detection) but to ignore the sequential omissions (drift rejection). They had to respond as fast and accurately as possible and received individual performance feedback in three breaks of 14 sec every four blocks.

The task consisted of 12 blocks with an average number of 160 trials (SD = 6.82) in a full-factorial 2 (Probability: high vs. low) × 2 (Event: switch vs. drift) design. This means that blocks either had a high or low probability of switches, paired with a high or low probability of drifts. Transitions between block types resulting from factor combination were balanced across the entire session. Event probabilities were individually staircased before the scanner session and probabilities for switches and drifts always adapted to the same extent. Here, participants performed 10 blocks with 80 trials each, starting with an event frequency of 17.5%. For a block performance higher (lower) than 75%, event frequency increased (decreased) with a rate of 2.5% in the subsequent block. The maximum reached frequency of events across the entire staircase session (M = 24.5%, SD = 1.7) served as maximum event frequency in unmixed blocks of the main experiment, in which switches and drifts occurred with the same frequency. Minimum event frequency was set to approximately one third of the respective individual maximum frequency. In mixed (i.e., high-switch and low-drift or vice versa) blocks, the difference between maximum frequency for both event types and minimum frequency for one event type served as maximum event frequency, whereas minimum frequency remained equal. In this way, difficulty level in terms of overall probability of events was kept constant across the experiment (with the exception of unmixed low-frequency blocks).

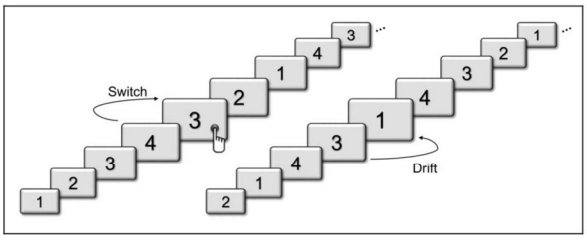

Figure 1. Schematic diagram of the task. Stimuli of a simple four-digit sequence continuously followed each other with a frequency of 1 Hz. Participants had to indicate a change in the direction of a sequence (switch), as displayed in the upper row, via button press. At the same time, they had to ignore the omission of a single digit (drift), as displayed in the lower row. The probability of occurrence of each respective type of sequence violation changed from block to block.

Stimulus presentation per block was pseudorandomized by using the stochastic universal sampling method (Baker, 1987). This method ensured a balanced distribution of event types across the block so that the observed event frequencies were in line with the expected frequencies.

fMRI Data Acquisition

Whole-brain imaging data were collected on a 3-T Siemens Magnetom Prisma MR tomograph (Siemens, Erlangen, Germany) using a 20-channel head coil. To minimize head motion, the head was tightly fixated with cushions. Functional images were acquired using a gradient T2*-weighted single-shot EPI sequence sensitive to BOLD contrast (64 × 64 data acquisition matrix, 192 mm field of view, 90° flip angle, repetition time = 2000 msec, echo time = 30 msec). Each volume consisted of 30 adjacent axial slices with a slice thickness of 4 mm and a gap of 1 mm, resulting in a voxel size of 3 × 3 × 5 mm. Images were acquired in ascending order along the AC–PC plane to provide a whole-brain coverage. Structural data were acquired for each participant using a standard Siemens 3-D T1-weighted MPRAGE sequence for detailed reconstruction of anatomy with isotropic voxels (1 × 1 × 1 mm) in a 256-mm field of view (256 × 256 matrix, 192 slices, repetition time = 2130, echo time = 2.28). Stimuli were projected on a screen that was positioned behind the participant's head. They were presented in the center of the field of vision by a video projector, and participants viewed the screen by a 45° mirror, which was fixated on the top of the head coil and adjusted for each participant to provide a good view of the entire screen.

Behavioral Data Analysis

Performance on the task was defined by hits (correct detection of switches), correct rejections of drifts, and, correspondingly, switch misses and false alarms at drifts. Discrimination index (P_r; probability of recognition of switches and drifts, i.e., (hits + 0.5/number of switches + 1) − (false alarms + 0.5/number of drifts + 1)) and bias index (B_r; response probability in an uncertain state, i.e., (false alarms + 0.5/number of drifts + 1)/(1 − P_r)) were calculated (Snodgrass & Corwin, 1988). Hit and correct rejection rate and RTs at hits and false alarms were compared by Student's paired t tests. To assess the relationship between hits and correct rejections, we calculated Pearson's correlation coefficient. To show that there was no relationship between the two measures, we additionally calculated

the attenuation adjusted correlation coefficient, which provides an estimate of the strength of a correlation assuming no measurement error. For this purpose, the correlation of the two variables (r_{xy}) was divided by the square root of their multiplied reliabilities (r_{xx} and r_{yy}; see Spearman, 1904). Here, we calculated split-half reliability, that is, Pearson's correlation coefficients between scores of the two halves of the test for both switch detection and drift rejection. If not stated otherwise, significance tests were performed at $\alpha = .05$, two-sided.

fMRI Data Analysis

fMRI Data Preprocessing

Brain image preprocessing and basic statistical analyses were conducted using LIPSIA software package, version 3.0 (Lohmann et al., 2001). As a first step, spikes in time series were corrected by interpolating them with adjacent time points. To correct for temporal offsets between the slices acquired in one scan, a cubic-spline interpolation was used. Additionally, individual functional magnetic resonance (EPI) images were motion-corrected with the first time-step as reference and six degrees of freedom (three rotational, three translational). Then, the average across all time points of this corrected data was used as reference scan for a second pass of motion correction. Motion correction estimates were inspected visually. A rigid linear registration with six degrees of freedom (three rotational, three translational) was performed to align the functional data slices with a 3-D stereotactic coordinate reference system. Rotational and translational parameters were acquired by coregistration of the first EPI magnetic resonance time step to the individual 3-D MPRAGE reference set. Anatomical datasets were normalized to the ICBM/MNI space by linear scaling. The resulting parameters were then used to transform all functional slices employing a trilinear interpolation. Resulting data had a spatial resolution of $3 \times 3 \times 3$ mm ($27\ mm^3$). Normalized functional images were spatially smoothed with a Gaussian kernel of 6 mm FWHM. A temporal high-pass filter of 1/128 HZ was applied to the data to remove low-frequency noise such as scanner drift. To prevent effects of physiological noise in the midbrain (e.g., pulsation artifacts), the component-based noise correction method (CompCor) was applied to the epoch-related analysis (see below) to reduce the temporal standard deviation of the BOLD signal (Behzadi, Restom, Liau, & Liu, 2007). During this application, the first few principal components of regions with high temporal variance are obtained and factored out via linear regression.

Design Specification

Statistical analysis was based on a least squares estimation using the general linear model (GLM) for serially autocorrelated observations (Friston et al., 1995; Worsley & Friston, 1995). Event- and epoch-related analyses were conducted in separated GLMs: The event-related analysis focused on BOLD signal changes during single trials to assess prediction error processing, whereas the epoch-related analysis included entire periods where either unstable or inflexible states were adjusted. Single trials and epochs were modeled as delta and box-car functions, respectively, and convolved with a canonical hemodynamic response function. In both models, the subject-specific six rigid body transformations obtained from residual motion correction were included as further covariates of no interest.

Flexible and stable responses to prediction errors. To analyze common and differential neural signatures of responses to both types of prediction errors, that is, switches and drifts, we calculated first-level regression models containing the specific events with an amplitude of one, that is, standard digits (STD), switches (SW), drifts (DR), and breaks of 14 sec. Only correct responses were analyzed, which comprised the full duration of the presented trial (1 sec). Because of the high event density, only events at a distance of at least two trials to the next modeled event were included. Furthermore, the GLM contained a separate regressor subsuming all button presses, that is, hits and false alarms. This controlled for motor response activity during switch versus drift processing inasmuch as only the first event type required a motor response whereas the second did not. This way, the switch effect, which would otherwise have concealed the drift effect, could be leveled. To provide further verification for the existence of the two networks, we calculated an additional GLM containing the specific error types, that is, switch misses and false alarms at drifts, which were contrasted with hits and correct rejections, respectively (for a detailed analysis, see Supplementary Material; https//figshare.com/s/e0bfd1e93bf80e57f6f0). Contrast images, that is, beta value estimates of the raw score differences between specified conditions, were generated for each participant.

Thresholds for flexible and stable state transitions driven by recent performance history. We expected midbrain dopaminergic activity to correspond to the experience-driven transitions to flexible and stable states. We therefore conducted an epoch-related analysis to assess neural activity emerging from performance history in response to different switch and drift probabilities in the recent past within an individually fitted time window. To estimate the participant-specific length of the time window, across which switch and drift probability were accumulated, logistic regressions were conducted for each subject. The regression model estimated the degree to which window length-based Shannon's surprise $I(x_i)$ for switches and drifts (Shannon, 1948) could predict (variance in) response accuracy for both types of events (hits and correct rejections).

Shannon's surprise can be used as a measure of anticipation success because it is based on the frequency of an

event $p(x_i)$ normalized by the sum of all event types over a defined window of recent events (see Equation 1).

Calculation of event probability:

$$p(x_i) = \frac{n(x_i) + 1}{\sum x_t + 1} \quad (1)$$

The surprise $I(x_i)$ of each event given by the negative logarithm of this probability quantifies the amount of information provided by the current stimulus dependent on the history of previous stimuli (see Equation 2).

Calculation of Shannon's surprise:

$$I(x_i) = -\ln p(x_i) \quad (2)$$

We conducted these regressions for sliding windows with a minimum length of 20 trials and a trial-wise increase up to the mean predefined block length of 160 trials. Subsequently, the respective window length that provided the minimum deviance, that is, the difference between the log-likelihood of the fitted model and the maximum possible likelihood, was chosen as subject-specific epoch duration in the fMRI analysis. A paired t test between these individually obtained deviance values and deviances of models determining surprise as a function of mean block length of 160 trials was calculated. This was done to validate the significance of fit improvement by the individual sliding window length.

On the basis of the derived window length, we then calculated the difference of error type per window (number of misses − number of false alarms) to reflect the bias of prior performance. High values correspond to rare responding, resulting in a high miss as well as a high correct rejection rate. In contrast, low values reflect a bias toward frequent responses resulting in a higher hit, but also higher false alarm rate. The GLM underlying the fMRI analysis included the parametric effect of this bias on neural activity within the respective subsequent period as the main regressor of interest. We included mean surprise at switches and at drifts per window as nuisance regressors in the GLM. This ensured that the effects of the previous error bias on activity within a current period could not be attributed to the probability of critical events within this period.

Group Analysis

To obtain group statistics, the resulting contrast images of all participants were entered into a second-level random-effects analysis using a one-sample t test across participants to test for significant deviation from zero. To assess differences between switch and drift processing, hits at switches were contrasted with drift rejections (SW > DR) and vice versa (DR > SW) in the GLM, which controlled for motor responses. Furthermore, we calculated the block-wise parametric effects for the error bias (BIAS). We corrected for multiple comparisons across all voxels using the threshold-free cluster enhancement (TFCE) method (Smith & Nichols, 2009). The significance level for whole-brain activations was set to $p < .05$ TFCE-corrected. Default TFCE parameters $H = 2$ and $E = 0.5$ were used.

ROI Analysis

To test for a specific role of the caudate nucleus in global prediction error processing, we assessed overlapping effects of switch- and drift-elicited activity using small volume correction (SVC) on the additive conjunction analysis [(SW > STD) ∩ (DR > STD)] at $p < .05$ TFCE-SVC-corrected. Anatomical masks of left and right caudate were defined based on the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Beta values of these ROIs, that is, left and right caudate, were extracted and correlated with P_r index. Alpha level was Bonferroni-corrected.

To investigate effects of error bias on dopaminergic midbrain activity, left and right SN ROIs were used for SVC. These ROIs were derived from the probabilistic atlas of the BG (ATAG; Keuken et al., 2014).

RESULTS

Behavioral Results

To assess participants' performance and response tendency on the task, we used signal detection theory measures mean discrimination index (P_r) and bias index (B_r; Snodgrass & Corwin, 1988). Mean P_r index was $M = 0.78$ ($SD = 0.14$), and mean B_r index was $M = 0.35$ ($SD = 0.27$). This bias toward conservative response thresholds across the whole group also translated into a significant difference between hits at switches $M = 84.31\%$ ($SD = 12.60$) and correct rejections at drifts ($M = 94.26\%$, $SD = 5.73$), $t(19) = 3.243$, $p = .004$. Mean RT at hits ($M = 953$ msec, $SD = 177$) did not differ significantly from mean RT at false alarms ($M = 890$ msec, $SD = 186$), $t(19) = 1.569$, $p = .133$. As we expected the B_r value to reflect trait impulsivity of the participants, we conducted a correlational analysis on B_r score with BIS-11 total score that, however, did not reveal a significant association ($r = .15$, $p = .36$).

To test our hypothesis that cognitive flexibility and cognitive stability would be functionally independent, we performed a correlation analysis between the rate of hits (detected switches) and the rate of correct rejections (ignored drifts). This analysis revealed no significant relationship between the two variables ($r = .025$, $a(r) = 0.16$, $p = .918$; Figure 2A), despite attenuation correction.

Individual drift and switch surprise rates were modeled on the basis of an individually fitted window of recent events for each subject. Mean trial number of the sliding window was $M = 40.76$ ($SD = 36.81$). The individually optimized logistic regressions fitted the data significantly better than those that were based on the mean block length of 160 trials ($t(19) = 7.31$, $p < .001$). Although participants showed an anticipation effect of drift processing,

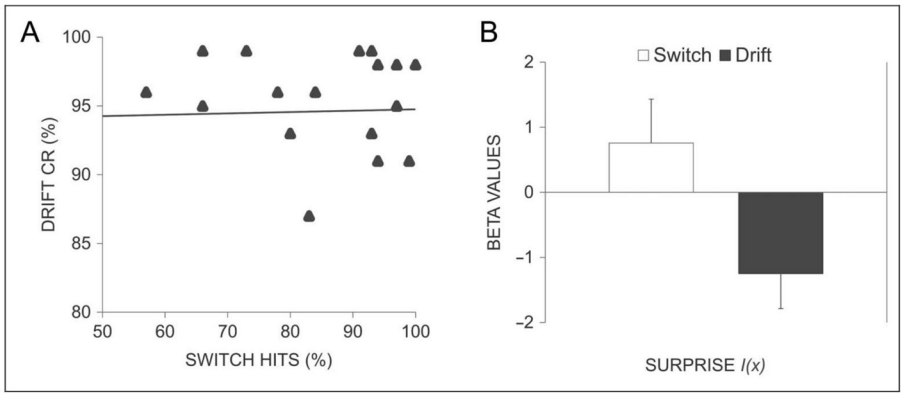

Figure 2. (A) Scatter plot of nonsignificant correlation between performance on switches and drifts, measured as percent correct responses toward switches (hits) and percentage of correctly withheld responses toward drifts (correct rejections, CR). (B) Beta values signifying the relationship between error rate on switches and drifts and switch and drift surprise $I(x)$. Switch surprise was positively correlated with correct responses; a lower drift surprise, (i.e., anticipation of drifts) was accompanied by a lower error rate.

participants did not adapt to environments with a high amount of switches: High surprise of drifts was related to a high chance of making an error, whereas high switch surprise was accompanied by lower error chance (Figure 2B).

Imaging Results

To assess differential cortical processing of switches and drifts, we contrasted BOLD signal changes between successfully detected switches and successfully rejected drifts and vice versa. We expected to find medial pFC (MPFC) and hippocampus in response to switches as a sign of updating predictions from long-term memory. In contrast, we hypothesized drift-specific activation in lateral prefrontal and premotor regions reflecting heightened demands on model stabilization.

Differential Cortical Networks for Flexible and Stable Responses

The switch-specific contrast estimate (SW > DR) revealed prefrontal activation of bilateral MPFC, including BA 9 and BA 10, extending into dorsal ACC, as well as of the right hippocampus (Figure 3A). The reverse contrast, that is, successful rejection of drifts (DR > SW), yielded BOLD signal changes in bilateral SMA and premotor cortex, portions of the triangular and opercular parts of the inferior frontal gyrus (IFG), and anterior insula (Figure 3B; Table 1). Results of an alternative GLM excluding motor responses as regressor of no interest and of the GLM, in which error types were contrasted with correct responses, are included in the Supplementary Material.

Striatal Activity toward Prediction Errors Associated with Task Performance

To assess BOLD signal changes during the processing of prediction errors, an additive conjunction of the contrasts switch versus standard digit and drift versus standard digit (SW > STD) ∩ (DR > STD) was computed. This contrast revealed the expected caudate nucleus activation at a threshold of $p < .05$, TFCE-corrected (R: $x = 8$, $y = 18$, $z = -2$; L: $x = -10$, $y = 18$, $z = -2$).

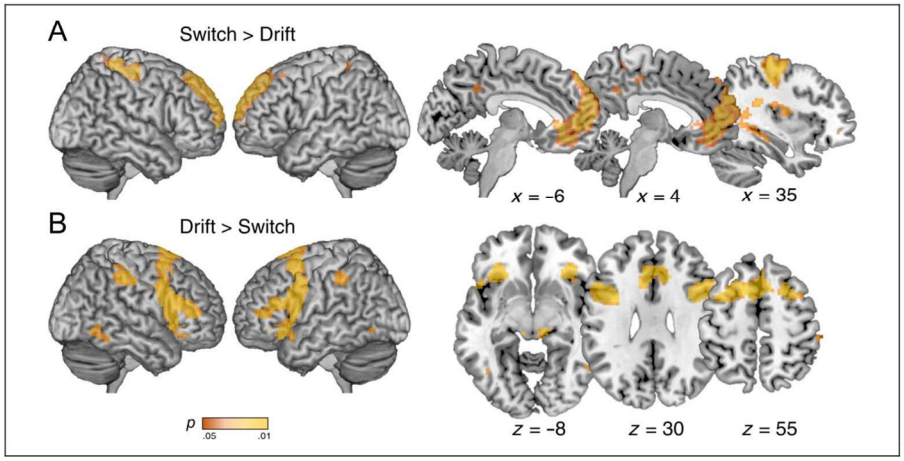

Figure 3. fMRI main effects at $p < .05$, whole-brain TFCE-corrected. (A) There was statistically significantly increased activation during switches in medial prefrontal and cingulate areas and in the right hippocampus. (B) Drifts elicited significant activation of BA 6 extending into IFG and anterior insula.

Table 1. fMRI Activations

Region	Side	BA	Cluster Size	MNI Coordinates			p^a
				x	*y*	*z*	
Switch > Drift							
Superior frontal gyrus	L	9	432	−21	57	33	10^{-4}
Anterior cingulate cortex	L	10	67986	−6	48	0	10^{-3}
Postcentral gyrus[b]	R	3	65745	21	−36	63	10^{-3}
Cuneus	R	18	3024	−6	−93	27	10^{-3}
Inferior temporal gyrus	R	20	135	54	−27	−24	10^{-2}
Drift > Switch							
Frontal inferior gyrus	R	48	1377	39	12	23	10^{-4}
Supplementary motor area	R/L	32	79002	0	15	48	10^{-3}
Supramarginal gyrus	R	40	999	54	−33	42	10^{-3}
Premotor cortex	L	6	81	−15	3	75	10^{-2}
Inferior parietal lobule	L	21	540	−48	−36	42	10^{-2}
Inferior temporal gyrus	R	20	189	51	−48	−15	10^{-2}
Angular gyrus	R	7	621	30	−57	45	10^{-2}

R = right; L = left; *x*, *y*, *z* = MNI coordinates of peak voxel activation.

[a]TFCE-corrected for multiple comparison.

[b]Extending into bilateral posterior cingulate cortex and right hippocampus.

Parameter estimates of right caudate activity significantly correlated with P_r ($r = .536, p = .007$, one-tailed) but not with B_r index ($r = .275, p = .121$, one-tailed) at an adjusted alpha level of .025. Left caudate activity was not related to either of the two measures (P_r: $r = .33$, $p = .075$, one-tailed; B_r: $r = .24$, $p = .153$, one-tailed; Figure 4). This correlation of striatal activation with P_r value suggests that prediction error processing in the striatum is associated with the ability to make the correct response toward surprising stimuli. This finding stands in contrast to the proposal that the striatum is limited to signaling any deviation from predictions per se.

SN Activity Reflects Adaptation of Flexible and Stable State Transitions

The epoch-based analysis revealed that activity in the left SN ($x = -12, y = -21, z = -18$) significantly correlated

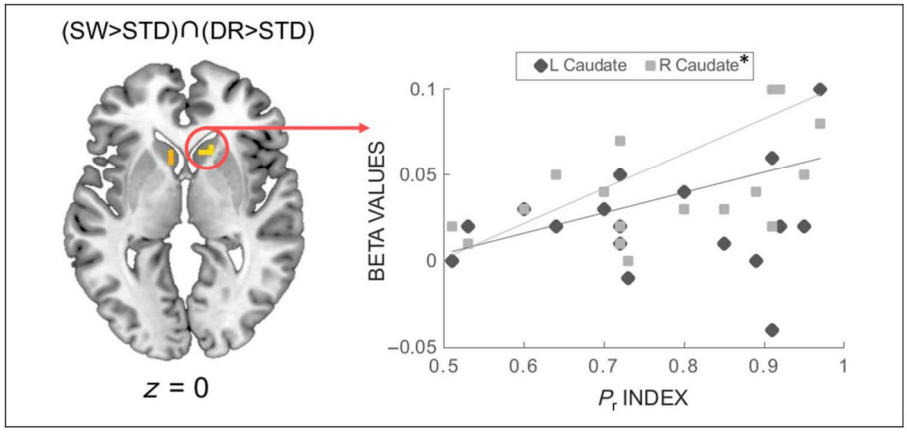

Figure 4. Results of caudate ROI analysis, reported at $p < .05$, TFCE-SVE-corrected. In the caudate ROIs, there was higher activation for both switches and drifts compared with standard digits. Activation during these critical events scaled with participants' ability to discriminate between events as indicated by behavioral P_r index.

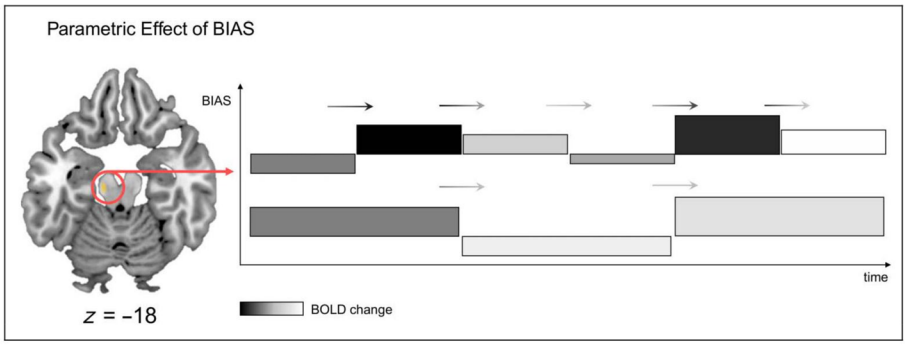

Figure 5. Parametric effect of previous error bias on current epoch-related processing revealed activation of left SN, reported at $p < .05$, TFCE-SVE-corrected. Schematic diagram depicts parametric analysis for two example participants: BOLD signal change in SN (reflected in bar color) depends on the error bias in the respective previous epoch (indicated by bar height and arrow). Bar width illustrates that epoch lengths were individually fitted.

(at $p < .05$, TFCE-SVC-corrected) with a bias toward a higher miss versus false alarm rate in the previous time window with an individually fitted length based on levels of volatility predicting participants' behavioral performance (Figure 5). The whole-brain effect of this analysis is provided in the Supplementary Material.

This finding suggests that activation of the left SN is responsible for adapting global thresholds for cognitive state transitions depending on recent performance history in response to local environmental demands.

In summary, we show that updating in response to behaviorally relevant switches and stabilization in face of irrelevant drifts activated separate cortical networks. A network consisting of MPFC and hippocampus was activated by hits at model switches, whereas the requirement of model stabilization, that is, correct rejections, elicited premotor and lateral pFC activation. In contrast, a prediction error signal in the caudate nucleus correlated with participants' ability to select the correct response. Moreover, reactive state adaptation driven by either too stable or too flexible behavior in the recent past was reflected in sustained activity of the dopaminergic midbrain.

DISCUSSION

In this study, we could show that different target regions of dopaminergic projections contribute to separate functions in the processing of unpredicted sensory stimuli. Specifically, responses to relevant and irrelevant prediction errors requiring either flexible updating or stable maintenance of internal models, respectively, take place within different cortical networks, suggesting that both functions act—at least in part—independent from each other. Discrimination of prediction errors in terms of these behavioral requirements rather than a global response probability bias was related to striatal activation increase. Additionally, we found that the dopaminergic midbrain plays a role in performance-history dependent transition thresholds between flexible and stable cognitive states. The failure to ignore drifts was accompanied by decreased SN activity, indicative of decreased DA activity; we propose that this activity decrease promotes transition into a more stable state with a higher emphasis on ignoring upcoming noise. In contrast, the failure to flexibly adapt in volatile environments led to increased SN activity, suggesting transition into a flexible cognitive state, increasing sensitivity toward changes.

Flexible Updating and Stable Maintenance as Functionally Independent Processes

To date, there is no clear evidence whether cognitive flexibility and stability in response to environmental changes are antagonistically related and depend on one common neural network or whether they rely on two separate, that is, neurally distinct and orthogonal mechanisms (e.g., Draheim, Hicks, & Engle, 2016; Hedden & Gabrieli, 2015; Armbruster, Ueltzhöffer, Basten, & Fiebach, 2012; Müller et al., 2007). This lack of knowledge is partly due to different operationalization approaches of the two concepts in terms of different cognitive control subprocesses (Miyake et al., 2000).

Cognitive stability is commonly measured by working memory delay tasks rendering representations distractor-resistant, thus, subsuming processes like active maintenance (Baddeley, 1986), shielding (Goschke & Dreisbach, 2008), and cognitive inhibition (Lavie, 2005). Cognitive flexibility, in contrast, is typically assessed by switching between different task sets, thus requiring maintenance and updating of task rule representations, as well as inhibition of the previously active task set (see Vandierendonck, Liefooghe, & Verbruggen, 2010, for a discussion). As Draheim et al. (2016) pointed out, results regarding the relationship between updating and working memory capacity furthermore depend on the choice of the dependent variable, that is, accuracy and/or RT.

In the current study, we therefore used a novel task in which long-term memory rather than working memory content enabled participants to predict the ongoing course of a sequence. In case of a violation of the current internal model, predictions implicated by this error either had to be stabilized or updated. Thus, in the context of the current study, cognitive stability refers exclusively to

the ability to shield the internal model from temporary violation, whereas flexibility comprises the ability to update the internal model because of permanent changes. If flexibility and stability were two extremes on the same dimension, we would expect that being inflexible leads to missing relevant events while helping to ignore irrelevant changes. At the same time, the ability to detect relevant events would lead to responses toward irrelevant prediction errors. In the present task, participants' performance could be driven by a set motor response threshold as shown in a negative correlation between switch detection and drift rejection. However, we did not find a corresponding relationship between flexible and stable responses, thus providing evidence that cognitive flexibility and stability rely on functionally independent processes. Because of the limited variability in our measure of cognitive stability that might have prevented us from finding a significant correlation between hits at switches and correct rejections of drifts, the finding of a missing relationship needs to be confirmed in future studies using a similar task.

Different Cortical Substrates of Cognitive Flexibility and Stability

Our hypothesis that cognitive flexibility and stability rely on independent processes is substantiated by the differential processing of switches and drifts on the cortical level. As hypothesized, we found a network comprising medial prefrontal regions, that is, BA 9 and BA 10, and the right hippocampal formation in response to correctly detected model switches. This suggests that this network plays a role in the top–down adaptation of working memory representations by retrieval of an alternative predictive model from long-term memory. This finding significantly extends previous studies where mesial BA 9 was found in response to predictable events compared with destabilized predictions (Kühn & Schubotz, 2012). More rostral portions of the MPFC have been implicated in guiding hippocampal encoding and retrieval when new information is integrated into existing knowledge (Schlichting & Preston, 2015; Preston & Eichenbaum, 2013; van Kesteren, Ruiter, Fernández, & Henson, 2012). Our findings suggest that this network provides top–down predictions, which initiate an immediate update of currently valid internal models.

We further hypothesized drift-specific activation of lateral pFC, which would reflect model stabilization (D'Esposito, 2007; Bilder et al., 2004; Cohen et al., 2002; Miller & Cohen, 2001). Either dorsal or ventral prefrontal portions were expected to be activated, depending on whether model content was stored visuospatially, that is, by circular sequence representation, or phonologically (see Rottschy et al., 2012, for a meta-analysis). Furthermore, previous studies have shown that the prediction of sequences primarily activates premotor and not necessarily prefrontal regions (Schubotz, 2007; Schubotz & von Cramon, 2003). Even increasing the demand on mnemonic representation of the sequence by occluding some of its stimuli did not recruit prefrontal areas but rather further boosted premotor activity (Schönberger, Hagelweide, Pelzer, Fink, & Schubotz, 2015). Thus, we expected the premotor network to be activated in response to irrelevant prediction errors. In line with our hypotheses, we observed that mental sequence completion and stabilization in case of drifts activated a network comprising SMA, premotor cortex, and portions of the IFG extending along the operculum into anterior insula. Because the common task strategy was subvocalization of the digit sequence, activation of IFG presumably reflects heightened verbal working memory load because of sequential interruptions (Fegen, Buchsbaum, & D'Esposito 2015; Shergill et al., 2002). Our results thus further substantiate that a network comprising not only lateral prefrontal but also premotor regions plays a basic role in the stabilization of predictive internal models that are stored in working memory.

Recognition of Prediction Error Types in the Striatum

Although the behavioral consequences of different types of prediction errors requiring updating or shielding of predictions are processed in different neural networks, our study further provides evidence that all types of surprising events are captured by the same (pre-) attention control system, presumably gated through the striatum. A number of recent studies suggest that the striatum is responsible for flexible updating and adaptation of cortical representations (e.g., Stelzel, Fiebach, Cools, Tafazoli, & D'Esposito, 2013; Cools et al., 2007; Dreisbach & Goschke, 2004). Moreover, there is evidence for a basic stimulus selection function of the striatum when faced with unpredicted sensory input (e.g., den Ouden, Danizeau, Roiser, Friston, & Stephan, 2010; Corlett et al., 2004; O'Doherty et al., 2004; Seymour et al., 2004).

In this study, we observed that caudate activity is related to selecting the correct response following prediction errors rather than being driven by a global response probability bias. This suggests that specific behavioral implications of both event types have been or are recognized at this processing stage. This novel finding extends the proposed input gating function to control cognitive and motor representations in the pFC (Chatham & Badre, 2015; Badre, 2012; Cools, 2011). Our data thus integrate the above-mentioned findings, suggesting that flexible stimulus processing in the striatum might comprise a selection process, which can entail adaptation, stabilization, or building of internal models.

Adaptation of Flexible and Stable States in the SN

Our results support the hypothesis that activity in the SN is associated with the transition between states of

cognitive flexibility and cognitive stability, driven by participants' performance in response to recent environmental demands. This finding delivers evidence in favor of recent computational models (Durstewitz & Seamans, 2008), which propose a dopaminergic modulation of cognitive states: A D1 receptor dominated state is associated with active maintenance, whereas DA action on D2 receptors promotes flexibility of the system. Furthermore, it has been proposed that tonic DA release balances transitions between different states by modulating the degree to which prior learning biases action selection (Humphries et al. 2012). The adjustment of each of the two states might thus be realized by presynaptic effects of tonic DA release: DA released in this manner acts as an inhibitory feedback signal and changes responsivity of the DA system in such a way as phasic responses in the dopaminergic midbrain become curtailed (O'Reilly & Frank, 2006; Schmitz, Benoit-Marand, Gonon, & Sulzer, 2003; Grace, 1991). Therefore, in this study, we associate the model of prefrontal function proposed by Durstewitz et al. (2000) with activation in the midbrain as a source of dopaminergic activity in pFC. We are the first to show that the disposition toward (too) stable or (too) flexible states differs not only between individuals but that these states also vary intraindividually dependent on the recent performance history in response to environmental demands.

Conclusion

Taken together, our data provide evidence that flexible and stable responses in short-term prediction error processing correspond to functionally independent functions but share a common neural substrate in the striatum, responsible for stimulus discrimination and corresponding response decisions. MPFC is associated with model update, whereas lateral pFC stabilizes working memory when faced with distraction. Furthermore, the adaptation of different cognitive states, resulting from performance history, is modulated by SN activation, emphasizing the likely role of tonic DA in setting a threshold for corresponding state transitions. Future studies can build on these findings, especially as they might shed new light on DA-related diseases, for example, Parkinson disease, in which a deficient interplay of flexibility and stability may contribute to the phenotype.

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Supplementary Material

Title: Frontostriatal Contribution to the Interplay of Flexibility and Stability in Serial Prediction

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1. Supplementary Behavioral Results

In order to assess the relationship between switch hits and correct rejections at drifts in dependence of their respective in-block occurrence probabilities, we calculated a repeated measures analysis of variance (RM-ANOVA) with the factors RESPONSE (hit, correct rejection) and PROBABILITY (high, low).
In case of an antagonistic relationship of both measures, the following effects would have been expected: As blocks in which switches and drifts occur with high and low probability, respectively, imply demands on cognitive flexibility, a high switch hit rate would be accompanied by a low rate of correct rejections. In contrast, in stable contexts with a high frequency of drifts but few switches a high amount of correctly rejected drifts would be associated with misses at switches. However, we did not find a significant interaction effect between the two measures ($F(1,19) = 1.056$, $p = .317$; Figure S1) providing further evidence that cognitive stability and flexibility are at least partially independent from each other.

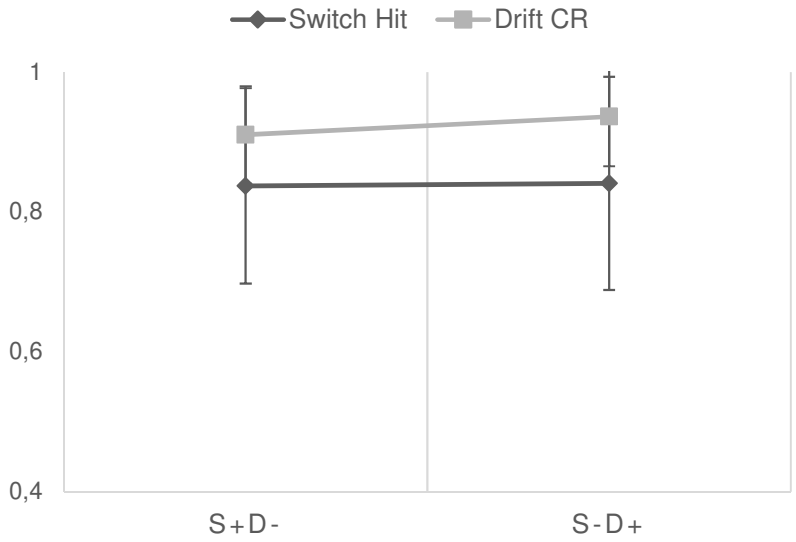

Figure S1. *No interaction effect between type of correct response (hit, correct rejection (CR)) and in-block occurrence probability (high (+), low (-)) of the corresponding events (switch (S), drift (D)) was observed. Error bars represent standard deviation.*

2. Supplementary fMRI Results

Results of a GLM without motor responses as regressor of no interest are displayed in Figure S2. As expected, the corresponding contrast estimate (SW>DR) revealed a strong activation of the motor network due to motor responses at switches. This shows that we successfully controlled for motor responses in our main contrast.

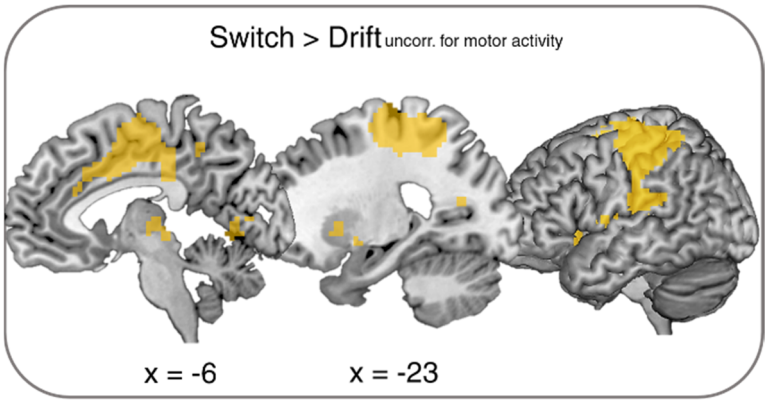

Figure S2. *fMRI main effects at p < .0001, whole-brain TFCE-corrected. When the GLM did not correct for motor responses by using an additional regressor subsuming all button presses, there was increased activation during switches in motor areas, i.e., primary motor and somatosensory cortex, cingulate motor areas, and putamen.*

We furthermore calculated a GLM which contained regressors for the specific error types, i.e., misses and false alarms. Because of different numbers of observations, we matched the number of hits and correct rejections per first-level regression model with the number of misses and false alarms, respectively. Results are reported at the level of $p < .001$ uncorrected, as no activation survived correction for multiple multiple comparison. Both contrasts (Hit > Miss as well as Correct Rejection > False Alarm) revealed activation of corresponding networks comparable to those yielded by contrast estimates of switches versus drifts and vice versa (Figure S3).

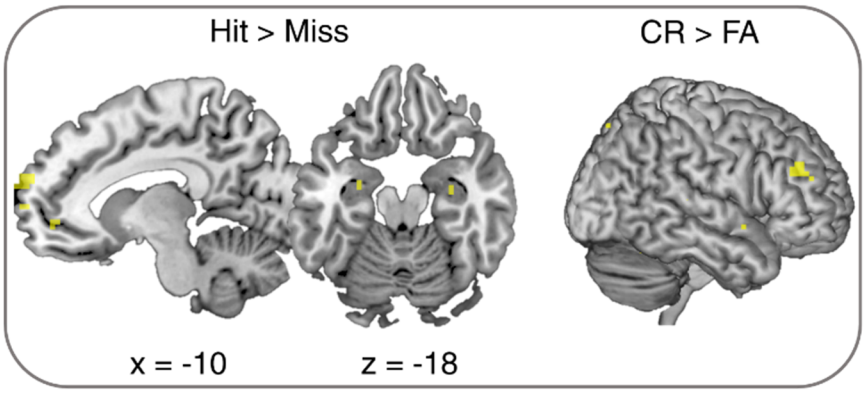

Figure S3. *fMRI main effects at p < .001, uncorrected. (a) Switch hits versus misses revealed activation of left mPFC, rostral ACC and bilateral hippocampus. (b) Correct rejections versus false alarms at drifts were accompanied by increased BOLD-signal change in right dlPFC. CR: Correct Rejection; FA: False Alarm.*

In order to provide further evidence for the involvement of dopaminergic pathways in modulating state transitions as reflected by an effect of previous error bias on epoch-related processing, we conducted a whole-brain parametric analysis at a significance level of $p < .001$, uncorrected. Beyond activation of left substantia nigra, this analysis revealed activation of left globus pallidus and left putamen suggesting a modulation of inputs to motor regions dependent on previous performance (Figure S4).

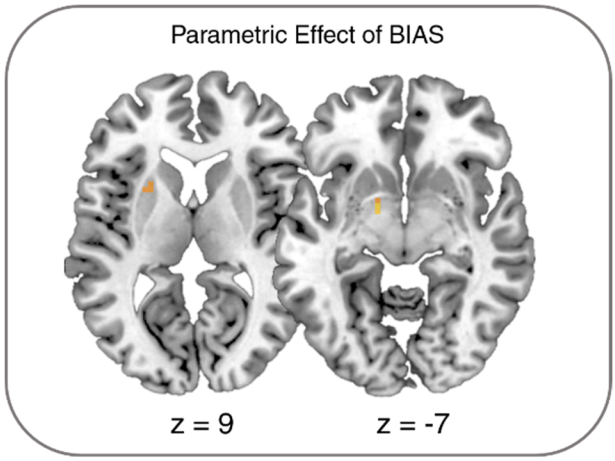

Figure S4. *A whole-brain parametric effect of previous error bias on current epoch-related BOLD signal was found in left putamen and left globus pallidus at p < .001 uncorrected.*

3.2 Study II: Association of Grey Matter Changes with Stability and Flexibility of Prediction in Akinetic-Rigid Parkinson's Disease

Running title: Association of Grey Matter Changes with Stability and Flexibility in PD

Ima Trempler, Ellen Binder, Nadiya El-Sourani, Patrick Schiffler, Jan-Gerd Tenberge, Anne-Marike Schiffer, Gereon R. Fink, Ricarda I. Schubotz (2018)

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ORIGINAL ARTICLE

Association of grey matter changes with stability and flexibility of prediction in akinetic-rigid Parkinson's disease

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Abstract
Parkinson's disease (PD), which is caused by degeneration of dopaminergic neurons in the midbrain, results in a heterogeneous clinical picture including cognitive decline. Since the phasic signal of dopamine neurons is proposed to guide learning by signifying mismatches between subjects' expectations and external events, we here investigated whether akinetic-rigid PD patients without mild cognitive impairment exhibit difficulties in dealing with either relevant (requiring flexibility) or irrelevant (requiring stability) prediction errors. Following our previous study on flexibility and stability in prediction (Trempler et al. J Cogn Neurosci 29(2):298–309, 2017), we then assessed whether deficits would correspond with specific structural alterations in dopaminergic regions as well as in inferior frontal cortex, medial prefrontal cortex, and the hippocampus. Twenty-one healthy controls and twenty-one akinetic-rigid PD patients on and off medication performed a task which required to serially predict upcoming items. Switches between predictable sequences had to be indicated via button press, whereas sequence omissions had to be ignored. Independent of the disease, midbrain volume was related to a general response bias to unexpected events, whereas right putamen volume correlated with the ability to discriminate between relevant and irrelevant prediction errors. However, patients compared with healthy participants showed deficits in stabilisation against irrelevant prediction errors, associated with thickness of right inferior frontal gyrus and left medial prefrontal cortex. Flexible updating due to relevant prediction errors was also affected in patients compared with controls and associated with right hippocampus volume. Dopaminergic medication influenced behavioural performance across, but not within the patients. Our exploratory study warrants further research on deficient prediction error processing and its structural correlates as a core of cognitive symptoms occurring already in early stages of the disease.

Keywords Parkinson's disease · Cognitive deficits · Prediction errors · Grey matter · MRI

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which results from depletion of dopamine (DA) production in the substantia nigra (SN). The degeneration of dopaminergic neurons in the SN progressively affects both subcortical and cortical areas along different neuronal pathways (Braak et al. 2003; Goedert et al. 2013). Apart from specific motor symptoms such as bradykinesia, rigidity, and resting tremor, changes in cortico-basal ganglia-cortical projections also result in initially subtle but progressive cognitive impairment (Muslimović et al. 2005; Chaudhuri and Schapira 2009; Kehagia et al. 2010). The question, which structural changes lead to which specific impairment, has moved into the focus of cognitive neuropsychology (see Biundo et al. 2016, for a review), but is thus far not answered conclusively.

Cognitive deficits in PD include impaired prediction of upcoming events implicated by experience-based internal models of the world that guide motor as well as cognitive control by (probabilistic) inference: For example, Schönberger et al. (2013) reported that patients show difficulties in predicting stimulus sequences and, moreover, that these difficulties are intra-individually correlated with the severity of motor dysfunctions. Other studies found compromised

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learning from prediction errors (PEs), i.e., mismatches between subjects' expectations and external events (Schott et al. 2007; Schonberg et al. 2010; Galea et al. 2012). PE processing deficiencies are likely to be caused by the disruption of DA production in PD since phasic DA release in the SN appears to be triggered by unpredicted external stimuli (Schultz and Dickinson 2000; Redgrave and Gruney 2006; Schiffer et al. 2015).

Beyond signalling surprise, violations of predictions can be differentiated based on their behavioural implications. They could either signal the need for adapting to lasting changes of the environment (thereby requiring flexible updating), or be caused by temporary distractors (requiring stabilisation of predictions). Irrespective of predictive functioning, Cools and D'Esposito (2011) suggest that optimal dopamine (DA) levels in frontostriatal circuits are responsible for balancing the trade-off between cognitive stability and flexibility. On the one hand, DA receptor activation in the striatum—one of the main target structures of SN projections—is associated with flexible gating of relevant information into working memory (Badre 2012; Chatham and Badre 2015; Frank et al. 2001; Cools et al. 2007; D'Ardenne et al. 2012). In contrast, DA in the lateral prefrontal cortex (PFC) is essential for stabilising working memory representations (Cohen et al. 2002; Miller and Cohen 2001; Bilder et al. 2004; D'Esposito 2007). According to the dual-state theory of working memory, representations in the PFC are regulated by so-called attractor networks, with either high or low energy barriers favouring either maintenance of the current representational state or flexible and fast switching among different states (Durstewitz and Seamans 2008). Regarding PD, there is evidence that in the early stages of PD, when DA depletion primarily affects the striatum, patients perform worse at flexible updating. On the contrary, the ability to maintain working memory content is not affected or can even be improved compared with healthy controls (Cools et al. 2003, 2009).

Within the specific scope of prediction, we recently found slightly different networks for stabilisation and flexible updating of internal models (Trempler et al. 2017). Here, stability was defined as the capacity to shield the internal model against unexpected irrelevant temporary changes, whereas flexible updating was required in response to unexpected, but lasting changes of the environment. Because of this operationalisation approach, the striatum was activated by either relevant or irrelevant sequential PEs highlighting striatal gating to control cognitive and motor representations in the frontal cortex (Chatham and Badre 2015; Cools 2011). Stabilisation was associated with activity of the inferior frontal gyrus (IFG), consistent with its role in active maintenance of working memory representations and inhibition (Baddeley 1986). In contrast, flexible adaptation was accompanied by activation of medial prefrontal cortex (mPFC) and the hippocampus contributing to updating and learning from PEs (Schlichting and Preston 2015; Schiffer et al. 2012). Owing to the evidence for an involvement of DA in prediction on the one hand, and in flexibility and stability on the other, the present study aimed at investigating whether stability and flexibility in the particular case of prediction are both impaired in PD. By reason of the various findings on the relationship between cognitive deficits and grey matter alterations in the striatum as well as in frontal and temporal regions in PD (see Kehagia et al. 2012, for a review on the progression of structural abnormalities in PD), we further explored whether deficient PE processing would relate to structural variations within a priori defined brain regions.

To this end, akinetic-rigid PD patients and healthy controls performed a task previously described in Trempler et al. (2017). The task requires monitoring of a digit sequence for order-violating items. Switches between predictable sequences need to be indicated via button press (requiring prediction flexibility), whereas digit omissions, drifts hereafter, should be ignored (requiring prediction stability). Using correlation analysis on the rate of correctly ignored drifts and detected switches, we first assessed whether (1) cognitive stability and cognitive flexibility of prediction would act in an antagonistic fashion in patients and not in healthy controls (Cools et al. 2003, 2009; Trempler et al. 2017). Moreover, we hypothesised that (2) patients compared with controls would show deficits in discriminating between irrelevant and relevant PEs and, as a result, impaired cognitive stability and flexibility as reflected in lower rates of drift rejection and switch detection, respectively. Since midbrain DA neurons are suggested to respond to unexpected events, (3) midbrain volume variations were expected to be associated with the probability to respond to surprising stimuli per se, i.e., a general response bias irrespective of stimulus identity (Redgrave and Gurney 2006). Striatal volume was (4) predicted to correlate with difficulties in discriminating between drifts and switches (Chatham and Badre 2015; Trempler et al. 2017). Furthermore, we expected (5) deficits in cognitive stability to be accompanied by structural alterations in IFG, which is known to be involved in maintaining working memory content and inhibition (Cohen et al. 2002; Fegen et al. 2015). In contrast, (6) reduced cognitive flexibility would correlate with inter-individual hippocampus volume and mPFC thickness differences due to the role of these regions in updating and learning (Schlichting and Preston 2015). Comparing correlation coefficients between the groups helped to quantify the specificity of the hypothesised brain-behaviour relationships. Finally, in view of the evidence for an involvement of DA in stability and flexibility of prediction, we (7) expected performance at switches and drifts to be partially improved by medication within and across patients and assessed whether daily medication dose would be associated with grey matter changes.

Materials and methods

Participants

23 right-handed patients with akinesia-rigidity dominant idiopathic Parkinson's disease (abbreviated as PD in the following) (6 females; 58.83 ± 9.24 years old; range 40–72 years) participated in the study. A group of 21 healthy participants (6 females; 60.05 ± 10.05 years old; range 36–74 years) similar to the patients regarding age and gender served as control subjects. Patients were acquired from the neurologic outpatient clinic of the University Hospital of Cologne, Germany. Only those patients that met the United Kingdom Parkinson´s Disease (UKPD) Society Brain Bank Criteria for idiopathic Parkinson's disease (Hughes et al. 1992) and no patients with atypical parkinsonian syndrome were included in the study, also indicated by a significant response to their individual dopaminergic medication. To select a clinically homogenous group and to minimize potential movement artefacts, only patients of the akinetic-rigid subtype according to a clinical judgment of an experienced movement disorder specialist were selected. No participant had undergone neurosurgical treatment for the disease or had a history of other neurological or psychiatric diseases. Symptoms of nine patients were left-dominant, and symptoms of eight patients were right-dominant (with onset of symptoms as criterion). All patients were tested once on their regular medication and once off medication to investigate whether DA medication could improve not only motor but also cognitive deficits resulting from the disease. Patients in the OFF-state were studied after overnight withdrawal of dopaminergic medication. The levodopa equivalent daily dose (LEDD) was calculated according to Tomlinson et al. (2010) and the severity of clinical symptoms was defined according to Hoehn and Yahr (1967) and to the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS III) (Fahn and Elton 1987). Hoehn and Yahr ratings ranged between I and III under regular medication. UPDRS III was assessed by a movement disorder specialist and additionally determined on the basis of video tapes by a second specialist blinded for the state of medication (see Supplementary Material). Patients and controls with any evidence of dementia or depression would have been excluded from the study. However, all participants scored between 19 and 30 points in the Parkinson Neuropsychometric Dementia Assessment (PANDA; 18–30 points = "age adequate cognitive performance") (Kalbe et al. 2008) and lower than 19 points in the Beck depression inventory-II (BDI-II; cut-off for depression: ≥ 20 points) (Hautzinger et al. 2006). Two patients were excluded due to difficulties in completing the main task. Thus, a total of 21 PD patients (6 females, 58.81 ± 9.89-years-old; range 40–72) were included in the analyses. For further assessment, all participants performed the two subtests "Divided Attention" and "Go/NoGo" of the TAP (Testbatterie zur Aufmerksamkeitsprüfung) (Zimmermann and Fimm 1993) and completed the Barratt Impulsiveness Scale (BIS-11; Patton et al. 1995). Table 1 summarises demographic data of patients and controls.

All subjects gave written informed consent prior to participation. The study was performed in accordance with the Declaration of Helsinki and had been approved by the ethics committee of the Medical Faculty of the University Hospital Cologne, Germany. Each participant submitted a signed informed consent notification and received reimbursement for participation afterwards (10 € per hour plus travel expenses).

Procedure and task

Healthy controls and PD patients attended the study on 1 and 3 days, respectively. Controls performed training, experiment, and additional assessments on the same day, whereas patients were first screened for being able to perform the task with their regular dopaminergic medication. The second day, 50% of patients were tested on medication and 50% were tested off medication. The third day was arranged in the same way as day two, except that the other 50% of patients were now tested off medication and vice versa. Healthy controls did not receive any medication.

Participants performed a slightly modified version of the paradigm as described in Trempler et al. (2017). They were presented with one of two different digit sequences, which allowed them to predict forthcoming input (ascending model: 1–2–3–4, descending model: 4–3–2–1) (Fig. 1). Digits continuously succeeded one another and were presented one at a time at the centre of the screen for 1 s, separated by an inter-stimulus interval of 100 ms. Sequences repeated constantly to enable the participants to predict the regular sequence. Switches between the sequences, i.e., directional changes, occurred at a random ordinal position within the initial sequence so that participants had to flexibly adapt their prediction according to the new direction of the presented sequence. In addition, single digits were omitted occasionally at variable positions without a temporal gap (drifts, hereafter). Contrary to switches, drifts disturbed the predictive process and required stabilisation of the internal model. Hence, the participants' task was to signal a switch from one model to the other by button press (switch detection), but to ignore the sequential omissions (drift rejection). Moreover, a motor control task was implemented to assess the individual mean reaction time. Here, one digit of the sequence repeated continuously, but maximally eight times until the participant pressed the response button. Baseline

Table 1 Demographic and clinical data of study population

Characteristics	Mean (± SD)			*p* value[a]
	Healthy controls	PD patients		
	(*n* = 21)	(*n* = 21)		
Age (years)	60.05 (10.05)	58.81 (9.89)		0.689
Female	60.17 (10.65)	58.17 (11.32)		0.759
Male	60.00 (10.18)	59.07 (9.68)		0.799
BDI-II	5.95 (4.93)	7.81 (4.69)		0.218
BIS-11	69.93 (6.28)	71.19 (4.84)		0.404
Attentional	16.52 (1.83)	17.10 (2.80)		0.438
Non-planning	22.43 (3.34)	24.20 (3.25)		0.091
Motor	30.86 (3.48)	29.90 (4.10)		0.421
PANDA	27.33 (2.31)	27.38 (3.01)		0.954
		OFF	ON	
UPDRS III	5.33 (3.02)	27.14 (9.46)	19.62 (7.48)	< 0.001**
TAP				
Divided attention	2.10 (2.07)	2.67 (2.60)	3.38 (4.30)	0.416
Go/NoGo	0.25 (0.72)	0.43 (1.12)	0.71 (2.24)	0.614
Disease duration[b]	–	4.29 (3.33)		–
LEDD	–	511.38 (290.33)		–

SD standard deviation, *PD* Parkinson's disease, *BDI* Beck's depression inventory, *BIS* Barratt impulsiveness scale, *PANDA* Parkinson neuropsychometric dementia assessment, *UPDRS* Unified Parkinson's Disease Rating Scale, *TAP* Testbatterie zur Aufmerksamkeitsprüfung, *LEDD* levodopa equivalent daily dose

**$p < 0.001$

[a]*p* value of independent *t* test or analysis of variance

[b]Years since PD diagnosis

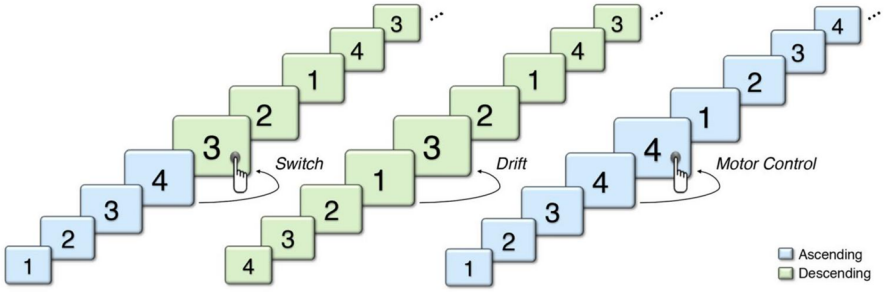

Fig. 1 Schematic diagram of the task. Stimuli of a simple 4-digit sequence continuously followed each other with a duration of 1 s and an inter-stimulus interval of 100 ms. Subjects had to indicate changes from ascending to descending sequences (and vice versa) (switch), as displayed in the left row, via button press. Moreover, they had to ignore the omission of a single digit (drift), as displayed in the middle row. During a motor control task, depicted on the right, one digit repeated continuously until the participant pressed the response button

trials with a 6 s presentation of a fixation cross were distributed equally across the experiment.

The task was binned into 12 blocks that either had a high or low probability of switches, either paired with a high or low probability of drifts. Each block consisted of an average number of 125 trials in a full-factorial 2 (probability: high vs. low) × 2 (event: switch vs. drift) design. Stimulus exposure per block was pseudo-randomised using the stochastic universal sampling method (Baker 1987). Results of this probability manipulation will be reported elsewhere.

The training session contained ten blocks of 80 trials each and a probability of 16% for switch or drift occurrence. To enable participants to get accustomed to the task, presentation speed started at 1400 ms per digit and adapted blockwise with a decrease of 50 ms if the participant reacted correctly to 75% of the events. In addition, patients performed

a short training directly prior to the main experiment consisting of three blocks with 80 trials at the main experiment's digit presentation speed of 1 s. The randomisation was programmed using MATLAB R2012b (The MathWorks Inc., Natick, MA, USA) and stimuli were presented using Presentation 13.1 (Neurobehavioral Systems, San Francisco, CA, USA).

Behavioural data analysis

Unpaired *t* tests were used to explore group differences in demographic variables. Derived from signal detection theory measures, task performance was assessed by hits (correct detection of switches), correct rejections (CRs) of drifts and, correspondingly, switch misses and false alarms at drifts. Differences in task measures between controls and patients OFF were regarded as effects of the disease, whereas differences between patients ON and OFF were interpreted as effects of DA medication. No comparisons between controls and patients ON were carried out due to lacking hypotheses about potential differences. Individual response time windows per participant were calculated from the mean reaction time plus two standard deviations as determined by the motor control task. If the participants pressed the button within this specific time window after a switch, their response was acknowledged as hit, whereas it counted as CR, if the participants did not press the button after a drift. There were no differences between the groups in the individual response time window length (controls ($M = 2432.38$, SD = 490.38) vs. patients OFF ($M = 2318.50$, SD = 649.79): $t(40) = 0.644$, $p = 0.511$; patients OFF vs. patients ON ($M = 2430.54$, SD = 800.24): $t(20) = 1.496$, $p = 0.15$).

A discrimination index [P_r; probability of recognition of switches and drifts, i.e., P_r = hit rate - false alarm rate] indicating the participants' ability to discriminate between drifts and switches and a bias index [B_r; response probability in an uncertain state, i.e., B_r = false alarm rate/$(1 - P_r)$] for an assessment of the overall motor threshold were calculated (Snodgrass and Corwin 1988). Data points per participants for each behavioural variable exceeding two standard deviations from the respective group mean were regarded as outliers and excluded from further analyses. This procedure resulted in exclusion of one healthy participant of analyses including the switch measure and the P_r index.

To assess the relationship between drift CRs and switch hits we calculated Pearson's correlation coefficients for each group separately. Comparisons between control participants and patients OFF regarding behavioural measures were carried out by an analysis of covariance (ANCOVA). B_r index served as a covariate as variations in drift CRs and switch hits can partly be explained by the individual probability to respond to surprising stimuli in general. Differences in CRs and hits between PD patients ON and OFF were assessed by paired *t* tests on the unstandardized residuals of the regression of hits and CRs on B_r index. Reaction times were calculated for each group separately and compared by either unpaired *t* tests to determine differences between controls and patients OFF or by paired *t* tests for differences between patients ON and OFF. Finally, we calculated the Pearson's correlation coefficient for an assessment of the relationship between LEDD and task performance in the ON-state. If not stated otherwise, significance tests were performed at $\alpha = 0.05$, one-sided, based on directional hypotheses with regard to the behavioural data. Statistical analyses were performed using IBM SPSS Statistics 22.

Brain imaging and data processing

Whole-brain imaging data of healthy controls and PD patients were collected at the Research Centre Jülich, Germany, on a 3 T Siemens TIM TRIO MRI scanner using a Tx/Rx CP head coil. Structural data were acquired for each participant using a standard Siemens 3D T1-weighted MPRAGE sequence for detailed reconstruction of anatomy with isotropic voxels ($1 \times 1 \times 1$ mm^3) in a 256 mm field of view (256×256 matrix, 172 slices, TR = 2250, TE = 3.03). In addition, functional images were acquired during the main task using a gradient T2*-weighted single-shot echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast. The corresponding results will be reported elsewhere.

Estimates of cortical thickness and volumetric segmentation were obtained using FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described in previous publications (Dale et al. 1999; Fischl and Dale 2000). The standardised processing includes motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter (WM) and deep grey matter (GM) volumetric structures, intensity normalization, tessellation of the GM/WM boundary, and automated topology correction. The FreeSurfer data were checked visually after preprocessing for any topological defects in the surface. For each subject, a triangular mesh was used to measure the distance from the pial surface to the GM/WM boundary for each hemisphere. A priori regions of interest (ROIs), i.e., bilateral portions of the inferior frontal gyrus (pars orbitalis, pars triangularis, pars opercularis), bilateral rostral anterior cingulate cortex (rACC) and superior frontal gyrus, based on gyral anatomical landmarks were parcellated on each hemisphere (Desikan et al. 2006). Subcortical GM volume measures for bilateral caudate nucleus, putamen and hippocampus were automatically extracted as part of the standard FreeSurfer pipeline. Midbrain segmentation was automatically performed by the application of a Bayesian

algorithm relying on a probabilistic atlas of the brainstem as described in Iglesias et al. (2015).

Statistical analysis of a priori ROIs

Thickness of left and right IFG was computed by averaging the extracted measures of pars orbitalis, pars triangularis, and pars opercularis due to the lack of specific hypotheses on the respective substructures. Thickness of left and right mPFC was computed by averaging measures of rACC and superior frontal gyrus as these regions correspond closest to the activation pattern found in our previous study (Trempler et al. 2017). Thickness per region was proportionally normalised by the mean thickness of the respective hemisphere. Volumes of subcortical ROIs, i.e., midbrain, caudate, putamen, and hippocampus, were normalised by the estimated total intracranial volume. Unpaired *t* tests were used to assess group differences in volume and thickness of the respective regions.

For cognitive measures, partial correlations, controlling for age, were performed between midbrain and B_r index for each group separately to investigate whether volume variations were associated with the probability to respond to surprising stimuli per se. Correlations between bilateral caudate and putamen volume and P_r index were analysed to determine the contribution of morphology of these regions to differences in the capacity to discriminate between different types of PEs. Furthermore, we examined the relationship between drift CRs and IFG thickness and between switch hits and hippocampus volume by partial correlations, controlling for age, for healthy controls and patients OFF. To investigate the specificity of these effects also the reversed correlations were calculated. Coefficients were compared between the groups to assess whether relationships were specific to the disease or could also apply to healthy controls. For bilateral tests, the alpha level was corrected to $p < 0.025$. Finally, we performed a regression analysis of GM measures on LEDD, controlling for age and disease duration.

Results

Group differences in task performance

To investigate differences in the relationship between cognitive stability and flexibility in patients and controls, we calculated and compared correlation coefficients between drift CRs and switch hits of each group separately. The correlation was more negative in patients OFF, $r = -0.073$, $p = 0.753$, compared with controls, $r = 0.345$, $p = 0.136$, and with patients ON, $r = 0.265$, $p = 0.246$, but the differences between these correlation coefficients did not reach significance (Controls vs. Patients OFF: $z = 1.28$, $p = 0.201$; Patients ON vs. Patients OFF: $z = 1.03$, $p = 0.303$). Thus, (1) there was a weak positive though non-significant relationship in controls and patients ON, but no systematic correlation in patients OFF (Fig. 2a).

Behavioural manifestations of deficits in cognitive stability were determined by comparisons of drift CRs of PD patients OFF and healthy controls, controlling for the general response bias as assessed by the B_r index. In contrast, impaired cognitive flexibility was measured by comparisons of switch hits of the two groups, controlling for the B_r index. In accordance with our hypothesis, (2) patients OFF compared with healthy controls had lower rates of both drift CRs, $F(1,39) = 3.085$, $p = 0.044$, and switch hits, $F(1,38) = 3.924$, $p = 0.028$. Accordingly, the P_r index that measures discrimination between drifts and switches significantly differed between the two groups, $t(39) = 2.062$, $p = 0.023$ (Fig. 2b). Reaction times of switch hits, [Controls ($M = 1394.47$, SD = 481.60) vs. Patients OFF ($M = 1485.77$, SD = 412.92): $t(39) = -0.522$, $p = 0.604$] and drift false alarms [Controls ($M = 1393.46$, SD = 584.41) vs. Patients OFF ($M = 1412.92$, SD = 743.73): $t(39) = -0.091$, $p = 0.928$] did not differ between the groups.

Contrary to our hypothesis, (7) patients ON and OFF did not differ in drift rejection, $t(20) = 0.413$, $p = 0.684$, and switch detection, $t(20) = 0.559$, $p = 0.582$. Likewise, there were no differences in the P_r index, $t(20) = 0.867$, $p = 0.396$. Finally, dopaminergic medication did not affect reaction times at switch hits [Patients ON ($M = 1494.73$, SD = 613.22) vs. Patients OFF: $t(19) = -0.673$, $p = 0.509$] and drift false alarms [Patients ON ($M = 1519.05$, SD = 557.90: $t(19) = -0.410$, $p = 0.687$]. However, focusing on the effects of individual dopaminergic medication dose on task performance across patients in the ON-state, we found a significant positive correlation between LEDD and the P_r index, $r = 0.404$, $p = 0.035$.

Group differences in GM measures

Patients compared with healthy controls exhibited a significant decrease of left caudate volume, $t(38) = 3.883$, $p < 0.001$, and differences in right caudate volume at a probability of significance close to the adjusted alpha level, $t(39) = 2.33$, $p = 0.025$. Midbrain, bilateral putamen and hippocampus volumes as well as IFG and mPFC thickness did not differ between the two groups ($p > 0.13$) (Fig. 3).

To explore whether left caudate atrophy contributes to morphological alterations in these apparently non-affected regions, we calculated a post hoc regression analysis of GM measures of midbrain, bilateral putamen, bilateral hippocampus, bilateral IFG and bilateral mPFC on left caudate volume, controlling for age. This analysis revealed a significant positive association with right hippocampus volume, $\beta = 0.647$, $p = 0.023$, but a significant negative relationship

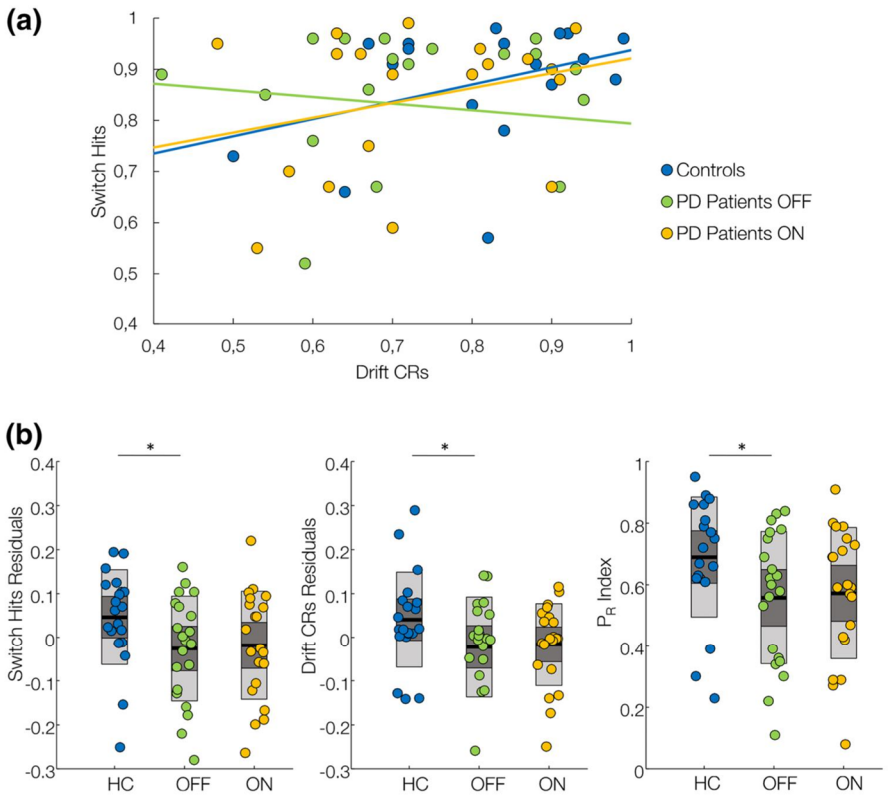

Fig. 2 **a** Scatter plot of correlation between switch hits and drift correct rejections (CRs) in healthy controls and akinetic-rigid Parkinson's Disease (PD) patients in the OFF- and ON-state. As expected, the two measures were not significantly correlated with each other. **b** Unstandardized residuals of the regression of B_r index on switch hits (left) and drift CRs (middle) and P_r index (right) of healthy control participants and patients OFF and ON. In all three measures, PD patients OFF significantly differed from controls, whereas there were no differences between patients OFF and ON. *$p < 0.05$, one-tailed

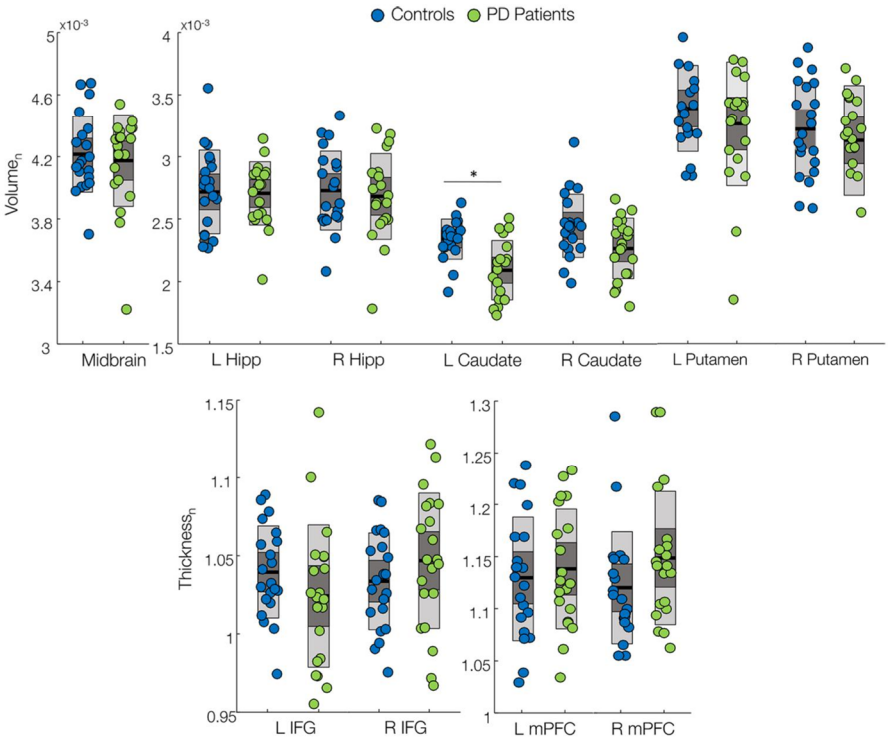

Fig. 3 Volume and thickness of different regions of interest of healthy controls and patients with akinetic-rigid Parkinson's Disease (PD). Only left caudate nucleus volume significantly differed between the two groups. R, Right; L, Left; Hipp, Hippocampus; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex. The n-subscript indicates that volume and thickness were normalised by estimated total intracranial volume and mean hemisphere thickness, respectively; *$p < 0.025$

with right IFG thickness, $\beta = -0.411$, $p = 0.007$, and left mPFC thickness, $\beta = -0.409$, $p = 0.019$, with $R^2 = 0.558$, $F(10,28) = 3.535$, $p = 0.004$.

Association of GM measures with PE processing

We hypothesised (3) a relationship between the response bias B_r and midbrain volume. Partial correlation controlling for age revealed a non-significant correlation in patients OFF, $r = 0.429$, $p = 0.059$, but a significant correlation in controls, $r = 0.473$, $p = 0.042$. Correlation became significant when considering the whole group, $r = 0.451$, $p = 0.002$ (Fig. 4a). In contrast, our hypothesis (4) of a relationship between the P_r index, which represents the ability to discriminate between different types of PEs, and caudate nucleus volume was not confirmed, neither for patients OFF nor for controls ($p > 0.404$). However, since there was a trend towards a significant correlation between bilateral putamen and P_r index in both groups [Controls: R (right): $r = -0.471$, $p = 0.042$, L (left): $r = -0.398$, $p = 0.093$; Patients OFF: R: $r = -0.455$., $p = 0.044$, L: $r = -0.401$., $p = 0.080$] we assessed the relationship across the whole sample revealing a significant association of P_r index with right, $r = -0.395$, $p = 0.012$, but not with left putamen, $r = -0.312$, $p = 0.050$ (Fig. 4b). Thus, volume of dopaminergic regions, i.e., midbrain and right putamen, was related to the probability to respond to surprising stimuli per se and to the ability to discriminate between them, respectively, though not specific to the disease.

We finally predicted disease-specific structural variations in (5) the IFG and (6) the mPFC and hippocampus to be related to deficits in cognitive stability and cognitive flexibility, respectively. Partial correlation analyses controlling for age revealed a significant negative correlation between CRs and right IFG thickness in patients OFF, but not in healthy controls. In contrast, switch hits of patients but not of controls correlated negatively with right hippocampus volume (Fig. 5).

Correlations appeared to be specific as there was no relationship between drift CRs and hippocampus volume or switch hits and IFG thickness as well as no differences in coefficients between the groups. However, contrary to our expectation left mPFC negatively correlated with drift CRs, but not with switch hits in patients only (Table 2).

Association of GM with medication

For an assessment of (7) the relationship between medication and GM, we performed a regression analysis of our GM measures on LEDD, controlling for age and disease duration. This analysis revealed a negative relationship between LEDD and right hippocampus, $\beta = -2.591$, $p = 0.049$, right caudate, $\beta = -2.960$, $p = 0.032$, and right putamen, $\beta = -2.916$, $p = 0.033$, with $R^2 = 0.947$, $F(7,31) = 6.807$, $p = 0.023$. Thus, patients with smaller volume of these regions might require a higher dose of dopaminergic medication. Note that left hippocampus, caudate, and putamen negatively relate to LEDD, albeit not reaching significance ($p > 0.052$) (see Table S3 in the Supplementary Material).

Discussion

In the present study, we investigated whether structural deviations in a priori defined brain regions of akinetic-rigid PD patients are accompanied by deficient processing of unpredicted stimuli that either had to be ignored (indicating cognitive stability) or detected (indicating cognitive flexibility). In sum, (1) there was no significant correlation between our behavioural measures of cognitive stability and flexibility in prediction, neither in patients on and off medication nor in healthy participants. (2) Both functions were affected in

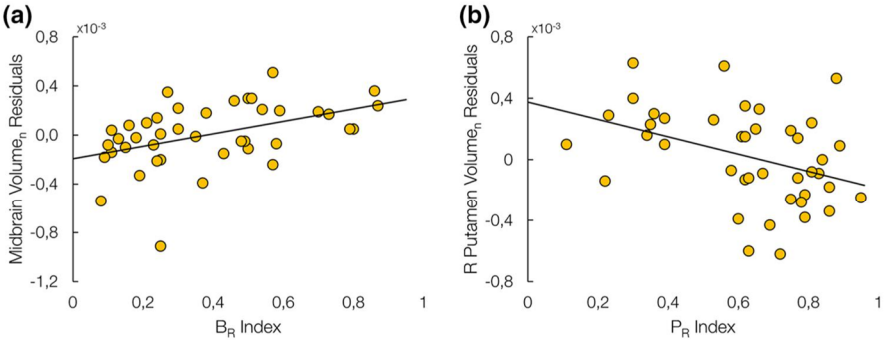

Fig. 4 Scatter plots of significant correlations between **a** residuals of midbrain (controlling for age) and B_r index indicating a general response bias to unexpected events and **b** between right putamen residuals (controlling for age) and P_r index measuring the ability to discriminate between different types of events across healthy controls and akinetic-rigid Parkinson's disease patients in the OFF-state. The n-subscript indicates that volume was normalised by estimated total intracranial volume

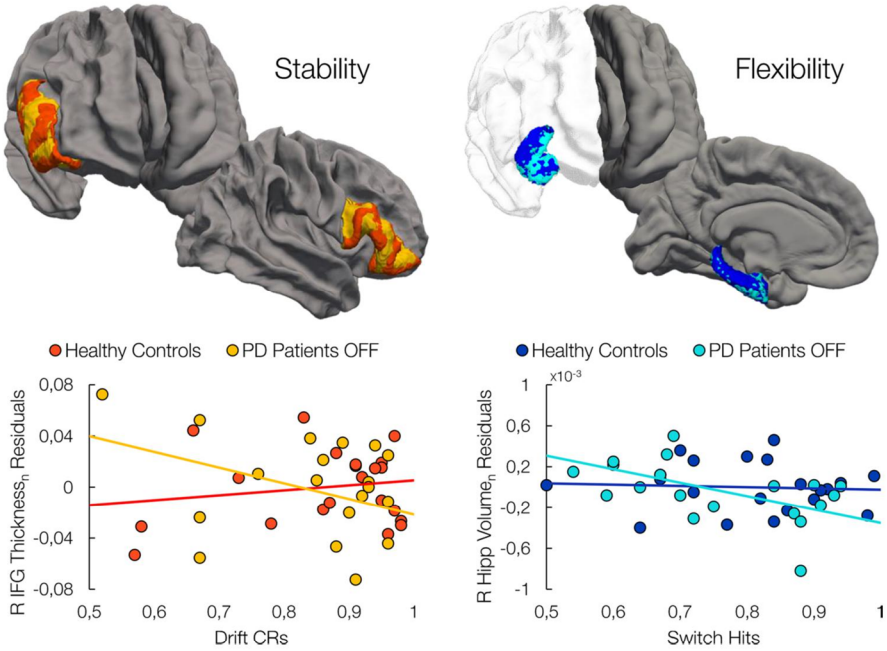

Fig. 5 Above, overlay of mean thickness of right inferior frontal gyrus (R IFG) and mean volume of right hippocampus (R Hipp) of healthy controls (in dark colour) and akinetic-rigid Parkinson's disease (PD) patients (in light colour). Mean thickness and volume did not significantly differ between the groups. Below, scatter plots displaying the relationship between measures of stability (drift correct rejections, CRs) and flexibility (switch hits) and unstandardized residuals of right IFG thickness and hippocampus volume, respectively, for healthy controls and PD patients OFF (controlled for age). There was a significant negative correlation between drift CRs and right IFG thickness and between switch hits and right hippocampus volume in patients, but not in controls

Table 2 Brain-Behaviour Correlations

		Drift CRs			Switch hits		
		Healthy controls	PD patients OFF	*z*-score	Healthy controls	PD patients OFF	*z*-score
Inferior frontal gyrus thickness$_n$	R	0.197	− 0.486*	2.19*	− 0.192	0.025	− 0.65
	L	0.346	− 0.107	1.40	0.122	0.156	− 0.1
Hippocampus volume$_n$	R	0.347	− 0.110	1.42	− 0.064	− 0.644*	2.07*
	L	0.355	− 0.086	1.37	− 0.243	− 0.467	0.76
Medial prefrontal cortex thickness$_n$	R	0.082	− 0.234	0.95	0.079	0.056	− 0.07
	L	0.290	− 0.600*	2.93*	0.395	− 0.028	− 1.32

Coefficients are partial correlations, controlling for age, between thickness and volume of the respective region and our measures of stability and flexibility. Fisher's z depicts differences of coefficients between healthy controls and patients off medication

The n-subscript indicates that volume and thickness were normalised by estimated total intracranial volume and mean hemisphere thickness, respectively

CRs correct rejections, *PD* Parkinson's disease, *R* right, *L* left

*Significant at $p < 0.05$, one-tailed

patients as reflected in difficulties in ignoring irrelevant and detecting relevant, but unpredicted events. Furthermore, data confirmed our hypothesis that (3) midbrain volume relates to a general response bias to unexpected events, though this was not specific to PD. Likewise, (4) right putamen volume related to the ability to discriminate between relevant and irrelevant events across the whole sample. (5) Morphological differences in right IFG were associated with variations in cognitive stability only in patients, whereas (6) differences in hippocampus volume related to specific deficits in flexible adaptation to relevant input. Contrary to our hypothesis, mPFC thickness correlated with our measure of stability in patients, but not in controls. Finally, (7) although we did not find performance differences between patients on and off medication, individual dose of medication positively correlated with discrimination ability across the patients in the ON-state. Increased daily medication dose was in turn associated with smaller right hippocampus, caudate and putamen volume.

Contribution of morphological variations to general PE detection

We found distinct patterns for the association of different anatomical structures with difficulties in dealing with

unpredicted events. Smaller midbrain was related to a lower probability to respond to unpredicted sensory input across the whole sample, i.e., independent of the disease. Phasic DA release in the midbrain projecting to the striatum is involved in signalling mismatches between anticipated and actual events (Redgrave and Gurney 2006), allowing for a fast adaptation of behaviour (D'Esposito and Postle 2015). Our results further suggest that structural variations in the midbrain matter with regard to differences in the ability to identify and respond to PEs as such. Moreover, patients compared with controls exhibited a reduced ability to discriminate different types of PEs which was negatively correlated with volume of the right putamen in the whole sample. This finding corresponds with previous studies on response selection especially within the domain of motor processing (Humphries et al. 2006; Lo and Wang 2006; Howard et al. 2017; Hiebert et al. 2014). It is suggested that the primary role of the basal ganglia entails the selection of behaviours represented in prefrontal and premotor areas to be executed. Cognitive representations within the frontal cortex are selected by striatal actions via caudate-prefrontal loops (Houk and Wise 1995; Jueptner and Weiller 1998) and then executed via the motor loop connecting the putamen to the lateral premotor cortex and the supplementary motor area (Alexander et al. 1986). The motor loop contributes to the prediction of upcoming events (see Schubotz 2007, for a review), and impaired performance in predicting stimulus sequences in PD has been found to be accompanied by motor loop dysfunction (Schönberger et al. 2015). Thus, although we could not replicate our previous finding of a relationship between caudate nucleus and discrimination ability in young healthy subjects (suggesting the involvement of the prefrontal loop) (Trempler et al. 2017), the relationship between thickness of the right putamen and discrimination ability emphasises the importance of overt motor aspects of discrimination ability or cognitive impact on motor control in older age.

Impaired cognitive stability and flexibility in PD

Compared with controls patients rejected and detected significantly lower amounts of drifts and switches, respectively, suggesting deficits in both cognitive stability and flexibility of prediction. It has been suggested that cognitive inflexibility in PD, i.e., difficulties in updating in response to relevant input, appears to be beneficial for stability by becoming less prone to distraction (Cool et al. 2003, 2009). It is noteworthy that unlike previous studies on the interplay of stability and flexibility, we here measured the two functions in a predictive setting. We define stability as the ability to shield the initial internal model that allows prediction of visual input in the face of distraction, thereby also inhibiting motor reactions. In contrast, flexibility refers to the ability to update the internal model in response to a lasting change, along with an appropriate motor reaction. To avoid confounds with working memory capacity influencing performance in both, stability and flexibility, we used an overlearned predictable digit sequence serving as the internal model. Thus, our operationalisation of stability and flexibility refers to the ability to deal with different types of PEs and is, thus, only partly comparable to previous studies. Usually, active maintenance of working memory content (without external input) plays a substantial role for stability (Durstewitz 2000), whereas flexibility is measured by switching between different tasks or task sets (Stelzel et al. 2010; Fröber and Dreisbach 2017). However, as Cools and D'Esposito (2011) point out it is conceivable that stability and flexibility are accomplished by two separate mechanisms that nevertheless influence and partly oppose each other.

Hence, in the present study we did not find a significant negative relationship between the rate of drift CRs and the rate of switch hits. Measures of cognitive stability and flexibility showed a non-significant trend towards a weak positive relationship in healthy controls and patients in the ON-state, whereas there was no relationship in the OFF-state. Thus, in case of prediction flexible updating might diminish with disease progression, but independent of the ability to reject irrelevant distractors (or vice versa). The weak positive relationship in controls and patients ON might point to some superior function modulated by DA, from which both stability and flexibility can profit, so that withdrawal results in a more incidental dealing with unpredicted events.

Structural correlates of cognitive stability and flexibility

We found that deficits in cognitive stability relate to higher thickness of right IFG (note that we will discuss possible mechanisms regarding the direction of this effect in the following section). The lateral PFC is responsible for stabilisation of working memory representations, i.e., active maintenance (Baddeley 1986) and cognitive inhibition in the face of distractors (Lavie 2005). The involvement of IFG in drift rejections in our previous and in the present study might point to heightened verbal working memory load in response to sequential interruptions because the common task strategy was subvocalization of the digit sequence (Shergill et al. 2002; Fegen et al. 2015). However, it has been suggested that particularly the right IFG is relevant for motor inhibition (see Aron 2007, for a review) and attentional control when facing salient stimuli (Hampshire et al. 2010). Structural abnormalities in the right IFG have been reported for neuropsychiatric disorders that are linked to impaired inhibition, such as attention-deficit hyperactivity disorder (Depue et al. 2010) and obsessive–compulsive spectrum disorders (Menzies et al. 2007). The present results further indicate

that higher thickness in the right, but not in the left IFG of PD patients is related to a decline in inhibitory control and maintenance of the internal model in face of unpredicted distractors. However, thickness of the left mPFC, activated in response to switches in our previous fMRI study (Trempler et al. 2017), was also associated with our measure of cognitive stability in the patient sample. As right IFG and left mPFC thickness negatively correlated with left caudate volume, changes within these two regions might contribute to the same dysfunctional profile in patients, namely overreacting to unexpected but irrelevant input. We suggest that frontal contribution to instable responses reflects impaired inhibition on the one hand (due to the involvement of right IFG) but also concurrent reliance on cognitive control over behavioural responses by recruitment of left mPFC (di Pellegrino et al. 2007; Alexander and Brown 2011). Thus, compensatory but mal-adaptive attentional resources might be recruited to maintain motor control to some degree in the early stage of the disease, whereby this results in rather unspecific and even unstable responses to unexpected stimuli (see Seidler et al. 2010, for a review).

Considering cognitive flexibility, right hippocampus volume negatively correlated with the rate of correctly detected switches in patients, but not in controls. In line with the hippocampus' role in updating and learning (Ross et al. 2009; Chen et al. 2011), morphological changes within this region might result in specific impairment in flexible dealing with behavioural relevant PEs. Structural changes of the hippocampus of PD patients have been found in several studies, commonly associated with a progression towards dementia, independent from frontal dysfunction (Shimada et al. 2009). It has been suggested that posterior cortical changes in PD are caused by cholinergic loss and not by dopaminergic (dys-)function (Hall et al. 2014). Although it is not provable by the present results whether deficits in flexible updating of prediction in PD result from changes in cholinergic transmission in temporal regions, they suggest subtle differences in morphology to be accompanied by cognitive deficits associated with learning and memory already in early stages of the disease.

Cerebral reorganisation in Parkinson's disease

It is not a trivial question why increased GM was related to cognitive performance deficits in the present study. Both GM increases and decreases in PD have been described in previous studies, and heterogeneous findings mirror the complexity of the underlying pathophysiology including multiple neurotransmitter deficiencies as well as genetic risk factors (see Biundo et al. 2016, for a review). Additionally, WM fractional anisotropy could be the underlying cause of the reported effects since it has been shown to contribute to variations in GM estimates (Villain et al. 2010; Freund et al. 2011; Henry et al. 2009). For instance, Price et al. (2016) found that a reduced prefrontal fractional anisotropy in addition to reduced GM caudate volume predicted processing speed of PD patients, which highlights the importance of GM-WM interactions for cognitive symptoms in PD.

One hypothesis is that cortical thickening may occur due to temporary compensatory, but inefficient cytoarchitectural reorganisation that cannot counterbalance cognitive decline (Rektorova et al. 2014). Evidence for this assumption is provided by a negative correlation between left caudate volume and thickness of right IFG and left mPFC in the present study suggesting that striatal volume loss is accompanied by compensatory thickening of target frontal regions. Biundo et al. (2013) proposed a non-linear progression of structural changes with patients initially exhibiting hyperactivation or thickening in task-relevant brain structures reflecting compensatory mechanisms, and subsequently developing hypoactivation or cortical thinning with disease progress. However, regarding the hippocampus its positive relationship with left caudate indicates hippocampus atrophy rather than thickening. Because smaller volume of the right hippocampus was associated with higher LEDD, which in term influenced PE discrimination ability, it may be possible that patients with decreased volume of these regions might benefit more from medication than those with higher volume and, as a result, perform better at switches. This would correspond with the suggestion of the inverted-U-shaped action of DA on cognitive functions according to which either too little or too much DA action can reduce performance on cognitive tasks (Cools and D'Esposito 2011). In line with this, some studies relate aberrant cerebral alterations to a hyperdopaminergic state induced by DA medication. DA is involved in modulating synaptogenesis, dendritic arborisation, and can induce cytotoxic long-term effects (Tessitore et al. 2016). Thickening of the anterior cingulate and orbitofrontal cortex in PD patients with impulse control disorder (Tessitore et al. 2016) as well as of the right IFG in levodopa induced dyskinesia has been reported (Cerasa et al. 2013). These findings indicate that DA medication might initially preserve cognitive and motor functions, at least to some degree, whereas other areas become hyperactive due to DA overdose, also accompanied by structural alterations. In this regard, future investigations of cognitive dysfunctions in PD should take possible paradoxical effects of DA medication into account (see Cools 2006, and; Vaillancourt et al. 2013, for a review).

Finally, the detected associations could also result from GM variations from birth, with subjects with thinner cortex and smaller subcortical volume being resistant to cognitive deficits, whereas subjects with thicker and larger structures are more prone to cognitive decline (Cerasa et al. 2013). This might also explain why we did not find differences

between the two groups in thickness and volume of the corresponding regions.

Medication effects

Contrary to our expectation, there was no difference between patients on and off medication in behavioural performance. Since most of the patients were in the early stage of the disease (Hoehn and Yahr ratings between I and III) the remaining neurons in the SN were possibly still capable of storing DA medication also in the off-state (Chase et al. 2013). Moreover, some of the patients took slow release dopaminergic medication and, due to ethical concerns, we decided not to affect these patients too much by longer-term withdrawal. Thus, although withdrawal affected motor performance as seen in significant differences in UPDRS-score between patients ON and OFF, the patients' cognitive functioning was possibly retained. Alternatively, loss of other neurotransmitters might contribute to deficits in stability and flexibility as operationalised in our study. As already mentioned, deficits in flexible updating of prediction may result from changes in cholinergic transmission in temporal regions. Moreover, there is growing evidence for noradrenaline depletion in PD (Delaville et al. 2011) that might cause cognitive inflexibility (Vazey and Aston-Jones 2012).

However, we found a positive relationship between the dose of individual dopaminergic medication and performance under medication across patients. This suggests that in the long run DA can indeed enhance the ability to identify and deal with different types of unpredicted events either requiring cognitive stability or flexibility, though short-term withdrawal does not provoke a significant drop in performance. In this connection, it is also interesting that—albeit not reaching the level of significance—there was a weak positive relationship between stability and flexibility in patients on medication (as observed in healthy controls), whereas the correlation was absent or rather negative in the OFF-state. Thus, stable and flexible responses to PEs appear to be influenced equally by dopaminergic medication.

Limitations

We acknowledge the relatively small sample size of 21 patients and its heterogeneity in terms of disease duration, PD subtypes, and stages as limitations of the current study. Future studies should elaborate on deficits in cognitive stability and flexibility of prediction, in particular because the reported effects could be more pronounced when examining a larger sample. To assess a non-linear progression of specific cerebral morphological patterns, longitudinal studies with a larger PD cohort including patients with mild cognitive impairment should be conducted. Regarding the small effects of medication, we acknowledge that we did not assess the presence or absence of medication fluctuations per patient. This could have been beneficial to take into account potential interactions with present task performance.

Furthermore, we are unable to rule out that participants missed, that is, did not detect drifts instead of actively rejecting them. Although there is no reason to assume that subjects would only signal switches (given the fact that there was no systematic relationship between switch misses and drift CRs), functional imaging could ensure that drifts elicited activity in areas associated with stability of prediction.

Finally, to understand the specific pathophysiological mechanisms causing grey matter changes multimodal studies and joint research between disciplines from subcellular or cellular to functional level are required. Therefore, we highlight our considerations on causes of cerebral reorganisation to be still speculative. However, deriving hypotheses on the DA-mediated interactions between cognitive PE processing and cerebral morphology, our exploratory study holds great potential for future investigations.

Conclusion

Taken together, our study is the first to show that inter-individual differences in cerebral morphology of akinetic-rigid PD patients are linked to deficits in cognitive processing of either relevant or irrelevant unpredicted sensory information. Deficient stabilisation is accompanied by disruption of dopaminergic frontostriatal circuits, which is reflected in cerebral alterations in prefrontal areas, whereas impaired updating of current predictions is associated with structural hippocampal alterations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Brain Structure and Function

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Supplementary Material

1. Supplementary Methods

1.1 UPDRS rating

UPDRS III of controls and patients was initially assessed by a movement disorder specialist and additionally determined on the basis of video tapes by a second neurologist blinded for state of medication. Because rigidity is not reliably measurable by video tapes, corresponding values of the second rater were missing. For this reason, we calculated the two-way mixed intraclass correlation coefficient (ICC) for the UPDRS III sum scores (dropping rigidity items) to estimate the overall agreement between the two examiners. Agreement was almost perfect for the mean ratings (ICC=0.89; 95% CI=0.81-0.93) such that we used the entire UPDRS III rating of the unblinded rater for our analyses.

2. Supplementary Results

2.1 Relationship between degree of motor symptoms and cognitive performance

To investigate whether motor and cognitive deficits would be associated with each other, we performed correlation analyses between the degree of motor impairment assessed by UPDRS III and cognitive performance, i.e. drift CRs and switch hits, across healthy controls and PD patients OFF. We found significant negative correlations between drift CRs and UPDRS III scores, r = -0.281, p = 0.036, and between switch hits and UPDRS III scores, r = -0.310, p = 0.024 (Figure S1) suggesting that cognitive and motor dysfunctions in PD partially overlap.

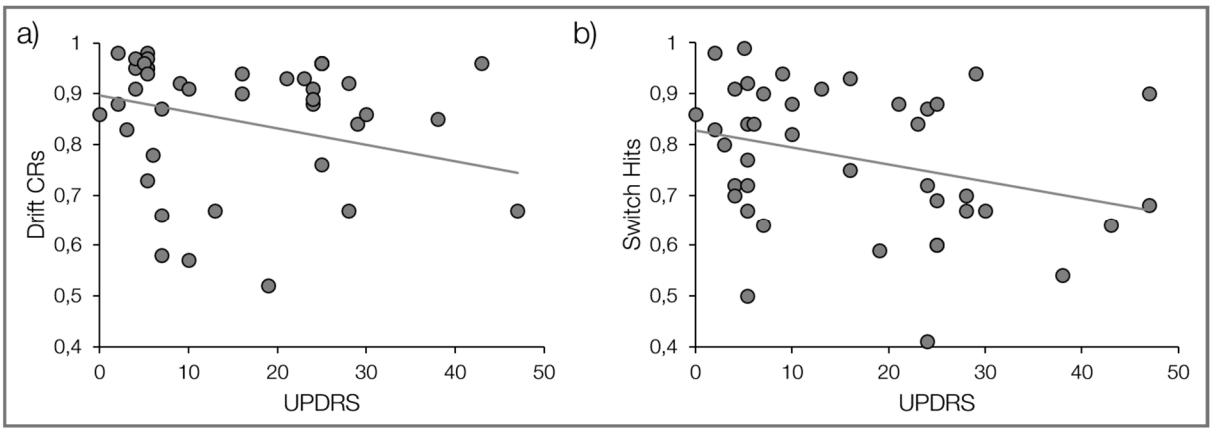

Fig. S1 Scatter plots of significant correlations between a) drift correct rejections (CRs) and UPDRS III, and b) switch hits and UPDRS III across healthy controls and patients OFF.

Note that patients with higher motor symptom scores including bradykinesia and rigor in fact showed a higher probability to respond when they should not, i.e. a higher false alarm rate. This further suggests that impaired flexibility is not automatically good for stability and vice versa. Future studies should investigate whether cognitive stability and flexibility relate to very specific motor symptoms of the disease.

2.2 Relationship between non-planning impulsivity and cognitive performance

Because the non-planning subscore of the BIS-11 questionnaire pointed towards a relevant difference between controls and patients, we conducted correlation analyses between this score and our task measures. BIS-11 questions refer to relatively stable traits, thus, patients filled in the questionnaire in the ON-state. We compared correlation coefficients between healthy controls and patients ON and OFF medication (Table S1).

Table S1. Correlations of BIS-11 non-planning score with behavioral measures.

	BIS-11 non-planning				
	ON	*z*-score HC-ON	HC	*z*-score HC-OFF	OFF
Switch Hits	0.25	1.66	-0.29	1.23	0.11
Drift CRs	0.11	0.66	-0.11	1.07	0.24
P_r Index	0.23	1.31	-0.20	1.44	0.27
B_r Index	0.03	0.45	-0.12	0.18	-0.18

BIS, Barrett Impulsiveness Scale; CRs, correct rejections; Fisher's z depicts differences of correlation coefficients between healthy controls and patients on and off medication.

Although not reaching significance, the direction of the correlation coefficients is nevertheless remarkable. Lower non-planning subscores reflecting higher self-control are accompanied by increased performance at switches and drifts in controls, whereas they go along with decreased hit and CR rates in patients ON and OFF. Thus, although this should be subject of future research, low non-planning impulsivity, probably experienced as everyday rigidity by the patients, appears to be reflected in difficulties in the spontaneous detection of and reaction to unpredicted stimuli. In contrast, the same trait might be beneficial for attentional control of ongoing prediction in controls.

2.3 Relationship between GM measures and LEDD

Detailed results of the regression analysis of GM measures on LEDD, controlling for age and disease duration, are depicted in Table S2.

Table S2. Summary of linear regression analysis predicting LEDD.

Variables	B	SE(B)	β	*T*	*P*
Age	-8.48	8.120	-0.302	-1.035	0.348
Disease duration	10.26	16.75	0.120	0.613	0.567
Midbrain	525184.32	366165.62	0.378	1.434	0.211
L Hipp	765906.65	472606.36	0.535	1.621	0.166
R Hipp	-1137662.86	439012.31	-1.106	-2.591	0.049*
L Caudate	1656440.87	654190.50	1.336	2.532	0.052
R Caudate	-1201217.54	405755.04	-.976	-2.960	0.032*
L Putamen	497517.81	199721.89	.659	2.491	0.055
R Putamen	-842510.13	288886.55	-.827	-2.916	0.033*
L IFG	223.31	966.77	.035	.231	0.826
R IFG	1845.49	1691.69	.284	1.091	0.325
L mPFC	-3220.43	1595.05	-.627	-2.019	0.099
R mPFC	-684.73	942.43	-.153	-.727	0.500

LEDD, levodopa equivalent daily dose; B, unstandardized coefficients; β, standardized coefficients; SE: standard error; L, Left; R, Right, Hipp, Hippocampus; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; *$p < 0.05$.

2.4 Levodopa equivalent daily dose

Table S3 depicts medication and levodopa equivalent daily dose (LEDD) of each patient.

Table S3. Individual medication and LEDD per participant.

Patient Number	Medication	LEDD
1	Azilect, Rotigotine	240
2	Azilect, Madopar, Sifrol	715
3	Azilect, Pramipexole	210
4	Levodopa, Piripedil	300
5	Amantadine, Levopar, Ropinirole	1095
6	Amantadine, Piripedil, Selegiline	471
7	Azilect, Sifrol, Rotigotine	317
8	Azilect, Levodopa	500
9	Amantadine, Azilect, Levodopa, Ropinirole	940
10	Amantadine, Azilect, Piripedil	400
11	Amantadine, Acilect, Levodopa, Pramipexole	930
12	Levobeta, Pramipexole, Selegiline	980
13	Azilect, Pramipexole	205
14	Azilect, Rotigotine	400
15	Levodopa	350
16	Ropinirole	80
17	Amantadine, Azilect, Levodopa	600
18	Dopadura, Pramipexole, Selegiline	710
19	Clarium, Madopar, Stalevo	257
20	Citalopram, Levodopa, Ropinirole	649
21	Azilect, Levodopa, Sifrol	390

LEDD, levodopa equivalent daily dose.

2.5 Motor symptom asymmetry

We tested for possible effects of motor symptom asymmetry (i.e. side of symptom onset) on our target behavioural and structural measures. However, asymmetry was not significantly related to any of these measures such that we did not include it as a noise regressor in further analyses (Table S4).

Table S4. Structural and behavioural data of PD patients with either left- or right-side dominance of motor symptoms

Characteristics	**Mean (± SD)**		***p* value[a]**
	Left (n = 9)	Right (n = 8)	
Midbrain Volume$_n$	0.0041 (0.0002)	0.0043 (0.0002)	0.689
Left Caudate Volume$_n$	0.0022 (0.0003)	0.0021 (0.0002)	0.759
Right Caudate Volume$_n$	0.0023 (0.0002)	0.0023 (0.0003)	0.799
Left Hippocampus Volume$_n$	0.0026 (0.0002)	0.0028 (0.0002)	0.218
Right Hippocampus Volume$_n$	0.0027 (0.0003)	0.0028 (0.0003)	0.404
Left IFG Thickness$_n$	1.019 (0.056)	1.021 (0.035)	0.438
Right IFG Thickness$_n$	1.041 (0.055)	1.052 (0.037)	0.091
Left mPFC Thickness$_n$	1.130 (0.062)	1.152 (0.064)	0.462
Right mPFC Thickness$_n$	1.140 (0.051)	1.143 (0.065)	0.929
	OFF		
UPDRS III	22.63 (3.34)	31.38 (11.61)	0.19
Drift CRs	0.87 (0.15)	0.86 (0.09)	0.89
Switch Hits	0.70 (0.10)	0.69 (0.18)	0.85
P$_r$ Index	0.57 (0.21)	0.55 (0.22)	0.57
	ON		
UPDRS III	15.38 (3.78)	23.88 (8.56)	0.08
Drift CRs	0.84 (0.14)	0.83 (0.14)	0.70
Switch Hits	0.69 (0.12)	0.74 (0.16)	0.52
P$_r$ Index	0.53 (0.23)	0.56 (0.24)	0.88

PD, Parkinson's disease; SD, standard deviation; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; UPDRS, Unified Parkinson's Disease Rating Scale; CRs, correct rejections. The n-subscript indicates that volume and thickness were normalised by estimated total intracranial volume and mean hemisphere thickness, respectively; [a]*p* value of analysis of variance.

3.3 Study III: Dopaminergic Modulation of Surprise: fMRI Evidence for Deficient Flexible Adaptation of Prediction in Parkinson's Disease

Running title: Dopaminergic Modulation of Surprise

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Dopaminergic modulation of surprise: fMRI evidence for deficient flexible adaptation of prediction in Parkinson's disease

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Abbreviated title: Dopaminergic modulation of surprise

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Abstract

While the ability to continually predict future states of the environment is an efficient principle of neural processing, the brain's sensitivity to and accentuation of unpredicted over predicted sensory signals plays a fundamental role in learning. According to the predictive coding account, dopamine is responsible for balancing the interplay between bottom-up input and top-down predictions by controlling the precision of surprise signals that guide learning.

Using functional MRI, we investigated whether dopamine-mediated neural surprise responses differ regarding the behavioural relevance of prediction errors. To this end, twenty-one male and female patients with Parkinson's disease (PD) on and off medication and eighteen healthy controls performed a digit prediction paradigm. During the task, violations of sequence-based predictions either signalled the need to adapt or to stabilise the current prediction. Furthermore, the probability of the violations varied across the experiment.

Controls but not patients off medication became more flexible when the probability of prediction errors increased. On the neural level, this learning deficit in patients was accompanied by altered signalling in the caudate nucleus and left hippocampus. In contrast, probability-dependent modulation of behaviour and neural responses was much less pronounced for irrelevant prediction errors. Also, dopaminergic medication could neither improve learning from prediction errors nor restore the physiological, neurotypical pattern.

Our findings point to a pivotal contribution of an intact dopamine system to learning from prediction errors regarding a flexibilization of predictions and behaviours. Still, they witness only poor effects of dopaminergic medication on learning in PD.

Significance Statement

Dopamine is proposed to play a key role in the build-up and adaptation of predictions about upcoming stimuli by modulating the precision of surprise signals to unexpected environmental changes. The present study investigated whether behavioural and neural surprise responses to either behaviourally relevant or irrelevant unexpected events are impaired in patients with Parkinson's disease. The dopaminergic deficit in patients contributed to an insufficient adaptation of behaviour and decreased surprise-driven learning signals in the striatum and the hippocampus in response to relevant events. These findings provide novel insight into the specificity of dopamine-mediated learning and corresponding deficits in Parkinson's disease.

Introduction

To behave adaptively, we need to adjust our expectations to persistent environmental changes while sustaining the pursuit of our action goals despite temporary distractions. Environmental changes that do not match our expectations, i.e. prediction errors, are known to cause phasic dopamine signalling in the midbrain. Thereby, they trigger bottom-up processing guiding the adjustment of predictions and the initiation of behaviour (Schultz and Dickinson, 2000; Redgrave and Gruney, 2006; Murty et al., 2011; D'Ardenne et al., 2012). This adjustment pertains to learning since future surprise can be minimised and behavioural implications of prediction errors become more predictable (Friston et al., 2014; Fiser et al., 2010). The influence of predictions on behaviour is suggested to be regulated by tonic dopamine action, determining the relative weight or *precision* of bottom-up prediction errors for top-down predictions (Friston et al., 2012). By regulating phasic dopamine release, tonic dopamine modulates the surprise-driven learning rate (Beeler et al., 2010; Humphries et al., 2012) and sets transition thresholds between flexible and stable states, favouring either bottom-up sensory input or top-down predictions (Barter et al., 2015; Yu et al., 2013; Trempler et al., 2017).

During learning, predictions are adapted to a particular context, based on the probabilistic structure of the past (Behrens et al., 2007). This contextual learning has been suggested to rely on the hippocampus (Shohamy and Adcock, 2010; Schapiro et al., 2014; Schlichting and Preston, 2012). Phasic dopamine release in the midbrain modulates hippocampal plasticity, whereas the output from the hippocampus, in turn, enhances dopaminergic signalling in the midbrain (Lisman and Grace, 2005; Kaminski et al., 2018). Moreover, dopamine levels in frontostriatal circuits balance the interplay

of flexibility and stability in response selection (Williams and Castner, 2006; Doll et al., 2011; Cools and D'Esposito, 2011). Here, the striatum assumes the role of a gate for relevant versus irrelevant input into working memory (Badre, 2012; Keeler et al., 2014). Concurrently, high or low energy barriers of attractor networks within the prefrontal cortex facilitate either shielding or updating of working memory representations (Durstewitz et al., 2000; Durstewitz and Seamans, 2008). These barriers are probably adjusted contingent on prioritisation of perceptual input utilising relevance (Summerfield and Egner, 2009; Rauss et al., 2011). However, it so far remains to be elucidated how dopamine contributes to the build-up of predictions for either flexible or stable behaviour in response to prediction errors.

In this fMRI study, we, therefore, compared the performance of healthy controls and patients with akinetic-rigid Parkinson's disease (PD) with and without medication during a digit prediction task. Participants were required to indicate the occurrence of digit rule *switches*, as behaviourally *relevant* violations leading to an update of the predictive rule (revealing flexibility), and to ignore short interruptions, referred to as *drifts* hereafter, as behaviourally *irrelevant* prediction errors provoking a shielding of the predictive rule (revealing stability). Importantly, the proportion of switch and drift occurrences changed over time. Varying probability and predictability of these events as measured by decay-dependent information theoretic quantities, i.e. *surprise* and *entropy* (Harrison et al., 2011), served as regressors for analysing behavioural performance and BOLD time series to assess learning from prediction errors. We expected that PD patients off medications would have problems to adopt flexible and stable states depending on the switch and drift probability, respectively (Friston et al., 2012). In controls compared with PD patients, substantia nigra activity was hypothesised to be modulated by both switch and drift surprise. In contrast, we

hypothesised an increased modulation of the activity of the caudate nucleus and the hippocampus by the probability of switches (Bestmann et al., 2008; Marshall et al., 2016). Regarding stabilisation, we expected a greater involvement of the inferior frontal gyrus (IFG) in response to surprising drifts in controls versus PD patients (Hampshire et al., 2010; Trempler et al., 2017, 2018). Finally, learning from prediction errors should improve with dopaminergic medication, also reflected in a restored surprise-dependent modulation of neural activation within the respective regions.

Materials and methods

Participants

Our sample was the same as reported in Trempler et al. (2018). 21 patients (6 females, mean age = 58.81 years, SD = 9.89, range = [40, 72]) meeting the United Kingdom Parkinson´s Disease (UKPD) Society Brain Bank Criteria for idiopathic Parkinson's disease (Hughes et al., 1992) were recruited via the neurologic outpatient clinic of the University Hospital of Cologne, Germany. Hoehn and Yahr ratings ranged between I and III under regular medication (Hoehn and Yahr, 1967). During the screening session, the severity of symptoms was further defined according to the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). Only patients of the akinetic-rigid subtype were selected, based on the judgment of an experienced movement disorder specialist. Patients did not show any signs of dementia or depression as assessed by the Parkinson Neuropsychometric Dementia Assessment (PANDA) (Kalbe et al., 2008) and the Beck depression inventory-II (BDI-II) (Hautzinger et al., 2006), respectively. The screening included a

training session to ensure that patients would be able to perform the task under their regular dopaminergic medication.

Patients were tested twice on their regular medication ("On"-state) and off medication ("Off"-state), i.e. after overnight withdrawal of dopaminergic medication (at least 10 hours after the last dose). Session order (Off-On and On-Off) was counterbalanced across the participants. Three of 21 healthy participants matched to the patients regarding age and gender were excluded from the present analyses because the task was slightly changed after they had been measured (i.e. rest trials were added). Thus, a group of 18 participants (5 females, mean age = 60.17 years, SD = 10.70, range [36, 74]) served as control subjects. Healthy controls did not receive any medication. They performed the training, the experiment, and all additional assessments on one day. No participant had undergone neurosurgical treatment for the disease or had a history of other neurological or psychiatric diseases.

The study was performed following the Declaration of Helsinki and had been approved by the ethics committee of the Medical Faculty of the University Hospital Cologne, Germany. Each participant submitted a signed informed consent notification and received reimbursement for participation plus travel expenses afterwards.

Task

During the task, a digit sequence was visually presented at the centre of a computer screen, in either ascending (1 – 2 – 3 – 4) or descending (4 – 3 – 2 – 1) order (Figure 1). To enable participants to predict forthcoming input the sequence repeated constantly, and digits succeeded one another for 1 s, separated by an inter-stimulus interval of 100 ms. Directional changes from ascending to descending digit sequences or vice versa (switches, hereafter) occurred at pseudorandom ordinal positions within

the initial sequence and had to be signalled by a button press (switch detection). Besides, single digits were omitted occasionally at variable positions without a temporal gap (drifts, hereafter), and participants were instructed to ignore these omissions (drift rejection). During a motor control task, which was implemented to assess the individual mean reaction time, one digit of the sequence repeated continuously but maximally eight times until the participant pressed the response button. A 6 s presentation of a fixation cross distributed across the experiment served as the baseline (i.e. rest trial).

To assess adaptation to different environments the task was binned into 12 blocks that either had a high or low probability of switches, either paired with a high or low probability of drifts. Each block consisted of an average number of 125 trials in a full-factorial 2 (probability: high vs. low) x 2 (event: switch vs. drift) design. Transitions between block types resulting from this factor combination were balanced across the session. Probabilities were based on a pilot study, which assessed the performance of 12 PD patients during a staircase procedure of the task with different switch and drift frequencies. As a result, the maximum event frequency in unmixed blocks, in which switches and drifts occurred with the same frequency, was set to 16 % (i.e. 8 % per event type) and minimum event frequency was set to 8 % (i.e. 4 % per event type). In mixed (i.e. high-switch and low-drift or vice versa) blocks, the maximum frequency was set to 12 %, whereas the minimum frequency was left at 4 %. In this way, the difficulty level regarding the overall probability of events was kept constant across the experiment (except for unmixed low-frequency blocks). Stimulus presentation was pseudorandomised using the stochastic universal sampling method (Baker, 1987), which ensured a balanced distribution of switches and drifts across the blocks.

The training consisted of ten blocks of 80 trials each and a probability of 16 % for switch or drift occurrence. To enable participants to get accustomed to the task, presentation speed started at 1400 ms per digit and adapted block-wise with a decrease of 50 ms provided that the participant correctly reacted to 75 % of the events. In addition, patients performed a short training before the scanner session with three blocks of 80 trials at the main experiment's digit presentation speed of 1 s. The randomisation was programmed using MATLAB R2012b (The MathWorks Inc., Natick, MA, USA) and stimuli were presented using Presentation 13.1 (Neurobehavioral Systems, San Francisco, CA, USA).

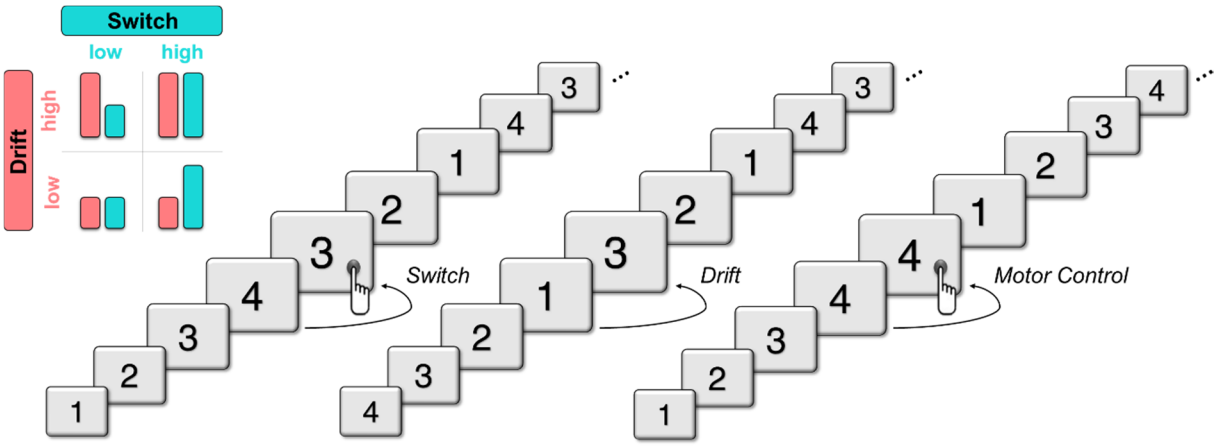

Figure 1. Schematic diagram of the task. Stimuli of a simple 4-digit sequence continuously followed each other with a duration of 1 s and an inter-stimulus interval of 100 ms. Subjects had to indicate changes from ascending to descending sequences (and vice versa) (switch), as displayed in the left row, via a button press. Moreover, they had to ignore the omission of a single digit (drift), as displayed in the middle row. During a motor control task, depicted on the right, one digit repeated continuously until the participant pressed the response button. As depicted in the top left diagram, the probabilities of switches and drifts varied block-wise across the experiment in a 2x2 design.

Probability model

In a Bayesian cognitive model, an observer's predictions of forthcoming sensory input are represented as probability distributions based on previous sensory input and prior knowledge. Due to the present task design, in which critical events were per se

rather improbable and, thus, unpredicted as opposed to frequent standard digits, it is not plausible to assume an ideal Bayesian observer, which would base estimation of probabilities of these events on *all* previous events. Instead, we supposed that the observer would not be able to remember distant events. Consequently, we made use of a time-dependent decay model derived from Harrison et al. (2011) in which distant events are weighted less than recent ones. According to their formula, the update of an observer's model at trial *N* is based on the weighted counts α of each type of event *k* (switch, drift, or standard digit), which are exponentially weighted by half-life τ:

$$\alpha_k(N) = \sum_{t \in T} \exp\left(-\frac{N-t-1}{\tau}\right) \delta(x_t = k)$$

This formula assumes that trial *N*-1 has the weight 1 (i.e. is fully weighted), while the weights of more distant trials decrease at an exponential rate. In the present paper, the weighted counts were computed based on the assumption that τ = 125, according to the mean block length. We also calculated counts weighted by other half-lives (see https://osf.io/n5ugp/) and found that results based on a specification of τ = 125 were sensitive to the prediction of response accuracy of controls versus PD patients. Furthermore, we computed the counts with and without taking rest trials into account. Either the counts of each event were reset after a rest trial (i.e. $T = \{B, B+1, \ldots, N-1\}$ where B indicates the index of the first observation after a rest trial), or rest trials were neglected during counting (i.e. $T = \{1, 2, \ldots, N-1\}$). The probability of a particular event *k* occurring at trial *N* can then be calculated as (Bernado & Smith, 1994):

$$\rho_k(N) = \frac{\alpha_k(N) + \alpha_k(0)}{\sum_{j=1}^{K} \alpha_j(N) + \alpha_j(0)}$$

In words, this probability is characterized by the weighted counts of event *k* relative to the sum of the counts of all possible events (switch, drift, and standard digit).

The prior counts $\alpha_k(0)$ before observing the first trial were set to 1/3 for all events representing an uninformative prior (Jeffreys, 1946). Moreover, like previous studies, we used information theoretic indices, i.e. *surprise* and *entropy*, to quantify the amount of information provided by the current stimulus that could predict response accuracy and neural responses (e.g. Strange et al., 2005; Bestmann et al., 2008; Mars et al., 2008). The surprise $I_k(N)$ of an event, i.e. its improbability, is given by the negative logarithm of the probability:

$$I_k(N) = -\log p_k(N)$$

Conversely, entropy measures the average surprise of all possible events and quantifies the expected information of events regarding their predictability:

$$H(N) = -\sum_{k=1}^{K} \rho_k(N)\, log\, \rho_k(N)$$

The varying extent to which each stimulus was locally unexpected, i.e. its surprise value (Figure 2), was used to explain error rates and fMRI BOLD response amplitudes at switches and drifts. In doing so, we aimed to assess whether learning differs between the two event types, and between healthy control participants and PD patients, regarding behavioural adaptation and its corresponding brain activity.

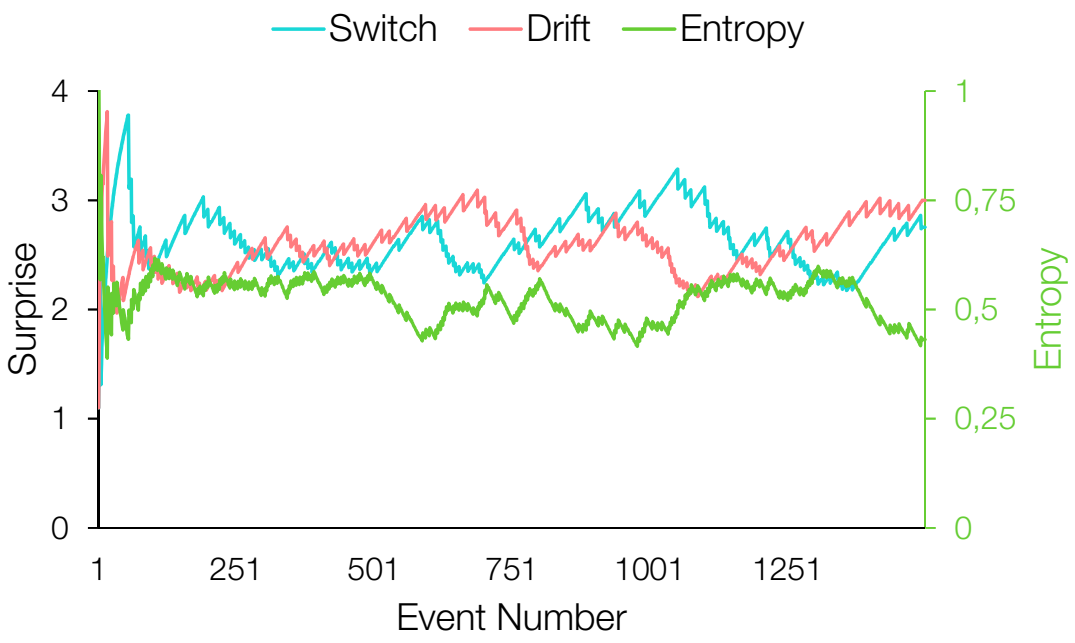

Figure 2. Illustration of the information theoretic measures *surprise,* for switches and drifts, and *entropy* varying over the course of the experiment of one example participant. Surprise values were used to predict the participant's performance and BOLD activity at switches and drifts.

fMRI data acquisition

Whole-brain imaging data were collected on a 3 Tesla Siemens Magnetom Prisma MR tomograph using a TRTX-head coil. To minimise head motion the head was tightly fixated with cushions. Functional images were acquired using a gradient T2*-weighted single-shot echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast (64 x 64 data acquisition matrix, 192 mm field of view, 90° flip angle, TR = 2000 ms, TE = 30 ms). Each volume consisted of thirty adjacent axial slices with a slice thickness of 4 mm and a gap of 1 mm, resulting in a voxel size of 3 x 3 x 5 mm. Images were acquired in ascending order along the AC-PC plane to provide a whole-brain coverage. Structural data were acquired for each participant using a standard Siemens 3D T1-weighted MPRAGE sequence for detailed reconstruction of anatomy with isotropic voxels (1 x 1 x 1 mm) in a 256 mm field of view (256 x 256 matrix, 192 slices, TR = 2130, TE = 2.28). Stimuli were

projected on a screen positioned behind the subject's head and were presented in the centre of the field of vision by a video-projector. Subjects viewed the screen by a 45° mirror, which was fixated on the top of the head coil and adjusted for each subject to provide a good view of the entire screen.

Behavioural data analysis

We assessed task performance by accurate detection of switches (hits), and correct non-responses to drifts (correct rejections), or, correspondingly, switch misses and false alarms at drifts. A motor control task was used to determine the 90%-quantile of each participant's reaction times. This quantile served as an individual time window, in which button presses in response to switches and drifts were acknowledged as hits and false alarms, respectively. Using Bayesian logistic multilevel models in R (R Core Team, 2018) via brms and Stan (Bürkner, 2017; Carpenter et al. 2017), these dichotomous responses were predicted by information theoretic indices (i.e., switch and drift surprise as well as entropy) in interaction with group and event type. For the factors group and event type, we used effect coding with -1 for healthy controls and 1 for patients off, -1 for patients on and 1 for patients off, and -1 for drifts and 1 for switches. Default priors of brms were used, which are weak or non-informative (Bürkner, 2017).

fMRI data preprocessing

Brain image preprocessing and basic statistical analyses were conducted using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; see: http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional images were slice-timed to the middle slice to correct for differences in slice acquisition time. To correct for

three-dimensional motion individual functional MR (EPI) images were realigned to the mean image and motion correction estimates were inspected visually. The anatomical scan was co-registered (rigid body transformation) to the mean functional image. Each subject's co-registered anatomical scan was segmented into native space tissue components. A group-specific template was created using DARTEL with default settings in SPM12. Functional images were then normalised to the MNI space by affine transformations using invertible and smooth deformations (flow fields) for each participant's native space to the template derived from the previous step through the DARTEL tool. Smoothing was also applied during DARTEL warping with a Gaussian kernel of 8 mm^3 full width at half-maximum.

Before subject-level analysis, a denoising procedure using the default settings of the CONN toolbox was performed on the EPI data. To this end, we used the BOLD signal derived from white matter masks and CSF, as well as motion correction parameters from the realignment stage of the spatial preprocessing as covariates of no interest. A 128 s temporal high-pass filter was applied to the data to remove low-frequency noise.

fMRI design specification

The statistical analysis was based on a least-squares estimation using the general linear model (GLM) for serially autocorrelated observations (Friston et al., 1995; Worsley and Friston, 1995). Our GLM included regressors coding for onsets and durations of events, which were then convolved with the canonical hemodynamic response function (HRF) and regressed against the observed fMRI data. The subject-specific six rigid-body transformations obtained from residual motion correction were

included as covariates of no interest. The GLM contained three regressors for the specific events, i.e. for the main effect of standard digits, switches, and drifts.

Moreover, we modelled variability in the BOLD amplitude to switches and drifts as a function of decay-dependent surprise and entropy, as outlined in detail above (cf. Probability model). We mean-centred each regressor before entering the GLM. Resting periods were not modelled and served as an implicit baseline (Pernet, 2014). Also, whenever two events were separated by less than 2 s (i.e. less than one TR), only the first one was included in the GLM, whereas the second was not modelled and treated as part of the implicit baseline.

Contrast images for variations of BOLD amplitudes with surprise at switches and drifts were generated for each participant. We performed region of interest (ROI) analyses to test for BOLD activation differences between the groups in the substantia nigra, the caudate nucleus, the hippocampus, and the IFG. Anatomically defined ROIs were created using the SPM Wake Forest University (WFU) Pickatlas toolbox (http://www.fmri.wfubmc.edu/cms/software, version 2.3) (Maldjian et al., 2003), except for the substantia nigra ROIs, which are not implemented in the WFU Pickatlas and were thus derived from the probabilistic atlas of the basal ganglia (ATAG; Keuken et al., 2014). For the ROI analyses, we extracted beta scores of switch and drift events and corresponding standard errors per voxel and subject. Using Bayesian linear multilevel models in R (R Core Team, 2018) via brms and Stan with default priors (Bürkner, 2017, Carpenter et al. 2017), we predicted the beta scores by group, event type, and ROI while accounting for dependencies between responses belonging to the same voxel or subject. Furthermore, varying degrees of uncertainty in the beta scores (i.e. varying standard errors) were accounted for by using an inverse-variance

weighting scheme with more precisely estimated scores receiving higher weight (Cooper et al., 2009; https://osf.io/n5ugp/).

Hypothesised differences between healthy controls and patients off, and between patients off and on, were tested for behavioural performance and beta values in the selected ROIs. The α-level was set to 5%, with a 95% credible interval for non-directional, and a 90% credible interval for directional hypotheses, respectively. Further, for directional hypotheses, we also report the posterior probability (*pp*) that the differences in neural activation between the groups show in the expected directions.

Results

Behavioural Results

Bayesian logistic multilevel models on surprise and entropy estimates were used to predict behavioural errors, that is, switch misses and false alarms at drifts of healthy controls versus PD patients off, and PD patients on versus off medication. When baseline trials were neglected (see Methods), we found that the modulation of error rate by surprise and entropy depended on event type and group. Regression coefficients and corresponding 95% credible intervals (CIs; i.e., Bayesian confidence intervals) for each predictor variable of these models are given in Table 1 for controls and PD patients off medication, and in Table 2 for PD patients on and off medication.

The results support an interaction effect of SWITCH SURPRISE X GROUP X EVENT TYPE, as well as an interaction effect of DRIFT SURPRISE X GROUP X EVENT TYPE. Figure 3 illustrates that in controls, higher switch surprise led to more missed switches but fewer false alarms at drifts. In PD patients off, the rate of missed switches decreased, and the rate of false alarm to drifts increased as a function of switch surprise. Interestingly, drift surprise did not modulate false alarms at drifts but corresponded to an increased

switch miss rate in controls and a decreased switch miss rate in patients. Moreover, we observed that increasing entropy affected the error rate at switches more than at drifts in controls only. Independently of their medication, patients revealed an interaction effect of SWITCH SURPRISE X EVENT TYPE and DRIFT SURPRISE X EVENT TYPE. However, there were no differences between patients off and on medication.

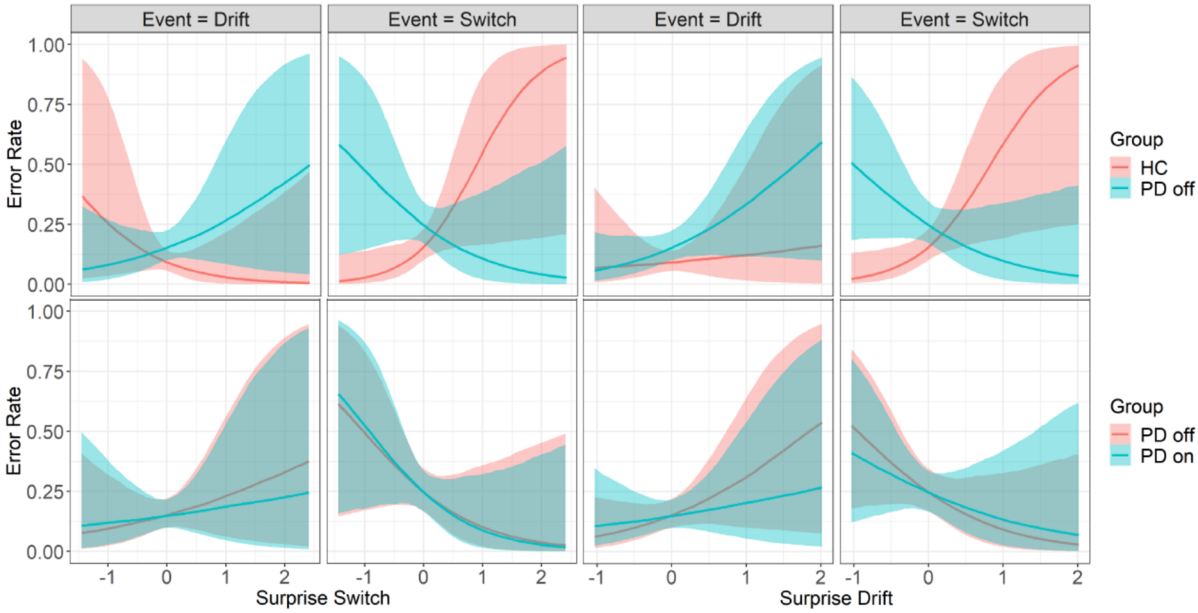

Figure 3. Behavioural data. Effect of mean-centred switch surprise (left panel) and drift surprise (right panel) on error rate at switches, i.e. misses, and at drifts, i.e. false alarms, in healthy controls (HC) and PD patients off (top panel) and in PD patients off and on medication (lower panel). The solid lines depict the regression fit, and the shaded areas show the 95% credibility intervals.

Table 1. Bayesian logistic multilevel model predicting errors of HC and patients off

Coefficient	*B*	l-95% CI	u-95% CI
Switch surprise	0.07	-0.77	0.93
Drift surprise	0.55	-0.27	1.33
Entropy	3.15	-2.05	7.95
Group: PD off	1.99	-0.66	4.55
Event type: Switch	-1.33	-3.87	1.28
Switch surprise x Group: PD off	-0.24	-1.10	0.68
Drift surprise x Group: PD off	-0.60	-1.41	0.27
Entropy x Group: PD off	-3.38	-8.43	1.97
Switch surprise x Event type: Switch	0.34	-0.52	1.19
Drift surprise x Event type: Switch	-0.12	-0.93	0.70
Entropy x Event type: Switch	3.23	-1.93	8.32
Group: PD off x Event type: Switch	3.14	0.65	5.55
Switch surprise x Group: PD off x Event type: Switch	-1.21	-2.03	-0.35
Drift surprise x Group: PD off x Event type: Switch	-0.97	-1.75	-0.18
Entropy x Group: PD off x Event type: Switch	-6.26	-11.05	-1.31

Table 2. Bayesian logistic multilevel model predicting errors of patients on and off

Coefficient	*b*	l-95% CI	u-95% CI
Switch surprise	-0.39	-1.19	0.40
Drift surprise	-0.16	-0.87	0.55
Entropy	-1.37	-5.84	2.95
Group: PD on	0.29	-1.91	2.51
Event type: Switch	1.24	-0.97	3.43
Switch surprise x Group: PD on	-0.10	-0.86	0.62
Drift surprise x Group: PD on	-0.04	-0.76	0.69
Entropy x Group: PD on	-0.59	-5.05	3.74
Switch surprise x Event type: Switch	-0.78	-1.51	-0.02
Drift surprise x Event type: Switch	-0.81	-1.53	-0.08
Entropy x Event type: Switch	-1.84	-6.26	2.60
Group: PD on x Event type: Switch	-0.47	-2.62	1.82
Switch surprise x Group: PD on x Event type: Switch	0.02	-0.75	0.76
Drift surprise x Group: PD on x Event type: Switch	0.24	-0.53	0.95
Entropy x Group: PD on x Event type: Switch	0.93	-3.60	5.25

fMRI Results

Bayesian linear multilevel models were employed to analyse how surprise at switches and drifts modulated the BOLD response in defined ROIs. Corresponding to the reported error rate effects, we addressed the hypothesised differences between healthy controls and PD patients off, and between patients on and off.

Caudate nucleus activity covaried negatively with switch surprise in controls but not in PD patients off medication, L (left): $b_{HC\text{-}Off}$ = -52.53, 90%-CI = [-104.57, -0.84], $pp(b < 0)$ = .95; R (right): $b_{HC\text{-}Off}$ = -50.96, 90%-CI = [-91.21, -14.07], $pp(b < 0)$ = .99 (Figure 4b). Contrary to our expectation, medication did not restore the neural activation within this region but resulted in a more positive covariation with switch surprise compared to patients off medication, L: $b_{On\text{-}Off}$ = 10.22, 90%-CI = [5.64, 14.89], $pp(b < 0)$ = .001; R: $b_{On\text{-}Off}$ = 11.09, 90%-CI = [6.63, 15.36], $pp(b < 0)$ = .001.

There were no differences between controls and PD patients off medication regarding a modulation of right hippocampus activity, $b_{HC\text{-}Off}$ = -8.43, 90%-CI = [-36.53, 20.18], $pp(b < 0)$ = .69. In contrast, left hippocampus activity covaried negatively with switch surprise in controls but positively in PD patients off medication, $b_{HC\text{-}Off}$ = -37.28, 90%-CI = [-68.38, -7.35], $pp(b < 0)$ = .98 (Figure 4c). Compared with PD patients off medication, left hippocampus activity was not modulated by switch surprise when patients were tested under medication, $b_{On\text{-}Off}$ = -11.06, 90%-CI = [-7.43, -14.60], $pp(b < 0) > .99$.

Unlike switch surprise, drift surprise covaried positively with activity in the respective regions. There was some evidence in favour of a stronger modulation of IFG activity by drift surprise in controls compared with PD patients off medication although it did not quite reach significance, L: $b_{HC\text{-}Off}$ = 25.66, 90%-CI = [-0.13, 52.65], $pp(b > 0)$ = .95; R: $b_{HC\text{-}Off}$ = 27.12, 90%-CI = [-2.39, 58.16], $pp(b > 0)$ = .94 (Figure 4d).

Finally, there were no clear differences between controls and patients off medication regarding a modulation of substantia nigra activity by switch surprise, L: $b_{HC\text{-}Off}$ = 4.72, 90%-CI = [-31.18, 41.61], *pp(b > 0)* = .58; R: $b_{HC\text{-}Off}$ = 26.51, 90%-CI = [-2.06, 54.84], *pp(b > 0)* = .93, and by drift surprise, L: $b_{HC\text{-}Off}$ = -2.71, 90%-CI = [-28.96, 22.98], *pp(b > 0)* = .43; R: $b_{HC\text{-}Off}$ = -8.85, 90%-CI = [-41.30, 22.64], *pp(b > 0)* = .33. In both groups, parameter estimates were close to zero, reflecting no modulation by switch and drift surprise (Figure 4a).

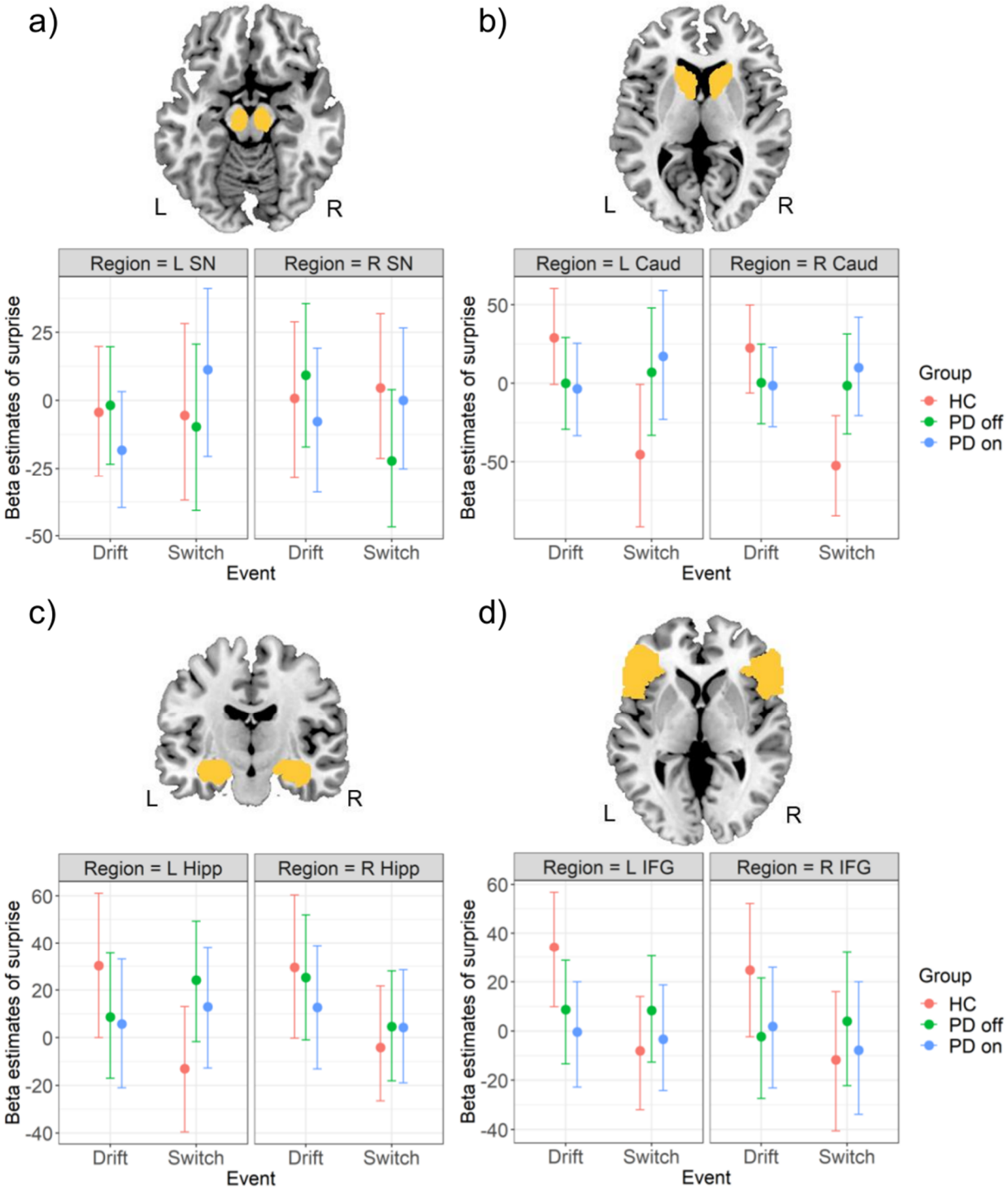

Figure 4. Region of interest fMRI data. Beta estimates of the continuous modulation of activity in the left (L) and right (R) **a)** substantia nigra (SN), **b)** caudate nucleus (Caud), **c)** hippocampus (Hipp), and **d)** inferior frontal gyrus (IFG) by surprise at switches and drifts in healthy controls (HC) and PD patients off and on medication.

Discussion

The present fMRI study aimed at gaining insight into how dopaminergic brain areas modulate learning from relevant and irrelevant prediction errors requiring either updating or stabilisation of current predictions, respectively. We found that probability and predictability of events differentially affected the error rate of healthy subjects and PD patients off medication at relevant prediction errors. In contrast, there were no differences between PD patients on and off medication. On the neural level, we observed a deficient modulation of surprise of relevant prediction errors by bilateral caudate nucleus and left hippocampus in PD patients off medication, with minor changes of surprise responses under medication. In the following, we will (1) discuss our behavioural findings on impaired probability-dependent flexible responding in PD patients, and (2) will then go into more detail regarding our fMRI results.

At switches but not at drifts, error rates of controls and PD patients were differentially affected by changes in the time-dependent probability of both events. Error rates decreased in controls in high-probability conditions; that is, over time healthy participants missed fewer switches when switch frequency was particularly high. Interestingly, increased *drift* probability did not change performance at drifts, but also improved flexible responding to switches. That is, both more switches and more drifts led to better detection of switches in healthy subjects, reflecting implicit learning from environments and hence the ability to flexibly adapt prediction and behaviour.

Compared to healthy controls, PD patients reacted less flexibly to switches in high-probability conditions, no matter whether on or off medication. This finding is consistent with recent studies reporting deficits in implicit contextual learning in PD patients (Perugini et al., 2016; Perugini and Basso, 2017). Our results thus support previous studies implicating dopamine in flexible responding to sensory prediction

errors (Galea et al., 2012; Iglesias et al., 2013). Moreover, the improvement of controls' flexible responding to switches in contexts requiring stabilisation against frequent drifts supports previous accounts, according to which dopamine sensitises behaviour to higher-level precision estimates by highlighting surprising input in predictable contexts (Bestmann et al., 2014; Marshall et al., 2016). Our results extend these findings by showing that contextual learning relies on teaching signals provided by *all* prediction errors but ultimately only impacts upon the reaction to relevant events.

In healthy controls, but not in PD patients off medication, BOLD amplitudes in the bilateral caudate nucleus and the left hippocampus increased with a higher probability of switch occurrence. The involvement of the caudate nucleus in predictive processing of relevant events is in accordance with findings from previous fMRI studies and computational models that highlighted dopamine signalling in the striatum in delivering gating input to frontal areas to allow flexible updating and adaptation of cortical representations (e.g., O'Reilly and Frank, 2006; Stelzel et al., 2013). Thereby, dopaminergic neurons do not only react to unpredicted events per se but also encode their precision by tonic dopamine release (Fiorillo et al., 2008; Friston et al., 2012). The relationship between tonic and phasic dopamine release (Grace, 1991) might provide an explanation why we did not find a modulation of substantia nigra activity by surprise: Learning from prediction errors could be accompanied by a relative decrease in phasic signalling within the substantia nigra but higher tonic release within the caudate nucleus (Schmitz et al., 2003; O'Reilly & Frank, 2006).

Notably, in our previous study using the same paradigm in healthy young participants, we found caudate activity in response to both switches and drifts (Trempler et al., 2017). This discrepancy may be because we employed decay-dependent surprise as a linear regressor in the present study. Indeed, results reveal a

caudate activation increase as a function of drift surprise in controls. This might suggest an increased phasic signalling in response to highly unexpected irrelevant events that decreases in the course of learning.

The hippocampus has been associated with contextual learning by extracting statistical information to create a representation of the environmental volatility (Schapiro et al., 2014; Schlichting and Preston, 2012; Kluger and Schubotz, 2018). Increasing hippocampal activation as a function of switch probability in healthy subjects but not in PD patients could reflect more frequent dopamine-mediated matching of top-down predictions with sensory input (Kumaran and Maguire, 2006). Responses in the hippocampus are hypothesised to enhance the processing of behaviourally relevant novel stimuli through a dopaminergic modulation of long-term potentiation (Lisman and Grace, 2005; Shohamy and Adcock, 2010). Moreover, projections from the dopaminergic midbrain to the hippocampus could enhance the likelihood of future retrieval of predictive models depending on the current goal and context (Scimeca and Badre, 2013; Roediger and Butler, 2011). However, dopamine has been suggested to be particularly responsible for learning from prediction errors regarding response selection (Marshall et al., 2016). Therefore, signals of environmental uncertainty in the hippocampus might also be encoded by other neurotransmitters such as noradrenaline or acetylcholine (Yu and Dayan, 2002; 2005). Dopamine release might interact with these neurotransmitter systems and thereby influence the hippocampal encoding of uncertainty using the goal-relevance of the incoming sensory input (Piciotto et al., 2012; Mizumori and Tryon, 2015; Aly and Turke-Browne, 2017).

Finally, we found no clear evidence for the hypothesised difference between controls and PD patients regarding the modulation of IFG activity by drift probability. However, though not reaching the level of significance, we found that the patients' but

not the controls' predictions became particularly prone to drifts when these were rare, and hence, highly surprising. Moreover, susceptibility to respond to rare drifts was accompanied by a (non-significant) decrease in IFG activation in the PD patients, as compared with healthy controls. Notably, previous studies showed even enhanced distractor-resistance in PD patients compared with healthy subjects (Cools et al., 2009). This alleged advantage in PD patients might result from inflexibility rather than stability, independent of the behavioural relevance of the stimulus (Uitvlugt et al., 2015). Our data suggest that - due to the patients' anticipation impairment - inflexibility (and alleged stability) had a particular impact upon high-probability conditions. Concurrently, patients possibly became more prone to deliver responses when stimuli became more surprising, while - probably due to deficient response selection - these responses remained somewhat arbitrary (Humphries et al., 2006; Trempler et al., 2018).

Dopaminergic medication did not restore learning from prediction errors in our sample. Previous studies revealed disparate findings regarding the impact of dopaminergic medication upon locomotor adaptive learning (Roemmich et al., 2015), feedback, and reinforcement learning (e.g. Cools et al., 2007; McCoy et al., 2018), and learning of uncertainty during decision-making (Perugini et al., 2016; Vilares and Kording, 2017). In PD patients on versus off medication, we found decreased surprise signals within the hippocampus and increased signals in the caudate nucleus. Consistent with the assumption of oppositional interactions between (habitual) striatal and (declarative) hippocampal learning systems, our findings might suggest that, although dopaminergic drugs could potentially increase the firing rate of striatal neurons, they do not enhance learning signals provided by the hippocampus (Foerde and Shohamy, 2011). As a result, predictive strategies cannot be adapted to increasing

demands on flexibility (conceivably due to the involvement of other neuromodulators) resulting in a breakdown of performance. However, to exhibit the contribution of dopamine to impaired learning in PD, future studies with direct neural recordings should measure dopaminergic neuron responses to prediction errors of varying precision, for example in patients undergoing deep brain stimulation surgery.

Our results further suggest that different temporal scales of integrating past events impact on behavioural and neural responses. In line with that, it has been suggested that the hierarchical organisation of the cortex is determined by specific timescales over which information is aggregated (Harrison et al., 2011; Kiebel et al., 2008). Moreover, subjects differ with regard to the number of samples they use when coding probabilities (Trempler et al., 2017) and the time they spend within one representational state (Vidaurre et al., 2017). Therefore, it is reasonable to assume that learning from the specific experiment's temporal dynamics contributes to the prediction of forthcoming input; that is, the accumulated evidence for an event to occur probably consists of an interplay of its absolute probability and the time elapsed since its last occurrence. Previous studies provided evidence for the role of dopamine in gathering information from the passage of time (Pasquereau and Turner, 2015; Tomassini et al., 2016), which could also explain the altered time perception in PD patients (e.g. Harrington et al., 1998). Future studies should thus elaborate on the dopaminergic modulation of learning from either relevant or irrelevant prediction errors by taking temporal aspects of prediction formation into account.

In sum, our study provides evidence that dopaminergic withdrawal in PD contributes to deficient learning from prediction errors, reflected in an impaired flexible adaptation of behaviour and decreased surprise-driven learning signals in the striatum and the hippocampus.

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4. General Discussion and Future Directions

4.1 Summary of the Presented Studies

In the presented studies, I was interested in the relationship and the neural correlates of flexible updating and stabilisation of prediction in response to unexpected environmental changes. Due to the evidence regarding the contribution of dopaminergic neurotransmission to cognitive flexibility and stability as well as to the encoding of the precision of prediction errors, I further examined a potential impairment of corresponding predictive processing in patients suffering from Parkinson's disease (PD).

In **Study I** (*Frontostriatal Contribution to the Interplay of Flexibility and Stability in Serial Prediction*; Trempler et al., 2017), I assessed the neural networks of updating and stabilisation of prediction in young healthy subjects. Furthermore, I tested whether dopaminergic regions support the transition between flexible and stable cognitive states. Results suggest that different cortical regions are activated by different types of prediction errors, dependent on their behavioural requirements. Flexible switching between internal models was accompanied by activation in the medial PFC (mPFC) and the hippocampus, whereas model stabilisation corresponded to activation of premotor areas and the inferior frontal gyrus (IFG). The caudate nucleus responded to both behaviourally relevant and irrelevant unexpected events and its activation was related to a successful response selection following these events. Finally, activity of the substantia nigra within specified time windows was predicted by a previous error bias, which varied intra-individually across the experiment in response to temporal environmental demands. In summary, Study I provides evidence for partially distinct functional mechanisms for flexible and stable responses to prediction errors but a common neural substrate in the striatum, which supports behavioural decisions. Moreover,

results suggest that, on a global level, the substantia nigra modulates the adoption of either more stable or more flexible states, thresholded by participants' individual performance history.

Following these results, in **Study II** (*Association of Grey Matter Changes with Flexibility and Stability of Prediction in Akinetic-Rigid Parkinson's Disease*; Trempler, Binder et al., 2018) I focused on potential deficits of flexible and stable responses to prediction errors in PD patients. I investigated whether such deficits would correspond with specific structural, that is, grey matter alterations in regions responsible for flexible and stable responses as revealed by Study I - in dopaminergic and frontal regions, and in the hippocampus. In healthy controls as well as in PD patients, there was an association between the volume of the midbrain and the participants' general response biases. In contrast, right putamen volume negatively correlated with response selection following prediction errors. As expected, PD patients were impaired in flexible updating, which was associated with the right hippocampus volume. Likewise, the PD patients' difficulties in ignoring irrelevant prediction errors positively related to thickness in frontal brain regions. Dopaminergic medication had no direct influence on behavioural performance, but daily medication dose was positively related to successful response selection across the patients. Taken together, Study II indicates deficient flexible and stable responses in prediction error processing in PD and suggests that these dysfunctions (and partly also interindividual differences in healthy subjects) are associated with the grey matter structure of related brain areas.

Finally, in **Study III** (*Dopaminergic Modulation of Surprise: fMRI Evidence for Deficient Flexible Adaptation of Prediction in Parkinson's Disease,* Trempler, Bürkner et al., 2018) I investigated the neural substrates of potential deficits in PD patients regarding an adoption of flexible and stable states, using the functional MRI data set of Study II. Specifically, I assessed differences between PD patients and healthy subjects in the probability-dependent processing of either relevant or irrelevant prediction errors. In healthy subjects but not in PD

patients, increasing probability of both types of unexpected events was accompanied by a lower miss rate of relevant events (i.e., a more flexible state) but not by a lower false alarm rate to irrelevant events (i.e., a more stable state). On the neural level, this flexible state was accompanied by an increased activation of the caudate nucleus and the left hippocampus in healthy controls but not in PD patients. Moreover, there was evidence for a greater involvement of the IFG in the processing of highly surprising irrelevant events in healthy controls compared to PD patients. Crucially, dopaminergic medication did not affect learning from prediction errors. However, it caused a decreased activity of the hippocampus and an increased activity of the caudate nucleus. In conclusion, Study III provides evidence for deficits in the flexible adaptation of prediction dependent on current environmental challenges in PD, which are not restored by dopaminergic medication.

In the following, I will discuss how flexibility and stability of prediction relate to each other and - against the backdrop of a potential involvement of dopamine - in what way both functions are impaired in PD.

4.2 The Relationship between Flexibility and Stability of Prediction

4.2.1 Measures of Flexible and Stable Behaviour

In the present studies, a focus was set on the relationship between flexibility and stability in the specific scope of predictive processing. I assumed that a distinction can be made between flexible and stable *responses* on the one hand, and flexible and stable predictive *states* on the other hand. Based on the results of the presented studies, Figure 2 summarises the proposed model of flexibility and stability of prediction.

Previous studies suggested that cognitive flexibility and stability oppose each other such that high stability would lead to inflexible behaviour, whereas high flexibility would result in instable responses to distractors (e.g., Armbruster et al., 2012; cf. section 1.1.3). In fact, relevant

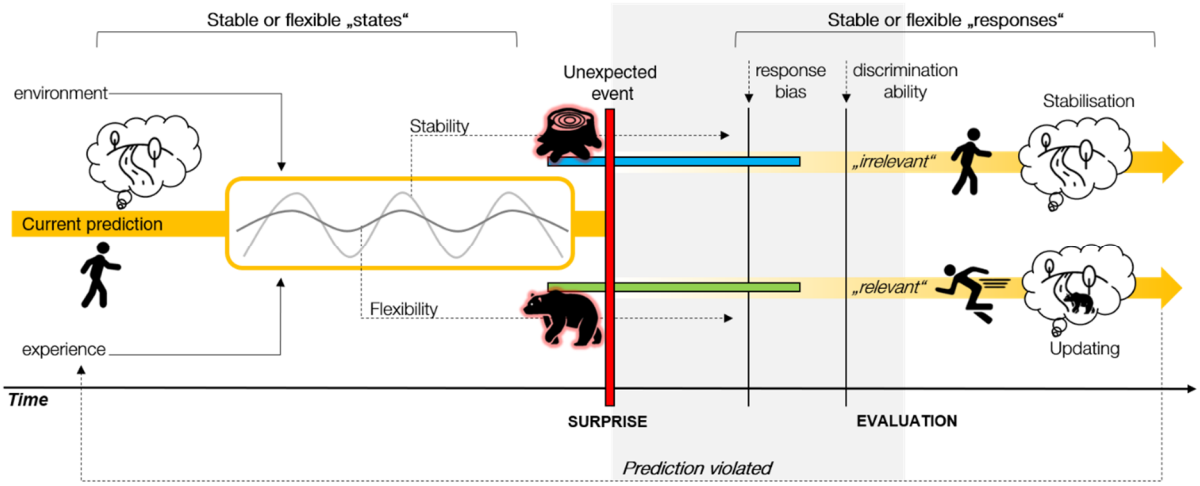

Figure 2. Proposed model of flexibility and stability of prediction. Here, the current prediction (broad yellow line) of a hiker consists of the route ahead. The hiker's predictive state can either be more stable or more flexible (corresponding to high or low precision of the prediction) depending on anticipated environmental challenges (for example the current bear population) as well as previous experiences (for example encounters with bears). Predictive states are schematised as basins in a potential landscape, with flatter valleys according to a more flexible state (dark grey graph) and deeper valleys according to a stable state (light grey graph) (adopted from Durstewitz & Seamans, 2008). As a result, an unexpected event conveys more or less surprise (red vertical line), accompanied by an initial motor reaction (response bias). However, the event itself can either be relevant (a bear) or irrelevant (a tree stub) with regard to an update of the current prediction and the behavioural consequences it entails. Accordingly, the subsequent processing of the unexpected event can outweigh the current response bias. It involves a final evaluation of the stimulus, which is suggested to depend on the individual ability to distinguish between stimuli of different relevance. Finally, the adequate behavioural response can be selected, and the current prediction is either stabilised or updated.

and irrelevant sensory inputs typically require opposing behaviours - a motor reaction or its inhibition, respectively. In this regard, reacting to relevant external events is an indicator of flexible behaviour, whereas ignoring irrelevant events serves as an indicator of sufficient stability. Derived from signal detection theory (Snodgrass & Corwin, 1988), I used corresponding measures to quantify the participants' flexible and stable response behaviour, i.e., hits at relevant events and correct rejections of irrelevant events, respectively. Due to these opposite response options, at least a portion of the trade-off between flexible and stable responding could rely on an individual response bias: the probability or tendency of someone to react to unexpected events per se, independent of an event's identity. In line with that,

previous research even suggests that the response bias - at least in recognition memory - reflects an individual trait-like predisposition (Kantner & Lindsay, 2012). If flexibility and stability were solely attributable to the tendency to either react or not to react to incoming sensory input, the two functions would act in opposite ways. However, no negative relationship between flexible and stable responses to prediction errors was observed in the presented studies. Instead, the measures of flexibility and stability of prediction showed a non-significant trend towards a weak positive relationship in young (Study I) as well as in in older healthy subjects and PD patients on medication (Study II). This suggests that individuals who are better at detecting relevant prediction errors concurrently tend to be better at ignoring irrelevant events. Thus, it rather seems that any superior capacity equally affects both flexibility and stability of prediction. Such a capacity could be the ability to distinguish between different types of stimuli reflecting a precondition of successfully balancing flexibility and stability. The discrimination ability enables the identification of a stimulus' relevance and the behavioural requirements that it entails. In this regard, our behaviour ideally depends on the relevance of the current sensory input rather than on a current (or even fixed) response bias (Cools & D'Esposito, 2011).

Moreover, I assumed that, on a more global level, different predictive states would influence performance and neural responses to prediction errors. The rationale behind this assumption was that stable states would correspond with highly precise top-down predictions and a low influence of upcoming (irrelevant) prediction errors. Conversely, flexible states can be suggested to be accompanied by a high expected precision of (relevant) prediction errors triggering an update of current predictions (Friston, 2010; Summerfield & Egner, 2009). The results of the presented studies indicate that behavioural and neural responses to unexpected events depend on such current predictive states. In an extension of findings of previous studies (Armbruster et al., 2012; Behrens et al., 2007; Jiang, Beck, Heller, & Egner, 2015), the present

results suggest that these states can vary intra-individually, dependent on previous experiences as well as on current environmental challenges.

In this context, I assumed that predictive states are represented on a specific time scale in the brain (Kiebel et al., 2008). This time scale can be represented by a particular time window across which the probability for the occurrence of an event (or rather its inverse *surprise* (Shannon, 1948)) is accumulated and can successfully predict the participants' neural and behavioural responses to this event. In Study I, the length of the time window was individually fitted based on the surprise of relevant and irrelevant events which best predicted the participants' responses to these events. Conversely, in Study III the participants' responses were predicted by surprise, which was determined by an equal window length for all participants, weighting recent events more than distant ones (Harrison, Bestmann, M. Rosa, Penny, & Green, 2011).[4] In Study I, a lower surprise of irrelevant events was related to correct responses to prediction errors (probably reflecting anticipation), whereas a lower surprise of relevant events was related to an increased rate of incorrect responses (probably reflecting increased difficulty). In contrast, in Study III healthy participants improved flexible responding as a function of the probability of both relevant and irrelevant upcoming events. These contradictory results of Study I and Study III may result from the different time scales used to predict the participants' behaviour. Since the mean time scale over which the incoming information was aggregated was much shorter in Study I than in Study III, it may be possible that stable states are built on a more temporary time scale and might depend on the retention of short-term environmental challenges rather than on long-term contextual learning required for the adoption of flexible

[4] The reason for these different approaches is that in Study I, I aimed at investigating whether substantia nigra activity can be predicted by performance within a specified time window whose length was assumed to differ between individuals. Thus, I was not primarily interested in whether surprise within a specific time window could successfully predict behavioural performance but in the window length itself. Conversely, explicitly searching for the window length that best predicts performance does not allow to test the respective effect of surprise on performance. Therefore, in Study III I had to specify an equal time window for all participants since I was interested in differences between PD patients and healthy controls in learning from prediction errors reflected in both behaviour and brain activity. Future studies could assess PD-specific differences in the window length that best predicts performance.

states. Thus, although the presented studies show that responding to prediction errors depends on current predictive states, future studies should strategically examine temporal aspects of the build-up of predictions for different environmental requirements.

4.2.2 Neural Correlates of Flexibility and Stability of Prediction

The present studies reveal both common and distinct neural substrates of flexibility and stability of prediction, substantiating the assumption that both functions act at least in part independent of each other (for an overview of the most relevant areas, see Figure 3).

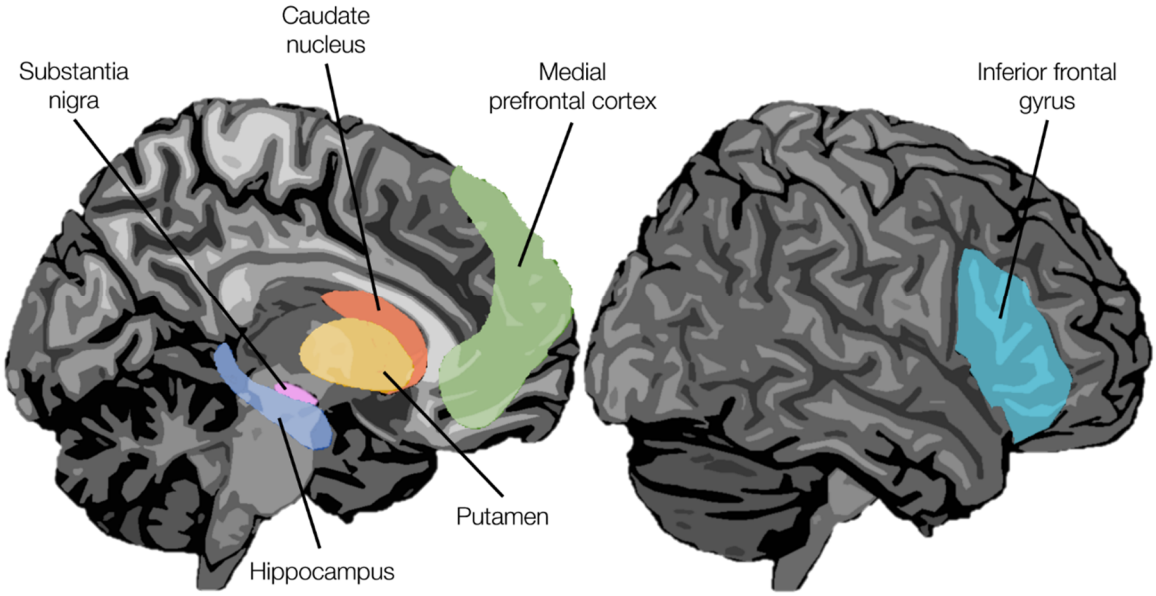

Figure 3. Brain regions responsible for balancing flexibility and stability of prediction. Note that these regions only illustrate the most relevant areas as focused on in the presented studies. Other brain regions as, for example, the premotor system and the cingulate cortex also play a role in flexibility and/or stability of prediction.

Cortical Networks

In Study I, I conducted a whole-brain analysis to test the hypotheses on the respective cortical networks for flexible and stable responses to prediction errors. For the processing of relevant versus irrelevant events, a network comprising mPFC and the right hippocampal

formation was found. The medial PFC has been associated with reporting prediction errors (W. Alexander & J. Brown, 2011, 2018) and with guiding the encoding of these prediction errors in the hippocampus (Schlichting & Preston, 2016; van Kesteren, Ruiter, Fernández, & Henson, 2012). The hippocampus, in turn, has been suggested to create representations of the environmental volatility (Kumaran & Maguire, 2006; Schiffer, Ahlheim, Wurm, & Schubotz, 2012). In line with this, Study III showed that probability-dependent processing of relevant prediction errors is accompanied by a left hippocampus activation increase in healthy older subjects. The presented studies indicate that the hippocampus supports flexible updating of predictions in response to relevant unexpected events and adopting a flexible state when these events become even more probable.

Regarding stability of prediction, the processing of irrelevant versus relevant prediction errors was found to be accompanied by activation of a network comprising portions of the premotor system and the IFG in Study I. The PM is associated with the sequential prediction of external events (Schubotz, 2007; Schubotz & Cramon, 2003), and SMA activity in particular has been observed during the mnemonic representation of predictable sequences - similar to what was required during the processing of irrelevant omissions in the present paradigm (Schönberger et al., 2015). Regarding the involvement of prefrontal areas, the involvement of the IFG is consistent with previous findings, according to which the lateral PFC plays a major role during working memory stabilisation (Bilder, Volavka, Lachman, & Grace, 2004; D'Esposito, 2007; E. Miller & Cohen, 2001). As discussed in the presented studies, IFG activation in response to irrelevant prediction errors might reflect either heightened verbal working memory load (Fegen, Buchsbaum, & D'Esposito, 2015; Shergill et al., 2002), attentional control when facing salient stimuli (Hampshire, Chamberlain, Monti, J. Duncan, & Owen, 2010), or the inhibition of motor responses (for a review, see Aron, Robbins, & Poldrack, 2014). Study III revealed an IFG activity increase as a function of the surprise of irrelevant

prediction errors, speaking in favour of its role in the control and inhibition of responses to highly salient stimuli. To clarify the exact role of an IFG involvement in the stabilisation of prediction, future studies could use a different stimulus material (e.g., circle instead of digit sequences to assess the effects of verbalisation) or match the required behavioural responses to the two types of prediction errors (e.g., either reacting to both or to neither of the two types of prediction error to assess the role of motor inhibition).

Dopaminergic Midbrain and the Striatum

Regarding the focus on the putative involvement of dopaminergic areas in flexibility and stability of prediction, Study I showed that activity in the substantia nigra is associated with the transition between flexible and stable states, driven by participants' performance in response to recent environmental demands. A participant's bias to respond too rarely successfully predicted an increase in substantia nigra activity. In turn, a bias to response too frequently was accompanied by a decrease in substantia nigra activity. Moreover, Study II showed that even a larger volume of the midbrain is accompanied by a higher probability to react to unpredicted sensory input, irrespective of its relevance. It has been found that midbrain volume positively relates to reward reactivity in the ventral striatum and the mPFC (Carlson, Foti, Harmon-Jones, & Proudfit, 2015). The present results further suggest that midbrain volume is associated with interindividual differences in reactivity to unexpected input in general. However, contrary to the expectation, no modulation of substantia nigra activity in healthy subjects in response to highly surprising prediction errors was observed in Study III. Schiffer et al. (2012) reported previously that the substantia nigra is particularly activated by the novelty of the sensory input and not by unpredicted input per se. Thus, it is possible that prediction errors in the present study were no longer novel and not that surprising as soon as participants had learned from these initially quite unexpected events (for a more detailed discussion, see section 4.4.1).

Finally, Study I revealed a BOLD signal increase in the caudate nucleus in response to both relevant and irrelevant prediction errors. The degree of activation was inter-individually related to the participants' ability to distinguish between the two types of events. This finding is in line with previous studies, supporting a striatal role in gating of and response selection to sensory input (Badre, 2012; Chatham & Badre, 2015). The assumption that the striatum is responsible for flexible updating (e.g., Cools et al., 2009; Stelzel, Basten, Montag, Reuter, & Fiebach, 2010) can be extended by the present results, which indicate that flexible processing in the striatum involves the decision of whether to adapt or to stabilise current predictions.[5] Interestingly, Study III revealed an increase of caudate activation with increasing probability of relevant events. This increase can be supposed to reflect the adoption of a more flexible state conceivably due to higher tonic dopamine release (Frank & O'Reilly, 2006; Schmitz, Benoit-Marand, Gonon, & Sulzer, 2003). In contrast, there was also an increase of caudate activation in response to highly surprising irrelevant events. This increase could reflect phasic signalling that decreases when it is learned that the input is rather irrelevant (for a discussion of the putative involvement of dopamine in dealing with prediction errors, see section 4.4.1). In Study II, putamen and not caudate volume was related to the ability to distinguish between relevant and irrelevant prediction errors. Given the primary connections of the caudate/anterior putamen and the posterior putamen with lateral prefrontal and (pre-)motor regions, respectively (G. Alexander et al., 1986; Di Martino et al., 2008), one could suggest that the caudate nucleus supports the selection of relevant information used to update predictions, whereas the putamen is associated with motor aspects of executing the correct response. This in line with previous findings from other domains (Argyropoulos, Tremblay, & Small, 2013; Jankowski, Scheef, Hüppe, & Boecker, 2009). However, future studies are warranted to further clarify the

[5] Note that the term *flexible* is here used in a different sense as usually used in the present thesis. In any case, it is evident that a precise clarification of the terms used, and the constructs described with them is of decisive importance for the interpretation of the results of various studies.

contribution of the caudate nucleus and the putamen, and cognitive and motor aspects of response selection in predictive processing.

4.3 Flexibility and Stability of Prediction in Parkinson's Disease

A potential impairment of the interplay of flexibility and stability of prediction in PD patients not only provides evidence for a central role of dopamine in prediction but can also have important clinical implications regarding a deeper understanding and potential treatment of the disease. Accordingly, Study II was dedicated to flexible and stable responses and their association with grey matter structure in PD. Study III investigated disease-specific difficulties in learning from prediction errors, i.e., in the adoption of flexible and stable states.

4.3.1 Behavioural Impairment of Flexibility and Stability

In Study II, PD patients exhibited both inflexible responses to relevant prediction errors and instable responses to irrelevant ones. Indicated by a lower discrimination index, PD patients are, thus, impaired in their sensitivity to detect relevant versus irrelevant changes. The finding of deficient flexible responses to relevant prediction errors is in line with a huge body of studies reporting inflexible updating in PD patients (Cools, 2001b; Lees & E. Smith, 1983). Intriguingly, Study III further showed that patients exhibit an impairment in learning from prediction errors to improve flexible responding. While healthy subjects become more flexible in highly volatile environments probably because prediction errors are given a greater weight (whereby volatility here refers to an increased rate of both irrelevant and/or relevant input), PD patients react to events when these are highly surprising. This difference between healthy subjects and PD patients further indicates an impairment in probabilistic learning from prediction errors in PD (Perugini & Basso, 2018; Perugini, Ditterich, & Basso, 2016): PD patients appear to find it more difficult to react to an increasing number of events insofar as

these events - due to deficits in learning from the previously observed input - could not be foreseen. This assumption could also provide an explanation for the inconsistent findings on cognitive stability in PD. As already mentioned, both enhanced and decreased distractor-resistance was reported previously (Cools et al., 2010; E.-Y. Lee et al., 2010). In Study II, when controlled for the participants' general response bias (assuming that this would, at least in part, control for the likely motor rigidity of the patients), PD patients showed not only impaired flexible but also impaired stable responding. This finding might indicate that the alleged enhanced stability, which was reported in some studies, actually results from the patients' (motor) inflexibility. Results from Study III partially support this interpretation. Patients detected more relevant but also tended to incorrectly indicate more irrelevant prediction errors in environments of a low compared to a high volatility. Thus, patients became more prone to deliver responses when unexpected stimuli were even more surprising. Conversely, inflexibility (i.e., alleged stability) had a greater impact in highly volatile environments: here, PD patients "missed" not only more relevant events but - to their advantage - also more irrelevant events instead of actively inhibiting them.

In summary, PD patients appear to be impaired in selecting the correct response to unexpected events: they are more prone to react to distracting events but also to miss important input. Thereby, they seem to reveal an impaired surprise-driven learning to adapt to changing environmental demands. However, since results depended on the time scale used to predict behavioural data, further studies could investigate whether PD patients also represent probabilities of upcoming relevant or distracting sensory input but on a different (probably shorter) time scale compared with healthy subjects.

4.3.2 Structural and Functional Correlates of Impaired Response Selection

Comparing grey matter structure between PD patients and healthy subjects in Study II revealed atrophy in the caudate nucleus in PD patients. Surprisingly, this atrophy was not related to impaired responses to prediction errors. Previous studies revealed inconsistent results regarding the relationship between caudate atrophy and cognitive impairment in PD (Alegret et al., 2001; Camicioli et al., 2009; Geng, Li, & Zee, 2006). The differences between these studies could be due to the heterogeneity of the patients samples regarding disease duration or different PD subtypes, but also to the respective method used for the segmentation of grey matter structures (Amiri et al., 2018). However, fMRI as used in Study III revealed a strong activation in the caudate nucleus in response to relevant events as a function of their probability in healthy subjects, yet no probability-dependent modulation of caudate activity in PD patients was detected. Striatal deactivation might impair bottom-up gating to frontal areas to allow flexible updating and adaptation of cortical representations (Frank & O'Reilly, 2006; Stelzel et al., 2010).

Intriguingly, the behavioural measures of flexibility and stability of prediction positively related to thickness and volume of specific regions in Study II. The direction of these effects could explain why there were, apart from caudate atrophy, no further grey matter differences between healthy subjects and PD patients. As thoroughly discussed in Study II, there could have been a compensatory thickening of grey matter in some patients that could still not counterbalance cognitive decline (Rektorova et al., 2014). Although morphological changes (mostly atrophy) of the hippocampus are commonly associated with a progression towards dementia, which occurs more likely in later stages of the disease (Bouchard et al., 2008; Camicioli et al., 2003), the present finding suggest that, even in early stages of PD, subtle differences in this region's morphology are accompanied by cognitive deficits associated with learning and flexible updating. In line with the assumed role of the hippocampus in contextual

learning and in building representations of the environmental volatility (Kluger & Schubotz, 2017; Schapiro, Gregory, B. Landau, McCloskey, & Turk-Browne, 2014), Study III revealed an activation increase of the hippocampus as a function of the probability of relevant events in healthy subjects. In contrast, the reverse pattern, i.e., increased activity in response to highly surprising events was found in PD patients. Thus, the patients' impairment in adopting a flexible state in highly volatile environments is accompanied by a relative decrease in hippocampus activation.

Regarding impaired stability of prediction, thickness of frontal regions, i.e., IFG and mPFC, was related to the deficits in inhibiting irrelevant prediction errors in PD. An association with IFG thickness was in accordance with the hypotheses, since this region was found to support inhibition of distractors in Study I. In line with that, Study III provided evidence for a difference between controls and PD patients regarding the modulation of IFG activity by the probability of irrelevant events. The susceptibility to respond to rare irrelevant events was accompanied by a decrease in IFG activation in PD patients compared with healthy controls. The additional involvement of the mPFC in Study II might suggest compensatory frontal mechanisms for inhibitory control in PD, though resulting in rather unspecific responses to unexpected stimuli (for a review on compensatory reliance on frontal regions for motor control during aging, see Seidler et al., 2010). However, this assumption ought to be tested by future studies, since it was assumed to find a relationship of mPFC thickness with the detection of relevant rather than with irrelevant events.

To sum up, behavioural deficits in responding to relevant and irrelevant prediction errors in PD are associated with the morphology of the hippocampus and frontal regions, respectively. Moreover, the impaired ability to adapt flexibility in volatile environments is associated with decreased hippocampal and caudate activity. Finally, there is some evidence in favour of decreased surprise signals to irrelevant events in IFG, which might relate to impaired inhibition

in PD patients. In view of the involvement of frontal areas in stability and the hippocampus in flexibility of prediction, future studies could investigate how impaired updating and stabilisation as two (at least partially) independent processes relate to the two cognitive profiles in PD patients that have been suggested by the dual-syndrome hypothesis: on the one hand disruptions of frontostriatal circuits are assumed to result in executive impairments, whereas on the other hand temporoparietal alterations are associated with a progression towards dementia (Kehagia et al., 2013).

4.3.3 Effects of Dopaminergic Medication and their Clinical Implications

Although medication caused an improvement of the patients' motor symptoms, it did not restore behavioural performance in the presented task measuring flexibility and stability of prediction. Patients on medication neither exhibited more correct responses nor did they adopt a more flexible state in volatile environments than under withdrawal. As already discussed in Study II, the overnight withdrawal may not have led to a complete withdrawal of dopamine availability: first, patients were in the early stage of the disease and there might have been still a sufficient number of dopamine producing neurons in the substantia nigra (Chase, Fabbrini, Juncos, & Mouradian, 1990). Second, in some cases, due to ethical concerns the duration of withdrawal was shorter than the half-time of the dopaminergic drugs. However, in view of the positive relationship between the dose of individual daily dopaminergic medication and the ability to distinguish between relevant and irrelevant prediction errors as found in Study II, medication might improve response selection at least in the long term.

Corresponding to previous studies reporting poor effects of dopaminergic medication on uncertainty learning (Perugini et al., 2016; Vilares & Kording, 2017), PD patients under medication did not improve regarding the adoption of more flexible states depending on current environmental demands in Study III. Interestingly, PD patients on versus off medication

exhibited decreased surprise signals within the hippocampus and increased surprise signals in the caudate nucleus. Previous research suggests oppositional interactions between the hippocampus and the striatum during learning: while the hippocampus has been associated with declarative memory and contextual learning, the striatum plays a role in implicit habit learning and in building stimulus-response associations (for a review, see Foerde & Shohamy, 2011; Goldfarb, Chun, & Phelps, 2016). Although the contribution of both regions to different types of learning is still a matter of debate, the present results indeed suggest an opposite modulation by dopaminergic medication: medication appears to enhance firing rate of striatal neurons in response to surprising relevant events but, concurrently, decreases contextual learning signals provided by the hippocampus. Future studies should elaborate on medication effects on learning signals and on the potential behavioural deficits that accompany these effects.

In line with the heterogeneous pathophysiology of the disease accompanied by the heterogeneous clinical picture (Biundo, Weis, & Antonini, 2016), cognitive symptoms appear to only partially respond to dopaminergic medication. Although medication successfully alleviates dysfunctions associated with overt motor execution, there is still debate whether medication also has beneficial effects on cognitive impairment (Solari, Bonito-Oliva, Fisone, & Brambilla, 2013). In the long run, there might even occur side effects of medication such as dyskinesia or impulse control disorders (Voon et al., 2017). Side effects could be traced back to dopamine overdose in some brain areas, which are initially not (yet) affected by dopamine degeneration (Cools, 2006; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). It has been reported that in the early stage of the disease, the most severe loss of nerve terminals is in the dorsal and posterior putamen, whereas the anterior and ventral striatum is relatively spared (Morrish, Sawle, & Brooks, 1996; Nandhagopal et al., 2009). Thus, since PD patients included in the presented studies were in the early stage of the disease, at least some of the presented findings might represent side effects of medication rather than initial effects of the disease.

Further studies are required to systematically disentangle the physiological causes of different cognitive symptoms in PD.

Consequently, non-pharmacological treatment that targets cognitive impairment in PD is becoming more widely endorsed (Eberling et al., 2014). There is evidence for the effectiveness of physical exercise, cognitive and nutritional interventions (see Goldman et al., 2018, for a topical discussion and review). With respect to predictive processing, Binder et al. (2014) showed previously that a training of serial prediction that engages sensorimotor circuits can improve motor functions in healthy older subjects. Thus, it seems promising to assess whether and, if so, which symptoms in PD could benefit from a training of serial prediction. In addition, future studies could investigate whether training could help the patients to improve their ability to distinguish different types of unexpected events as well as to adapt predictions to different environmental demands.

4.4 Dopamine, Predictive Processing, and Cognitive Motor Control

4.4.1 Evidence for the Role of Dopamine in Predictive Processing

Phasic dopaminergic neurotransmission in the midbrain has been shown to signal prediction errors allowing a fast adaptation of behaviour (D'Esposito & Postle, 2015; Redgrave & Gurney, 2006). Because of the short latency of the phasic dopamine signal (~100ms), incoming sensory input has probably not yet been identified at the time of dopamine release (Redgrave, Prescott, & Gurney, 1999). It is therefore suggested that phasic dopamine release is rather triggered in response to any unpredicted stimulus, independent of its value (den Ouden, Kok, & Lange, 2012). However, by modulating phasic dopamine release, tonic dopamine, which acts over longer time scales (minutes to hours), can bias response selection (Dreher & Burnod, 2002); cf. section 1.2.1). Accordingly, the modulation of substantia nigra activity by transitions between flexible and stable states as reported in Study I might reflect tonic dopamine

release setting motor thresholds dependent on previous performance. The influence of tonic dopamine release on phasic responses may also provide an explanation why activity of the substantia nigra was not modulated by the probability of unexpected events in Study III. Learning from prediction errors that became more predictable themselves could have been accompanied by a decrease of phasic dopamine transmission in this region. In line with this, substantia nigra activity was modulated by surprise when rest trials were taken into account during the calculation of probabilities. Considering rest trials resulted in a shorter time scale over which probabilities were sampled to predict the participants' behaviour and neural activity. Though in this case, learning from prediction errors was not mapped onto behaviour, the substantia nigra revealed a corresponding surprise signal in response to highly unexpected relevant events (for corresponding (additional) analyses of Study III see https://osf.io/n5ugp/).

Concurrently, the increase of caudate nucleus activity as a function of increased probability (and, thus, decreased surprise) of relevant prediction errors found in Study III could also reflect tonic dopamine action, which is suggested to encode the precision of prediction errors over longer time scales (Fiorillo, Tobler, & Schultz, 2003; Friston et al., 2012). The anticipation of flexible updating in the course of learning from relevant events reduces overall surprise, which leads to reduced evoked responses (i.e., phasic discharges) to the respective events (Y. Yu et al., 2013). Associating these findings with models, which propose that flexible and stable states are realised by dopamine acting on specific receptor classes (Durstewitz & Seamans, 2008), caudate nucleus activity may reflect increased D2 receptor stimulation. This stimulation results in an inhibition of the indirect pathway of the basal ganglia and, thus, in disinhibition of thalamocortical connections (Frank & O'Reilly, 2006; cf. section 1.2.2).

Interestingly, there was no corresponding activation increase for the adoption of a stable state in any of the brain areas targeted by Study III that would render the system resistant to an increased probability of irrelevant prediction errors. For example, activity in the IFG rather

increased when irrelevant events were highly unexpected. It can be assumed that this increased activity reflects phasic dopaminergic discharges reporting "changes in the current context and signal a change in the relative precision (uncertainty)" (Friston, 2012). Environments in which irrelevant prediction errors are more probable might rather lead to a decrease in tonic signalling resulting in greater responses (i.e., phasic discharges) to highly unexpected irrelevant events. Remarkably, the encoding of the precision of prediction errors by tonic dopamine thereby not only accounts for the degree of surprise but also for the behavioural relevance of sensory input.

Thus, given the structural and functional changes in the IFG in PD patients, one might speculate that these also result from dopamine deficiency. PFC circuits have been suggested to rely heavily on dopamine neurotransmission (Seamans & Yang, 2004). It is proposed that phasic dopamine release in the PFC provides signals to update working memory representations (Servan-Schreiber, 1990; Seamans & Yang, 2004). The dual-state model suggests that D2-receptor activation in the PFC renders prefrontal representations more flexible to allow for simultaneous but relatively weak (i.e., little precise) representations, whereas a D1-dominant state is associated with much more stable (i.e., highly precise) representations (Durstewitz & Seamans, 2008). Regarding the involvement of the IFG in particular, Wimber et al. (2011) observed higher IFG-mediated interference suppression in carriers of the Met allele compared to carriers of the Val allele of the COMT Val108/158Met polymorphism, which is associated with higher PFC dopamine availability. Moreover, caudate dopamine function has been found to be associated with IFG activity during working memory maintenance (S. Landau, Lal, O'Neil, Baker, & Jagust, 2009). Conceivably, different morphology and activity associated with stabilisation against irrelevant prediction errors in PD patients, as found in the presented studies, might point to deficient dopamine function in the IFG.

Regarding the hippocampus, it has been suggested that long-term potentiation in response to relevant novel stimuli is triggered by a dopamine-dependent loop formed by the

hippocampus and the dopaminergic midbrain (Kamiński et al., 2018; Lisman & Grace, 2005; Shohamy & Adcock, 2010). Phasic release in the midbrain modulates hippocampal plasticity for memory formation, whereas the output from the hippocampus enhances dopaminergic signalling in the midbrain. However, other neurotransmitters such as noradrenaline or acetylcholine might also be responsible for the encoding of environmental uncertainty in the hippocampus (A. Yu & Dayan, 2002, 2005) but interact with dopamine release regarding adaptive reactions to unexpected events (Bestmann, Ruge, Rothwell, & Galea, 2015; L. Marshall et al., 2016). The integrity of the cholinergic system determines memory performance in healthy elderly (Richter et al., 2014) and posterior cortical changes in PD have been associated with cholinergic loss resulting in deficits in learning and memory, i.e., a progression towards dementia (Hall et al., 2014). Moreover, previous work highlights the role of noradrenaline depletion due to neuron loss within the locus coeruleus in PD, which is suggested to cause cognitive inflexibility (Delaville, Deurwaerdère, & Benazzouz, 2011; Vazey & Aston-Jones, 2012). Thus, to really exhibit the contribution of dopamine to flexibility and stability of prediction, further research is warranted to more directly measure dopaminergic neuron responses associated with prediction errors. For example, positron emission tomography studies (Sawada et al., 2012), pharmacological intervention studies using D2 agonists (Cameron, Wallace, Al-Zughoul, Kayser, & D'Esposito, 2018; Stelzel, Fiebach, Cools, Tafazoli, & D'Esposito, 2013), or imaging genetic studies using groups of different genotypes associated with dopamine metabolism (Nolan, Bilder, Lachman, & Volavka, 2004; E. Rosa, D. Dickinson, Apud, Weinberger, & Elvevåg, 2010; Stelzel et al., 2010) could be conducted. Apart from that, prospective studies could investigate flexibility and stability of prediction in other neuropsychiatric diseases such as schizophrenia and attention deficit hyperactivity disorder in which dopamine dysfunctions are suggested to play a key pathological role.

4.4.2 The Relationship between Cognitive and Motor (Dys-)Functions

A starting point of this thesis was the postulation that motor and cognitive control rely on the same (or similar) principles, namely principles of predictive processing, that account for the intertwining of cognitive and motor functions. Hence, the operationalisation of flexibility and stability of prediction was based on the assumption that flexible updating of current predictions implies - at least in most cases - a corresponding motor reaction, whereas a stabilisation against irrelevant prediction errors can be associated with the inhibition of motor responses to these distractors. The presented results clearly indicate a contribution of rather "non-motor" regions (i.e., caudate nucleus, hippocampus and IFG) to the interplay of the two functions and, thus, to the selection of correct (motor) responses to prediction errors. By playing a key role in signalling prediction errors and in encoding their precision, dopamine has been suggested to be involved in both gating of relevant input to update cortical representations and selecting the respective motor responses implied by them. Correspondingly, impaired flexible and stable responses in PD patients were not only associated with differences in the structure and activity of these regions, but also with the severity of the patients' motor symptoms (cf. supplementary material of Study II). Previous studies reported a relationship between the severity of freezing of gait and lower scores of frontal tests (Amboni, Cozzolino, Longo, Picillo, & Barone, 2008; Vandenbossche et al., 2011). Domellöf, Elgh, and Forsgren (2011) described an association between bradykinesia and working memory and cognitive flexibility, whereas postural instability was related to visuospatial functioning. These associations were still persistent one year after the initial assessment (Domellöf, Forsgren, & Elgh, 2013). The present results further indicate that motor symptoms in PD (apart from cognitive functions) not only result from a motor loop dysfunction and corresponding deficits in initiating movements but also rely on deficits in dealing with unexpected input per se. Considering, in turn, the evidence for the contribution of the premotor loop to purely cognitive functions (Schubotz, 2007) and

corresponding deficits in PD (Hagelweide et al., 2018; Schönberger et al., 2013; Schönberger et al., 2015), the differentiation between cognitive and motor functions as well as accordingly assigned brain regions seems rather vague.

Even though the present task to measure flexibility and stability of prediction required a motor reaction, this reaction was externally guided by the instruction to indicate a directional change in the digit sequence by button press. Hence, flexibility and stability of prediction were operationalised in the context of perceptual inference, where prediction errors are minimised by an update of current predictions (Feldman & Friston, 2010). Reactive motor responses accompanying these updates can be distinguished from the internally guided movements that we constantly produce to influence our environment in accordance with our current goals. Thus, during active inference, the environment is actively changed in a way that the sensory input conforms to our predictions (Adams et al., 2013; Friston, 2010). Future studies should investigate the difference between motor reactions that accompany updates of predictions due to (immutable) changes of the environment on the one hand, and motor actions causing changes of the environment by oneself on the other hand. Using the present paradigm, the detection of a directional change by button press could, for example, produce a reversal of the directional change such that the sequence is presented again in the original order.

Finally, investigating whether the behavioural and neural effects of flexibility and stability of prediction can be transferred to other domains might prove important. For example, principles of perceptual and active inference are suggested to pertain to action observation (Kilner, Friston, & Frith, 2007; Urgen & L. Miller, 2015) and to emotional processing in the context of interoceptive inference (Seth, 2013; Seth & Friston, 2016). With regard to previous findings on deficits in action representation (Poliakoff, 2013) as well as in emotion recognition (Argaud, Vérin, Sauleau, & Grandjean, 2018) in PD, future research could address the question whether these deficits also rely on an impaired predictive processing in the respective domain.

5. Conclusion

Maintaining the delicate balance between flexibility and stability of prediction is illustrative of the fascinating human abilities that we take for granted in our everyday life. People might notice this natural aptitude only when they are no longer able to anticipate and to cope with environmental challenges.

The studies composing the present thesis provide evidence that the selection of either flexible or stable responses in prediction error processing correspond to partially independent functions. Moreover, they indicate a role of dopamine in corresponding response decisions following relevant or irrelevant prediction errors. Importantly, patients suffering from Parkinson's disease displayed an impairment in both responding to and learning from prediction errors, probably due to a deficit in utilising the respective relevance of the sensory input. The patients' deficiencies were accompanied by changes in the underlying structure and activity of brain regions associated with dopamine function.

The presented studies provide a further step towards a deeper understanding of the role of dopamine and an impairment of predictive processing in Parkinson's disease, thereby offering a multitude of starting points for future studies. The notion that motor and cognitive control employ a unified principle of predictive processing, whose impairment is a core of the patients' symptoms, warrants further investigations in due course.

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Abbreviations

ACC	anterior cingulate cortex
BOLD	blood-oxygen-level-dependent
COMT	catechol-*O*-methyltransferase
dlPFC	dorsolateral prefrontal cortex
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
M1	primary motor area
MCI	mild cognitive impairment
Met	Methionin
mPFC	medial prefrontal cortex
MSN	medium spiny neurons
OFC	orbitofrontal gyrus
PD	Parkinson’s disease
PM	premotor cortex
SMA	supplementary motor area
sMRI	structural magnetic resonance imaging
SPT	serial prediction task
SRTT	serial reaction time task
Val	Valin

List of Figures

Curriculum Vitae

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Master thesis Psychology (Dali Gamsakhurdashvili)

Publications

Trempler, I., Binder, E., El-Sourani, N., Schiffler, P., Tenberge, J. G., Schiffer, A. M., Fink, G. R., & Schubotz, R. I. (2018). Association of grey matter changes with stability and flexibility of prediction in akinetic-rigid Parkinson's disease. *Brain Structure and Function, 223(5), 2097-2111*.

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Declarations

Declarations by the candidate documenting **open-science activities** and **on the consideration of ethical aspects** as part of the doctoral process and disclosure of **personal contribution** for manuscripts completed by two or more authors (cumulative dissertations)

Doctoral candidate: Ima Trempler

Title of dissertation: Neurocognitive Mechanisms of Flexibility and Stability of Prediction and their Impairment in Parkinson's Disease

1. Documentation of **open-science activities**

Manuscript 1

	Yes	No	If yes, please specify the source
Pre-registration		X	
Publication of data		X	
Publication of analysis scripts		X	
Publication of materials		X	
Open access publication		X	

Manuscript 2

	Yes	No	If yes, please specify the source
Pre-registration		X	
Publication of data		X	
Publication of analysis scripts		X	
Publication of materials		X	
Open access publication		X	

Manuscript 3

	Yes	No	If yes, please specify the source
Pre-registration		X	
Publication of data	X		available via https://osf.io/n5ugp/ as soon as the manuscript is published
Publication of analysis scripts	X		
Publication of materials	X		
Open access publication		X	

2. Declaration on **the consideration of ethical aspects**

Study number	**Source (manuscript / chapter of dissertation):** e.g. study 1 in paper 2, study 1 described in chapter 4	**Was the study reviewed by an ethics commission?**	
		yes	**No**
1	Manuscript 1	X	
2	Manuscript 2 & 3	X	

3. Declaration of one's **personal contribution** to the submitted academic manuscripts by two or more authors

Manuscript 1

Title	Frontostriatal contribution to the interplay of flexibility and stability in serial prediction		
Author(s)	Ima Trempler, Anne-Marike Schiffer, Nadiya El-Sourani, Christiane Ahlheim, Gereon R. Fink, Ricarda I. Schubotz.		
Publication status:	not yet submitted		(please mark with X)
	submitted		
	in review		
	in revision		
	accepted		
	published	X	
Journal	Journal of Cognitive Neuroscience		
Year of publication	2017		

Description of your own contribution in the case of joint authorship:

- partly responsible for the study's conception and design
- collecting, processing, analysing and interpreting data
- mainly responsible for drafting and revising the manuscript
- marked as corresponding author

Manuscript 2

Title	Association of grey matter changes with stability and flexibility of prediction in akinetic-rigid Parkinson's disease		
Author(s)	Ima Trempler, Ellen Binder, Nadiya El-Sourani, Patrick Schiffler, Jan-Gerd Tenberge, Anne-Marike Schiffer, Gereon R. Fink, Ricarda I. Schubotz		
Publication status:	not yet submitted		(please mark with X)
	submitted		
	in review		
	in revision		
	accepted		
	published	X	
Journal	Brain Structure & Function		
Year of publication	2018		

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Manuscript 3

Title	Dopaminergic modulation of surprise: fMRI evidence for deficient flexible adaptation of prediction in Parkinson's Disease		
Author(s)	Ima Trempler, Paul-Christian Bürkner, Nadiya El-Sourani, Ellen Binder, Paul Reker, Gereon R. Fink, Ricarda I. Schubotz		
Publication status:	not yet submitted		(please mark with X)
	submitted		
	in review	X	
	in revision		
	accepted		
	published		
Journal	Journal of Neuroscience		
Year of publication			

Description of your own contribution in the case of joint authorship:

- partly responsible for the study's conception and design
- mainly responsible for data collection*
- mainly responsible for processing, analysing and interpreting data
- mainly responsible for drafting the manuscript
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* same data as collected in manuscript 2

Place, Date

Signature of the doctoral candidate