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Opinion

Paradoxical Decision-Making: A Framework for Understanding Cognition in Parkinson's Disease

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People with Parkinson's disease (PD) show impaired decision-making when sensory and memory information must be combined. This recently identified impairment results from an inability to accumulate the proper amount of information needed to make a decision and appears to be independent of dopamine tone and reinforcement learning mechanisms. Although considerable work focuses on PD and decisions involving risk and reward, in this Opinion article we propose that the emerging findings in perceptual decision-making highlight the multisystem nature of PD, and that unraveling the neuronal circuits underlying perceptual decision-making impairment may help in understanding other cognitive impairments in people with PD. We also discuss how a decision-making framework may be extended to gain insights into mechanisms of motor impairments in PD.

Highlights

People with PD show both motor and cognitive impairments that are often attributed to different dopaminergic systems.

Cognitive impairments in people with PD are broadly defined as impairments in executive function, they are thought to involve frontostriatal circuits, and many are explained by too much or too little dopamine.

Medial cortical–basal ganglia circuits are implicated in adjusting decision thresholds in conditions of sensory conflict in people with PD.

People with PD show impaired decision-making when those decisions involve the evaluation of rewarding outcomes. Recent work on perceptual decision-making in people with PD reveals additional impairments in processing memory information leading up to choice.

A Decision-Making Framework for PD

Perceptual decision-making is the process by which we evaluate the sensory world and choose a course of action based on sensory evidence. At times we may be uncertain about the evidence, and in such cases an effective decision-making strategy would be to combine external, sensory information with internal information, such as the recollection of a previous, similar experience. In the Bayesian framework of decision-making, these conscious or unconscious memories of past experiences are called priors. Priors influence decisions before and possibly during the acquisition of new information. We recently discovered that people with PD exhibit impairments at combining prior information with current, sensory information compared to healthy participants while performing a perceptual decision-making task. The impairment appeared regardless of medication status, suggesting that non-dopaminergic circuits may play a role [1–3]. We propose that these recent findings expose what may be a fundamental dysfunction associated with faulty basal ganglia (BG) processing. In this Opinion article we review recent evidence from the perceptual decision-making literature in people with PD and healthy controls, as well as in monkeys, that implicates the BG in perceptual decision-making. We focus on decision processes leading up to a choice of action, rather than on decisions depending on the evaluation of outcome value, which is more commonly studied in PD. We also discuss our opinion that considering PD symptoms in a decision-making framework may explain some of the cognitive and motor symptoms seen in PD. Cognitive and motor impairments in PD are usually interpreted as arising from dysfunction in two different circuits, both involving dopamine. The framework proposed here has the advantage of explaining both by a single mechanism.

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People with PD Show Impaired Integration of Memory and Sensory Information during Perceptual Decision-Making

In our recent study, participants discriminated the orientation of a visual stimulus (a Glass pattern) that varied in the strength of the sensory information present (Figure 1). Both healthy participants and people with PD performed well when the strength of the sensory information was high, but, not surprisingly, both sets of participants performed less well as the strength of the sensory information decreased (Figure 1C,D, grey). In this perceptual decision-making task, the orientation of some of the Glass pattern stimuli was associated with different probabilities of occurrence, allowing participants to learn that information implicitly (i.e., develop priors) and use the prior infomation to guide their decisions when the available sensory information was less informative. After learning the priors, healthy control participants were able to use them to guide their decisions in conditions of sensory uncertainty. By contrast, patients with PD were impaired at using these priors (*cf* black and grey lines in Figure 1C,D). A popular model that explains much of the data on perceptual decision-making is the drift diffusion model (DDM; Box 1 for more details). In this model, incorporating priors can lead to a bias in decision-making through two mechanisms – adjusting the starting point of evidence accumulation to be closer to the boundary for the more frequent orientation, or increasing the rate of evidence accumulation for the more frequent orientation. The former is equivalent to a change in a decision criterion in a signal detection theory framework, whereas the latter is equivalent to a change in perceptual sensitivity [4]. Modeling our data with the DDM revealed that healthy participants implemented a decision bias towards the more frequent orientation by adjusting (i) the starting point of evidence accumulation for both stimulus features, and (ii) the drift rate, but only for the stimulus feature that occurred more often, thus reducing the amount of evidence required to make a decision in a stimulus-specific manner (Figure 1E,G). People with PD adjusted their drift rate in a stimulus-specific manner, suggesting that the brain had some knowledge of the priors (Figure 1H), but they showed an inability to adjust the starting point of evidence accumulation (Figure 1F), resulting in an impaired expression of the bias for the more frequent orientation. These results demonstrate that, first, people with PD are unimpaired at making perceptual decisions in the presence of clear sensory information, indicating intact perceptual and motor processes in this task. However, performance degrades when prior information must be combined with specific stimulus features to guide decisions. We suggest that deficits in combining information from past experience with sensory information is central to a broad range of cognitive deficits present in PD, and may even explain some of the enigmatic motor symptoms found in PD.

Impaired Integration of Memory and Sensory Information May Underlie Many Cognitive Problems in PD

Cognitive deficits affect a large proportion of people with PD at the time of diagnosis, and an even higher proportion as the disease progresses [5–8]. The deficits seen at the time of diagnosis or soon thereafter often involve changes in executive function and may substantially impact quality of life [9–12]. For example, people with PD show impairment on the Wisconsin card-sorting task, a task that involves set shifting and assesses cognitive flexibility [13–15]. In set-shifting tasks, participants must learn a rule to solve a problem, and when the rule changes they must learn the new rule and adjust their behavior accordingly. People with PD fail to apply the new rule in set shifting tasks. However, they fail in a characteristic way: they learn the initial rule normally, but when the rule changes their performance becomes poor but not random. Instead, they perseverate – they continue to use the previous rule even though it is no longer valid.

Another well-documented deficit in PD is on tasks requiring response planning and problem solving. In these types of tasks (such as the Tower of Hanoi) one must evaluate the current state

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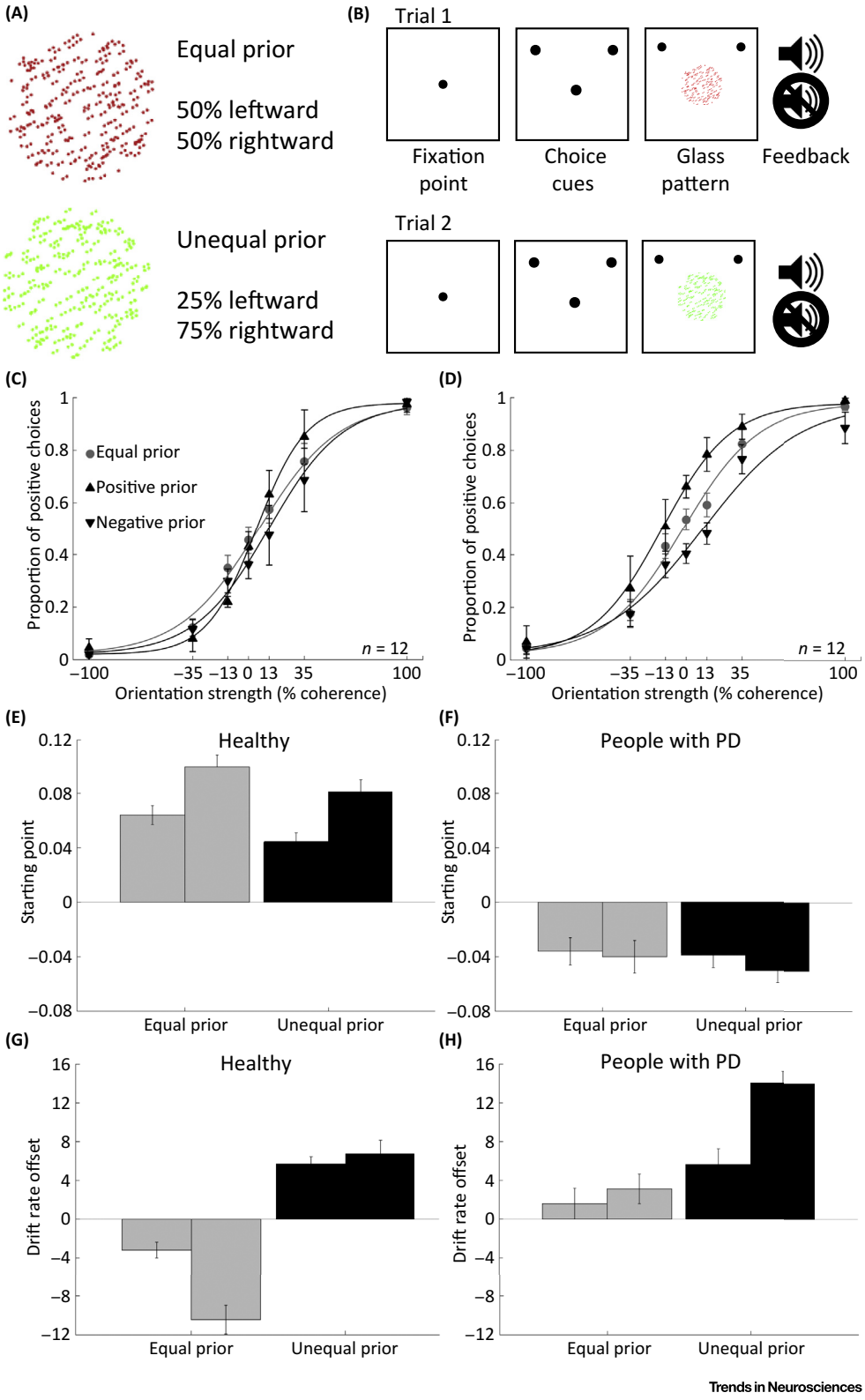

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Box 1. Drift Diffusion Model Schematic

A popular model of perceptual decision-making, particularly in two-choice tasks, is the drift diffusion model (DDM) [4,130–132] (Figure I). According to the DDM, noisy sensory evidence is accumulated (Figure IA, blue line) until it reaches one of two boundaries representing the two options (Figure I, black solid lines), and a decision is made. The distance between the starting point (Figure I, red dot) and the boundary is the decision threshold, which represents the amount of information necessary to make one or the other decision. The starting point of evidence accumulation is equivalent to the decision criterion in the signal-detection theory model of decision-making [4]. In unbiased decisions, the distance between the starting point and the two boundaries is equal. The quality of the sensory information determines the rate of evidence accumulation (drift rate), and decisions are therefore fast and accurate when sensory information is strong, but slow and inaccurate when sensory information is weak (green arrows, strong stimuli; black dashed arrow, very weak stimulus). The DDM provides insight into how priors are incorporated to bias decisions. One way is to shift the starting point of evidence accumulation towards the boundary that is associated with the more frequent stimulus, according to the prior (Figure IB). In this way, less evidence is needed to cross that boundary, and that decision would be made more frequently. We found that healthy people performing the perceptual decision-making task adjust their starting point to reflect the more frequent orientation, whereas people with PD are impaired at this [1] (Figure 1E,F). The other mechanism is a change in the drift rate offset (Figure IC). An offset is added to the drift rate such that, even in the absence of sensory evidence, the process drifts towards one of the decision boundaries. In our task, two differently colored stimuli were used and we applied an equal orientation prior to one colored stimulus and an unequal orientation prior to the other colored stimulus. Both healthy people and people with PD adjusted their drift rate offset in a stimulus-specific manner, consistent with the priors [1] (*cf* Figure 1G,H). Thus, healthy people use a combination of starting-point adjustments and drift rate offset changes to implement a bias in our perceptual decision-making task. People with PD could adjust the drift rate offset in a stimulus-specific manner, indicating the brain had knowledge of the prior but were unable to adjust their starting point of evidence accumulation. Adapted, with permission, from [1].

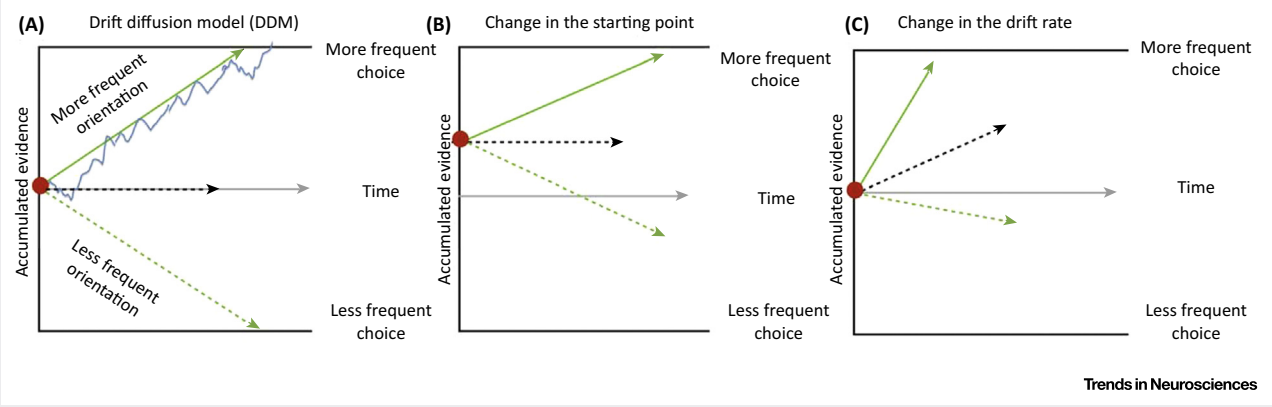

Figure I. DDM Schematic. (A) In two-choice tasks, noisy sensory evidence is accumulated over time (blue line), and a decision is made when the evidence crosses one of the two decision bounds (black lines). In the absence of a bias, evidence accumulation begins at the center of the two bounds, referred to as the starting point (red dot). The distance between the starting point of evidence accumulation and the bound is the amount of evidence required for a decision, also referred to as a decision threshold. The average rate at which evidence accumulates is referred to as the drift rate, and this reflects the strength of the sensory evidence. For example, when the orientation signal in the Glass pattern is strong, decisions are fast and likely to be accurate, as reflected by the positive drift rate (green arrow). By contrast, when the orientation signal in the Glass pattern is weak, evidence accumulates slowly and can lead to inaccuracies (black dashed arrow). The grey arrow indicates advancing time. (B) Adjusting the starting point towards one bound (red dot), translates to less evidence being required to reach that decision and choosing that option more frequently, similar to adjusting a decision criterion to be more liberal in signal-detection theory. (C) Changes in the drift rate offset (angle between black dashed line and green solid line) results in faster evidence accumulation, and this also results in one of the options being chosen more frequently. Adapted, with permission, from [1].

Figure 1. Memory-Based Perceptual Decision-Making Task [1]. (A) Manipulation of prior information: equal numbers of red and green Glass patterns were randomly interleaved over the course of the session; however, stimuli of one color had an equal probability of being leftward or rightward (equal prior); whereas for stimuli of the other color, one of the orientations occurred threefold more often than the other (unequal prior). Thus, participants needed to integrate color, orientation, and likelihood to determine the decision, similarly in some aspects to the weather-prediction task. The color and orientation were randomly interleaved across trials, and which orientation occurred more often was counterbalanced across participants ([1] for further information). (B) A schematic showing the sequence of a trial: the fixation point appears, followed by the two alternative choice targets and then by the Glass pattern. Participants reported their decision as soon as it was made. A tone occurred at the end of correct trials and no sound occurred for incorrect trials. (C) The proportion of leftward (positive) choices is plotted against the orientation strength for 12 age- and sex- matched healthy participants. The grey points and lines show the data and the logistic fits in the equal prior trials (50:50), whereas the black arrows and lines show the data for unequal positive prior trials (75:25, upward arrow) or the unequal negative prior trials (25:75, downward arrow). (D) Same as in (C) for 12 medicated people with Parkinson's disease (PD). (E) Parameter estimates for the starting point of evidence accumulation in the first and second half of the session for the healthy participants of (C). Grey bars indicate the starting point for the equal prior; black bars indicate the starting point for the unequal prior. A positive starting point indicates that the process starts closer to the decision boundary associated with the more frequent orientation. A negative starting point indicates that the process starts closer to the opposite boundary, inconsistent with the prior. (F) As in (E) for the group of people with PD shown in (D). (G) As in (E) for the drift rate offset. A positive value of the drift rate offset indicates that the process drifts towards the bound associated with the more frequent choice according to the priors. (H) As in (F) for the drift rate offset. Error bars are ± SEM. Adapted, with permission, from [1].

of the problem and plan subsequent moves to approach the desired goal state [16]. People with PD are generally slower than healthy control participants in performing tasks that assess problem solving, and show longer thinking times before making moves, resulting in a slower rate of achieving the solution. Importantly, these impairments are independent of the slower movement times generally seen in people with PD [17–21]. People with PD also show impairments in learning when arbitrary stimulus–response associations are learned gradually and incrementally, without awareness [22–24]. The weather-prediction task assesses this type of learning. In this example of a probabilistic learning task, participants are instructed to predict the weather (sun or rain) on individual trials based on a subset of cards with shapes on them. On each trial, participants choose either 'sun' or 'rain' based on the cards that are presented on the trial. If the response is correct, a high tone and a smiling face appear. If the response is incorrect, a low tone and a frowning face appear. Unknown to participants, the stimulus configurations are associated with the outcomes probabilistically, such that the features on each card represent the likelihood of an outcome, and these likelihoods can be combined to reach a choice. The probabilistic nature of the stimulus–outcome associations leads to gradual learning rather than memorization of the outcomes of individual trials. This type of learning depends on trial-by-trial feedback, and participants choose the alternative associated with more correct choices according to what they experienced in the past. Patients with PD perform poorly on the weather-prediction task, providing evidence for impaired probabilistic learning. These same patients show intact declarative memory for the training episode [23]. Together with the finding that patients with amnesia are able to show relatively normal learning on the weather-prediction task, these data provide strong evidence for the idea of multiple memory systems, including an implicit memory system involving the BG and an explicit or declarative memory system involving medial temporal lobe structures. However, the results from the weather-prediction experiment do not identify why people with PD are impaired. They also do not rule out interpretations other than impaired probabilistic learning. For example, people with PD may be impaired at learning the likelihoods of the outcomes given the cues, or they may be unable to translate their experience into appropriate actions. Although somewhat different from our perceptual decision task, the weather-prediction task requires participants to integrate the memory of the outcome of particular stimulus features on previous trials with the current stimulus features to update the likelihoods of the cards. Therefore, another possibility is that people with PD may be impaired at integrating the previous outcome information with the stimulus features appearing on the cards. Follow-up work shows that healthy participants performing the weather-prediction task use a multicue strategy, that is, they learn the outcome associated with a combination of multiple cues, whereas people with PD use a suboptimal singleton strategy, that is, they learn to choose based only on those trials with a single cue [23]. Thus, the impairment in performance on the weather-prediction task in people with PD could be interpreted as an impairment in integrating past experience with multiple cues to arrive at a decision, similar to the impairment we find in perceptual decision-making. One possibility is that people with PD are impaired at adjusting their decision criterion (equivalent to adjusting the starting point of evidence accumulation in the DDM framework) when a combination of sensory and memory information is required. If so, then the observed impairment in learning may stem from a difficulty in decision-making rather than in learning *per se.*

Many of the apparently heterogeneous cognitive impairments in PD share features with our perceptual decision-making task and the weather-prediction task in that they all require integration of multiple sensory cues and memory. For example, in the Wisconsin card-sorting task, people must learn to associate multiple stimulus features to outcomes and they must apply that rule according to cues provided. People with PD perform the Wisconsin card-sorting task well initially, indicating that they learned the rule appropriately. Even though the stimulus

features are complex, there is no memory component to this part of the task – the cue and the possible matches are always present. The problem in performance of the Wisconsin card-sorting task appears after the rule changes, and participants must remember the previous rule to ensure that they no longer apply it. Thus, the impairment appears when people with PD must integrate memory information with multiple stimulus features to inform a decision. Along these lines, we predict that if participants were to perform a version of the Wisconsin card-sorting task that institutes a delay such that memory is required, people with PD would also show impairment in the initial learning. To what extent this integration process requires dopamine is unknown. Next, we briefly review what is known about dopamine and cognitive function and dysfunction.

Dopamine and Cognition in PD

Proposed in the late 1980s, the 'dopamine overdose hypothesis' explains a curiosity discovered from studies of people with PD while on and off their dopaminergic medications [14,25–32]. Dopaminergic medication improves motor and cognitive deficits mediated by the dorsolateral striatal–dorsolateral prefrontal cortical circuit, whereas the medication impairs cognitive functions mediated by the ventral striatal–orbitofrontal cortical circuit [13,33–40]. The dorsolateral striatal–dorsolateral prefrontal cortical circuit is most affected in PD compared to the relatively spared ventral striatal–orbitofrontal cortical circuit [41–43]. Thus, all of the cognitive impairments observed in PD, at least at the early stages, are generally considered to result from altered dopaminergic tone, either too much or too little, in the striatum and/or prefrontal cortex.

The role of dopamine in reinforcement learning has tremendous explanatory power for several cognitive impairments in PD. The reinforcement–learning model suggests that dopamine tone regulates the ability of people with PD to learn arbitrary stimulus–response associations from feedback. This view rests on the idea that dopamine signals a reward-prediction error [44–50]. For example, people with PD can perform an arbitrary stimulus–response association task well when positive feedback is used and they are on their dopaminergic medications. When off their dopaminergic medications, performance with positive feedback worsens, whereas performance based on negative feedback improves [48]. These results are interpreted in light of the role of dopamine in signaling reward – when on dopaminergic medications, the phasic increase in dopamine release in response to positive reward occurs normally, whereas off dopaminergic medications it does not. When off medications, the phasic decrease in dopamine release with negative reinforcement occurs normally, whereas the phasic release with positive reinforcement does not. It is difficult to explain impairments in the weather-prediction task based on dopamine loss because impairments in performance persist even when people with PD are optimally medicated at the time of testing [23]. Of course, an implicit assumption is that the reward-prediction error signal encoded by the phasic activation of dopamine neurons is intact in people with PD while on medication, but that assumption remains in question [51].

Does the reinforcement-learning model explain impairments in memory-based decision-making? A key feature of our memory-based perceptual decision task discussed earlier is the ability to separate learning, decision-making, perceptual, and motor processes. The equal prior condition controls for perceptual and motor processes. If individuals can perform this aspect of the task, it follows that they can see the orientation and make the appropriate motor response to report their choice, and they can adjust decision thresholds normally. The unequal prior trials provide an assay of learning/memory and decision-making. If people show biases in decision-making, they are able to learn the prior information and use it to make choices. If they fail to show biases, the impairment can arise from either impaired learning or impaired decision-making processes, but modeling and task requirements can dissociate these. Another key

feature of our task is that it assesses the integration of memory and sensory information during the decision process leading up to a choice. Much of the work on decision-making in PD focuses on value-based decision-making or decisions based on risk or reward [52–55]. The key to these types of decisions is the outcome. In perceptual decision-making tasks such as the one we described, the focus is on the processes leading up to a decision. We argue that five observations indicate that the impairment in expressing a decision bias during our perceptual decision task is unlikely to arise from a dopamine-dependent learning process or impaired evaluation of outcomes. First, modeling the data from people with PD using the DDM showed that they could adjust their drift rate in a stimulus-specific manner, indicating that the brain was aware of the prior, but their choice performance remained impaired, resulting from an impaired ability to adjust a starting point of evidence accumulation. Second, when explicitly informed of the priors in the decision task, eliminating the need for learning, people with PD continued to show impairment [1]. Third, people with PD show impaired performance regardless of whether they are on or off their medications [1,2]. Fourth, people with dopa-unresponsive focal dystonia show impaired performance similar to people with PD [2]. Fifth, we assessed directly the ability of people with PD to learn the prior from positive and negative feedback, by analyzing win–stay and lose–shift strategies, and found that all participants used the same win–stay, lose–shift strategies [2]. In line with these findings, a recent study showed that dopaminergic medications have no effect on learning from positive or negative reinforcement [56], and evidence from animals suggests that dopamine fluctuations are not causally related to reward learning [57–59]. Together, this suggests that different mechanisms may underlie memory integration during perceptual decision-making and value-based decision-making impairments in PD.

Many cognitive symptoms of PD likely result from alterations in dopamine signaling. However, it is crucial to keep in mind that PD is a multisystem disease that involves neurotransmitter systems and circuits other than dopamine [9,41,60,61]. To what extent cognitive dysfunction involves mechanisms and circuits that overlap with the motor circuits that are dependent upon dopamine and are impaired in PD is unknown. Further, the extent to which other neural circuits and transmitter systems are involved in cognitive impairment, particularly in early stages of the disease, is not well understood [9,62,63]. In the next section we discuss how impaired sensory and memory integration may represent a deficit that could also extend to movement control in PD.

Impaired Integration of Memory and Sensory Information May Extend to Movement in PD

Many of the cognitive impairments seen in people with PD are considered to result from dopaminergic treatments, as described by the overdose hypothesis, in which excessive dopaminergic stimulation of the intact ventral striatal–orbitofrontal cortical circuit produces impairment in cognition [14,31,64]. As such, at this stage of our understanding of PD, cognitive and motor impairments are often considered separately and are thought to reflect dysfunction in distinct neuronal dopaminergic circuits [53–55,65–68]. However, there is growing recognition that cognitive impairment in PD may be part of the degenerative disease process itself, such as the accumulation of α-synuclein, that affects many different neuronal cell types [11,69] and may even precede the onset of motor symptoms, which appear after extensive dopaminergic neuronal cell loss [62,70,71]. Our recent discovery of impaired decision-making in people with PD that appears regardless of medication status is in line with these new ideas, and raises the possibility that some cognitive and motor impairments in PD may share circuits. People with PD show impaired perceptual decision-making, compared to healthy controls, when these decisions require the integration of memory and sensory information. By contrast, for decisions based on sensory evidence alone, people with PD perform similarly to healthy controls. The perceptual decision-making impairment we uncovered and some of the motor

impairments observed in people with PD show striking similarities. For example, many people with PD show two enigmatic, and in appearance, opposite, motor behaviors that occur in the presence of conflicting sensory information or in the absence of sensory information: freezing of gait (FoG) and paradoxical movement. Paradoxical movement is the ability of people with PD to normalize their gait pattern when sensory cues are provided to guide the movement. If people with PD walk in the presence of transverse lines drawn on the ground, their stride length, speed, and cadence to varying extents become nearer to normal. In the absence of this sensory information, the gait of people with PD is slower and occurs with small shuffling steps, referred to as festination [72–74]. Conversely, FoG, the inability to initiate walking and/or the sudden halting of walking, is exacerbated in the presence of conflicting sensory cues – for example when passing through a doorway (Box 2) [75–77]. The ability of sensory cues to overcome gait abnormalities as in paradoxical movement parallels our finding in decision-making. FoG in the presence of conflicting sensory cues may result from impaired decision-making under sensory conflict [78,79]. Lastly, dopaminergic medications have variable effects on paradoxical movement and FoG [80–83], suggesting that FoG and paradoxical movements may have a multifactorial etiology involving the perceptual decision-making impairment (non-dopaminergic) and

Box 2. Freezing of Gait (FoG) in PD – A Clinical Example of the Importance of Priors

FoG and associated falls in PD are a significant source of morbidity in these people. FoG is a clinical example of a motor symptom in PD that may have its origins in an impaired ability to integrate multiple cues including priors for decisions. Normal locomotion requires the integration of visual, vestibular, and proprioceptive cues, and prior information can presumably be used to resolve conflicts in sensory signals during locomotion (Figure IA,B). For example, conflicting visual and vestibular signals have the potential to reduce the speed of gait in healthy people, whereas in people with PD these can cause transient cessation of gait, referred to as FoG (Figure IC). Because a key role of priors in decision-making is to minimize perceptual uncertainty, a possibly way to minimize FoG might be to minimize this dependence on priors and enhance the perceptual information leading to locomotion.

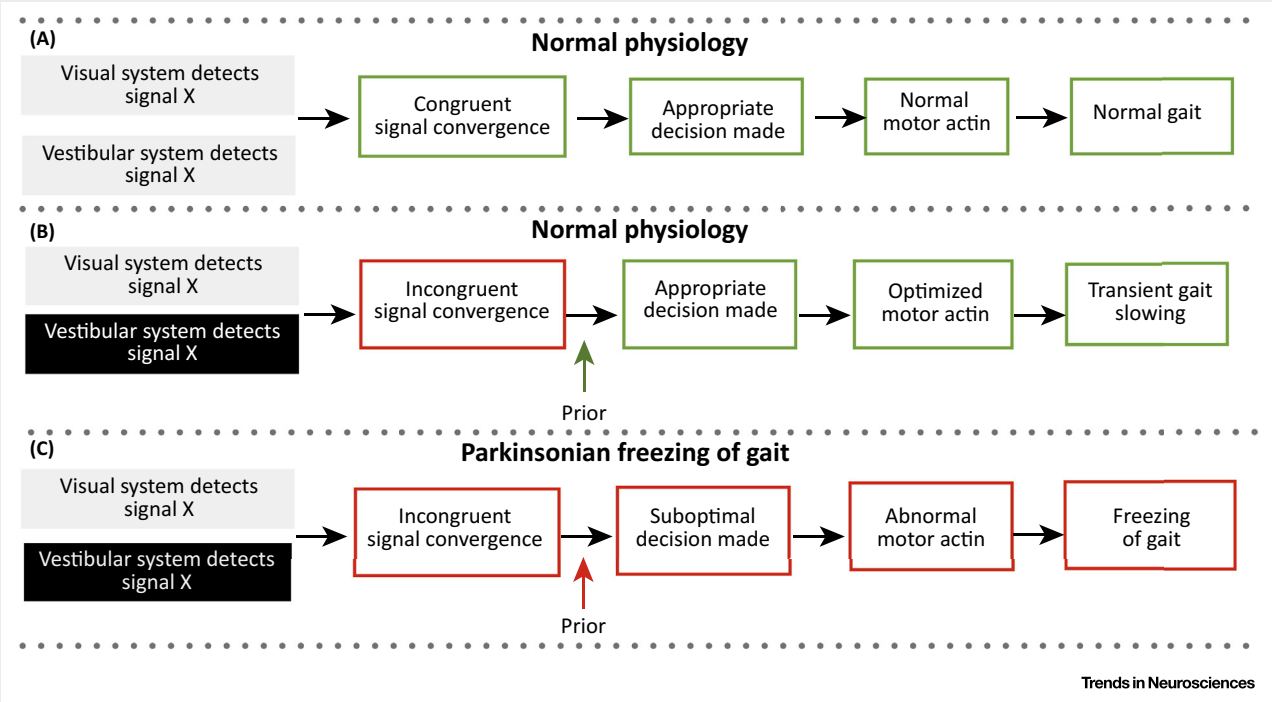

Figure I. FoG in PD. (A) Normal gait in the presence of congruent visual and vestibular signals. Green boxes indicate steps leading to normal gait production. (B) In the presence of conflicting sensory cues, indicated by the black box and the red outlined box, prior information (upward green arrow) can resolve the conflict in a healthy individual and result in only a normal and transient slowing of gait. (C) In PD, the failure of the ability to integrate prior information (red upward arrow) may lead to an impaired ability to adjust the decision criterion and thus to suboptimal decisions and FoG.

dopaminergic circuits. The broader framework we propose is one based in decision-theory; specifically, that dysfunctional basal ganglia circuits lead to impairments in adjusting decision thresholds for cognition and action specifically when memory information is required. The next challenge is to determine the circuits in the striatum and its output nuclei that integrate multiple sources of information, determine how the integration is performed, and establish how these circuit alterations lead to adjustments or failures in adjustments of decision thresholds, particularly when sensory and memory information must be integrated. In what follows we discuss current thinking on the role of the BG in decision-making.

The Role of the Basal Ganglia in Decision-Making

Perceptual decision-making is a dynamic process that involves the accumulation of sensory evidence and an end-point when a sufficient amount of evidence has been accumulated. In the context of evidence accumulation models, the end-point is referred to as the decision boundary [4,84] (Box 1). The amount of sensory evidence required to reach the decision boundary is the decision threshold, and the starting point of evidence accumulation is analogous to the decision criterion in signal-detection theory [4]. Decision thresholds determine the time and accuracy of a decision: when the decision threshold is set high (either by an increase in the bound or a decrease in the starting point), more information must be accumulated, resulting in slower but generally more accurate decisions. Conversely, when the decision threshold is set low, decisions are faster and less accurate. Models based on evidence accumulation to a decision bound, of which the DDM is a popular one, combined with neuronal recordings from animals performing perceptual decision-making tasks, have led to important breakthroughs in our understanding of how the brain makes perceptual decisions (e.g., [85,86]). Much emphasis is placed on understanding where and how sensory evidence is accumulated, and this work shows involvement of the lateral intraparietal cortex (but see [87]), the medial intraparietal cortex, the dorsolateral prefrontal cortex, the supplementary motor area (SMA), and even the superior colliculus in the brainstem and the caudate nucleus of the BG [87–102]. Many of these regions are also implicated in evidence accumulation in humans [1,103–106]. The question of where in the brain decision thresholds are set receives comparatively little attention in the animal literature, but some progress has been made recently in monkey (e.g., [107]) and in human work (e.g., [108]).

Evidence in humans suggests that BG nuclei are involved in adjusting decision thresholds in tasks that require speed–accuracy trade-offs. In these tasks, participants are cued to respond quickly, resulting in less-accurate and less-cautious decisions, or to respond accurately, resulting in slower and more cautious decisions. An fMRI study reported that the anterior striatum and the pre-SMA show blood oxygen level-dependent (BOLD) signal activation in response to cues instructing participants to make a motion–direction discrimination under time pressure, compared to when participants made decisions without time pressure [108]. Using a similar task with high-resolution diffusion tensor imaging, the same authors identified correlations between the structural connectivity of the pre-SMA and striatum and flexibility of the participants in adjusting their decision thresholds [106]. These results support the hypothesis that cortical–BG circuits are involved in adjusting decision thresholds under speed–accuracy demands. Similarly, evidence from electrophysiological recordings in people with PD undergoing deep brain stimulation therapy (DBS) reveals correlations between neuronal activity recorded in the medial prefrontal cortex (mPFC) and subthalamic nucleus (STN), as well as changes in decision thresholds in conditions of decision conflict when participants must choose the more rewarding of two stimuli based on previously learned associations. The observed correlations between mPFC and the STN can be reversed by STN-DBS, suggesting a causal role for the STN in decision threshold adjustments [109]. More recent findings show that low frequency (2–8 Hz) oscillatory activity in the STN correlates with changes in the decision

threshold on a trial-by-trial basis [103,110,111]. The results from this body of work support the hypothesis that the mPFC and the STN work together to increase decision thresholds when decisions require caution, as in the case of sensory conflict. The STN is thought to 'buy time' by raising the decision threshold, such that more evidence can be accumulated before committing to a decision [112,113]. Ongoing research is aimed at clarifying the role of dysfunctional oscillations in PD, their relationship to decision-making and whether altered oscillations are a cause or a result of the disease process [114].

The role of the mPFC–STN in decision-making is similar to that proposed for this circuit in movement generation [115,116]. A careful analysis of DDM model parameters suggests that the STN does not simply slow movement but actually increases the time of evidence accumulation to inform the decision. That changes in STN activity were observed well before choice execution is also consistent with a role in decision processes rather than in movement [103,111]. Electrophysiological experiments introducing STN alterations of decision thresholds and recordings from evidence-accumulation areas of the brain will be required, however, to test this hypothesis definitively. Another question that remains unknown based on work in humans is whether the direct cortical–STN (hyperdirect) pathway is responsible for the modulations of decision threshold or whether corticostriatal processing is also involved [105,106,112,117–120]. Theoretical work suggests that the cortico–BG–superior colliculus circuit controls decision thresholds. In this model, informed by data from monkeys performing a random dot motion-direction discrimination task [89], the decision threshold is determined by the weight of corticostriatal synapses, which determines how much drive is needed to suppress the output of the BG, which in turn releases the superior colliculus from inhibition. This latter act is a report of the crossing of the decision threshold resulting in a commitment to a choice [121,122]. Some support for a role for the caudate in decision-making comes from electrophysiological recordings made in monkeys during performance of the random dot motion-direction discrimination task. Caudate neurons show activity associated with evidence accumulation approximately similar to that seen in cerebral cortex, and stimulation of the caudate alters decision-making performance [101,123]. Evidence from monkeys suggests that the superior colliculus, which receives direct input from the BG, establishes the starting point of evidence accumulation [107]. It remains an open question whether the caudate participates in the formation of a decision or whether it simply mirrors evidence accumulation taking place in cortex [124]. Very recent work in mice suggests that the caudate plays a role in establishing perceptual decision criteria [125], consistent with our proposed role for the BG in memory-based perceptual decision-making discussed here.

Concluding Remarks and Future Perspectives

In this Opinion article we reviewed some recent evidence suggesting that people with PD are impaired at integrating sensory and memory evidence for perceptual decisions. This novel cognitive impairment in people with PD highlights several issues that we raise for consideration. First, because PD involves BG impairment and the BG receive input from virtually the entire cerebral cortex, the cognitive impairment seen in people with PD reinforces the view that the BG are uniquely positioned to integrate the information from multiple sources that is required for cognitive processing [126,127]. This privileged anatomy also places the BG in a unique position to play a key role in decision-making [128]. Therefore, a crucial task for the future will be to unravel the details of the neuronal circuits that underlie our ability to combine memory and sensory information to make effective decisions. What cortical areas encode prior information, and how is this information conveyed to the BG? Where in the BG does cortical sensory information terminate, and what are the circuits and computations within the BG that lead to the integration of sensory and memory information? Parallel experiments in humans and

electrophysiological studies in monkeys performing these decision-making tasks while exploring cortical–BG relationships will be crucial in the effort to unravel these circuits and computations. A second issue we raise here for discussion is the role of dopamine in cognition more broadly, and in memory and decision-making more specifically. It is incontrovertible that dopamine is involved in motor impairments in PD and even in some cognitive deficits found in PD. Nevertheless, dopaminergic dysfunction alone cannot explain all PD symptomatology. Some motor symptoms, such as paradoxical movement and FoG, are resistant to dopamine therapy, and the memory-based perceptual decision-making impairment we uncovered is also resistant. Future experiments should be geared at determining the role of dopamine in specific aspects of cognitive function, and, given the growing recognition that PD is a multisystem disease [129], effort should be made to explore the possibility that other neurochemical systems also play a role in cognitive impairments.

Finally, our recent modeling effort to understand the mechanism underlying the memory-based decision making impairment in PD provides a novel framework for understanding many PD symptoms more broadly. When decisions require memory information, people with PD show an impaired ability to adjust the starting point of evidence accumulation (or the criterion in static models of decision-making such as signal-detection theory). We propose that a framework based on the neuroscience of decision-making may help us to understand both cognitive and motor symptoms seen in people with PD. When decisions require the combination of memory and sensory information, people with PD fail to make optimal decisions, such as is seen in the weather-prediction task, the memory-based perceptual decision-making task, and even in the Wisconsin card-sorting task. Conversely, when decisions are based purely on sensory evidence, people with PD show improvements in performance. This paradoxical decision-making – improved performance with sensory information, or impaired performance when integrating multiple stimulus features and memory – is strikingly similar to that seen in the motor impairments of people with PD; sensory cues can help movement in some cases or hinder movement in other cases, and movements are more likely to be impaired in the absence of sensory information to guide them. We propose that both these phenomena may reflect an underlying impairment in the adjustment of decision criteria, particularly when memory is involved. Future work should be aimed at explaining the relationships between cognition and action in PD, and how computational approaches to decision-making may help to shed light on enigmatic PD symptomology (see Outstanding Questions).

Outstanding Questions

Where in the brain are decision thresholds determined?

Do motor and cognitive deficits in people with PD share the same dysfunctional circuits?

People with PD show impairments in decisions that require the evaluation of outcomes, particularly when the outcomes are rewarded. People with PD also show impairments integrating memory and sensory information for perceptual decisions. Do these two types of decision-making share mechanisms, or are the circuits mediating these behaviors different?

People with PD show impaired integration of memory and sensory information. Is this impairment unique to memory information, or does it apply also to multisensory integration?

Do other neurotransmitter systems known to be affected in PD also play a role in perceptual and memory decision-making impairment?

If STN activation increases decision thresholds, would inactivation of STN decrease decision thresholds, and would it rescue the ability to express a decision bias in people with PD?

PD is a heterogeneous disorder that manifests in different forms. Specifically, some people have tremor-dominant PD, whereas others have akinesia-dominant PD. Is there a relationship between cognitive impairment and specific motor symptoms in PD? Are there interactions between the impact of DA on cognition and movement?

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