What are people with Parkinson's disease really impaired on when it comes to making decisions? A meta-analysis of the evidence.

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Highlights

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What are people with Parkinson's disease really impaired on when it comes to making decisions? A meta-analysis of the evidence

Agata Ryterska, Marjan Jahanshahi, Magda Osman*

- We review studies investigating decision-making in Parkinson's disease.
- We conduct a meta-analysis of the results of these studies.
- Discrete feedback and dopaminergic medication affect decision-making in PD.
- No support found for general decision-making impairment in PD.

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Review

What are people with Parkinson's disease really impaired on when it comes to making decisions? A meta-analysis of the evidence

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ABSTRACT

Parkinson's disease (PD) is associated with motor and cognitive impairment caused by dopamine dysregulation in the basal ganglia. Amongst a host of cognitive deficits, evidence suggests that decision-making is impaired in patients with PD, but the exact scope of this impairment is still unclear. The aim of this review was to establish which experimental manipulations commonly associated with studies involving decision-making tasks were most likely to generate impairments in performance in PD patients. This allowed us to address the question of the exact scope of the decision-making deficits in PD and to hypothesize about the role of the basal ganglia in decision-making processes. We conducted a meta-analysis of available literature, which revealed that the two key predictors of impairment in PD were the feedback structure of the decision-making task and the medication status of patients while performing the tasks. Rather than a global impairment in decision-making ability, these findings suggest that deficiencies in choice-behaviour in patients with PD stems from dysfunctions at the outcome evaluation stage of the decision-making process.

Contents

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder primarily associated with degeneration of dopamine-producing neurons in the substantia nigra pars compacta. This degeneration affects the functioning of the other basal ganglia nuclei, particularly the putamen, which results in the primary motor symptoms of bradykinesia (slowness of movement), akinesia (poverty of action), tremor and rigidity. Other symptoms of PD, not related to motor functioning, include certain psychiatric disorders (such as depression, apathy, anxiety, hallucinations and delusions) and deficits in cognitive functioning. It is these cognitive deficits, and more specifically deficits in decision-making, which are the focus of this review. In the main, we discuss if the impairments in decision-making observed in PD suggest a general deficit affecting all stages of the decision-making process, or whether this deficit is limited to a specific stage. We attempt to address this question in view of the available experimental evidence and discuss the implications for the role of the basal ganglia in decision-making.

1.1. General cognitive dysfunction in Parkinson's disease

Traditionally, the view has been that the basal ganglia are purely motor structures that are important for selection and execution of movement. Their role in cognitive functioning has been recognized more recently because of the intimate connectivity of the basal ganglia with areas of the frontal cortex which are involved in executive functions (e.g. Alexander et al., 1986; Middleton and Strick, 1994) (for a review see Middleton and Strick, 2000). Cognitive impairments observed in people with PD, in whom the basal ganglia are affected, provide further support for the importance of the basal ganglia for cognitive functioning.

Cognitive dysfunction in PD can range from mild cognitive impairment (MCI), found in the early stages of illness, to dementia in patients in advanced stages of the disorder (Dirnberger and Jahanshahi, 2013; Dubois et al., 2007; Emre et al., 2010; Kehagia et al., 2010; Litvan et al., 2012) and impact on important abilities, such as decision-making (Brand et al., 2004; Mimura et al., 2006; Pagonabarraga et al., 2007). Executive dysfunction in PD is characterized by deficits in internal control of attention, set-shifting, planning, reduced ability to perform two tasks concurrently, deficits in inhibitory control, and conflict resolution (Dirnberger and Jahanshahi, 2013). Impairment of executive function in Parkinson's disease is thought to be associated with the dysfunction of the associative fronto-striatal loop between the caudate nucleus and the dorsolateral prefrontal cortex (e.g. Cools et al., 2002; Marie et al., 1999).

Dopaminergic medication has been shown to be effective in alleviating many of the motor symptoms associated with PD. However, it can have variable effects on cognitive function, either improving, or in some cases impairing performance on specific tests. For instance, with dopaminergic medication, performance on many tests mediated by the motor or associative circuit improves, whereas performance on tests mediated by the limbic (ventral striatum-anterior cingulate) or orbitofrontal (caudate-orbitofrontal cortex) circuits tends to worsen (Cools, 2001; Gotham et al., 1988; Jahanshahi et al., 2010; Swainson et al., 2000). More specifically, dopaminergic medication successfully alleviates some working memory, cognitive sequencing and task switching impairments in PD (MacDonald and Monchi, 2011). At the same time this medication has been linked to impairments in conditional associative learning, probabilistic reversal learning, and incremental learning with feedback (e.g. Cools, 2001; Cools et al., 2003, 2007; Gotham et al., 1988; Jahanshahi et al., 2010). To account for this puzzling set of findings, the 'dopamine overdose' hypothesis (Gotham et al., 1988; Cools et al., 2003) proposes that while dopaminergic medication has beneficial effects in the areas of the brain most affected in the early stages of the disease, such as the dorsal striatum, it causes overdosing in the parts less affected, such as the ventral striatum.

1.2. Specific cognitive dysfunction in Parkinson's disease: decision-making

In addition to the variable effects of dopaminergic medication on tests of cognitive functioning, another major source of variability in PD patients' performance is the indices of performance themselves, namely the tests. Studies of decision-making ability in PD are a case in point (Osman, 2011). For instance, some experiments using tasks designed to mimic risky decision-making (e.g. Iowa Gambling Task (IGT)) revealed impairments in decision-making in PD (e.g. Brand et al., 2004; Kobayakawa et al., 2008; Mimura et al., 2006). Studies utilizing tasks designed to mimic everyday decision-making (e.g. Dynamic decision-making tasks (DDM)), on the other hand, observed no such deficits (e.g. Osman et al., 2008; Witt et al., 2006). Consequently, inconsistent results presented in the literature on decision-making in PD may stem from methodological issues: given that the tests of decision-making differ considerably, results from various studies may not be comparable. Without careful evaluation, this can lead to a distorted picture of the actual decision-making impairments in PD.

1.3. Objectives and structure of the review

Our aim is to comprehensively review the pattern of findings that emerge from studies investigating PD patients' performance on different decision-making tasks. Our goal is to identify the exact nature of the deficits and the influence of task characteristics and medication status on decision-making performance in PD. The first part of the review introduces the tasks that are commonly used to study decision-making in PD, and discusses the specific experimental manipulations that are associated with impairments, including medication status. Next, the general findings of a meta-analysis of 38 studies investigating decision-making impairments in PD are presented. The results of the meta-analysis are evaluated and discussed in the concluding section of this article with a particular focus on the implications of these findings for the role of the basal ganglia in decision-making.

2. Decision-making stages and tasks

Evidence has shown that decision-making relies on several processing steps which are supported by different brain areas and neurotransmitter systems (Delazer et al., 2009; Kable and Glimcher, 2009; Rangel et al., 2008). Decision-making is typically conceptualized as a process that involves the representation and assignment of

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values and probabilities to different options, from which an action then follows from a choice made, after the outcome of the action is evaluated (e.g. Rangel et al., 2008). The ventromedial prefrontal cortex (VmPFC) (Chib et al., 2009; Fellows and Farah, 2007; Glascher et al., 2009; Lebreton et al., 2009), striatum (Brooks et al., 2010; Lau and Glimcher, 2008; Litt et al., 2011; O'Doherty et al., 2006) and anterior cingulate cortex (ACC) (Croxson et al., 2009; Kennerley et al., 2006; Rushworth and Behrens, 2008; Walton et al., 2007) are thought to be crucial for assigning value to available options. Lateral prefrontal and parietal cortex (especially lateral intraparietal area, superior colliculus and frontal eye fields) (Glimcher and Sparks, 1992; Gottlieb, 2007; Kiani et al., 2008; Roitman and Shadlen, 2002; Shadlen and Newsome, 2001) were found to be important for selecting options based on the values assigned to them. Brain areas such as the premotor cortex and anterior cingulate cortex (Ernst and Paulus, 2005; Van Veen and Carter, 2002) are thought to be responsible for movement execution and action monitoring. Finally, the dorsal/ventral striatum (Kurniawan et al., 2013; Phillips and Everling, 2012; van der Meer and Redish, 2009; Yamada et al., 2011), ACC (Cai and Padoa-Schioppa, 2012; Kennerley and Wallis, 2009; Seo and Lee, 2007; Walton and Mars, 2007) and amygdala (Baxter et al., 2000; Trepel et al., 2005) are claimed to be important for evaluating the outcomes of the decision-making process. Taken together, this body of work supports the idea that decision-making consists of several steps mediated by different brain structures, amongst which the basal ganglia play an important role.

Further evidence for the important role of the basal ganglia structures such as the striatum in decision making processes comes from studies investigating decision making in patients with PD. Decision-making in this population has been investigated using a variety of tasks. Most of these tasks were designed to assess the accuracy of choices between options, based on the assumption that people will learn some information (cues) about the options and how reliable that information is (validity) in order to maximize their reward (i.e. gain the most possible wins over the course of the task). Good performance on these tasks necessitates learning about the relationship between options, outcomes, and in some cases also rewards. The options will have different informational content (cues), which may be indicative of the potential underlying structure of the task (i.e. the associations between the cues and the outcome). The task may provide trial-by-trial information revealing outcome feedback (correct/incorrect), and/or the reward for a correct/incorrect outcome (gains/losses). By utilizing feedback or reward information it is possible to devise strategies that enable the decision maker to maximize their total wins. Outcome feedback usually, in the form of binary 'correct/incorrect' information, refers to the performance on a given trial, and is independent of performance on previous trials – in other words it is discrete. In some tasks, however, outcome feedback is provided in the form of cumulative information; this means that it carries information from one trial to the next (e.g. deviation from a target value that is set at the start of the experiment), allowing the decision maker to monitor their on-going performance as it changes over consecutive trials. Despite this basic set up, common for most decision-making tasks, there are marked differences between the tasks as well.

2.1. Tasks used to study decision-making in PD

Tasks used to study decision-making can be divided into two categories (see Fig. 1), those that examine decision-making under risk, and those examining decision-making under uncertainty. This is actually an economically informed distinction originally proposed by Knight (1921) and is based on the agent's sources of knowledge regarding outcomes and probabilities. Knight's distinction between risk and uncertainty outlines that decision-making under *risk* refers to situations in which probabilities are known (or knowable) (e.g. games of chance), whereas situations of *uncertainty* are characterized as cases where probabilities are neither logically deducible nor can they be inferred from the information presented in the task (Meder et al., 2013; Osman, 2011; Trepel et al., 2005). One factor to bear in mind is that the distinction between tasks that examine decision-making under risk and decision-making under uncertainty is not a clear cut one. One reason for this is that tasks that examine both risk and uncertainty also include a learning component, in which participants attempt to infer the underlying probabilities. This in turn implies that there are likely to be potential differences in performance which is based on differences in the learning processes employed by participants, rather than the underlying structure of the risky situation they are trying to make decision on. This is especially the case in task such as the Iowa Gambling Task where differences in performance can be attributed to either differences in learning or differences in risk preference. In many decision-making tasks that involve a learning component, it is not always possible to unambiguously separate out the two.

2.1.1. Tasks investigating decision-making under risk

When we make decisions under risk, some estimation of an outcome can be calculated, such as betting on a certain number landing face-up when throwing a dice. Take, for instance, the *Game of Dice Task (GDT)*. Here, participants are asked to place a bet on a number that will come up on the dice, just before it is rolled. They can choose between (A) single number (e.g. 4), (B) two numbers (2 or 4), and (C) three numbers (1, 2, 5). They receive outcome feedback (i.e. the actual result of the dice roll), and information about reward (how much they won or lost). The task is set up so that the more likely the probability of winning (e.g. option C) the lower the reward. When comparing performance of patients with PD on medication with performance of healthy controls (HCs), the former tended to choose the riskier options A and B more often than the latter (e.g. Brand et al., 2004; Euteneuer et al., 2009). However, when immediate feedback was removed (i.e. participants did not receive any information about the actual outcome of the dice roll) risky behaviour dropped (e.g. Labudda et al., 2010).

An alternative to the GDT is the Cambridge Gambling Task (CGT). Participants are presented with a row of 10 boxes which can be either red or blue, and are asked to place a bet on whether a token has been hidden under a red or a blue box. The proportion of red and blue boxes changes from trial to trial. In this task participants are aware of the risk associated with each option, and are expected to adjust their betting behaviour to the number of red and blue boxes. For example, when seven blue and three red boxes are presented, participants are expected to indicate that the token is hidden under a blue box. Following this choice, participants are invited to place a bet (in a form of a percentage of their current task credit) on whether or not they believe their decision will prove to be correct. Cools et al. (2003) reported that compared to age matched healthy controls (HCs) PD patients on medication exhibited abnormal betting behaviour which was suggestive of impulsivity; they tended to make bets quicker than PDs off medication and HCs. On the other hand, Delazer et al. (2009) showed that in an adapted version of the task (Probability-Associated Gambling Task) PD patients on medication performed just as well as HCs. However, it has to be noted that no measures of impulsivity were included in this particular version of the CGT task.

2.1.2. Tasks investigating decision-making under uncertainty

In tasks examining decision-making under uncertainty the probabilities associated with different outcomes occurring are unknown. It would be akin to betting on the number 2 coming up on a die, but not knowing if the die rolled from trial to trial is 6-sided or 12-sided. A popular task used to study decision-making under

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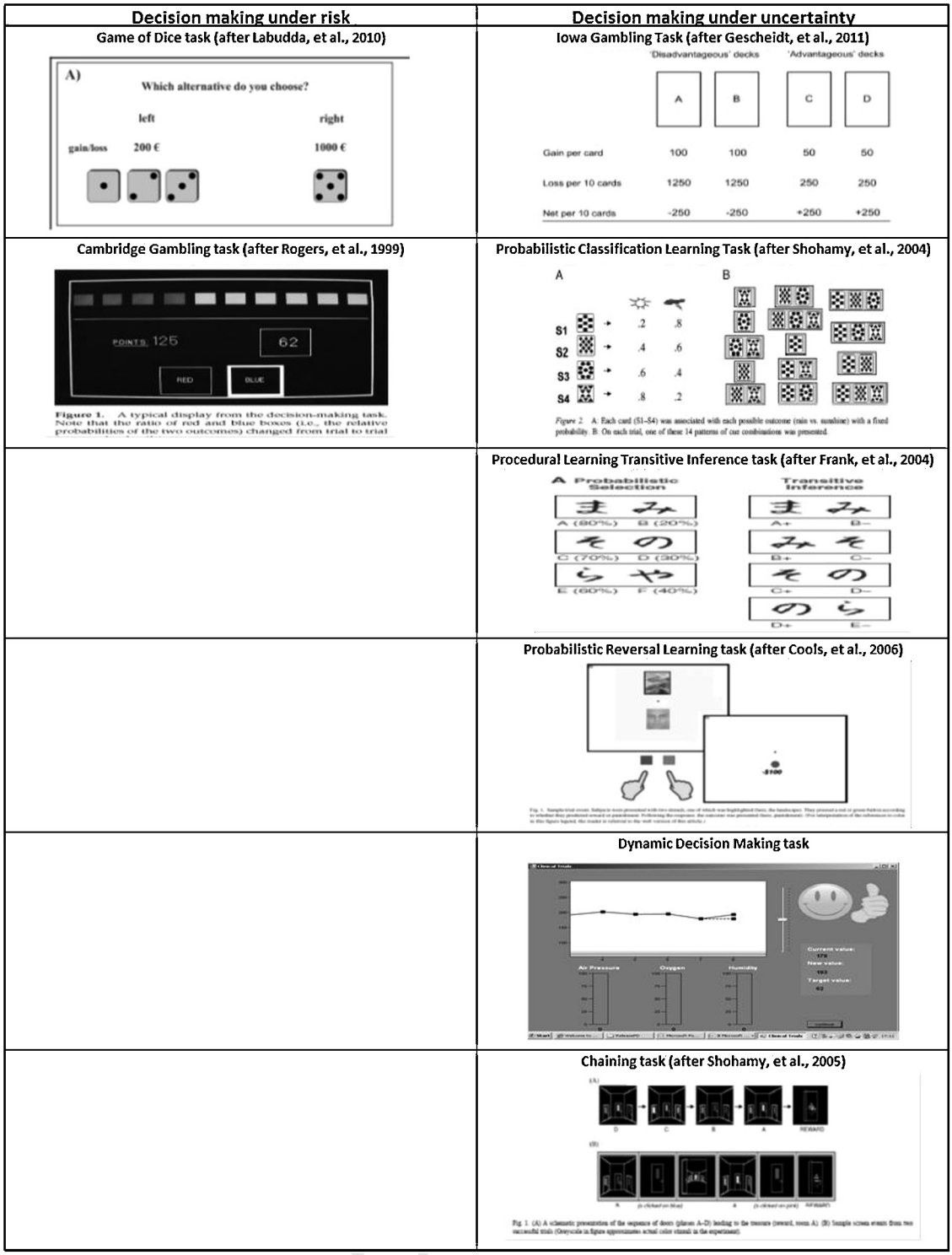

Figure 1. A typical display from the decision-making task. Note that the ratio of red and blue boxes (i.e., the relative probabilities of the two outcomes) changed from trial to trial.

Figure 2. A: Each card (S1–S4) was associated with each possible outcome (rain vs. sunshine) with a fixed probability. B: On each trial, one of these 14 patterns of cue combinations was presented.

Fig. 1. Tasks commonly used to study decision-making in Parkinson's disease.

uncertainty in patients with PD is the *Iowa Gambling Task* (IGT). In the IGT participants are presented with 100 or so trials, and on each trial they are required to choose between four decks of cards. Unbeknownst to the participants two of the decks are advantageous (small gains, but also small losses – consistent selection leads to net profit) and two are disadvantageous (large gains, but also large losses – consistent selection leads to net loss). Participants receive trial-by-trial information about the gains or losses following their selection, and performance is indexed by subtracting the overall number of disadvantageous selections from the advantageous selections. Here again, the pattern of findings is mixed. Some studies (Euteneuer et al., 2009; Poletti et al., 2010; Stout et al., 2001; Thiel et al., 2003) show that patients with PD make selections consistent with those of a healthy sample, while others show that PD patients make more disadvantageous selections (Czernecki et al., 2002; Delazer et al., 2009; Ibarretxe-Bilbao et al., 2009; Kobayakawa et al., 2008; Mimura et al., 2006; Pagonabarraga et al., 2007; Perretta et al., 2005).

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The set-up of the *Probabilistic Classification Learning Task* (PCL) differs markedly from the IGT primarily because rather than selecting from four options, in the PCL participants predict a binary outcome based on a combination of 1, 2 or 3 different cues. Each cue is independently associated with each outcome with a fixed probability, and each outcome occurs equally often. A good example of a PCL task is the Weather Prediction Task (WPT) (Knowlton et al., 1994), which is used widely in studies of procedural learning in PD (e.g. Poldrack et al., 2001; Shohamy et al., 2004a; Witt et al., 2002). In the WPT, participants are presented with 100 or so trials, in which on every trial they see a combination of tarot cards (maximum number is four) and from this configuration of cards they are asked to predict an outcome (i.e. whether it will be rainy or sunny). The actual outcome is determined by a probabilistic rule based on the combinations of cards, and in actual fact each card is partially an accurate predictor of the outcome (Gluck et al., 2002). Usually outcome feedback is presented on a trial-by-trial basis and in some variations reward information is also presented. In general PD patients on medication are thought to be impaired on this task (e.g. Knowlton et al., 1996; Mattox et al., 2006; Sage et al., 2003; Perretta et al., 2005; Wilkinson et al., 2008; Witt et al., 2002), showing limited learning of the relationship between cues and outcomes, represented by near chance levels of performance.

Another type of probabilistic learning task that involves decision-making under uncertainty is *Probabilistic Reversal Learning* (PRL). The task consists of two stages, starting with a simple probabilistic visual discrimination task. Here participants need to learn to choose the one of two stimuli which is associated with greater probability of positive feedback. The stimuli usually take the form of different coloured patterns presented on a computer screen (e.g. Swainson et al., 2000). Participants choosing the 'correct stimuli' receive positive feedback (e.g. 'smiley face' picture) on 80% of the trials. Half way through the task (usually after 40–50 trials) the contingencies are reversed without warning, so that the previously 'incorrect' stimulus becomes correct and vice versa. The participants need to be able to alter their behaviour in response to changing reinforcement contingencies, and while HCs show adaptive behaviour, PD patients on medication tend to stick to their initial choice after the reversal much more often than HCs (e.g. Cools, 2001; Cools et al., 2006; Peterson et al., 2009; Swainson et al., 2000).

Procedural Learning Transitive Inference Task (PLTIT) is somewhat different from the tasks described above, as it comes in two versions: probabilistic (where the outcome might differ from trial to trial, irrespective of participant choices) and deterministic (where the outcome is predetermined and depends solely on participants' choices). In the deterministic version of the task participants are presented with a pair of stimuli, each of which have either positive (+) or negative (−) feedback associated with them. Four pairs that are typically presented are (A+ B−) (B+ C−) (C+ D−) and (D+ E−). On each trial participants are presented with a pair of Japanese symbols (meaningless for them) and asked to choose the one more likely to be associated with positive feedback. No reward is given for the correct answer. Nevertheless, to obtain positive, rather than negative feedback, participants need to learn to select the correct stimulus in each pair. To do this, they need to learn the transitive relationship between the stimuli. Stimuli near the top of the hierarchy (e.g. A and B) develop positive net associative strengths, whereas those at the bottom develop negative net associative strengths (e.g. D and E). The probabilistic version of the task differs from the deterministic in that each of the stimulus pairs presented over trials is unique (e.g. AB, CD, EF). In each stimulus pair one of the stimuli is associated with a greater probability of receiving positive feedback and participants need to learn to choose this stimulus. According to Frank et al. (2004) PD patients on medication are more sensitive to positive than negative feedback, and the evidence from the probabilistic and deterministic version of the PLTIT task revealed exactly that. Moreover, the opposite was found for PD patients off medication, with the results showing that they were reliably better at avoiding negative stimuli at the lower end of the hierarchy.

Along the same lines as the PLTIT, the Chaining task also requires participants to learn the ordering of relevant information. In the Chaining task participants learn through trial and error the correct sequence of coloured doors to complete the task. In this computer-based environment participants have to guide a character through 4–6 different rooms to reach a goal (an outside world or a hidden treasure). In each room they are presented with a set of three doors of different colours. Participants need to learn which door is correct in each room. When the correct door is chosen participants move on to the next room, and in the final room participants reach the outside world/hidden treasure. No monetary reward is usually offered for completing the whole sequence correctly. Contrary to the results of most of the studies described above, PD patients performed just as well as HCs during this task when on dopaminergic medication, i.e. they were able to learn a correct sequence of doors as quickly as HCs and were as accurate as HCs (Shohamy et al., 2005). However, when tested off medication, PD patients were significantly worse than HCs (Nagy et al., 2007; Shohamy et al., 2005).

Finally, what differentiates Dynamic Decision-making (DDM) tasks from all the aforementioned tasks is that there is an underlying causal structure between the cue (input) information and the outcome (output), and participants make decisions by directly manipulating the values of the inputs. A good example of a DDM task is the Sugar Factory task, designed by Berry and Broadbent (1984). It is a computer-based environment in which participants take on a role of a sugar factory manager. Participants usually have about 40 trials to learn to reach and maintain a specific output value (e.g. level of sugar production) by manipulating the value of the cue (e.g. the number of workers employed) (Berry and Broadbent, 1984). The task is dynamic because the output value changes directly as a result of the actions of the decision maker, but can also change independently of their choices according to the type of probabilistic structure that is embedded in the task. On each trial participants receive cumulative outcome feedback informing them of the output value they have achieved over several trials. In general PD patients on medication perform just as well as HCs on this task based on their ability to reach and maintain the output value to the target level (Osman et al., 2008; Rutledge et al., 2009; Witt et al., 2006).

2.1.3. Summary of differences in decision-making tasks

All of the tasks described above involve an element of learning either through outcome feedback or through information about rewards. Differences in the learning processes employed to infer the underlying probabilities within a task might have direct influence on the results of different studies. Furthermore, none of the tasks involve the same underlying cue–outcome relationship, which in itself dictates the probabilities of certain outcomes occurring. In addition, some tasks examine decision-making under uncertainty, whereas others look at decision-making under risk. All this might impact the way people make decisions on these tasks. In fact, human and animal studies suggest that the probabilities of different outcomes occurring have direct consequences for shaping the preferences between options (e.g. Bechara et al., 1997; Brand et al., 2006; Delazer et al., 2009; Kahneman and Tversky, 1979). Therefore, the decision-making process might look differently when the probabilities of different outcomes occurring are known (decision-making under risk) as compared to when they have to be estimated by the decision maker (decision-making under uncertainty). This needs to be taken into account when investigating decision-making in PD on different types of tasks. Moreover,

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the tasks used to study decision-making in PD differ in terms of various other characteristics, such as the feedback structure and cover stories, which might have a direct impact on PD patients' performance as well. Consequently, it is crucial to take these factors into account when comparing PD patients' performance on different decision-making tasks.

Because of the differences in methodologies between the studies examining decision-making in PD, the results of these studies are difficult to compare directly. Identifying the factors associated with experimental design that impact decision-making processes in PD could potentially give us more insights into the specific deficits concerning decision-making in these patients. It could also give us insights into why there are so many inconsistencies in the patterns of findings reported in studies of decision-making in PD. In the next section we focus on the potential factors that, based on the existing literature, are most likely to lead to deficits: type of task environment (uncertain or risky; probabilistic or deterministic), type of feedback, and medication status of patients (on or off medication) (Osman, 2011).

2.2. Experimental manipulations associated with decision-making tasks and their influence on decision-making in PD

2.2.1. Task environment

Cue–outcome relationship. The rule governing the cue-outcome relationship in the tasks discussed can be either deterministic or probabilistic. In deterministic environments certain cues are invariably followed by certain outcomes. In probabilistic environments, cues predict certain outcomes with a specific probability. The type of rule governing the cue outcome relationship in an environment is thought to influence the type of learning that takes place (Osman, 2011). For instance, probabilistic environments are thought to trigger learning that has been described as procedural (Knowlton et al., 1994, 1996). If we return to work discussed earlier in the section on the link between cognitive functions and the role of the basal ganglia, then there is some evidence that dopamine deficiency in the basal ganglia leads to impaired procedural learning (e.g. Faure et al., 2005; Saint-Cyr et al., 1995; Wilkinson and Jahanshahi, 2007). In addition, the nigral dopaminergic system has been shown to be important for learning to make choices in environments with probabilistic reward contingencies (Peterson et al., 2009). Taken together, this would mean that PD patients should be more impaired when the decision-making environment is probabilistic than deterministic, because probabilistic environments typically invoke procedural learning that has been suggested to be impaired in PD. However, Frank et al. (2004) tested PD patients' performance on two tasks – probabilistic and deterministic versions of the PLTIT, and found no significant differences in performance between the groups. Moreover, an example of a probabilistic decision-making environment is DDM tasks, but they also fail to show impairment in performance in PDs. Clearly the impact of probabilistic and deterministic cue–outcome relationships on performance in PDs has not been settled.

Risk vs. uncertainty. As suggested before, it is possible that the results of the studies conducted thus far differ because the tasks employed involve either decision-making under risk (GDT, CGT) or uncertainty (e.g. IGT, DDM and PCL) (e.g. Delazer et al., 2009). Many of the tasks used to examine decision-making in PD *de facto* measure decision-making under risk. Euteneuer et al. (2009) suggested that PD patients are specifically impaired on decision-making under risk (as measured by GDT), but not under uncertainty (as measured by IGT). In contrast, Delazer et al. (2009) found PD patients were impaired on tasks examining decision-making under uncertainty (as measured by IGT), but not under risk (as measured by a version of the CGT). Clearly whether risk and/or uncertainty lead to poor decision-making in PD is an important but unsettled matter.

2.2.2. Feedback structure

Studies conducted so far suggest that the feedback structure could potentially influence PD patients' performance on decision-making tasks. For example, evidence from fMRI studies conducted on healthy volunteers suggest that ventral striatum might be involved in feedback processing during WPT task (Poldrack et al., 2001; Seger and Cincotta, 2005), which in turn could result in impaired feedback processing in PD patients in whom this structure is affected. This is supported by several studies indicating that impaired performance of PD patients might result from impaired processing of trial-by-trial outcome feedback. PD patients have been shown to be able to make advantageous decisions in a gambling scenario when all the necessary information was explicitly given, and no outcome feedback was provided (Minati et al., 2011). Furthermore, Shohamy et al. (2004b) compared performance on the WPT with outcome feedback and without (e.g. a paired associate (PA) version in which PD patients were presented with cues and outcomes simultaneously). PD patients in the no-feedback condition outperformed those in the feedback condition. Shohamy et al. (2008) interpreted this as evidence for impaired incremental feedback-based learning in PD (Shohamy et al., 2008). Schmitt-Eliassen et al. (2007) replicated these findings in a modified version of the WPT task, in which the no-feedback condition merely observed the cue–outcome associations. However, when Wilkinson et al. (2008) replicated Shohamy et al.'s (2004b) study using similar techniques to Schmitt-Eliassen et al. (2007), they reported that compared to a healthy age matched group PD patients were impaired on both feedback and no-feedback versions. The findings of the studies conducted thus far do not provide a clear answer as to whether the presence of feedback influences PD patients' performance on decision-making tasks.

What adds to the confusion is that tasks used to examine decision-making in PD have utilized two different types of feedback. In some tasks (e.g. WPT) the feedback is discrete, which means that it only informs people about the success of their actions on a given trial. Such feedback provides very little information about the rule underlying cue–outcome relationship (i.e. task structure – underlying association between cues, outcome probabilities, and rewards), unless it is tracked over time, which puts a stress on working memory. For example, if a given cue is associated with a given outcome 80% of the time, then feedback that informs participants that on this particular trial the cue was followed by this particular outcome does not help in any way to discover the rule governing the cue outcome relationship in this task, unless people have a significant degree of exposure to the task. In tasks that use cumulative feedback (e.g. DDM), on the other hand, people are provided with information about their performance relative to a target across several trials. This kind of feedback makes it much easier for participants to discover the rule guiding the cue outcome relationship, because they can track their performance more easily without burdening their working memory. Using the example described above, if a given cue is associated with a given outcome 80% of the time, then feedback that informs participants that on past five trials this particular cue was followed by this particular outcome on four occasions, makes it easier for participants to figure out what the cue–outcome relationship actually is. In general studies utilizing discrete feedback tend to find PD patients to be impaired (e.g. Knowlton et al., 1996; Perretta et al., 2005; Sage et al., 2003), whereas studies utilizing cumulative feedback usually find decision making in PD to be intact (e.g. Osman et al., 2008, Witt et al., 2002). Consequently, it seems that when informational content of feedback is rich, frequent, or in some cases not provided

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at all, these situations seems to assist PD patients in learning and decision-making (Shohamy et al., 2004b; Witt et al., 2006).

2.3. Experimental manipulation associated with medication status of PD patients

In addition to task design, one of the factors that have been proposed to have a profound effect on PD patients' performance on decision-making tasks is whether they are tested on or off their dopaminergic medication. Pharmacological therapy available for PD patients focuses on restoring depleted levels of the neurotransmitter dopamine in the brain. The midbrain dopaminergic system is thought to play a crucial role in learning from feedback (e.g. Shohamy et al., 2004b) and reward processing (Hollerman et al., 2000; Schultz, 2002). Previous studies suggest that in normal populations learning from positive and negative feedback depends on the phasic changes of firing of dopamine neurons (e.g. Aubert et al., 2000; Floresco et al., 2003). Unexpected reward is associated with phasic bursts of activity in dopamine neurons (Schultz et al., 1993), while omission of an expected reward results in dips in activity (Hollerman and Schultz, 1998). It has been proposed that phasic release of dopamine acts as a "temporal difference" error signal that indicates whether the occurrence of a reward or a stimulus signalling reward is better (phasic increase, positive prediction error) or worse (phasic pause or dip, negative prediction error) than expected; while continued tonic activity signifies that things are as expected (Montague et al., 1996, 2004; Schultz and Dickinson, 2000).

A decrease in dopamine levels in PD is associated with degeneration of the dopamine-producing cells in the substantia nigra pars compacta, and this is thought to result in substantial disruption of the processes described above. Consequently, it could be hypothesized that PD patients should perform worse in decision-making tasks than HCs when tested off medication, when the dopamine levels are decreased, but just as well (or nearly as well) when tested on medication, which partially restores the dopamine levels in the brain. However, evidence suggests that PD patients tend to perform better when tested off medication, rather than on medication on some tasks such as the WPT, CGT, IGT, PRL or concurrent discrimination task (e.g. Cools, 2001; Cools et al., 2003, 2006; Jahanshahi et al., 2010; Kapogiannis et al., 2011; Shohamy et al., 2006; Swainson et al., 2000). Several explanations for this phenomenon have been proposed. Frank et al. (2004) hypothesized that dopaminergic medication impairs PD patients' ability to learn from negative feedback. Alternatively, poor performance in decision-making tasks may reflect the fact that dopaminergic medication causes an overdose of dopamine in parts of the basal ganglia such as the central striatum less affected by the disease in the early stages (Gotham et al., 1988). It is important, however, to bear in mind that several studies have also reported that there are no differences in performance on Iowa Gambling Task and Weather Prediction Task between patients on and off medication (e.g. Czernecki et al., 2002; Wilkinson et al., 2008), which suggests that the effect of medication on decision-making tasks in PD is not straightforward.

2.4. Summary of experimental manipulations that influence decision-making in PD

It is clear from the findings discussed that there are candidate features of decision-making tasks and experimental factors that may explain the inconsistent pattern of findings associated with decision-making in PD. However, without a detailed evaluation of the pattern of findings reported in each study, there is no basis for drawing any strong conclusions. Therefore, we conducted a simple exploratory meta-analysis of the main findings of studies employing the tasks reviewed in this article.

The specific manipulations that were examined were the decision-making paradigm (decision-making under risk vs. uncertainty), environment (probabilistic vs. deterministic), feedback structure of the task (discrete vs. other), and medication status (on vs. off dopaminergic medication). Also, to investigate the proposal that PD patient's impaired performance is a result of slower rates of learning (i.e. that people with PD are capable of learning about the underlying cue–outcome associations, but require more trials to achieve it) the number of trials in each test was entered into the analysis as well. The electronic search of databases in January 2013 using key words 'Parkinson's disease' and 'decision-making' identified 363 results. Following the examination of titles and abstracts we excluded all reviews and animal studies. Given that we were only interested in tasks in which successful performance would require intact processing of all stages of the decision-making process described in Section 2, we excluded tasks not employing the basic set-up described above. We also excluded studies which examined PD patients suffering from impulse control disorders (e.g. pathological gambling), unless these studies included PD patients without these disorders and their healthy peers as control groups. Consequently, 32 papers were selected, and further 20 studies were identified based on reference lists. From the list of 52 studies, those which did not have age-matched healthy participants as a control group were eliminated from the analysis (e.g. Rossi et al., 2010). Two studies examining performance of PD patients who had Deep Brain Stimulation surgery were also excluded (Halbig et al., 2004; Wilkinson et al., 2011). This resulted in 38 studies which were included in the final analysis. Each study was then classified according to the four manipulations described above. Binary values were assigned to each of the relevant categories (e.g. 'patients interviewed off medication' assigned numerical value of 1, 'patients interviewed on medication' assigned numerical value of 2). Each study was described using the appropriate numerical values for each category. For each study the outcome on performance was recorded (i.e. 1, patients with PD performed as well as HCs; 2, showed impairments). The next step of the analysis was to conduct a logistic regression to find the task characteristics that could influence the results of studies examining decision-making processes in PD patients.

3. Results

38 studies from the past 18 years were analyzed (earliest: 1994; most recent: 2012) – 60 separate experiments of decision-making in PD (studies with PD patients ON and OFF med, or with different types of feedback were counted as separate instances of PD patients performing the task – these were labelled as separate tests). PD patients were found to be impaired relative to HCs on 39 experiments (65% of all experiments). Logistic regression analysis was performed to assess the impact of the decision-making paradigm, environment (i.e. the rule governing the cue–outcome relationship), feedback, and medication status on the likelihood that PD patients would be impaired on decision-making tasks. The criterion variable was whether or not PD patients were impaired on the decision-making task compared to healthy age-matched controls. Only the significant results of this analysis are reported. The full model containing all predictors was statistically significant, $\chi^2(5, N = 60) = 22.75$, $p < .001$, indicating that the model was able to distinguish between impaired and unimpaired PD patients. The model as a whole explained between 33.4% (Cox and Snell R square) and 45.5% (Nagelkerke R squared) of the variance in PD patients' performance on the decision-making tasks, and correctly classified 82.1% of cases.

As shown in Table 1, two of the independent variables (feedback and medication status) made a unique statistically significant contribution to the model. Thus the following question can

Table 1
Logistic regression predicting likelihood of impaired performance in PD patients.

	B	S.E.	Wald	df	Sig.	Odds ratio	95% C.I. for odds ratio	
							Lower	Upper
Paradigm	0.826	1.08	0.59	1	0.44	2.28	0.278	18.81
Environment	0.76	0.96	0.63	1	0.429	2.14	0.32	14.05
Feedback	3.222	1.09	8.76	1	0.003	25.07	2.97	211.8
Medication status	2.69	0.8	11.43	1	0.001	14.79	3.1	70.54
Trial no.	0	0.002	0.6	1	0.43	1	0.99	1
Constant	−5.65	1.93	8.56	1	0.003	0.003		

be answered: *Which experimental manipulations associated with decision-making tasks are most likely to generate impairments in performance in patients with PD?* The strongest predictor of impaired performance was the presence of discrete feedback, recording an odds ratio of 25.1. PD patients presented with discrete trial-by-trial feedback were significantly more likely to show impaired performance as compared with cumulative feedback or no feedback at all, controlling for all other factors in the model. The odds ratio of 14.8 for the medication status indicated that PD patients on medication were significantly more likely to show impaired performance on decision-making tasks compared to PD patients off medication, controlling for other factors in the model.

4. Discussion

The result of our meta-analysis revealed that presentation of discrete feedback and testing patients with PD on medication are more likely to lead to poorer performance on decision-making tasks in these patients. In light of this, we can now begin to answer the following two questions: *Is general decision-making ability affected in PD? How can the deficits identified in decision-making in PD contribute to our understanding of the role of the basal ganglia in decision-making?*

4.1. Is general decision-making ability affected in PD?

One of the main questions regarding decision-making in people with PD is whether it is general decision-making ability that is impaired in PD, or is the impairment actually a by-product of a deficit affecting a more specific cognitive function. Based on the results of this meta-analysis it seems more plausible that PD is associated with specific deficits in feedback processing which is associated with the outcome evaluation stage of the decision-making process.

4.1.1. Evaluation of outcome feedback

The results of this meta-analysis suggest that PD patients are adversely affected by discrete feedback when making decisions. Impairments in feedback processing in PD are likely to affect evaluation of the outcomes, which is the final stage of the decision-making process, resulting in impairments observed on some decision-making tasks in PD. However, the impairments of feedback processing in PD seem to be limited to discrete feedback, which begs the question: Why only discrete feedback?

It can be argued that it is not the presence of feedback per se that impairs learning and decision-making in PD, but rather it is the absence of information about the cue–outcome relationship. For instance, Todd and Hammond (1965) suggested that outcome feedback in most MCPL tasks (which is often discrete) is not informative of how people should appropriately weight the cues, which could have negative effects on task performance (Hammond et al., 1973). Consistent with this view, in many studies in which feedback failed to provide critical information about the cue–outcome relationship, impaired incremental learning in HCs, similar to that reported in PD patients, was observed (e.g. Knowlton et al., 1996; Shohamy et al., 2004b; Smith and McDowall, 2006). Moreover, when task relevant information was available through feedback in MCPL tasks it was shown to benefit participant's performance (Hammond et al., 1973; Harries and Harvey, 2000). An example of an environment in which outcome feedback is directly related to the structure of the underlying task is DDM task. In DDM tasks cumulative outcome feedback provides participants with important information regarding the cue–outcome relationships, which may be why PD patients' performance is as good as HCs (e.g. Osman et al., 2008). Thus, we would argue that when a decision-making task is sequential and involves choices which have effects on the reward (e.g. WPT/IGT) or on the outcome (DDM) then a feedback structure that is consistent with this incremental learning will facilitate accurate performance in PD. Discrete feedback, on the other hand, disrupts the incremental process of updating task information, which especially affects the performance of PD patients, in whom the mechanisms responsible for processing and updating information based on prediction errors is already impaired. Therefore, whenever feedback does not provide important information about the task structure, this will affect PD patients' performance.

4.1.2. Medication status

The results of the current meta-analysis also suggest that PD patients tend to perform better on decision-making tasks when they are examined off rather than on their usual medication. However, this is not true for all decision-making tasks. This suggests that dopaminergic medication also does not affect the global decision-making ability, but rather some components of this process.

The fact that PD patients on medication tend to perform worse on some decision-making tasks, when considered in the context of the dopamine "overdosing" hypothesis (Cools et al., 2003; Gotham et al., 1988), suggests that some components of the decision-making process in PD might depend on parts of the brain less affected at the early stages of the disease, which become 'overdosed' with dopamine after administration of dopaminergic medication. In PD neurodegeneration the striatum progresses in a well-defined manner, with the dorsal striatum affected earlier in the disease than the ventral striatum. Given this, processes that involve the ventral striatum to a greater extent, such as stimulus-reward learning (e.g. MacDonald et al., 2013), are adversely affected by dopaminergic medication in patients with PD. This in turn might explain why PD patients on medication are found to be impaired on some decision-making tasks, for the reason that these tasks may rely to a great extent on associative stimulus-reward learning processes. It can be hypothesized, therefore, that dopaminergic medication does not impair decision-making per se, instead, PD impairs certain components of the decision-making process, such as outcome evaluation, which in turn relies heavily on reward processing mediated by the ventral striatum. This, in turn, results in poor performance of PD patients on medication on decision-making tasks providing participants with certain types of feedback.

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4.2. How can the deficits identified in decision-making tasks in PD contribute to our understanding of the role of the basal ganglia in decision-making?

Given the comprehensive nature of our meta-analysis, we hoped that the factors we included would also give us insights into the role of the basal ganglia in decision-making. Basal ganglia have been shown to be important with respect to a range of cognitive functions such as working memory (e.g. Frank et al., 2001; O'Reilly and Frank, 2006), habit learning (e.g. Knowlton et al., 1996; Grahn et al., 2008), reinforcement learning (Bullock et al., 2009) and category learning (Seger, 2008; Shohamy et al., 2008). Crucially, there are findings from several studies which suggest that basal ganglia might be important for decision-making processes (e.g. Brand et al., 2004; Mimura et al., 2006; Pagonabarraga et al., 2007). However, as highlighted in this review, not all of the evidence supports a critical role for basal ganglia in decision-making given that patients with PD could perform as well as HCs on a variety of decision-making tasks. Furthermore, variability in the effects of dopaminergic medication on decision-making in PD along with the differences between tasks commonly used to assess decision-making in this population has made drawing conclusions about the role of the basal ganglia in decision-making difficult, until now. Consequently, the aim of this review was to evaluate the evidence available from studies on decision-making in PD to identify the key factors influencing the performance of PD patients, which could potentially inform us about the role of the basal ganglia in these processes.

Based on the pattern of results obtained from PD patients so far it seems that basal ganglia are especially important for evaluating the outcomes of the decision-making process in scenarios in which feedback of a particular type is presented. They seem to play a crucial role for successful decision-making when discrete outcome feedback is the only source of information about the underlying structure of the task. In such circumstances learning about the task takes place mainly by forming stimuli-reward associations, mediated by the striatum. When such learning is impaired as a consequence of dopaminergic imbalance in the basal ganglia, making optimal decisions becomes especially difficult. The findings from the studies reviewed in this paper suggest that in such circumstances dropping the feedback altogether, or replacing it with cumulative feedback could be advantageous for decision-makers.

In addition, the results of this meta-analysis suggest that the other key factor that greatly impairs decision-making in PD is dopaminergic medication, which again seems to impair a specific stage rather than a global decision-making process. Considering that the most reliable support for the overdosing hypothesis comes from studies using discrete feedback structure (such as WPT or PRL tasks) (e.g. Cools et al., 2006; Jahanshahi et al., 2010; Shohamy et al., 2006; Swainson et al., 2000), it is possible that the overdosing effect also depends on the feedback structure of the task. Overdosing of dopamine in PD patients taking L-dopa primarily affects ventral striatum, a structure which is important for reward processing (e.g. Haber and Knutson, 2009), especially for processing of intrinsic reward (e.g. self-rated good performance – how good I think I am/achievement – how good I hope to be) (e.g. Lutz et al., 2012; Satterthwaite et al., 2012) and outcome feedback (Tricomi and Fiez, 2008). Therefore, what might actually be impaired in patients with PD while on medication is the processing of intrinsic rewards provided by outcome feedback. This should not affect PD patients' learning when feedback provides information about the underlying structure of the task as well. The reason for this is that, if it is easy to track one's own performance and improve performance because outcome feedback is tied to the inherent structure of the task, then when performance dips decision makers should find it easier to adapt their strategies to improve their performance. So, there is less of a burden on processes concerning intrinsic rewards. However, when the only information feedback provides in a decision making tasks is whether you were 'good' (coherent with participants' predictions, therefore rewarding) or 'bad' (inconsistent with participants' predictions, therefore not rewarding), and moreover, is only tangentially connected to the cue–outcome associations, then being able to correctly process intrinsic rewards might be much more important for the learning process. This would mean that overdosing of dopaminergic medication would have the biggest impact on performance when feedback provided in the task was not informative of the underlying structure of the task, hence the successful incorporation of the information provided by feedback depended on correct reward processing. We would therefore predict that the more remote the feedback is to the underlying structure of the task, the greater the impairments in PD on medication, and the greater the effect of overdosing.

4.3. Conclusion

The current review set out to determine the scope of decision-making impairments in people with Parkinson's disease. This was achieved by investigating the pattern of findings in decision-making tasks associated with manipulations of task environment (deterministic vs. probabilistic), paradigm (risk vs. uncertainty), feedback (discrete, continuous), number of trials, and medication status of patients. The results suggest that discreet feedback and dopaminergic medication generate the most significant impairments to decision-making behaviour in PD. The latter adds further support to the dopamine overdosing hypothesis. At the same time we found no evidence that factors such as task environment (probabilistic vs. deterministic) or task paradigm (decision-making under risk or under uncertainty) influence decision-making in PD. The implications of these findings are that Parkinson's disease does not lead to a global impairment in decision-making ability, as some studies would propose, but rather impairs processing in the final stage of the decision-making process, namely the evaluation of the outcome. We speculate that this is associated with difficulties in processing feedback which does not contain sufficient information about the task structure. This current finding adds to our understanding of the role of the basal-ganglia in the decision-making process, pointing to their importance for the reward processing evaluative component of decision-making.

Uncited references

Q3

Gescheidt et al. (2012), Kobayakawa et al. (2010), Moody et al. (2004), Myers et al. (2003) and O'Doherty et al. (2004).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2013.10.005.

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