Psychophysiological evidence for impaired reward anticipation in Parkinson’s disease

Samuel T. Mattox a,b, Fernando Valle-Inclán c, Steven A. Hackley b,*

a Department of Neurology, University of Missouri, Columbia, USA
b Department of Psychological Sciences, University of Missouri, Columbia, USA
c Department of Psychology, University of La Coruña, Spain

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Abstract

Objective: According to a widely held view, mesencephalic dopamine neurons mediate feedback-based learning by broadcasting an error signal that indexes the difference between anticipated and actual response-contingent reward. The present experiment tested whether impaired learning of a probabilistic classification task by individuals with Parkinson’s disease (PD) is associated with abnormal reward expectation.

Methods: The stimulus-preceding negativity (SPN), a brain potential known to reflect anticipation of motivationally significant events, was compared for blocks in which subjects anticipated high or low monetary rewards and punishments.

Results: The SPN was reduced in amplitude in patients relative to controls in the high monetary incentive condition. Furthermore, whereas the SPN varied in size as a function of cue complexity for control subjects, it did not for patients.

Conclusions: These results suggest that anticipatory processes within cortical portions of the reward system are impaired by PD.

Significance: These data support previous claims that the SPN offers an electrophysiological index of activity within cortical portions of the reward pathway, and that reinforcement-based learning is impaired in PD.

Keywords: Event-related potentials; Basal ganglia; Parkinson’s disease; Learning and memory

1. Introduction

There is now extensive evidence that mesencephalic dopamine (DA) neurons and their target structures play a central role in the processing of motivationally relevant stimuli. For example, single unit studies in nonhuman primates indicate that cells distributed throughout the striatum, ventral midbrain, and orbitofrontal cortex are active when rewards are expected or presented (Hikosaka et al., 1989; Schultz et al., 1992; reviewed in Schultz et al., 2000). In addition, neuroimaging experiments in humans have documented increased blood flow/oxygenation within these same regions in response to various types of reward, including money (Delgado et al., 2000; Elliott et al., 2003; Knutson et al., 2001; Thut et al., 1997), good-tasting food (McClure et al., 2003); cocaine (Breiter et al., 1997), generic pleasant photographs (Lane et al., 1997), and photographs of beautiful faces (Aharon et al., 2001).

A widely accepted functional interpretation of mesencephalic DA neurons is that they serve to modulate synaptic plasticity. Dopaminergic cells promote feedback-based learning by transmitting an error signal reflecting the difference between anticipated and actual response-contingent rewards (Schultz, 1998; Schultz et al., 2000). The existence of a diffusely broadcast learning signal with this characteristic is consistent with the most influential contemporary theory of conditioning (Rescorla and Wagner, 1972) and with connectionist models of learning and memory derived from this theory (e.g., Waelti et al., 2001).

Given the severe deterioration of midbrain DA pathways in Parkinson’s disease (Agid et al., 1987), it seems
reasonable to examine impaired reward processing as a possible explanation for the learning deficits that characterize this disorder. Neuroimaging evidence for impaired reward processing in PD has been provided by Künig and colleagues (2001). These authors showed that monetary rewards produce blood flow increases in the caudate and putamen on both sides of the brain in control subjects. By contrast, increases were seen only in a small portion of the left caudate in the PD participants of their study.

A disadvantage of such hemodynamic approaches is that poor time resolution precludes investigating pathological variation in reward anticipation and receipt with the millisecond-level precision needed to follow neural activity. (But see Knutson et al., 2003, for fMRI analyses that distinguish reward anticipation vs. receipt.) The current study was conducted to help address this deficit in the literature. Specifically, an event-related brain potential (ERP) associated with reward anticipation was recorded during a well-characterized task in which PD patients are known to exhibit poor performance.

1.1. Feedback-based learning

The weather prediction task, introduced by Knowlton et al. (1994), involves feedback-based learning of probabilistic stimulus–response associations. Participants are required to sort stimuli into two categories on a trial-and-error basis, with a certain degree of inconsistency imposed in the feedback. This inconsistency is intended to prevent subjects from adopting declarative, rule-based strategies. Instead, participants are encouraged to rely on implicit, gradually acquired, stimulus–outcome associations. Single and double dissociation studies have demonstrated that PD patients are selectively impaired in this type of learning (Knowlton et al., 1996; Witt et al., 2000).

More recent evidence suggests that it is trial-by-trial feedback and reward rather than probabilistic categorization that is crucial for revealing Parkinsonian learning deficits (Shohamy et al., 2004; see also Ashby et al., 2003). Shohamy and colleagues demonstrated that in a nonfeedback probabilistic classification task, one in which subjects learned by simply observing cue–outcome associations, PD patients did as well as controls during subsequent behavioral testing. A second version of the task did document group differences. In this version, participants first saw the cue display, tried to guess the outcome, and then received response-contingent feedback and reward. Participants with Parkinson’s disease performed more poorly than did those who were neurologically normal. Strengthening these conclusions, a parallel fMRI study using only healthy subjects showed that the feedback version of the task produced greater striatal activation than the observational version (Poldrack et al., 2001).

1.2. The stimulus-preceding negativity (SPN)

The main goal of our study was to investigate whether anticipation of feedback and rewards is impaired in PD. Anticipatory processes were assessed using the stimulus-preceding negativity (SPN), an ERP that appears to specifically reflect the expectation of motivationally relevant stimuli (reviewed in Van Boxtel and Böcker, 2004). For example, this slow cortical potential has been observed prior to emotion-inducing slides (Klorman and Ryan, 1980; Simon et al., 1979), electric shocks (Böcker et al., 2001), performance feedback (Damen and Brunia, 1994), and monetary rewards (Kotani et al., 2001).

Because monetary rewards, electric shocks, performance feedback, and emotion-inducing slides are likely to attract attention, one might infer that the SPN simply reflects anticipatory attention. There are three arguments against this inference: First, Damen and Brunia (1994) compared the SPN prior to three types of task-relevant stimuli: instructional cues, task stimuli, and performance feedback displays. A clear SPN was obtained in that study only prior to the feedback display, the most motivationally relevant of these stimuli. Second, whereas manipulating the perceptual difficulty of an anticipated stimulus would be expected to influence the size of an attention-related brain wave, no such effect has been found for the SPN (Hillman et al., 2000; Kotani and Aihara, 1999). Finally, parallel neuroimaging and dipole modeling studies indicate that the generators of SPN include structures involved in the processing of feedback and rewards. Specifically, the putative SPN generators are lateral prefrontal cortex (BA 9/10/44/45), inferior parietal lobe (BA 40), and right insular cortex (Böcker et al., 1994; Brunia et al., 2000; Ohgami et al., 2003; Tsukamoto et al., in press).

In the present study, Knowlton’s weather prediction task was modified in several ways in order to optimize investigation of the SPN. A delay was imposed between response and feedback to reduce overlap between movement-related potentials and the subsequent SPN. The cues and outcome were jointly redisplayed after feedback, to minimize working memory load during the interval in which SPN appeared. The magnitude of monetary reward/punishment was manipulated across blocks to better reveal group differences that are specific to the motivational aspect of reward anticipation.

The neuropsychological and electrophysiological data reviewed above lead to the following predictions: if performance deficits in the weather task are due to impaired processing of feedback and rewards, as hypothesized by Shohamy and colleagues (2004), a reduction in amplitude of the SPN should be observed for the patient group. This group difference should interact with the size of the monetary rewards and punishments, on the assumption that it is specifically related to the motivational/emotional aspect of feedback. The failure to obtain such an interaction would leave open the possibility that reduced SPN amplitudes might reflect, for example, a deficit in anticipatory attention or in preparation to process numerical data.
2. Methods

2.1. Participants

Twenty clinically diagnosed patients with idiopathic Parkinson’s disease were assessed. Patients withdrew from all antiparkinsonian medications during the night preceding the experimental session. The average withdrawal period of 15 h would not be enough to achieve full clearance of antiparkinsonian drugs nor yield an asymptotically stable “off” state. However, emotional processes are known to be enhanced by dopaminergic medication (e.g., Tessitore et al., 2002), so overnight withdrawal might reasonably be expected to accentuate group differences in our study. A longer withdrawal period would have achieved better drug clearance but would have imposed a greater burden on our participants.

Thirteen of the patients were male, seven were female. The mean age for this group was 69.00 years (SD = 8.91, range 51–84). Mean duration of the illness was 4.98 years (SD = 5.47, range 1–23). Patients were mildly impaired, as indicated by both the Hoehn and Yahr Scale (1967) and the Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn and Elton, 1987). The patients’ scores on these symptom scales averaged 1.70 (SD = 0.66, range 1–3) and 28.60 (SD = 11.43, range 10–47), respectively. See Table 1 for details.

The control group included 32 neurologically normal, age-matched individuals (24 male, 8 female). Their mean age was 69.19 years (SD = 5.87, range 50–80). A larger sample of control subjects was recruited because it was originally planned to match various subsets of the control group to the PD group with respect to task performance, age, years of education, Geriatric Depression Scale score (GDS; Sheikh and Yesavage, 1986), Snaith–Hamilton Pleasure Scale score (SHAPS; Snaith et al., 1995), and the Total Memory Composite Score of the Weschler Memory Scale – Third Edition Abbreviated (WMS-III Abbreviated). However, this turned out to be unnecessary because patients and controls were not significantly different on any of the demographic or psychometric measures other than task performance (see Table 1).

Participants were nondemented, had no other neurological disorder, and were not taking antidepressant, anxiolytic, or antipsychotic medication. They gave their written, informed consent prior to the session and were paid $40.00 in addition to their net winnings earned during the probabilistic classification tasks.

2.2. Probabilistic classification task

Two parallel versions of the weather prediction category learning task (Knowlton et al., 1994; Witt et al., 2000) were employed, which we refer to as the “weather task” and “stock market task.” All stimuli were displayed on a 32 × 23 cm color monitor at a distance of 50 cm. On every trial, a display of one, two, or three cards from a set of four possible cards was presented in a horizontal array at the center of the screen. On each card was a unique geometric design (i.e., four different arrangements of polygons or circles for the weather task and a different set of designs for the stock market task). Participants indicated their response either with a left-hand finger using a key on the left side of the keyboard or with a right-hand finger on the right side of the keyboard. In the stock market task, participants made left- and right-hand responses based on the “leading economic indicators” to predict whether the market would be “up” or “down.” In the weather task, the cards were used to predict outcomes of “sunny” or “cloudy.” Left/right-hand assignments were not counter-balanced with respect to trial outcome, due to the number of other variables that had to be balanced across groups (see Data Analysis, below). The cards remained on the computer screen until the participant made a key press.

The cards were independently and probabilistically related to each outcome, such that the overall probability of the cards was 75%, 57%, 43%, and 25% for one outcome (e.g., sunny). Complementary probabilities associated the cards with the other outcome (cloudy). For displays with more than one card, outcomes were determined by the average probability.

2.3. Recordings

Participants were seated in a dark, sound attenuated room, with their head positioned on a chin rest in front of the computer monitor to minimize head and jaw movements. All electrophysiological recordings were obtained with 9-mm tin electrodes. Monopolar EEG was recorded at F3, F4, C3, C4, FPz, Fz, Pz, and Oz (bandpass, 0.01–30 Hz), rereferenced off-line to digitally averaged mastoids. Peri-ocular and FPz electrodes were affixed with adhesive collars; all others were held in place with a nylon electrode cap (Electro-Cap International, Inc.). Bipolar
vertical and horizontal electro-oculograms (v and hEOG) were obtained using the same bandpass as the EEG (0.01–30 Hz). Spontaneous facial EMG was recorded with a bipolar pair of electrodes positioned over the left m. zygomaticus major (smile) and m. corrugator supercilii (knitted brow) using a bandpass of 0.3–300 Hz. These recordings were intended to confirm the hedonic impact of rewards and punishments in control subjects and in patients not suffering from facial masking. All electrode impedances were below 10 kΩ. scalp leads were usually below 3 kΩ.

Digitization of the electrophysiological signals was carried out continuously at 250 Hz. EMG was full-wave rectified prior to signal averaging. The recording epochs used for signal averaging can be considered to be both response- and stimulus-locked, as stimulus presentation was linked to the participant’s key press. The delay from the participant’s response until feedback stimulus onset was constant at 2000 ms. Epochs were 8000 ms in length, which included 2000 ms preceding and 6000 ms following the key press response. Prior to signal averaging, eye movement artifacts were removed using the method of Gratton et al. (1983). Small stimulus displays were used during the learning task to further minimize eye movements. Epochs were rejected if EEG at any channel exceeded ±70 μV, or if facial EMG exceeded 150 μV. These criteria resulted in at least 80% retention of all experimental trials for signal averaging.

2.4. Procedure

The session began at 9:00 a.m. with acquisition of informed consent. The next step, in the case of patients, was administration of Hoehn and Yahr and UPDRS assessments. Subsequently, all participants were given a practice block of trials to familiarize them with the timing and event structure of the two habit learning tasks. Practice trials were similar to experimental trials with the exceptions that the four predictor cards for the practice were distinguished simply by colors, and the relationship between the cards and the outcomes was random.

In experimental blocks (as in practice blocks), each trial began with presentation of the predictor cards. Participants were instructed to make a one-finger key press with the response button that corresponded to their prediction of the weather or stock market outcome, whichever was being performed in that half of the experiment. The subjects were told that “speed is not important, but try not to take more than a few seconds on each trial.” Thus, slow responders (e.g., bradykinetic PD patients off medication) were not disadvantaged by a reaction time criterion.

After a response, the cards disappeared and a fixation cross appeared at the center of the screen for 2 s. After this delay (referred to as the “prefeedback interval”), a feedback display appeared. If the response for the trial was correct, then the feedback display consisted of a green rectangle with the amount of money won indicated in text (e.g., “+$0.75”). If the response was incorrect then the rectangle was red in color, and the amount of money lost was shown. The feedback display remained on the screen and after 1.5 s (the “redisplay interval”) the predictor cards for that trial were again presented, partially overlaying the feedback. The redisplay screen remained on for 2.5 s, and then the screen darkened for the intertrial interval of 2 s. In summary, the events within a trials were: card display, key press, fixation point, feedback, card redisplay, and intertrial interval.

The weather and stock market tasks were administered in separate halves of the experimental session. One of the two tasks was designated as the low incentive condition, in which participants won or lost $0.05 for correct or incorrect answers, respectively (range of possible net winnings/losses: -$4.90 to +$4.90). The other task was designated as the high incentive condition (±$0.75; possible range −$73.50 to +$73.50). Size of the payoff was manipulated rather than comparing reward to nonreward in order to avoid a confound with preparation to process numerical data. The order of task type (weather or stock market) and incentive condition were balanced within the two subject groups. By way of example, one-fourth of the PD patients began the high incentive ($0.75/trial) version of the weather task as soon as they finished the practice blocks. Then, in the second half of their experimental session, these subjects played the stock market game under conditions in which they could win or lose only a nickel on each trial.

Each task consisted of 98 trials. During a 25-s break between the first and second half of each task and also at the end of the tasks, the amount of net winnings appeared on the screen. After the second task, patients resumed their medication before beginning the psychometric assessments. The MMSE, WMS-III Abbreviated, GDS and SHAPS were administered at this time.

2.5. Data analysis

2.5.1. Behavior

As in previous probabilistic categorization experiments, “percentage correct” or “percentage of optimal responding” was defined as a prediction that corresponded to the most probable outcome for that trial. For example, in the weather task, if a card was presented and was associated with the answer “sunny” 75% of the time, then the correct response would have been “sunny,” regardless of the actual outcome for that particular trial. The mean number of correct responses was computed separately for each of the 7 blocks of 14 trials in each task. The factors Group (PD or control), Incentive (low or high), Task Order (whether the high incentive condition was performed first or second), and Trial Block were included in a $2 \times 2 \times 2 \times 7$ mixed ANOVA.

2.5.2. Electrophysiology

The amplitude of the stimulus-preceding negativity (SPN) was defined as the average voltage during the 200-ms interval immediately preceding feedback. Two
ERPs reflecting response preparation and execution, the “movement-related potential” (MRP) and its subcomponent, the lateralized readiness potential (LRP), were analyzed to assess contamination of SPN by motor artifacts. MRP amplitude was defined as the mean voltage across the interval −1100 ms to −100 ms prior to the key press. The LRP, an index of hand-specific motor cortex activity, was computed by subtracting waveforms recorded ipsilateral to the responding hand from those obtained at contralateral sites, and then averaging across left- and right-hand trials (De Jong et al., 1988). The mean amplitude of the LRP was analyzed for two time intervals, the 300 ms immediately preceding key press and the 200 ms interval prior to feedback (i.e., the SPN-measurement interval). The former was used to assess group differences in motor cortex activity, and the latter, to evaluate contamination of the SPN by volume conducted motor cortex potentials. Zygomaticus and corrugator EMG amplitudes were computed as the mean voltage across the interval 900–3900 ms following feedback. Unfortunately, EMG data were available for only 10 patients and 18 control subjects, due to experimenter error. The error was corrected midway through the two groups; therefore, counterbalancing for incentive condition order was not compromised.

For the main analysis, amplitude measures were subjected to a mixed ANOVA that included the variables Group (PD or control), incentive (high or low), valence (monetary gain or loss), task order (whether the high incentive task was performed first or second), lateralization (left or right-hemisphere), and anteriority (frontal or central). An additional ANOVA was computed to clarify scalp distribution in some cases. These analyses included the variables group, incentive, valence, and mid-sagittal location (midline electrodes Fpz, Fz, Cz, and Pz; the Oz channel was excluded because of high noise levels). These ANOVAs were repeated for a subset of the participants that were matched for task performance. Twenty of the 32 control participants were selected to match the patient group with regard to overall task performance, thereby equating the number of reward and punishment trials across groups. These post hoc groups were balanced for task order. Finally, an additional set of analyses (described below) assessed group differences in task strategy.

3. Results

3.1. Performance

Fig. 1 presents overall performance for PD patients and controls collapsed across the two tasks. The main effect of group was significant ($F[1,48] = 9.90, p = 0.05$). Replicating prior research on feedback-based learning (e.g., Knowlton et al., 1996), PD patients were found to perform worse than control subjects (Fig. 1). There was no main effect for incentive level or interaction of this factor with group, but the trends were illuminating. Consistent with our SPN data and with a previous behavioral study (Shohamy et al., 2004, discussed below), patients actually tended to perform worse when nontrivial rewards were offered (61.6% and 65.1% correct for high and low incentive conditions, respectively). Overt performance did not differ between the two conditions for control subjects (68%, high incentive vs. 67.8%, low incentive).

A number of order effects were observed. An interaction of incentive and task order, which reflected differences between the first and second half session due to practice, was highly significant ($F[1,48] = 12.31, p < 0.01$). A significant main effect of block was also obtained ($F[6,288] = 5.83, p < 0.01$). Performance improved sharply between the first two blocks and then improved only gradually over the last five blocks. Finally, PD-versus-control differences varied as a function of task order ($F[1,48] = 3.97, p = 0.05$). Simple effect analyses of this interaction indicated that patients’ performance was better when the low incentive task was performed first and the high incentive task second ($F[1,18] = 5.23, p < 0.05$). By contrast, there were no performance differences as a function of incentive condition order for control subjects.

3.2. Movement-related potentials

The preresponse negativity, measured from −100 ms to −1100 ms prior to key press documented a main effect of electrode position ($F[1,48] = 8.19, p < 0.01$) such that the MRP was most negative at central scalp sites overlying motor cortex. An additional ANOVA with mid-sagittal sites as levels of the electrode position factor also yielded a main effect ($F[3,144] = 21.17, p < 0.01$), confirming that negativity was greatest at Cz. A main effect of task order ($F[1,48] = 6.16, p = 0.016$) reflected the fact that subjects who were assigned the high incentive condition first and the low incentive second exhibited larger premovement negativities than did subjects performing the tasks in the opposite order. Although a main effect for lateralization was not significant, mean amplitudes revealed slightly more negativity over left-hemisphere than right, which is oppo-
site to the pattern that is typically observed for SPN (e.g., Damen and Brunia, 1994) and that was observed in the present study (see below).

For the lateralized readiness potential (LRP), no significant group differences were found for the preresponse or prefeedback measurement windows for this very easy motor response. The LRP waveform shows hand-specific motor cortex activation prior to, during, and after the key press (Fig. 2). By the time of the SPN-measurement interval (200 ms before feedback), motor activity had substantially declined toward the baseline for both groups. Taken together, these results indicate that group differences in SPN amplitude (described below) are unlikely to be due to overlapping movement-related potentials.

3.3. Zygomaticus and corrugator EMG

Zygomaticus (smile) activity was expected to be larger for win than lose trials, whereas the opposite pattern was predicted for corrugator (furrowed brow). No effects of group or incentive emerged, but a significant effect of valence was obtained (zygomaticus, \(F[1,26] = 10.81, p < 0.01\); corrugator, \(F[1,26] = 5.72, p = 0.02\)). For both muscles, greater activity occurred after monetary losses than gains. Signal-averaged EMG waveforms for rewards and penalties were essentially superimposed until 800 ms after feedback. At that point, larger amplitudes were seen for penalties than rewards. Thus, the EMG measures were sensitive to the motivational valence, but the pattern for zygomaticus activity was opposite to that which was predicted. On-line video monitoring suggested that this was due to smirks and grimaces (movements kinematically similar to smiles) following negative feedback.

3.4. Stimulus-preceding negativity

As would be predicted under the hypothesis that reward anticipation is altered by Parkinson’s disease, the interaction of group and incentive was significant \((F[1,48] = 7.22, p = 0.01); see Fig. 3\). There was a tendency for SPN amplitudes to be larger prior to high rewards/penalties than prior to low ones for the control group. By contrast, PD patients showed the reversed pattern \((F[1,18] = 7.81, p = 0.01)\). Looking at the interaction another way, SPN amplitudes were greater for control than PD participants during the high incentive task \((F[1,48]=7.61, p < 0.01)\) but not the low.

Main effects were obtained for the electrode position variables of lateralization \((F[1,48] = 29.56, p < 0.01)\) and anteriority \((F[1,48] = 4.22, p < 0.05)\) across sites F3, F4, C3, and C4. As is commonly observed, the SPN had a right-hemisphere, frontal maximum (see Fig. 4 for a portrayal of laterality effects in control subjects). A separate ANOVA that included the midline electrode variable (Fpz, Fz, Cz, and Pz) also yielded a significant effect \((F[1,48] = 16.00, p < 0.01)\) with a maximum amplitude for SPN at the frontal polar site, Fpz. The absolute maximum was at the frontopolar site which, although consistent with fMRI studies of monetary reward (e.g., Knutson et al., 2003), differs from previous SPN studies. Many earlier studies that lacked explicit rewards reported that SPN was largest at the F4 electrode (Van Boxtel and Böcker, 2004).

An incentive-by-task order interaction documented SPN amplitude differences between the first and second task \((F[1,48] = 5.91, p = 0.02)\). Greater negativity was observed
for whichever task was performed in the second half of the experimental session.

In the analyses for which control and patient groups ($N = 20$ per group) were matched for performance and hence, for average number of rewards, all previously described main effects and interactions were confirmed. This implies that the attenuated SPNs observed in PD patients were unlikely to be due to reduced interest in the task as a result of infrequent rewards.

An additional set of analyses examined the possible effect of strategy differences on the SPN. Previous research has shown that when the weather task is first being learned, both PD patients and controls tend to adopt simple strategies. These include focusing on a single cue (e.g., clustered diamonds = sunny) or learning what to predict on one-cue trials but just guessing when two or three cards are shown (Shohamy et al., 2004). After this initial phase, neurologically normal participants quickly advance to a strategy in which they treat multicue displays as Gestalten, gradually learning to associate them with specific outcomes. By contrast, people whose brains have been damaged by Parkinson’s disease persist with simple strategies even after days of training (Shohamy et al., 2004).

We reasoned that if PD patients use strategies in which they focus on single cues, there should not be much variation in their SPN amplitudes between one-cue and three-cue trials, whereas control subjects should treat these trials differently. Specifically, when controls are testing their hypotheses about triplet arrays, feedback would have a high information value and therefore be associated with large SPNs (Kotani et al., 2003). We tested these predictions by conducting analyses of variance using factors of group, task order, cue type (1- vs. 3-cue displays), valence, incentive, and electrode site.

Concurrent with these predictions, a group × cue type × incentive interaction was obtained at both the lateral electrode sites ($F[1,38] = 6.09, p < 0.02$) and the mid-sagittal sites ($F[1,38] = 5.94, p < 0.02$). In the high incentive condition, control subjects showed larger SPNs on three-than on one-card trials, whereas there was no difference for patients (see Fig. 5). Separate analyses for the two groups showed that number of cues had no effect for patients ($F[1,12] = 0.05, p = 0.82$) but had a rather large effect on control participants’ SPN amplitudes ($F[1,26] = 9.88, p < 0.01; $ lateral sites).

These results are consistent with previous evidence (Shohamy et al., 2004) that PD patients mainly use relatively simple strategies. On trials with inherently conflicting, three-card displays, they may limit their attention to a single, salient cue. By contrast, control participants attempt to use more sophisticated multicue strategies, at least when high incentives make the extra effort worthwhile.

4. Discussion

We recorded electrophysiological activity associated with rewards and feedback to examine whether PD patients exhibit abnormal anticipatory processing of these stimuli during feedback-based category learning tasks. Tasks of this sort have been shown in previous work to yield poor performance in PD patients when response-contingent feedback and rewards are given, but normal performance when participants simply learn by observation (Shohamy et al., 2004). We expected prefeedback abnormalities because research in normal humans and monkeys (Knutson et al., 2003; Schultz et al., 2000) indicates that feedback-based learning involves anticipatory processes within cortical areas innervated by mesencephalic dopamine cells, cells that degenerate in Parkinson’s disease. Using a noninvasive electrophysiological measure, we showed that anticipatory processing of rewards and feedback is indeed altered by Parkinson’s disease.
4.1. Manipulation checks

Consistent with much prior research (e.g., Knowlton et al., 1996), PD patients in our study performed more poorly than age- and psychometrically matched control subjects in the probabilistic classification task. The manipulation of incentive level did not generate significant differences in task performance, probably because only a small amount of money was involved and there was a high base level of social motivation in both tasks (participants knew their performance was being monitored). Covert measures, however, demonstrated that the incentive manipulation did have an effect. Specifically, group differences in SPN amplitudes were observed only in the high incentive condition, and it was only in this condition that control subjects exhibited differential processing of easy, one-cue versus difficult, three-cue displays. Facial EMG and video monitoring provided clear evidence that the rewards, penalties, and feedback mattered to the subjects. About 800 ms after participants were informed that they had guessed wrong and therefore had lost money, subjects in both groups often knitted their brows and either grimaced or smirked.

4.2. Movement-related potentials

Before interpreting results regarding the SPN, it is important to rule out contaminating effects of movement-related brain potentials, most of which are also negative and largest over frontal cortex. The extent and time course of movement-related activity were assessed using the lateralized readiness potential (LRP, see Fig. 2), which is a well-established index of motor cortex activity (Eimer, 1998; Miller and Hackley, 1992).

Several features of the observed movement-related potentials argue that they did not contribute to group differences in SPN measures. First, whereas the SPN increased in amplitude as the feedback display grew imminent, the LRP decreased steadily toward baseline. Movement-related potentials had essentially decayed to negligible levels at the time the SPN was measured. Second, the SPN was significantly larger over the right than left hemisphere (Fig. 4), consistent with most previous studies (e.g., Damen and Brunia, 1994), whereas movement-related potentials exhibited a nonsignificant trend in the opposite direction. Third, the SPN varied systematically as a function of cue and reward condition, whereas the two measures of movement-related activity did not. Fourth, the duration of movement-related potentials including the late portion that could potentially overlap with the SPN was no greater than in similar previous studies at this laboratory and others. Finally, in a follow-up study using a slightly longer prefeedback interval (3000 instead of 2000 ms; Hackley, Hebert, Valle-Inclan and Oh, in preparation), the MRP and SPN were separated by clear return to baseline.

4.3. Paradoxical effects of incentive level

Although the observed interaction of group with incentive level for SPN amplitude constitutes evidence that reward anticipation is altered by PD, it is surprising that the patients actually exhibited reduced amplitude SPNs in the high relative to the low incentive condition. Also, their performance tended to be worse in the high incentive condition. These findings are paradoxical, but they are similar to the pattern observed by Shohamy and colleagues (2004) in a behavioral study. As noted earlier, their PD participants performed about the same as controls in a version of the probabilistic categorization task in which learning was based simply on observing cue–outcome associations. In the other version of the task, in which participants actively responded to the cues with predictions and then received feedback and rewards, the patients’ accuracy was significantly reduced.

One way to summarize this odd pattern of results is as follows: Parkinson’s patients actually learn less and exhibit smaller SPN amplitudes when significant rewards are provided (+$1.00 in their study; ±$0.70 in ours) than when either no rewards or only trivially small rewards and penalties are given. Shohamy and coauthors were not able to offer an explanation, but they did point out that failure to abandon the feedback-based learning strategy might have been related to impaired task-switching ability, which is often attributed to fronto-striatal circuitry. We can only add that the learning signal broadcast by a degraded dopamine system might not just be attenuated, but distorted as well.

4.4. Understanding the SPN

Recent studies of the SPN have tended to stick closely to the time-interval production paradigm with which Brunia and colleagues (e.g., Brunia and Damen, 1988) first convincingly distinguished this slow wave from other components of the contingent negative variation. Our study examined a different task, subject population, and set of manipulated variables. Consequently, it provided new information about the nature of the SPN. Our results showed that SPN amplitude varies as a function of learning, reaching larger amplitudes in the second half of the experimental session, in parallel with practice effects on task performance. In normal participants, the SPN was also larger on more difficult trials, those with three as opposed to one cue. This is consistent with neurobiological evidence that activity within mesencephalic dopamine pathways is related to reward uncertainty (Mirenowicz and Schultz, 1996). Subjects were presumably more uncertain about whether a reward would be received on trials that were difficult.

Finally and most importantly, group differences in our study provide further evidence that the SPN specifically reflects anticipatory activity within cortical portions of
the reward system (Kotani et al., 2001, 2003). In both groups of participants, the SPN was largest at the electrode closest to mesial orbitofrontal cortex, Fpz, a region shown in previous fMRI studies to be sensitive to monetary rewards (e.g., Knutson et al., 2003). More importantly, we found that the SPN was grossly abnormal in individuals whose dopamine system had been degraded by Parkinson’s disease and who had been withdrawn from dopamine-replacement medication. The paradoxical patterning of these effects raises new questions, questions that may profitably be addressed by future research.

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