



## Effects of asymmetric dopamine depletion on sensitivity to rewarding and aversive stimuli in Parkinson's disease

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### ARTICLE INFO

#### Article history:

Received 15 September 2012

Received in revised form

1 February 2013

Accepted 5 February 2013

Available online 17 February 2013

#### Keywords:

Dopamine

Parkinson's disease

Hemispheric asymmetry

Approach

Avoidance

### ABSTRACT

The onset and progression of Parkinson's disease (PD) motor symptoms is generally asymmetric, reflecting differential extent of nigral pathology and resulting dopamine depletion in each of the hemispheres. Given the role of dopamine in processing rewarding and aversive events, and considering findings associating asymmetric neural activity with differential sensitivity to positive and negative stimuli, the current study examined the possibility that dopamine asymmetry in PD is related to differential approach and avoidance tendencies. An original task assessing and comparing sensitivity to positive and negative probabilistic feedback was administered to 29 right-handed participants with idiopathic PD, 16 with predominant right-side and 13 with predominant left-side motor symptoms, to compare the two groups. As dopamine replacement therapy (DRT) has shown different effects on reward and punishment processing, all participants were assessed in both off- and on-medication states. As predicted, when off medication, participants with relatively greater dopamine deficit in the left hemisphere minimized losses better than they increased gains, while those with a greater right hemisphere deficit showed a trend toward the opposite pattern. Medication reversed the relationship between gain and loss sensitivity in the left-hemisphere PD group, but not in the right-hemisphere group. Particularly in the left-hemisphere PD group, findings support the possibility that subcortical dopaminergic asymmetry is reflected in behaviorally-expressed approach and avoidance tendencies. Furthermore, the effects of DRT on approach and avoidance appear to interact with asymmetry, shedding light on previous conclusions regarding the role of dopamine in reinforcement processing.

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### 1. Introduction

Dopamine is central to neural processes underlying motivational control, with a widely accepted role in processing rewarding events and guiding goal-directed behavior, as well as known involvement in responding to aversive stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). Accordingly, it has been proposed that the processing of positive and negative feedback and, more broadly, the relative tendency towards approach-related behaviors versus avoidance of aversive stimuli, is affected in populations in which the dopaminergic system is known to be compromised, among them patients with Parkinson's disease (PD). In PD, degeneration of dopaminergic cells in ventrolateral parts of the substantia nigra (SN) leads to depleted dopamine levels in striatal projection areas, particularly the posterior putamen (Bjorklund & Dunnett, 2007; Hornykiewicz & Kish, 1984).

Projections from the dorsal striatal area to cortical areas involved in motor control lead to the cardinal motor symptoms associated with PD. Loss of dopaminergic neurons in the ventral tegmental area and disruption of pathways from more ventral parts of the SN to the nucleus accumbens and caudate nucleus, which are associated with higher emotional and motivational functions (Middleton & Strick, 2000a,b), result in various non-motor manifestations of the disease (Bernal-Pacheco, Limotai, Go, & Fernandez, 2012; Cools, 2006). In this context, abnormalities in processing and learning from reinforcement have indeed been reported in PD (Bodi et al., 2009; Frank, Seeberger, & O'Reilly, 2004; Palminteri et al., 2009; Shohamy, Meyers, Kalanithi, & Gluck, 2008).

In the majority of individuals with PD, the onset of motor symptoms is asymmetric (Elbaz et al., 2005; Toth, Rajput, & Rajput, 2004; Uitti et al., 2005), presenting as more severe on either the left side or the right side of the body. While its etiology is unclear (Djaldetti, Ziv, & Melamed, 2006), this asymmetry is known to be associated with asymmetric degeneration of dopaminergic neurons in the substantia nigra (Kempster, Gibb, Stern,

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& Lees, 1989) and, more generally, with asymmetry in dopaminergic transmission in the striatum (Leenders et al., 1990; Tatsch et al., 1997). Furthermore, it often persists throughout the progression of the disease (Djaletti et al., 2006).

Davidson (2004) has proposed that differential sensitivity to positive and negative stimuli is associated with relatively asymmetric patterns of activation in anterior cortical regions, with several clinical and laboratory observations suggesting that left prefrontal cortex plays a more significant role in approach behavior, while right prefrontal cortex underlies withdrawal behavior and behavioral inhibition (Sutton & Davidson, 1997). As cortical asymmetries have been attributed to input from asymmetric subcortical neurochemical systems (Trevorthen, 1996), the dopaminergic system among them, it is suggested that dopamine asymmetry may play a role in modulating sensitivity to reward and punishment. The asymmetric dopamine depletion that leads to lateralized motor symptoms in PD presents a distinctive opportunity to examine this possibility.

In a study examining approach and avoidance tendencies in PD, as expressed in the self-reported personality measures novelty seeking and harm avoidance, respectively, Tomer and Aharon-Peretz (2004) reported asymmetry-based effects, in line with Davidson's (2004) model. The aim of the current study was to determine whether this relationship between differential patterns of dopaminergic asymmetry and self-reported approach and avoidance tendencies would be expressed behaviorally, on a measure specifically designed to compare sensitivity to positive and negative feedback. Based on the aforementioned findings associating relatively greater left- and right-hemisphere activity with approach and withdrawal behavior, respectively, it was hypothesized that patients with a relatively greater degree of dopamine loss in the left-hemisphere ("left-hemisphere PD," predominantly right-side motor symptoms) would be more sensitive to punishment than to reward, while the opposite would be true for patients with relatively greater dopamine loss in the right-hemisphere ("right-hemisphere PD," predominantly left-side motor symptoms). It was further predicted that relative sensitivity to reward versus punishment would be correlated with a relative measure of motor asymmetry in the PD group as a whole.

The dopamine-based medications used to treat PD have repeatedly been shown to affect reward and punishment processing in differential ways (Bodi et al., 2009; Frank et al., 2004; Palminteri et al., 2009; van Wouwe, Ridderinkhof, Band, van den Wildenberg, & Wylie, 2012), raising the possibility that medication interacts with asymmetry to determine approach and avoidance tendencies among asymmetric, medicated patients. Participants in the current study were thus assessed in both off-medication and on-medication states, such that the main and interactive effects of both asymmetry and medication could be evaluated. Predictions about possible interactions between medication and asymmetry can be considered in the context of the 'dopamine overdose hypothesis' (Cools, 2006; Gotham, Brown, & Marsden, 1988). Attempting to explain the detrimental effects of systemically increased dopamine levels on some cognitive functions, this model suggests that dopaminergic medications such as L-dopa normalize dopamine levels in depleted areas, while increasing levels excessively in areas that are less affected (Cools, Barker, Sahakian, & Robbins, 2001; Swainson et al., 2000). While this model was formulated based on evidence that striatal dopamine depletion in PD is expressed earlier and more significantly in dorsolateral areas than in more ventral areas (Kish, Shannak, & Hornykiewicz, 1988), the idea that performance on cognitive tasks may be disrupted by either reducing or increasing optimum dopamine levels can also be applicable with respect to asymmetry. Namely, when dopamine depletion is

greater in one hemisphere than in the other, the addition of dopaminergic medications may ameliorate deficits in the more depleted hemisphere while excessively increasing dopamine levels in the other. Thus, medication is expected to alter the relationship between the two task conditions in each of the groups.

## 2. Methods

### 2.1. Participants

Twenty-nine right-handed participants with idiopathic Parkinson's disease were recruited from the patient population of the Parkinson's Disease and Movement Disorders Clinic at the Sheba Medical Center. All participants gave written informed consent and the study was approved by the local ethics committee.

Major psychiatric disorder predating the onset of PD, insulin-dependent diabetes, history of head trauma involving loss of consciousness, other neurological disease, history of drug or alcohol abuse, and surgical relief of PD symptoms were grounds for exclusion. All participants were non-demented and scored 28 or above on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), which was administered at the time of testing. Participants satisfying Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) criteria for any Axis I psychiatric diagnosis were also excluded.

All participants were on stable doses of medication when recruited for the study. Use of some form of levodopa-based (L-dopa-based) medication was required for inclusion; additional medications included dopamine agonists (17 participants), rasagiline (14 participants), selegiline (7 participants), amantadine (13 participants), entacapone (13 participants), anticholinergic medications (5 participants), and antidepressant medications (5 participants). L-dopa dose, agonist dose, and a calculated L-dopa equivalence dose incorporating both types of medications (Evans et al., 2004) were documented for each participant. The group was divided according to the side of onset of motor symptoms (13 left-onset motor symptoms, or right-hemisphere PD; 16 right-onset of motor symptoms, or left-hemisphere PD), as determined by documentation of their neurological examinations at the time of diagnosis and confirmed in a neurological examination at the time of testing.

### 2.2. Measures

General demographic information was collected including age, sex, and years of formal education, and the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) were administered.

The motor examination portion (items 18–31) of the United Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987) was used to assess the severity of Parkinsonian motor deficits in the PD groups, for each side of the body and for both sides combined.

#### 2.2.1. Gain–loss sensitivity (GLS) task

An original computerized task that assesses and compares sensitivity to positive and negative probabilistic feedback under separately-administered conditions was used. In each condition, four decks of cards, numbered 1–4, are graphically presented on the screen and the participant is instructed to select one card in each of 100 trials by pressing the key on the keyboard corresponding to the number of the deck of choice. After each selection, one of two feedback options is presented. In the reward condition, the participant either gains (+10) or does not gain (0) ten points (virtual money), while in the punishment condition, the participant either loses (–10) or does not lose (0) ten points. Unbeknownst to participants, the probabilities of the two feedback types vary between the decks, with decks corresponding to 80%, 70%, 60%, and 50% chances of gaining ten points or losing ten points in the reward or punishment conditions, respectively. Thus, the task enables direct comparison of responses to positive versus negative feedback, as well as examination of sensitivity to small changes in feedback probability.

In the reward condition, participants begin with no points, and are given the following instructions: "You will be presented with four decks of cards: 1, 2, 3, 4. In each trial, select one card from the deck of your choice by pressing the corresponding key on the keyboard. Each time you choose a card, you may earn money—sometimes you will and sometimes you will not. Some decks are better than others and you are completely free to move from deck to deck whenever you want to and as many times as you choose. The goal of the game is to earn as much as possible. Please treat the game money as though it were real, and make your decisions as though they involved your own money." In the punishment condition, participants begin with 1000 points, and are given instructions that vary from the reward condition instructions only in that they explain that money may or may

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