CORTEX 49 (2013) 2834–2844

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

Hemispheric dissociation of reward processing in humans: Insights from deep brain stimulation

Stefano Palminteri [a,b], Giulia Serra [b], Anne Buot [b], Liane Schmidt [a,b], Marie-Laure Welter [b] and Mathias Pessiglione [a,b,*]

[a] Motivation, Brain and Behavior (MBB) Team, Institut du Cerveau et de la Moelle Epinière (ICM), Hôpital de la Pitié-Salpêtrière, Paris, France
[b] Inserm UMR 975, CNRS UMR 7225, Université Pierre et Marie Curie (UPMC – Paris 6), Hôpital de la Pitié-Salpêtrière, Paris, France

ARTICLE INFO

Article history:
Received 21 August 2012
Reviewed 26 November 2012
Revised 10 January 2013
Accepted 5 February 2013
Action editor Marco Catani
Published online 29 March 2013

Keywords:
Reinforcement learning
Incentive motivation
Hemispheric dissociation
Deep brain stimulation
Parkinson's disease

ABSTRACT

Rewards have various effects on human behavior and multiple representations in the human brain. Behaviorally, rewards notably enhance response vigor in incentive motivation paradigms and bias subsequent choices in instrumental learning paradigms. Neurally, rewards affect activity in different fronto-striatal regions attached to different motor effectors, for instance in left and right hemispheres for the two hands. Here we address the question of whether manipulating reward-related brain activity has local or general effects, with respect to behavioral paradigms and motor effectors. Neuronal activity was manipulated in a single hemisphere using unilateral deep brain stimulation (DBS) in patients with Parkinson's disease. Results suggest that DBS amplifies the representation of reward magnitude within the targeted hemisphere, so as to affect the behavior of the contralateral hand specifically. These unilateral DBS effects on behavior include both boosting incentive motivation and biasing instrumental choices. Furthermore, using computational modeling we show that DBS effects on incentive motivation can predict DBS effects on instrumental learning (or vice versa). Thus, we demonstrate the feasibility of causally manipulating reward-related neuronal activity in humans, in a manner that is specific to a class of motor effectors but that generalizes to different computational processes. As these findings proved independent from therapeutic effects on parkinsonian motor symptoms, they might provide insight into DBS impact on non-motor disorders, such as apathy or hypomania.

1. Introduction

Incentive motivation and instrumental learning: these two reward-related processes are often confounded, as they are naturally intermingled in real-life situations. The crucial difference is that the reward is known before engaging the action in incentive motivation and after completing the action in instrumental learning. Incentive motivation is the process through which reward prospects activate particular behaviors (Berridge, 2004; Haggard, 2008). Instrumental learning is the process through which obtained rewards increase the propensity to repeat particular behaviors (Skinner, 1938; Thorndike, 1911). There is ample evidence that reward expectation and obtainment are represented in fronto-striatal

* *Corresponding author*. 47 Bd de l'Hôpital, 75013 Paris, France.
E-mail address: mathias.pessiglione@gmail.com (M. Pessiglione).
0010-9452/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cortex.2013.02.014

circuits and modulated by dopaminergic transmission (Kable and Glimcher, 2009; Knutson and Cooper, 2005; O'Doherty, 2004; Salamone and Correa, 2002; Schultz, 2006). However, it remains unclear whether the reward representations used in instrumental learning and incentive motivation involve the same neural structures. A first aim of the present study was to examine whether manipulating neural activity in fronto-striatal circuits conjointly affects incentive motivation and instrumental learning performance.

In folk psychology, rewards impact on the mind and behavior of a subject taken as a whole, not on some sub-part of that person. However, the neural implementation of reward processing raises the possibility that a sub-personal system might be affected while others are not. Previously we have provided evidence for this phenomenon in both incentive motivation and instrumental learning paradigms (Palminteri et al., 2009a; Schmidt et al., 2010). Behavioral and neuroimaging data suggested that the two hemispheres can represent different reward expectations, which might influence both action selection (which hand to move) and action energization (with how much vigor). However, the evidence was only correlational and could not conclude a causal relationship between reward representations and behavioral outputs. A second aim of the present study was to provide direct evidence that unilaterally manipulating reward representation can affect the participation of one specific hemisphere to reward-based action selection and energization.

To manipulate activity in fronto-striatal circuits we chose to investigate deep brain stimulation (DBS) in Parkinson's disease (PD), as it was shown to enhance motivation for food reward and to improve reward-based action learning (Serranova et al., 2011; van Wouwe et al., 2011). In first approximation, PD is due to a degeneration of dopaminergic neurons that induces motor symptoms (akinesia, rigidity, tremor), which can be alleviated using dopaminergic enhancers or DBS in the subthalamic nucleus (STN-DBS). Several studies have consistently reported that dopamine depletion impairs reward-based approach learning but favors punishment-based avoidance learning, this pattern being reversed by dopamine enhancers (Bodi et al., 2009; Cools et al., 2009; Frank et al., 2004; Palminteri et al., 2009b; Pessiglione et al., 2006). A plausible explanation for dopamine enhancers effects is that tonic dopamine release adds a constant to reward prediction errors, such that positive reinforcement following reward is amplified, whereas negative reinforcement following punishment is diminished. We reasoned that STN-DBS, which has a similar impact as dopamine enhancers on motor symptoms, might also amplify neural encoding of reward magnitude. A third aim of this study was to validate the assumption that reward magnitude is amplified under STN-DBS.

To address our three questions, we tested PD patients with unilateral STN-DBS using both our incentive motivation and instrumental learning tasks (Fig. 1A and B). Each patient was tested twice, once with left and once with right electrode simulation, allowing within-patient comparison of task performance to assess unilateral DBS effects. In order to get reference points for disease and treatment effects we also included healthy controls and PD patients with bilateral STN-DBS On and Off. Our working hypothesis was that brain reward sensitivity is reduced in PD patients but inflated by STN-DBS, as it is with dopamine enhancers. Thus, a first prediction was that unilateral STN-DBS should amplify incentive effects on force production when applied contralaterally to the working hand. In addition, the hypothesized similarity between STN-DBS and levodopa effects implies that low-probability cues (mostly associated with negative reinforcement) should be better learned when stimulation is off, whereas high-probability cues (mostly associated with positive reinforcement) should be better learned when stimulation is on (see Fig. 2A and B). A second prediction was therefore that STN-DBS should also improve (respectively, impair) instrumental learning in conditions where the contralateral option is associated to high (respectively, low) reward probability. As a control, bilateral STN-DBS should have no effect in our instrumental learning paradigm, since impaired learning from negative prediction error (missed reward) should cancel improved learning from positive prediction error (obtained reward).

2. Materials and methods

2.1. Subjects

The study was approved by the local ethical committee of the Pitié-Salpêtrière Hospital. All participants provided informed written consent prior to participation. We included 16 patients with PD, all implanted bilaterally with electrodes for high frequency stimulation (DBS, Medtronic®) in the STN. Patients were tested either six months ($n = 8$) or twelve months ($n = 8$) after surgery. Exclusion criteria were: cognitive dysfunction and concomitant psychiatric condition. We also included eight age-matched healthy subjects, screened for any history of neurological or psychiatric disease and concomitant psychotropic medication. As they were mostly relatives accompanying patients to the hospital, they shared the same socio-economic background. All PD patients and healthy subjects were right handed (see Table 1 for a summary of demographic and clinical data).

2.2. Instrumental learning task

PD patients and healthy subjects performed a probabilistic instrumental conditioning task with two motor responses (left or right) and two monetary outcomes (.5€ or nothing). The same task has been previously used to demonstrate the lateralization of reward representations (Palminteri et al., 2009a) and the detrimental effects of dopamine receptor antagonists (Worbe et al., 2011). It was programmed on a PC using Cogent 2000 software (Wellcome Trust Center for Neuroimaging, London, UK), running as a MatLab® toolbox.

The task comprised three independent learning sessions, each containing new cues to be learned. Learning sessions lasted 11 min, contained 96 trials and employed four different pairs of visual cues, which were letters taken from the Agathodaimon font. Each cue was associated with a stationary reward probability (25 or 75%). The four cue pairs were randomly constituted and assigned to the four possible combinations of probabilities (25/25, 25/75, 75/25, 75/75%). As far as