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Dopaminergic modulation of the trade-off between probability and time in economic decision-making

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Abstract
Studies on animals and humans have demonstrated the importance of dopamine in modulating decision-making processes. In this work, we have tested dopaminergic modulation of economic decision-making and its neural correlates by administering either placebo or metoclopramide, a dopamine D2-receptor antagonist, to healthy subjects, during a functional MRI study. The decision-making task combined probability and time delay with a fixed monetary reward. For individual behavioral characterization, we used the Probability Time Trade-off (PTT) economic model, which integrates the traditional trade-offs of reward magnitude-time and reward magnitude-probability into a single measurement, thereby quantifying the subjective value of a delayed and probabilistic outcome. A regression analysis between BOLD signal and the PTT model index permitted to identify the neural substrate encoding the subjective reward-value. Behaviorally, medication reduced the rate of temporal discounting over probability, reflected in medicated subjects being more prone to postpone the reward in order to increase the outcome probability. In addition, medicated subjects showed less activity during the task in the postcentral gyrus as well as frontomedian areas, whereas there were no differences in the ventromedial orbitofrontal cortex (VMOFC) between groups when coding the subjective value.

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The present study demonstrates by means of behavior and imaging that dopamine modulation alters the probability-time trade-off in human economic decision-making.

1. Introduction

Reports on animals and humans have established the importance of the dopaminergic system in reward-encoding and decision-making processes. Studies on macaques have shown that neurons capable of encoding value-related elements are located in the striatum (Lau and Glimcher, 2008; Samejima et al., 2005). In humans, the striatum is not only active during the evaluation of the primary reward characteristics (Knutson et al., 2007; McClure et al., 2007) but it also encodes subjective value (De Martino et al., 2009; Hsu et al., 2009; Kable and Glimcher, 2007). Dopaminergic treatment used in Parkinson's disease (PD) induces impulsivity among other adverse effects (Ceravolo et al., 2010; Merims and Giladi, 2008). The modification of dopamine levels in PD patients with impulse control disorders (ICD) has been associated with a devaluation of a delayed reward (Voon et al., 2010). The acute administration of levodopa to healthy controls had an effect on reward-related behavior, predisposing subjects to select shorter delay options although, the administration of a dopamine antagonist, haloperidol, did not produce significant behavioral changes (Pine et al., 2010). Previous work has also shown that acute administration of dopamine antagonists effectively modified reward related behaviors such as gambling (Tremblay et al., 2010) and instrumental learning (Eisenegger et al., 2014; Pessiglione et al., 2006). In rats decision-making under uncertainty was influenced by a striatal D2/3 receptor antagonist, increasing risk aversion (Cocker et al., 2012; St Onge and Floresco, 2009). A proposed mechanism for these effects has been to consider dopamine a neurotransmitter driving motivation towards rewards (Berridge et al., 2009). Use of different dopamine antagonists in decision-making paradigms may help to further unravel the role of dopamine in reward related human behaviors.

A choice often involves both the passage of time before an outcome is reached and uncertainty regarding the outcome. Examples are investment decisions that lead to uncertain payoffs in the future, or consumption decisions that involve comparing alternative paths with different delays and uncertain gratification. However, most studies in the field of economics have focused on the study of the trade-off between reward magnitude and probability, and between reward magnitude and delay separately. Reflections on the primacy of time or probability discounting have been mainly based on parallels in the trade-off between reward magnitude and probability, and reward magnitude and delay; for a review see Berns et al. (2007). In this work, we aimed to elucidate which brain areas are involved during the decision-making process when both delay and risk are being concurrently evaluated. Aside from the intrinsic increase in value when a reward is received with higher probability, which can thus be traded against an increase in delay, a trade-off between delay and risk is central in many instances of decision making in modern society. Fields where a trade-off between time and probability of reward is needed when making decisions include project management where more time intensive procedures may increase the probability of success of a project, in environmental economics where more time consuming applications of policy decisions can modify the chances of obtaining the desired outcome and in health economics where the length of treatments can influence the probability of a preferred outcome. This kind of interaction between time and risk in decision making is also in line with classical foraging theory models in which the probability of a reward is weighted against the effort or time required for an animal to obtain it (Real and Caraco, 1986).

To shed light on the role of dopamine in the trade-off between probability and delay, we measured the impact of a dopamine D2 receptor (D2R) antagonist, metoclopramide, on the behavioral and functional outcome of a probability-time trade-off paradigm, using functional magnetic resonance imaging (fMRI). Metoclopramide, a derivative of benzamide, acts by antagonizing the dopamine D2 receptor in the peripheral and central nervous systems, as it easily crosses the blood brain barrier (Liu et al., 2009). Its short-term-use good safety profile (Friedman et al., 2011) and short lasting effect led us to consider it as an interesting D2R antagonist. In addition, we have previously demonstrated that a single dose of metoclopramide is capable of altering cerebral perfusion in humans (Fernandez-Seara et al., 2011).

We hypothesized that the administration of metoclopramide would increase the willingness of subjects to wait for a less risky reward (i.e. a reward with higher probability), when compared to the administration of placebo. It was also expected that medication would modify activity in striatal regions, which present the highest density of D2Rs, or in frontal regions involved in decision-making. The VMOFC has been proposed to be a key region in the valuation of rewards and hence was considered a priori a key area to search for activations related to the assignation of subjective value and the difference in this assessment between groups (Bartra et al., 2013; Levy and Glimcher, 2012).

2. Experimental procedures

2.1. Subjects

Two groups of subjects were evaluated, in a single-blind, placebo controlled study. The medicated group (MG) consisted of 15 subjects, six females (age=24.0±3.4 years: mean±standard deviation (SD)), who received an oral dose (10 mg) of metoclopramide (commercial name *Primperan*) one hour prior to entering the scanner. The pharmacokinetic properties of the drug are included in Supplementary material. The second group followed the same experimental procedure, but taking a placebo (an identical capsule with 10 mg of starch). The placebo group (PG) consisted of 14 subjects, 10 females (age=23.0±1.9 years). Participants were recruited among the student body of the Medical School and were