Brain Stimulation 5 (2012) 116–123

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Effect of continuous theta burst stimulation of the right dorsolateral prefrontal cortex on cerebral blood flow changes during decision making

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ARTICLE INFO

Article history:
Received 28 October 2011
Received in revised form
7 March 2012
Accepted 8 March 2012
Available online 10 April 2012

Keywords:
rTMS
Theta burst stimulation
Dorsolateral prefrontal cortex
Decision making
Impulsivity
Delay discounting task

ABSTRACT

Decision making is a cognitive function relaying on a complex neural network. In particular, the right dorsolateral prefrontal cortex (DLPFC) plays a key role within this network. We used positron emission tomography (PET) combined with continuous theta burst transcranial magnetic stimulation (cTBS) to investigate neuronal and behavioral changes in normal volunteers while performing a delay discounting (DD) task. We aimed to test whether stimulation of right DLPFC would modify the activation pattern of the neural circuit underlying decision making during the DD task and influence discounting behavior.

We found that cTBS of the right DLPFC influenced decision making by reducing impulsivity and inducing participants to favor large but delayed rewards instead of immediate but small rewards. Stimulation also affected activation in several prefrontal areas associated with DD. In particular, we observed a reduced regional cerebral blood flow (rCBF) in the ipsilateral DLPFC (BA 46) extending into the rostral part of the prefrontal cortex (BA 10) as well as a disrupted relationship between impulsivity (*k*-value) and rCBF in these and other prefrontal areas.

These findings suggest that transcranial magnetic stimulation of the DLPFC influences the neural network underlying impulsive decision making behavior.

Introduction

It has been demonstrated that both humans and experimental animals generally value immediate reward more than delayed reward. In everyday life, individuals tend to compare potential benefit versus cost and choose the most valuable option under a given situation. During this decision making process, people may assign different weights to rewards, with time playing an important factor in calculating the value of that reward.

Frequently, individual characteristics such as personality and personal preferences guide this decision making process. Impulsivity is a personality trait that is considered to play an important role in decision making. This behavior is associated with actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes [1]. As a measure of impulsivity, delay discounting (DD) is a behavioral analytic approach utilized to understand how each individual makes a choice between a smaller reward given immediately and a larger reward given after a time delay. This metric can therefore be used to assess impulsivity [2]. Significantly elevated discounting tendencies are observed in various patient groups with impulsive behavior. For example, drug abusers or pathological gambler, obsessive compulsive disorder and attention deficit hyperactivity disorder patients show larger preference for immediate but smaller reward then delayed but larger reward in a DD task [3–5].

Thus far, there have been a number of studies that have tried to investigate the neural substrates underlying the decision making process associated with the DD paradigm. These reports have documented the involvement of different areas in the prefrontal cortex (PFC) including the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MePFC) with the anterior cingulated cortex (ACC) and the orbitofrontal cortex (OFC), along with the

The authors report no financial or other conflict of interest relevant to the subject of this article.

A.P.S. is supported by a grant from the Canadian Institutes of Health Research (MOP 110962), Canada Research Chair Program and Edmond J. Safra Philanthropic Foundation.

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doi:10.1016/j.brs.2012.03.007

Table 1
Characteristics of the participants.

Characteristic	
Age	22.6 y (S.D = 2.7)
Gender	
Female	50%
Male	50%
Education	14.5 y (1.3)
BDI	2.0 (2.1)
BIS	
Total	58.0 (10.0)
Motor	21.6 (4.1)
Attention	14.9 (3.6)
Non-planning	21.6 (4.6)

BDI = Beck Depression Inventory; BIS = Barratt Impulsivity Scale-11.

inferior parietal region and ventral striatum (i.e. nucleus accumbens) [6–17].

Despite functional neuroimaging studies providing some insight on the neural control of DD decisions, imaging alone suffers from the limitation that it can only provide neuronal correlates of cognitive performance and often cannot determine a causal relation between observed brain activity and behavioral performance [18,19]. Thus, the specific functional relevance (active role vs simple epiphenomenon) of those structures during DD remains to be established.

There is evidence that the right hemisphere plays an important role in inhibiting impulsive behavior. In particular, the DLPFC along with the inferior frontal cortex and OFC are critical for response inhibition [20–23]. Recently, using non-invasive stimulation tools such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), some studies have suggested that the right DLPFC may affect decision making [24–27] by modulating its neuronal excitability. In particular, we were able to show that cTBS of the right DLPFC reduced the discounting rate (*k*-value) during the DD task compared to sham stimulation providing evidence that cTBS-induced modulation of cortical excitability of the right DLPFC may reduce impulsive decision making [28].

The aim of the present study was to extend our previous observations [28] to investigate, during $H_2^{15}O$ positron emission tomography (PET), whether TBS-induced changes in the level of excitability of the DLPFC in the right hemisphere would affect the activations elsewhere associated with decision making during DD and interfere with impulsivity level.

Methods

Subjects

Eight right-handed young healthy subjects (mean age: 22.6 ± 2.7 y; age range: 18–27 y; 4 women) were enrolled in this study. Exclusion criteria included history of psychiatric and/or neurological disorder, including epilepsy, any previous exposure to stimulant drugs, head injury, pregnancy, and migraine. Handedness was assess using the Edinburgh Handedness Inventory [29]. Applicants with a laterality index lower than 40 for Edinburgh Handedness Inventory were excluded from the study. Subjects were screened as well for depression using the Beck Depression Inventory (BDI) with an exclusion criterion of a score of >10. A trait measure of impulsivity was collected using the Barratt Impulsivity Scale-11 (BIS). The BIS is a self-reported questionnaire containing 30 questions on a 4-point Likert scale reflecting frequency of occurrence. Scoring yields a total score and three subscale scores: attention (rapid shifts and impatience with complexity), motor (impetuous action) and non-planning (lack of future orientation) [30] scores. Higher scores indicate higher impulsivity. The mean values for our subjects are presented in Table 1. Written informed consent was obtained in all cases before the study enrollment; the study protocol was approved by the Ethical Committee of the Center for Addiction and Mental Health Research, University of Toronto.

Behavioral task

This study used three behavioral tasks: delay discounting (DD), magnitude discrimination and a physical discrimination task (Fig. 1). The magnitude discrimination and physical discrimination tasks were used as control tasks. These control tasks were designed to be identical to the DD task with regards to visual perception, motor effects, number of trials and number of choice options in each trial. The choice stimuli were presented on the screen for 3 s and the inter-stimulus interval was 2 s.

In each trial of the DD task, the amounts of monetary reward for immediate and delay options were decided by the fixed *k*-value, and the delay time were based on the hyperbolic function of delay discount, $V = A/(1 + kD)$, where V is the value of the delayed outcome (i.e. the indifference value), A is the delayed reward, D is the length of the delay, and k expresses the steepness of the discount function [31–33]. Based on this function, higher *k*-values are associated with preference for immediate small-size reward and lower *k*-values show a preference for delayed large-size reward. Thus, low *k*-values are an index of minor impulsivity. Subjects were instructed to express a preference judgment between two hypothetical rewards shown on a computer screen. All reward choices were made by pressing either the ← or → key on keyboard with the subject's dominant hand (right hand for all subjects). The available time delays were 6 in total (1 week, 3 weeks, 3 months, 6 months, 1 year, and 3 years). The predefined *k*-values were 0.0005, 0.0028, 0.0050, 0.0275, 0.05, 0.075, 0.1, 0.3, 0.5 and 0.7; the same number of trials was assigned for each *k*-value.

In the magnitude preference task (i.e. control task), subjects had to express a preference between two hypothetical rewards shown on a computer screen just like in the DD task but there was no temporal delay component. In the physical discrimination task

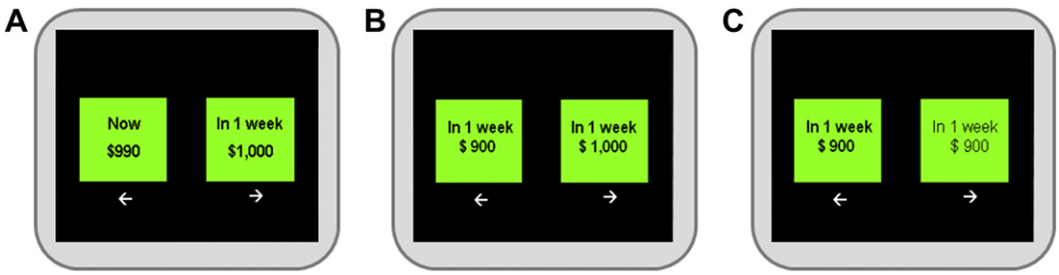

Figure 1. Examples of each behavioral task. (A) Delay discounting task, (B) Magnitude discrimination task, (C) Physical discrimination task.