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Review article

Prefrontal cortex and impulsivity: Interest of noninvasive brain stimulation

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ABSTRACT

Introduction: Impulsivity has been reported in many psychiatric conditions and includes deficits in several cognitive functions such as attention, inhibitory control, risk taking, delay discounting and planning. Many studies have shown that noninvasive brain stimulation (NIBS) techniques modulate the activity of the prefrontal cortex and the functions involved in impulsivity.
Objective: This article aims to review the literature on the effect of NIBS on impulsivity in healthy subjects aged 18–65 years old, and to highlight research avenues to develop therapeutic alternatives for such disorders.
Method: We performed a systematic review of the literature in the PubMed database following PRISMA method with "transcranial magnetic stimulation", "repetitive transcranial magnetic stimulation", "transcranial direct current stimulation", "inhibition", "risk", "impulsive behavior", "attention", "reward", "delay discounting", "delay task", "planning", "prefrontal cortex" as key words.
Results: We selected fifty-six studies showing modulation of the cognitive functions involved in impulsivity through NIBS.
Conclusions: The data led us to consider new therapeutic alternatives in impulsive disorders by modulating prefrontal cortex activity through NIBS.

Contents

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1. Introduction

Impulsivity is involved in our daily decisions and actions. It is characterized by poorly anticipated and inappropriate hasty behaviors that may have negative consequences. Impulsive subjects have difficulties anticipating the effects of their behaviors, learning from the negative repercussions of past actions and appropriately control inhibition (Evenden, 1999). Impulsivity is a multidimensional concept; according to the current most consensual model, it includes poorly attending to relevant stimuli and suppressing irrelevant information, as well as deficient action planning, heightened delay aversion as well as increased risk taking (Barratt, 1985; Horn et al., 2003; Dalley et al., 2011; Eysenck and Eysenck, 1977).

Impulsivity disorders have been reported in many psychiatric conditions such as depression, schizophrenia, behavioral or substance-related addictions, obsessive compulsive disorders, cluster B personality disorders (*e.g.*, borderline or antisocial personality disorders), hyperactivity, aggressive and suicidal behaviors (Plutchik and Van Praag, 1989; Gvion et al., 2015). Impulsive disorders may partly explain the high suicide rates associated with such diseases. Furthermore, suicide attempters show a deficit of attention (Jollant et al., 2011), inhibition (Richard-Devantoy et al., 2012), delay discounting (Jollant et al., 2005), and increased risk taking (Adams et al., 1973). Today, suicide is a major public health problem with high mortality, especially in people with psychiatric disorders. According to World Health Organization (WHO), there were 804,000 deaths by suicide in 2012, being one every 40 s. Besides, the risk of repetition is 30 times greater after a previous suicide attempt. Repetition most frequently occurs within the year following the suicide attempt, with higher risk in the first two weeks (WHO, 2015). Such information has led us to consider new specific therapeutic avenues to reduce impulsivity associated with suicide attempts.

The study of patients with brain lesions and neuroimaging studies have contributed to the identification of various elementary cognitive functions and neuronal substrates involved in impulsivity (Aron et al., 2004; Pattij and Vanderschuren, 2008). The prefrontal cortex (PFC) may be one substrate playing a key role in cognitive control, which determines goals and how to achieve them. The subdivision of the PFC remains unclear and may vary depending on the authors. Some authors divide the PFC in three faces (lateral, ventral or orbital and medial). The lateral face is itself divided in two subdivisions: the dorsolateral prefrontal cortex (DLPFC) including the middle frontal gyrus (lateral part of Brodmann's area 9–BA 9 and BA 46) and the ventrolateral prefrontal cortex (VLPFC) including the inferior frontal gyrus (IFG) BA 44, 45 and 47. The orbital frontal cortex (OFC) including the ventromedial prefrontal cortex (VmPFC) is located in the ventral and medial part of prefrontal cortex, BA 10, 11, 12. The superior medial face is composed by the dorsomedial prefrontal (DmPFC) which includes the anterior cingulate cortex (ACC) on BA 24 and 32 and the medial part of BA 9. DLPFC and VLPFC are more closely connected to sensory cortex and receives projections from somatosensory, auditory and visual information from the occipital, temporal and parietal cortices. The DLFPC, especially the BA 46 is closely connected to pre-motor area such as the supplementary motor area, pre-supplementary motor area and sends projections to the frontal eye field (FEF). On the other hand, orbital PFC is closely connected to the temporal limbic structures (hippocampus, amygdala and hypothalamus) critical for long-term memory and the processing of internal states such as affect and motivation. The different regions of the PFC are also interconnected allowing a crossroad, a place of interaction of different information from different brain structures. Lateral PFC is also connected to limbic structures via the medial PFC (Goldman-Rakic, 1995; Miller and Cohen, 2001; O'Reilly, 2010). The PFC may modulate certain essential functions such as inhibitory control, attention, planning, risk taking and delay discounting (Aron et al., 2004; Gazzaley and Nobre, 2012; Nee and Jonides, 2008). Prefrontal cortex hypoactivity may result in deficits in these functions and lead to greater cognitive and motor impulsivity (Dalley et al., 2011).

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are noninvasive brain stimulation (NIBS) techniques that modulate brain activity in the area beneath the stimulation site and remote areas through connected neuronal networks. These techniques can thus be used as investigation tools for cortical functioning through induced virtual reversible lesions. TMS consists in applying an electric field that modifies neuronal activity through an electric coil placed over the scalp of the subject. Repetitive TMS (rTMS) involve applying regular trains of TMS over a target cortical region. According to works on the motor cortex, the effect of rTMS depends on stimulation frequency: low-frequency rTMS ($\leq$1 Hz) reduces while high-frequency increases ($\geq$5 Hz) the excitability of the targeted cortical area (Maeda et al., 2000; Pascual-Leone et al., 1994). More recent TMS approaches have been developed which involve the application of high-frequency (50 Hz) bursts of stimuli at theta frequencies, so called theta-burst stimulation (TBS). The temporal pattern in which these bursts are applied determines whether the protocol is facilitatory or depressant. In this way, intermittent TBS (iTBS) increases the cortical excitability whereas continuous TBS (cTBS) decreases it (Huang et al., 2005). This depression of cortical excitability would be dependent on *N*-methyl-D-aspartate glutamate receptors (NMDAR) (Muller et al., 2014; Funke and Benali, 2011; Ridding and Ziemann, 2010; Pascual-Leone et al., 1994). On the other hand, tDCS consists in delivering continuous electric current passing through two saline soaked sponge electrodes placed over the subject's skull. According to Bindman et al. (1964) who studied the effects of brief polarizing currents on the cerebral cortex, weak direct currents, delivered by intracerebral or epidural electrodes, modulate cortical activity and excitability. The anode increases cortical activity whereas the cathode sustainably reduces it. This neuromodulation can be stable long after the end of stimulation from few minutes to several hours. These effects share some features with the well-characterized phenomena of long-term potentiation (LTP) and long-term depression (LTD). The long-lasting effects are protein synthesis-dependent and accompanied by modifications of intracellular cAMP and calcium levels. By this way tDCS could increase or decrease neuronal activity and also modulate behavior and the effects depend of the duration and the current density of the stimulation (Nitsche et al., 2008).

In light of these neurophysiological data, many authors took an interest in the effect of NIBS techniques on suicide and the various dimensions of impulsivity. George et al. (2014) recently demonstrated that intensive high-frequency rTMS applied over the PFC was well-tolerated and favored decreased suicidal ideation in suicidal inpatients. Their results were however not statistically significant when comparing patients undergoing active with patients undergoing sham rTMS. Desmyter et al. (2014) also highlighted some effects of rTMS on suicidal ideation in patients with depression receiving PFC stimulation. Hence, better knowledge of the effects of NIBS on impulsivity may help define potential targets