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Review

Non-invasive brain stimulation and the autonomic nervous system

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HIGHLIGHTS

- Non-invasive Brain Stimulation (NIBS) can be applied to the investigation of the autonomic nervous system (ANS) function and, conversely, ANS measures can shed light into the neurobiological mechanisms of NIBS.
- Significant modification of ANS activity in half of the reported NIBS studies, but the optimal parameters of NIBS and ANS assessments remain unclear.
- Based on a review NIBS/ANS studies using a predefined framework, we propose some methodological recommendations for future NIBS studies investigating the ANS.

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are non-invasive methods of brain stimulation (NIBS) that can induce significant effects on cortical and subcortical neural networks. Both methods are relatively safe if appropriate guidelines are followed, and both can exert neuromodulatory effects that may be applied to the investigation of the autonomic nervous system (ANS). In addition, ANS measures can shed important light onto the neurobiologic mechanisms of NIBS. Here we present a systematic review on studies testing NIBS and ANS simultaneously. We structure our findings into four broad (not mutually exclusive) categories: (i) studies in which ANS function was modified by NIBS versus those in which it was not; (ii) studies in which NIBS was used to understand ANS function, (iii) studies in which ANS was used to understand NIBS mechanisms and (iv) NIBS/ANS studies conducted in healthy subjects versus those in patients with neuropsychiatric diseases. Forty-four articles were identified and no conclusive evidence of the effects of NIBS on ANS was observed, mainly because of the heterogeneity of included studies. Based on a comprehensive summary of this literature we propose how NIBS might be further developed to enhance our understanding of the cortical mechanisms of autonomic regulation and perhaps to modulate autonomic activity for therapeutic purposes.

Contents

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1. Introduction

In recent years, techniques for non-invasive brain stimulation (NIBS) have become increasingly used in fundamental and clinical neuroscience. Here we focus on two techniques: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), which have been studied most intensively (Fregni and Pascual-Leone, 2007). Both methods have provided relevant information about cortical excitability in healthy subjects as well as relevant advances in the treatment of several clinical conditions (Fregni and Pascual-Leone, 2007). Despite the increased use of these techniques, their mechanisms of action remain poorly understood. In addition, the relative impact of rTMS and tDCS on different parts of the nervous system has received limited attention. Here we concentrate specifically on the effects of rTMS and tDCS on the autonomic nervous system (ANS) and on the use of ANS to understand the mechanisms of rTMS and tDCS.

NIBS is a useful technique to understand cortical control of ANS. Previous studies have demonstrated that modulation of motor cortex results in significant changes in muscle sympathetic nerve activity (Macefield et al., 1998; Silber et al., 2000). In addition, the ANS has been increasingly used as an outcome measure in NIBS studies in order to understand the broad effects of these techniques including their safety profile. However, while there is clear evidence of autonomic effects of brain stimulation on animals (Yasui et al., 1991; Sequeira et al., 1995; Tavares et al., 2004), recent articles found conflicting results on the relationship of NIBS and ANS (Lai et al., 2010; Näsi et al., 2011; Vandermeeren et al., 2010; Brunoni et al., 2013). Therefore, it is important to consider the two-way relationship between central modulation and ANS function that can be used to explore both NIBS mechanisms and ANS function.

In his context, given the mixed results of studies of NIBS combined with ANS measures and lack of pivotal studies in this area, we performed a systematic review to assess the relationship between non-invasive cortical stimulation and ANS using the following framework: (i) studies separated by those in which ANS function was changed by NIBS versus those in which it was not; (ii) studies in which NIBS was used to understand ANS function, (iii) studies in which ANS was used to understand NIBS mechanisms and (iv) NIBS/ANS studies conducted in healthy subjects versus those in patients with neuropsychiatric diseases.

Finally, because there are no guidelines for establishing parameters to induce and quantify cortical autonomic plasticity using NIBS, we also explored these issues in the present review.

2. Methods

2.1. Literature search

For TMS, we searched for articles published from 1985, when the first study of TMS was released using current TMS parameters (Barker et al., 1985). For tDCS, we searched for studies published from 1998, when modern stimulation protocols were adopted (Priori et al., 1998). We explored articles in the following databases: Medline, Scopus, Web of Science and Google Scholar. Fig. 1 shows the search strategy and the results after careful inclusion and exclusion processes. The autonomic variables were chosen after a systematic review of autonomic tests in the current literature (Ravits, 1997; Low, 2003; Freeman, 2005; Hilz and Dütsch, 2006).

2.2. Literature selection: inclusion and exclusion criteria

We included (1) all original articles that reported TMS and tDCS effects in humans and (2) articles written in English. We therefore excluded the following articles: (1) animal studies; (2) case reports; (3) letters; (4) editorials; (5) articles reporting duplicate data; (6) review articles and, finally (7) articles addressing the effects of non-invasive stimulation applied to other parts of nervous system apart from the brain.

2.3. Data extraction

After careful review of articles, the authors defined the most relevant variables to be extracted from the articles (see below). Then, for each study, two authors extracted data independently (P.S. and O.P.) and two other authors (M.S. and F.F.) checked data extraction. Any discrepancies were resolved by consensus with the corresponding author (F.F.) if necessary.

We elaborated a structured checklist in order to extract the following variables:

(i) *Demographic and clinical characteristics:* Total number of subjects, gender (absolute number of males and females), age (years) and clinical condition (healthy versus non-healthy subjects);
(ii) *Study characteristics:* Year of publication, presence of control group, level of blinding (open, single- or double-blinded) and study design (parallel, crossover or case series designs); In order to assess the quality of reports of the clinical trials we used Jadad scores (Jadad et al., 1996), spanning from 0 to 5 points according to presence of randomization (0 to 2 points), blinding (0 to 2 points), withdrawals report (1 point).
(iii) *Stimulation characteristics:* For TMS we noted the presence and type of sham, site of stimulation in the scalp (M1, DLPFC and others), intensity (% of motor threshold), number of pulses before the autonomic measurements, shape of the coil (circular versus figure-of-eight), type of stimulation (single versus repetitive) and frequency of stimulation (if repetitive). For tDCS, we also included stimulation montage and polarity, dose of electric current, duration of session (min), current intensity (mA), size of electrodes (cm^2), and current density (mA/cm^2). Tables 1–6 display the most rele-