Clinical Neurophysiology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Non-invasive brain stimulation and the autonomic nervous system

Pedro Schestatsky [a,b,c], Marcel Simis [c,d], Roy Freeman [e], Alvaro Pascual-Leone [f], Felipe Fregni [c,f,*]

[a] Programa de Pós-Graduação em Ciências Médicas da Universidade Federal do Rio Grande do Sul, Brasil
[b] Departament of Internal Medicine, Universidade Federal do Rio Grande do Sul, Brazil
[c] Laboratory of Neuromodulation, Department of Physical Medicine & Rehabilitation, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[d] Division of Neurology, Santa casa de São Paulo Medical School, SP, Brazil
[e] Autonomic and Peripheral Nerve Laboratory, Department of Neurology, Beth Israel Deaconess Medical Center, USA
[f] Berenson-Allen Center for Noninvasive Brain Stimulation, Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Accepted 14 March 2013
Available online xxxx

Keywords:
Non-invasive brain stimulation
Transcranial magnetic stimulation
Transcranial direct current stimulation
Autonomic nervous system
Systematic review

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

* Corresponding author at: Laboratory of Neuromodulation, Spaulding Rehabilitation Hospital, Harvard Medical School, 125 Nashua Street #727, Boston, 02114 MA, USA. Tel.: +1 617 573 2195; fax: +1 617 975 5322.
E-mail address: fregni.felipe@mgh.harvard.edu (F. Fregni).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.03.020

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

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

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

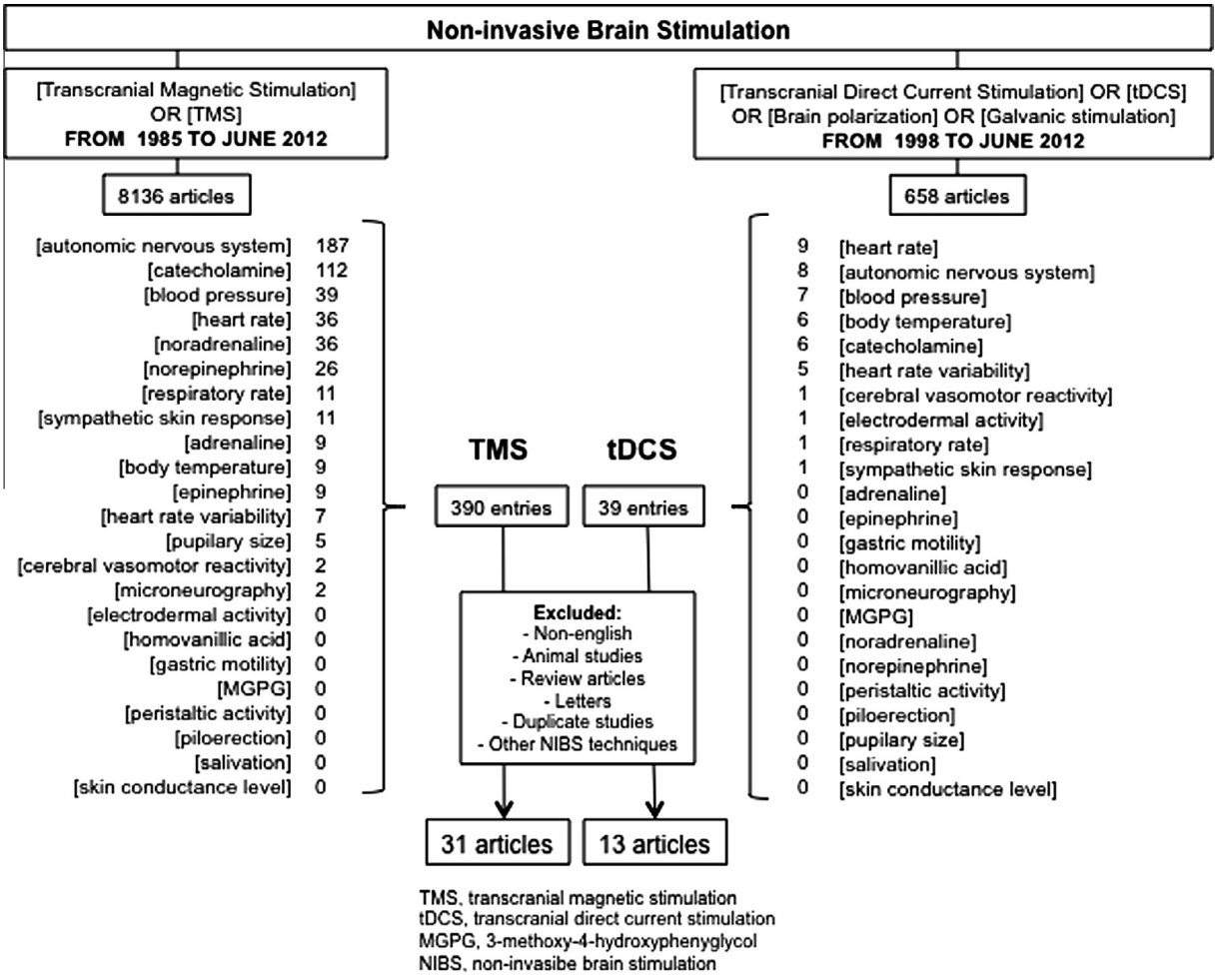


Fig. 1. Search strategy for articles dealing with NIBS and ANS.

current density (mA/cm^2). Tables 1–6 display the most relevant parameters addressed for each NIBS technique. For both NIBS techniques (TMS and tDCS) we noted the number of sessions preceding the autonomic recordings;

(iv) *Autonomic function measurement characteristics:* Positive versus negative ANS findings (we classified studies as "ANS+" and "ANS−"); classification of ANS outcome (whether autonomic variables were the main or secondary outcome of the study); and main study goals (whether the main objective was to understand the function of ANS using NIBS as a tool or if the study was designed to understand NIBS mechanisms of safety using ANS parameters. Finally, the type of autonomic variables, the timeframe for measurement of the autonomic parameters with respect to brain stimulation and the presence of absence of provocative maneuvers to elicit autonomic responses were assessed.

2.4. Data analysis

All analyses were performed using Statistical Package for the Social Sciences, version 16.0 (USA). For the first category of our framework hypothesis we performed an exploratory analysis in which we ran initially univariate logistic regression models considering the outcome (yes/no) for the autonomic variables as the dependent binary variable and selected independent variables. Subsequently, we ran. a multivariate logistic regression model including independent variables chosen according to clinical importance and also according to our univariate analysis (reported in Tables 5 and 6). The goal of this model was to assess significant predictors of ANS findings in NIBS studies. A value of $p < 0.05$ was used to define statistical significance. For the second, third and fourth categories of our framework, due to the data heterogeneity and small sample sizes, most of the results were reported in a descriptive manner.

3. Results

Our initial search strategy yielded 8136 articles on TMS and 658 articles on tDCS. We then cross-referenced these with each of the selected ANS tests (Fig. 1). With this strategy of combining NIBS with those autonomic tests, we reduced the references to 390 and 39 entries for TMS and tDCS, respectively. After applying the exclusion criteria, 34 studies on TMS and 13 studies on tDCS were retrieved for full-text assessment. In this step, a further 3 TMS studies were excluded, two because of duplicated data and one because it was a letter with no original data in it. Therefore, 31 articles on TMS and 13 articles on tDCS were included, resulting in a total of 44 articles for detailed analyses. The quality of studies measured by Jadad scores was 0.5 ± 0.5 for TMS and 0.8 ± 0.4 for tDCS ($p = 0.06$).

3.1. Overall effects of NIBS on the ANS

As above mentioned, 31 TMS articles were identified, enrolling 350 healthy subjects and 173 patients, totaling 523 subjects. Fifteen articles (48.4%) showed an association between TMS and

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

Table 1
Individual characteristics of TMS studies showing ANS alterations.

Author	*N*, status	What to study?	Frequency	Sham	Study design	Blinding	Site of stimulation (side)	Intensity % MT	Pulses (total)	Sessions	Autonomic tests	Provocative maneuvers	Autonomic recording
Rossini et al. (1993)	25, healthy	NIBS	Single	Yes	Cross-over	Single	M1 (R)	120	ND	ND	SSR	None	Concomitant
Macefield et al. (1998)	8, healthy	ANS	Single	Yes	Cross-over	Open	M1 (R/L), vertex	100	ND	ND	HR, BP, RR, MICR	None	Concomitant
Silber et al. (2000)	10, healthy	ANS	Single	No	Cross-over	Open	Frontal, parietal and occipital	ND	ND	ND	MICR	None	Concomitant
Filippi et al. (2000)	10, healthy	NIBS	Single	No	Case series	Open	M1 (R)	110	ND	ND	HR, SSR	Respiratory	Concomitant
Yoshida et al. (2001)	32, healthy	NIBS	0.2	Yes	Cross-over	Single	Vertex	90	280	4	HRV	None	>1 min
van Honk et al. (2002)	10, healthy	NIBS	0.6	No	Cross-over	Open	DLPFC (R)	130	ND	1	HR	Figures of angry faces	ND
Jenkins et al. (2002)	19, healthy	NIBS	1	No	Cross-over	Open	DLPFC (L)	100	2000	2	HR, BP	None	ND
van Honk et al. (2003)	8, healthy	NIBS	2	Yes	Cross-over	Single	Parietal (R)	90	4800	2	HR, SCL	None	ND
Clarke et al. (2006)	42, migraine	NIBS	Single	No	Case series	Open	Painful area	ND	ND	ND	HR, HRV	None	Concomitant
Yukimasa et al. (2006)	26, depression	NIBS	20	No	Case series	Open	DLPFC (L)	80	8000	10	CAT	None	>1 min
Udupa et al. (2007)	27, depression	NIBS	15	No	Parallel	Open	MI (L)	100	18000	12	HRV	None	>1 min
Vernieri et al. (2009)	29 healthy; 5 stroke	NIBS	17	Yes	Parallel	Double	M1 and occipital (L)	ND	2040	5	CVR	None	ND
Yozbatiran et al. (2009)	12, stroke	NIBS	20	No	Case series	Open	M1 (ND)	90	1600	1	CVR, BP	None	>1 min
Goldie et al. (2010)	6, healthy	NIBS	Single	No	Case series	Open	ND	ND	ND	ND	HRV	None	Concomitant
Lai et al. (2010)	8, schizophrenia	NIBS	1	Yes	Cross-over	Single	Temporo-parietal cortex (L)	90	ND	11	HRV	None	ND

NA = not applicable; ND = not described; HR = Heart rate; BP = Blood pressure; HRV = Heart rate variability; SCL = Skin conductance level; SSR = Sympathetic skin response; RR = Respiratory rate; CVR = Cerebral vasomotor reactivity; BT = Body temperature; MICR = Microneurography; CAT = Catecholamines; PSIZ = Pupillary size.

ANS (Group TMS ANS+ articles), whereas sixteen articles (51.6%) did not find this association (Group TMS ANS− articles). Regarding tDCS, 13 studies were identified, comprising of 342 healthy subjects and only 10 patients, totaling 352 subjects. Six studies (46.2%) found a significant association between tDCS and ANS alterations (Group tDCS ANS+). Tables 1–4 show the individual characteristics of TMS and tDCS studies, respectively, according to its effects on ANS.

We report the results from this review according to our proposed framework.

3.2. Framework – category I: studies separated by those in which the ANS function was changed by NIBS versus those in which it was not

There were no significant demographic or clinical predictors for ANS alterations associated with NIBS. Regarding stimulation characteristics, univariate analysis showed that the only significant predictors of ANS alterations were the type of TMS stimulation (single-pulse TMS) and the number of tDCS sessions. Single-pulse TMS – probably because of its transitory effect over autonomic function – and a high number of tDCS sessions – because of the cumulative effects – were more likely to induce ANS changes after NIBS. Another possibility is that single pulse TMS might have induced larger autonomic responses because of the novelty of stimulus when compared to the habituated and therefore less pronounced autonomic responses induced by rTMS. No other significant findings were observed for the other stimulation parameters for either TMS or tDCS.

In most of the NIBS studies that showed ANS alterations, either the M1 or DLPFC were used as the target for NIBS. However, other stimulation areas were also associated with ANS alterations induced by NIBS, such as parietal (Silber et al., 2000; van Honk et al., 2003; Lai et al., 2010), occipital (Silber et al., 2000; Vernieri et al., 2009), frontal (Silber et al., 2000) and vertex (Macefield et al., 1998; Yoshida et al., 2001) regions for TMS studies, and temporal region (Montenegro et al., 2011) for tDCS studies.

The number of studies that aimed to analyze ANS changes as a primary outcome was higher in ANS+ group in comparison with ANS− group for either NIBS methods (80% versus 30% for TMS and 66% versus 20% for tDCS studies; $p = 0.01$). The most commonly autonomic tests used for either NIBS technique (Figs. 2 and 3) were the absolute heart rate (HR), blood pressure evaluation (BP) and heart rate variability (HRV), followed by the functional sweating tests.

The provocative maneuvers in which ANS alterations were detected were respiratory movements (Filippi et al., 2000; Locher et al., 2006) and the use of figures with angry facial expressions (van Honk et al., 2002). The side of scalp stimulation (right versus left) was not a significant predictor for either TMS or tDCS studies. Tables 5 and 6 show the study characteristics according to the NIBS effects on the ANS.

Multivariate analysis showed that none of these variables remain significant when adjusted to the other covariates, suggesting that potential significant findings from univariate analysis may be a result of confounding factors – i.e., the association between single-pulse TMS and significant fluctuations in ANS may be due to other factors in studies with single-pulse TMS.

3.3. Framework – category II: studies in which NIBS was used to understand ANS function

In this category, NIBS was used to understand the impact of cortical modulation on the ANS function and therefore provide

Table 2
Individual characteristics of TMS studies showing no ANS alterations.

Author	*N*, status	What to study?	Frequency	Sham	Design	Blinding	Site of stimulation (side)	Intensity %MT	Pulses (total)	Sessions	Autonomic tests	Provocative maneuvers	Autonomic recording
Pascual-Leone et al. (1993)	9, healthy	NIBS	1 to 15	No	Cross-over	Open	M1 (R/L)	167.5	2353	1	HR, BP	None	ND
Jahanshahi et al. (1997)	6, healthy	NIBS	25	No	Cross-over	Open	M1 (L)	110	200	1	HR, BP	None	ND
Foerster et al. (1997)	13, healthy	NIBS	20	Yes	Cross-over	Single	M1 (R/L), Fz,	120	10	1	HR, BP	None	<1 min
Niehaus et al. (1998)	30, healthy	ANS	10	Yes	Cross-over	Open	M1 (?)	130	42	1	SSR	None	<1 min
Strafella et al. (2001)	8, healthy	NIBS	10	No	Cross-over	Open	DLPFC, occipital (L)	100	450	1	BT, EDA, RR	No	ND
Clark et al. (2000)	18, healthy	NIBS	20	Yes	Parallel	Single	DLPFC, parietal (R)	90	ND	1	HR, BP	None	>1 min
Pecuch et al. (2000)	20, healthy	ANS	20	Yes	Cross-over	Single	M1 (L)	110	150	1	HR, BP, CBF	None	ND
Niehaus and Guldin (2001)	22, healthy	ANS	10 and 20	Yes	Cross-over	Single	Frontal, parieto-occipital (ND)	130	56	1	PSIZ	None	<1 min
Locher et al. (2006)	6, healthy	NIBS	Single	No	Case series	Open	Vertex	ND	ND	ND	RR	Respiratory movements	Concomitant
Zwanzger et al. (2007)	11, healthy	NIBS	1	Yes	Cross-over	Single	DLPFC (R)	120	1800	1	HR	None	ND
Sibon et al. (2007)	10, healthy	NIBS	10	No	Cross-over	Open	DLPFC, occipital (L)	90	450	3	HR, RR, BT, SCL	None	>1 min
Osuch et al. (2009)	9, PTSD	NIBS	1	Yes	Cross-over	Double	DLPFC (R)	100	36000	20	CAT	None	>1 min
Van den Eynde et al. (2011)	38, bulimia	NIBS	10	Yes	Parallel	Double	DLPFC (L)	110	ND	1	HR, BP	None	ND
Nakatani-Enomoto et al. (2011)	8	NIBS	Single	No	Case series	Open	M1 (L)	90	1440	1	HR, BP	None	Concomitant
Kuppuswamy et al. (2011)	6, SCI	NIBS	5	Yes	Parallel	Single	M1 (ND)	80	900	5	HR, BP, SSR	None	>1 min
Näsi et al. (2011)	23	NIBS	0.5, 1 and 2	No	Parallel	Open	M1 (L)	75	800	8	HR, BP	None	ND

NA = not applicable; ND = not described; HR = Heart rate; BP = Blood pressure; HRV = Heart rate variability; SCL = Skin conductance level; SSR = Sympathetic skin response; RR = Respiratory rate; CVR = Cerebral vasomotor reactivity; BT = Body temperature; MICR = Microneurography; CAT = Catecholamines; PSIZ = Pupillary size.

insight into the cortical–subcortical ANS relationship. Seven (out of 31) TMS articles aimed to study ANS function by using TMS (Table 1). No articles using tDCS to study the ANS function were found in this review. All the aforementioned TMS studies enrolled healthy subjects (119) with a mean age of 29.8 ± 3.8 years old. The most common type of study design was an open-label, cross-over trial. Regarding stimulation parameters, although repetitive TMS (rTMS) was more frequently used (57.1%), 3 articles used single-pulse TMS to disrupt cortical function and measure ANS effects. The most commonly used target was the left M1. The mean intensity was 110% with 90 pulses and 3 sessions on average. There were no preferences of coil type and, in only 57.1% of cases sham stimulation was included using a sham coil (Niehaus et al., 1998; Macefield et al., 1998; Niehaus and Guldin, 2001) or placing the active coil at 90° in relation to the scalp (Pecuch et al., 2000). With respect to autonomic assessment, the most commonly used tests were heart rate frequency/variability and blood pressure levels, followed by microneurography, sweating tests, pupil size and respiration rates evaluations. In 71.4% of the studies, the autonomic measurement was done concomitantly to the stimulation, without autonomic provocative maneuvers. Positive effects of TMS over the ANS were seen in 42.9% of the articles and, among all autonomic tests, HRV was the only one with significant association with autonomic changes ($\chi^2 = 6.359$; $p = 0.018$). From this analysis, it was clear that most of the studies aimed to map cortical areas associated with ANS modulation, therefore the use of open-label studies, healthy subjects and single-pulse TMS design was appropriate.

3.4. Framework – category III: studies in which ANS was used to understand NIBS mechanisms

In this category, ANS measurements were used to understand the broad behavioral effects of NIBS including safety of NIBS. Twenty-four out of 31 TMS articles (77.4%) and 13 out of 13 tDCS articles (100%) aimed to investigate NIBS mechanisms and safety using autonomic assessments. Ten articles (8 TMS, 2 tDCS) were found that investigated NIBS safety.

3.4.1. TMS studies (framework – category III)

Contrary to the articles from *Framework – Category II*, in which no studies with patients were found, 62.5% of TMS articles that aimed to study NIBS mechanism enrolled subjects with a variety of clinical conditions (See also Section 3.5 for further information on study of patients). The mean age of all subjects (healthy and patients) was 35.28 ± 8.34 years old. The study designs were similar to those used shown in *Framework – Category II*. The quality of studies indexed by Jadad scores was slightly higher in comparison with those from TMS studies designed to assess ANS function (Jadad scores of 1.0 ± 0.8 versus 0.7 ± 0.9; $p = 0.2$). Unlike the *Framework – Category II*, when ANS was used to study NIBS mechanisms, repetitive TMS was more frequently used (the average number of pulses per session was 1011). Single-pulse TMS was used in only 16.7% of the studies. The most commonly used autonomic tests were also similar, but other outcomes were also used, such as heart variability using power spectrum analysis, cerebral vasomotor reactivity, body temperature, and catechol-

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

Table 3
Individual characteristics of tDCS studies showing ANS alterations.

Author	*N*, status	What to study?	Stimulation electrode position	Reference electrode position	Polarity	Design	Blinding	Current density (mA/cm^2)	Dur (min)	Sessions	Autonomic tests	Provocative maneuver	Autonomic recording
Beeli et al. (2008)	35, healthy	NIBS	DLPFC (L)	Ipsilateral Mastoid	A/C/S	Parallel	Single-blinded	0.04	5.5	1	SCL	Pictures-induced stress	<1 min
Vernieri et al. (2010)	10, healthy	NIBS	M1 (R)	Ipsilateral Arm	A/C	Crossover	Open	0.03	15	1	HRV, CVR	None	ND
Montenegro et al. (2011)	20, healthy	NIBS	Temporal (L)	Supraorbital (R)	A/S	Crossover	Single-blinded	0.06	20	1	HRV	None	ND
Binkofski et al. (2011)	15, healthy	NIBS	M1 (R)	Forehead (L)	A/S	Crossover	Single-blinded	NA	20	1	BP	None	ND
Knotkova et al. (2012)	10, major depression	NIBS	DLPFC (L)	Supraorbital (R)	A	Crossover	Open	0.06	20	10	HR, BP	None	ND
Brunoni et al. (2013)	20, healthy	NIBS	DLPFC (L)	DLPFC (R)	A/C/S	Parallel	Single-blinded	0.04	33	1	HRV	Pictures-induced stress	>1 min

ND = not described; A = Anodal; C = Cathodal; S = Sham; HR = Heart rate; BP = Blood pressure; HRV = Heart rate variability; SCL = Skin conductance level; SSR = Sympathetic skin response; RR = Respiratory rate; CVR = Cerebral vasomotor reactivity; BT = Body temperature; MICR = Microneurography; CAT = Catecholamines; PSIZ = Pupillary size.

Table 4
Individual characteristics of tDCS study showing no ANS alterations.

Author	*N*, status	What to study?	Stimulation electrode position	Reference electrode position	Polarity	Design	Blinding	Current density (mA/cm^2)	Dur (min)	Sessions	Autonomic tests	Provocative maneuver	Autonomic recording
Accornero et al. (2007)	20, healthy	NIBS	Occipital cortex	Neck	A/C	Parallel	Open	0.03	10	1	HR, BP, BT	None	>1 min
Flöel et al. (2008)	19, healthy	NIBS	Superior temporal	Supraorbital (R)	A/C/S	Crossover	Double-blinded	0.03	20	1	HR, BP	None	>1 min
Koenigs et al. (2009)	25, healthy	NIBS	Frontopolar (R/L)	Arm	A/C/S	Crossover	Double-blinded	0.05	35	1	SCL	None	<1 min
Karim et al. (2010)	44, healthy	NIBS	Frontopolar (R)	Parietal (L)	A/C/S	Parallel	Double-blinded	0.04	13	1	SCL	Stressful situation	ND
Vandermeeren et al. (2010)	30, healthy	NIBS	Medial frontal	Tibia (R)	A/C/S	Parallel	Single-blinded	0.03	20	1	HR, BP, RR	Stressful situation	>1 min
de Vries et al. (2010)	38, healthy	NIBS	Inferior frontal	Supraorbital (R)	A/S	Parallel	Single-blinded	0.03	20	1	HR, BP	None	>1 min
Raimundo et al. (2012)	50, healthy	NIBS	M1 (L)	Supraorbital (R)	A/S	Parallel	Double-blinded	0.03	20	1	HR, BP, RR, BT	None	>1 min

ND = not described; A = Anodal; C = Cathodal; S = Sham; HR = Heart rate; BP = Blood pressure; HRV = Heart rate variability; SCL = Skin conductance level; SSR = Sympathetic skin response; RR = Respiratory rate; CVR = Cerebral vasomotor reactivity; BT = Body temperature; MICR = Microneurography; CAT = Catecholamines; PSIZ = Pupillary size.

amine levels measurements. In only 12.5% of the studies, the autonomic measurement was done simultaneously with TMS stimulation and in 45.8% of cases the autonomic tests were performed 1 min after the stimulation. In some cases, autonomic assessments were completed after hours (Vernieri et al., 2009), days (Yozbatiran et al., 2009; Kuppuswamy et al., 2011) or even weeks (Yukimasa et al., 2006; Udupa et al., 2007) after TMS. Autonomic provocative maneuvers were performed in only 12.5% of cases and the overall significant effects of TMS over ANS was 54.1%.

3.4.2. tDCS studies (framework – category III)

From the initially selected tDCS studies (13 articles), all of them aimed to analyze NIBS mechanisms and safety using autonomic functional tests. Among those, 46.2% found positive effects of tDCS on autonomic assessments. Most of the studies were done in healthy subjects with a mean age of 28.7 ± 8.7 years old and Jadad score of 1.5 ± 1.5. In 6 of them, the classic M1 or DLPFC anodal montages were used, but in the other 7 articles, less common stimulation sites were observed, such as occipital (Accornero et al., 2007), superior temporal (Flöel et al., 2008), inferior frontal (de Vries et al., 2010) and temporal (Montenegro et al., 2011) areas in which only the later significantly altered the ANS after stimulation. As expected, due to the intrinsic characteristics of tDCS, most of these studies used sham stimulation (76.9%) and measured autonomic function 1 min away from stimulation. Most of the positive ANS effects were attributed to anodal stimulation, but in two articles, cathodal stimulation induced significant autonomic modifications in both DLPFC (Beeli et al., 2008) and M1 (Vernieri et al., 2010) spots. The most frequently used autonomic tests can be seen in Fig. 3, in which provocative maneuvers were performed in only 38.5% of cases.

In summary, in contrast to *Framework – Category II*, in this category, most of the studies included the use of protocols aimed at inducing long-lasting neuroplasticity with tDCS and rTMS. Futhermore, this category showed more studies in patients as well as more follow-up assessments.

3.5. Framework – category IV: NIBS/ANS studies conducted in healthy subjects versus patients with neuropsychiatric diseases

Only 10 out of 44 articles assessed the association between NIBS and ANS in patients (9 TMS, 1 tDCS). The clinical conditions varied. In TMS studies, disorders such as migraine, depression, stroke,

Table 5
Global characteristics of TMS studies with positive association with ANS alterations versus studies in which no ANS alterations were found.

Parameters	ANS altered by TMS ($N = 15$)	ANS unaltered by TMS ($N = 16$)	p
Demographic and clinical characteristics			
Subjects (mean/study)	17.36 (11.2)	15.38 (9.22)	0.260
Clinical condition (%)			
Healthy	60	81.2	
Non-healthy	40	18.8	0.354
Age (years)	35.10 (9.05)	32.95 (6.81)	0.610
Gender (mean/study)			
Male	10.86 (8.43)	8.36 (5.87)	0.404
Female	8.50 (9.29)	7.71 (7.93)	0.619
Stimulation characteristics			
Type of stimulation (%)			
Repetitive	60.0	93.8	
Single	40	6.2	0.037*
Frequency (Hz)	8.53 (9.11)	11.64 (7.87)	0.197
Coil (%)			
Figure-of-eight	58.3	71.4	
Circular	41.7	28.6	0.263
Sham (%)	40	56.2	0.366
Site of stimulation (%)			
MI	50	50	
DLPFC	21.4	37	
Other	28.6	12.5	0.312
Side of stimulation (R:L)	4:4	3:8	0.642
Intensity (% MT)	100 (14.83)	108.16 (23.57)	0.203
Number of Pulses (mean)	5245.71 (6180.84)	3434.9 (9812.45)	0.865
Number of Sessions	5.33 (4.47)	3.13 (5.08)	0.658
Pulses/session	1111.14 (789.39)	671.62 (844.65)	0.577
Autonomic measurement characteristics			
ANS as primary outcome (%)	80	56.2	0.152
Safety aim (%)	20	37.5	0.433
Time stimulation-recording (%)			
Concomitant	14.3	6.7	
<1 min	42.9	60	
>1 min	42.9	33.3	0.609
Provocative maneuvers (%)	13.3	6.2	0.505

All analyses were done using unpaired t tests and Fisher's exact test.

schizophrenia, posttraumatic stress disorder, bulimia and spinal cord injury were tested. In tDCS studies only patients with depression and HIV were evaluated. The mean age of the patients was 41.9 ± 7.2 years old. In most of TMS studies dealing with patients, an open-label and parallel design studies was assessed. The quality of studies was generally poor, according to Jadad scores (1.2 ± 1.0). Regarding stimulation protocols, most of the articles used rTMS with an average of 1048 pulses/session and 8 sessions applied over the left M1 or DLPFC. Most of the autonomic assessments were done after 1 min of stimulation, with no previous autonomic provocative maneuvers. Similarly, heart rate variability using power spectrum was the most used tool to assess NIBS mechanisms. A positive effect of NIBS over the ANS was found in 66.7% of the studies with patients.

4. Discussion

Our findings can be summarized in seven main points: (1) half of the NIBS studies failed to show significant changes in ANS outcomes; (2) there are no significant predictors of NIBS-induced ANS changes when adjusting for multiple variables; (3) there is a lack of studies assessing ANS effects in neurological disorders and lack of studies using provocative maneuvers to study both NIBS mechanisms and ANS function; (4) there is no consensus on the best parameters of stimulation necessary to induce significant modifications in autonomic function; (5) parameters of stimulation and study design seem to differ in studies assessing NIBS mechanisms with ANS parameters versus studies assessing the ANS function with NIBS; (6) autonomic tests used have a different sensitivity to ANS changes and only the HRV showed a significant association with autonomic fluctuations; and (7) most of the clinical studies have low Jadad scores, therefore indicating that studies have several limitations in the report and/or methodology.

From approximately 9000 NIBS (TMS/tDCS) articles in the available literature, we found only 44 studies analyzing NIBS effects on the ANS and approximately half of these studies showed a significant association between NIBS and changes in the autonomic tests. This was considered an unexpected finding given the strong body of evidence on cortical modulation of sympathetic and parasympathetic responses in animals. For instance, in the prefrontal cortex, two regions have well-defined autonomic control: the medial (mPFC) and lateral prefrontal cortex (Tavares et al., 2004). Also, electrical stimulation applied to motor and premotor areas in the rat, cat and monkeys can also elicit well-defined cardio-autonomic responses (Sequeira et al., 1995). Finally, Yasui et al. (1991) found that stimulation of different regions of the insular cortex triggers cardiovascular responses consistently.

One of the main reasons to explain why only half of the reviewed studies did not show ANS changes in response to NIBS is the poor specificity and penetration of brain stimulation induced currents over the specific brain regions. For instance, Yasui et al. (1991) found that stimulation of different regions of the insular cortex could raise different cardiovascular responses in the same subject: stimulating the anterior commissure with microelectrodes, increased HR and sustained BP were obtained, whereas the stimulation of posterior insular cortex leads to decreased HR and BP together. These findings illustrate well the technical diffi-

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

Table 6
Global characteristics tDCS studies with positive association with ANS alterations versus studies in which no ANS alterations were found.

Parameters	ANS altered by tDCS ($N = 6$)	ANS unaltered by tDCS ($N = 7$)	p
Demographic and clinical characteristics			
Subjects (mean)	18.33 (9.30)	34.57 (17.20)	0.113
Clinical condition (%)			
Healthy	83.3	100	
Non-healthy	16.7	0	0.462
Age (years)	31.38 (12.01)	25.95 (2.84)	0.09
Gender (mean/study)			
Male	10.83 (7.67)	17.17 (8.11)	0.653
Female	7.50 (7.76)	18.17 (11.44)	0.218
Stimulation characteristics			
Stimulation electrode (%)			
MI	33.3	14.3	
DLPFC	50	0	
Frontal	0	42.9	
Other	16.7	42.9	0.022*
Reference electrode (%)			
Cephalic	33.3	42.9	
Extra-cephalic	66.7	57.1	0.308
Polarity (%)			
Anodal/Cathodal	33.3	57.1	
Anodal	50	28.6	
Cathodal	16.7	14.3	0.672
Side of stimulation (Right:Left)	2:4	1:3	0.906
Current intensity (mA)	1.50 (0.44)	1.21 (0.56)	0.863
Surface (cm^2)	35.20 (0.44)	36.29 (7.74)	0.095
Current density (mA/cm^2)	0.04 (0.01)	0.03 (0.009)	0.657
Duration (min)	18.92 (8.91)	19.71 (7.88)	0.967
Sham (%)	66.7	85.7	0.559
Number of Sessions	2.50 (3.67)	1 (0.01)	0.020*
Autonomic measurement characteristics			
ANS as main outcome (%)	60.0	42.9	0.391
Safety as the aim (%)	16.7	14.3	1.0
Time stimulation-recording (%)			
<1 min	50	28.6	
>1 min	50	71.4	0.008*
Provocative maneuvers (%)	33.3	42.9	0.725

All analyses were done using unpaired t tests except *Fisher's exact test.

culties in performing NIBS in humans, in which the electrical current induced into the cortex reaches only few centimeters in depth in a non-selective way. Indeed the relatively low spatial focality of TMS and tDCS may result in current being induced in two functionally opposite areas – i.e., whereas one area increases blood pressure, an adjacent cortical areas may have a contrary effect. Theoretically, TMS is a more adequate tool to investigate ANS function because of its focality over cortical autonomic areas. One strategy that might help to focus the stimulation to a specific target is the use of neuronavigation to better localize the area to be stimulated by TMS (Bashir et al., 2011) or, in case of tDCS, the use of a high-definition stimulation (Borckardt et al., 2012) or simply reducing the size of stimulation electrode/increasing the size of the reference electrode (Nitsche et al., 2007).

Using the first category of our framework for selecting articles, we were able to appraise differences between those articles that found positive ANS alterations and those that did not. This analysis is useful to identify predictors of ANS alterations. Although we found some significant results in the univariate analysis, these variables did not remain significant in the multivariate adjusted analysis. The likely main reason here is that parameters were variable across studies, and therefore, the power for the adjusted analysis was limited.

Although the adjusted analysis failed to show significant relationships, some univariate significant findings are interesting to be briefly discussed. We found that single-pulse TMS studies are more likely to report ANS changes. One interesting aspect here is that single-pulse TMS is not able to induce autonomic plasticity. Due to the lack of sham stimulation in most of these studies (Table 1), the authors from these studies were unable to exclude the role of arousal provoked by the stimuli, rather than a direct stimulation of autonomic pathway. One option to disentangle these effects is to separate autonomic changes secondary to arousal versus activation of autonomic centers is the use of scales to assess unpleasantness of the stimulation using a simple visual analogue scale such as Foerster et al. (1997) performed. Another way is to apply the State-Trait Anxiety Inventory (Rosin and Nelson, 1983) scale. If strong correlations between these scores and autonomic responses are found, vegetative changes due to arousal effect – and not due to direct autonomic activation – is more likely. Therefore, measuring the levels of anxiety and arousal in studies addressing ANS is of paramount importance for future investigations.

We found relatively less tDCS studies as compared to TMS studies using ANS measurements. Most of the tDCS studies were in healthy subjects and employed a single session of tDCS. One finding that needs to be further investigated is the impact of number of sessions. One study on tDCS for depression using repeated sessions showed significant effects on heart rate and blood pressure (Knotkova et al., 2012). It has been shown that repeated sessions of tDCS induce prolonged behavioral effects (Shekhawat et al., 2013). Other tDCS parameters that are also important to be considered are mean current density, duration of stimulation and electrodes montage. In fact, it is known already that larger current densities may induce effects on deeper cortical structures (DaSilva et al., 2012). Therefore, the use of increased current density – by using smaller and

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

more focal stimulation electrodes (Nitsche et al., 2007) – may be beneficial in future studies addressing the effects of tDCS over the ANS.

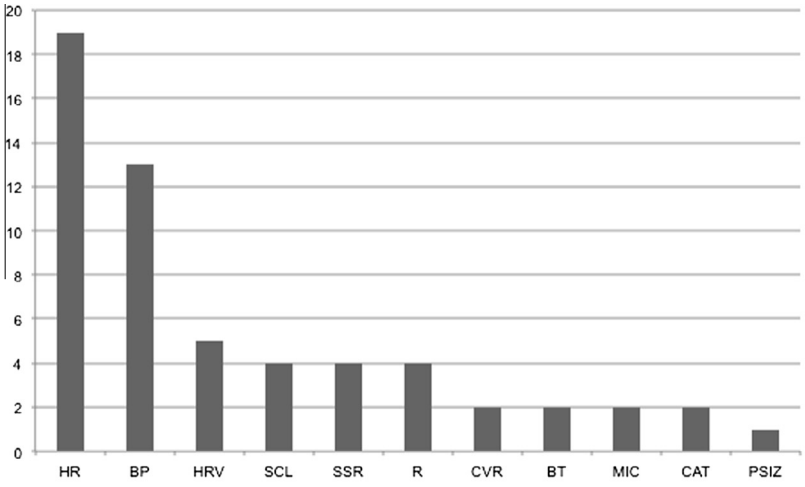
According to the studies with positive effects of NIBS on ANS, the M1 and DLPFC were the most used areas for triggering autonomic responses. Indeed, according to some authors, there is a strong correlation between the sympathetic activity and M1 (Schlindwein et al., 2008) and DLPFC (Henderson et al., 2012). However, according to our review, other brain areas, apart from M1 and DLPFC also showed promising effects in modulating ANS function, such as parietal (Silber et al., 2000; van Honk et al., 2003; Lai et al., 2010), occipital (Silber et al., 2000; Vernieri et al., 2009), frontal (Silber et al., 2000), vertex (Macefield et al., 1998; Yoshida et al., 2001) and temporal (Montenegro et al., 2011) regions. In the case of tDCS the effects of stimulation might be related not only due to the position of the anode, but also to the combined action of the cathode electrode. For instance, Montenegro et al. (2011), in order to reach the insular cortex, one of the key areas for autonomic control, placed the anode over T3 area according to the international EEG 10–20 system. These authors found significant changes in autonomic parameters and discussed that some of these effects may be due to the reference electrode placed at the contralateral supraorbital region. Therefore, it is important to consider the site of both electrodes positioning with the aid of computer-based tDCS modeling (Bikson et al., 2012).

Regarding TMS, other targets have been implicated in the ANS modulation in humans, such as the spinal cord (Paxton et al., 2011) and cerebellum (Demirtas-Tatlidede et al., 2011). Therefore, these two regions (spinal cord and cerebellum) should be further explored in future studies addressing ANS modulation induced by NIBS.

Another important consideration when choosing the stimulation target is the hemisphere of stimulation. We found no differences of ANS effects according to the hemisphere of NIBS stimulation. However, there are some studies suggesting lateralization for brain-related autonomic areas associated with some ANS functions. For instance, it has been shown that the left insular cortex would be related to parasympathetic autonomic activity, whereas the right insular cortex would mediate sympathetic autonomic activity (Oppenheimer et al., 1992; Brunoni et al., 2011). For instance, direct cortical stimulation in humans can increase or decrease BP and HR, depending on the side of cortex stimulated (Oppenheimer et al., 1992). Consequently, because of the side of stimulation might potentiate NIBS effects on autonomic function, it is important to consider this issue in future NIBS/ANS studies.

One relevant issue when considering NIBS to study ANS function is whether the goal is to induce plasticity (for instance with protocols of rTMS or tDCS) or only transient disruption (for instance with single pulse TMS). This is critical as to modify study design. For example, studies using protocols to induce long-lasting plastic changes should plan to conduct longer follow-up autonomic assessments (hours, days and weeks) as previously shown (Yukimasa et al., 2006; Udupa et al., 2007; Vernieri et al., 2009; Yozbatiran et al., 2009; Kuppuswamy et al., 2011). Another important issue to be considered when planning NIBS/ANS studies is the type of TMS coil. Whereas the figure-of-eight coil is the preferred method for focal stimulation, (Wassermann et al., 1992), the circular coil is recommended to obtain current distribution in larger and deeper areas (Sekino and Ueno, 2004) or those coils proposed by Deng et al. (2013) that can more reliable target deep brain structures.

The correct use of an adequate control group is also a matter of concern. Although most of the reviewed studies used a sham control group, the type of sham stimulation was quite variable throughout them. For instance, in the study of Lai et al. (2010), the control group consisted in leaving the patients at rest in a bed without TMS. On the other hand, Yoshida et al. (2001) used a circular coil for testing and figure-of-eight coil for sham stimulation. Both authors found a positive association between TMS and acute alterations on HRV, but using those types of sham stimulation, these effects could have been attributed to other factors apart from the TMS i.e., auditory click or further arousal effects induced by the figure-of-eight coil. In another study (Osuch et al., 2009), the rTMS coil was placed at a 45° to the head, producing nerve and muscle stimulation on the face and scalp. Although it has been used in previous studies (George et al., 1997; Kimbrell et al., 1999) some authors have suggested it has a significant active component (Loo et al., 2000). If this is true, false negative results could have been obtained. Actually, the quality of sham stimulation is crucial for analyzing the effects of NIBS on vegetative responses, since autonomic responses are known to be very liable to any stimuli, including imagery (Papadelis et al., 2007). Therefore, in order to compare groups reliably, the sham should be as similar as possible to real stimulation, but without inducing any active physical en-



HR = Heart rate; BP = Blood pressure; HRV = Heart rate variability; SCL = Skin conductance level; SSR = Sympathetic skin response; RR = Respiratory rate; CVR = Cerebral vasomotor reactivity; BT = Body temperature; MIC = Microneurography; CAT = Catecholamines; PSIZ = Pupillary size

Fig. 2. The most common used autonomic tests in TMS studies.

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

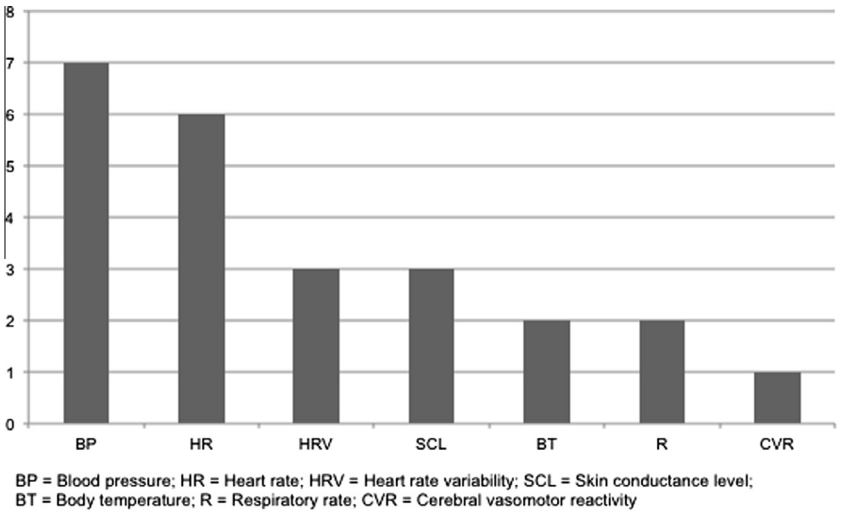


Fig. 3. The most common used autonomic tests in tDCS studies.

ergy. In order to improve the quality of sham stimulation some special coils have been developed. For instance, Okabe and Ugawa (2003) developed a sham coil that also delivered electrical co-stimulation to the skin and Arana et al. (2008) claimed that the best sham condition is achieved with individual titration of the electrical stimulation intensity. In the same way, Rossi et al. (2007) also have created a new method of sham stimulation, known as real electromagnetic placebo, in which a fake wood-made coil, with the same shape as a real TMS coil, is attached to the real coil. For tDCS, perhaps the best is to use subthreshold stimulation. Indeed, O'Connell et al. (2012) proposed that ideal blinding for tDCS would be reached with the use of 1 mA stimulation and positive results from studies using 2 mA should be interpreted with caution.

Given the effects of TMS and tDCS in neuroplasticity and the results we have shown in this review, it is expected that both techniques would have an therapeutic effect on several diseases in which the ANS plays a major role, such as arterial hypertension (Esler, 2000), heart failure (Li and Patel, 2003), obesity (Seals and Bell, 2004), diabetes (Esler et al., 2001), migraine (Shechter et al., 2002), obstructive sleep apnea complications (Lurie, 2011), parkinsonian symptoms (Iodice et al., 2011), vasovagal syncope (Kanjwal et al., 2011), septic shock (Pancoto et al., 2008), primary palmar hyperhidrosis (Schestatsky et al., 2011), complex regional pain syndrome (Marinus et al., 2011) and postural tachycardia syndrome (Mathias et al., 2011). In these conditions one potential approach to be tested is the use of a closed loop system – for instance, NIBS is triggered by increase in autonomic activity (i.e., blood pressure) – rather than off-line basis, in order to optimize brain plasticity and consequently clinical positive outcomes (Priori et al., 2009).

A potential explanation for the lack of association between NIBS and ANS could be the suboptimal use of autonomic tests. The most commonly used tests were the variation of blood pressure and heart rate in response to brain stimulation. Although easily performed, both tests may be insensitive to subtle ANS changes when performed without challenge or provocative maneuvers. According to Low (2003), heart rate in response to deep breathing – a classic autonomic provocative maneuver – is probably preferable to most others, since both afferent and efferent pathways are vagal, most patients are able to cooperate with the procedure, and the confounding variables are well studied and easy to detect. However, a more sensitive approach may be simply to include multiple autonomic outcome variables measure its changes in response to additional provocative maneuvers, such as Valsalva maneuver, lower body negative pressure, postural change or pharmacological interventions.

Few of the analyzed studies specified subjects and environmental conditions before autonomic tests were performed. These are all important factors that might have affected autonomic responses and include room temperature and humidity, stress, exhaustion, use of medications that might interfere with cortical or autonomic excitability (Low, 2003; Hilz and Dütsch, 2006). We found that HRV was the more sensitive test in predicting ANS changes. Indeed, Ziegler et al. (1992) evaluated cardiovagal function in 261 patients with diabetes of different severity using HRV and found excellent accuracy in the diagnosis of autonomic dysfunction. Electrodermal activity (SCL or SSR), although very liable to external background stimuli, it is considered a good index of arousal, which is an important confounding factor in autonomic studies and, therefore its use should be encouraged to help to disentangle arousal versus plastic autonomic effects in NIBS studies. Other techniques such as QSART and microneurography, although very accurate means of assessing sympathetic function, are unable to detect preganglionic dysfunction and do not provide information on the parasympathetic branch of the ANS (Illigens and Gibbons, 2009). Finally, it is important to underscore that, although CVR provides consistent data on NIBS studies (Vernieri et al., 2009, 2010), there is still no standardization of the technique and, therefore, its use cannot be recommended systematically. Finally, the use of brain derived neurotrophic factor measurement (BDNF) has been linked to plastic effects in anesthetized animals (Gersner et al., 2011) and also might help to select specific forms or neurostimulation depending on BDFN polymorphism i.e., variants Val/Met (Jayasekeran et al., 2011; Cirillo et al., 2012). Therefore this could be also used for future studies on autonomic NIBS-induced plasticity.

In summary, to date, there is no conclusive evidence of the effects of NIBS on ANS, including its potential therapeutic effect for autonomic disorders. While positive results have frequently been reported in both open-label and randomized controlled studies, several treatment parameters, such as location, frequency, intensity and duration, have been used unsystematically, making the interpretation of the results difficult and providing little guidance on what treatment parameters may be the most useful to modulate ANS parameters. Further studies with ANS function as a primary outcome and NIBS on other brain areas with specific stimulation parameters will be helpful to understand cortical control of ANS function and also potential therapeutic strategies for ANS disorders. Finally, novel strategies of stimulation such as primed 1 Hz stimulation (Iyer et al., 2003) or theta burst TMS stimulation (Huang et al., 2005) also in combination with tDCS (Hasan et al., 2012) might offer advantages to modulate ANS function as

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

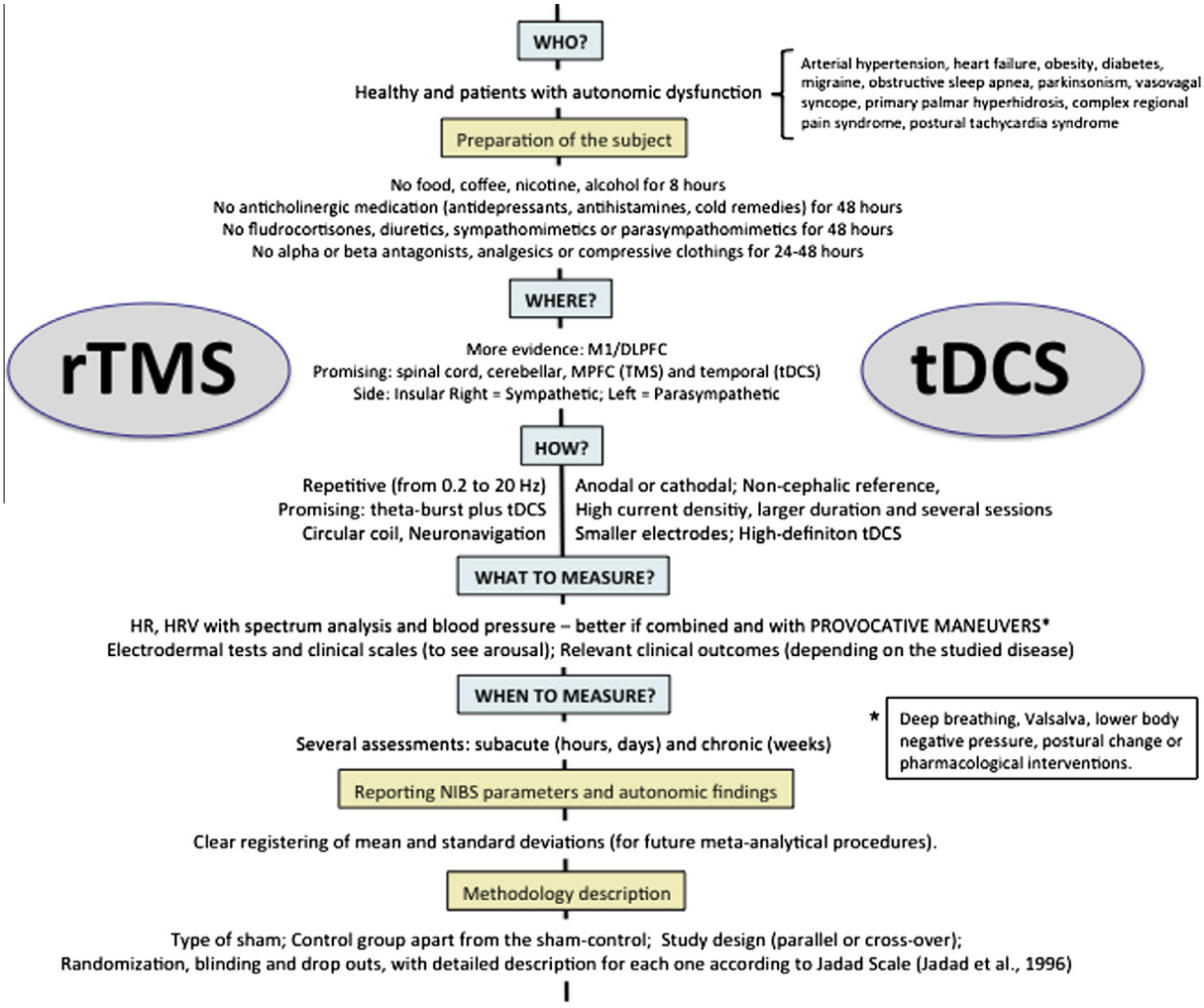


Fig. 4. Recommendations for studies using NIBS and ANS.

they may induce longer lasting effects on neuroplasticity (Fregni and Pascual-Leone, 2007).

Based on the data presented in this article, some methodological recommendations are proposed for future NIBS studies involving the ANS (Fig. 4).

Acknowledgements

The authors are grateful to Olivia Tousignant-Pienkos for her assistance during the data collection, to Fernanda Queiros for her assistance in data analysis and to Deborah Nadler for her assistance in copyediting this manuscript. We also want to thanks the grant from CAPES-Brazil: BEX 9605/11-5 (PS) and 9722/11-4 (MS).

References

Accornero N, Li Voti P, La Riccia M, Gregori B. Visual evoked potentials modulation during direct current cortical polarization. Exp Brain Res 2007;178:261–6.

Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder, et al. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? Brain Stimul 2008;1:44–51.

Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1:1160–7.

Bashir S, Edwards D, Pascual-Leone A. Neuronavigation increases the physiologic and behavioral effects of low-frequency rTMS of primary motor cortex in healthy subjects. Brain Topogr 2011;24:54–64.

Beeli G, Casutt G, Baumgartner T, Jäncke L. Modulating presence and impulsiveness by external stimulation of the brain. Behav Brain Funct 2008;4:33.

Bikson M, Rahman A, Datta A, Fregni F, Merabet L. High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. Neuromodulation 2012;15:306–15.

Binkofski F, Loebig M, Jauch-Chara K, Bergmann S, Melchert UH, Scholand-Engler, et al. Brain energy consumption induced by electrical stimulation promotes systemic glucose uptake. Biol Psychiatry 2011;70:690–5.

Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. J Pain 2012;13:112–20.

Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011;14:1133–45.

Brunoni AR, Vanderhasselt MA, Boggio PS, Fregni F, Dantas EM, Mill, et al. Polarity- and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol. Psychoneuroendocrinology 2013;38:58–66.

Cirillo J, Hughes J, Ridding M, Thomas PQ, Semmler JG. Differential modulation of motor cortex excitability in BDNF Met allele carriers following experimentally induced and use-dependent plasticity. Eur J Neurosci 2012;36:2640–9.

Clark L, McTavish SF, Harmer CJ, Mills KR, Cowen PJ, Goodwin GM. Repetitive transcranial magnetic stimulation to right prefrontal cortex does not modulate the psychostimulant effects of amphetamine. Int J Neuropsychopharmacol 2000;3:297–302.

Clarke BM, Upton AR, Kamath MV, Al-Harbi T, Castellanos CM. Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain 2006;7:341–6.

Dasilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache 2012;52:1283–95.

de Vries MH, Barth AC, Maiworm S, Knecht S, Zwitserlood P, Flöel A. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J Cogn Neurosci 2010;22:2427–36.

Demirtas-Tatlidede A, Freitas C, Pascual-Leone A, Schmahmann JD. Modulatory effects of theta burst stimulation on cerebellar nonsomatic functions. Cerebellum 2011;10:495–503.

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

Deng ZD, Lisanby SH, Peterchev AV. Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul 2013;6:1–13.
Esler M. The sympathetic system and hypertension. Am J Hypertens 2000;13:99S–105S.
Esler M, Rumantir M, Wiesner G, Kaye D, Hastings J, Lambert G. Sympathetic nervous system and insulin resistance: from obesity to diabetes. Am J Hypertens 2001;14:304S–9S.
Filippi MM, Oliveri M, Vernieri F, Pasqualetti P, Rossini PM. Are autonomic signals influencing cortico-spinal motor excitability? a study with transcranial magnetic stimulation. Brain Res 2000;881:159–64.
Flöel A, Rösser N, Michka O, Knecht S, Breitenstein C. Noninvasive brain stimulation improves language learning. J Cogn Neurosci 2008;20:1415–22.
Freeman R. Autonomic peripheral neuropathy. Lancet 2005;365:1259–70.
Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 2007;3:383–93.
Foerster A, Schmitz JM, Nouri S, Claus D. Safety of rapid-rate transcranial magnetic stimulation: heart rate and blood pressure changes. Electroencephalogr Clin Neurophysiol 1997;104:207–12.
George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154:1752–6.
Gersner R, Kravetz E, Feil J, Pell G, Zangen A. Long-term effects of repetitive transcranial magnetic stimulation on markers for neuroplasticity: differential outcomes in anesthetized and awake animals. J Neurosci 2011;31:7521–6.
Goldie J, McGregor C, Murphy B. Determining levels of arousal using electrocardiography: a study of HRV during transcranial magnetic stimulation. Conf Proc IEEE Eng Med Biol Soc 2010;2010:1198–201.
Hasan A, Hamada M, Nitsche MA, Ruge D, Galea JM, Wobrock, et al. Direct-current-dependent shift of theta-burst-induced plasticity in the human motor cortex. Exp Brain Res 2012;217:15–23.
Henderson LA, Stathis A, James C, Brown R, McDonald S, Macefield VG. Real-time imaging of cortical areas involved in the generation of increases in skin sympathetic nerve activity when viewing emotionally charged images. Neuroimage 2012;62:30–40.
Hilz MJ, Dütsch M. Quantitative studies of autonomic function. Muscle Nerve 2006;33:6–20.
Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.
Illigens BM, Gibbons CH. Sweat testing to evaluate autonomic function. Clin Auton Res 2009;19:79–87.
Iodice V, Low DA, Vichayanrat E, Mathias CJ. Cardiovascular autonomic dysfunction in MSA and Parkinson's disease: similarities and differences. J Neurol Sci 2011;310:133–8.
Iyer MB, Schleper N, Wassermann EM. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 2003;23:10867–72.
Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
Jahanshahi M, Ridding MC, Limousin P, Profice P, Fogel W, Dressler, et al. Rapid rate transcranial magnetic stimulation–a safety study. Electroencephalogr Clin Neurophysiol 1997;105:422–9.
Jayasekeran V, Pendleton N, Holland G, Payton A, Jefferson S, Michou, et al. Val66Met in brain-derived neurotrophic factor affects stimulus-induced plasticity in the human pharyngeal motor cortex. Gastroenterology 2011;141:827–36.
Jenkins J, Shajahan PM, Lappin JM, Ebmeier KP. Right and left prefrontal transcranial magnetic stimulation at 1 Hz does not affect mood in healthy volunteers. BMC Psychiatry 2002;2:1.
Kanjwal K, Sheikh M, Karabin B, Kanjwal Y, Grubb BP. Neurocardiogenic syncope coexisting with postural orthostatic tachycardia syndrome in patients suffering from orthostatic intolerance: a combined form of autonomic dysfunction. Pacing Clin Electrophysiol 2011;34:549–54.
Karim AA, Schneider M, Lotze M, Veit R, Sauseng P, Braun, et al. The truth about lying: inhibition of the anterior prefrontal cortex improves deceptive behavior. Cereb Cortex 2010;20:205–13.
Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 1999;46:1603–13.
Knotkova H, Rosedale M, Strauss SM, Horne J, Soto E, Cruciani, et al. Using transcranial direct current stimulation to treat depression in HIV-infected persons: the outcomes of a feasibility study. Front Psychiatry 2012;3:59.
Koenigs M, Ukueberuwa D, Campion P, Grafman J, Wassermann E. Bilateral frontal transcranial direct current stimulation: failure to replicate classic findings in healthy subjects. Clin Neurophysiol 2009;120:80–4.
Kuppuswamy A, Balasubramaniam AV, Maksimovic R, Mathias CJ, Gall A, Craggs, et al. Action of 5 Hz repetitive transcranial magnetic stimulation on sensory, motor and autonomic function in human spinal cord injury. Clin Neurophysiol 2011;122:2452–61.
Lai IC, Yang CC, Kuo TB, Shieh KR. Transcranial magnetic stimulation for auditory hallucination in severe schizophrenia: partial efficacy and acute elevation of sympathetic modulation. Psychiatry Clin Neurosci 2010;64:333–5.
Li YF, Patel KP. Paraventricular nucleus of the hypothalamus and elevated sympathetic activity in heart failure: the altered inhibitory mechanisms. Acta Physiol Scand 2003;177:17–26.
Locher C, Raux M, Fiamma MN, Morélot-Panzini C, Zelter M, Derenne, et al. Inspiratory resistances facilitate the diaphragm response to transcranial stimulation in humans. BMC Physiol 2006;6:7.
Loo CK, Taylor JL, Gandevia SC, McDarmont BN, Mitchell PB, Sachdev PS. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? Biol Psychiatry 2000;47:325–31.
Low PA. Testing the autonomic nervous system. Semin Neurol 2003;23:407–21.
Lurie A. Hemodynamic and autonomic changes in adults with obstructive sleep apnea. Adv Cardiol 2011;46:171–95.
Macefield VG, Taylor JL, Wallin BG. Inhibition of muscle sympathetic outflow following transcranial cortical stimulation. J Auton Nerv Syst 1998;68:49–57.
Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery, et al. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637–48.
Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. Postural tachycardia syndrome–current experience and concepts. Nat Rev Neurol 2011;8:22–34.
Montenegro RA, Farinatti Pde T, Fontes EB, Soares PP, Cunha FA, Gurgel, et al. Transcranial direct current stimulation influences the cardiac autonomic nervous control. Neurosci Lett 2011;497:32–6.
Nakatani-Enomoto S, Hanajima R, Hamada M, Mochizuki H, Kobayashi S, Enomoto, et al. Some evidence supporting the safety of quadripulse stimulation (QPS). Brain Stimul 2011;4:303–5.
Näsi T, Mäki H, Kotilahti K, Nissilä I, Haapalahti P, Ilmoniemi RJ. Magnetic-stimulation-related physiological artifacts in hemodynamic near-infrared spectroscopy signals. PLoS One 2011;6:e24002.
Niehaus L, Meyer BU, Röricht S. Magnetic stimulation over different brain regions: no differential effects on the elicited sympathetic skin responses. Electroencephalogr Clin Neurophysiol 1998;109:94–9.
Niehaus L, Guldin B, Meyer B. Influence of transcranial magnetic stimulation on pupil size. J Neurol Sci 2001;182:123–8.
Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang, et al. Shaping the effects of transcranial direct current stimulation of thehuman motor cortex. J Neurophysiol 2007;97:3109–17.
O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, Moseley, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2 mA. PLoS One 2012;7:e47514.
Okabe S, Ugawa Y, Kanazawa I. Effectiveness of rTMS on Parkinson's disease study group. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord 2003;18:382–8.
Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42:1727–32.
Osuch EA, Benson BE, Luckenbaugh DA, Geraci M, Post RM, McCann U. Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. J Anxiety Disord 2009;23:54–9.
Pancoto JA, Corrêa PB, Oliveira-Pelegrin GR, Rocha MJ. Autonomic dysfunction in experimental sepsis induced by cecal ligation and puncture. Auton Neurosci 2008;138:57–63.
Papadelis C, Kourtidou-Papadeli C, Bamidis P, Albani M. Effects of imagery training on cognitive performance and use of physiological measures as an assessment tool of mental effort. Brain Cogn 2007;64:74–85.
Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato, et al. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol 1993;89:120–30.
Paxton RJ, Malcolm MP, Newsom SA, Richards JC, Rynn GM, Bell C. Sympathetic responses to repetitive trans-spinal magnetic stimulation. Clin Auton Res 2011;21:81–7.
Pecuch PW, Evers S, Folkerts HW, Michael N, Arolt V. The cerebral hemodynamics of repetitive transcranial magnetic stimulation. Eur Arch Psychiatry Clin Neurosci 2000;250:320–4.
Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport 1998;9:2257–60.
Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? Brain Stimul 2009;2:241–5.
Raimundo RJ, Uribe CE, Brasil-Neto JP. Lack of clinically detectable acute changes on autonomic or thermoregulatory functions in healthy subjects after transcranial direct current stimulation (tDCS). Brain Stimul 2012;5:196–200.
Ravits JM. AAEM minimonograph #48: muscle sympathetic activity testing. Muscle Nerve 1997;20:919–37.
Rossi S, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi, et al. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). Clin Neurophysiol 2007;118:709–16.
Rosin L, Nelson 3rd WM. The effects of rational and irrational self-verbalizations on performance efficiency and levels of anxiety. J Clin Psychol 1983;39:208–13.
Rossini PM, Opsomer RJ, Boccasena P. Sudomotor skin responses following nerve and brain stimulation. Electroencephalogr Clin Neurophysiol 1993;89:442–6.
Schestatsky P, Callejas MA, Valls-Solé J. Abnormal modulation of electrodermal activity by thermoalgesic stimuli in patients with primary palmar hyperhidrosis. J Neurol Neurosurg Psychiatry 2011;82:92–6.
Schlindwein P, Buchholz H-G, Schreckenberger M, Bartenstein P, Dieterich M, Birklein F. Sympathetic activity at rest and motor brain areas: FDG–PET study. Autonomic Neurosci 2008;143:27–32.

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020

Seals DR, Bell C. Chronic sympathetic activation: consequence and cause of age-associated obesity? Diabetes 2004;53:276–84.
Sekino M, Ueno S. Numerical calculation of eddy currents in transcranial magnetic stimulation for psychiatric treatment. Neurol Clin Neurophysiol 2004;2004:88.
Sequeira H, Ba-M'Hamed S, Roy JC. Fronto-parietal control of electrodermal activity in the cat. J Auton Nerv Syst 1995;53:103–14.
Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. Neurology 2002;58:422–7.
Shekhawat GS, Stinear CM, Searchfield GD. Transcranial direct current stimulation intensity and duration effects on tinnitus suppression. Neurorehabil Neural Repair 2013;27:164–72.
Sibon I, Strafella AP, Gravel P, Ko JH, Booij L, Soucy, et al. Acute prefrontal cortex TMS in healthy volunteers: effects on brain 11C-alphaMtrp trapping. Neuroimage 2007;34:1658–64.
Silber DH, Sinoway LI, Leuenberger UA, Amassian VE. Magnetic stimulation of the human motor cortex evokes skin sympathetic nerve activity. J Appl Physiol 2000;88:126–34.
Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001;21:RC157.
Tavares RF, Antunes-Rodrigues J, De Aguiar Corrêa FM. Pressor effects of electrical stimulation of medial prefrontal cortex in unanesthetized rats. J Neurosci Res 2004;77:613–20.
Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Raju TR, Gangadhar BN. Modulation of cardiac autonomic functions in patients with major depression treated with repetitive transcranial magnetic stimulation. J Affect Disord 2007;104:231–6.
Eynde F, Claudino AM, Campbell I, Horrell L, Andiappan M, Stahl, et al. Cardiac safety of repetitive transcranial magnetic stimulation in bulimic eating disorders. Brain Stimul 2011;4:112–4.
Van Honk J, Hermans EJ, d'Alfonso AA, Schutter DJ, van Doornen L, de Haan EH. A left-prefrontal lateralized, sympathetic mechanism directs attention towards social threat in humans: evidence from repetitive transcranial magnetic stimulation. Neurosci Lett 2002;319:99–102.
Van Honk J, Schutter DJ, Putman P, de Haan EH, d'Alfonso AA. Reductions in phenomenological, physiological and attentional indices of depressive mood after 2 Hz rTMS over the right parietal cortex in healthy human subjects. Psychiatry Res 2003;120:95–101.
Vandermeeren Y, Jamart J, Ossemann M. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci 2010;11:38.
Vernieri F, Maggio P, Tibuzzi F, Filippi MM, Pasqualetti P, Melgari, et al. High frequency repetitive transcranial magnetic stimulation decreases cerebral vasomotor reactivity. Clin Neurophysiol 2009;120:1188–94.
Vernieri F, Assenza G, Maggio P, Tibuzzi F, Zappasodi F, Altamura, et al. Cortical neuromodulation modifies cerebral vasomotor reactivity. Stroke 2010;41:2087–90.
Wassermann EM, McShane LM, Hallett M, Cohen LG. Noninvasive mapping of muscle representations in human motor cortex. Electroencephalogr Clin Neurophysiol 1992;85:1–8.
Yasui Y, Breder CD, Saper CB, Cechetto DF. Autonomic responses and efferent pathways from the insular cortex in the rat. J Comp Neurol 1991;303:355–74.
Yoshida T, Yoshino A, Kobayashi Y, Inoue M, Kamakura K, Nomura S. Effects of slow repetitive transcranial magnetic stimulation on heart rate variability according to power spectrum analysis. J Neurol Sci 2001;184:77–80.
Yozbatiran N, Alonso-Alonso M, See J, Demirtas-Tatlidede A, Luu, et al. Safety and behavioral effects of high-frequency repetitive transcranial magnetic stimulation in stroke. Stroke 2009;40:309–12.
Yukimasa T, Yoshimura R, Tamagawa A, Uozumi T, Shinkai K, Ueda, et al. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. Pharmacopsychiatry 2006;39:52–9.
Ziegler D, Laux G, Dannehl K, Spüler M, Mühlen H, Mayer, et al. Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. Diabet Med 1992;9:166–75.
Zwanzger P, Eser D, Völkel N, Baghai TC, Möller HJ, Rupprecht, et al. Effects of repetitive transcranial magnetic stimulation (rTMS) on panic attacks induced by cholecystokinin-tetrapeptide (CCK-4). Int J Neuropsychopharmacol 2007;10:285–9.

Please cite this article in press as: Schestatsky P et al. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol (2013), http://dx.doi.org/10.1016/j.clinph.2013.03.020