A meta-analysis of non-invasive brain stimulation and autonomic functioning: Implications for brain-heart pathways to cardiovascular disease

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ABSTRACT

Given the intrinsic connection between the brain and the heart, a recent body of research emerged with the aim to influence cardiovascular system functioning by non-invasive brain stimulation (NIBS) methods such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Despite the implications of cardiovascular activity modulation for therapeutic purposes, such effects of NIBS have not yet been quantified. The aim of this study was to meta-analyze studies on NIBS effects on blood pressure (BP), heart rate (HR) and its variability (HRV). PubMed and Scopus databases were searched for English language studies conducted in humans. Twenty-nine studies were eligible for the analyses. Pooled effect sizes (Hedges' g) were compared. Random effect models were used. NIBS was effective in reducing HR ($g = .17$) and enhancing HRV ($g = .30$). A marginal effect emerged for BP ($g = .21$). Significant moderators were the stimulation technique and the site of stimulation. Results show that NIBS affects cardiovascular and autonomic nervous system activity, confirming a potential pathogenic brain-heart pathway to cardiovascular disease.

Keywords: Meta-analysis, Non-invasive brain stimulation, Transcranial magnetic stimulation, Transcranial direct current stimulation, Autonomic nervous system, Cardiovascular

Contents

1. Introduction
2. Methods
 - 2.1. Literature search and study selection
 - 2.2. Coding
 - 2.3. Data analyses
 - 2.4. Moderator Analyses
3. Results
 - 3.1. Blood Pressure
 - 3.1.1. Moderator analysis
 - 3.2. Heart Rate
 - 3.2.1. Moderator analysis
 - 3.3. Heart Rate Variability
 - 3.3.1. Moderator analysis
4. Discussion
5. Limitations and conclusion

1. Introduction

Cardiovascular disease (CVD) has been recognized as the most common cause of death in the world, accounting for 30% of all mortality (Lee and Cooper, 2009). Hypertension is one of the primary risk factors for heart disease and stroke, the leading causes of death worldwide. In fact, the World Health Report 2002 identified hypertension, or high blood pressure, as the third ranked factor for disability-adjusted life years. One-quarter of the world's adult population has hypertension and modeled projections indicate an increase to 1.15 billion hypertensive patients by 2025 in developing countries. As a consequence, hypertension places a heavy burden on society and overall economic activity. Moreover, as the population ages, the economic impact of CVD on health care systems will become even greater (Bromfield and Muntner, 2013).

A growing body of research demonstrates that psychosocial stresses play a crucial role in the development of CVD (e.g., Cuffee et al., 2014), mainly via its effects on the autonomic nervous system. A non-invasive measure, resulting from the dynamic interplay between the fast acting parasympathetic nervous system and the relatively slower sympathetic nervous system, is heart rate variability (HRV). HRV has been proposed as an index of the degree to which the autonomic nervous system provides flexible and adaptive regulation to environmental stress (Thayer and Lane, 2000; 2009). Indeed, acute and chronic psychosocial stress not only increases heart rate (HR) but also significantly reduces HRV in both human (e.g., Jarczok et al., 2013; Schubert et al., 2009) and animals (see Sgoifo et al., 2014 for a review).

Despite the role of the brain in determining what is stressful to the individual, neuroimaging methods have only recently been directed at understanding these brain-body pathways (McEwen and Gianaros, 2010). Existing findings suggest that the orbitofrontal, anterior cingulate, and insular brain regions act as a network to process the motivational aspects of environmental stimuli and support adaptive cardiovascular reactions to stressors (Gianaros and Sheu, 2009; Gianaros et al., 2012). A more extensive body of research exists on the identification of the reciprocal interrelations between the autonomic nervous system and brain areas, the so-called Central

Autonomic Network (Benarroch, 1993). Taken together, these findings pointed to the primary importance of the brain in the pathophysiology of essential hypertension (e.g., Julius and Majahalme, 2000). In fact, the brain is implicated in the initiation of high blood pressure and changes in brain function, structure, and organization correlate with the presence of hypertension early in its course (see Jennings and Zanstra, 2009 for a review).

Nevertheless, most research in the field is correlational, and experimental manipulation is necessary to increase our insight in the causal relationship between cortical functioning and cardiovascular responses. In this context, techniques for non-invasive brain stimulation (NIBS) are an interesting tool to investigate such a relationship.

To date, the NIBS techniques that have been most intensively studied with reference to the cardiovascular and autonomic systems are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). High frequency rTMS and anodal tDCS are able to enhance the excitability of the stimulated hemisphere, while low frequency rTMS and cathodal tDCS can suppress it.

TMS is a non-invasive tool for the electrical stimulation of neural tissue (Barker et al., 1985) that can be applied as single pulses of stimulation, depolarizing neurons and evoking measurable effects. Repetitive TMS consisting of trains of stimuli has the potential to modify excitability of the cerebral cortex at the stimulated site and at remote areas along functional anatomical connections (see Rossini et al., 2010 for a review).

TDCS differs from TMS as it does not induce neuronal firing by supra-threshold neuronal membrane depolarization but rather modulates spontaneous neuronal network activity via the application of weak electrical currents to different cortical areas. At the neuronal level, the primary mechanism of action is the induction of polarity-dependent changes in cortical excitability (Priori et al., 1998). Animal and human studies have provided insight regarding the mechanisms underlying tDCS effects on neuroplasticity and showed that tDCS could induce specific changes in neuropsychological, psychophysiological and motor activity as a function of targeted brain areas

(see Brunoni et al., 2012 for a review).

Despite accumulating evidence on the effects of NIBS on the cardiovascular system, such effects have not yet been systematically quantified. Up to now, only a systematic review has been conducted on the topic, highlighting the heterogeneity of included studies and the impossibility to draw conclusive evidence of the effects of NIBS on cardiovascular and autonomic systems (Schestatsky et al., 2013). This is mainly due to the fact that most of existing studies have been designed with the aim to understand the safety of NIBS using cardiovascular parameters and not to study the brain-heart connections.

To overcome these limitations, the aim of the present work was to quantify existing evidence supporting the effects of NIBS on the cardiovascular and autonomic nervous systems. In choosing our outcome measures, we decided to focus on those physiological markers that play a role as established risk factors for cardiovascular disease, such as blood pressure (BP), HR, and HRV. Resting high BP (e.g., Wilson et al., 1998) and HR have been shown to be independent risk factors for cardiovascular disease and mortality (Custodis et al., 2013) and prolonged low HRV has been associated with cardiovascular disease (Thayer et al., 2010 for a review).

The research question of the present study is: “Can NIBS techniques be effectively used to significantly reduce BP and HR and increase HRV?”. Given the role of these biomarkers in the development of cardiovascular disease, these observations will allow us to construct theoretical models for translational science, ultimately to inform the development of personalized prevention strategies. To better inform therapeutic interventions, an integrative investigative approach is called for, combining techniques including functional brain imaging and detailed autonomic monitoring.

2. Methods

2.1. Literature search and study selection

Two search strategies were used to systematically collect empirical studies of the effects of NIBS on BP, HR, and HRV. First, Medline (<http://www.pubmed.com>) and Scopus databases were

searched for English-language publications through January 10th 2016. Separate searches were conducted for the following keywords: *Transcranial Magnetic Stimulation* OR *TMS* combined with *blood pressure*, *heart rate*, *heart rate variability*, *cardiovascular*, and *autonomic nervous system*. The same searches were then repeated for *Transcranial Direct Current Stimulation* OR *tDCS*.

Second, the reference lists of previous systematic reviews were searched for relevant studies.

The search was limited to English-language publications and human samples. Inclusion criteria for our analysis were as follows: a) use of TMS or tDCS, b) recorded BP, HR, and/or HRV, and c) utilized a design suitable for calculating one or more effect sizes. Reasons for exclusion were: a) review articles, b) case reports; c) articles examining the effects of NIBS applied to other parts of nervous system apart from the brain.

A total of 730 results were retrieved. Comparison of the retrieved titles identified 264 studies that were duplicates, thus leaving 466 abstracts for further evaluation (see Figure 1). The current series of meta-analyses is based on data extracted from 29 studies that met the inclusion criteria (see Table 1 and references marked with an asterisk in the reference list) and had BP, HR, and HRV as outcomes. Among the 29 studies, additional data (not published in the reviewed article but needed to calculate effect sizes or to run moderator analyses) were received for 4 studies.

Guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force, 1996) were used to define the HRV measurements to include in the pertinent meta-analysis. We decided to focus on vagally-mediated HRV because, to date, this is the only HRV measure that has definite structural and functional brain correlates (Thayer et al., 2012; Winkelmann et al., in press). Studies that reported respiratory sinus arrhythmia (RSA), root-mean-square successive RR-interval difference (RMSSD); mean successive difference (MSD); or any spectral measure in the high frequency (HF) range of 0.15 - 0.4Hz (natural log transform (lnHF), normalized (HF n.u.) or absolute power (absHF)) were included in our meta-analysis that had HRV as the outcome measure. Given the sequential inclusion of HRV measures, low-frequency HRV (LF-HRV) was not considered because it is not strictly a

measure of vagally-mediated HRV and its interpretation is controversial (e.g., Reyes Del Paso et al., 2013). For this reason, LF-HRV would require a separate meta-analysis comprising the other non-vagal HRV measures, which would be beyond the scope of the present meta-analysis.

2.2. Coding

A standardized data coding form was developed to extract the following information from each study: a) authors and publication year; b) study design; c) characteristics of the study sample (age, sex, size, subgroups); d) NIBS method used; e) outcomes of interest; f) adjusted covariates; and g) brief results. Following the indications of Cooper (2009), each study (and each participant) was included only once in one of our meta-analyses.

Each research article was read and analyzed by 2 members of the research team. Intercoder agreement was 100%.

For tDCS, when both anodal and cathodal stimulation were present (and compared with sham stimulation), we opted for the anodal versus sham for two reasons: a) we were interested in stimulation (and not in inhibition) of cortical areas; b) whereas it is well established that anodal tDCS increases cortical excitability, the effects of cathodal tDCS are still a matter of debate (e.g., Monte Silva et al., 2010).

For TMS, when high- and low-frequency forms of stimulation were used, we chose the high-frequency stimulation due to findings from the existing systematic review suggesting that high-frequency TMS might be the optimal strategy to evoke cardiovascular and autonomic system responses (Schestatsky et al., 2013).

When both left- and right-sided stimulation were used, we based our choice on theoretical and empirical assumptions on the lateralized properties of cortical structures.

A study conducted by Pascual-Leone et al. (1993) has been excluded from the analyses because it had 9 participants, each of them stimulated at different frequencies and in different scalp positions.

The quality of evidence was assessed with a modified version of the Newcastle-Ottawa Scale (NOS; Wells et al., 2011). We modified the criteria so that the subcategories would be applicable to psychophysiological studies. In our modified NOS scale the maximum score that could be achieved by a study was 7 stars (see Appendix A for the methodological quality scores attributed to each study included in the present meta-analyses).

2.3. Data analyses

For each study (or subsample of a study), we calculated a Hedges' g effect size. Based on conventional standards, effect sizes of g equal to .20, .50, and .80 were considered small, medium, and large, respectively (Cohen, 1988). The g coefficient represents the difference between responding to a NIBS induction and responding to a control condition (baseline or sham) divided by the pooled standard deviation (Hedges & Olkin, 1985). Effect sizes indicating bigger decreases in BP and HR and increases in HRV (change scores from baseline) associated with NIBS compared to a control condition got a positive sign.

Calculation of effect sizes was based on means, standard deviations, difference in mean scores, P values, and sample sizes of the groups. When not presented explicitly, the mean change in each group was obtained by subtracting the final mean from the baseline mean. When the standard deviation (SD) of the changes was not provided, we imputed a change-from-baseline standard deviation using a correlation coefficient as indicated by Higgins and Green (2011): $SD_{\text{change}} = \sqrt{(SD_{\text{baseline}}^2 + SD_{\text{final}}^2 - (2 * \text{Corr} * SD_{\text{baseline}} * SD_{\text{final}}))}$. When only standard errors (SE) were provided, standard deviations were obtained by applying the following formula $SD = SE * \sqrt{n}$ (Higgins & Green, 2011). When studies did not provide raw data to calculate effect sizes and instead provided statistics (e.g., t), we applied transformation formulas to convert to g (Lipsey & Wilson, 2001). When a paper reported $p < .05$ or $n. s.$, we computed Hedges' g with p -values of .045 and 1 (one-tailed), respectively, which likely yielded a highly conservative estimate of the effect size. For studies reporting RR interval values (duration of 1 heartbeat in milliseconds), HR

was calculated and its corresponding variance was estimated proportionally to the RR interval variance. Where citations reported multiple vagally-mediated HRV indices, a hierarchical inclusion was implemented to prevent conflation of effect size estimates as follows: HF power only, next RSA only, next RMSSD only, next MSD only, or else pNN50 only.

The effect sizes were computed in ProMeta Version 2.0 (Internovi). Random-effects models were used in all the analyses as they account for the amount of variance caused by differences between associations as well as differences among participants within associations. ProMeta also computed 95% confidence intervals (*CI*) around the point estimate of an effect size. The Q and I^2 statistics were used to assess heterogeneity among studies. A significant Q value indicates a lack of homogeneity of findings among studies. I^2 values of .25, .50, and .75 correspond to low, moderate, and high between-trial heterogeneity, respectively.

The problem of publication bias was estimated informally by using a funnel plot of effect size against standard error for asymmetry and formally by using Begg and Mazumdar's rank correlations, and Egger's regression intercept test. We did not rely on failsafe N because, despite its popularity, it has been considered inadequate and problematic as a method to assess publication bias (e.g., Becker, 2005). In fact, as reported by Higgins and Green (2011), the estimate of fail-safe N is highly dependent on the assumed mean effect for the unpublished studies and runs against the principle to concentrate on the size of the estimated effect and the associated confidence intervals, rather than on whether the P value reaches a particular, arbitrary threshold. Publication bias is mostly due to the tendency of journals and authors to publish studies with positive results rather than those with negative or non-significant results. Moreover, studies with small sample sizes need to detect larger effects to be published compared with studies with large samples.

As the main aim of a meta-analysis is to aggregate over all data, we first run the analyses including the entire set of studies and then subsequently re-run them without some potential outliers, to examine the impact of these specific studies. Potential outliers were excluded if they had statistically significant standardized residuals (Ellis, 2010).

Statistics reported in this meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009) statement (see Appendix B for PRISMA checklist).

2.4. Moderator analyses

For each outcome we examined how the size of the association varied as a function of mean age (years), sex (% of women), stimulation intensity (high versus low), stimulation duration (min), number of sessions, presence of a sham condition (yes versus no), site of stimulation (motor cortex, PFC, or other), sample (healthy versus pathological), presence of a stressful task/condition (yes versus no), if the aim was to test the effects of NIBS on the cardiovascular system (yes versus no), and methodological quality (0–7).

Sex was examined as a moderator in light of reported prominent sex differences in the neural control of the autonomic nervous system (e.g., Nugent et al., 2011). Stimulation intensity, duration, and number of sessions are crucial factors affecting the outcome of TMS (Robertson et al., 2003) and tDCS (Kekic et al., 2015). The presence of sham stimulation is crucial for analyzing the effects of NIBS on cardiovascular responses, since the parasympathetic nervous system rapidly responds to almost every type of stimuli, including internal thoughts (Ottaviani et al., 2016). As to sample status, it is important to establish if TMS and tDCS can be considered as powerful tools for prevention only or also for therapy. It would be particularly relevant to establish if NIBS is effective for pathological conditions that are critically characterized by autonomic nervous system dysfunctions. Lastly, given the above-mentioned role of stress for CVD risk, it is important to examine whether NIBS is effective in reducing not only cardiovascular activation at rest but also in response to stressors.

A minimum of 4 studies for each subgroup was required for the moderation analysis.

Continuous moderators were evaluated using meta-regression (i.e., age, sex, stimulation duration, number of sessions, methodological quality), while categorical moderators were entered

as grouping variables in the effect size calculations. For continuous moderators, the sign of the coefficient indicates the direction of the relation between NIBS and cardiovascular response.

3. Results

Table 1 discloses the specific contrast or test that were used to extract effect sizes in the present series of meta-analyses. Studies marked with an asterisk in the table and figures indicate potential outliers.

3.1. Blood pressure

Analysis of 13 studies (300 subjects) showed a marginally significant association between NIBS and diminished BP ($g = .21$, 95% CI $(-.02, .44)$, $p = .069$) in a heterogeneous set of studies ($Q(12) = 32.7$, $p = .001$; $I^2 = 63.3$). Figure 2 shows the forest plot. We did not find evidence of asymmetry using a classic funnel plot (see Appendix C, panel a), Begg's rank test ($Z = 0.49$; $p = .63$), or Egger's regression test (intercept = -1.04 , $t = -0.37$, $p = .72$). No potential outliers emerged in this meta-analysis.

3.1.1. Moderation analysis

No significant moderators emerged in this meta-analysis.

3.2. Heart rate

The meta-analysis showed significant associations between NIBS and decreased HR (18 studies; 348 subjects; $g = .17$, 95% CI $[.01, .33]$, $p = .04$), which was small in size. Figure 3 presents the forest plot. Significant heterogeneity was shown by the Q and I^2 statistics, $Q(17) = 31.2$, $p = .02$; $I^2 = 45.5$. Kendall's tau excluded the presence of a publication bias ($Z = 0.11$; $p = .91$), and this was confirmed by Begg and Mazumdar's rank correlation test (intercept = -0.47 , $t = -0.26$, $p = .80$) and by the funnel plot (see Appendix C, panel b). No potential outliers were identified.

3.2.1. Moderation analysis

To have a comparable number of studies in each subgroup, in this meta-analysis the site of stimulation had to be recoded in PFC versus other, thus aggregating M1 and other.

Contrasting studies with and without a sham condition yielded significant differences, $Q(1) = 5.08, p = .02$, with HR decreases after NIBS only in studies that did not include such a condition ($g = .36, 95\% \text{ CI } [.10, .62], k = 8, n = 140$) compared with those that did ($g = .01, 95\% \text{ CI } [-.15, .16], k = 10, n = 208$). It has to be noted that only studies without a sham condition showed substantial heterogeneity, $Q(7) = 15.7; p = .03; I^2 = 55.3$.

The site of stimulation played a marginally significant role as a moderator, $Q(1) = 3.26, p = .06$, with only studies that stimulated the PFC showing effects of NIBS on HR ($g = .37, k = 8, n = 148$ vs $g = .09, k = 9, n = 185$) in two homogeneous sets of studies.

A trend toward significant differences was also found on the basis of the type of stimulation used, $Q(1) = 2.89, p = .08$, with significant HR decreases to NIBS only in studies that used TMS ($g = .23, 95\% \text{ CI } [.04, .42], k = 14, n = 254$) compared with studies using tDCS ($g = -.04, 95\% \text{ CI } [-.29, .21], k = 4, n = 94$). Only studies using TMS showed substantial heterogeneity, $Q(13) = 27.2; p = .01; I^2 = 52.2$.

3.3. Heart rate variability

The overall combined effect size for the total set of 15 studies (328 subjects) was significant ($g = .30, 95\% \text{ CI } [.02, .58], p = .04$; see Figure 4 for the forest plot) in a heterogeneous set of studies, $Q(14) = 60.97, p < .0001; I^2 = 77.04$.

Evidence of publication bias was detected by an asymmetrical funnel plot (see Appendix C, panel c). The bias was neither confirmed by Begg's rank test ($Z = -0.74; p = .46$), nor by Egger's regression test (intercept = -3.63, $t = -1.60, p = .13$).

Exclusion of an extreme outlier (Hamner et al., 2015) significantly increased the effect size (g

= .42, 95% CI [.21, .63], $p < .0001$) but not heterogeneity, $Q(13) = 30.5$; $p = .004$; $I^2 = 57.4$. After outlier exclusion, the funnel plot was no longer asymmetrical.

3.3.1. Moderation analysis

Contrasting studies using TMS with studies using tDCS yielded a significant difference, $Q(1) = 6.36$, $p = .01$, with only the first being able to detect effects on HRV in response to the stimulation ($g = .60$, $k = 8$, $n = 165$ vs $g = -.10$, $k = 7$, $n = 163$). Both sets of studies presented significant heterogeneity, $Q(12) = 17.4$, $p = .02$; $I^2 = 59.9$ and $Q(12) = 28.5$, $p < .0001$; $I^2 = 78.9$, respectively. Outlier removal had no impact on this moderation analyses.

The site of stimulation emerged as a marginally significant moderator, $Q(2) = 4.63$, $p = .08$, with studies that stimulated the PFC ($g = .43$, $k = 6$, $n = 153$) and other areas such as Cz, T3, pain-related areas and the scalp (5 cm anterior to the hand area on parasagittal plane) ($g = .56$, $k = 5$, $n = 109$) but not studies stimulating the M1 area ($g = -.44$, $k = 4$, $n = 66$). It has to be noted that only studies stimulating other areas and M1 showed substantial heterogeneity, $Q(4) = 13.2$; $p = .01$; $I^2 = 69.7$ and $Q(3) = 27.6$; $p < .0001$; $I^2 = 89.1$, respectively.

4. Discussion

In a series of meta-analyses we investigated the association between NIBS and BP, HR, and increased HRV. HR and (marginally) BP were diminished, whereas HRV was enhanced by NIBS. Even if effects were only small, moderator analysis suggested that there is the potential for larger effects if future studies take a series of precautions as described here below. Overall, effects were bigger in studies that used TMS instead of tDCS and stimulated the PFC instead of the primary motor cortex or other brain regions (mainly Cz, T3, and pain-related areas).

First, studies using TMS were more effective than those using tDCS with up to medium effects on HRV. This result is not surprising if we consider the technical difficulties in performing tDCS in humans, in which the electrical current induced into the cortex reaches only a few centimeters in

depth in a non-selective way. Theoretically, TMS is a more adequate tool to investigate ANS function because of its focality over cortical autonomic areas (Tremblay et al., 2014).

Second, the PFC appeared to be the golden target to stimulate to obtain effects on the cardiovascular system. Unfortunately, as shown in Table 1 most of the examined studies did not have cardiovascular changes as their target and only recorded HR and BP for safety issues. In general, most research on the effects of NIBS has focused on the motor cortex, because of the ease of obtaining the motor-evoked potential as an objective measure of the effectiveness of brain stimulation. This is an unfortunate circumstance given that this site of stimulation was found to be the least effective to reduce cardiovascular activation. Not surprisingly, the PFC was associated with the most effective stimulation in terms of HR reductions and HRV increases. The PFC plays a critical role in the representation of both internal and external context in the brain and the use of such information to regulate behavior and peripheral physiology. Animal and human pharmacological blockade, lesion, functional and structural neuroimaging studies implicate the PFC in the regulation of cardiovascular autonomic activity (Ahern et al., 2001; Buchanan et al., 2010; Gianaros, Van Der Veen, & Jennings, 2004; Lane et al., 2009; Ter Horst & Postema, 1997; Winkleman et al., in press). Moreover, a meta-analysis of brain regions associated with HRV identified the PFC as a core area in the regulation of HRV (Thayer et al., 2012). The present findings complement this literature and suggest that this region may be a fruitful site for potential intervention in both psychological and physiological dysregulation. Future NIBS are needed to more fully understand the precise stimulation parameters that might be most beneficial.

Although we made an attempt to consider sample composition in our moderator analyses, this analysis is inadequate (healthy versus pathological) to fully clarify the role of such a crucial factor on the effects of NIBS at a cardiovascular level. The lack of significant moderation effects should not be taken as a sign of NIBS being equally effective in healthy and pathological subjects, given the substantial heterogeneity in the pathological sample (major depressive disorder, autism spectrum disorder, migraine, bulimia nervosa, stroke, and spinal cord injury). Given the promising

result of the present meta-analysis, it is indeed possible that NIBS would emerge to be particularly effective for a specific disease or psychopathological condition in which the autonomic or cardiovascular systems play an important role. From a clinical perspective, brain stimulation has the aim to induce long-term changes in cortical excitability. Unfortunately, none of the examined studies was prospective or had an adequate follow-up assessment. The present meta-analytic findings highlight the need for prospective studies in order to test the stability of the effects of NIBS techniques on the cardiovascular and autonomic nervous systems and further elucidate mediating and confounding factors.

Another surprising result was the lack of differences between studies examining resting cardiovascular parameters and studies having participants under a stressful task or condition. Again, this may be due to the heterogeneity of the examined stressful conditions, which ranged from pain induction, to emotional pictures viewing, strenuous exercise and even pharmacologically induced panic attack. Moreover, being that cardiovascular functioning was only a secondary outcome measure in most studies, it has to be noted that the assessment of BP, HR, and HRV was often far from the gold standard.

The present series of meta-analyses quantified the efficacy of NIBS in modifying several established risk factors for CVD and provide preliminary -although modest- support to the suggested use of NIBS as a further therapeutic tool for arterial hypertension (Cogiamanian et al., 2010).

5. Limitations and conclusion

Several limitations need to be acknowledged. First, we did not include studies published in languages other than English. Fortunately, analyses suggest that publication bias is unlikely to have influenced our results. In fact publication bias appeared in only one of the examined physiological variables (HRV) and seemed to be related to the presence of an extreme outlier.

Second, there was marked heterogeneity across studies, the sources of which subgroup analyses

were unsuccessful in identifying. To address this limitation, random-effects models were used in all the analyses. Nevertheless, there are likely to be several other important moderators that we did not consider.

Also, the effects of NIBS on other cardiovascular parameters, such as peripheral resistance or cardiac output, could not be quantified by the present meta-analysis due to the lack of studies. The assessment of multiple physiological markers is likely to increase the robustness of findings and therefore should be taken as another target for future studies.

Taken together, our series of meta-analyses suggests promising evidence that NIBS could be tested as a potential therapeutic tool to diminish HR and enhance HRV. The modest but significant sizes of the effects of NIBS seem comparable with those of lifestyle interventions such as smoking cessation or increased physical exercise (Baena et al., 2014). It is important to keep in mind, however, that with the exception of one study conducted on patients after stroke, none of the other examined studies had a sample composed by patients with cardiovascular problems. For this reason, in the current stage these techniques may yield a potential for prevention rather than therapy. Clearly, there is a need for studies using TMS on the appropriate brain site (PFC or even better vmPFC), conducted on both at risk patients and controls, with a more sophisticated cardiovascular assessment and lasting for more than the short assessment that characterizes basic research.

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Appendix

Appendix A. Adapted version of the Newcastle-Ottawa Scale used in the present study for quality assessment.

Newcastle-Ottawa Scale adapted (maximum 7 stars)

Selection: (Maximum 2 stars)

1) Representativeness of the general population sample:

- a) Truly representative of the average in the target population. * (all subjects or random sampling)
- b) Somewhat representative of the average in the target population. * (non-random sampling)
- c) Selected group of users.
- d) No description of the sampling strategy.

2) Sample size:

- a) Justified and satisfactory. *
- b) Not justified.

Confounds: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis.

For within-subject or correlational studies, confounding factors are controlled for or the sample has acceptable homogeneity.

- a) The study controls for the most important factors (Age, gender, BMI, baseline physiology). *
- b) The study control for any additional factor (sham condition). *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome (physiological variable):

a) Acceptable length, method of recording, artifact correction. **

b) Not the gold standard measurement but described. *

c) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

Appendix B. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2; no limitations due to space constraints; no registration number
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No registered review protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7, Figure 1.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-11, Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, 12-13

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2, Figure 3, Figure 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix C
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix C. Funnel plots for meta-analysis on a) blood pressure, b) heart rate; and c), heart rate variability.

a)

b)

c)

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Figure Captions

Fig. 1. Flow chart showing study selection for the meta-analysis.

Fig. 2. Forest plot for meta-analysis on NIBS effects on blood pressure

Fig. 3. Forest plot for meta-analysis on NIBS effects on heart rate.

Fig. 4. Forest plot for meta-analysis on NIBS effects on heart rate variability.

95% CI

Aslaksen et al. 2014	-0.67 / 0.36
Flöel et al. 2008	-0.41 / 0.41
Foerster et al. 1997	0.23 / 1.36
Gulli et al. 2013	-0.66 / 0.35
Hamner et al. 2015	0.40 / 1.58
Jahanshahi et al. 1997	-0.51 / 0.78
Jenkins et al. 2002	0.30 / 1.29
Kuppuswamy et al. 2011	-0.24 / 0.68
Pecuch et al. 2000	-0.11 / 0.71
Raimundo et al. 2012	-0.44 / 0.60
Udupa et al. 2011	0.13 / 0.83
Van den Eynde et al. 2011	-0.94 / 0.25
Yozbatiran et al. 2009	-0.95 / 0.11
Overall (random-effects model)	-0.02 / 0.44

95% CI

Berger et al. 2015	-0.30 / 0.54
Cabrerizo et al. 2014	-0.83 / 0.33
Casanova et al. 2014	0.20 / 1.19
Clarke et al. 2006	0.20 / 0.91
Floel et al. 2008	-0.43 / 0.43
Gulli et al. 2013	0.14 / 1.35
Hamner et al. 2015	-0.48 / 0.48
Jahanshahi et al. 1997	-0.61 / 0.74
Jenkins et al. 2002	0.30 / 1.29
Kuppuswamy et al. 2011	-0.89 / 0.11
Pecuch et al. 2000	-0.51 / 0.34
Raimundo et al. 2012	-0.71 / 0.38
Sibon et al. 2007	-0.23 / 0.95
Udupa et al. 2011	-0.21 / 0.49
Van den Eynde et al. 2011	-0.22 / 1.03
Vitor-Costa et al. 2015	-0.61 / 0.53
Yozbatiran et al. 2009	-0.53 / 0.53
Zwanzger et al. 2007	-0.47 / 0.63
Overall (random-effects model)	0.01 / 0.33

Table 1

Studies included in the meta-analysis and conditions/comparisons used to derive effect sizes.

Studies	<i>n</i>	Wo (%)	Age	Stim type	Status	Sham	Stim site	Intensity	Sessions	Goal	Durat	Task	Contrast	Hedges' <i>g</i> (MA)
Aslaksen et al. (2014)	51	51	23.1	tDCS	Healthy	Yes	M1	2 mA	1	No	7	Pain induction (heat)	Response to pain (change score from baseline) in sham vs anodal condition	-0.12 (SBP); -0.19 (DBP)
Berger et al. (2015)	20	100	23.3	TMS	Healthy	Yes	dIPFC	10 Hz	1 ¹	Yes	15	Emotional pictures	Response to high negative pictures in the HF active vs sham conditions	0.12 (HR ²)
Brunoni et al. (2013a)	46	76.2	43.9 ³	tDCS	MDD	Yes	F3	2 mA	12	Yes	30	No	Pre to post-treatment changes in completers assigned to placebo in sham vs anodal condition	0.06 (lnHF-HRV)
Brunoni et al. (2013b)	20	85	24.9	tDCS	Healthy	Yes	dIPFC	1.5 mA	1	Yes	33	Neutral and negative images	Response to negative stimuli	0.10 (HF-HRV)

														(minus neutral) in sham vs anodal condition	
Cabrerizo et al. (2014)	10	30	25 ³	TMS	Healthy	No	M1	10 Hz	1	Yes	5	No	Baseline vs during stimulation	-0.25 (HR); 0.00 (HF-HRV)	
Casanova et al. (2014)	18	22.2	13.1	TMS	ASD	No	dIPFC	0.5 Hz	18	Yes	12	No	First vs last session	0.73 (HR ⁴); 0.77 (HF-HRV)	
Clancy et al. (2014)	14	50	34.5 ³	tDCS	Healthy	Yes	M1	1 mA	1	Yes	15	No (semi-supine)	Change score from baseline in sham vs anodal condition	-0.22 (HF-HRV)	
Clarke et al. (2006)	33	85.7	41.4	TMS	Migraine	No	pain area ⁵	-	1	Yes	-	No	Pre vs post stimulation	0.55 (HR); 1.16 (HF-HRV)	
De Putter et al. (2015)	38	80.3 ³	23.1 ³	tDCS	Healthy	Yes	dIPFC	2 mA	1	Yes	25	Relax	Sham vs anodal groups (plus working memory training)	0.24 (HF-HRV)	
Flöel et al. (2008)	19	47.4	25.6	tDCS	Healthy	Yes	posterior part of the perisylv. area	1 mA	1	No	20	Language learning paradigm	Change score from baseline in sham vs anodal condition	-0.00 (SBP); -0.00 (DBP); 0.00 (HR)	
Foerster et al.	13	-	27.8	TMS	Healthy	Yes	C3, C4,	20 Hz	1	No	0.008	No	Sham vs	0.85	

(1997)							Fz, Pz						active conditions	(SBP); 0.85 (DBP) ⁶ -0.24 (SBP); -0.07 (DBP); 0.80 (HR ⁸); 0.68 (HRV: HF n.u.)
Gulli et al. (2013)	12	41.7	35	TMS	Healthy	No	OFC	0.7 Hz	2 ⁷	Yes	8	No	Baseline vs recovery post right-stimulation	1.58 (SBP); 0.40 (DBP); 0.00 (HR); -2.38 (HF-HRV) 0.21 (SBP); 0.05 (DBP); 0.06 (HR ⁸)
Hamner et al. (2015)*	15	46.6	25.5 ³	tDCS	Healthy	Yes	M1	2 mA	1	Yes	40	Pain induction (Cold Pressor Task)	Response to pain (change score from baseline) in sham and anodal condition	0.79 (MAP); 0.83 (HR ⁸)
Jahanshahi et al. (1997)	6	33.3	33.3	TMS	Healthy	No	M1	20 Hz	2	No	-	No	Pre vs post stimulation (2 blocks)	0.25 (SBP); 0.20 (DBP); -0.39 (HR)
Jenkins et al. (2002)	20	50	24.6	TMS	Healthy	No	dlPFC	1 Hz	2	No	60-s blocks/ 15-s breaks	No ⁹	Effect of left site stimulation (before vs after) ¹⁰	
Kuppuswamy et al. (2011)	15	20	39.7	TMS	Spinal cord injury	Yes	sensori-motor	5 Hz	5	Yes	15	No (sitting)	Pre- to post-treatment in active vs sham	

Montenegro et al. (2011)	20	0	30 ³	tDCS	Healthy	Yes	T3	2 mA	1	Yes	20	No (sitting) ¹¹	Main effect of stimulation in the entire group	0.33 (HF-HRV) ¹²
Okano et al. (2015)	10	0	33	tDCS	Healthy (cyclists)	Yes	T3	2 mA	1	Yes	20	Incremental maximal cyclist test	HRV during the test in sham vs anodal condition	0.44 (HRV _{3 ms} threshold)
Pecuch et al. (2000)	20	55	32	TMS	Healthy	Yes	Frontal lobe	10/20 Hz	2	No	6	No	Pre vs post stimulation	0.23 (DBP); 0.37 (SBP); -0.09 (HR ⁸)
Raimundo et al. (2012)	50	64	30.5	tDCS	Healthy	Yes	C3	1 mA	1	Yes	20	No (sitting)	Change score from baseline in sham vs anodal condition	0.11 (SBP); 0.05 (DBP); -0.16 (HR)
Remue et al. (2015)	19	100	21.8	TMS	Healthy	Yes	dIPFC ⁷	20 Hz	1	Yes	10	Stress induction (negative feedback)	Response to stress induction (T2) in the active vs sham condition	0.72 (rMSSD)
Sibon et al. (2007)	10	50	24.7 ³	TMS	Healthy	Yes ¹⁰	dIPFC	10 Hz	1	No	30 ³	No	Change score from baseline in sham vs active condition	0.36 (HR)

Udupa et al (2007)	27	29.6	32.6	TMS	MDD	No	M1	15 Hz	12	Yes	12	No	Pre vs post stimulation	0.40 (rMSSD)
							scalp 5 cm anterior to the hand area on parasagittal plane							0.35 (SBP); 0.60 (DBP); 0.14 (HR); 0.19 (HRV)
Udupa et al. (2011)	30	55.2	30.5	TMS	MDD	No		15 Hz	12	Yes	12	No	Pre vs post stimulation	
Van den Eynde et al. (2011)	37	86.8	-	TMS	Bulimia nervosa	Yes	dIPFC	10 Hz	1	No	20 ³	No	Response after 20 rTMS trains (minus baseline) in sham vs active condition	-0.28 (SBP); -0.41 (DBP); 0.40 (HR)
Vitor-Costa et al. (2015)	11	0	26	tDCS	Healthy	Yes	M1	2 mA	1	Yes	13	Constant load test (cycling)	Response after exhaustion in anodal vs sham conditions	-0.04 (HR)
Yoshida et al. (2001)	16	0	29 ³	TMS	Healthy	Yes ¹⁴	Cz	0.2 Hz	4	Yes	5.8	No (sitting)	Before vs after stimulation	0.74 (HF-HRV)
Yozbatiran et al. (2009)	12	16.6	67	TMS	Stroke	No	M1	20 Hz	1	No	20	No	Pre vs immediately post TMS	-0.56 (SBP); -0.28 (DBP); 0.00 (HR ⁸)
Zwanzger et al. (2007)	11	54.5	26	TMS	Healthy	Yes	dIPFC	1 Hz	1	Yes	30	Pharmacologically induced	Maximim HR response after sham	0.08 (HR ¹⁵)

Note. MA = Meta-analysis; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MAP = Mean Arterial Pressure; HR = Heart Rate; HF-HRV = High Frequency-Heart rate variability; rMSSD = Root Mean Square of the Successive Differences; MDD = Major Depression Disorder; Wo = Women; Stim = Stimulation; Durat = Stimulation duration; tDCS = Transcranial direct Current Stimulation; TMS = Transcranial Magnetic Stimulation; ASD = Autism Spectrum Disorder; M1 = Primary Motor Cortex; dlPFC = Dorsolateral prefrontal cortex; OFC = Orbitofrontal cortex; * Potential outlier; ¹ The study included two sessions but we only considered the HF stimulation; ² Phasic cardiac response; ³ Estimated value; ⁴ RR intervals; ⁵ N = 19 in temporal, n = 24 in occipital, and n = 8 in frontal areas; ⁶ The study also included HR as an outcome but insufficient data were provided for ES computation; ⁷ Stimulation on right and left side; ⁸ Pulse rate; ⁹ Before and after the stimulation participants underwent a series of tasks (Digit Symbol Substitution and Verbal Fluency Task); ¹⁰ The study also had a right/left site stimulation that yielded non-significant effects; ¹¹ Controlled breathing; ¹² The study found a significant effect on HF-HRV in athletes only; ¹³ Left occipital stimulation used as sham; ¹⁴ Not included in the analyses due to missing data; ¹⁵ Maximum HR peak.

Table 2

Quality assessment performed using the Newcastle-Ottawa Scale adapted.

Studies	Quality Score (0-7)	Selection (0-2)	Confounds (0-2)	Outcome (0-3)
Aslaksen et al. (2014)	5	2	1	2
Berger et al. (2015)	6	2	2	2
Brunoni et al. (2013a)	7	2	2	3
Brunoni et al. (2013b)	5	1	1	3
Cabrerizo et al. (2014)	3	0	0	3
Casanova et al. (2014)	5	1	1	3
Clancy et al. (2014)	6	2	1	3
Clarke et al. (2006)	5	2	0	3
De Putter et al. (2015)	4	1	1	2
Flöel et al. (2008)	4	1	1	2
Foerster et al. (1997)	2	0	1	1
Gulli et al. (2013)	3	0	0	3
Hamner et al. (2015)*	4	1	1	2
Jahanshahi et al. (1997)	3	0	0	3
Jenkins et al. (2002)	4	1	1	2
Kuppuswamy et al. (2011)	4	1	1	2
Lai et al. (2010)	2	0	1	2
Montenegro et al. (2011)	4	1	1	2
Okano et al. (2015)	3	0	1	2
Pecuch et al. (2000)	4	1	1	2
Raimundo et al. (2012)	5	2	1	2
Remue et al. (2015)	4	1	1	2
Sibon et al. (2007)	4	1	1	2
Udupa et al. (2007)	6	2	1	3
Udupa et al. (2011)	6	2	1	3
Van den Eynde et al. (2011)	4	1	1	2
Vitor-Costa et al. (2015)	5	2	1	2
Yoshida et al. (2001)	4	1	1	2
Yozbatiran et al. (2009)	4	1	0	3
Zwanzger et al. (2007)	4	1	1	2

Note: * = potential outliers.