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REVIEW

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The effects of noninvasive brain stimulation on heart rate and heart rate variability: A systematic review and meta-analysis

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Abstract

Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation and transcranial direct current stimulation are widely used to test the involvement of specific cortical regions in various domains such as cognition and emotion. Despite the capability of stimulation techniques to test causal directions, this approach has been only sparsely used to examine the cortical regulation of autonomic nervous system (ANS) functions such as heart rate (HR) and heart rate variability (HRV) and to test current models in this regard. In this preregistered (PROSPERO) systematic review and meta-analysis, we aimed to investigate, based on meta-regression, whether NIBS represents an effective method for modulating HR and HRV measures, and to evaluate whether the ANS is modulated by cortical mechanisms affected by NIBS. Here we have adhered to the PRISMA guidelines. In a series of four meta-analyses, a total of 131 effect sizes from 35 sham-controlled trials were analyzed using robust variance estimation random-effects meta-regression technique. NIBS was found to effectively modulate HR and HRV with small to medium effect sizes. Moderator analyses yielded significant differences in effects between stimulation of distinct cortical areas. Our results show that NIBS is a promising tool to investigate the cortical regulation of ANS, which may add to the existing brain imaging and animal study literature. Future research is needed to identify further factors modulating the size of effects. As many of the studies reviewed were found to be at high risk of bias, we recommend that methods to reduce potential risk of bias be used in the design and conduct of future studies.

KEYWORDS
heart rate, heart rate variability, meta-regression, noninvasive brain stimulation, transcranial direct current stimulation, transcranial magnetic stimulation

1 | INTRODUCTION

Over the past three decades, noninvasive brain stimulation (NIBS) techniques have become increasingly important in cognitive neuroscience. They provided significant advances by identifying causal links between specific cortical brain structures and their respective cognitive, affective, sensory, and motor functions (Dayan et al., 2013). In this systematic review and meta-analysis, we evaluate

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the impact of NIBS on several indicators for autonomic nervous system activity, namely heart rate (HR) and different measures of heart rate variability (HRV). We will focus on transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which are the NIBS techniques most frequently used. Understanding whether and how NIBS should be used to modulate HRV and HR is crucial to design future studies that aim to investigate the underlying mechanisms of cortical regulation of autonomic nervous system (ANS) functions.

1.1 | Neuroanatomical pathways of heart rate and heart rate variability regulation

The autonomic regulation of the heart has been suggested to be realized by the interplay of several cortical regions, including the medial prefrontal cortex (MPFC) and the insular cortex, higher subcortical regions including the amygdala, the bed nucleus of the stria terminalis (BNST), several areas and nuclei of the hypothalamus (e.g., paraventricular nucleus, dorsomedial hypothalamic nucleus), the periaqueductal gray (PAG), and brainstem regions including the parabrachial nucleus (PBN), the nucleus of the solitarius tract (NTS), the nucleus ambiguous (NA), the area postrema, the locus coeruleus, the dorsal motor nucleus of the vagus (DMNV), and the rostral (RVLM) and caudal (CVLM) ventrolateral medulla (Benarroch, 1993; Smith et al., 2017). Together, these interconnected areas form the so-called central autonomic network (CAN, Benarroch, 1993). Accordingly, the MPFC, including the anterior cingulate cortex (ACC), and the insular cortex are involved in the regulation of hierarchically lower level regions of the CAN such as the amygdala by integrating both cortical perceptual representations of one's bodily or visceral states and conceptual interpretations of this perceptual input (Smith et al., 2017). The amygdala, which has been found to be crucially involved in detecting novel and relevant stimuli, is highly connected to the entire cortex and subcortical structures alike (Liddell et al., 2005). While afferent outputs serve to modulate attention and cognitive processing of the perceived stimuli, efferent projections to the hypothalamic nuclei and the PAG lead to the initiation of autonomic and behavioral responses to those stimuli (Liddell et al., 2005; Silvani et al., 2016; Smith et al., 2017). Signals from the amygdala are then transferred by the hypothalamus and the PAG to the nuclei of the lower brainstem and the medulla through bidirectional connections (Silvani et al., 2016). In addition to projections from the hypothalamus and PAG, the brainstem receives visceral afferents that reach the NTS through cranial, sacral, and thoracolumbar neural pathways. There, the signals are relayed to the PBN, from where they are transmitted to the hypothalamus, the amygdala, and the insula (Jänig, 2006, Napadow et al., 2008). The primary outcome of the CAN is projected through preganglionic sympathetic neurons of the RVLM and parasympathetic neurons of the NA and DMNV, which innervate all internal organs via stellate ganglia and the vagus nerve, respectively (Silvani et al., 2016). The function of the heart as one of these effector organs is thus under permanent regulation of the CAN (Benarroch, 1993). To study this constant mediating effect of the cardiac autonomic outflow of the CAN on beat-to-beat dynamics of the heart, analysis of HR and HRV are the prevailing approaches utilized (Smith et al., 2017; Thayer & Lane, 2009).

Significance

Both heart rate and heart rate variability have been identified as significant markers for cardiovascular health as well as for cognitive functioning and emotional well-being. In this paper, we performed a series of meta-analyses to examine whether noninvasive brain stimulation (NIBS) serves as an effective tool for influencing cardiovascular functions and, consequently, as a promising approach in research and therapy. Results show that NIBS hold the potential to effectively influencing cardiovascular measures. Stimulation of distinct brain areas seem to cause diverging cardiovascular responses. Stimulation of prefrontal and motor cortex were found to produce larger effects than stimulation of temporal regions.

While HR is defined by the number of heartbeats within a given period of time (usually within one minute), HRV is understood as the temporal variability in beat-to-beat intervals between consecutive heartbeats (Malik et al., 1996). HRV can be described by different metrics using frequency domain, time domain, and nonlinear measurements. Commonly, three frequency components are differentiated in the spectral profile (Berntson et al., 1997; Malik et al., 1996). The high-frequency (HF-HRV) band (0.15 to 0.40 Hz), when measured at a respiratory rate of 9–24 cycles per minute, can be considered to quantify the effect of respiration on HR, known as respiratory sinus arrhythmia (RSA; del Paso et al., 2013; Laborde et al., 2017, Malik et al., 1996). HF-HRV is further widely used as an index of cardiac vagal control. In this regard, however, various studies have shown that HF-HRV is suitable as a marker of cardiac vagal control only under certain conditions (Grossman & Taylor, 2007). The low-frequency (LF-HRV) component of HRV (0.04–0.15 Hz) is assumed to be produced by primarily parasympathetic but also sympathetic influences and may provide information about control mechanisms of baroreflex (Goldstein et al., 2011) as well as vasomotor tone (del Paso et al., 2013). The LF-HRV has further been demonstrated to be highly influenced by different respiratory patterns at frequencies between 0.15 and 0.4 Hz and may reflect RSA when measured at a respiratory rate lower than nine cycles per minute (<0.15 Hz) (Beda et al., 2014; Kromenacker et al., 2018). The very-low-frequency (VLF-HRV) band of HRV (0.0033–0.04 Hz) represents long-term control mechanisms including hormonal and thermoregulation for instance (Berntson et al., 1997; Malik et al., 1996).

In the time domain, the root mean square of successive differences (RMSSD) is the predominantly used approach to estimate vagally mediated HRV (vmHRV). Although being less affected

by respiratory influences than HF-HRV (Penttilä et al., 2001), a high correlation is found between both measures (Kleiger et al., 2005). The RMSSD further correlates with the percentage of successive normal sinus RR intervals more than 50 ms (pNN50) which is suggested to reflect cardiac vagal tone as well (Shaffer & Ginsberg, 2017). Further time-domain HRV measures are the standard deviation of all RR intervals (SDNN), the HRV triangular index, the peak valley analysis, also called peak-to-through analysis, and the Porges-Bohrer method (Laborde et al., 2017; Shaffer & Ginsberg, 2017).

A large body of research demonstrates relationships between both HR and (primarily vagally mediated) HRV at rest, and cardiovascular and mental health as well as cardiorespiratory/physical fitness (Buchheit, 2014; Hillebrand et al., 2013; Perna et al., 2020; Thayer & Lane, 2000). Previous research has further shown associations between vmHRV both at rest and changes in vmHRV in response to different situations and several cognitive processes such as emotion regulation and executive functioning (Forte et al., 2019; Laborde et al., 2018; Thayer & Lane, 2000, 2007). While resting vmHRV may serve as a proxy of cognitive resources to adapt to environmental demands, changes in vmHRV are hypothesized to reflect processes of cognitive adaptation at the autonomic level (Laborde et al., 2018; Thayer & Lane, 2000, 2007).

A variety of studies, including primarily imaging and lesion studies, have confirmed the influence of various brain regions hypothesized to be part of the CAN on HR and HRV (e.g., Critchley et al., 2003; Hilz et al., 2006; Napadow et al., 2008; Sclocco, Beissner, et al., 2016). The results of these studies indicate that different components of the CAN contribute to varying degrees to the regulation of the various cardiovascular measures. Pharmacological blockade of the left or right prefrontal cortex, for instance, resulted in an increase in HR that was associated with a decrease in HF-HRV but not with changes in LF-HRV (Thayer et al., 2009). Similar patterns appear to be present also in the insular cortex, where modulation of its activity by invasive stimulation (Chouchou et al., 2019) or emotional auditory stimuli (Nguyen et al., 2016) was associated with changes in HF-HRV but not in LF-HRV. Comparable dissociations could further be found in other cortical (e.g., ACC), subcortical (e.g., amygdala), and brainstem regions (e.g., LC, NTS, and PAG), as well as in the functional connectivities between these areas (Chang et al., 2013; Critchley et al., 2003; Mather et al., 2017). These findings corroborate the assumption that the various cardiovascular measures are regulated, at least in part, by different underlying neural regulation mechanisms, and thus represent the functioning of distinct neurophysiological systems (Berntson et al., 1997).

Recent research on the neural regulation of the ANS further suggests that brain regions not traditionally defined as part of the CAN (e.g., motor cortex, hippocampus, precuneus, lingual gyrus, etc.) are also involved in its complex interactions, suggesting that a variety of brain regions act as moderators of ANS activity and thus of HR and HRV (Reisert et al., 2021; Sklerov et al., 2019; Valenza et al., 2019). According to the results of two recent meta-analyses, the extent to which a particular brain region, or even a specific subdivision within that brain region, contributes to ANS activity may depend on the task to be solved or the situation to adapt to (Beissner et al., 2013, Thayer et al., 2012). One illustrative finding in this regard comes from Critchley et al. (2003), who used fMRI to not only identify task-independent HRV-related brain regions, but also areas linked to changes in HRV during the execution of specific tasks. The authors revealed activity in orbitofrontal areas during a n-back task and in somatomotor areas during an isometric handgrip exercise, which were associated with changes in HRV. Furthermore, Sclocco, Kim, et al. (2016) reported for instance that activity in the visual cortex moderates parasympathetic outflow, which was measured by the high-frequency range of HRV during motion sickness.

Based on these results, it has been suggested that some portion of the neural activity previously attributed to only cognitive functions instead indicates autonomic processing, which via cortico-subcortical pathways produces bodily responses for contextually adaptive behavior appropriate for these higher order functions (Beissner et al., 2013, Critchley et al., 2003, Thayer & Lane, 2000). The neurovisceral integration model represents an exemplary approach that explains the relationship between HRV and cognitive processes by suggesting that activity in different areas of the prefrontal cortex during emotion and self-regulation modulates subcortical cardioacceleratory circuits of the CAN via inhibitory pathways (Thayer et al., 2009; Thayer & Lane, 2000, 2007).

These assumptions and models made in humans, though, are based almost exclusively on correlational results from brain imaging or lesion studies. Previous studies have shown that the effects of NIBS are not limited to the cortical target regions, but also extend to subcortical areas such as the thalamus or striatum via network-level effects (Bestmann et al., 2004; Beynel et al., 2020; Nonnekes et al., 2014). Given its ability to modulate not only the neuronal activity of circumscribed cortical regions but also that of cortico-subcortical networks, NIBS represents a promising opportunity to systematically investigate underlying mechanisms of correlations between neuronal activity and both HR and HRV detected in initial brain imaging studies. The potential of NIBS has led to increased numbers of publications in the past years. This increase in empirical research provides the opportunity to test via meta-analysis, whether NIBS represents an effective method for modulating HR and HRV and to evaluate whether ANS is regulated via cortical mechanisms.

1.2 | Transcranial magnetic stimulation and transcranial direct current stimulation

TMS is based on the Faraday's principles of electromagnetic induction (Walsh, 1998) and generates a magnetic field, which passes through the skull to induce a current within the brain. This current leads to a depolarization of cortical axons in the area above which the TMS coil is held (Pascual-Leone et al., 2000). In particular, the use of repetitive transcranial magnetic stimulation (rTMS) has become established in modern neuroscientific

research (Bestmann, 2008; Klomjai et al., 2015). rTMS delivers repeated single magnetic impulses of defined frequency and intensity, which cause changes in cortical activity that outlast the stimulation period (Hoogendam et al., 2010; Maeda et al., 2000a). Both intensity and frequency of the magnetic pulses are crucial parameters affecting duration and direction of the TMS-induced effects. Classically, high-frequency (HF) rTMS pulses ≥ 5 Hz are thought to increase cortical excitability, whereas low-frequency (LF) stimulations around 1 Hz decrease cortical excitability (Siebner et al., 2009). However, considerable interindividual variability of effects has been noted for decades for most, if not all, stimulation protocols, with a large proportion of individuals exhibiting neutral or opposite effects from the standard effect (Corp et al., 2020; Maeda et al., 2000b; Schilberg et al., 2017). Although the exact physiological mechanisms of rTMS on the brain are not fully understood, rTMS may trigger the same mechanisms underlying synaptic plasticity. Thus, it is suggested that rTMS acts on the brain through mechanisms such as long-term potentiation (HF-rTMS) and long-term depression (LF-rTMS) (Esser et al., 2006; Hoogendam et al., 2010)

TDCS, in contrast to TMS, does not induce a suprathreshold neuronal membrane depolarization required for the initiation of an action potential. Instead, in tDCS, a weak current (1–2 mA) delivered through sponge electrodes placed on the scalp is thought to cause polarization of cortical neurons (Nitsche et al., 2008; Priori et al., 2009). In addition, tDCS differs from TMS in terms of spatial resolution and has low focality in comparison to TMS (Woods et al., 2016). While anodal tDCS is thought to result in tonic depolarization of cortical neurons and thus has an excitatory effect on the stimulated area, cathodal tDCS is thought to result in tonic hyperpolarization and thus inhibition of the stimulated regions (Brunoni et al., 2011). However, similar to TMS, there is substantial interindividual variability in the responses of individuals undergoing tDCS application (Chew et al., 2015; López-Alonso et al., 2015). Size, direction, and duration of the neuroplastic (after-) effects of tDCS depend on various stimulation parameters, such as current intensity and direction, electrode size and position, stimulation duration, and multiple interindividual factors (Agboada et al., 2019; Li et al., 2015; Nitsche et al., 2008; Weller et al., 2020). Both techniques have been widely used to stimulate different cortical regions to study their role during various cognitive, affective, and behavioral processes (Levasseur-Moreau et al., 2013). In contrast, the use of NIBS to study the involvement of different cortical regions in the regulation of the ANS is scarce.

Based on our literature search conducted in PubMed, Web of Knowledge, and PsycInfo, we found only two previous attempts to systematically review or quantify the effects of NIBS on the ANS to date (Makovac et al., 2017; Schestatsky et al., 2013). These reviews found either no or small to medium effects of NIBS on the ANS. Both reviews acknowledge the limited interpretability of their results, which arises from the heterogeneity of the experimental designs, the stimulation parameters and the samples investigated in the reviewed studies as well as from methodological deficiencies such as the lack of sham stimulation. To address these issues, we included only sham-controlled randomized trials in the current meta-analysis and additionally aimed to extract any parameters regarding brain stimulation, sample characteristics, and study design from the trials that may act as moderators of the effect of NIBS on HR/HRV based on the current literature. This approach seems promising to guide future trials in developing efficient study designs and stimulation parameters which allow for comparability of results.

Previous studies have already shown that personal characteristics such as age (Ghasemian-Shirvan et al., 2020; Jandackova et al., 2016), sex (Huber et al., 2003; Koenig & Thayer, 2016), and the presence of physical or mental illness (Kemp & Quintana, 2013) may influence HR, HRV, and the effects of brain stimulation. It is further well-established that different stimulation parameters, such as frequency, number, and intensity of the pulses in TMS, current intensity and reference electrode placement in tDCS, or duration and direction (excitatory and inhibitory) of stimulation influence strength and direction of the effects produced (Klomjai et al., 2015; Siebner et al., 2009; Thair et al., 2017). Additionally, the strength of NIBS effects as well as HR/HRV (re-)activity are subject to temporal and task-dependent influences. Therefore, the timing of the stimulation and of the HR/HRV measurement as well as the presence/absence of a task and the nature of that task were included in our analyses as potential influential factors. Given the evidence on neural regulation of HR/HRV (re-)activity, we accounted for the impact of different brain regions on the ANS by eliciting both the region of stimulation and the stimulated hemisphere as further moderators.

Previous research further corroborates the assumption that different cardiovascular measures reflect different physiological systems regulated by different neuronal circuitries (Berntson et al., 1997; Critchley et al., 2003). Therefore, in contrast to previous work, we decided not to subsume the various HRV measures under the umbrella term "HRV" and to perform a separate meta-analysis for each cardiovascular measure (i.e., HR and various HRV variables).

The ability of NIBS to manipulate the neuronal activity of cortical regions, unlike other brain imaging techniques, may allow us to investigate which regions are causally involved in the increase or decrease of HR or HRV. This work aimed to quantify the effects of NIBS on HR and HRV based on current studies in the field to evaluate whether NIBS presents an appropriate method to alter HR and HRV and, thus, to study the underlying cortical mechanisms involved in the regulation of autonomic functions. In addition, we critically reviewed the existing studies with regard to their design, their stimulation parameters, and the sample examined to provide insights into particularly suitable study parameters.

2 | METHODS

This systematic review and meta-analysis were preregistered in PROSPERO (CRD42020196005). The guidelines of the Preferred

Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) were followed in planning and conducting the systematic review and meta-analysis (Moher et al., 2010).

2.1 | Systematic literature search and study selection

The literature search was conducted according to PRISMA. The search, conducted in PubMed, Web of Knowledge, and PsycInfo, included articles published between 1985 and 2020. Search terms used were ("Heart rate" OR "HRV" OR "Heart rate variability" OR "RSA" OR "RMSSD" OR "pnn50" OR "SDNN" OR "HF" OR "LF" OR "r-r interval" OR "vagal" OR "vagus" OR "parasympathetic" OR "autonomic nervous system" OR "ANS" OR "cardiovascular") AND ("Non-invasive brain stimulation" OR "NIBS" OR "Neurostimulation" OR "Transcranial Magnetic Stimulation" OR "TMS" OR "rTMS" OR "Transcranial direct current stimulation" OR "tDCS" OR "theta burst stimulation" OR "iTBS" OR "cTBS" OR "Neuromodulation").

In this literature search, 2547 results were retrieved from PubMed, 1888 from Web of Knowledge, and 948 from PsycInfo. After the identification and removal of 550 duplicates among the initial results, we obtained a total sample of 4833 studies. Titles and abstracts of these articles were screened and if potentially relevant to the analyses, the full text of that paper was read. In a second step, we performed a citation network analysis in which all articles cited by those originally considered suitable or citing these articles themselves were scanned for further relevant studies. In a final step, all corresponding authors of the articles classified as suitable were asked for unpublished data. Figure 1 outlines the detailed study selection procedure.

Only quantitative articles written in English were considered eligible for inclusion. Inclusion criteria were informed using Population, Intervention, Comparison, Outcome, Study type (PICOS) guidelines (Brown et al., 2006), summarized in Table 1.

Reasons for exclusion were: (1) review articles, (2) case reports, (3) animal studies, (4) articles using other NIBS techniques than TMS and tDCS, (5) articles examining the effects of NIBS applied to other parts of the nervous system than to the brain.

Our literature research and inclusion criteria resulted in a final sample of 34 studies and one unpublished data set that were incorporated in our analyses. Twenty-six of these studies used tDCS to stimulate the brain, and nine used TMS. Methodological quality of all included studies was evaluated using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) (Sterne et al., 2019) (Table 2).

2.2 | Data extraction

The following data were extracted from each study: (a) authors and publication year, (b) characteristic of the study sample (age, sex, population type), (c) experimental design (within vs. between-subject design, time point of HR/HRV measurement, time point of stimulation, presence of a certain tasks), (d) NIBS method used, (e) stimulation parameter (general parameter: duration, stimulation site, laterality, single vs. multiple sessions, excitatory vs. inhibitory; TMS: frequency, intensity, total number of pulses; tDCS: current strength, and anodal and cathodal placement), and (f) cardiovascular outcomes. In determining the cardiovascular outcome measures to be used for our analyses, we oriented ourselves along the Guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Malik et al., 1996) and, based on these, planned to extract the following measures: HR, HF-HRV, and LF-HRV (absolute power), RMSSD, RSA, pNN50, and SDNN. Both raw and log-transformed values were extracted for all measures listed. Normalized units of HF and LF-HRV as well as the LF/HF ratio were not extracted for further analyses as these measures and their mathematical expression are based on the flawed, simplifying assumption of autonomic reciprocity, meaning that autonomic control can be viewed as a continuum extending from parasympathetic to the sympathetic (del Paso et al., 2013). Data extraction was performed by the first author and double-checked by the last author.

2.3 | Data analyses

The effect size calculated for each study or study subsample was Hedges'*g*, representing the difference between response to actual NIBS and the response to sham stimulation divided by the pooled standard deviation (Hedges & Olkin, 2014). Hedges'*g* was chosen as results were not reported uniformly across studies, reporting both raw and log-transformed values as well as only *F* and *t* statistics in some studies. Since we were only interested in whether NIBS can influence HR and HRV and not in the exact direction of these effects, all effect sizes received a positive sign regardless of the direction of change in HR and HRV. Hedges'*g* as well as the standard error of g and the sampling variance were calculated by using Comprehensive Meta-analysis, version 3 (Borenstein, 2009) and the spreadsheet from Lakens, version 4.2 (Lakens, 2013). When the mean difference between pre- and postmeasurement of both study groups was presented explicitly in the studies or could be calculated from raw data provided, the effect size was calculated using these data. When the difference between pre- and poststimulation measurement was not available, authors were contacted and asked to provide the (raw) data needed. In case of no response, or data not being provided by the authors, calculations were based on either the mean values during or after stimulation or alternatively on the reported statistics (i.e., *F* and *t* values). If none of these statistics were reported, the study was excluded from the analysis.

Based on their design (multiple measurement time points, stimulation parameters, etc.), many studies reported multiple outcomes. These multiple outcomes are generally nonindependent, which means that effect sizes are correlated within a study. However, these within-study correlations are rarely reported (Riley, 2009). Because

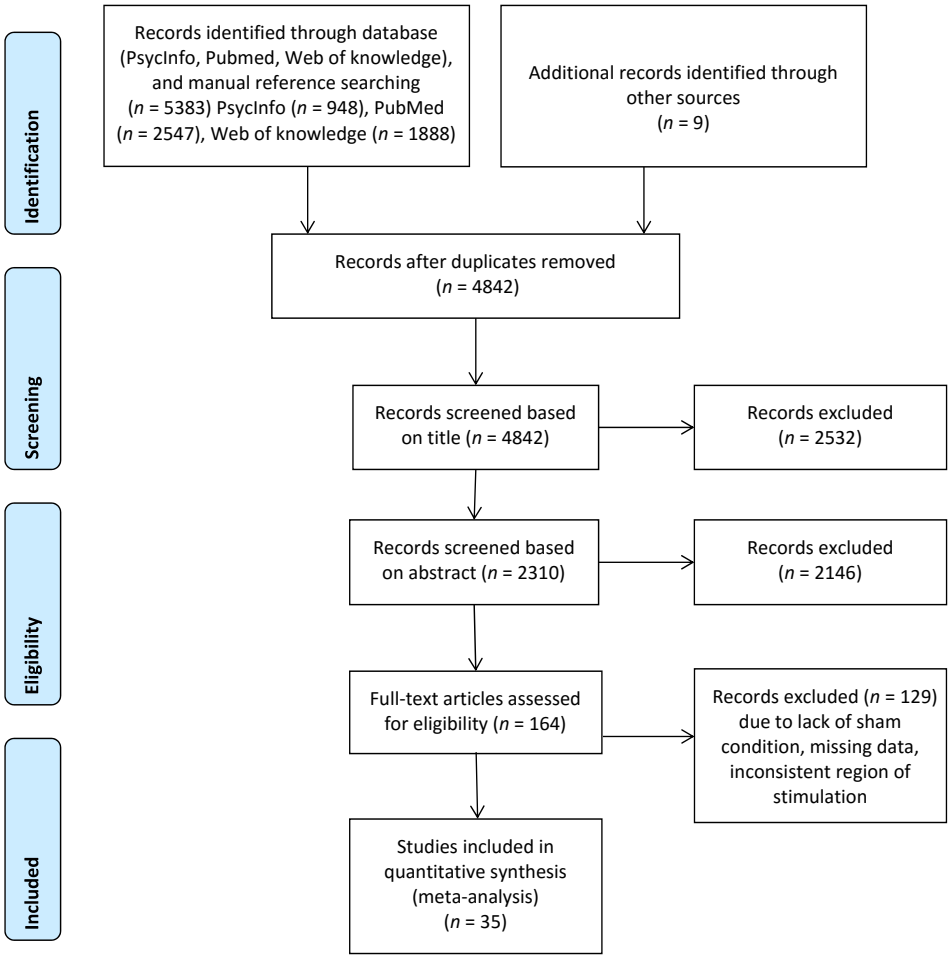

FIGURE 1 Flow diagram showing the process of screening and article selection

TABLE 1 PICOS criteria for inclusion

PICOS	Inclusion criteria
Population	Healthy humans and any patient groups of all ages
Intervention	Single or multiple TMS or tDCS sessions
Comparison	With sham-stimulated control group or with sham stimulation condition
Outcomes	Changes in heart rate and heart rate variability metrics (HR, HF-HRV, LF-HRV, RMSSD, RSA, pNN50, SDNN)
Study type	Sham -controlled randomized trials

Abbreviations: HF-HRV, high-frequency absolute power; LF-HRV, low-frequency absolute power; RMSSD, root mean square of successive RR interval differences; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

these unknown statistical dependencies pose problems for conventional meta-analytic methods, we used robust variance estimation (RVE) to run multiple random-effects meta-regressions for each of the cardiovascular measures (Hedges et al., 2010; Pustejovsky & Tipton, 2021). RVE performs a robust estimation of effect size weights and standard errors and further models statistically dependent effect sizes, thus accounting for both correlational structures of multiple outcomes within studies. Multiple outcomes in our study sample were neither attributable to a purely correlative nor a purely hierarchical effect structure. That is, multiple effect sizes per study resulted from multiple measurements per subject within one study, from examining multiple independent samples within one study, or both. Thus, we used a working model that accounts for both correlative and hierarchical effects, as recommended in Pustejovsky and Tipton (2021). To perform the analyses, we used the *rma.mv()* function of the *metafor* package (Viechtbauer, 2010) and both the *coef_test()* and the *conf_int()* functions of the *clubSandwich* package (Pustejovsky, 2020) in R, software version 4.0.2 (R Core Team, 2020).

TABLE 2 Results of the risk of bias 2 analysis

Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Angius et al. (2016)	🔴	🟡	🟢	🟡	🟡	🔴
Angius et al. (2018)	🔴	🟡	🟢	🟡	🟡	🔴
Angius et al. (2019)	🟡	🟡	🟢	🟡	🟡	🟡
Baldari et al. (2018)	🔴	🟡	🟢	🟡	🟡	🔴
Barwood et al. (2016)	🔴	🟡	🟢	🟡	🟡	🔴
Berger et al. (2017)	🔴	🟡	🟢	🟡	🟡	🔴
Brunoni, Kemp, et al. (2013)	🔴	🟡	🟢	🟢	🟡	🔴
Brunoni, Vanderhasselt, et al. (2013)	🔴	🟡	🟢	🟡	🟡	🔴
Carnevali et al. (2019)	🔴	🟡	🟢	🟡	🟡	🔴
Ciccone et al. (2019)	🔴	🟡	🟢	🟡	🟡	🔴
Clancy et al. (2014)	🔴	🟡	🟢	🟢	🟡	🔴
da Silva et al. (2017)	🔴	🟡	🟢	🟡	🟡	🔴
De Putter et al. (2015)	🔴	🟡	🟢	🟡	🟡	🔴
Era et al. (2021)	🔴	🟡	🟢	🟡	🟡	🔴
Erdogan et al. (2018)	🔴	🟡	🟢	🟡	🟡	🔴
Germano-Soares et al. (2017)	🔴	🟡	🟢	🟡	🟡	🔴
Hamner et al. (2015)	🔴	🟡	🟢	🟡	🟡	🔴
Heinz et al. (2020)	🟡	🟡	🟢	🟡	🟡	🟡
Holgado et al. (2019)	🔴	🟡	🟢	🟡	🟢	🔴
Iseger, Arns, et al. (2020)	🔴	🟡	🟢	🟢	🟡	🔴
Kao et al. (2020)	🟡	🟡	🟢	🟡	🟡	🟡
Lee et al. (2019)	🔴	🟡	🟢	🟡	🟡	🔴
Nikolin et al. (2017)	🔴	🟡	🟢	🟡	🟡	🔴
Notzon et al. (2015)	🔴	🟡	🟢	🟡	🟡	🔴
Ottaviani et al. (2018)	🔴	🟡	🟢	🟡	🟡	🔴
Park et al. (2019)	🔴	🟡	🟢	🟡	🟡	🔴
Petrocchi et al. (2017)	🔴	🟡	🟢	🟢	🟡	🔴
Poppa et al. (2020)	🔴	🟡	🟢	🟡	🟡	🔴
Pulopulos et al. (2020)	🔴	🟡	🟢	🟢	🟢	🔴
Raimondo et al. (2012)	🔴	🟡	🟢	🟡	🟡	🔴
Remue et al. (2016)	🔴	🟡	🟢	🟡	🟡	🔴
Sauvaget et al. (2018)	🟡	🟡	🟢	🟡	🟡	🟡
Thomas et al. (2020)	🔴	🟡	🟢	🟡	🟡	🔴
Valenzuela et al. (2019)	🔴	🟡	🟢	🟡	🟡	🔴
Van den Eynde et al. (2011)	🟡	🟡	🟢	🟡	🟡	🟡

🟢 Low risk; 🟡 Some concerns; 🔴 High risk.

In order to account for dependency, we set ρ to the recommended value of 0.80 (Tanner-Smith & Tipton, 2014).

Heterogeneity was assessed using the Q statistics. A significant Q value reflects a lack of homogeneity between the findings among studies. Furthermore, τ^2 and ω^2 were calculated indicating the variance of the distribution of the true study effects between and within studies, respectively (Pustejovsky & Tipton, 2021; Veroniki et al., 2016).

Subsequent moderator analyses were performed using random-effects meta-regression with RVE. Meta-regression has recently been recommended for moderator analysis since it allows multiple moderators to be included in a single model, unlike other approaches such as the use of multiple subgroup comparisons (Pigott & Polanin, 2020). In an initial step, all predefined moderators were included in the random-effects model. Moderators included in the model are shown in Tables 3–6. In a second step, applying an information-theoretic approach (Burnham & Anderson, 2004), we performed model selection based on Akaike weights to identify the most likely and parsimonious model among all alternatives retaining NIBS technique and stimulated brain area in each model, as they represent the two main points of interest of our analyses. Model selection was accomplished using the *dredge* function from the R package *MuMIn* (Bartoń, 2013). We further performed Wald tests with the default Hotelling's T_z^2 small sample correction from the *clubSandwich* package to calculate post hoc tests on categorical (dummy-coded) variables that were incorporated as covariates.

To detect extreme outliers and influential effect sizes, we proceeded according to the recommendations of Viechtbauer and Cheung (2010). Accordingly, we identified extreme outliers and influential effect sizes by inspecting the *z*-value of the standardized residuals and Cook's distance plot, respectively. Effect sizes with *z*-values above 1.96 were classified as extreme outliers. These effect sizes were removed for further analyses if Cook's distance plot revealed that they also had a significant influence on the results. To test for publication bias, we used the so-called Egger's sandwich test (Rodgers & Pustejovsky, 2020). This refers to the application of RVE to a traditional Egger's regression test (Sterne & Egger, 2005). In the Egger's regression test, the effect size estimate is regressed on a measure of its precision (usually the standard error of the effect size) weighted by their inverse variance. If the intercept of this regression test differs significantly from zero, the overall relationship between the precision and the size of the studies included in the data set is asymmetric and thus biased. Previous research has shown that the results of the Eggers' regression test are misleading when applied to Hedges'*g* because of an artifactual correlation between Hedges'*g* and its standard error leading to an inflated Type 1 error (Pustejovsky & Rodgers, 2019). Following the recommendations from Pustejovsky and Rodgers (2019), we applied the Egger's sandwich test by modifying the random-effects models to include $\sqrt{W_i}$ (instead of the standard error of the effect sizes) as a moderator, where $\sqrt{W_i} = 2 / \sqrt{n_i}$. Because we performed a separate analysis for each of the extracted cardiovascular measures, the above steps were followed for each of the respective analyses.

3 | RESULTS

3.1 | Heart rate

3.1.1 | Study characteristics

Study characteristics that were collected and examined as potential moderators for the full sample of studies can be found in Table 3. The mean sample size of the total sample of 20 studies was 21.5 (SD = 11.9). TMS was used for neural modulation in five studies and tDCS in 15 studies. Brain areas targeted by NIBS were the dorsolateral prefrontal cortex (dlPFC), insular cortex, and temporal regions in both left and right hemispheres, as well as the left and central primary motor cortex (M1). Since targeting the temporal cortex in many studies was intended to stimulate the insular cortex, and due to the also very small number of studies, both brain regions were combined in all subsequent statistical analyses. In 15 of the 20 studies, NIBS-induced behavioral changes in emotional, cognitive, and physical tasks were assessed in addition to cardiovascular changes. Tasks included, for instance, emotional perception tasks (Berger et al., 2017), stress tests (Carnevali et al., 2019; Era et al., 2021), and various athletic tasks such as cycling (e.g., Angius et al., 2019; Holgado et al., 2019), running (Park et al., 2019), and resistance exercise (Germano-Soares et al., 2017). While 19 studies performed NIBS on healthy participants (including trained athletes), one study (Van den Eynde et al., 2011) examined a psychiatric sample (bulimic eating disorder).

3.1.2 | Risk of bias

Assessing the risk of bias using RoB2 (Sterne et al., 2019), we identified 17 studies (85 %) with overall high risk and three studies (15 %) with some concerns. Domains coded with some concerns primarily included deviations from planned measures, measurement of outcomes, and selection of reported outcomes. The overall high risk was caused mainly by the high risk of bias in the randomization process (see Table 2).

3.1.3 | Publication bias and outlier diagnostics

Diagnostics for publication bias and influential outliers were performed on a total sample of 19 studies and one unpublished data set (Baldrai et al., 2020) including 429 participants and 41 effect sizes. Egger's sandwich test revealed no evidence for publication bias in the included sample, $t = 1.48$, $df = 8.50$, $p > .05$. One effect size (Ottaviani et al., 2018) was identified as outlier and influential case by our outlier diagnostics. The analyses reported in the following were performed after excluding this observation.

3.1.4 | Meta-analytic results

The analysis from 40 effect sizes from a total of 19 studies ($N = 391$) yielded significant associations between NIBS and changes in HR, $g = 0.25$, $t(13.6) = 4.91$, $p < .001$, 95% CI [0.14; 0.36] (Figure 2). Significant heterogeneity was shown by the *Q* statistics, $Q(39) = 103.69$, $p < .001$; $\tau^2 = 0.006$; $\omega^2 = 0.015$. Taking into account

the premise that NIBS technique and brain areas are mandatorily included in our model, model selection considering Akaike weights identified a model with only these two moderators as the most likely one (see Table 7). A subsequent moderator analysis revealed no significant moderators.

3.2 | High-frequency HRV

3.2.1 | Study characteristics

Study characteristics that were collected and examined as potential moderators for the full sample of studies can be found in Table 4. The mean sample size of the total sample of 15 studies was 32.3 (SD = 22.7). TMS was used for neural modulation in three studies and tDCS in 12 studies. Brain regions targeted were the left dlPFC, left and right hemispheric insular/temporal regions, and the left and central M1. One study from Lee et al. (2019) was the only one to apply neurostimulation over frontocentral regions. Therefore, it was not included in the meta-analytical calculations reported below. Six studies examined cardiovascular changes in addition to NIBS-induced behavioral changes in emotional (Brunoni, Vanderhasselt et al., 2013; Hamner et al., 2015), cognitive (De Putter et al., 2015; Nikolin et al., 2017), physical (Heinz et al., 2020), and other kinds of tasks (e.g., breathing task; Poppa et al., 2020). While 10 studies performed NIBS on healthy participants, three studies examined psychiatric samples including patients with depression (Brunoni, Kemp et al., 2013; Iseger, Arns, et al., 2020) and schizophrenia (Kao et al., 2020). Two further studies examined samples with other pathologies, such as chronic lower back pain (Lee et al., 2019) and stroke (Heinz et al., 2020). Three of these patient studies (Brunoni, Kemp et al., 2013; Kao et al., 2020; Lee et al., 2019), unlike the remaining studies, did not examine the acute effects of NIBS on HF-HRV but rather examined changes in HF-HRV after completion of longer term NIBS therapy.

3.2.2 | Risk of bias

Evaluation of the risk of bias by the use of RoB2 (Sterne et al., 2019) identified 13 studies (86.7%) with overall high risk and two studies (13.3%) with some concerns. Domains coded with some concerns primarily included deviations from planned measures, measurement of outcomes, and selection of reported outcomes. The overall high risk was caused mainly by the high risk of bias in the randomization process (see Table 2).

3.2.3 | Publication bias and outlier diagnostics

Diagnostics for publication bias and influential outliers were performed on a total sample of 14 studies including 420 participants and 34 effect sizes. Egger's sandwich test revealed no evidence for publication bias in the included sample, $t = 0.46$, $df = 5.41$, $p > .05$. Two effect sizes (Clancy et al., 2014) were identified as outliers and influential cases by our outlier diagnostics. The analyses reported in the following were performed after excluding these observations.

3.2.4 | Meta-analytic results

The analysis from 32 effect sizes from a total of 14 studies ($N = 420$) yielded significant associations between NIBS and changes in HF-HRV, $g = 0.22$, $t(8.77) = 4.11$, $p = .002$, 95% CI [0.10; 0.35] (Figure 3). Significant heterogeneity was shown by the Q statistics, $Q(31) = 93.22$, $p < .001$; $\tau^2 = 0.00$; $\omega^2 = 0.03$. Considering that NIBS technique and brain areas are mandatorily included in our model, model selection using Akaike weights identified a model with the moderators NIBS technique, brain area, and stimulation duration as the most likely model (see Table 8). A subsequent moderator analysis revealed nonsignificant effects of NIBS technique, $F(1, 3.79) = 5.23$, $p = .087$, and stimulation duration, $\beta = -0.0003$, $SE < 0.001$, $t(3.35) = 2.79$, $p = .061$ on effect size. Studies using TMS produced average effect sizes smaller than studies using tDCS, $\beta = -0.279$, $SE = 0.122$, $p = .087$. Furthermore, there was a nonsignificant effect of brain area on effect size, $F(2, 3.83) = 6.46$, $p = .06$. Post hoc Wald tests revealed that stimulation of dlPFC was associated with significant higher effect sizes than stimulation of temporal/insular regions, $\beta = -0.337$, $SE = 0.087$, $F(1, 7.93) = 14.84$, $p = .004$. Our analyses detected no significant difference in effect size between stimulation of M1 and dlPFC, $\beta = 0.116$, $SE = 0.161$, $F(1, 2.97) = 0.52$, $p = .524$ or between stimulation of M1 and temporal/insular cortex, M1, $\beta = -0.453$, $SE = 0.217$, $F(1, 3.10) = 4.38$, $p = .125$.

3.3 | Low-frequency HRV

3.3.1 | Study characteristics

Study characteristics that were collected and examined as potential moderators for the full sample of studies can be found in Table 5. The mean sample size of the total sample of 12 studies was 33.27 (SD = 12.7). TMS was used for neural modulation in two studies and tDCS in 10 studies. Brain regions targeted were the left dlPFC, left and right hemispheric insular/temporal regions, and the left and central M1. One study from Lee et al. (2019) was the only one to apply neurostimulation over frontocentral regions. Therefore, it was not included in the meta-analytical calculations reported below. Five studies examined cardiovascular changes in addition to NIBS-induced behavioral changes in emotional (Brunoni, Vanderhasselt et al., 2013; Hamner et al., 2015), cognitive (Nikolin et al., 2017), physical (Heinz et al., 2020), and other kinds of tasks (e.g., breathing task; Poppa et al., 2020). While eight studies performed NIBS on healthy participants, four studies examined psychiatric samples (Iseger, Arns, et al., 2020; Kao et al., 2020) and samples with other pathologies (Heinz et al., 2020; Lee et al., 2019). Two of these patient studies (Kao

TABLE 3 Characteristics of all included studies with HR as an outcome measure

Study	Sample size[a]	Female (%)	Population type	Mean age (years)	NIBS	Brain area	Aimed stimulation direction
Angius et al. (2016)	12	00.0	Healthy	23.0	tDCS	L M1	Excitatory
Angius et al. (2018)	12	50.0	Healthy	21.8	tDCS	L TC/Insula R TC/Insula	Excitatory
Angius et al. (2019)	12	25.0	Healthy	23.0	tDCS	L dlPFC	Excitatory
Baldari et al. (2018)	10	00.0	Healthy	27.0	tDCS	Central M1	Excitatory Inhibitory
Baldrai et al. (2020)	10	100	Healthy	/	tDCS	Central M1	Excitatory Inhibitory
Barwood et al. (2016)	6	00.0	Healthy	21.0	tDCS	L TC/Insula	Excitatory
Berger et al. (2017)	20	100	Healthy	23.5	TMS	R dlPFC	Excitatory Inhibitory
Carnevali et al. (2019)	30	00.0	Healthy	23.5	tDCS	L dlPFC	Excitatory
Era et al. (2021)	32	50.0	Healthy	22.2	TMS	L dlPFC L M1	Inhibitory
Erdogan et al. (2018)	16	62.5	Healthy	25.0	tDCS	Central M1	Excitatory
Germano-Soares et al. (2017)	12	00.0	Healthy	19.0	tDCS	L M1	Excitatory
Hamner et al. (2015)	15	46.7	Healthy	25.0	tDCS	L M1	Excitatory
Holgado et al. (2019)	36	00.0	Healthy	27.0	tDCS	L dlPFC	Excitatory Inhibitory
Ottaviani et al. (2018)	37	67.6	Healthy	26.8	tDCS	L TC/Insula	Excitatory
Park et al. (2019)	12	00.0	Healthy	27.4	tDCS	Central M1	Excitatory
Poppa et al. (2020)	24	58.3	Healthy	25.9	TMS	R TC/Insula	Excitatory Inhibitory
Raimondo et al. (2012)	50	64.0	Healthy	30.5	tDCS	L M1	Excitatory
Sauvaget et al. (2018)	30	10.0	Healthy	37.3	TMS	R dlPFC	Inhibitory
Thomas et al. (2020)	17	35.5	Healthy	25.1	tDCS	L dlPFC	Excitatory Inhibitory
Van den Eynde et al. (2011)	38	86.8	Psychiatric patients	29.9	TMS	L dlPFC	Excitatory

Abbreviations: dlPFC, dorsolateral prefrontal cortex; L, left; M1, primary motor cortex; R, right; TC, temporal cortex; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

[a]Not included as a moderator.

Task	Time point of stimulation	Time point of measurement	Stimulation duration (s)	Sessions	Design	ROB2
Physical	Before measurement and resting	After stimulation and during task	600	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and during task	1200	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and during task	1800	Single	Within	Some concerns
Physical	Before measurement and resting	After stimulation and resting (pretask), after stimulation and during task	1200	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and resting (pretask), after stimulation and during task	1200	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and during task	1200	Single	Within	High risk
Emotional other	Before measurement and resting	After stimulation and during task	900 270	Single	Within	High risk
Emotional	During measurement and resting, during measurement and during task, before measurement and during task	During stimulation and resting, during stimulation and during task, after stimulation and after task	900	Single	Between	High risk
Emotional cognitive	Before measurement and resting	After stimulation and during task	20	Single	Within	High risk
No task	Before measurement and resting	During stimulation and resting	600	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and after task	1200	Single	Within	High risk
Emotional	Before measurement and resting	After stimulation and after task	2400	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and during task	1200	Single	Within	High risk
Emotional	During measurement and during task	During stimulation and during task	900	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and during task	1200	Single	Within	High risk
Other No task	Before measurement and resting	After stimulation and resting, after stimulation and during task	160, 40	Single	Within	High risk
no task	Before measurement and resting	After stimulation and resting	1200	Single	Between	High risk
No task	Before measurement and resting	After stimulation and resting	360	Single		Some concerns
Physical	During measurement and during task	During stimulation and during task	1200	Single	Within	High risk
No task	Before measurement and resting	After stimulation and resting	1200	Single	Between	Some concerns

TABLE 4 Characteristics of all included studies with HF-HRV as an outcome measure

Study	Sample size[a]	Female (%)	Population type	Mean age (years)	NIBS	Brain area	Aimed stimulation direction
Brunoni, Vanderhasselt et al. (2013)	93	66.7	Psychiatric patients	42.2	tDCS	L dlPFC	Excitatory
Brunoni, Kemp et al. (2013)	20	85.0	Healthy	24.9	tDCS	L dlPFC	Excitatory Inhibitory
Ciccone et al. (2019)	18 20	55.5 50.0	Healthy	21.6 21.0	tDCS	L TC/Insula R TC/Insula	Excitatory
Clancy et al. (2014)	22	50.0	Healthy	21-48	tDCS	L M1	Excitatory Inhibitory
De Putter et al. (2015)	63	84.1	Healthy	23.1	tDCS	L dlPFC	Excitatory
Erdogan et al. (2018)	16	62.5	Healthy	25.0	tDCS	Central M1	Excitatory
Hamner et al. (2015)	15	46.7	Healthy	25.0	tDCS	L M1	Excitatory
Heinz et al. (2020)	12	33.3	Other patients	59	tDCS	L TC/Insula	Excitatory
Iseger, Arns, et al. (2020)	15	66.7	Psychiatric patients	32.0	TMS	L dfPFC	Excitatory
Kao et al. (2020)	60	55.0	Psychiatric patients	44.3	tDCS	L dlPFC	Excitatory
Lee et al. (2019)	21	/	Other patients	47.6	TMS	Central frontal	Excitatory
Nikolin et al. (2017)	20	45.0	Healthy	22.8	tDCS	L dlPFC	Excitatory
Petrocchi et al. (2017)	34	58.8	Healthy	43.7	tDCS	L TC/Insula	Excitatory
Piccirillo et al. (2016)	50	54.0	Healthy	50.1	tDCS	L TC/Insula	Excitatory
Poppa et al. (2020)	24	58.3	Healthy	25.9	TMS	R TC/Insula	Excitatory Inhibitory

Abbreviations: dlPFC, dorsolateral prefrontal cortex; L, left; M1, primary motor cortex; R, right; TC, temporal cortex; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

[a]Not included as a moderator.

et al., 2020; Lee et al., 2019), unlike the remaining studies, did not examine the acute effects of NIBS on LF-HRV but rather examined changes in LF-HRV after completion of longer term NIBS therapy.

3.3.2 | Risk of bias

Evaluating the risk of bias by means of RoB2 (Sterne et al., 2019), we identified 10 studies (83.3%) with overall high risk and two studies (16.7%) with some concerns. Domains coded with some concerns primarily included deviations from planned measures, measurement of outcomes, and selection of reported outcomes. The overall high risk was mainly due to the high risk of bias in the randomization process (see Table 2).

3.3.3 | Publication bias and outlier diagnostics

Diagnostics for publication bias and influential outliers were performed on a total sample of 11 studies including 245 participants and 31 effect sizes. Egger's sandwich test revealed no evidence

Task	Time point of stimulation	Time point of measurement	Stimulation duration (s)	Sessions	Design	ROB2
No task	Long term	After completion of treatment course	1800	Multiple	Between	High risk
Emotional Other	During measurement and during task	During stimulation and during task	1980	Single	Within	High risk
No task	During measurement and resting, before measurement and resting	During stimulation and resting, after stimulation and resting	1200, 1800	Single	Within	High risk
No task	During measurement and resting, before measurement and resting	During stimulation and resting, after stimulation and resting	900	Single	Within	High risk
Cognitive	Before measurement and resting	After stimulation and after task	1500	Single	Between	High risk
No task	Before measurement and resting	During stimulation and resting	600	Single	Within	High risk
Emotional	Before measurement and resting	After stimulation and after task	2400	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and resting (pretask), after stimulation and after task	1200	Single	Within	Some concerns
No task	During measurement and resting	During stimulation and resting	190	Multiple	Within	High risk
No task	Long term	After completion of treatment course, follow-up	1200	Multiple	Between	Some concerns
No task	Long term	After completion of treatment course, follow-up	600	Multiple	Between	High risk
Cognitive	During measurement and resting, during measurement and during task, before measurement and during task	During stimulation and resting, during stimulation and during task, after stimulation and after task, after stimulation and during task	900	Single	Between	High risk
No task	During measurement and resting	During stimulation and resting	900	Single	Within	High risk
No task	During measurement and resting	During stimulation and resting	900	Single	Within	High risk
Other No task	Before measurement and resting	After stimulation and resting, after stimulation and during task	160, 40	Single	Within	High risk

for publication bias in the included sample, $t = -0.38$, $df = 2.48$, $p > .05$. No outliers or influential cases were identified by our outlier diagnostics.

3.3.4 | Meta-analytic results

The analysis from 31 effect sizes from a total of 11 studies ($N = 245$) yielded significant associations between NIBS and changes in LF-HRV, $g = 0.51$, $t(9.27) = 3.25$, $p = .009$, 95% CI [0.15; 0.86] (Figure 4). Significant heterogeneity was shown by the Q statistics, $Q(30) = 291.03$, $p < .001$; $\tau^2 = 0.13$; $\omega^2 = 0.17$. Taking into account the premise that NIBS technique and brain areas are mandatorily included in our model, model selection considering Akaike weights identified a model with only these two moderators as the most likely one (see Table 9). A subsequent moderator analysis revealed nonsignificant effects of targeted brain area, $F(2, 3.58) = 5.57$, $p = .079$, on study effect size. Post hoc Wald tests revealed that stimulation of M1 was

TABLE 5 Characteristics of all included studies with LF-HRV as outcome measure

Study	Sample size[a]	Female (%)	Population type	Mean age (years)	NIBS	Brain area	Aimed stimulation direction
Brunoni, Vanderhasselt et al. (2013)	20	85.0	Healthy	24.9	tDCS	L dlPFC	Excitatory Inhibitory
Ciccone et al. (2019)	18 20	55.5 50.0	Healthy	21.6 21.0	tDCS	L TC/Insula R TC/Insula	Excitatory
Clancy et al. (2014)	22	50.0	Healthy	21-48	tDCS	L M1	Excitatory Inhibitory
Erdogan et al. (2018)	16	62.5	Healthy	25.0	tDCS	Central M1	Excitatory
Hamner et al. (2015)	15	46.7	Healthy	25.0	tDCS	L M1	Excitatory
Heinz et al. (2020)	12	33.3	Other patients	59	tDCS	L TC/Insula	Excitatory
Iseger, van Bueren, et al. (2020)	15	66.7	Psychiatric patients	32.0	TMS	L dfPFC	Excitatory
Kao et al. (2020)	60	55.0	Psychiatric patients	44.3	tDCS	L dlPFC	Excitatory
Lee et al. (2019)	21	/	Other patients	47.6	TMS	Central frontal	Excitatory
Nikolin et al. (2017)	20	45.0	Healthy	22.8	tDCS	L dlPFC	Excitatory
Piccirillo et al. (2016)	50	54.0	Healthy	50.1	tDCS	L TC/Insula	Excitatory
Poppa et al. (2020)	24	58.3	Healthy	25.9	TMS	R TC/Insula	Excitatory Inhibitory

Abbreviations: dlPFC, dorsolateral prefrontal cortex; L, left; M1, primary motor cortex; R, right; TC, temporal cortex; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

[a]Not included as a moderator.

associated with significant higher effect sizes than stimulation of temporal/insular regions, $\beta = -1.121$, SE = .314, $F(1, 3.79) = 12.7$, $p = .025$. There were no significant differences in effect size between stimulation of dlPFC and insular/temporal regions, $\beta = -0.294$, SE = 0.232, $F(1, 4.41) = 1.61$, $p = .268$, and between stimulation of M1 and dlPFC, $\beta = -0.827$, SE = 0.388, $F(1, 4.53) = 3.56$, $p = .109$.

3.4 | Root mean square of squared distance (RMSSD)

3.4.1 | Study characteristics

Study characteristics that were collected and examined as potential moderators for the full sample of studies can be found in Table 6. The mean sample size of the total sample of 12 studies was 35.7 (SD = 25.9). TMS was used for neural modulation in five studies and tDCS in seven studies. Brain regions targeted were the left and right dlPFC as well as left and right hemispheric insular/temporal regions. One study from Valenzuela et al. (2019) was the only one to apply NIBS over left M1 and was therefore excluded from subsequent statistical analyses reported below. Eight studies examined cardiovascular changes in addition to NIBS-induced behavioral changes in emotional (Carnevali et al., 2019; Era et al., 2021; Ottaviani et al., 2018; Pulopulos et al., 2020; Remue et al., 2016), cognitive (De Putter et al., 2015; Era et al., 2021), physical (Heinz et al., 2020), and other kinds of tasks (e.g., breathing task; Poppa et al., 2020). While nine studies performed NIBS on healthy participants, two studies examined psychiatric samples with patients with depression (Brunoni, Kemp et al., 2013; Iseger, Arns, et al., 2020). In

Task	Time point of stimulation	Time point of measurement	Stimulation duration (s)	Sessions	Design	ROB2
Emotional Other	During measurement and during task	During stimulation and during task	1980	Single	Within	High risk
No task	During measurement and resting, before measurement and resting	During stimulation and resting, after stimulation and resting	1200, 1800	Single	Within	High risk
No task	During measurement and resting, before measurement and resting	During stimulation and resting, after stimulation and resting	900	Single	Within	High risk
No task	Before measurement and resting	During stimulation and resting	600	Single	Within	High risk
Emotional	Before measurement and resting	After stimulation and after task	2400	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and resting (pretask), after stimulation and after task	1200	Single	Within	Some concerns
No task	During measurement and resting	During stimulation and resting	190	Multiple	Within	High risk
No task	Long term	After completion of treatment course, follow-up	1200	Multiple	Between	Some concerns
No task	Long term	After completion of treatment course, follow-up	600	Multiple	Between	High risk
Cognitive	During measurement and resting, during measurement and during task, before measurement and during task	During stimulation and resting, during stimulation and during task, after stimulation and after task, after stimulation and during task	900	Single	Between	High risk
No task	During measurement and resting	During stimulation and resting	900	Single	Within	High risk
Other No task	Before measurement and resting	After stimulation and resting, after stimulation and during task	160, 40	Single	Within	High risk

another study (Heinz et al., 2020), NIBS was applied to a sample of patients with stroke. A study by Brunoni, Kemp et al. (2013) was the only study that did not examine the acute effects of NIBS, but rather examined the long-term effects over the course of NIBS-based depression treatment.

3.4.2 | Risk of bias

Assessing the risk of bias using RoB2 (Sterne et al., 2019), we identified 11 studies (91.7%) with overall high risk and one study (8.3%) with some concerns. Domains coded with some concerns primarily included deviations from planned measures, measurement of outcomes, and selection of reported outcomes. The overall high risk was mainly due to high risk of bias in the randomization process (see Table 2).

3.4.3 | Publication bias and outlier diagnostics

Diagnostics for publication bias and influential outliers were performed on a total sample of 11 studies including 420 participants and 29 effect sizes. Egger's sandwich test revealed no evidence for publication bias in the included sample, $t = 1.42$, $df = 3.48$, $p > .05$. One effect size (Ottaviani et al., 2018) was identified as outlier and influential case by our outlier diagnostics. The analyses reported in the following were performed after excluding this observation.

TABLE 6 Characteristics of all included studies with RMSSD as outcome measure

Study	Sample size[a]	Female (%)	Population type	Mean age (years)	NIBS	Brain area	Aimed stimulation direction
Brunoni, Kemp et al. (2013)	93	66.7	Psychiatric patients	42.2	tDCS	L dlPFC	Excitatory
Carnevali et al. (2019)	30	00.0	Healthy	23.5	tDCS	L dlPFC	Excitatory
Ciccone et al. (2019)	18 20	55.5 50.0	Healthy	21.6 21.0	tDCS	L TC/Insula R TC/Insula	Excitatory
De Putter et al. (2015)	63	84.1	Healthy	23.1	tDCS	L dlPFC	Excitatory
Era et al. (2021)	32	50.0	Healthy	22.2	TMS	L dlPFC L M1	Inhibitory
Heinz et al. (2020)	12	33.3	Other patients	59	tDCS	L TC/Insula	Excitatory
Iseger, Arns, et al. (2020)	15	66.7	Psychiatric patients	32.0	TMS	L dfPFC	Excitatory
Ottaviani et al. (2018)	37	67.6	Healthy	26.8	tDCS	L TC/Insula	Excitatory
Poppa et al. (2020)	24	58.3	Healthy	25.9	TMS	R TC/Insula	Excitatory Inhibitory
Pulopulos et al. (2020)	75	100	healthy	21.1	TMS	L dlPFC	Excitatory
Remue et al. (2016)	19	100	Healthy	21.8	TMS	L dlPFC R dlPFC	Excitatory
Valenzuela et al. (2019)	8	00.0	Healthy	20.0	tDCS	L M1	Excitatory

Abbreviations: dlPFC, dorsolateral prefrontal cortex; L, left; R, right; TC, temporal cortex; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

[a]Not included as a moderator.

3.4.4 | Meta-analytic results

The analysis from 28 effect sizes from a total of 10 studies ($N = 382$) yielded significant associations between NIBS and changes in RMSSD, $g = 0.34$, $t(6.3) = 5.52$, $p = .001$, 95% CI [0.19; 0.49] (Figure 5). Significant heterogeneity was shown by the Q statistics, $Q(27) = 142.13$, $p < .001$; $\tau^2 = 0.00$; $\omega^2 = 0.04$. Considering that NIBS technique and brain areas are mandatorily included in our model, model selection using Akaike weights identified a model with the moderators NIBS technique, brain area, and study design as the most likely model (see Table 10). A subsequent moderator analysis revealed a significant effect of brain area, $F(1, 2.36) = 27.5$, $p = .023$, on effect size. Thus, trials targeting the dlPFC produced larger effect sizes than trials targeting insular/temporal regions, $\beta = -0.314$, SE = 0.059.

4 | DISCUSSION

In a series of four meta-analyses, we systematically quantified the effects of NIBS (i.e., TMS and tDCS) on HR and different HRV metrics (HF-HRV, LF-HRV, RMSSD). As such, we demonstrated both TMS and tDCS to effectively alter HR and HRV with small to medium effect sizes. We further found that trials produced effects of different magnitude depending on the brain site targeted by NIBS. The objective of this study was

Task	Time point of stimulation	Time point of measurement	Stimulation duration (s)	Sessions	Design	ROB2
No task	Long term	After completion of treatment course	1800	Multiple	Between	High risk
Emotional	During measurement and resting, during measurement and during task, before measurement and during task	During stimulation and resting, during stimulation and during task, after stimulation and after task	900	Single	Between	High risk
No task	During measurement and resting, before measurement and resting	During stimulation and resting, after stimulation and resting	1200, 1800	Single	Within	High risk
Cognitive	Before measurement and resting	After stimulation and after task	1500	Single	Between	High risk
Emotional Cognitive	Before measurement and resting	After stimulation and during task	20	Single	Within	High risk
Physical	Before measurement and resting	After stimulation and resting (pretask), after stimulation and after task	1200	Single	Within	Some concerns
No task	During measurement and resting	During stimulation and resting	190	Multiple	Within	High risk
Emotional	During measurement and during task	During stimulation and during task	900	Single	Within	High risk
Other No task	Before measurement and resting	After stimulation and resting, after stimulation and during task	160, 40	Single	Within	High risk
Emotional	Before measurement and resting, during measurement and resting	During stimulation and resting, after stimulation and resting, after stimulation and during task, after stimulation and after task	560	Single	Between	High risk
Emotional	Before measurement and resting	After stimulation and during task, after stimulation and after task	560	Single	Within	High risk
No task	Before measurement and resting	After stimulation and resting	1200	Single	Within	High risk

to investigate whether NIBS may serve as a viable method to explore the mechanisms underlying the neural regulation of the ANS and thus to test existing theories. To this end, we additionally sought to identify predictors such as NIBS technique and stimulated brain area, as well as other predictors related to the study design, experimental procedure, stimulation parameters, subjects, and study quality that had a significant impact on the observed effects. In contrast to the previous research by Schestatsky et al. (2013) and Makovac et al. (2017), we only included sham-controlled studies and further pursued a different meta-analytic approach that allowed us the consideration of multiple, statistically dependent effect sizes per study by applying robust variance estimation. As sham stimulation allows controlling for placebo effects (Dissanayaka et al., 2018), the integration of only sham-controlled trials ensures that the effect sizes analyzed are primarily based on cortical modulation by NIBS and not placebo effects. The analysis of multiple effect sizes per study has additional advantages such as a gain in information that may be lost in univariate approaches (see Jackson et al., 2011; Riley et al., 2017). Thus, the additional data obtained this way enabled us to perform a respective meta-analysis for different cardiovascular measures without having to pool them as in previous works. The results of our random-effects meta-regression analyses show that both TMS and tDCS are capable of modulating HR and several metrics of HRV, as both techniques exerted rather small to medium but

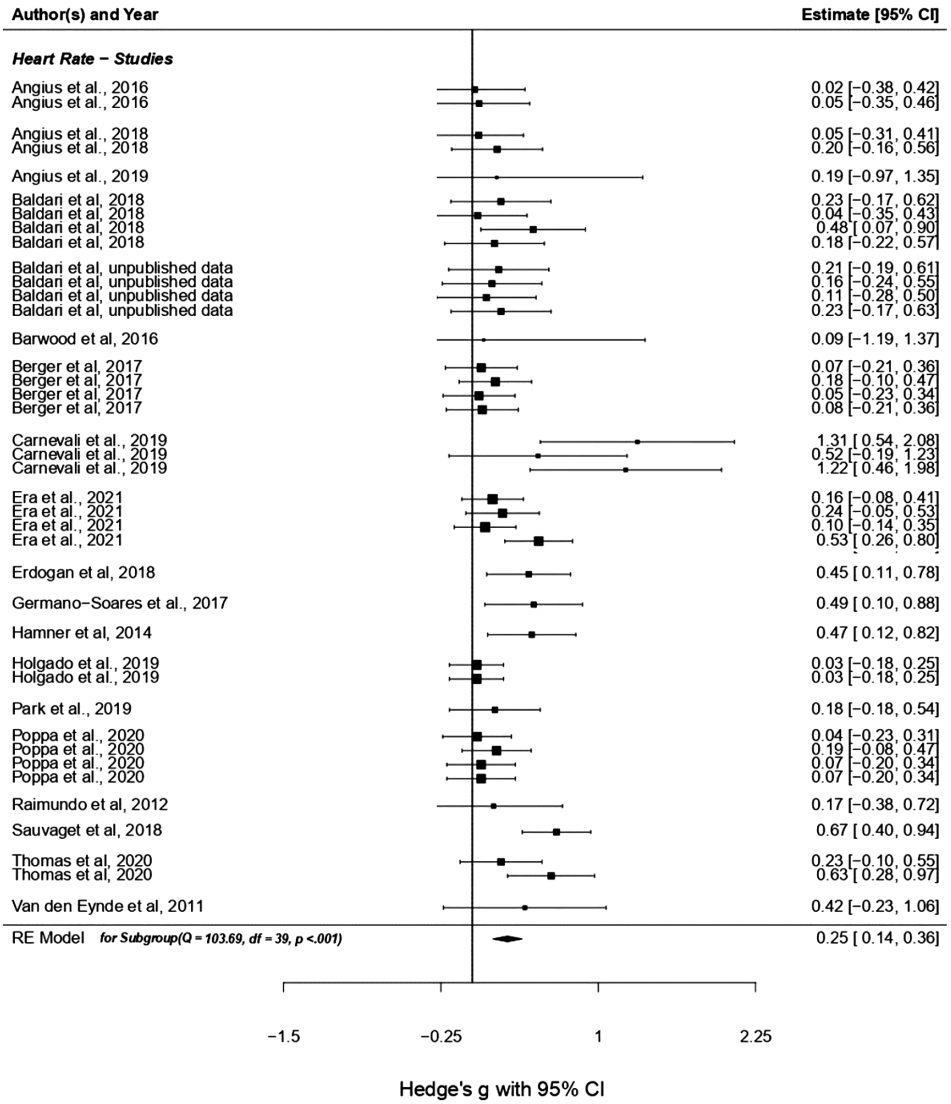

FIGURE 2 Forest plot for meta-analysis on NIBS effects on heart rate

TABLE 7 Estimates from meta-regression moderator analysis of HR studies

Moderator	Estimate	*t*	SE	*df*	95 % Confidence interval		*F*	*df* num	*df* den	*p*
					Lower	Upper				
Intercept	0.388	3.08	0.126	4.54	0.054	0.723				.03*
Brain area							2.11	2	1.85	.33
M1	−0.167	−1.43	0.12	2.18	−0.630	0.295				.27
TC/Insula	−0.267	−2.50	0.11	2.01	−0.723	0.190				.12
NIBS							0.05	1	5.48	.82
TMS	−0.032	−0.23	0.14	5.48	−0.378	0.314				.82

Abbreviations: M1, primary motor cortex; NIBS, noninvasive brain stimulation; TC, temporal cortex; TMS, transcranial magnetic stimulation.
*$p < .05$.

statistically relevant effects. These results are in line with the previous findings from Schestatsky et al. (2013) and Makovac et al. (2017).

We further tried to identify different factors related to study design, experimental procedure, study quality, stimulation parameters, and subjects that significantly influence the magnitude of

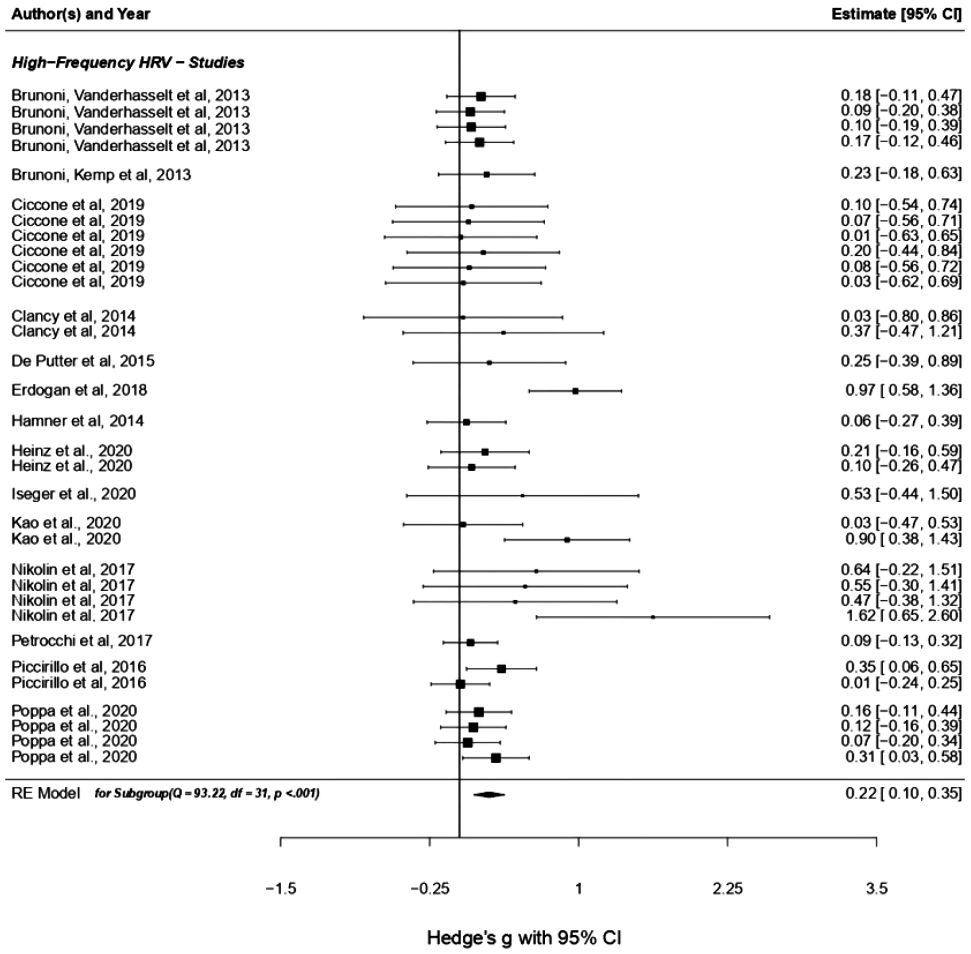

FIGURE 3 Forest plot for meta-analysis on the effects of NIBS on HF-HRV

TABLE 8 Estimates from meta-regression moderator analysis of HF-HRV studies

					95 % Confidence interval					
Moderator	**Estimate**	***t***	**SE**	***df***	**Lower**	**Upper**	***F***	***df* num**	***df* den**	***p***
Intercept	0.817	4.03	0.202	4.27	0.267	1.370				.013*
Brain area							6.46	2	3.83	.059
M1	0.116	0.72	0.161	2.97	−0.401	0.634				.524
TC/Insula	−0.337	−3.85	0.087	7.93	−0.538	−0.135				.004*
NIBS							5.23	1	3.79	.087
TMS	−0.279	−2.29	0.122	3.79	−0.626	0.067				.087
Duration	−0.0003	−2.79	<0.001	3.35	−0.0007	0.0001				.061

Abbreviations: M1, primary motor cortex; NIBS, noninvasive brain stimulation; TC, temporal cortex; TMS, transcranial magnetic stimulation.
*$p < .05$.

the effects of NIBS on HR and HRV. In a first step, we performed a model selection based on Akaike weights to select from all possible predictors those that form the most likely and parsimonious model. Based on our research goal to investigate whether rTMS and tDCS are appropriate tools to explore the neuronal and neuroanatomical structures of ANS regulation, respectively, brain area and NIBS technique were mandatorily included as predictors in each of the four models. The model selection process showed that the addition of only very few predictors in isolated models led to an increase of respective model likelihood. Hence, no additional predictor enhanced respective model likelihood in the analyses concerning HR and LF-HRV. While inclusion of stimulation duration produced the most likely HF-HRV model, adding study design as a predictor variable in the meta-regression resulted in the model with the highest

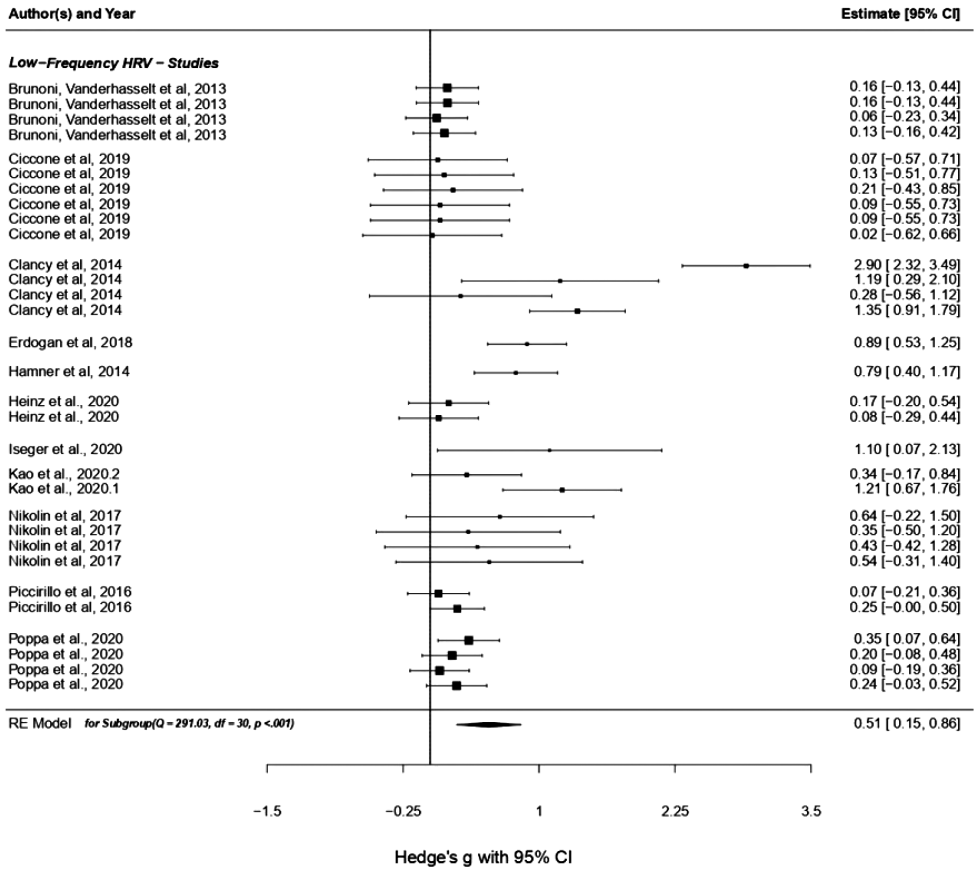

FIGURE 4 Forest plot for meta-analysis on the effects of NIBS on LF-HRV

TABLE 9 Estimates from meta-regression moderator analysis of LF-HRV studies

Moderator	Estimate	*t*	SE	*df*	95 % Confidence interval		*F*	*df* num	*df* den	*p*
					Lower	Upper				
Intercept	0.382	1.62	0.235	1.91	−0.677	1.440				.252
Brain area							5.57	2	3.58	.079
M1	0.827	2.13	0.388	3.56	−0.306	1.960				.109
TC/Insula	−0.294	−1.26	0.232	4.41	−0.915	0.327				.268
NIBS							0.92	1	1.96	.439
TMS	0.201	0.96	0.210	1.96	−0.716	1.119				.439

Abbreviations: M1, primary motor cortex; NIBS, noninvasive brain stimulation; TC, temporal cortex; TMS, transcranial magnetic stimulation.

likelihood in the analysis of the RMSSD trials. In a second step, we performed moderator analyses using the identified meta-regression models to examine whether the included predictor variables were significant moderators and thus explained heterogeneity between the respective trials.

In these analyses, we found the effect of the brain area targeted by NIBS to be different for specific cardiovascular measures. While there was no evidence that stimulation of distinct brain regions affects HR differently, region-specific differences in NIBS effects were found for the individual HRV measures. In line with the results from Makovac et al. (2017), NIBS produced the largest effects on both measures of vmHRV (i.e., HF-HRV and RMSSD) when applied over the dlPFC. These results are consistent with current theories of neural regulation of autonomic cardiac control (e.g., Porges, 2007; Thayer et al., 2009). In particular, the neurovisceral integration model (Thayer et al., 2009), as well as the frontal-vagal network theory of major depressive disorder (Iseger, van Bueren, et al., 2020), ascribe a prominent role to the (dorsolateral) prefrontal cortex in this regard. According to both theories, increased activity in the PFC is associated with more effective top-down control over emotion and self-regulatory processing and simultaneously leads to the inhibition of subcortical networks. This eventually leads to augmented vagal

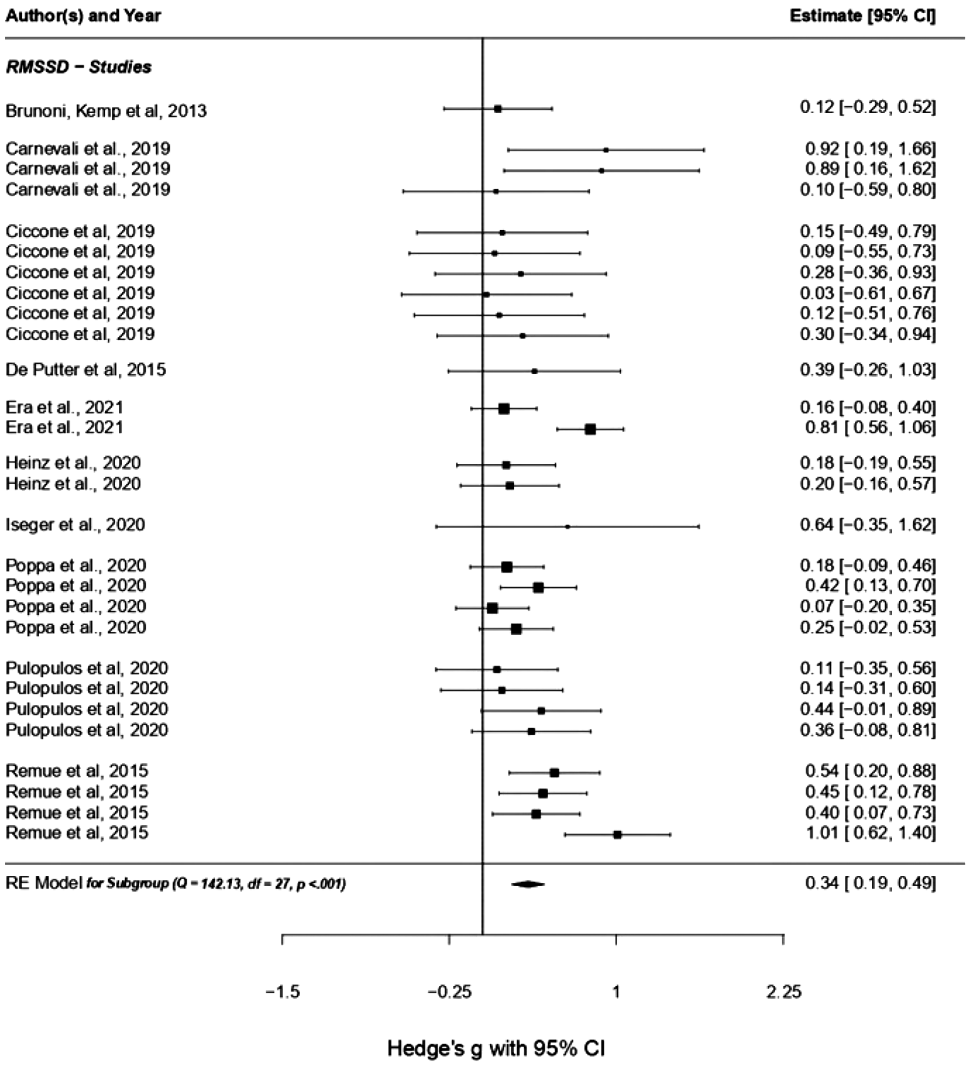

FIGURE 5 Forest plot for meta-analysis on the effects of NIBS on RMSSD

TABLE 10 Estimates from meta-regression moderator analysis of RMSSD studies

Moderator	Estimate	*t*	SE	*df*	95 % Confidence interval		*F*	df num	df den	*p*
					Lower	Upper				
Intercept	0.297	3.11	0.110	3.11	0.045	0.640				.071
Brain area							27.5	1	2.36	.023*
TC/insula	−0.314	−5.24	0.059	2.36	−0.538	−0.090				.023*
NIBS							0.01	1	2.25	.913
TMS	0.008	0.12	0.068	2.25	−0.257	0.274				.913
Design							7.91	1	2.67	.076
Within	0.219	2.81	0.078	2.67	−0.047	0.485				.076

Abbreviations: NIBS, noninvasive brain stimulation; TC, temporal cortex; TMS, transcranial magnetic stimulation.
*$p < .05$.

activity, which is reflected by increased levels in the vmHRV. These assumptions have already been supported by a variety of correlative results at brain imaging, psychophysiological, and behavioral levels alike. Thus, high vmHRV is associated with higher self- and emotion regulation capacity (Laborde et al., 2018; Thayer et al., 2009) as well as higher prefrontal activity (Beissner et al., 2013; Thayer

et al., 2012). Conversely, individuals with low vmHRV, for instance, exhibit deficient emotional processing (e.g., Steinfurth et al., 2018) as well as altered physiological responses to environmental demands (Brosschot et al., 2017), and have a higher risk of depression (Kemp & Quintana, 2013), which is characterized by disturbed prefrontal activity (Koenigs & Grafman, 2009).

The insula as another key node within the neurovisceral integration model as well as further brain areas located in the temporal lobe such as the hippocampus have also been associated with the regulation of the ANS. Along with numerous neuroimaging data (e.g., Ansakorpi et al., 2004; Bär et al., 2016; Marins et al., 2016; Nagai et al., 2010), studies in animals and patients with temporal lobe epilepsy provided significant findings in this regard. In particular, invasive electrical stimulation of the insular cortex or the hippocampus (Ruit & Neafsey, 1988; Sanchez-Larsen et al., 2021), as well as resection of these structures or even the entire temporal lobe (de Morree et al., 2016; Dericioglu et al., 2013), have been shown to induce substantial changes in cardiovascular function. The insular cortex appears to contribute to autonomic control in a highly complex manner, much of which is still unclear. As such, electrical stimulation of different subdivisions of the anterior and posterior portions of the insula in both humans and animals have been demonstrated to provoke different cardiovascular responses (e.g., Chouchou et al., 2019 Oppenheimer et al., 1992; Yasui et al., 1991). While these findings suggest a pivotal impact of temporal structures on cardiovascular regulation, in the presented analyses of all cardiovascular measures, we found trials in which NIBS was applied to temporal regions to yield smaller effects compared to those where other brain regions were targeted. A relatively simple possible explanation for this arises from a look at the stimulation parameters as well as the technical and physical properties of the stimulation methods used. While there are well-studied alternatives to neuronavigation for localization of the dlPFC and M1 (e.g., Holmes & Tamè, 2019; Seibt et al., 2015; Trapp et al., 2020), for instance, there are hardly any for other brain regions, including the insula. Not surprisingly, we observed in our analyses that the predominant reference localizing the insular cortex was the 10-20 EEG system, which is generally considered inadequate for finer grained positioning as well as for accounting for interindividual anatomical differences (Herwig et al., 2003, Rich & Gillick, 2019; Silva et al., 2021). Another challenge in targeting the insula, hippocampus, and deeper brain areas in general is their neuroanatomical location. Many of today's standard TMS and tDCS devices, which were also largely used in the studies reviewed in this article, can reach deeper regions only at the expense of stimulation intensity or focality (Deng et al., 2013; Foerster et al., 2018; Thair et al., 2017). Given these methodological and technical limitations, it seems very likely that the application of NIBS over the temporal cortex resulted in widespread untargeted stimulation of the target areas. This rather uncontrolled stimulation of temporal structures involved in autonomic control, such as the functional subdivisions of the insula, may have resulted in highly inconsistent cardiovascular responses in the respective trials. Recent technical developments in the field of NIBS such as high-definition tDCS (HD-tDCS) or the double cone (DC) coil and the H-coil in TMS have enabled more focal stimulation of deeper cortical regions (Datta et al., 2009; Edwards et al., 2013; Kuo et al., 2013; Lu & Ueno, 2017; Schecklmann et al., 2020). As these devices have already demonstrated their feasibility and efficacy, particularly in the clinical setting (Kreuzer et al., 2015), their utility in investigating the contribution of deeper cortex regions such as the insular or cingulate cortex and their respective subregions to autonomic cardiac control should be explored in future studies. Furthermore, recent studies have shown that not only the depth of a particular cortical region but also its thickness may influence the outcome of NIBS interventions. As such, the cortical thickness of regions such as the prefrontal (Bulubas et al., 2019; Filmer et al., 2019), cingulate (Baeken et al., 2021; Boes et al., 2018), and motor cortex (Conde et al., 2012) was found to predict the efficacy of NIBS targeting these areas. In addition, it has been reported that cortical thickness of prefrontal and insular regions positively correlates with the measures of resting HRV (Koenig et al., 2021). As cortical thickness seems to be a factor contributing to the intra- and interindividual variability in the efficacy of NIBS, it appears interesting to examine whether resting HRV, as a potential proxy for prefrontal or insular cortical thickness, can be utilized in predicting the magnitude of NIBS-induced effects on HR and HRV.

The third brain area that has been frequently targeted in the studies reviewed here is the M1. The motor cortex has played only a minor role in many of the current theories and models of neural control of the ANS so far (e.g., Benarroch, 1993; Thayer et al., 2009). In our analyses, however, there were no significant differences in NIBS-induced changes in HR, HF-HRV, or RMSSD between stimulation of the M1 and that of the dlPFC or temporal cortex. Regarding LF-HRV, stimulation of M1 even produced the largest effects. Although links between motor cortex activity and ANS control, including cardiovascular regulation (Critchley et al., 2003, Williamson et al., 2006), have been demonstrated in both animal models and human studies (Levinthal & Strick, 2012; Masuki & Nose, 2009; Silber et al., 2000), the exact relationships remain unclear. The fact that stimulation of M1 yielded the largest effects on changing LF-HRV may reflect an involvement of the motor cortex in the regulation of the baroreflex and is thus consistent with previous results indicating similar relationships (e.g., Goodwin et al., 1972; Raven et al., 2002; Smith et al., 2006). Future studies utilizing NIBS may serve to elucidate the contribution of the motor cortex on cardiovascular regulation.

In addition to brain area, we identified few other factors to act as moderators of the effects of NIBS on cardiovascular measures. Only the two factors' stimulation duration and NIBS technique were found to exert effects on the stimulation-induced changes in HF-HRV. Our analyses revealed slightly decreasing effect sizes with increasing duration of the stimulation protocols. It has already been pointed out several times that a longer stimulation duration does not necessarily equate to greater effects and that after a certain duration the effects can even reverse (Hassanzahraee et al., 2020; Thair et al., 2017). Moreover, in the field of TMS, new shorter rTMS protocols such as theta burst stimulation (TBS) have been shown to be more effective than conventional longer rTMS protocols in many

trials (Cárdenas-Morales et al., 2010; Di Lazzaro et al., 2011; Iezzi et al., 2011). However, as these results were primarily obtained from motor cortex excitability and associated measures of movement-evoked potentials (MEP), it remains to be determined whether these mechanisms also hold for the modulation of cardiovascular or autonomic measures in general.

Contrary to the analyses of the other cardiovascular measures and to results from cognitive neuroscience, where rTMS produced comparable or greater effects than tDCS in modulating cognitive processes (e.g., Begemann et al., 2020; Brunoni & Vanderhasselt, 2014) here, we found tendencies of rTMS being less effective than tDCS in altering HF-HRV. This may be explained by more frequent and adverse side effects that accompany rTMS, such as pain, headaches, or anxiety (Matsumoto & Ugawa, 2016). While these side effects may not directly influence cognitive outcomes assessed after stimulation, they have a lasting impact on ANS activity and have already been found to influence the effects of NIBS on cardiovascular measures (Poppa et al., 2020). Although this explanatory approach should be taken cautiously, we strongly recommend that the assessment of subjective states and sensations such as anxiety, pain, or stress before, during, and after stimulation and their inclusion in statistical analyses should become standard practice in future studies using NIBS.

While optimal conditions as well as potential confounders largely remain unknown, we suggest based on our findings that TMS and tDCS are useful methods to modify cardiovascular measures and to examine different brain areas for their involvement in ANS regulation. Despite a large number of studies that report correlations between cardiovascular and (neuro-)physiological or behavioral measures, there are currently few attempts to experimentally manipulate HR or HRV with the aim of investigating causal relations between domains. Based on our findings, we consider both TMS and tDCS to be highly promising methods for this endeavor, as both techniques not only have the potential to alter HRV, but have also demonstrated their combinability with behavioral and brain imaging methods in previous research (Bergmann et al., 2016). Combination of different methodological approaches will allow to systematically investigating whether NIBS-induced changes in HR and HRV can be causally related to the changes in activity in the stimulated cortical areas or in the broader neural networks connected to those areas. This may further help to verify or clarify existing theories about the involvement of specific brain regions in CVC and, on the other hand, shed light on the role of brain regions that have so far been less in the focus of interest. Since recent attempts in the field of cognitive neuroscience combining NIBS with the use of EEG (Ozdemir et al., 2020) and fMRI (De Pisapia et al., 2019; Hallam et al., 2016) have already proven fruitful, we see great potential in this approach to gather further knowledge about the structure, functions, and outcome measures of the CAN.

Further research efforts in this direction could provide important insights and benefits in areas such as cognitive and affective neuroscience or in therapeutic applications, as the ANS does not function independently of the CNS but is closely related to both cognitive and emotional brain functions (Critchley et al., 2013; Hugdahl, 1996). Thus, a variety of mental or affective disorders have been demonstrated to be accompanied by autonomic imbalances (Gillie & Thayer, 2014; Mulcahy et al., 2019). Conversely, diseases of autonomic control of the heart, such as arrhythmia or hypertension, seem to be associated with functional and structural changes at the cortical level as well as with cognitive deficits (Carnevale et al., 2020; Naumczyk et al., 2017; Silva et al., 2019). While, to our knowledge, there have been no attempts to employ NIBS to intervene in cardiovascular diseases at a cortical level, there are initial studies examining whether and how NIBS treatment affects cardiovascular parameters in mental disorders (e.g., Brunoni, Kemp et al., 2013; Iseger, van Bueren, et al., 2020). While neither a tDCS (Brunoni, Kemp et al., 2013) nor a TMS (Iseger, van Bueren, et al., 2020) intervention resulted in chronic changes in HRV or HR of depressed patients, Iseger, van Bueren, et al. (2020) found acute effects during single TMS sessions.

In addition, it should be noted that while our analyses found no evidence of publication bias in our sample, we identified many studies that were at high risk for bias according to RoB2 (Sterne et al., 2019). The high risk of bias in the present sample arises primarily from the largely inadequate reporting of the randomization process, making it unclear, for instance, what method was used for randomization and whether the allocation sequence was concealed to the experimenters. Recent findings have demonstrated that unclear or inadequate randomization processes may lead to bias in the form of inflated estimates of intervention effects. However, this has been shown to hold primarily for subjective outcome measures rather than objective measures such as HR or HRV (Page et al., 2016). Further concerns arise from the fact that the researchers who delivered the NIBS interventions or assessed study outcomes were not blinded or that reporting was unclear in this regard. Given the nature of NIBS, conducting double blinding may require additional effort or personnel, for instance in TMS interventions that require assessment of resting motor threshold in addition to the intervention itself, regardless of whether the intervention is real or sham. However, to minimize bias, we encourage researchers to find and adhere to feasible double-blind methods when using NIBS to study autonomic cardiac regulation as well as other outcome measures. Given the lack of reports of predefined analysis plans in the present sample, we further recommend that in future studies, data should be analyzed in a blinded fashion according to predefined analysis plans reported in the manuscript or even preregistered with journals or open-access repositories. Together with conducting multicenter studies, this would help to prevent selective reporting (e.g., reporting only those cardiovascular measures that were affected by NIBS).

In sum, we believe that NIBS can contribute to a better understanding of the relationships between cognitive, emotional, and autonomic processes on a cortical level. NIBS may thus represent a promising tool to advance our knowledge of ANS dysfunction, such as in cardiac arrhythmias, hypertension, or mental disorders, by studying cortical regulation of ANS functions in clinical populations, and to serve as a therapeutic tool at the CNS level in future.

5 | LIMITATIONS AND CONCLUSION

Despite its strengths, certain limitations of this meta-analysis should be acknowledged. While we defined a large totality of potential influencing factors, our model selection approach identified only few of them as influential moderators. Given the small number of studies with many of them being underpowered due to relatively small sample sizes (see Tables 3–6), the power to identify potential moderators was limited. We further did not include stimulation parameters specific to the respective method such as TMS coil design or size of tDCS electrodes as potential moderators. Including these factors in our chosen approach of analyzing TMS and tDCS studies together would not have been methodologically appropriate, in our view. Whether certain technique specific parameters may be more efficient in altering cardiovascular measures than others should be object of future research. Moreover, we decided to only use absolute values of effect sizes for our analyses. This can lead to changes in the sampling distribution which may result in misleading results when using conventional meta-analytic approaches (Morrissey, 2016). Therefore, secondary analyses of all models for the overall effect size and all Egger's sandwich tests were performed using the recommended "analyze-then-transform" approach (Morrissey, 2016), which were comparable to the results of the primary analyses. The results can be found in the supplementary material. We further considered only quantitative English language articles. However, our analyses found no evidence that our results were influenced by publication bias.

In summary, the results of our meta-regression indicate that both TMS and tDCS have the potential to exert a modulatory effect on HR and HRV. Hence, we conclude that their use, particularly in combination with brain imaging techniques, holds great potential to investigate the underlying mechanisms of neural regulation of the ANS. However, given the shortage of detected moderators in our models, we believe it is imperative to replicate previous findings and conduct well-designed future studies to identify parameters related to study design, stimulation, and study population that influence the magnitude of stimulation effects on HR and HRV. Given the high risk of bias in many of the studies reviewed, the reported results should be interpreted with caution. To reduce potential sources of bias in future studies, we recommend that their design and conduct be guided by the Cochrane risk of bias guidelines.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

AUTHOR CONTRIBUTIONS

All authors approved the submission of the final version of this paper. *Conceptualization*, M.S., S.L., and M.R.; *Methodology*, M.S., S.L., and S.H.; *Validation*, M.S. and S.L., *Formal Analysis*, M.S.; *Data Curation*, M.S. and S.L.; *Writing – Original Draft*, M.S.; *Writing – Reviewing & Editing*, M.S., S.L., S.H., and M.R.; *Visualization*, M.S.; *Supervision*, S.L., S.H., and M.R.; *Project Administration*, M.S., S.L., and M.R.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with respect to their authorship or the publication of this article.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.25062.

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