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Non-Invasive Brain Stimulation to Investigate Language Production in Healthy Speakers: A Meta-Analysis

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Non-invasive brain stimulation (NIBS) has become a common method to study the interrelations between the brain and language functioning. This meta-analysis examined the efficacy of transcranial magnetic stimulation (TMS) and direct current stimulation (tDCS) in the study of language production in healthy volunteers. Forty-five effect sizes from 30 studies which investigated the effects of NIBS on picture naming or verbal fluency in healthy participants were meta-analysed. Further sub-analyses investigated potential influences of stimulation type, control, target site, task, online vs. offline application, and current density of the target electrode. Random effects modelling showed a small, but reliable effect of NIBS on language production. Subsequent analyses indicated larger weighted mean effect sizes for TMS as compared to tDCS studies. No statistical differences for the other sub-analyses were observed. We conclude that NIBS is a useful method for neuroscientific studies on language production in healthy volunteers.

Keywords: language production, meta-analysis, picture naming, verbal fluency, TMS, tDCS

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Introduction

Transcranial magnetic (TMS) and direct current stimulation (tDCS) are non-invasive brain stimulation (NIBS) techniques that are increasingly used to investigate causal relationships between language functions and their underlying neuronal processes. The aim of this combined review and meta-analysis is to examine the efficacy and reliability of NIBS as an intervention method to study the neural correlates of language production in healthy volunteers. Prior meta-analyses on the effects of transcranial direct current stimulation (tDCS) on verbal fluency and picture naming have provided diverging results. Both Horvath, Forte, and Carter (2015) and Price, McAdams, Grossman, and Hamilton (2015) analysed performance changes in semantic production and word learning tasks, with the first finding no effect, but the latter reporting a reliable modulation of task performance. Furthermore, Westwood and Romani (2017) found no effect of tDCS on language production performance across production and reading tasks. Our present review offers an overview and meta-analysis of studies which measured changes in verbal fluency and picture-naming performance during or following the administration of tDCS or transcranial magnetic stimulation (TMS). Furthermore, by differentiating between different experimental parameters, we aim to provide a more detailed picture with respect to the usefulness of NIBS studies that investigate language production in healthy volunteers.

Picture naming (i.e., the production of a noun or verb in response to a visually presented stimulus) is the most direct way to measure language production performance. Cortical activity during this task has been located in a large left frontotemporal network stretching from the interior frontal to posterior superior temporal and inferior parietal regions (Indefrey, 2011; Indefrey & Levelt, 2004). Using TMS, which applies an ultra-short electromagnetic pulse that creates an electric current in superficial cortical nerve tissue, an engagement of the posterior superior temporal gyrus (pSTG), middle temporal gyrus (MTG), anterior temporal lobe (ATL), and inferior frontal gyrus (IFG) has been demonstrated (Acheson, Hamidi, Binder, & Postle, 2011; Mottaghy et al., 1999; Pobric, Jefferies, & Lambon Ralph, 2007, 2010, Schuhmann, Schiller, Goebel, & Sack, 2009, 2012; Shinshi et al., 2015; Sparing et al., 2001; Töpper, Mottaghy, Brügmann, Noth, & Huber, 1998; Wheat et al., 2013). Furthermore, cortical

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excitability can be modulated by applying a constant weak electric current between two electrodes affixed on the scalp. Although the vast majority of the electric field is shunted, a small yet significant portion of the field reaches the superficial layers of the cortex (Nitsche et al., 2008). Research on the human motor cortex has shown that anodal tDCS increases spontaneous neural firing and cortical excitability, while cathodal tDCS reduced spontaneous neural firing and lowered cortical excitability (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). Its potential to modulate underlying cortical tissue together with the facts that tDCS is not associated with serious adverse advents and allows for better (double) blinding procedures as compared to TMS has contributed to its increased use in cognitive neuroscience. Indeed, a number of studies have reported significant effects from applying anodal tDCS over the left STG and dorsolateral prefrontal cortex (DLPFC) on object and action naming (Fertonani, Brambilla, Cotelli, & Miniussi, 2014; Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). Interestingly, NIBS typically only affects naming latencies, but not error rates, in picture naming tasks.

Next to the classic picture naming tasks, a number of studies have also investigated the effects of tDCS and TMS on naming latencies in the semantic blocking and picture-word interference paradigm. In semantic blocking tasks, naming latencies are compared between semantically homogeneous (i.e., containing words from the same semantic category) and heterogeneous blocks (i.e., semantically unrelated words). Retrieving and producing semantically related words in a row typically results in longer naming latencies compared to producing semantically unrelated words. This semantic interference (SI) effect is taken as evidence for competitive selection of target responses (e.g., Belke, Meyer, & Damian, 2005; Damian, Vigliocco, & Levelt, 2001; Kroll & Stewart, 1994) and has been localised predominantly in the left temporal cortex (de Zubicaray, Johnson, Howard, & McMahon, 2014; Indefrey, 2011). Confirming this, studies applying tDCS (Meinzer, Yetim, McMahon, & de Zubicaray, 2016; Pisoni, Papagno, & Cattaneo, 2012) or TMS (Krieger-Redwood & Jefferies, 2014) before or during semantic blocking tasks reported an involvement of pSTG, but not IFG. These studies provide first evidence that processes involving lexical selection and retrieval can be targeted using NIBS. However, it should be kept in mind that behavioral effects were numerically small (see also Westwood et al., 2017, Experiment 2, for statistical null effects of tDCS across the left IFG in a semantic blocking task).

The picture-word interference (PWI) paradigm allows for the chronometric investigation of speech production processes on the timescale of tens of milliseconds (e.g., Damian & Martin, 1999; Schriefers, Meyer, & Levelt, 1990). Participants are asked to name pictures while ignoring a visually or auditorily presented distractor word, the relatedness of which to the target word is systematically varied. Typically, a semantically related distractor (e.g., *"cow"* when the target word is *"sheep"*) increases naming latencies compared to an unrelated distractor, while a phonologically related distractor (e.g., *"sheet"*) speeds up naming latencies. Varying the onset of the distractor relative to picture presentation (stimulus-onset asynchrony, SOA) enables researchers to examine the time course of speech planning with respect to the individual representational levels involved. Recall that lexical-semantic processing has been associated with the left MTG, while phonological processing has been located in the left STG (Indefrey, 2011; Indefrey & Levelt, 2004). In line with this, Henseler, Mädebach, Kotz, & Jescheniak (2014) reported a decrease of associative facilitation (i.e., when the distractor is associatively related vs. unrelated to the target word, e.g. *"boat"* and *"port"*) under MTG as opposed to IFG and sham stimulation (anodal tDCS). Furthermore, Pisoni, Cerciello, Cattaneo, & Papagno (2017) found reduced phonological facilitation following anodal tDCS to the STG, but no such effect when IFG was stimulated.

Finally, a number of studies also measured performance changes in response to TMS or tDCS in verbal fluency tasks (see also Horvath et al., 2015; Price et al., 2015). In these tasks, participants are asked to produce as many words as possible from a given semantic category (i.e., semantic fluency) or starting with a given letter (i.e., letter fluency) within a time constraint. High fluency scores reflect unimpaired speech production on the semantic or phonological level, respectively. Neuroimaging evidence has shown that both tasks involve left frontal, temporal, and parietal regions, with dissociable activity in the MTG in the semantic and in the IFG in the letter fluency task (Birn et al., 2010). Previous studies investigating the effect of tDCS on verbal fluency have provided ambiguous

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results. While some studies report increased verbal fluency during or after tDCS (IFG: Cattaneo, Pisoni, & Papagno, 2011; Iyer et al., 2005; Penolazzi, Pastore, & Mondini, 2013; Pisoni, Mattavelli, et al., 2017; DLPFC: Vannorsdall et al., 2012), others did not obtain such an effect (IFG: Ehlis, Haeussinger, Gastel, Fallgatter, & Plewnia, 2016; Vannorsdall et al., 2016; DLPFC: Cerruti & Schlaug, 2009).

To date, there are still many unknowns about the influence of different stimulation parameters on the behavioural (language production) effect induced by NIBS. In order to quantify the overall effect of NIBS observed across studies and to examine individual subsets contrasting different experimental parameters, we performed a meta-analysis evaluating the behavioural performance changes during language production tasks in healthy participants. With respect to language production, rather small effect sizes of tDCS treatment for clinically relevant populations (Hartwigsen & Siebner, 2013) raise the question whether this method is a useful tool in altering language production in healthy speakers, and previous meta-analyses which investigated fewer studies are inconclusive (Horvath et al., 2015; Price et al., 2015; Westwood & Romani, 2017), as they analysed fewer studies and used diverging methods. Here, unlike these previous studies, we investigated the absolute effect sizes obtained by the application of tDCS or TMS. The direction of behavioural effects caused by NIBS (i.e., improving or disrupting performance) is difficult to predict. For instance, TMS across left temporal and inferior parietal regions has been shown to both enhance (Acheson et al., 2011; Mottaghy et al., 1999; Sparing et al., 2001; Töpper et al., 1998) and impede picture naming performance (Pobric et al., 2007, 2010; Schuhmann et al., 2012). Furthermore, the dissociation of performance improvement in response to anodal tDCS as opposed to performance decline in response to cathodal tDCS as documented for the motor cortex (Nitsche & Paulus, 2000) has been shown to be more complex for higher cognitive functions (Hill, Fitzgerald, & Hoy, 2016; Jacobson, Koslowsky, & Lavidor, 2012). For example, Fertonani et al. (2010) found (descriptive) interference in picture naming from cathodal tDCS in Experiment 1, but (descriptive) facilitation from cathodal tDCS in Experiment 2. Furthermore, a recent study reported significant facilitation from cathodal tDCS across the left pSTG in a lexical decision task (Brückner & Kammer, 2017). Given these inconsistent result patterns in both TMS and tDCS studies, we centred this meta-analysis on the question whether NIBS changes *overall* performance compared to a baseline condition, regardless of whether this change is positive or negative. Furthermore, to our knowledge, no meta-analysis has yet quantified the efficacy of TMS on inducing changes in language production in healthy speakers. Finally, by contrasting subsets of studies in regard to a number of methodological aspects (i.e., stimulation site, control condition, experimental tasks, online vs. offline stimulation, and current density of the target electrode), we intend to investigate more detailed aspects of applying NIBS in healthy speakers.

Methods

Study selection and analysis

To find eligible studies, we first conducted a literature search in PubMed, querying for the any combination of the search terms ("language") AND ("tDCS", "TMS", "transcranial direct current stimulation", OR "transcranial magnetic stimulation") published up until January 2018. Additionally, the reference lists of previous reviews and meta-analyses (Hartwigsen, 2015; Horvath et al., 2015; Monti et al., 2013; Price et al., 2015) were screened to avoid overlooking suitable studies. Figure 1 provides a flowchart of the different phases of the relevant literature search.

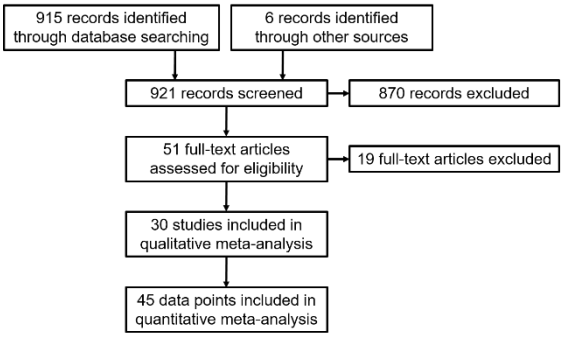

Figure 1. Flowchart of literature search for the meta-analysis.

Eligibility criteria were the following:

(1) A single session of tDCS or TMS was applied to the left hemisphere of the cerebral cortex in right-handed participants;

(2) Participants were adult healthy, young native speakers;

(3) The main dependent variable was either naming latency in a picture naming task or number of words generated in a verbal fluency

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task;

(4) The stimuli were either categories or letters (for the verbal fluency tasks), or pictures triggering single-word utterances (i.e., nouns or verbs, for picture-naming tasks). Studies using printed words as stimuli were omitted in order to avoid potential confounds with reading ability, as were studies that required the production of multi-word utterances or in which a mixture of verbal fluency and picture naming was used;

(5) All relevant data were provided either in the paper or by the authors upon request, or could be extracted from figures in the publication;

(5) The article was published in a peer-reviewed English-language journal;

(6) The study was approved by a medical ethical committee or review board.

Data synthesis and analysis

The literature search identified 30 eligible studies. Studies of which the full texts were screened, but which did not meet the inclusion criteria, are listed in Supplementary Table 1, along with a reason for their exclusion. For the eligible studies, the means, standard deviations, and sample sizes for all experimental and control conditions were collected (naming latencies for the picture naming tasks and number of words generated for the verbal fluency tasks). If this information was provided in graphs rather than tables, the relevant values were extracted using the software Plot Digitizer (http://plotdigitizer.sourceforge.net/). Additionally, if the reported data were not sufficient or inconsistent, the corresponding author of the paper in question was contacted and asked to provide this information. If an experiment reported several conditions (e.g., in terms of semantic category and naming cycle for semantic blocking tasks or in terms of different distractor conditions in PWI tasks), the reported values were averaged for the stimulation and the control condition in order to receive an estimate of overall effect of stimulation. All data points were coded in terms of their treatment (TMS vs. tDCS), the control condition (sham vs. no stimulation), the stimulated brain region (IFG, MTG, STG, DLPFC, IPL, or ATL), the task used (picture naming, semantic blocking, picture-word interference, or semantic fluency), the time of NIBS application (online vs. offline), and the current density of the target electrode.

For all reported comparisons (i.e., stimulation vs. control conditions) we calculated Hedges' *d* (Rosenberg, Adams, & Gurevitch, 2000). This is an adaptation of Hedges' *g* (Hedges & Olkin, 1985) – calculated as the difference between the mean of the experimental condition and the mean of the control condition, divided by the pooled standard deviation – which takes into account the often low sample sizes in previously published stimulation studies by multiplying the effect size with a small sample size correction. We were interested in the magnitude of the effect so we calculated the absolute effect size values. In order to avoid entering several data points from one experiment into the analysis, effect sizes originating from a single experiment were aggregated to yield a single measure per experiment. However, if several control conditions were tested which allowed for a more specific comparison of experimental variables (e.g., comparing cathodal and anodal stimulation, or different brain regions within one experiment), separate effect sizes per experiment were entered into the analysis.

We computed the cumulative effect size (i.e., the aggregated magnitude of the included studies' effect sizes, $\bar{E}$) and the 95% confidence intervals (CI) using a weighted average (Hedges & Olkin, 1985). All effect sizes were entered in a random effects model. As estimates of study heterogeneity, we report Q and I^2 values.

All effect size calculations and summary analyses were conducted using *MetaWin* (version 2.1, Rosenberg, Adams, & Gurevitch, 2000) and the *metafor* package (version 1.9-9, Viechtbauer, 2010) in *R* (version 3.3.3, R Core Team, 2017). Additional ANOVAs were run using the *ez* package (version 4.4.0, Lawrence, 2016).

Results

In total, 45 effect sizes originating from 30 studies including 655 healthy participants were analysed (Table 1). None of the studies reported any adverse events after applying stimulation. A significant effect of NIBS was found for behavioural performance ($Z = 5.214$, $p < .0001$), indicating that applying NIBS is capable of modulating speech production processes in healthy speakers. The overall weighted mean effect size for all included studies was 0.289 (95% CI: 0.181 – 0.398). The test for heterogeneity was not significant ($Q = 25.248$, $p = .990$), showing that the variance between studies was not larger than is to be expected when including random sample error. Rosenberg's fail-safe number for all studies was 274, implying that at least 274 studies publishing null effects would be required to invalidate the significant effect of NIBS on behavioural performance in

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Table 1
Overview of the studies included in the meta-analysis.

study	stimulation details*	target area**	task	*N*	mean age	sham?	behavioural effect of stimulation
(1) Acheson, Hamidi, Binder, & Postle (2011)	TMS, 10 Hz, 100 ms before picture onset, 100 % MT	MTG (−69, −39, −2)	picture naming	12	24.5 (*SD* = 4.2)	no	shorter naming latencies and speech duration following TMS
(2) Acheson, Hamidi, Binder, & Postle (2011)	TMS, 10 Hz, 100 ms before picture onset, 110 % MT	STG (−64, −38, −13)	picture naming	same as (1)		no	no effect
(3) Cappa, Sandrini, Rossini, Sosta, & Miniussi (2002)	TMS, 20 Hz, at picture onset, 90% MT	DLPFC (between F3 and F5)	picture naming (actions)	9	29 (range: 25-32)	yes	faster naming latencies compared to sham TMS to vertex
(4) Cappa, Sandrini, Rossini, Sosta, & Miniussi (2002)	TMS, 20 Hz, at picture onset, 90% MT	DLPFC (between F3 and F5)	picture naming (objects)	same as (3)		yes	no effect
(5) Cattaneo, Pisoni, & Papagno (2011)	tDCS, anodal, offline (20 min), 2 mA, rSO region as reference, CD: 0.057	IFG (between T3-Fz and F7-Cz)	verbal fluency (semantic and phonemic)	10	23.6 (*SD* = 3.2)	yes	higher fluency scores following tDCS
(6) Cerruti & Schlaug (2009)	tDCS, anodal and cathodal, online, 1 mA, rSO region as reference, CD: 0.061	DLPFC (F3)	verbal fluency (phonemic)	18	25.5 (*SD* = 2.6)	yes	no effect
(7) Chouinard, Whitwell, & Goodale (2009)	TMS, 10 Hz, 5 pulses at picture onset, 90% MT	LOC (−52, −62, −12) IFG (MNI not provided)	picture naming	12	26.5 (range: 21-29)	yes	higher naming latencies following TMS compared to sham TMS to PPC
(8) Ehlis, Haeussinger, Gastel, Fallgatter, & Plewnia (2016)	tDCS, anodal, offline (20 min), 1 mA, rSO region as reference, CD: 0.029	IFG (between C3, F3 and F7)	verbal fluency (semantic and phonemic)	23	32.1 (*SD* = 10.5)	yes	no effect
(9) Ehlis, Haeussinger, Gastel, Fallgatter, & Plewnia (2016)	tDCS, cathodal, offline (20 min), 1 mA, rSO region as reference, CD: 0.029	IFG (between C3, F3 and F7)	verbal fluency (semantic and phonemic)	23	24.3 (*SD* = 2.4)	yes	no effect
(10) Fertonani, Rosini, Cotelli, Rossini, & Miniussi (2010), Exp. 1	tDCS, anodal and cathodal, offline (8 min), 2 mA, right shoulder as reference, CD: 0.057	DLPFC (8 cm frontally and 6 cm laterally away from Cz)	picture naming	12	24.1 (*SD* = 3.7)	yes	overall no effect, when calculating difference scores to account for between-participant variability: faster

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							naming latencies following anodal tDCS, no effect of cathodal tDCS
(11) Fertonani, Rosini, Cotelli, Rossini, & Miniussi (2010), Exp. 2	tDCS, anodal and cathodal, offline (10 min), 2 mA, right shoulder as reference, CD: 0.057	DLPFC (8 cm frontally and 6 cm laterally away from Cz)	picture naming	12	21.8 (*SD* = 1.0)	yes	faster naming latencies following anodal tDCS, no effect of cathodal tDCS
(12) Fertonani, Brambilla, Cotelli, & Miniussi (2014)	tDCS, anodal, online and offline (10 min), 2 mA, right shoulder as reference, CD: 0.057	DLPFC (8 cm frontally and 6 cm laterally away from Cz)	picture naming	20	21.2 (*SD* = 0.9)	yes	faster naming latencies during and following anodal tDCS
(13) Henseler, Mädebach, Kotz, & Jescheniak (2014)	tDCS, anodal, online, 2 mA, rSO region as reference, CD: 0.08	IFG (−50, 15, 29) MTG (−56, −48, −2)	PWI (associative and semantic)	36	26.2 (*SD* = 3.0)	yes	no main effect of tDCS associative facilitation during IFG and sham tDCS, but not during MTG tDCS no effect of tDCS on semantic interference
(14) Krieger-Redwood & Jefferies (2014)	TMS, 1 Hz, offline, 10 min, 120 % MT	IFG (−45, 19, 18)	semantic blocking	16	20.8 (*SD* = 2.4)	no	no main effect of TMS reduced semantic facilitation in first cycle following TMS
(15) Krieger-Redwood & Jefferies (2014)	TMS, 1 Hz, offline, 10 min, 120 % MT	MTG (−54, −49, −2)	semantic blocking	same as (11)		no	no main effect of TMS reduced semantic facilitation in first cycle following TMS
(16) Meinzer et al. (2012)	tDCS, anodal, online, 1 mA, rSO region as reference, CD: 0.029	IFG (between T3-F3 and F7-C3 and midpoint between F7-F3)	verbal fluency (semantic)	20	26.7 (*SD* = 3.8)	yes	higher fluency scores during tDCS
(17) Meinzer, Yetim, McMahon, & de Zubicaray (2016)	tDCS, anodal, online, 1mA, rSO region as reference, CD: 0.029	IFG (between T3-Fz and F7-Cz) STG (−53, −46, −5)	semantic blocking	24	24.7 (*SD* = 4.6)	yes	no overall effect of tDCS reduced semantic interference during IFG tDCS in cycles 2 – 4 reduced semantic interference during MTG tDCS in cycles 2 – 6
(18) Mottaghy et al. (1999)	TMS, 20 Hz, offline (2s), 55% MSO	IFG (between F5 and	picture naming	16	28.1 (*SD* = 3.6)	yes	faster naming latencies immediately after STG TMS

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		F7) STG (Cp5)					no effect of IFG TMS
(19) Penolazzi, Pastore, & Mondini (2013)	tDCS, anodal, offline (20min), 2mA, varying reference positions, CD: 0.057	IFG (between T3-F3 and F7-C3)	verbal fluency (semantic)	90	21.6 (*SD* = 0.2)	yes	higher fluency scores following tDCS with rSO region as reference in second post-measurement (i.e., about 18min after stimulation)
(20) Pisoni, Papagno, & Cattaneo (2012), Exp. 1	tDCS, anodal, offline (20min), 2mA, rSO region as reference, CD: 0.057	STG (−53, −46, −5)	semantic blocking	12	22.4 (*SD* = 2.9)	yes	longer naming latencies following tDCS larger semantic interference following tDCS
(21) Pisoni, Papagno, & Cattaneo (2012), Exp. 2	tDCS, anodal, offline (20 min), 2 mA, rSO region as reference, CD: 0.057	IFG (between T3-Fz and F7-Cz)	semantic blocking	12	21.8 (*SD* = 2.1)	yes	shorter naming latencies following tDCS no effect on semantic interference
(22) Pisoni, Cerciello, Cattaneo, & Papagno (2017), Exp. 1	tDCS, anodal, offline (20 min), 2 mA, rSO region as reference, CD: 0.08	STG (CP5)	PWI (phonological)	12	22.0 (*SD* = 2.4)	yes	reduced phonological facilitation following tDCS
(23) Pisoni, Cerciello, Cattaneo, & Papagno (2017), Exp. 2	tDCS, anodal, offline (20 min), 2 mA, rSO region as reference, CD: 0.08	IFG (between Fz-T3 and Cz-F7)	PWI (phonological)	12	25.0 (*SD* = 3.5)	yes	no effect of tDCS on phonological effect overall, slower naming latencies following anodal tDCS
(24) Pisoni, Mattavelli, et al. (2017)	tDCS, anodal, offline (20 min), 0.75 mA, rSO as reference, CD: 0.047	IFG (not provided)	verbal fluency (phonemic and semantic)	18	27.7 (*SD* = 5.3)	yes	higher fluency rate following tDCS
(25) Pobric, Jefferies, & Lambon Ralph (2007)	TMS, 1Hz, offline (10 min), 120 % MT	ATL (−53, 4, −32)	picture naming	11	21.7 (*SD* = 4.1)	no	slower naming latencies following TMS
(26) Pobric, Jefferies, & Lambon Ralph (2010)	TMS, 1Hz, offline (10 min), 120 % MT	ATL (−53, 4, −32)	picture naming	9	20.2 (*SD* = 2.1)	no	slower naming latencies following TMS
(27) Pobric, Jefferies, & Lambon Ralph (2010)	TMS, 1Hz, offline (10 min), 120 % MT	IPL (−49, −44, 48)	picture naming	same as (27)		no	slower naming latencies following TMS
(28) Schuhmann, Schiller, Goebel, & Sack (2009)	triple-pulse TMS 150, 225, 300, 400, or 525 ms after picture onset, 40 Hz, online, 120 % MT	IFG (−51, 13, 24)	picture naming	10	23.2 (*SD* = 2.1)	yes	no main effect of stimulation increased naming latencies following TMS at 300ms after picture onset

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(29) Schuhmann, Schiller, Goebel, & Sack (2012)	triple-pulse TMS 150, 225, 300, 400, or 525 ms after picture onset, 40 Hz, online, 120 % MT	MTG (−59, −45, 16)	picture naming	same as (25)		no	no main effect of stimulation increased naming latencies following TMS at 225 ms and 400 ms after picture onset
(30) Schuhmann, Schiller, Goebel, & Sack (2012)	triple-pulse TMS 150, 225, 300, 400, or 525 ms after picture onset, 40 Hz, online, 120 % MT	STG (−57, −45, 16)	picture naming	same as (25)		no	no main effect of TMS increased naming latencies following TMS at 400 ms after picture onset
(31) Shinshi et al. (2015)	triple-pulse TMS 150, 225, 300, 375, or 450 ms after picture onset, 40 Hz, online, 100 % MT	IFG (−49, 24, 19)	picture naming	12	23.1 (*SD* = 3.3)	yes	no main effect of TMS increased naming latencies following TMS 300 and 375 ms after picture onset
(32) Smirni et al. (2017)	TMS, 1 Hz, offline, 90 % MT	~IFG (F7)	verbal fluency (phonemic)	22 (subset of 44)	23.9 (*SD* = 3.0)	yes	lower fluency rate following TMS
(33) Sparing et al. (2001), Exp. 1	TMS, 1 Hz, offline (40 s), 55 % MSO	IFG (between F5 and F7) STG (CP5)	picture naming	10 (subset of 16)	29 (range: 22-38)	yes	no effect
(34) Sparing et al. (2001), Exp. 2	TMS, 20 Hz, offline (2 s), 35 %, 45 %, and 55 % MSO	STG (CP5)	picture naming	6 (subset of 16)	29 (range: 22-38)	yes	shorter naming latencies 1 min after TMS at 55% MSO
(35) Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink (2008)	tDCS, anodal and cathodal, online (7 min) and offline, 2 mA, vertex (Cz) as reference, CD: 0.057	STG (CP5)	picture naming	15	26.9 (*SD* = 3.7)	yes	no main effect of tDCS shorter naming latencies directly after anodal tDCS
(36) Vannorsdall et al. (2012)	tDCS, anodal, online, 1 mA, vertex (Cz) as reference, CD: 0.074	DLPFC (F3)	verbal fluency (phonemic and semantic)	12	37.9 (*SD* = 11.3)	yes	no main effect of tDCS higher fluency rate in semantic task during stimulation
(37) Vannorsdall et al. (2012)	tDCS, cathodal, online, 1 mA, vertex as reference, CD: 0.074	DLPFC (F3)	verbal fluency (phonemic and semantic)	12	33.5 (*SD* = 8.7)	yes	no main effect of tDCS descriptively, lower fluency rate in phonemic task during tDCS

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(38) Vannorsdall et al. (2016)	tDCS, anodal, offline (20 min), 2 mA, rSO as reference, CD: 0.057	IFG (between T3-Fz and F7-Cz)	verbal fluency (phonemic and semantic)	14	22.3 (*SD* = 2.4)	yes	no effect
(39) Westwood, Olson, Miall, Nappo, & Romani (2016), Exp. 1A	tDCS, anodal, online, 1 mA, rSO region as reference, CD: 0.11	IFG (F7)	picture naming	18	21.0 (*SD* = 2.8)	yes	no effect
(40) Westwood, Olson, Miall, Nappo, & Romani (2016), Exp. 1B	tDCS, anodal, online, 1.5 mA, rSO region as reference, CD: 0.06	IFG (F7)	picture naming	20	21.0 (*SD* = 2.9)	yes	no effect
(41) Westwood, Olson, Miall, Nappo, & Romani (2016), Exp. 1C	tDCS, anodal, online, 1.5 mA, right cheek as reference, CD: 0.06	MTG (between T3 and T5)	picture naming	18	19.8 (*SD* = 2.8)	yes	no effect
(42) Westwood, Olson, Miall, Nappo, & Romani (2016), Exp. 2	tDCS, anodal, online, 1.5 mA, rSO region as reference, CD: 0.06	IFG (F7)	semantic blocking	17	21.0 (*SD* = 2.4)	yes	no effect
(43) Wheat et al. (2013)	single-pulse TMS 75, 100, 125, 225, 300, or 500 ms after picture onset, online, 150 % MT	IFG (−40, 5, −7)	picture naming	10	21.5 (*SD* = 1.8)	yes	no main effect of TMS longer naming latencies following stimulation at 225 and 300 ms after picture onset
(44) Wirth et al. (2011)	tDCS, anodal, online, 1.5 mA, right shoulder as reference, CD: 0.06	DLPFC (between F3 and AF3)	semantic blocking	20	23.5 (*SD* = 3.7)	yes	no main effect of stimulation smaller semantic interference during stimulation
(45) Wirth et al. (2011)	tDCS, anodal, offline (≈37 min, i.e., following experiment (41)), 1.5 mA, right shoulder as reference, CD: 0.06	DLPFC (between F3 and AF3)	picture naming	same as (41)		yes	no effect

Note. All target areas refer to the left hemisphere. IFG = inferior frontal gyrus; STG = superior temporal gyrus; MTG = medial temporal gyrus; ATL = anterior temporal lobe; DLPFC = dorsolateral prefrontal cortex; LOC = lateral-occipital complex; PPC = posterior parietal cortex; IPL = inferior parietal lobule; rSO region = right supraorbital region. MT = motor threshold; MSO = maximum stimulator output. PWI = picture-word interference.
* The current density (CD; in mA/cm²) refers to the current density of the target electrode as entered into the analysis reported in Section 3.6.
** MNI coordinates or positions according to the 10-20 EEG referencing system are provided.

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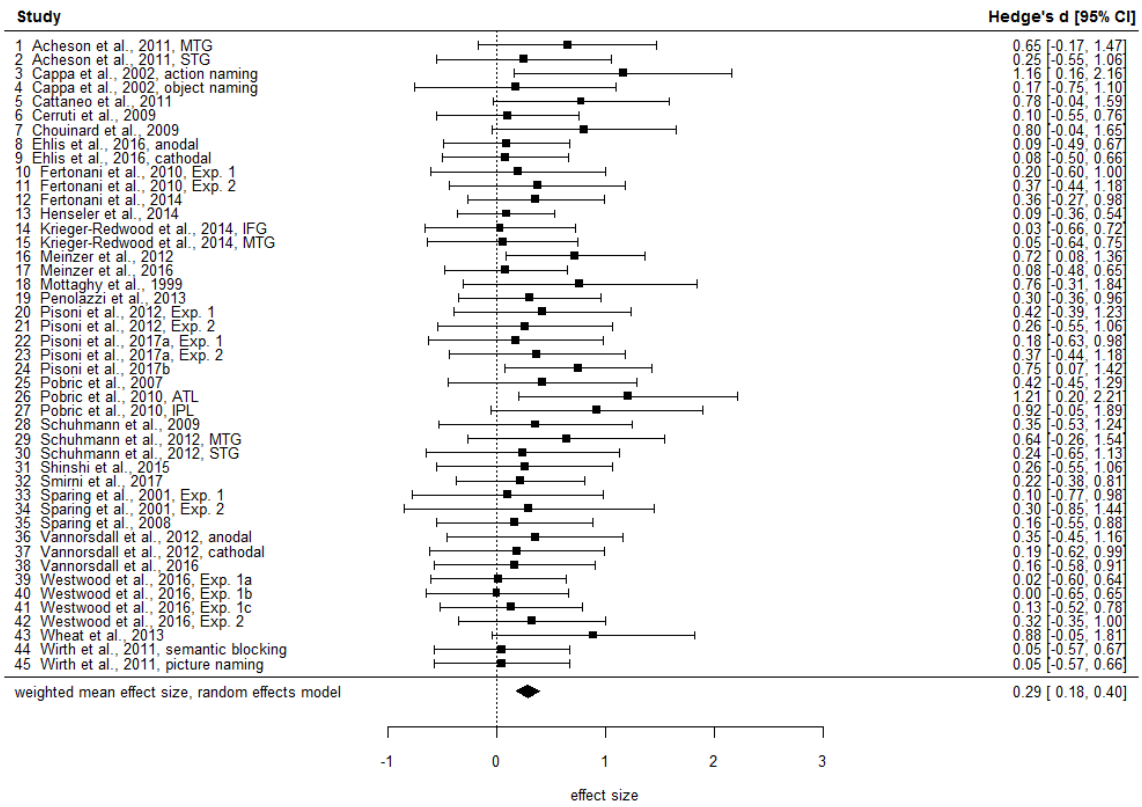

Figure 2. Forest plot of the effect sizes of the studies included in the meta-analysis investigating the efficacy of non-invasive brain stimulation as a tool of investigating language production in healthy participants.

language production. Figure 2 displays the effect sizes and 95% confidence intervals for all included studies.

Overall, our results suggest that NIBS appears to be an effective tool to modulate behaviour even in healthy participants. It should however be noted that the applied tDCS and TMS parameters used in the studies varied considerably. We therefore performed additional analyses to examine differences between stimulation type (tDCS vs. TMS), the applied control condition (sham vs. no stimulation), stimulation area (frontal vs. temporal), task (picture naming vs. verbal fluency), online vs. offline application, and current density of the target electrode. The results for these sub-analyses are summarised in Table 2.

TMS vs. tDCS

In order to investigate the efficacy of stimulation separately for TMS (N = 16) and tDCS (N = 26), respectively, separate meta-analyses were performed for the two stimulation techniques. The outcomes revealed significant weighted mean effect sizes of 0.225 (95% CI: 0.094 – 0.356) for the tDCS studies and 0.388 (95% CI: 0.178 – 0.598) for the TMS studies (see Figure 3). Furthermore, an ANOVA comparing the effect sizes yielded a significant main effect of stimulation type ($F(1,43) = 7.583$, $p = .009$, $\eta^2_G = .150$), indicating that the effect sizes for the TMS studies were significantly higher than those for the tDCS studies.

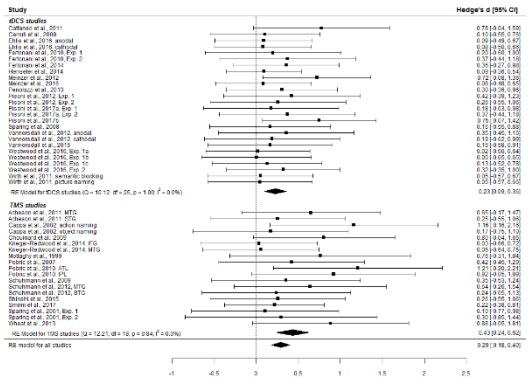

Figure 3. Forest plot of effect sizes, broken down by stimulation method (tDCS vs. TMS).

Sham vs. no stimulation as a control condition

To investigate a possible difference in NIBS efficacy depending on type of control condition, we compared studies that were sham-controlled (N = 36) to those that were not (N = 9). An ANOVA yielded no significant main effect of control condition ($F(1,43) = 2.148$, $p = .150$, $\eta^2_G = .048$). However, separate summary analyses revealed a descriptively larger effect size for studies which were not sham-controlled ($\bar{E}$ = 0.410, 95% CI: 0.133 – 0.686)

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Table 2
Results of meta-analysis, for all studies and specific subsets.

Comparison	*N*	$\bar{E}$	95% CI	*Z*	*p*	*Q*	*p*	I^2	Fail-safe
overall	**45**	**0.289**	**0.181 – 0.398**	**5.214**	**< .0001**	**25.248**	**.990**	**0.00**	**274**
				tDCS vs. TMS					
tDCS only	26	0.225	0.094 – 0.356	3.369	< .001	10.116	.996	0.00	51
TMS only	19	0.430	0.235 – 0.625	4.331	< .001	12.209	.836	0.00	74
				sham vs. no sham					
sham-controlled	36	0.267	0.149 – 0.386	4.429	< .0001	17.882	.993	0.00	148
not sham-controlled	9	0.410	0.133 – 0.686	2.903	.004	6.505	.591	0.00	11
				frontal vs. temporal					
frontal stimulation	27	0.275	0.139 – 0.411	3.953	< .001	14.344	.968	0.00	83
temporal stimulation	12	0.336	0.101 – 0.572	2.800	.005	5.454	.907	0.00	13
				picture naming vs. verbal fluency					
picture naming	24	0.356	0.192 – 0.521	4.239	< .0001	15.125	.890	0.00	89
verbal fluency	11	0.316	0.114 – 0.518	3.066	.002	6.366	.784	0.00	16
				online vs. offline					
online NIBS	23	0.280	0.131 – 0.428	3.700	< .001	13.225	.927	0.00	59
offline NIBS	22	0.301	0.141 – 0.461	3.678	<.001	11.987	.940	0.00	56
				current density of target electrode					
< 0.05 mA/cm²	5	0.308	0.013 – 0.603	2.046	.041	4.986	.289	16.13	2
0.06 – 0.07 mA/cm²	17	0.226	0.054 – 0.398	2.576	.010	3.898	.999	0.00	13
> 0.08 mA/cm²	4	0.124	-0.182 – 0.430	0.797	.425	0.505	.918	0.00	0

compared to those that were ($\bar{E}$ = 0.267, 95% CI: 0.149 – 0.386) (see Figure 4).

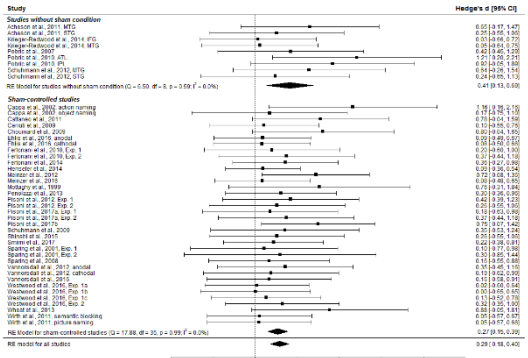

Figure 4. Forest plot of effect sizes, broken down by control condition (sham vs. no sham).

Frontal vs. temporal NIBS

The majority of the studies targeted areas within the left frontotemporal language network. To investigate whether one of these regions is more susceptible to NIBS, we selected studies targeting frontal regions including the left DLPFC and the left IFG (*N* = 27), and temporal regions including the left MTG, STG, and ATL (*N* = 12). An ANOVA comparing the effect of NIBS on these two regions provided no evidence for differences in effect sizes ($F(1,37) = 0.437$, p = .513, η^2_G = .012). That is, both frontal and temporal NIBS influenced language production in healthy speakers, with no quantitative difference in the magnitude of the effect between the two target locations (for frontal regions: $\bar{E}$ = 0.275, 95% CI: 0.139 – 0.411; for temporal regions: $\bar{E}$ = 0.336, 95% CI: 0.101 – 0.572; see Figure 5).

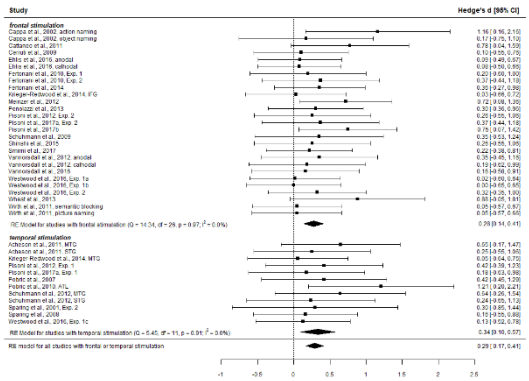

Figure 5. Forest plot of effect sizes, broken down by stimulation region (frontal vs. temporal).

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Picture naming vs. verbal fluency

To examine whether NIBS is more efficient for verbal fluency or picture naming tasks, we compared studies measuring verbal fluency (N = 11) with pure picture naming studies (N = 24; excluding picture-word interference and semantic blocking tasks to avoid potential confounds due to additional experimental conditions). An ANOVA provided no evidence for a difference in effect sizes between these types of tasks ($F(1,33) = 0.597$, $p = .445$, $\eta^2G = .018$). Separate summary analyses yielded descriptively comparable effect sizes and confidence intervals for verbal fluency tasks ($\bar{E} = 0.316$, 95% CI: 0.114 – 0.518) and picture naming tasks ($\bar{E} = 0.356$, 95% CI: 0.192 – 0.521) (see Figure 6).

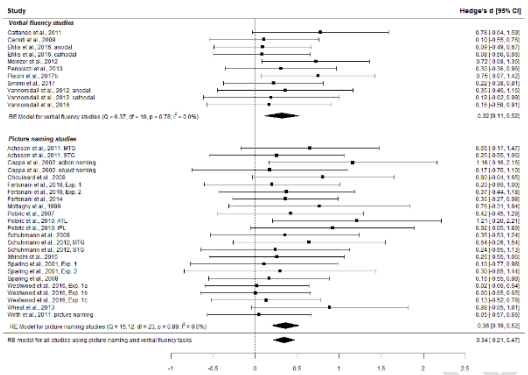

Figure 6. Forest plot of effect sizes, broken down by task (verbal fluency vs. picture naming).

Because frontal and temporal cortical regions are involved differentially in the tasks employed in the examined studies (see Introduction), we additionally investigated whether there are differences in effect sizes for these regions as a function of task (see Supplementary Table 2). An ANOVA including the factors region (i.e., frontal vs. temporal) and task (i.e., picture naming, semantic blocking, and picture-word interference tasks)[1] yielded no evidence for an interaction of these two factors ($F(2,22) = 0.175$, $p = .840$, $\eta^2_G = .016$). However, it should be noted that sample sizes for these particular sub-analyses were very small (ranging between 2 and 11 studies). Thus, future studies are needed to allow for a more reliable estimate.

Online vs. offline

To investigate the possible influence of applying NIBS prior to or during the execution of the experimental task, we compared studies that used an offline protocol ($N = 22$) with studies that used an online protocol ($N = 23$). An ANOVA provided no evidence for a quantitative difference between these two protocols ($F(1,43) = 0.031$, $p = .860$, $\eta^2_G = .001$), and effect sizes were descriptively comparable for both protocols (online: $\bar{E} = 0.280$, 95% CI: 0.131 – 0.428; offline: $\bar{E} = 0.301$, 95% CI: 0.141 – 0.461; see Figure 7).

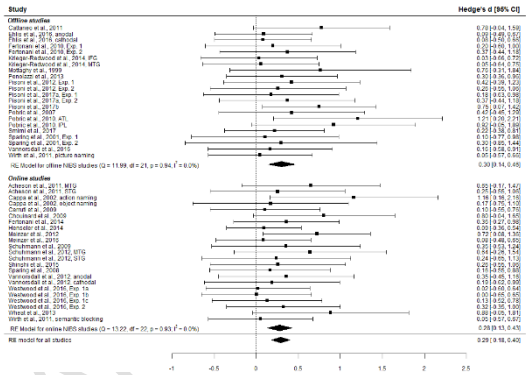

Figure 7. Forest plot of effect sizes, broken down by application time (online vs. offline).

Current density of the target electrode

Finally, we investigated whether the current density of the target electrode in tDCS studies has a differential effect on performance. We treated current density as a categorical variable split in three categories (low: current density ≤ 0.05 mA/cm²; medium: current density between 0.06 and 0.07 mA/cm²; high: current density ≥ 0.08 mA/cm²). An ANOVA yielded no significant main effect of current density ($F(2,23) = 0.747$, $p = .485$, $\eta^2_G = .061$). Descriptively, the largest effects were observed with low ($\bar{E} = 0.308$, 95% CI: 0.013 – 0.603) and medium current densities ($\bar{E} = 0.226$, 95% CI: 0.054 – 0.398), whereas current densities above 0.08 mA/cm² showed no significant effect size ($\bar{E} = 0.124$, 95% CI: -0.182 – 0.430; see Figure 8). However, it needs to be noted that most studies used current densities which we classified as "medium" (typically with a surface area between 25 and 35 cm² and a current intensity of 1.5 to 2 mA), whereas both the "low" and the "high" category are less common, thus reducing the statistical power for these groups.

[1] For this analysis, fluency tasks had to be removed because no single study has examined the effect of NIBS over temporal regions during these tasks. However, we ran additional sub-analyses for fluency tasks following frontal stimulation, both averaged across and broken down by task type (semantic vs. letter fluency). Interestingly, studies examining semantic fluency reported a stronger effect of NIBS over frontal regions, although Birn et al. (2010) showed that the left IFG is activated more during letter compared to semantic fluency tasks.

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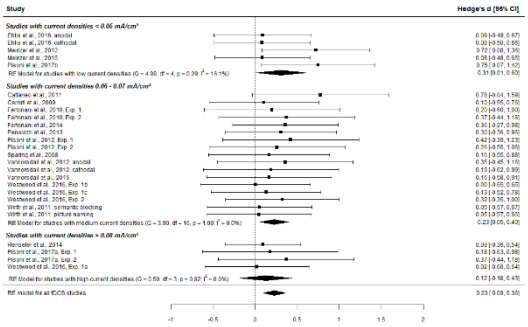

Figure 8. Forest plot of effect sizes, broken down by current density of active electrode (≤ 0.05 mA/cm² vs. 0.06 – 0.07 mA/cm² vs. ≥ 0.08 mA/cm²).

Discussion

The current meta-analysis evaluated the efficacy of non-invasive brain stimulation on performance changes in language production tasks in healthy speakers. As we have reviewed in the Introduction, studies which investigated the effects of NIBS on language production performance in healthy speakers show mixed results. Importantly, the methodological approaches vary substantially between studies as well, for example, with respect to the stimulation technique, site, duration, control condition and behavioural paradigm. While there is study-specific evidence for the efficacy of NIBS in language production research, the methodological variability between studies is large. As a result, it is not clear to what extent these differences affect the behavioural outcome.

To this end, we meta-analysed the effect sizes from studies measuring picture naming latencies or verbal fluency scores in healthy participants in which either TMS or tDCS was applied to probe the causal involvement of specific cortical areas in unimpaired language production. The overall effect size for all studies combined was small, but comparable to the results found in other meta-analyses investigating the influence of NIBS on cognitive function in healthy participants (e.g., Brunoni & Vanderhasselt, 2014; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Hill, Fitzgerald, & Hoy, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016; Schutter & Wischnewski, 2016). A potential reason for this relatively small effect size is that no clear-cut experimental standards exist. This introduces a large methodological variability between studies, which hampers both their comparability as well as the efficacy of the stimulation to effectively induce performance changes. For instance, for TMS studies, no valid threshold procedure (like motor-evoked potentials for the motor cortex or phosphene induction for the visual cortex) exists to reliably determine individual thresholds. Previous studies on language production used stimulation intensities between 100 and 120 % of the individual motor threshold or fixed stimulation intensities for all participants. In both cases, however, it is unclear if such a measure is the most reliable way to stimulate areas outside of the motor cortex. Inducing speech arrest may be a possible way of quantifying individual "speech thresholds". Following Pascual-Leone, Gates, & Dhuna (1991), who had successfully induced speech arrest in epileptic patients by applying rTMS to Broca's area, Epstein et al. (1996) contrasted the effect of stimulation frequencies between 4 and 32 Hz in a counting task. They found that applying 20 or 40 pulses over a period of five seconds (i.e., at 4 and 8 Hz, respectively) allowed for the induction of complete speech arrest without excessive muscle disturbances or pain sensations of the participants, which led the authors to conclude that this frequency was suitable for widespread application, e.g., to measure speech lateralization (see also Epstein et al., 1999). However, to the best our knowledge, none of the TMS studies that investigated language production in healthy participants has used this procedure. Similarly, for tDCS studies, individual cortical susceptibility to stimulation may differ (Parazzini, Fiocchi, Liorni, & Ravazzani, 2015), inducing different levels of excitability between participants. Also, the placement of the reference electrode, the size of both the target and reference electrode, as well as the stimulation frequencies vary substantially between studies, which hampers comparability between studies because different montages and intensities cause different electric field distributions across the cortex (Bastani & Jaberzadeh, 2013; Bastani, Jaberzadeh, Paulus, Rothwell, & Lemon, 2013; Bikson et al., 2017; Bikson, Datta, Rahman, & Scaturro, 2010; Rampersad et al., 2014; Saturnino, Antunes, & Thielscher, 2015). Further resources should be invested to explore the parameter space that allows for a reliable modulation of production performance while reducing the amount of inter- and intraindividual variability in the response to NIBS. Crucially, our results provide no evidence that applying NIBS online vs. offline, as well as the current density of the target electrode, affect weighted effect sizes.

On another note, different tasks might be differentially sensitive to performance changes

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induced by NIBS. We have shown that performance in both verbal fluency and pure picture naming tasks can be effectively modulated using NIBS. However, we cannot make a conclusive point with respect to the efficacy of NIBS in more specific picture naming paradigms (i.e., PWI, semantic blocking), as we have focused our analysis on the *overall* effect of NIBS as opposed to more specific experimental conditions. Westwood & Romani (2017) provide some evidence that at least tDCS may not be useful for examining semantically specific effects during language production. However, it should be noted that their analysis is based on a small number of experiments, so clearly more studies are needed before strong conclusions can be drawn.

It needs to be noted that the apparent advantage of TMS over tDCS is confounded with the physical sensations induced by either method. While participants typically cannot reliably differentiate between verum and sham tDCS, TMS arguably induces a stronger physical sensation at the stimulation site. Although some studies use so-called placebo coils or stimulate several areas (i.e., including at least one control region which is not expected to affect the outcome), many so far have only compared performance with real TMS to performance *without* the application of TMS. Evidently, in these cases, participants know when they are being stimulated and this could bias the results. We also wish to stress that for the TMS group, we pooled studies applying low-frequency (1 Hz) rTMS with studies using high-frequency (≥ 10 Hz) single- or triple-pulse TMS, which have different effects on cortical excitability. However, further subdividing the TMS studies was not meaningful given the very small sample sizes. Despite the larger effect sizes of TMS compared to tDCS, this finding should be thus treated with caution.

In conclusion, NIBS is a viable method to investigate the relations between cortical regions and language production in healthy volunteers and can contribute to the understanding of the neurobiology underlying unimpaired language production. Nevertheless, more fundamental studies are needed to explore under which conditions its efficacy can be homogenised within and between participants. Additionally, studies applying tDCS over several sessions, as is practice in clinical studies, may provide further insights into how efficacy can be improved.

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Supplementary Table 1
List of excluded studies and reason for exclusion.

Study	Reason for exclusion
Fertonani et al. (2014), older participant sample	old participants (mean age: 66.5 years)
Holland et al. (2011)	old participants (mean age: 69.0 years)
Lifshitz-Ben-Basat & Mashal (2017)	old participants (mean age: 69.4 years)
Cappelletti, Fregni, Shapiro, Pascual-Leone, & Caramazza (2008)	words as stimuli
Finocchiaro et al. (2008)	words as stimuli
Holland & Lambon Ralph (2010)	words as stimuli
Nozari & Thompson-Schill (2013)	words as stimuli
Oliveri et al. (2004)	words as stimuli
Pope & Miall (2012)	words as stimuli
Runnqvist et al. (2016)	words as stimuli
Shapiro, Pascual-Leone, Mottaghy, Gangitano, & Caramazza (2001)	words as stimuli
Spielmann et al. (2017)	words as stimuli
Tremblay & Gracco (2009)	words as stimuli
Arnold & Nozari (2017)	production of multi-word utterances
Fiori, Cipollari, Caltagirone, & Marangolo (2014)	production of multi-word utterances
Nozari, Arnold, & Thompson-Schill (2014)	production of multi-word utterances
Brunyé et al. (2015)	semantic association task
Jeon & Han (2012)	mixture of picture naming and verbal fluency
Cerruti & Schlaug (2009), Experiment 2	data could not be provided
Iyer et al. (2005)	data could not be provided
Mottaghy, Sparing, & Töpper (2006)	data could not be provided
Töpper et al. (1998)	data could not be provided
Schuhmann et al. (2012), IFG stimulation	same data as in Schuhmann et al. (2009)

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Supplementary Table 2

Results of sub-analysis examining the efficacy of NIBS by cortical region (frontal vs. temporal) and task.

Comparison	*N*	$\bar{E}$	95% CI	*Z*	*p*	*Q*	*p*	I^2	Fail-safe
					frontal				
picture naming	9	0.223	-0.019 – 0.464	1.807	.071	3.519	.898	0.00	0
fluency	11	0.316	0.114 – 0.518	3.066	.002	6.366	.784	0.00	16
letter fluency	7	0.206	-0.053 – 0.465	1.559	.119	3.793	.705	0.00	0
semantic fluency	7	0.300	0.038 – 0.562	2.246	.025	3.230	.780	0.00	3
semantic blocking	4	0.154	-0.191 – 0.499	0.877	.381	0.531	.912	0.00	0
PWI	1	–							
					temporal				
picture naming	11	0.388	0.130 – 0.645	2.948	.003	5.351	.867	0.00	14
fluency	0	–							
semantic blocking	3	0.150	-0.235 – 0.536	0.764	.445	0.550	.760	0.00	0
PWI	2	0.110	-0.281	0.500	.583	0.034	.854	0.00	0

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