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Review article

Treatment effect variability in brain stimulation across psychiatric disorders: A meta-analysis of variance

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ABSTRACT

Noninvasive brain stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are promising add-on treatments for a number of psychiatric conditions. Yet, some of the initial excitement is wearing off. Randomized controlled trials (RCT) have found inconsistent results. This inconsistency is suspected to be the consequence of variation in treatment effects and solvable by identifying responders in RCTs and individualizing treatment. However, is there enough evidence from RCTs that patients respond differently to treatment? This question can be addressed by comparing the variability in the active stimulation group with the variability in the sham group. We searched MEDLINE/PubMed and included all double-blinded, sham-controlled RCTs and crossover trials that used TMS or tDCS in adults with a unipolar or bipolar depression, bipolar disorder, schizophrenia spectrum disorder, or obsessive compulsive disorder. In accordance with the PRISMA guidelines to ensure data quality and validity, we extracted a measure of variability of the primary outcome. A total of 130 studies with 5748 patients were considered in the analysis. We calculated variance-weighted variability ratios for each comparison of active stimulation vs sham and entered them into a random-effects model. We hypothesized that treatment effect variability in TMS or tDCS would be reflected by increased variability after active compared with sham stimulation, or in other words, a variability ratio greater than one. Across diagnoses, we found only a minimal increase in variability after active stimulation compared with sham that did not reach statistical significance (variability ratio = 1.03; 95% CI, 0.97, 1.08, $P = 0.358$). In conclusion, this study found little evidence for treatment effect variability in brain stimulation, suggesting that the need for personalized or stratified medicine is still an open question.

1. Introduction

The emergence of noninvasive brain stimulation for the treatment of various psychiatric conditions has brought promising possibilities. Stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been used as add-on treatment (Brunoni et al., 2019) and have convinced with their minimal risk profile (Rossi et al., 2009), the prospect of noninvasively interfering with neuronal transmission, and the easy-to-use application. Popularity, particularly for TMS, increased considerably after the Food and Drug Administration's (FDA, 2011) approval of its application as an add-on to the conventional therapy for major depressive disorder in 2008 and obsessive–compulsive disorder (OCD) in 2018.

Consistent evidence for the superiority of TMS or tDCS over sham for other psychiatric disorders is lacking so far. Positive symptoms in schizophrenia are one such example: the initially promising results (Hoffman et al., 1999, 2000, 2003) developed into a more heterogeneous picture over the years (Marzouk et al., 2019). One explanation for this might be the drop in effect sizes over time (Leucht et al., 2017; Slotema et al., 2012). Another reason, often brought up by both

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researchers and clinicians (including ourselves; Homan et al., 2012), is to assume variability in treatment effects in brain stimulation (Guerra et al., 2017). This assumption has motivated the idea to personalize medicine by identifying responders to treatment through predictive biomarkers (Drysdale et al., 2017; Pizzagalli et al., 2018; Rolle et al., 2020; Webb et al., 2018).

However, the question remains whether there is enough evidence to conclude that patients do indeed differ in their response to noninvasive brain stimulation over and above the variability seen in response to sham stimulation. In addition, the extent of such variability would be important as well, as it would determine the corresponding need for personalized psychiatry. One way to address this question is by comparing the variance between treatment and control groups of randomized, controlled trials (RCT) (Nakagawa et al., 2015). Greater variability in the active stimulation group would indicate that there is a component of variation, the patient-by-treatment or subgroup-by-treatment interaction, indicating variability of treatment effects (Cortés et al., 2019). This approach has recently been used in the context of antipsychotics (Winkelbeiner et al., 2019) and antidepressants (Munkholm et al., 2020; Plöderl and Hengartner, 2019; Volkmann et al., 2020). Perhaps surprisingly, most of these meta-analyses found little evidence for treatment effect variability (Munkholm et al., 2020; Plöderl and Hengartner, 2019; Volkmann et al., 2020; Winkelbeiner et al., 2019).

To evaluate the heterogeneity in treatment effects for noninvasive brain stimulation (TMS and tDCS), we used the same approach of examining variability ratios in RCTs with patients across psychiatric diagnoses (unipolar depression, schizophrenia spectrum disorder, OCD, and bipolar disorder). We hypothesized that (1) the often claimed treatment effect variability in brain stimulation would be indicated by increased variability after active stimulation compared with sham, reflected by an overall variability ratio (VR) of greater than one. Further, we hypothesized that (2) the variability ratio is not dependent on the diagnostic group or (3) stimulation method.

2. Methods

2.1. Selection criteria

We included all studies that met the following eligibility criteria: (1) study population of adult patients with a psychiatric diagnosis of either an affective disorder, schizophrenia spectrum disorder, or OCD; (2) using noninvasive brain stimulation including TMS and tDCS; (3) RCTs or crossover trials; (4) published in a peer-reviewed English journal; (5) no case reports, case series, opinion pieces; (6) no animal research.

2.2. Search strategy

We conducted a comprehensive search of the electronic database MEDLINE (PubMed.gov) from January 1999 – August 2020 with the following combination of keywords: “depression” or “MDD” or “unipolar”; “bipolar” or “mania” and “transcranial magnetic stimulation” or “rTMS” or “TMS” or “transcranial direct current stimulation” or “tDCS”; “obsessive compulsive disorder” or “OCD” or “obsession” or “compulsion” and “transcranial magnetic stimulation” or “rTMS” or “TMS” or “transcranial direct current stimulation” or “tDCS”; “psychosis” or “schizophrenia” or “positive symptoms” or “auditory hallucinations” or “thought disorder” or “delusions” or “hallucinations” or “thinking” or “disorganization” and “transcranial magnetic stimulation” or “rTMS” or “TMS” or “transcranial direct current stimulation” or “tDCS”. The only search filters that were applied were “human”, and “English language”. In addition to the electronic database search, we searched the references of recent reviews and meta-analyses (Gold et al., 2019; Kubera et al., 2015; Lefaucheur et al., 2014, 2017; Moseley et al., 2016; Slotema et al., 2014; Vicario et al., 2019).

2.3. Data extraction

In adherence with the PRISMA guidelines (Moher et al., 2015), independent researchers (G.C., L.H., A.J., E.J., W.M., and M.N.) conducted the literature search and screened the articles, eliminated duplicates, decided whether the article met the inclusion criteria, and extracted all relevant data from the final articles (Supplementary Fig. 1). The same researchers assessed then the risk of bias of the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011). The independent searches, data extraction, and risk ratings were compared by S.H., discrepancies investigated, and resolved by discussion.

We extracted an available variance measure (standard deviation, standard error, or confidence interval) and means for the primary outcome measure at baseline and outcome for the active and sham group. Additionally, we extracted information on the study design, sample size, participants’ characteristics (diagnosis, treated symptom, sex, and age), stimulation parameters (targeted hemisphere, number of sessions, and whether neuronavigation was used), and the effect size. For TMS studies, we extracted also target location and stimulation frequency. For tDCS studies, we extracted also electrode placement of the anode and cathode and stimulation intensity.

Note that in cases of multi-arm RCTs, we omitted study arms that were not relevant to the question of this meta-analysis (Higgins et al., 2019). For example, we omitted the arm of one study (Brunoni et al., 2013a) in which TMS as an add-on to sertralin was compared to sham, while we included the arm in which TMS as a stand-alone treatment was compared to sham.

2.4. Data preprocessing

The majority of the included studies were RCTs (88%), with crossover trials making up only a small percentage (12%). Nevertheless, the inclusion of crossover trials required additional considerations (Higgins et al., 2019). We decided to exclude the second period of each crossover trial thus treating the trial as if it was a parallel trial. To check that this approach did not lead to biased results we conducted sensitivity analyses including also the second period of crossover trials (Supplementary Fig. 2). Of note, variance measures and means had to be estimated from figures for 21 (14%) comparisons. In the case of multi-arm trials, in which more than one arm of the RCT was considered relevant to this meta-analysis (Bais et al., 2014; Blumberger et al., 2012a,b, 2016; Brunoni et al., 2013a; Elbeh et al., 2016; Fitzgerald et al., 2012; George et al., 2000; Höppner et al., 2003; Loo et al., 2018; Padberg et al., 1999; Paillère Martinot et al., 2010; Pallanti et al., 2010; Slotema et al., 2011; Speer et al., 2014; Stern et al., 2007; Su et al., 2005; Theleritis et al., 2017; Triggs et al., 2010), we divided the sample size of the sham group by the number of intervention arms while retaining standard deviation (s) and mean (Higgins et al., 2019). This allowed us to create multiple pair-wise comparisons for those studies.

For the analysis, we used the pre-post difference scores to account for baseline differences. For the 21 (14 %) comparisons that reported raw outcome scores, we calculated the mean pre-post difference score (M_Δ) with

$$M_\Delta = M_{outcome} - M_{baseline}$$

The calculation of the respective standard deviation (s_Δ) is less straightforward with (Abrams et al., 2005; Higgins et al., 2008)

$$s_\Delta = \sqrt{s^2_{active} + s^2_{sham} - (2 \times \rho \times s_{active} \times s_{sham})}$$

and required an approximation for the overall correlation coefficient (ρ). Thus, we used the 20 (13 %) comparisons for which the standard deviation for the active and sham groups for baseline (t_0), outcome (t_1), and pre-post difference scores was available to calculate the correlation

coefficient for the active (ρ_{active}) and sham (ρ_{sham}) group, respectively, with

$$\rho_{active} = \frac{s^2_{active_{t0}} + s^2_{active_{t1}} - s^2_{active_{\Delta}}}{2 \times s_{active_{t0}} \times s_{active_{t0}}}$$

Next, we averaged over ρ_{active} and ρ_{sham} to obtain one correlation coefficient per comparison. Finally, we averaged over the 20 comparisons and used this average coefficient ($\rho_{average} = 0.59$) for imputation in the calculation of s_{Δ} (Higgins and Green, 2011; Higgins et al., 2019). While this approach was possible for the majority of comparisons, there were 5 comparisons for which the standard deviation of the percentage pre–post difference was reported (Boggio et al., 2008; Bose et al., 2019; Cook et al., 2019; Fregni et al., 2006; Schutter et al., 2009) and 4 comparisons (Carmi et al., 2019; Li et al., 2014) for which the range of the pre–post difference scores but provided no information on the raw outcome scores. Therefore, those studies had to be excluded. To test that the imputed values did not lead to biased results, we ran sensitivity analyses with the lower and the upper bound of the available correlation coefficients (Supplementary Fig. 3).

2.5. Statistical analysis

The variance of the active groups comprises the same variance components (within-patient variation, regression to the mean, and measurement error) as the sham group, with the only difference that the active group can comprise also a treatment-by-patient or treatment-by-subgroup interaction. This variance component reflects response differences between patients or subgroups. Thus, in the case of individual response difference, we would expect an increased variability (VR > 1) in the active group compared with sham. To test this, we calculated the log variability ratio (lnVR) for each comparison of active stimulation (TMS or tDCS) vs sham with (Hedges and Nowell, 1995)

$$\ln VR = \ln\left(\frac{s_{active}}{s_{sham}}\right) + \frac{1}{2(n_{active} - 1)} - \frac{1}{2(n_{sham} - 1)}$$

where s_{active} and s_{sham} were the standard deviations of the pre-post difference scores, and n_{active} and n_{sham} the respective sample sizes (Nakagawa et al., 2015). The corresponding sampling variance (s^2_{lnVR}) (Nakagawa et al., 2015) for each study was defined as

$$s^2_{lnVR} = \frac{1}{2(n_{active} - 1)} + \frac{1}{2(n_{sham} - 1)}$$

We weighted each lnVR with the inverse of its s^2_{lnVR} (Viechtbauer, 2010). To quantify the true individual response, after adjusting for within-patient variability and regression to the mean (Cortés et al., 2019; Hecksteden et al., 2015), we fitted a random-effects model stratified by diagnostic group. For better interpretability, we transformed the results back from the log scale: VR greater than 1 indicating greater variability under active stimulation compared with sham and a VR smaller than 1 indicating less variability under active stimulation compared with sham. In addition, we calculated subgroup analyses where sufficient data were available (studies in depression and schizophrenia). For transparency and completeness, we calculated preliminary subgroup analyses for studies in bipolar disorder and OCD.

Finally, we calculated the standardized mean difference (SMD) as a general effect size measure to compare our analysis with previous reports. By taking the log of the ratio of means, the SMD was centered symmetrically around zero, yielding Hedges' *g* (Viechtbauer and Viechtbauer, 2017). We also plotted the SMDs against year of publication stratified by diagnostic group to examine the relationship of the effect sizes and time.

2.6. Data and code availability

All analyses were performed in R (version 3.5.2) (R Core Team, 2018), the calculation of VR and SMD was done with the R package *metafor* (version 2.4.0) (Viechtbauer and Viechtbauer, 2017). This paper was written using *knitr* (version 1.28) (Knitr, 2020) in RStudio (version 1.2.5042) (RStudio and Team, 2015). All data and code are freely available online to ensure reproducibility (https://osf.io/6w947/). This study was pre-registered on the Open Science Forum platform (https://osf.io/8uxec).

3. Results

3.1. Descriptive statistics

A total of 130 studies were included that investigated treatment with active TMS or tDCS in depression (Anderson et al., 2007; Avery et al., 2006; Baeken et al., 2013, 2015, 2019; Benadhira et al., 2017; Berman et al., 2000; Blumberger et al., 2012a, 2016; Bortolomasi et al., 2007; Boutros et al., 2002; Bretlau et al., 2008; Brunoni et al., 2013a,b, 2014, 2017; Bulubas et al., 2019; Carpenter et al., 2017; Carretero et al., 2009; Dunlop et al., 2020; Fitzgerald et al., 2003, 2006, 2012; Garcia-Toro et al., 2001a,b; George et al., 1997, 2000, 2010; Hausmann et al., 2004; Herwig et al., 2007; Holtzheimer et al., 2004; Höppner et al., 2003; Huang et al., 2012; Januel et al., 2006; Kang et al., 2016; Klein et al., 1999; Koerselman et al., 2004; Kreuzer et al., 2012; Krstic et al., 2014; Lee and Kim, 2018; Leuchter et al., 2015; Loo et al., 2010a, 2012, 2018; Manes et al., 2001; Mogg et al., 2008; Mosimann et al., 2004; Müller et al., 2006; Nongpiur et al., 2011; Nord et al., 2019; O'Reardon et al., 2007; Padberg et al., 1999; Paillère Martinot et al., 2010; Pallanti et al., 2010; Palm et al., 2012; Pascual-Leone et al., 1996; Rao et al., 2019; Ray et al., 2011; Rigonatti et al., 2008; Rossini et al., 2005; Rumi et al., 2005; Salehinejad et al., 2017; Sharafi et al., 2019; Slotema et al., 2011; Speer et al., 2014; Stern et al., 2007; Su et al., 2005; Theleritis et al., 2017; Triggs et al., 2010; Vigod et al., 2019; Wang et al., 2017; Zheng et al., 2010), schizophrenia (Bais et al., 2014; Barr et al., 2012; Blumberger et al., 2012b; Brunelin et al., 2012; Chang et al., 2018; de Jesus et al., 2011; Dlabac-de Lange et al., 2015; Hoffman et al., 2000, 2003, 2005; Fitzgerald et al., 2008; Fröhlich et al., 2016; Garg et al., 2016; Hajak et al., 2004; Holi et al., 2004; Jandl et al., 2006; Jeon et al., 2018; Kantrowitz et al., 2019; Kimura et al., 2016; Klirova et al., 2013; Koops et al., 2015; Li et al., 2016; Loo et al., 2010b; McIntosh et al., 2004; Mondino et al., 2018; Paillère-Martinot et al., 2017; Palm et al., 2016; Poulet et al., 2004; Prikryl et al., 2013; Quan et al., 2015; Rabany et al., 2014; Rollnik et al., 2000; Rosa et al., 2007; Saba et al., 2006; Slotema et al., 2011; Smith et al., 2015; Wobrock et al., 2015), OCD (Arumugham et al., 2018; Bation et al., 2019; Elbeh et al., 2016; Gomes et al., 2012; Gowda et al., 2019; Haghighi et al., 2015; Harika-Germaneau et al., 2019; Hawken et al., 2016; Jahangard et al., 2016; Kang et al., 2009; Mansur et al., 2011; Mantovani et al., 2010, 2013; Pelissolo et al., 2016; Prasko et al., 2006; Shayganfard et al., 2016), and bipolar disorder (Dolberg et al., 2002; Fitzgerald et al., 2016; Hernández-Ribas et al., 2013; Kaptsan et al., 2003; Loo et al., 2018; Praharaj et al., 2009; Tavares et al., 2017) compared with sham over the last 24 years. Some studies compared more than one active stimulation to sham which is why we considered 155 comparisons in this meta-analysis. We excluded the second period of 12 crossover trials (Baeken et al., 2013, 2015; Brunoni et al., 2013b; Fitzgerald et al., 2003; George et al., 1997; Haghighi et al., 2015; Jandl et al., 2006; Jahangard et al., 2016; Klirova et al., 2013; Loo et al., 2010b; Palm et al., 2012; Shayganfard et al., 2016) and dropped 1 study's arm (Brunoni et al., 2013a) that was irrelevant for this meta-analysis. Importantly, none of the included studies used a design such as a repeated crossover trial that would have allowed to estimate individual response directly (Senn, 2016).

Overall, a total of 5748 patients were included. Of these 3654 (64%) had a diagnosis of unipolar or bipolar depression, 1482 (26%) schizophrenia spectrum disorder, 388 (7%) OCD, and 224 (4%) bipolar disorder. The majority of comparisons investigated brain stimulation in medicated patients (130, 84%), while only a minority was performed in

unmedicated patients (21, 14%) and only 1 (0.6%) included also medication-naive patients. For 3 (2%) comparisons information of medication status was not given (for more information see Supplementary Tables 8–14). Considering the potential impact of medication status on our results, we performed sensitivity analyses (see Supplementary Fig. 4).

Further, 106 (82%) studies investigated TMS and 24 (18%) tDCS compared with sham. Our evaluation of the risk of bias showed that 51 (39%) studies had a high risk of bias, while only 21 (16%) a low risk. For 58 (45%) studies the risk was unclear (see Supplementary Fig. 5). Therefore, we conducted sensitivity analyses to investigate the reliability of our results (see Supplementary Fig. 6). For more details on the included studies see Supplementary Fig. 7 and Supplementary Tables 1–14.

3.2. Variability ratio

We found no evidence for increased variability after active stimulation compared with sham across diagnostic groups and stimulation methods (VR = 1.03, 95% CI: 0.97, 1.08, $P = 0.358$; Fig. 1 and Supplementary Fig. 8). We estimated that 3% of the total variance was due to heterogeneity in true effects and not attributable to sampling variance. The subgroup analyses by stimulation method showed that only for TMS studies in schizophrenia there was an 8% increase in variability evident after active compared with sham stimulation (VR = 1.08, 95% CI: 1.01, 1.17, $P < 0.05$; Fig. 1; see also Supplementary Figs. 9 & 10). For studies in depression, there was no evidence for increased variability, irrespective of stimulation method (Supplementary Figs. 11 & 12). There was also no evidence for increased variability in the subgroup analyses in bipolar disorder and OCD (Supplementary Figs. 13–16) which, however, had only few studies available and should therefore be considered preliminary, as was the case for the preliminary.

3.3. Mean effect size

Additionally, we calculated the standardized mean differences to obtain an index of the effectiveness of brain stimulation. Overall, we found a medium to large effect size (SMD = 0.54, 95% CI: 0.32, 0.75, $P < 0.001$; Fig. 2) across diagnostic groups. This indicates that noninvasive brain stimulation was on average more effective than sham and is in line with previous meta-analyses in depression (TMS: odds ratios between 1.69 and 7.44; Brunoni et al., 2017; Mutz et al., 2018; tDCS: odds ratio = 4.17; Mutz et al., 2018), schizophrenia (Hedges' g between 0.39 and 0.63; Slotema et al., 2010; Shi et al., 2014), and OCD (Hedges' $g = 0.45$; Trevizol et al., 2016).

Further, we found a statistically significant inverse relationship of effect sizes and year of publication for the studies in patients with a schizophrenia spectrum diagnosis, but not for any of the other diagnostic groups (Supplementary Fig. 17).

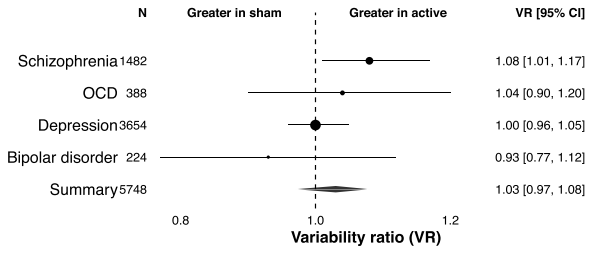

Fig. 1. Variability ratio by disorder. The forest plot shows the VR together with its 95% confidence interval (CI) for active stimulation vs sham by disorder. Within the diagnostic groups, the variance was not significantly increased by the stimulation (TMS or tDCS) compared with sham, except for studies in patients on the schizophrenia spectrum.

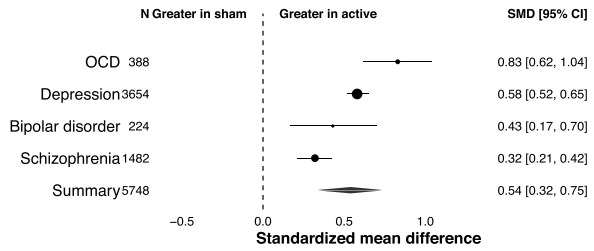

Fig. 2. Standardized mean difference. The forest plot shows the standardized mean difference (SMD) together with its 95% confidence interval (CI) for active stimulation vs sham by disorder. The overall effect size was greater for active stimulation compared with sham for all disorders.

4. Discussion

The observed variability in clinical trials and clinical practice is often viewed as proof that patients differ in their response to noninvasive brain stimulation over and above the variability seen in response to sham stimulation. If this was true, one would expect that active stimulation should increase variability compared with sham stimulation. Yet, the empirical evidence in this study does not support this assumption in general. Only for studies in patients with a schizophrenia spectrum disorder, variability was increased after active compared with sham stimulation. Nevertheless, our analysis allow no conclusions as to whether this was due to differences between individuals or between subgroups, as both would lead to increased overall variability compared with sham. Yet, the size of this variability increase was modest. Consistent with previous meta-analyses, our study also found support for the overall efficacy of brain stimulation across disorders, even though a substantial risk of bias because of the mostly small studies has to be acknowledged.

Our findings lend at least some support for the recent trend in psychiatry to personalize treatment (Korte et al., 2015; Ozomaro et al., 2013) in general and brain stimulation in particular (Drysdale et al., 2017; Olbrich et al., 2015; Winkelbeiner et al., 2018). One reason for this trend might be that the initially promising potential of noninvasive brain stimulation (George, 2019) for the treatment of psychiatric and neurological conditions (Brunoni et al., 2017; Lefaucheur et al., 2014, 2017; Mutz et al., 2018; Shi et al., 2014; Slotema et al., 2014; Trevizol et al., 2016), has started to wear off. Despite medium to large effect sizes from depression trials (George et al., 2010; O'Reardon et al., 2007), the promised beneficial effects did not appear to show in all patients. While some improved, others appeared to remain unchanged or even deteriorated. These observed outcome differences leave patients and clinicians unsatisfied, and researchers tempted to assume variation in treatment effects. Naturally, this has motivated the search for biomarkers to identify those patients who are likely to respond more favorably to treatment and tailor treatments accordingly. Yet, despite encouraging attempts (Drysdale et al., 2017; Pizzagalli et al., 2018; Webb et al., 2018; Winkelbeiner et al., 2018), (that occasionally did receive some push-back; Dinga et al., 2019; Mihalik et al., 2020) so far no reliable and clinically applicable biomarkers have been identified for treatment response prediction in individuals or subgroups.

One of the challenges in predicting treatment response might be rooted in the assumption that treatment effects vary in clinical trials and clinical practice. More often than not is this assumption the result of a somewhat arbitrary distinction between "responders" and "non-responders" (Homan and Kane, 2018; Senn, 2018). Yet, the presence of other variance components that might explain a majority of the outcome variance is sometimes overlooked (Senn, 2015). Thus, evaluating variances can give a first hint about whether a personal or subgroup element of response is indeed present in the data (Nakagawa et al., 2015). Our results provide some evidence for the presence of such treatment effect variability, driven mostly by studies in patients on the schizophrenia

spectrum who were treated with TMS. For those studies, variability was slightly increased after TMS compared with sham. This deviates from similar recent meta-analyses of antipsychotic drug trials (Winkelbeiner et al., 2019; McCutcheon et al., 2019) and antidepressant drug trials (Munkholm et al., 2020; Plöderl and Hengartner, 2019; Volkmann et al., 2020), where little evidence for treatment effect variability was found. However, after excluding all studies with a high risk of bias the VR increase for schizophrenia did not reach significance anymore (Supplementary Fig. 6).

Notably, our results for the overall mean effect size of brain stimulation is largely in line with previous meta-analyses in depression (TMS: odds ratios between 1.69 and 7.44; Brunoni et al., 2017; Mutz et al., 2018; tDCS: odds ratio = 4.17; Mutz et al., 2018), schizophrenia (Hedges' g between 0.39 and 0.63; Slotema et al., 2010; Shi et al., 2014), and OCD (Hedges' $g = 0.45$; Trevizol et al., 2016). In addition, we found a negative correlation of effect size and publication year for schizophrenia studies, which was also in line with previous studies (Leucht et al., 2017; Slotema et al., 2012). This effect might be explained by the larger sample sizes ($N > 70$) of more recent studies (Brunoni et al., 2017; George et al., 2010; O'Reardon et al., 2007; Quan et al., 2015; Wobrock et al., 2015), while the initial RCTs were performed in treatment groups of 10 or less patients (Padberg et al., 1999; Paillère Martinot et al., 2010; Speer et al., 2014; Baeken et al., 2013, 2015; George et al., 1997; Holtzheimer et al., 2004; Lee and Kim, 2018; de Jesus et al., 2011; Rosa et al., 2007; Saba et al., 2006; Jahangard et al., 2016; Mantovani et al., 2010, 2013; Shayganfard et al., 2016). Such small sample studies have low average statistical power (Amad et al., 2019; Button et al., 2013), which can be consequential. Chances are lower to detect the "true" effect that actually reflects a statistically significant result. Thus, effect sizes are overestimated which reduces chances of reproducibility.

What are the clinical implications of our results for the treatment with noninvasive brain stimulation? This meta-analysis provided some evidence to expect individual or subgroup differences in response to brain stimulation. One explanation might be the presence of subgroups that might have responded differently to brain stimulation with the more severely ill patients improving less or not at all and the less ill patients improving more (Cortés et al., 2019). Such a case would argue for "stratified medicine" rather than "personalized medicine", in which subgroups of patients receive varying treatments. Thus, the analysis of variability ratios does not allow to distinguish between those cases, i.e. patient-by-treatment and subgroup-by-treatment interactions (Winkelbeiner and Homan, 2019). However, although we did find evidence for treatment effect variability, the overall extent of such variability was modest and most pronounced for schizophrenia, and even for schizophrenia the confidence interval ranged from 1% to 17%, indicating that the need for personalized or stratified medicine, respectively, could be anything from minimal to moderate. It is therefore an open question whether these findings are strong enough to warrant the search for predictive biomarkers, no matter how promising the approach (Cocchi and Zalesky, 2018; Jog et al., 2019; Olbrich et al., 2015).

5. Limitations

Some limitations merit comment. First, we used the variability ratio and not the coefficient of variation ratio (CVR) because of the absence of a mean-variance relationship for the majority of disorders (Supplementary Fig. 18) and no relationship between the standardized mean differences and the lnVR. This suggests that there was no mean-variance scaling and no further need to controlling for the mean (Supplementary Fig. 19). Using the CVR would have been problematic because the logarithm can only be taken from positive values. Thus, negative mean values cannot be dealt with without losing information. Using pre-post difference scores can result in negative values in the case of worsening of symptoms ($\bar{x} < 0$) or zero values in the case of no symptom change ($\bar{x} = 0$) from baseline to outcome. More importantly, the CVR is scale dependent. For values on the interval scale with a mean close to zero but a standard deviation far from zero, the CVR becomes arbitrarily large and the mean-variance proportionality which makes the CVR meaningful is lost. Therefore, the CVR should only be used for outcome data on the ratio scale with a true zero (Mills et al., 2003). Alternatively, a Bayesian meta-regression approach could be used (Volkmann et al., 2020). Second, some of the subgroup analyses had only few studies available which limits statistical power and increases uncertainty. This was the case, e.g. for studies in patients with bipolar disorder for which only 7 comparisons were eligible. Third, the standard deviation of pre-post difference was not available for 134 (86%) comparisons and had to be calculated by imputing the correlation coefficient. To ensure that this did not lead to biased results, we ran sensitivity analyses which showed that the results remained unchanged (Supplementary Fig. 3). Fourth, our results do not allow conclusions about potential biomarkers of response to active or sham stimulation. A number of biomarkers have been previously investigated, including brain-derived neurotrophic factor plasma levels (Brunoni et al., 2014), receptors (Brunoni et al., 2015), network segregation (Fan et al., 2019), brain activation (Fitzgerald et al., 2007), functional connectivity (Ge et al., 2019), and EEG markers (Isserles et al., 2018). Of those, only network segregation, functional connectivity, and an EEG marker were found to predict response to active but not sham stimulation. Yet, before those candidate biomarkers can be applied clinically, these findings need to be replicated in larger samples. Last, the majority of the included studies were rated as having high risk of bias, which suggests a low quality of evidence. This was due to various factors such as not clearly defined primary outcome measures, incomplete or selective data reporting, potentially misleading report of outcome data, and failure to report baseline data. We undertook various measure to account for these shortcomings (see Section 2) and excluded the studies that did not report the values needed to infer the necessary values. In addition, we performed sensitivity analyses excluding the studies for which values had been inferred. The results of the sensitivity analyses showed almost identical results as the main analyses.

6. Conclusion

This study found little evidence for treatment effect variability in brain stimulation, suggesting that the need for personalized or stratified medicine is still an open question.

Conflict of interest

SH, WM, AJ, NM, GC, LH, EJ, MN, SV, ES, TD, and PH report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neubiorev.2020.11.033.

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