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Motor cortical plasticity in schizophrenia: A meta-analysis of Transcranial Magnetic Stimulation – Electromyography studies

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ABSTRACT

Background: Several lines of investigations converge upon aberrant synaptic plasticity as a potential pathophysiological characteristic of schizophrenia. In vivo experiments using neuromodulatory perturbation techniques like Transcranial Magnetic and Direct Current Stimulation (TMS & tDCS) have been increasingly used to measure 'motor cortical plasticity' in schizophrenia. A systematic quantification of cortical plasticity and its moderators in schizophrenia is however lacking.
Method: The PubMed/MEDLINE database was searched for studies up to December 31st, 2017 that examined case-control experiments comparing neuromodulation following single-session of TMS or tDCS. The primary outcome was the standardized mean difference for differential changes in motor evoked potential (MEP) amplitudes measured with single-pulse TMS (MEP Δ) between patients and healthy subjects following TMS or tDCS. After examining heterogeneity, meta-analyses were performed using fixed effects models.
Results: A total of 16 datasets comparing cortical plasticity (MEP Δ) between 189 schizophrenia patients and 187 healthy controls were included in the meta-analysis. Patients demonstrated diminished MEP Δ with effect sizes (Cohen's *d*) ranging from 0.66 (LTP-like plasticity) to 0.68 (LTD-like plasticity). Heterosynaptic plasticity studies demonstrated a greater effect size (0.79) compared to homosynaptic plasticity studies (0.62), though not significant ($P = 0.43$). Clinical, perturbation protocol- and measurement-related factors, and study quality did not significantly moderate the aberrant plasticity demonstrated in schizophrenia.
Conclusions: Schizophrenia patients demonstrate diminished LTP- and LTD-like motor cortical plasticity, which is not influenced by the various clinical and experimental protocol related confounders. These consistent findings should encourage the use of perturbation-based biomarkers to characterize illness trajectories and treatment response.

1. Introduction

Cortical plasticity is conceptualized as an intrinsic attribute of the nervous system that enables its ongoing, adaptive modification in response to a multitude of environmental stimuli (Pascual-Leone et al., 2005). This dynamic malleability of the nervous system (structural and functional) in response to neuronal activity triggered by internal or external stimuli is thought to be central to its processing of learning and adaptive behavior (Hart and Hobert, 2018). There have been incremental advances to our understanding about the precise synaptic morphological changes that govern neuronal plasticity and remodeling. These processes maintain the numerous overlapping and interconnected neural circuits that support brain function and are also implicated in brain disease states. For instance, the dynamic interplay between activity-regulated genes (e.g., *arc*/arg*3.1*) and presynaptic (e.g., neurexin) or postsynaptic (e.g., neuregulin) cell-adhesion molecules in shaping the excitatory and inhibitory circuit-level plasticity is critical in maintaining normal brain functions and is implicated in the genesis of severe neuropsychiatric disorders including schizophrenia (Leslie and Nedivi, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Südhof, 2017).

Various lines of human neuroimaging and animal research suggest that the core manifestations of schizophrenia and its neurodevelopmental trajectories can be understood as resulting from aberrant neuronal plasticity or dysplasticity that encompasses hypoplastic cognitive and volitional neural systems, as well as, hyperplastic salience detection and emotion processing systems (Keshavan et al., 2015). In

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keeping with these hypotheses, the last couple of decades have witnessed a rise of non-invasive, in vivo brain stimulation experiments to induce and quantify cortical plasticity responses in patients with schizophrenia (Cohen et al., 1998; Pascual-Leone et al., 1999). For example, Transcranial Magnetic Stimulation (TMS), by means of its ability to induce neuronal action potentials can be employed as both, a neuromodulator – to induce plastic change, and, as a neurophysiological probe – to quantify the degree of plastic change, in combination with electromyography (EMG), electroencephalography (EEG) or functional magnetic resonance imaging (fMRI). In contrast, Transcranial Direct Current Stimulation (tDCS) can alter resting membrane potentials of underlying neurons and hence be used as a pure neuromodulator.

Such techniques potentially enable researchers to quantify the 'dysplasticity' in schizophrenia. As a novel investigational approach, they do provide an excellent opportunity to translate these results from experimental laboratories to clinical practice informing us about potential neural markers that identify at-risk states, support diagnoses and predict treatment outcomes or even select personalized treatments. The central concept (Fig. 1) supporting these in vivo brain stimulation experiments is to use an external cortical perturbation (successive

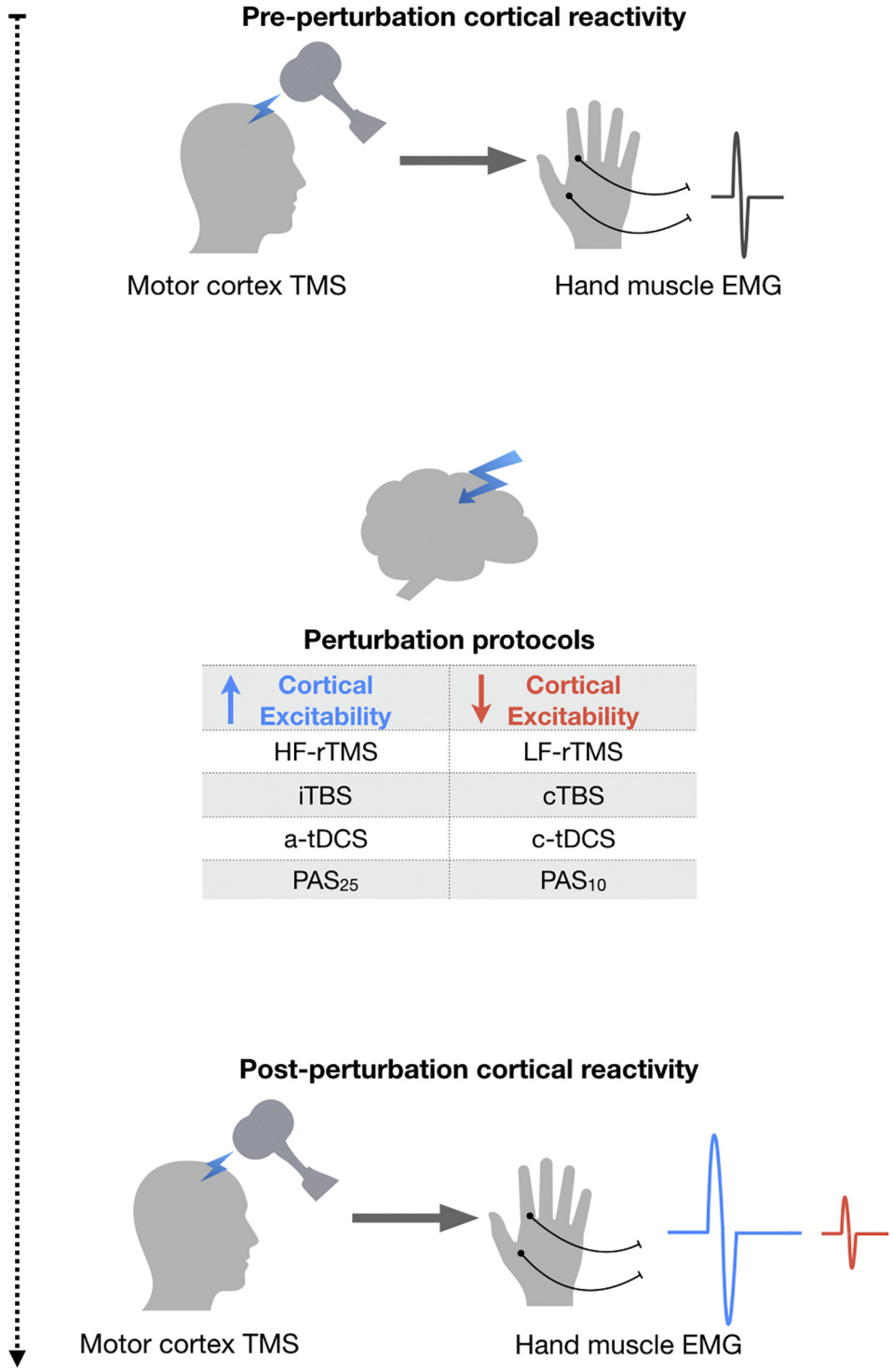

Fig. 1. Illustration of TMS-EEG or TMS-EMG cortical plasticity experiments.

electric or magnetic fields) and measure the magnitude and duration of change in cortical reactivity induced by this perturbation by means of TMS-EEG or TMS-EMG protocols (Freitas et al., 2013). Such perturbation-based remodeling of brain reactivity provides us with unique insights into local and network-level dynamics that can complement traditional resting-state and task-induced brain reactivity measurements. Importantly, such approaches would be translatable and thus enable reliable bridging of animal to human model systems (Diester et al., 2015).

Over the years, several experiments have now attempted to quantify and compare cortical plasticity in schizophrenia and healthy individuals using such perturbation protocols and their variants (Bhandari et al., 2016; Hasan et al., 2013a; Voineskos et al., 2013). The ability of these protocols to cause in vivo transitory cortical reactivity increases or decreases (Cooke and Bliss, 2006) parallels the commonly observed in vitro long-term potentiation/depression (LTP/LTD)-like experience-dependent synaptic plasticity accompanying Hebbian learning and memory (Artola et al., 1990; Toni et al., 1999). Despite having diverse mechanistic foundations, these perturbation protocols (TMS or tDCS), appear to have a final common individual-specific LTP/LTD-like effect that can be quantified by TMS-EMG (most common) or TMS-EEG measurements (Fig. 1) as changes in the amplitudes of motor evoked potentials (MEPs) or TMS-evoked EEG potentials (TEPs), respectively.

Several studies demonstrate impaired LTP-like and LTD-like cortical plasticity in schizophrenia (McClintock et al., 2011), however these perturbation protocols induce changes that tend to be fragile and variable – a function of not just the biological state or experimental protocol of perturbation and measurement, but also of the pre-stimulation neuronal state of the stimulated cortical area (Huang et al., 2017). A systematic quantification of cortical plasticity aberrations in schizophrenia is however lacking. Moreover, the experimental or patient-related factors that contribute to the variability in cortical plasticity can potentially refine our current understanding about the characteristics of cortical plasticity in schizophrenia. This exercise will also be a step forward in standardizing experimental protocols for employment in future perturbation-based biomarker studies.

In this context, we performed a meta-analysis of studies examining cortical plasticity in schizophrenia using perturbation-based strategies, with the aim to (a) quantify the magnitude of cortical plasticity abnormality in schizophrenia, and (b) study the moderating influence of patient-related (e.g., age, gender, duration of illness, medication dose, symptoms) and experiment-related (e.g., perturbation and recording techniques, methodological rigor) factors on cortical plasticity in schizophrenia.

2. Method

2.1. Study selection

Two authors (UMM and MVT) independently searched the PubMed/MEDLINE databases for studies up to December 31st 2017 using the following key phrases "(neuronal plasticity [Medical Subject Heading] OR cortical plasticity [in titles or abstracts] AND schizophrenia [Medical Subject Heading])". In addition, manual search of bibliographic cross-referencing from selected studies and reviews was performed to ensure no potential studies were excluded. Studies were included in the meta-analysis if they reported sufficient data (means and standard deviations, graphs, inferential statistics) to compute effect size measures from case-control experiments examining changes in cortical reactivity as measured using investigational Transcranial Magnetic Stimulation (TMS) protocols in patients with schizophrenia and healthy controls, following any perturbation intervention (e.g., TMS, tDCS). There were a total of 401 hits, of which, 13 studies providing 16 datasets were included in the meta-analysis. Data from three studies were not used in the meta-analysis as two of these studies (Strube et al., 2015b, 2015a) had subjects pooled from studies already included and one study did not provide sufficient data that could be used to compute effect size measures (Zhou et al., 2017). Fig. 2 provides details of the study selection process.

2.2. Data analysis

Standardized Mean Differences (Cohen's *d*) were derived from sample size, means and standard deviations. If group mean ± SD were not reported, they were extracted from graphs using Plot Digitizer Software (Huwaldt and Steinhorst, 2014). If we could not extract these values from graphs, group * time interaction effect F values or t values for each cortical reactivity parameter were used along with the sample sizes of the two groups to derive Cohen's *d* and its variance using the *MAd* package (Del Re and Hoyt, 2014) in R statistical programming language version 3.4.3 (R Core Team, 2014). This derivation of standardized mean differences is based on existing guidelines (Cooper et al., 2009) and has been used in earlier meta-analyses (Wykes et al., 2011). Among the various motor cortical reactivity measurements, MEP change was the commonest, followed by resting motor threshold (RMT) and cortical silent period (CSP). An omnibus meta-analysis was performed to examine if perturbation methods induced differential changes in MEP amplitudes with single pulse TMS (MEP Δ) between patients and healthy controls irrespective of the expected direction – LTD- or LTP-like plasticity using the *metafor* package in R (Viechtbauer, 2010). A positive effect size indicated greater induction of MEP Δ by the neuromodulatory method in healthy subjects compared to schizophrenia patients. Subsequently, secondary meta-analyses were conducted on studies examining LTD- and LTP-like plasticity protocols to determine if the effects were consistent across different types of cortical plasticity being examined. Consistency of the computed mean weighted effect sizes were tested with the Cochran's Q test of heterogeneity. Based on the tests of heterogeneity, random or fixed effects models were implemented for the meta-analyses. Publication bias was examined by visualization of funnel plots and performing Egger's regression test and rank correlation test for funnel plot asymmetry. Leave-one-out sensitivity analyses were conducted for determining consistency and robustness of results. An alpha probability error significance level of <0.05 (two-tailed) was used for the random/fixed effects models, test for heterogeneity, publication bias and moderator analyses. Meta-regression analyses were performed using mixed-effects modeling in *metafor* package in R (Viechtbauer, 2010) to independently control for (entered one by one) the effects of differences in perturbation protocol related parameters, clinical and socio-demographic parameters, cortical reactivity measurement related parameters, as well as, the classificatory system used to diagnose schizophrenia (ICD 10 or DSM IV).

2.3. Methodological rigor and reporting quality ratings

Each of the 13 studies that were included for the meta-analysis were rated for methodological rigor and reporting quality. A tailor-made checklist was designed with a scoring system. The checklist was designed with the items that are relevant to various nuances of assessing change in cortical reactivity (as measured using TMS) following a perturbation method (e.g., ensuring proper matching of cases and controls, recording and eliminating potential confounding variables, a-priori outcome definitions, etc. – see Table S2 in Supplementary material for details). The checklist provided a maximum score of 21 and a proportion of the maximum score derived for each study/dataset was used in the meta-regression analysis.

3. Results

3.1. Summary of included studies (Table 1)

Neuromodulatory perturbation protocols used in these 13 studies included low frequency repetitive TMS (LF-rTMS), continuous theta

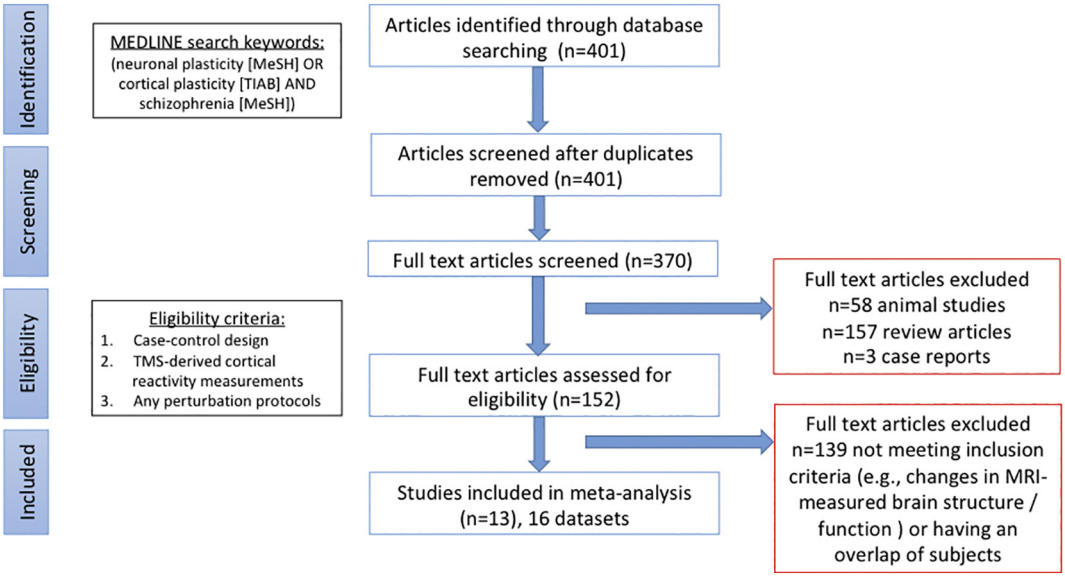

Fig. 2. Flowchart representing the study selection process.

burst stimulation (cTBS), cathodal and anodal tDCS and paired associative stimulation (PAS). The site of delivery of these perturbation protocols was the left motor cortex hand area (M1) in all studies except Oxley et al. (2014) (left premotor cortex) and Hasan et al. (2013a) (bilateral M1). The neurophysiological probe used in these studies to determine and quantify cortical reactivity was always single-pulse TMS-EMG, recorded predominantly from the right hand muscles (first dorsal interosseous or abductor pollicis brevis). The average sample size across the 16 datasets was 16 patients and 15 healthy subjects, who had a mean duration of illness of 5.78 ± 1.15 years, receiving antipsychotic medications amounting to a cumulative average of 396.56 ± 82.92 mg of chlorpromazine equivalents per day.

Most studies found a diminished or equivocal (Hasan et al., 2011; Strube et al., 2016) cortical plasticity response (MEP Δ), and two found an opposite pattern of change in cortical reactivity as compared to healthy subjects – MEP facilitation with LF-rTMS (Oxley et al., 2004) and MEP suppression with 300 pulses of cTBS (Hasan et al., 2015). It is noteworthy that, none of the studies included in the meta-analysis demonstrated an exaggerated plasticity response. Five studies reported data on changes in RMT. While the two LF-rTMS protocols reported an increase in RMT in healthy subjects but not in schizophrenia patients (Fitzgerald, 2004; Oxley et al., 2004), the three cathodal tDCS protocols reported no group difference in RMT change (Hasan et al., 2013c; Hasan et al., 2012a, 2012b). CSP was reported to be unchanged in three (Hasan et al., 2013c; Hasan et al., 2012b, 2011) of four cathodal tDCS studies, while one LF-rTMS study reported diminished CSP in healthy subjects but not in schizophrenia patients (Fitzgerald, 2004). Meta-analyses were performed only for the results reported on MEP Δ and not for changes in CSP or RMT because of the small number and heterogeneous nature of study designs. While the focus of most studies was on comparing the magnitude of plastic change induced, several studies also reported differences in time-courses of the plastic change between groups. Both these PAS studies demonstrated a group-difference (diminished MEP facilitation) at later time-points – 20 min (Ribolsi et al., 2017) and 30 min (Frantseva et al., 2008) following the PAS protocol. Other studies also recorded cortical reactivity across multiple time-points, but they did not report any significant time-course difference and hence performed further analyses with average post-stimulation MEPs across all time-points (e.g., Hasan et al., 2013c, 2013b; Hasan et al., 2015). The PAS method of Ribolsi et al. used a cortico-cortical pairing of TMS-pulses, as opposed to other PAS studies that used the traditional pairing of median nerve stimulation with motor cortex stimulation. See Table S1 in Supplementary material for more details regarding experimental protocols, clinical data and quality measures.

3.2. Meta-analysis

A total of 13 studies providing 16 datasets comparing cortical plasticity measures (MEP Δ) between an overall number of 189 schizophrenia patients (mean age 32.29 years; 68.1% males) and 187 healthy controls (mean age 31.78 ± 3.4 years; 66.36% males) were included in the meta-analysis. One dataset did not measure MEP Δ (Daskalakis et al., 2008), and hence the primary meta-analysis for change in MEP following a perturbation method was run on 15 datasets. There was good consistency in the effect sizes across all the 15 datasets [Q (df = 14) = 6.46, $P = 0.953$]. The meta-analysis, performed using the fixed-effects model, revealed significantly diminished motor cortical plasticity responses in the patient group, with an effect size of 0.673 (95% CI, 0.49 to 0.86; $P < 0.0001$). There were no potential outliers and influential cases as identified by the leave-one-out (estimates ranging from 0.64 to 0.7) and influence functions. There was little suggestion towards a publication bias as observed from the funnel plot and non-significant tests of plot symmetry (Egger's regression z = 0.34, $P = 0.73$; Kendall's tau rank correlation tau = 0.29, $P = 0.14$). We then included the study by Daskalakis et al., which measured thumb angular displacement as a measure of plasticity following an exercise protocol, as this also is likely to indicate LTP-like plasticity properties. The plasticity impairment in the patient group persisted with an effect size of 0.68 (95% CI, 0.49 to 0.86; $P < 0.0001$) by applying a fixed-effects model [Q (df = 15) = 6.6720, $P = 0.9661$]. The forest plots depicting these results are included in Figs. 3 and 4; funnel plots for these analyses are given in the Supplementary material.

3.3. Moderator effects

3.3.1. Examining differences based on plasticity categories

We categorized plasticity measurements based on two principles. The first principle depended on whether the perturbation protocol was likely to facilitate excitability (LTP-like; nine datasets) or inhibition (LTD-like; seven datasets) in the motor cortex. The second principle depended on whether plasticity was induced by activating one set of synapses (homosynaptic plasticity; 12 datasets) or simultaneous paired activation of two sets of synapses (heterosynaptic plasticity; four datasets). Secondary meta-analyses for LTD-/LTP-like plasticity, and

Table 1
Summary of different studies examining plasticity differences between patients with schizophrenia and healthy subjects.

Datasets	Year	Perturbation method	Cortical reactivity	Subjects	Summary	Plasticity (MEP Δ) in SZ
Long term depression (LTD) – like plasticity						
Transcranial Magnetic Stimulation (TMS) perturbation protocols						
Oxley et al. (2004)[#]	2004	LF-rTMS	MEP[$] RMT SICI	12 SZ (DSM IV) 12 HS	LF-rTMS produced MEP suppression in HS as expected, but there was MEP facilitation in SZ. RMT increased in HS but reduced in SZ; there was no significant between group difference in SICI change	↔
Fitzgerald (2004)	2004	LF-rTMS	MEP[$] RMT	26 SZ (DSM IV) 18 HS	LF-rTMS produced significantly reduced MEP suppression in SZ, compared to HS. There was no significant difference between medicated and non-medicated SZ. LF-rTMS produced an increase in RMT and diminished CSP duration in HS, but not SZ	↓
Hasan et al. (2015) (cTBS600)	2015	cTBS	MEP	10 SZ (ICD 10) 10 HS	c-TBS-600 produced significant MEP suppression in HS but not in SZ	↓
Transcranial Direct Current Stimulation (tDCS) perturbation protocols						
Hasan et al. (2012b)	2012	c-tDCS	MEP RMT CSP	21 SZ (ICD 10) 21 HS	c-tDCS produced significantly reduced (a) MEP suppression and (b) CSP duration elongation in SZ compared to HS. The RMT change was not significant in either groups	↓
Hasan et al. (2013b)	2013	Left c-tDCS	MEP	9 SZ (ICD 10) 9 HS	Left c-tDCS produced reduced MEP suppression in SZ compared to HS	↓
Hasan et al. (2012a)	2012	c-tDCS	MEP RMT CSP	18 SZ (ICD 10) 18 HS	c-tDCS produced significantly reduced MEP suppression on the stimulated and contralateral hemispheres in SZ compared to HS. There were no group differences in effects of c-tDCS on RMT or CSP	↓
Hasan et al. (2013c)	2013	c-tDCS	MEP RMT CSP	15 SZ (ICD 10) 15 FDR 10 HS	c-tDCS produced significantly reduced MEP suppression on the stimulated and contralateral hemispheres in SZ compared to HS. RMT and CSP showed no group differences after c-tDCS	↓
Long Term Potentiation (LTP) – like plasticity						
Transcranial Magnetic Stimulation (TMS) perturbation protocols						
Hasan et al. (2015) (cTBS300)	2015	cTBS	MEP	10 SZ (ICD 10) 10 HS	c-TBS-300 produced significant MEP suppression in SZ, but MEP facilitation in HS	↔
Transcranial Direct Current Stimulation (tDCS) perturbation protocols						
Hasan et al. (2011)	2011	a-tDCS	MEP CSP SICI ICF	22 SZ (ICD 10) 22 HS	a-tDCS produced significantly reduced MEP facilitation in multiple-episode SZ compared to recent-onset SZ and HS. There was no group difference for change in CSP, SICI and ICF	↓/≈
Hasan et al. (2013b)	2013	Left c-tDCS + Right a-tDCS	MEP	9 SZ (ICD 10) 9 HS	Left c-tDCS + Right a-tDCS produced significantly reduced MEP facilitation in SZ compared to HS	↓
Strube et al. (2016) (a-tDCS)	2016	a-tDCS	MEP SICI ICF	20 SZ (ICD 10) 20 HS	a-tDCS demonstrated MEP facilitation in SZ and HS. SICI and ICF did not show any group differences following a-tDCS	≈
Paired associative stimulation (PAS) perturbation protocols						
Frantseva et al. (2008)	2008	PAS	MEP	15 SZ or SA (DSM IV) 15 HS	PAS produced significantly reduced MEP facilitation in SZ compared to HS	↓
Ribolsi et al. (2017)	2017	PAS	MEP	12 SZ (DSM IV) 12 HS	Parieto-motor PAS produced reduced and slower MEP facilitation in SZ (more so in the left hemisphere), compared to HS	↓
Strube et al. (2016) (PAS)	2016	PAS	MEP SICI ICF	20 SZ (ICD 10) 20 HS	PAS produced significantly reduced MEP facilitation in SZ as compared to HS. SICI and ICF did not show any group differences following PAS	↓
Bridgman et al. (2016)	2016	PAS	MEP	9 SZ (DSM IV) 10 HS	Reduced MEP facilitation following PAS in SZ as compared to HS[a]	↓
Others						
Daskalakis et al. (2008)	2008	Exercise	Angular displacement	20 SZ (6 antipsychotic free) (DSM IV), 20 HS	Exercise induced significantly reduced mean angular displacement in SZ compared to HS, irrespective of their medication status	↓

Note: SZ = schizophrenia patients; HS = healthy subjects; SA = schizoaffective disorder; FDR = first degree relatives; MEP = motor evoked potentials; RMT = resting motor threshold; CSP = cortical silent period; SICI = short interval intracortical inhibition; ICF = intracortical facilitation; c-tDCS = cathodal tDCS; a-tDCS = anodal tDCS; cTBS = continuous theta burst stimulation; all perturbation protocols were delivered to the motor cortex, except [#]Oxley et al., which was delivered to the premotor cortex; all MEP recordings were performed using SI_{1mV} as the stimulation dose, except [$]Oxley et al., and [$]Fitzgerald et al., where the stimulating doses ranged between 102% to 120%RMT; MEP Δ = change in motor evoked potential amplitudes following a neuromodulatory perturbation protocol; ↓ = lesser than healthy subjects; ≈ = same as healthy subjects; ↔ = opposite to healthy subjects.

[a] Results reported from the placebo arm of the study.

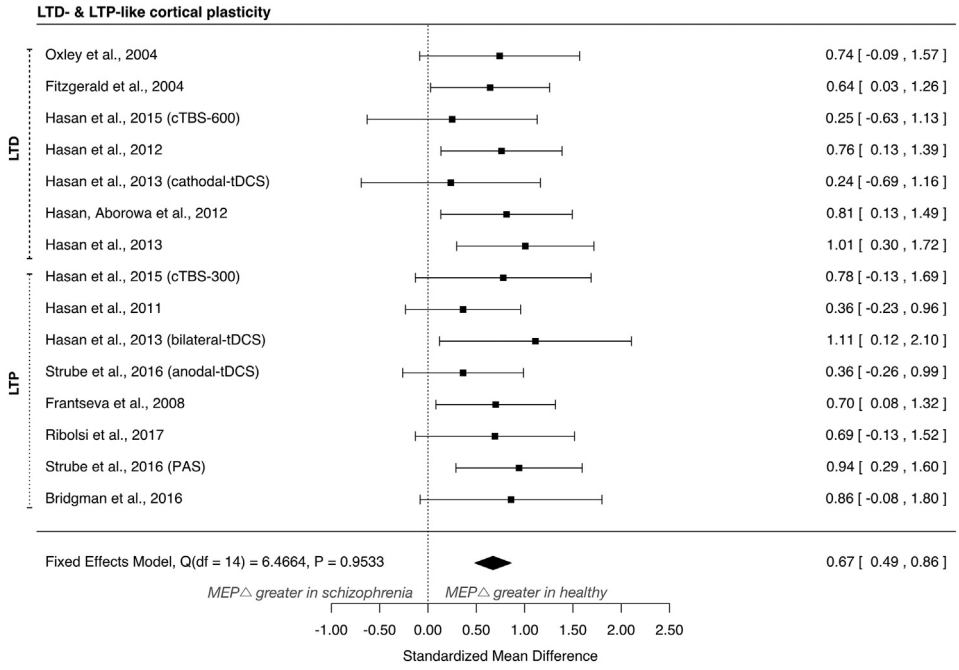

Fig. 3. Cortical plasticity (MEP Δ) meta-analysis forest plot for all datasets. Forest plot for cortical plasticity (MEP Δ) meta-analyses between schizophrenia patients and healthy subjects; MEP Δ = change in motor evoked potential amplitudes following a neuromodulatory perturbation protocol. See Supplementary Table S1 for more details.

homosynaptic/heterosynaptic plasticity studies were also performed using the fixed effects model, as tests of heterogeneity were not significant for inconsistent effect sizes. LTD-like plasticity deficits were seen in schizophrenia patients with an effect size of 0.68 (95% CI, 0.41 to 0.95; $P < 0.0001$), while LTP-like plasticity deficits were present with an effect size of 0.66 (95% CI, 0.41 to 0.92; $P < 0.0001$). Similarly, homosynaptic plasticity deficits were present with an effect size of 0.62 (95% CI, 0.41 to 0.84; $P < 0.0001$), and heterosynaptic plasticity deficits were present with an effect size of 0.79 (95% CI, 0.43 to 1.16; $P < 0.0001$). The type of plasticity abnormality in the patient group [LTD-like vs. LTP-like; $Q\ (1) = 0.01$, $P = 0.92$ and homosynaptic vs. heterosynaptic; $Q\ (1) = 0.61$, $P = 0.43$] did not significantly moderate the overall abnormality. None of the datasets were identified as outliers that could have potentially influenced the results in a significant manner.

3.3.2. Examining effects of the perturbation protocols used

Two studies each examined cortical plasticity by using TMS and cTBS methods, three studies used anodal-tDCS and four studies each used PAS and cathodal-tDCS. Only one study examined use-dependent plasticity by implementing an exercise protocol to change angular displacement of thumb twitches induced by single pulse TMS. We examined the moderating effects of both, general (e.g., exercise, TMS, PAS, tDCS) and specific (e.g., exercise, TMS, PAS, TBS, cathodal-tDCS or anodal-tDCS) type of perturbation protocols on the results and found no significant effect of one particular method [16 datasets, $Q\ (1) = 2.05$, $P = 0.82$ and 15 datasets, $Q\ (1)$ 0.62, $P = 0.73$ respectively]. However, on examining the bubble-plot comparing weighted effect sizes against perturbation protocols, there was an indication that the results coming from LF-rTMS and PAS studies were closer to the true effect size (0.68) determined in the meta-analysis (Fig. 4).

3.3.3. Examining effects of clinical and socio-demographic variables

Mean age of the subjects in each study [16 datasets, $Q\ (1) = 0.31$, $P = 0.57$], proportion of males recruited [16 datasets, $Q\ (1) = 0.27$, $P = 0.59$], classificatory system followed to diagnose schizophrenia [16 datasets, $Q\ (1) = 0.13$, $P = 0.71$], symptom severity (13 datasets, PANSS total scores) [$Q\ (1) = 0.01$, $P = 0.96$], duration of illness [11 datasets, $Q\ (1) = 0.01$, $P = 0.93$], chlorpromazine equivalents [16 datasets, $Q\ (1) = 0.02$, $P = 0.86$] and global functioning of patients [11 datasets, $Q\ (1) = 0.07$, $P = 0.79$], did not have a moderating effect on the plasticity differences between the two study groups across the datasets.

3.3.4. Examining effects of TMS/tDCS experimental variables

Similarly, results were not significantly moderated by baseline resting motor threshold of patients [10 datasets, $Q\ (1) = 0.216$, $P = 0.64$] and controls [10 datasets, $Q\ (1) = 0.20$, $P = 0.65$], baseline amplitude of motor evoked potential of patients [13 datasets, $Q\ (1) = 0.17$, $P = 0.67$], stimulation intensity used to measure motor evoked potentials [14 datasets, $Q\ (1) = 0.01$, $P = 0.92$], and the number of trials [15 datasets, $Q\ (1) = 0.001$, $P = 0.97$] averaged to determine cortical excitability (motor evoked potentials). Stimulator device type did not moderate the results for cortical plasticity differences as measured using TMS [eight datasets, $Q\ (1) = 0.49$, $P = 0.48$] and tDCS [seven datasets, $Q\ (1) = 0.88$, $P = 0.34$] neuromodulatory perturbation protocols. Quality of the individual studies rated on a continuum also did not significantly alter the outcome [16 datasets, $Q\ (1) = 0.41$, $P = 0.52$].

4. Discussion

We found that schizophrenia patients had impairments in cortical plasticity outcomes measured using TMS-EMG experiments with effect sizes ranging from 0.66 (LTP-like plasticity) to 0.68 (LTD-like plasticity). Heterosynaptic plasticity studies demonstrated a greater effect size (0.79) compared to homosynaptic plasticity studies (0.62), though not statistically significant ($P = 0.43$). Clinical, perturbation protocol-related and cortical reactivity measurement-related factors did not significantly moderate the aberrant plasticity demonstrated in schizophrenia patients. Quality of individual studies also did not have a moderating effect on plasticity outcomes between the two groups studied. None of the indices indicated potential publication bias. These findings suggest an overall moderate effect size of cortical plasticity impairment in schizophrenia. These findings can be interpreted within three contexts - clinical, study methodological and neurobiological.

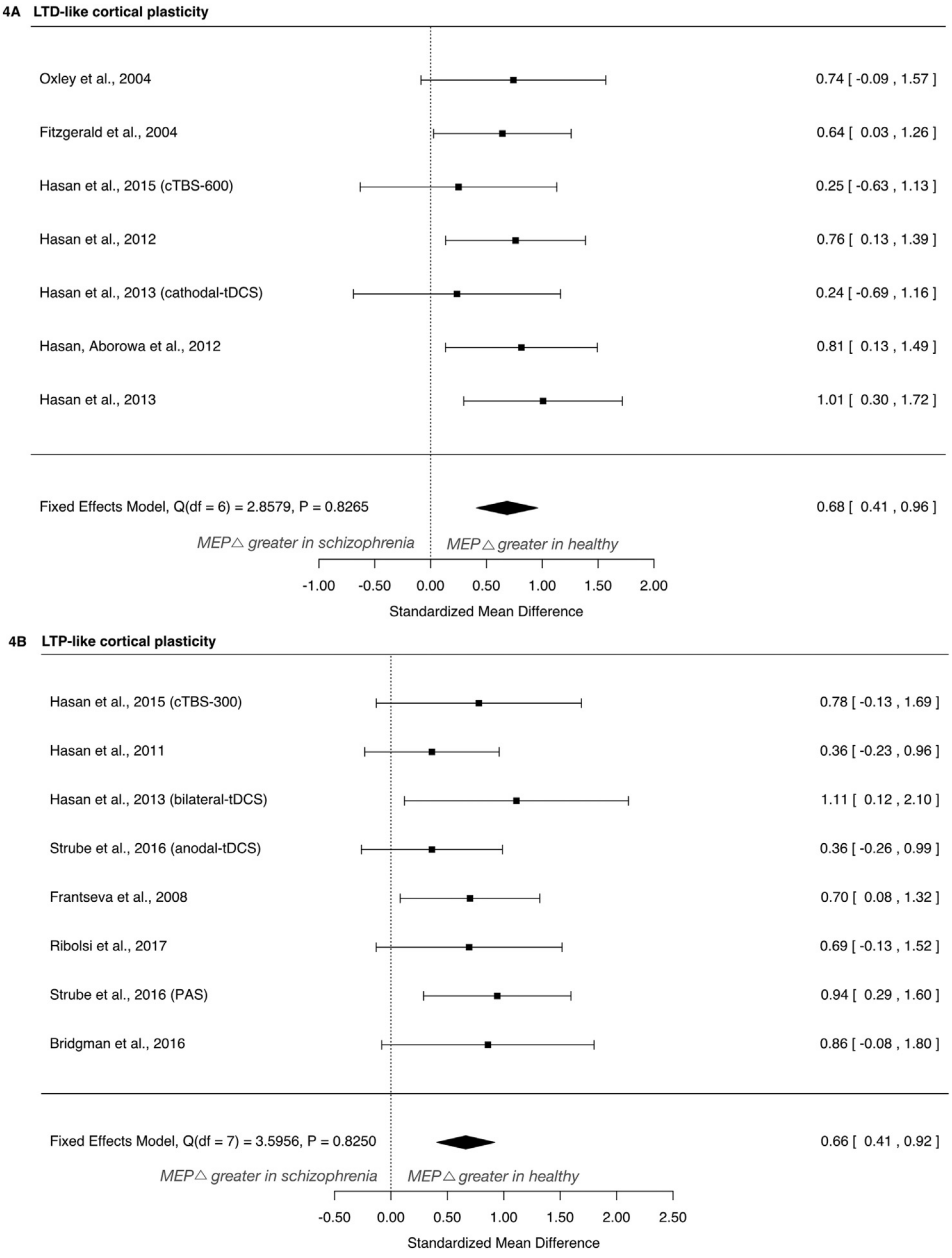

Fig. 4. Cortical plasticity (MEP Δ) meta-analysis forest plots for LTD-like and LTP-like cortical plasticity. A and B are forest plots for LTD-like and LTP-like cortical plasticity (MEP Δ) meta-analyses respectively; MEP Δ = change in motor evoked potential amplitudes following a neuromodulatory perturbation protocol. See Supplementary Table S1 for more details.

Among clinical scenarios, earlier studies in patients with schizophrenia have reported that the illness course and medication status determined plasticity outcomes. One study that examined recent-onset and multiple-episode chronic schizophrenia patients reported diminished cortical plasticity only in the chronic patient group (Hasan et al., 2011). This could either suggest a neurotoxic effect of chronic schizophrenia or an effect of antipsychotic medications – dopamine receptor blockade with sulpiride diminished motor cortical plasticity responses in healthy subjects (Nitsche et al., 2006). However, in our pooled sample analysis, duration of illness did not moderate the cortical plasticity outcomes significantly. Nearly all the studies included in the meta-analysis recruited stable patients on antipsychotic medications with a mean duration of illness ~5.78 years (4.4 to 7.6 years range). There were two studies (Daskalakis et al., 2008; Fitzgerald, 2004) that recruited un-medicated patients; neither of them reported significant differences in cortical plasticity responses between medicated and un-medicated patients. Nevertheless, the sample sizes of un-medicated or recent-onset patients in these studies were ≤10. We believe this would have made the pooled sample underpowered to detect any moderating effect of these potential confounding variables. In addition, we did not observe any moderating effect of cumulative antipsychotic dose (in chlorpromazine equivalents) on the cortical plasticity group-differences. However, there is also a possibility that altered plasticity may in fact antedate – and perhaps be causally related to – the manifestation of clinical symptoms of schizophrenia. Aberrant LTD-like motor cortical plasticity was indeed reported in a cathodal-tDCS study in non-psychotic first-degree relatives of individuals with schizophrenia (Hasan et al., 2013c). Longitudinal studies will be better able to examine the translational potential of such neuromodulatory perturbation protocols in identifying individuals who are at risk for psychotic disorders.

Another clinical source of variation could be the smoking status of patients. A pooled analysis of earlier studies demonstrated impaired LTD-like cortical plasticity only in non-smoking schizophrenia patients, but normal LTD-like cortical plasticity responses in schizophrenia patients

who were chronic smokers (Strube et al., 2015a). Interestingly, varenicline, a partial agonist at the α4β2 nicotinic acetylcholine receptor, increased LTP-like cortical plasticity in schizophrenia patients who were non-smokers. These findings highlight not only the cholinergic regulation of *N* methyl D aspartate (NMDA)-mediated glutamatergic neurotransmission (and thereby plasticity) in schizophrenia (Marchi et al., 2015), but also emphasize the need for meticulous patient selection during recruitment in such studies. This is crucial, especially given the large response variability observed across diverse neuromodulatory perturbation protocols (López-Alonso et al., 2015; van der Kamp et al., 1996). Unfortunately, smoking status was not routinely reported in most studies, and hence we could not perform a meta-regression to examine its moderating effects on cortical plasticity outcomes in this analysis. Yet another potential clinical confounding effect could be mediated by diabetes, which often presents with subtle neurocognitive deficits and is known to be highly comorbid in individuals with schizophrenia (Annamalai et al., 2017). Early reports suggest impaired LTP-like cortical plasticity effects assessed using intermittent theta burst stimulation in patients with type-2 diabetes mellitus (Fried et al., 2016). None of the studies included in this analysis provided information on comorbid diabetes and hence we could not examine its effect on cortical plasticity outcomes. Lastly, brain atrophy, by means of a resulting greater scalp-to-brain distance and added current shunting in the cerebrospinal fluid spaces, could also reduce perturbation effects (Wagner et al., 2007). Since patients with schizophrenia also have varying degrees of brain atrophy (Padmanabhan et al., 2015; Walton et al., 2018), MRI brain imaging to correct for scalp-to-brain distance coupled with projective studies where intensity is accordingly adjusted would be desirable.

From a study methodological standpoint, we examined different perturbation-protocols and the cortical reactivity measurement using TMS-EMG set-up. In summary, none of the above moderated the between-group cortical plasticity outcome in a significant manner. This is despite the various perturbation methods having potentially different, yet inconclusive cellular and network-level mechanisms that have a final common output that resembles LTP/LTD-like experience dependent synaptic plasticity (Huang et al., 2017). However, bubble-plot observations suggested LF-rTMS and PAS perturbation protocols to have less fluctuating effect sizes that were closer to the true, overall effect-size (Fig. 5) as compared to other methods. Newer perturbation methods like theta burst stimulation (Huang et al., 2005), quadripulse stimulation (Ugawa, 2016), quadripulse theta burst stimulation (Jung et al., 2016) and high-definition tDCS (Kuo et al., 2013) that are likely to induce more robust and less variable cortical reactivity changes have not been sufficiently studied in the schizophrenia population. Given the rapid advancements in engineering newer perturbation protocols, it is important that the newer methods are applied in a clinical population after careful experiments that demonstrate their robustness in terms of validity with respect to putative neurobiological underpinnings, and test-retest reliability. We now know form healthy subject experiments that there is a minimum number of trials to record MEPs that is needed to achieve sufficient test-retest reliability of cortical inhibition and plasticity outcomes with neuromodulatory protocols (Chang et al., 2016). However, we did not find a significant moderation of differential cortical plasticity outcomes by the number of trials used in the included studies to measure MEPs (see Supplementary material). The absence of sham stimulation protocols in any of these experiments should also merit a deliberation on possible placebo effects the perturbation protocols could have had on motor cortical reactivity changes. For example, it is known that a sense of expectation and anticipation result in motor cortical excitability changes (Lou et al., 2013). Such expectancy related placebo effects on motor cortical physiology, though not elaborately characterized, could be avoided by either having sham stimulations to account for the sensory effects or alternative control strategies like

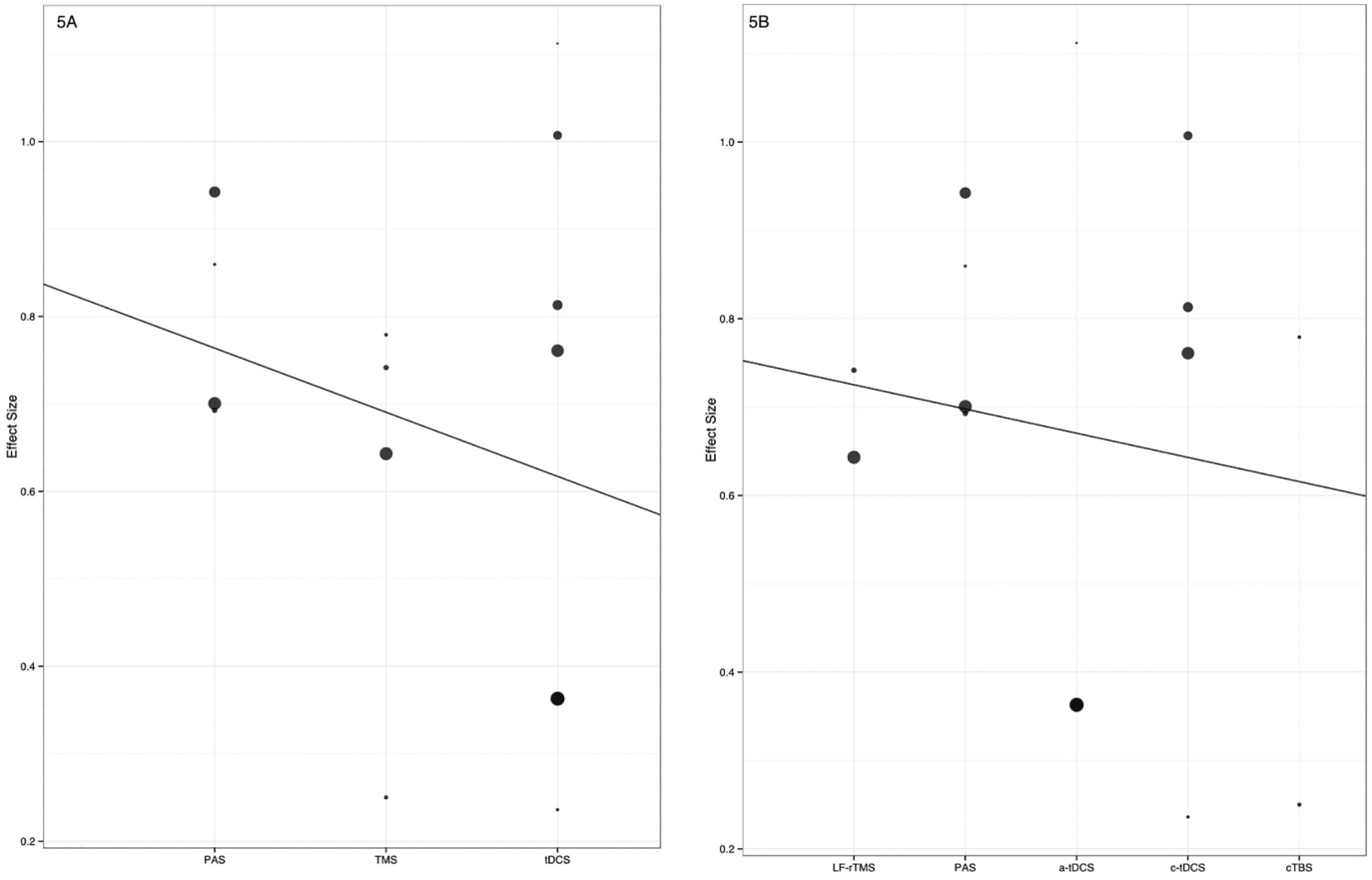

Fig. 5. Bubble plots of effect sizes representing cortical plasticity (MEP Δ) impairments in schizophrenia patients compared to healthy subjects. X-axes (A: generic division & B: specific division) represent the different neuromodulatory perturbation protocols used in the selected studies and Y-axes represent the effect sizes (size of the circle is weighted for sample size.

stimulating a non-motor brain region (Duecker and Sack, 2015). There were very few studies that examined time-course effects of the various neuromodulatory perturbation protocols on MEP Δ between groups. Similarly, there was limited data about effects on other cortical reactivity measures (e.g., RMT and CSP) thus limiting conclusive inferences. These could be the focus of future studies.

Lastly, the overarching diminished cortical plasticity (LTP/LTD-like or homo/heterosynaptic) responses to a range of non-invasive brain stimulation perturbation protocols in schizophrenia partly validates the 'dysplastic' brain model of schizophrenia (Keshavan et al., 2015), especially with respect to the hypo-plasticity observed in most studies. There was insufficient data to systematically examine the association between hypoplastic motor cortical changes and symptom dimensions in the patient group. This is understandable since most studies had recruited stable schizophrenia patients. Examining motor cortical plasticity in actively symptomatic or resistant patients with schizophrenia and patients with homogenous sets of symptoms will enable testing of the aberrant hyper-plasticity that is hypothesized as to be related to some symptom dimensions like affective instability and phasic exacerbations of positive symptomatology (Keshavan et al., 2015). Nevertheless, a diminished plastic brain response to perturbation protocols in schizophrenia lays emphasis on the role of an aberrant, hypofunctioning NMDA receptor system and its downstream effects on maintaining dendritic arborization, glial density, myelination and an optimal excitation/inhibition balance (Friston et al., 2016; Stephan et al., 2009) necessary for optimal network-level brain functioning. Incidentally, the activity-dependent trafficking of the NMDA receptors between synaptic and extra-synaptic sites is also central to optimal synaptic plasticity and experience-dependent learning (Lau and Zukin, 2007). While there is consistent evidence of a diminished motor cortical plasticity response in schizophrenia, very little is known about its specificity to schizophrenia. Indeed, cortical plasticity has been systematically evaluated and found to be abnormal in individuals with depression (Kuhn et al., 2016), autism (Oberman et al., 2016; Pedapati et al., 2016), Alzheimer's dementia (Koch et al., 2017). However, there are no head-to-head comparisons of how cortical plasticity varies across these diverse psychiatric disorders.

Restricting our interpretation on cortical plasticity in schizophrenia to data emerging from TMS-EMG studies focusing on the motor cortex alone might reveal only a partial understanding of its complex pathophysiology. Hence, the importance of TMS-EEG/MRI studies that could provide information with better temporo-spatial and molecular resolution cannot be underestimated. Indeed, evidence from parallel investigations comparing electroencephalographic event related potentials evoked by tetanized auditory stimuli (Mears and Spencer, 2012) and visual high frequency stimulation (Cavus et al., 2012) suggest potentiation deficits in schizophrenia; these deficits also have an association with their neurocognitive performance (Jahshan et al., 2017) and functional outcomes (Kantrowitz et al., 2016). To the best of our knowledge, there are no studies that have combined the assessment of motor and sensory cortex plasticity in schizophrenia. This is an important research gap, which can be addressed by combining motor and non-motor plasticity experiments, especially because the developmental critical periods for cortical plasticity are likely to differ across specialized cortical processes supported by distinct cortical neural networks. As a next step, it needs to be evaluated whether cortical plasticity aberrations observed in the motor cortex parallel those in other cortical regions. The emergence of TMS-EEG cortical plasticity methods (Chung et al., 2017) has the potential to bridge this gap in the near future by enabling readouts from motor, as well as, non-motor cortical areas.

It is possible that each of the perturbation protocols used to elicit a neuroplastic response acts via different neurophysiological and neurochemical mechanisms that are relevant to the pathophysiology of schizophrenia (Wilson et al., 2018). The cortical-level in vivo plasticity elicited using such methods need not always directly correlate with LTP- and LTD-like synaptic-level plasticity, as the cortical-level plasticity is potentially influenced by a range of complex mechanisms such as sliding thresholds, metaplasticity and an optimal cortical excitatory–inhibitory balance (Hensch, 2005). This provides us with the unique opportunity to examine (a) the behavioral correlates of diverse cortical plasticity properties in schizophrenia and (b) their longitudinal trajectories over distinct illness phases that parallel brain development and potentially represent a brain health index (Freitas et al., 2013). Meticulous homogenous subject selection, standardized neuromodulatory protocol delivery, recording and measuring potential confounding variables (e.g., smoking status, comorbid diabetes, genotyping of important plasticity-related polymorphisms) will go a long way in reducing the inter-individual response variability. Implementing these refined approaches can potentially improve the reliability of cortical plasticity responses, and the true inter-subject variability can then be utilized as potential markers of response to not only non-invasive brain stimulation therapies (Osoegawa et al., 2018), but also to antipsychotic medications and cognitive training interventions in schizophrenia.

In conclusion, this meta-analysis of TMS-EMG studies demonstrated hypoactive mechanisms of motor cortical plasticity in patients with schizophrenia as compared to healthy subjects. These deficits were reported in largely stable schizophrenia groups and were not moderated by clinical factors, methodological variability (perturbation-method or cortical reactivity recordings) or study quality. Future studies need to focus on examining the specificity, behavioral correlates and developmental trajectories of these cortical plasticity responses in schizophrenia. Potential clues towards heterogeneous responses (e.g., smoking status, illness stage and medication status, comorbid diabetes and specific genotypes) need to be systematically measured and accounted for. The robust findings in terms of moderate effect size deficits in cortical plasticity in schizophrenia should encourage future studies to examine this novel investigational protocol to supplement conventional neuroimaging and electrophysiological experiments as disease biomarkers.

Conflict of interest statement

Dr. APL was partly supported by the Sidney R. Baer Jr. Foundation, the NIH (R01MH100186, R01HD069776, R01NS073601, R21 NS082870, R21 MH099196, R21 NS085491, R21 HD07616), the Football Players Health Study at Harvard University, and Harvard Catalyst | The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758). Drs. UMM, MVT, JP and MSK have no biomedical financial interests or potential conflicts of interest to declare. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIMHANS, Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health, or the Sidney R. Baer Jr. Foundation. Dr. APL is listed as an inventor on several issued and pending patents on the real-time integration of Transcranial Magnetic Stimulation with electroencephalography and magnetic resonance imaging.

Contributions

UMM performed the literature search, conducted the meta-analysis and drafted the manuscript. MVT also performed the literature search, tabulated all the data and edited the manuscript. JP provided expert-guidance to plan the analysis, gave inputs on performing the meta-analysis and edited the manuscript. APL provided expert-guidance in planning the analysis and edited the manuscript. MSK conceptualized the study, provided expert-guidance to plan the analysis and contributed to editing the manuscript.

Role of the funding source

The funding agency had no role to play in the content and drafting of this manuscript.

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Appendix A. Supplementary data

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