Transcranial magnetic stimulation neurophysiology of patients with major depressive disorder: a systematic review and meta-analysis

Megumi Kinjo1, Masataka Wada1, Shinichiro Nakajima1, Sakiko Tsugawa1, Tomomi Nakahara1, Daniel M. Blumberger2, Masaru Mimura1 and Yoshihiro Noda1

1Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan and 2Department of Psychiatry, Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

Abstract

Major depressive disorder (MDD) is a mental illness with high socio-economic burden, but its pathophysiology has not been fully elucidated. Recently, the cortical excitatory and inhibitory imbalance hypothesis and neuroplasticity hypothesis have been proposed for MDD. Although several studies have examined the neurophysiological profiles in MDD using transcranial magnetic stimulation (TMS), a meta-analysis of TMS neurophysiology has not been performed. The objective of this study was to compare TMS-electromyogram (TMS-EMG) findings between patients with MDD and healthy controls (HCs). To this end, we examined whether patients with MDD have lower short-interval cortical inhibition (SICI) which reflects gamma-aminobutyric acid (GABA)A receptor-mediated activity, lower cortical silent period (CSP) which represents GABA B receptor-mediated activity, higher intracortical facilitation (ICF) which reflects glutamate N-methyl-D-aspartate receptor-mediated activity, and the lower result of paired associative stimulation (PAS) paradigm which shows the level of neuroplasticity in comparison with HC. Further, we explored the effect of clinical and demographic factors that may influence TMS neurophysiological indices. We first searched and identified research articles that conducted single- or paired-pulse TMS-EMG on patients with MDD and HC. Subsequently, we extracted the data from the included studies and meta-analyzed the data with the comprehensive meta-analysis software. Patients with MDD were associated with lower SICI, lower CSP, potentially higher ICF, and lower PAS compared with HC. Our results confirmed the proposed hypotheses, suggesting the usefulness of TMS neurophysiology as potential diagnostic markers of MDD.

Introduction

Overview of depression

Major depressive disorder (MDD) is one of the most common psychiatric disorders, which affects >264 million people worldwide (GBD, 2017 Disease & Injury Incidence, 2018). Depression is associated with a high mortality rate, with a hazard ratio of 1.61 (Pratt, Druss, Manderscheid, & Walker, 2016) and a particularly high suicide rate. These factors, in part, have contributed to the large societal, medical and economic burden of this disease. The first line of treatment for MDD includes psychotherapy and pharmacotherapy; however, at least one-third of patients are resistant to these treatments (Ionescu, Rosenbaum, & Alpert, 2015). Therefore, it is important to elucidate the pathophysiology of MDD to develop effective strategies for treatment-resistant depression.

Disrupted excitatory and inhibitory balance in MDD

Several lines of evidence suggest that there is an imbalance between cortical excitability and inhibition in patients with MDD, whereby there is excessive cortical excitability and reduced cortical inhibition (Gabbay et al., 2017; Sanacora, Treccani, & Popoli, 2012). For example, previous studies have reported decreased gamma-aminobutyric acid (GABA) concentrations and increased glutamate concentrations in the brain of patients with MDD, using proton magnetic resonance spectroscopy (1H-MRS) (Bhagwagar et al., 2008; Moriguchi et al., 2019; Sanacora et al., 2004). In addition, ketamine, which is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, represents an effective treatment...
Depression Rating Scale; CDRS-R, Children in several brain regions including the prefrontal cortex (PFC) imaging studies have noted a reduction of functional connectivity mediated activity. Furthermore, functional magnetic resonance imaging studies have noted a reduction of functional connectivity in several brain regions including the prefrontal cortex (PFC) may be lower in patients with MDD compared to healthy controls (HCs) (Noda et al., 2018; Pittenger & Duman, 2008).

| Author Year | N (controls/patients) | Age (SD) (controls/patients) | %female (controls/patients) | Depression severity (SD) | Patients' characteristics (medicated or unmedicated, VD, etc) | Key findings |
|-------------|-----------------------|------------------------------|-----------------------------|--------------------------|-------------------------------------------------------------|--------------|
| Bella et al. (2011) | 10/15 | 67.7 (3.9)/70.5 (6.6) | 50.0/53.3 | HRSD-17: 14.9 (6.4) | VD | No difference in SICI, CSP, and ICF between groups |
| Bhandari et al. (2018) | 34/48 | 69.1 (8.9)/67.9 (6.9) | 58.8/60.4 | MADRS; 25.9 (4.9) | Late life depression | Lower neuroplasticity induced by PAS in patient group |
| Concerto et al. (2013) | 11/11 | 67.36 (3.75)/62.45 (7.64) | 45.5/50.0 | HRSD-17: MDD 20.27 (4.41), VD 15.91 (7.23) | Divided into MDD group and VD group | No difference in SICI and ICF between patient group and control group, longer CSP in MDD group and no difference in CSP between VD group and control group |
| Croarkin et al. (2013) | 22/24 | 13.77 (2.18)/13.87 (2.11) | 50.0/58.3 | CDRS-R: 58.9 (8.5) | Unmedicated | No difference in SICI and CSP between groups, higher ICF in patient group |
| Croarkin et al. (2014) | 19/14 | 13.9 (2.2)/14.0 (2.1) | 57.9/57.1 | CDRS-R: 59.0 (9.6) | Unmedicated | No difference in LICI between groups |
| Kuhn et al. (2016) | 27/27 | 37.3 (10.3)/38.7 (11.2) | 48.1/44.4 | BDI-II: 23.6 (NA) | Medicated | No difference in neuroplasticity induced by PAS between groups |
| Lefaucheur et al. (2008) | 35/35 | 43 (NA)/56 (16.6) | 51.4/60.0 | MADRS: 32.1 (8.3) | Medicated | Lower SICI in patient group, no difference in CSP and ICF between groups |
| Levinson et al. (2010) | 25/60 | 43.84 (8.95)/47.17 (11.2) | 52.0/63.3 | HRSD-17: 18.6 (11.4) | Divided into TRD group, unmedicated group and medicated euthymic group | No difference in SICI and ICF between groups, shorter CSP in patient group |
| Lewis et al. (2018) | 20/54 | 14.2 (1.76)/15.8 (1.76) | 45.0/64.8 | CDRS-R: 42.9 (13.9) | Divided into depression groups with and without suicidal behavior | No difference in SICI, LICI, and ICF between groups, shorter CSP in patient group |
| Maeda et al. (2000a, 2000b) | 8/8 | 44.9 (NA)/46.8 (NA) | 25.0/37.5 | BDI: 21.5 (11.6) | TRD and unmedicated | No difference in SICI and ICF between groups |
| Münchau et al. (2005) | 6/7 | 39.0 (NA)/43.6 (NA) | 33.0/71.4 | BDI: 56.8 (5.9) | Depressed epilepsy patients and medicated | No difference in SICI and CSP between groups, higher ICF in patient group |
| Pennisi et al. (2016) | 15/16 | 63.8 (7.2)/68.1 (8.6) | NA | HRSD-17: 14.8 (6.1) | VD | Higher SICI in patient group, no difference in CSP and ICF between groups |
| Player et al. (2013) | 23/23 | 38.5 (13.1)/38.0 (12.8) | 56.5/56.5 | MADRS: 30.7 (3.4) | NA | Lower neuroplasticity induced by PAS in patient group |
| Steele et al. (2000) | 19/16 | 40.17 (11.5)/43.1 (8.9) | 68.4/75.0 | BDI: 24.9 (8.8) | NA | longer CSP in patient group |
| Veronezi et al. (2016) | 21/60 | 28.0 (8.0)/37.7 (9.3) | 47.6/68.3 | HRSD-17: 21.7 (3.8) | Divided into atypical, melancholic, and undifferentiated MDD groups | No difference in SICI and ICF between groups, shorter CSP in patient group |

MDD, major depressive disorder; VD, vascular depression; TRD, treatment-resistant major depressive disorder; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; CDRS-R, Children’s Depression Rating Scale-Revised; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory second edition; SICI, short-interval cortical inhibition; LICI, long-interval cortical inhibition; CSP, cortical silent period; ICF, intracortical facilitation; PAS, paired associative stimulation.

approach for treatment-resistant depression (McGirr et al., 2015). Taken together, these findings suggest that patients with depression may have disrupted GABA and glutamate NMDA receptor-mediated activity. Furthermore, functional magnetic resonance imaging studies have noted a reduction of functional connectivity in several brain regions including the prefrontal cortex (PFC) (Zeng et al., 2012), as well as a reduction of PFC volumes in patients with MDD (Botteron, Raichle, Drevets, Heath, & Todd, 2002). These findings support the notion that neuroplasticity in the PFC may be lower in patients with MDD compared to healthy controls (HCs) (Noda et al., 2018; Pittenger & Duman, 2008).
Cortical excitability, inhibition, and neuroplasticity can be measured by TMS paradigms. Output measures of TMS can be assessed in two ways: coupling of TMS with peripheral electromyography (EMG) or with concurrent electroencephalography (EEG) (Farzan et al., 2013). Single- and paired-pulse TMS paradigms have been shown to assess intracortical facilitation (ICF), and intracortical inhibition, which includes short-interval cortical inhibition (SICI) and long-interval cortical inhibition (LICI) (Chen, 2000). SICI consists of a subthreshold condition pulse and suprathreshold test pulse with an interstimulus interval of 1–5 ms and is thought to reflect GABA_A receptor-mediated activity (Hanajima et al., 1998; Ilić et al., 2002; Ziemann,
LICI is composed of a suprathreshold condition pulse and test pulse with an interstimulus interval of 100–200 ms (Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997). LICI is thought to reflect GABA\(\text{B}\) receptor-mediated activity. GABA\(\text{B}\) activity can also be measured using a TMS paradigm known as cortical silent period (CSP), whereby a strong test pulse is delivered during a voluntary muscle contraction (McDonnell, Orekhov, & Ziemann, 2006; Siebner, Dressnandt, Auer, & Conrad, 1998; Wilson, Lockwood, Thickbroom, & Mastaglia, 1993). In contrast to these measures, ICF is thought to be a measure of cortical excitability, specifically glutamate NMDA receptor-mediated activity (Hunt & Castillo, 2012). ICF consists of a subthreshold condition pulse and suprathreshold test pulse with an interstimulus interval of 10–15 ms (Liepert, Schwenkreis, Tegenthoff, & Malin, 1997; Ziemann et al., 1996). An additional TMS paradigm called short-latency afferent inhibition (SAI) is an index of the central cholinergic activity (Tokimura et al., 2000). SAI is measured by delivering TMS over the M1 immediately after contralateral peripheral median nerve stimulation, which attenuates the motor-evoked potential (MEP) (Tokimura et al., 2000). Furthermore, neuroplasticity can be indexed using a TMS paradigm called paired associative stimulation (PAS). This paradigm combines repeated electrical stimulation to the peripheral median nerve of the wrist with TMS to the contralateral primary motor cortex, for over 30 min (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). Depending on the time interval between the PNS and TMS pulses, PAS can induce either long-term potentiation (LTP)-like (e.g. ∼25 ms interval) and long-term depression (LTD)-like (e.g. ∼10 ms interval) neuronal activity (Buonomano & Merzenich, 1998).

Fig. 2. The results of meta-analyses for the SICI, CSP, and ICF paradigms, when VD was included in MDD. Favors A (left side): HC. Favors B (right side): MDD.

4 Megumi Kinjo et al.

https://doi.org/10.1017/S0033291720004729 Published online by Cambridge University Press
Previous studies of TMS neurophysiological paradigms in MDD

As mentioned earlier, research suggests that patients with MDD may have excessive cortical excitability and reduced cortical inhibition, in addition to lower levels of neuroplasticity in the PFC. Several neurophysiological studies using TMS in patients with MDD have attempted to establish support for these hypotheses (Kaskie & Ferrarelli, 2018); however, the results of these studies are inconsistent. Therefore, continued research is necessary in order to elucidate if these hypotheses are valid.

Aim of this review study

Here, we conducted a systematic review and meta-analysis to compare TMS-EMG indices between patients with MDD and HC. Our hypotheses were as follows: patients with MDD would have lower GABA<sub>A/B</sub> receptor-mediated activity, higher glutamate NMDA receptor-mediated activity, and lower levels of neuroplasticity compared to HC. In addition, we explored the effects of clinic-demographic factors such as age, sex, and depression severity on the TMS findings in patients with MDD.

Methods

Search strategy

Research articles written in English were screened by three reviewers using EMBASE, Medline, and PsycINFO from the earliest record to 29 April 2019. The search terms included ‘non-invasive brain stimulation’ or ‘TMS’ or ‘transcranial magnetic stimulation’, ‘brain activity’ or ‘brain waves’ or ‘EEG’ or ‘electroencephalogram’ or ‘electroencephalography’ or ‘EMG’ or ‘MEP’ or ‘motor evoked potential’ or ‘neurophysiology’ or ‘neuroplasticity’ or ‘plasticity’ or ‘plastic’ or ‘short interval intracortical inhibition’ or ‘SICI’ or ‘intracortical facilitation’ or ‘ICF’ or ‘long interval intracortical inhibition’ or ‘LICI’ or ‘paired associative stimulation’ or ‘PAS’ or ‘short latency afferent inhibition’ or ‘SAI’ or ‘contralateral silent period’ or ‘CSP’, and ‘depression’.

Inclusion criteria

Studies were included in the analysis if they met the following criteria: (1) depression was diagnosed by operational diagnostic criteria; (2) TMS-EMG was conducted using any of the following paradigms, SICI, LICI, ICF, SAI, PAS, or CSP; and (3) results were included for both patients with depression and HCs. Various types of depression, such as atypical depression and melancholic depression, were also included. Vascular depression was also included for both patients with depression and HCs.

Analysis

The meta-analyses and meta-regression analyses were conducted using the comprehensive meta-analysis (CMA) Software (Biostat Inc.). Outcome variables were denoted as standardized mean differences (SMD). A 95% confidence interval (CI) was calculated following summary statistics. Study heterogeneity was evaluated using the I<sup>2</sup> statistic with I<sup>2</sup> ≥50% indicating significant heterogeneity. When a two-sided p value was <0.05, it was statistically considered to be significant. Further, we conducted meta-regression analyses to examine the effects of additional factors including patients’ age, gender rate, and severity of depression. For the severity of the depression factor, the Hamilton Rating Scale for Depression (HRSD) with 17 items was selected for the moderator variable. Studies that included the Montgomery–Åsberg Depression Rating Scale (MDARS), Beck Depression Inventory (BDI), or BDI-II scores, were converted to HRSD scores, as there are strong correlations between HRSD score and correlation coefficients of r = 0.88, r = 0.73, and r = 0.74, respectively (Furukawa et al., 2019, Heo, Murphy, & Meyers, 2007). The formula used for the conversion of the MADRS to the HRSD was: HRDS17 = –1.58 + 0.86 × MADRS (Heo et al., 2007). For the conversion of scores on the BDI or BDI-II to the HRSD, published data from a previous study were used (Furukawa et al., 2019, Table 2).

For the included studies with missing data values, we supplemented them using one of the following options: (1) contacting the authors for additional data or (2) enlarging the graphic charts, if present, and measuring the data values with R Studio Software or a ruler. Thus, we also conducted the analyses only on the studies that had complete data and confirmed if the pattern of findings held the same.

Risk of bias of the included studies

We used the risk of a bias assessment tool for non-randomized studies (Kim et al., 2013) to assess the risk of bias for the following factors: the selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. The assessment is shown in online Supplementary Fig. S1.

Publication bias

The publication bias was assessed by Egger’s test using the CMA Software.

Results

Out of 882 initial records, 16 studies were included in this meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement flow diagram is presented in online Supplementary Fig. S2. The characteristics of the included studies are detailed in Table 1. There were nine studies which measured SICI (Bajbouj et al., 2006; Concerto et al., 2013; Croarkin et al., 2013; Lefaucheur et al., 2008; Levinson et al., 2010; Lewis et al., 2018, 2019; Maeda, Keenan, & Pascual-Leone, 2005, 2008, 2009; Veronezi et al., 2016), two studies for LICI (Croarkin et al., 2014; Lewis et al., 2018), nine studies for CSP (Bajbouj et al., 2006; Concerto et al., 2013; Croarkin et al., 2013; Lefaucheur et al., 2008; Levinson et al., 2010; Lewis et al., 2018; Münchau et al., 2005; Steele, Glabus, Shajahan, & Ebmeier, 2005; Veronezi et al., 2016), nine studies for ICF (Bajbouj et al., 2006; Concerto et al., 2013; Croarkin et al., 2013; Lefaucheur et al., 2008; Levinson et al., 2010; Lewis et al., 2018, 2019; Maeda et al., 2009a, 2009b; Münchau et al., 2005; Veronezi et al., 2016), and three studies for PAS (Bhandari et al., 2018; Kuhn et al., 2016; Player et al., 2013). There were no studies that examined the SAI paradigm that met the inclusion criteria. Due to the insufficient number of studies, we did not conduct the meta-analysis on the LICI and SAI paradigms.
**Meta-analysis**

The results of the meta-analysis for SICI, CSP, ICF and PAS are shown in Fig. 1.

SICI and CSP values were smaller in the MDD group compared to the HC group (SICI: SMD = −0.22, CI −0.42 to −0.020, p = 0.031; CSP: SMD = −0.49, CI −0.69 to −0.29, p < 0.001). In contrast, ICF values were greater in patients with MDD compared to HCs (SMD = 0.22, CI 0.171–0.42, p = 0.034). MEP values generated using the PAS paradigm were smaller in the MDD group compared to the HC group (SMD = −0.66, CI −0.96 to −0.36, p < 0.001). Further, for the PAS paradigm, all of the three studies included in this systematic review indicated LTP-like activity.

**The analyses when the studies with missing data values were excluded**

There were four studies measuring SICI (Concerto et al., 2013; Levinson et al., 2010; Maeda et al., 2000a, 2020b; Münchau et al., 2005), one study for CSP (Levinson et al., 2010), three studies for ICF (Levinson et al., 2010; Maeda et al., 2000a, 2020b; Münchau et al., 2005), and two studies for PAS (Bhandari et al., 2018; Player et al., 2013) which had missing data values. Thus, we measured the values from graphic charts in the articles using R Studio Software or a ruler. When these studies with missing data values were excluded from the analyses, the pattern of the findings still remained. However, the finding of ICF became non-significant in this analysis (SICI: SMD = −0.38, CI −0.62 to −0.14, p = 0.0020; CSP: SMD = −0.37, CI −0.59 to −0.15, p = 0.0010; ICF: SMD = 0.18, CI −0.050 to 0.41, p = 0.12). On the other hand, we could not conduct the analysis of the PAS paradigm since there was only one study left.

**The effect of VD on the results**

Three studies employed the SICI, CSP, and ICF paradigms in patients with VD, while no studies were found in this population using the PAS paradigm. When VD was included for the analysis of the SICI paradigm, the result for the meta-analysis became non-significant (SMD = −0.098, CI −0.28 to 0.085, p = 0.30). For the analysis of the CSP paradigm, the result remained significant (SMD = −0.34, CI −0.53 to −0.16, p < 0.001). Similarly, for the ICF paradigm, the result remained significant when VD was included (SMD = 0.27, CI 0.085 to 0.45, p = 0.004) (Fig. 2).

**Meta-regression analysis**

Meta-regression analyses were conducted for the SICI, CSP, and ICF paradigms, while they could not be conducted for the PAS paradigm due to the insufficient number of studies.

First, patients’ age was not associated with the SMD of the SICI, CSP, or ICF paradigms between patients with MDD and HCs (SICI: slope = −0.0084, CI −0.032 to 0.015, p = 0.24; CSP: slope = 0.013, CI −0.027 to 0.052, p = 0.26; ICF: slope = −0.018, CI −0.049 to 0.012, p = 0.12). The scatter plots are displayed in online Supplementary Fig. S3.

Second, the proportion of female patients was not associated with the SMD of the SICI, CSP, or ICF paradigms between patients with MDD and HCs (SICI: slope = 0.019; CI −0.0076 to 0.045, p = 0.083; CSP: slope = 0.018, CI −0.028 to 0.063, p = 0.23; ICF: slope = 0.027, CI −0.012 to 0.066, p = 0.085). The scatter plots are displayed in online Supplementary Fig. S4.

Finally, the severity of depression as assessed by the HRSD-17 was not associated with the SMD of the SICI and CSP paradigms between patients with MDD and HCs (SICI: slope = −0.037, CI −0.10 to 0.030, p = 0.14; CSP: slope = 0.052, CI −0.074 to 0.18, p = 0.21), while it was associated with higher SMDs in the ICF paradigm (slope = 0.15, CI 0.048–0.26, p = 0.0023). The scatter plots are displayed in online Supplementary Fig. S5.

**Publication bias**

Egger’s test showed no publication bias in the analysis of the SICI, CSP, ICF, and PAS paradigms. The funnel plots are displayed in online Supplementary Fig. S6.

**Risk of bias**

The risk of bias of the included studies is summarized in online Supplementary Fig. S1. For ‘random sequence generation’, the risk of bias was ‘unclear’ for four studies which did not mention the method of recruitment of participants. The risk of bias for ‘incomplete outcome data’ was ‘unclear’ for one study which did not specify how data was excluded. For ‘selective reporting’, the risk of bias was ‘unclear’ for all studies since we did not have access to the experimental protocols.

In addition, no specific sponsorship bias was identified for the included studies in this review, as none of the studies were funded by the private sector. Although some studies received funding from companies, those companies was not likely to affect the results because their business was not related to TMS neurophysiology. Other than these studies, some of the included studies mentioned that they were funded by some foundations which were not likely to make sponsorship bias. The other studies stated that they had no conflict of interest, or did not mention about conflict of interest.

**Discussion**

This meta-analysis compared GABA<sub>A</sub> receptor-mediated activity, glutamate NMDA receptor-mediated activity, and neuroplasticity between patients with MDD and HC through comprehensive TMS-EMG neurophysiological indices. Our analyses revealed that compared to HCs, patients with MDD have lower SICI, CSP, and probably higher ICF, with small effect sizes, and lower PAS, with a medium effect size (Fig. 1). These results suggest that patients with MDD have lower GABA<sub>A</sub>B receptor-mediated activity, a lower level of neuroplasticity, and might have higher glutamate NMDA receptor-mediated activity compared with HC. These findings provide support for the proposed cortical excitatory and inhibitory imbalance hypothesis and neuroplasticity hypothesis of MDD. Taken together, our results suggest that out of the five TMS paradigms, lower values of SICI, CSP, and PAS paradigms, and higher ICF could represent biomarkers for MDD, which can be used to distinguish MDD patients from HCs. In contrast to our ICF finding, a previous meta-analysis of glutamatergic neurometabolite levels in MDD as measured by 1H-MRS revealed decreased glutamate + gluta- mine levels in the medial frontal cortex in patients with MDD (Moriguchi et al., 2019). This discrepancy may be due to differences in the region of interest and the modality of measurement. For example, TMS measures functional neural dynamics, while...
CSP), and vice versa. That is, when the excitability of one hemisphere increases (i.e. increased SICI and increased ICF), the inhibitory properties of the contralateral hemisphere also increases in response (i.e. increased ICF and decreased SICI). This finding suggests the existence of a bidirectional cross-talk between motor cortex hemispheres. Our analyses on SICI and CSP were not. This discrepancy is possibly due to the lack of information provided.

When studies of VD were included in the sub-analysis, the group differences in SICI no longer remained significant and differences in CSP became smaller. In contrast, the inclusion of the VD studies increased the group differences of the ICF paradigm (Fig. 2). The majority of patients with VD exhibit dementia-like disruption in cortical excitability and decrease in cortical inhibition (Alexopoulos et al., 1997; Issac, Chandra, & Nagaraju, 2013). Our meta-analyses indicated that patients with VD showed higher cortical excitability and higher cortical inhibition compared to the analysis where they were not included. Thus, our ICF findings were in line with previous research, whereas our analyses of SICI and CSP were not. This discrepancy is possibly due to the compensatory mechanism of interhemispheric inhibition. That is, when the excitability of one hemisphere increases (i.e. increased ICF), the inhibitory properties of the contralateral hemisphere also increases in response (i.e. increased SICI and CSP), and vice versa.

The results of meta-regression on patients’ sex suggest that cortical functions of the M1, including GABA_{A/B} and glutamate NMDA receptor-mediated activity, may not be significantly influenced by age (online Supplementary Fig. S3). In general, however, neurophysiological activities have been shown to decrease with age (Talelli, Ewas, Waddingham, Rothwell, & Ward, 2008). This discrepancy was possibly due to the small number of included studies. Further research with a larger number of studies is needed to confirm the effect of age on these neurophysiological indices.

The results of meta-regression on patients’ sex suggest that cortical functions of the M1, including GABA_{A/B} and glutamate NMDA receptor-mediated activity, do not differ between males and females (online Supplementary Fig. 4). A previous TMS study found a significant difference in TMS-induced MEPs of the lower limbs but not of the upper limbs between males and females (Cantone et al., 2019). This may be because the sex difference in the distance of the corticospinal tract from the M1 to the upper limbs is relatively smaller compared to the lower limbs. In the present systematic review, all of the studies included in this meta-analysis assessed TMS-EMG of the upper limbs. Thus, MEPs measured from the upper limbs may not detect subtle sex differences. In contrast, a previous study explored the effects of female hormones such as estrogen and progesterone on cortical excitability and found significantly higher motor threshold values at the first dorsal interosseous muscle using TMS applied to the M1 in women with amenorrhea compared to women in the early follicular stage (Chagas et al., 2018). This, therefore, highlights a potential difference in cortical functions of the M1 between males and females. Our analysis did not include information regarding the menstrual cycle of the study samples due to the lack of information provided.

The result of meta-regression on the severity of depression for the ICF paradigm suggests that the worse the HRSD-17 score, the higher the glutamate NMDA receptor-mediated activity (online Supplementary Fig. S5). Therefore, ICF may represent a state marker of MDD. In contrast, the results of meta-regression on depression severity for the SICI and CSP paradigms show no correlations between HRSD-17 scores and GABA_{A/B} receptor-mediated activity (online Supplementary Fig. S5). Taken together, our results suggest that while SICI and CSP may be biomarkers of MDD, it is difficult to evaluate the state of depression from the inhibitory function of the corticospinal tract.

There are several novel therapeutic strategies for MDD that target the neurophysiological bases of MDD. For instance, ketamine, a non-competitive antagonist of the NMDA receptor (Anis, Berry, Burton, & Lodge, 1983), is now used in refractory depression at some specialized medical institutions. Since patients with MDD have higher ICF compared to HCs, ketamine may rapidly suppress hyperexcitation in glutamate NMDA receptor-mediated activity, resulting in improvement of depression symptoms.

Another promising pharmacological treatment for MDD is a novel GABA_{A} receptor positive allosteric modulator known as SAGE-217 (3α-hydroxy-3β-methyl-21-(4-cyano-1H-pyrazol-1′-y)-19-nor-5β-pregn-20-one) (Martinez Botella et al., 2017). Our SICI findings showing that GABA_{A} receptor-mediated activity may be lower in patients with MDD compared to HCs is suggestive of the effectiveness of SAGE-217 for the treatment of MDD.

Some neurosteroids have also been shown to affect the state of depression. For example, estrogen attenuates GABA_{A/B} receptor-mediated activities (Lagarde, Wagner, Ronneklev, & Kelly, 1996; Mukherjee et al., 2017). However, no relationship was found between the proportion of females in the included studies and GABA_{A/B} receptor-mediated inhibitory functions in the present meta-regression analysis (see online Supplementary Fig. S4). Another neurosteroid example is allopregnanolone, which is a positive allosteric modulator of the GABA_{A} receptor (Faroni & Magnaghi, 2011). Allopregnanolone also stimulates GABA synthesis by increasing the level of glutamic acid decarboxylase of 67 kDa, resulting in the activation of both GABA_{A/B} receptor-mediated activities (Magnaghi et al., 2010). The results of our analyses on SICI and CSP suggest the effectiveness of allopregnanolone as a potential treatment for MDD in women. In support of this, allopregnanolone has recently been approved by the FDA to treat postpartum depression, a condition that is associated with disrupted GABAergic functioning due to a rapid postpartum drop in progesterone (Walton & Maguire, 2019).

Other than pharmacotherapy, repetitive TMS (rTMS) has emerged as a promising treatment for treatment-resistant depression. rTMS is thought to exert its therapeutic effect through the induction of neuroplasticity in both excitatory and inhibitory synapses (Lenz et al., 2016). Our PAS analysis indicates a lower level of neuroplasticity in patients with MDD compared to HCs, thus suggesting that rTMS could be a useful treatment to target the underlying pathophysiological impairments associated with depression.

The present study has several limitations. First, we failed to perform the meta-analysis for the PAS due to the limited number of the included studies, warranting further research on PAS in MDD. Ongoing investigation as the field continues to grow would improve the accuracy and reliability of the results.
Second, for some studies, we had to impute the results from figures using R Studio software or a ruler which also impacted the accuracy of the findings. When the studies with missing data were excluded from the analyses, the difference of the ICF results between HCs and patients with MDD became non-significant. Therefore, ICF findings in patients with MDD should be interpreted with caution at this time. Further research on the ICF paradigm is needed comparing larger sizes of patients with MDD and HCs. Third, the concomitant medication administered to patients with MDD was not standardized across the studies. Furthermore, as mentioned earlier, the effect of hormonal fluctuation due to the menstrual cycle in females on neurophysiological findings was not considered as a confounding factor. Additionally, there are other potential confounding factors that could affect the results, including, alcohol, drugs, smoking, and physical activity that were not measured in the studies (Huang et al., 2017; Kähkönen, Wilenius, Nikulin, Ollikainen, & Ilmoniemi, 2003; Kalivas & O’Brien, 2008). Finally, three studies using the scales of depression other than HRS-D-17, MADRS, and BDI (Bajbouj et al., 2006; Croarkin et al., 2013; Lewis et al., 2018) could not be included in the meta-regression since the scales other than these three did not correlate with HRS-D-17 score, which we selected as the moderator variable.

In summary, our results provided support for the cortical excitatory and inhibitory imbalance hypothesis as well as the neuroplasticity hypothesis. The present systematic review and meta-analyses on TMS neurophysiology in MDD warrants further research with larger sample sizes to replicate our findings and the consideration of potential confounding factors that may affect neural activity as mentioned above. Finally, given the results of this study, TMS neurophysiology has the potential not only to distinguish MDD from HCs but also to be a useful neuroscientific tool to elucidate the pathophysiology of MDD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720004729

Acknowledgement. The authors would like to acknowledge the assistance of Michelle Goodman for editing related to grammar and language.

Conflict of Interest. None.

References
Alexopoulos, G. S., Meyers, B. S., Young, R. C., Kakuma, T., Silbersweig, D., & Charlson, M. (1997). Clinically defined vascular depression. The American Journal of Psychiatry, 154(4), 562–565.
Anis, N. A., Berry, S. C., Burton, N. R., & Todd, R. D. (2002). Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biological Psychiatry, 51(4), 342–344.
Buonomano, D. V., & Merzenich, M. M. (1998). Cortical plasticity: From synapses to maps. Annual Review of Neuroscience, 21, 149–186.
Cantone, M., Lanza, G., Vinciguerra, L., Puglisi, V., Ricceri, R., Fiscarco, F., … Pennisi, M. (2019). Age, height, and sex on motor evoked potentials. Translational data from a large Italian cohort in a clinical environment. Frontiers in Human Neuroscience, 13, 185.
Chagas, A. P., Monteiro, M., Mazer, V., Baltar, A., Marques, D., Carneiro, M., … Monte-Silva, K. (2018). Cortical excitability variability: Insights into biological and behavioral characteristics of healthy individuals. Journal of the Neurological Sciences, 390, 172–177.
Chen, R. (2000). Studies of human motor physiology with transcranial magnetic stimulation. Muscle & Nerve. Supplement, 9, S26–S32.
Concerto, C., Lanza, G., Cantone, M., Pennisi, M., Giordano, D., Spampinato, C., … Bella, R. (2013). Different patterns of cortical excitability in major depression and vascular depression: A transcranial magnetic stimulation study. BMC Psychiatry, 13, 300.
Croarkin, P. E., Nakonezny, P. A., Husain, M. M., Melton, T., Buyukdura, J. S., Kennard, B. D., … Daskalakis, Z. J. (2013). Evidence for increased glutamatergic cortical facilitation in children and adolescents with major depressive disorder. Jama Psychiatry, 70(3), 291–299.
Croarkin, P. E., Nakonezny, P. A., Lewis, C. P., Zaccariello, M. J., Huxhall, I. E., Husain, M. M., … Daskalakis, Z. J. (2014). Developmental aspects of cortical excitability and inhibition in depressed and healthy youth: An exploratory study. Frontiers in Human Neuroscience, 8, 669.
Faroni, A., & Magnaghi, V. (2011). The neurosteroid allopregnanolone modulates specific functions in central and peripheral glial cells. Frontiers in Endocrinology, 2, 103.
Farzan, F., Barr, M. S., Hoppenbrouwers, S. S., Fitzgerald, P. B., Chen, R., Pascual-Leone, A., & Daskalakis, Z. J. (2013). The EEG correlates of the TMS-induced EMG silent period in humans. Neuroimage, 83, 120–134.
Furukawa, T. A., Reijnders, M., Kishimoto, S., Sakata, M., DeRubeis, R. J., Dimidjian, S., … Cuipiers, P. (2019). Translating the BDI and BDI-II into the HAMD and vice versa with equipercentile linking. Epidemiology and Psychiatric Sciences, 29, e24.
Gabbay, V., Bradley, K. A., Mao, X., Ostrower, R., Kang, G., & Shungu, D. C. (2017). Anterior circulate cortex γ-aminobutyric acid deficits in youth with depression. Translational Psychiatry, 7(8), e1216.
GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. The Lancet, 392(10159), 1789–1858.
Hanajima, R., Ugawa, Y., Terao, Y., Sakai, K., Furubayashi, T., Machii, K., & Kanazawa, I. (1998). Paired-pulse magnetic stimulation of the human motor cortex: Differences among I waves. The Journal of Physiology, 509 (Pt 2), 607–618.
Heo, M., Murphy, C. F., & Meyers, B. S. (2007). Relationship between the Hamilton depression rating scale and the Montgomery-Asberg depression rating scale in depressed elderly: A meta-analysis. The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry, 15(10), 899–905.
Huang, Y.-Z., Lu, M.-K., Antal, A., Classen, J., Nitsche, M., Ziemann, U., & Chen, R. (2000). Studies of human motor physiology with transcranial magnetic stimulation. The Journal of the Collegium Internationale Neurophysiologicum, 11(S), S25–S26.
Bhandari, A., Lissemore, I. J., Rajji, T. K., Mulsant, B. H., Cash, R. F. H., Noda, Y., … Blumberger, D. M. (2018). Assessment of neuroplasticity in late-life depression with transcranial magnetic stimulation. Journal of Psychiatric Research, 105, 63–70.
Botteron, K. N., Raichle, M. E., Drevets, W. C., Heath, A. C., & Todd, R. D. (2003). Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biological Psychiatry, 51(4), 342–344.
https://doi.org/10.1017/S0033291720004729
Ionescu, D. F., Rosenbaum, J. F., & Alpert, J. E. (2015). Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues in Clinical Neuroscience*, 17(2), 111–126.

Issac, T. G., Chandra, S. R., & Nagaraju, B. C. (2013). Transcranial magnetic stimulation in patients with early cortical dementia: A pilot study. *Annals of Indian Academy of Neurology*, 16(4), 619–622.

Kähkönen, S., Wilenius, J., Nikulin, V. V., Ollikainen, M., & Ilmoniemi, R. J. (2003). Alcohol reduces prefrontal cortical excitability in humans: A combined TMS and EEG study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 28(4), 747–754.

Kalivas, P. W., & O’Brien, C. (2008). Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 33(1), 166–180.

Kaskie, R. E., & Ferrarelli, F. (2018). Investigating the neurobiology of schizophrenia and other major psychiatric disorders with transcranial magnetic stimulation. *Schizophrenia Research*, 192, 30–38.

Kim, S. Y., Park, J. E., Lee, Y. J., Seo, H.-J., Sheen, S.-S., Hahn, S., … Son, H.-J. (2013). Testing a tool for assessing the risk for bias for nonrandomized studies showed moderate reliability and promising validity. *Journal of Clinical Epidemiology*, 66(4), 408–414.

Kuhn, M., Mainberger, F., Feige, B., Maier, J. G., Wirminghaus, M., Limbich, L., … Nissen, C. (2016). State-dependent partial occlusion of cortical LTP-like plasticity in major depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 41(6), 1521–1529.

Lagrange, A. H., Wagner, E. J., Ronnekleiv, O. K., & Kelly, M. J. (1996). Estrogen rapidly attenuates a GABAB response in hypothalamic neurons. *Neuroendocrinology*, 64(2), 114–123.

Lefaucheur, J. P., Lucas, B., Andraud, F., Hogrel, J. Y., Bellivier, F., Del Cul, A., … Paillère-Martinot, M. L. (2008). Inter-hemispheric asymmetry of motor corticospinal excitability in major depression studied by transcranial magnetic stimulation. *Journal of Psychiatric Research*, 42(5), 389–398.

Lenz, M., Galanis, C., Müller-Dahlaus, F., Opitz, A., Wierenga, C. J., Szabó, G., … Vlachos, A. (2016). Repetitive magnetic stimulation induces plasticity of inhibitory synapses. *Nature Communications*, 7, 10020.

Levinson, A. J., Fitzgerald, P. B., Favalli, G., Blumberger, D. M., Duigl, M., & Daskalakis, Z. J. (2010). Evidence of cortical inhibitory deficits in major depressive disorder. *Biological Psychiatry*, 67(5), 458–464.

Lewis, C. P., Nakonezny, P. A., Blacker, C. J., Vande Voort, J. L., Port, J. D., … Rosenbaum, J. F., & Alpert, J. E. (2015). Pharmacological approaches to the challenge of treatment-resistant depression. *Molecular Psychiatry*, 24(7), 952–964.

Mulkherjee, J., Cardarelli, R. A., Cantaut-Belair, Y., Deeb, T. Z., Srivastava, D. P., Tyagarajan, S. K., … Moss, S. J. (2017). Estradiol modulates the efficacy of synaptic inhibition by decreasing the dwell time of GABAa receptors at inhibitory synapses. *Proceedings of the National Academy of Sciences of the United States of America*, 114(44), 11763–11768.

Münchau, A., Langosch, J. M., Gerschlager, W., Rothwell, J. C., Orth, M., & Trimble, M. R. (2005). Mirtazapine increases cortical excitability in healthy controls and epilepsy patients with major depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 76(4), 527–533.

Nakamura, H., Kitagawa, H., Kawaguchi, Y., & Tsuji, H. (1997). Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *The Journal of Physiology*, 498( Pt 3), 817–823.

Noda, Y., Zomorrodhi, R., Vila-Rodriguez, F., Downar, J., Farzan, F., Cash, R. F. H., … Blumberger, D. M. (2018). Impaired neuroplasticity in the prefrontal cortex in depression indexed through paired associative stimulation. *Depression and Anxiety*, 35(5), 448–456.

Pennisi, M., Lanza, G., Cantone, M., Ricceri, R., Stampinato, C., Pennisi, G., … Bella, R. (2016). Correlation between Motor Cortex excitability changes and cognitive impairment in vascular depression: Pathophysiological insights from a longitudinal TMS study. *Neural Plasticity*, 2016, 8154969.

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: A convergence of mechanisms. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 33(1), 88–109.

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P., Martin, D., … Loo, C. K. (2013). Neuroplasticity in depressed individuals compared with healthy controls. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 38(11), 2101–2108.

Pratt, L. A., Druss, B. G., Manderscheid, R. W., & Walker, E. R. (2016). Excess mortality due to depression and anxiety in the United States: Results from a nationally representative survey. *General Hospital Psychiatry*, 39, 39–45.

Sanacora, G., Gueorguieva, R., Epperson, C. N., Wu, Y.-T., Appel, M., Rothman, D. L., … Mason, G. F. (2004). Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Archives of General Psychiatry*, 61(7), 705–713.

Sanacora, G., Testranci, G., & Popoli, M. (2012). Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders. *Neuropsychopharmacology*, 62(1), 65–77.

Siebner, H. R., Dressnandt, J., Auer, C., & Conrad, B. (1998). Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle & Nerve*, 21(9), 1209–1212.

Steele, J. D., Glabus, M. F., Shajahan, P. M., & Ebmeier, K. P. (2000). Increased cortical inhibition in depression: A prolonged silent period with transcranial magnetic stimulation (TMS). *Psychological Medicine*, 30(3), 565–570.

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain: A Journal of Neurology*, 123(Pt 3), 572–584.

Talelli, P., Ewas, A., Waddington, W., Rothwell, J. C., & Ward, N. S. (2008). Neural correlates of age-related changes in cortical neurophysiology. *NeuroImage*, 40(4), 1772–1781.

Tokimura, H., Di Lazzaro, V., Tokimura, Y., Oliviero, A., Proface, P., Insola, A., … Rothwell, J. C. (2000). Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *The Journal of Physiology*, 523(Pt 2), 503–513.

Veronezi, B. P., Moffa, A. H., Carvalho, A. F., Gallhardoni, R., Simis, M., Bensehor, I. M., … Bronuni, A. R. (2016). Evidence for increased motor cortical facilitation and decreased inhibition in atypical depression. *Acta Psychiatrica Scandinavica*, 134(2), 172–182.
Walton, N., & Maguire, J. (2019). Allopregnanolone-based treatments for postpartum depression: Why/how do they work? *Neurobiology of Stress, 11*, 100198.

Wilson, S. A., Lockwood, R. J., Thickbroom, G. W., & Mastaglia, F. L. (1993). The muscle silent period following transcranial magnetic cortical stimulation. *Journal of the Neurological Sciences, 114*(2), 216–222.

Zeng, L.-L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., … Hu, D. (2012). Identifying major depression using whole-brain functional connectivity: A multivariate pattern analysis. *Brain: A Journal of Neurology, 135*(Pt 5), 1498–1507.

Ziemann, U., Rothwell, J. C., & Ridding, M. C. (1996). Interaction between intracortical inhibition and facilitation in human motor cortex. *The Journal of Physiology, 496*(Pt 3), 873–881.