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Hemispheric asymmetry of motor cortex excitability in mood disorders – Evidence from a systematic review and meta-analysis

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HIGHLIGHTS

- During major depressive episodes there is lower left than right-hemisphere cortical excitability.
- During bipolar depression there is lower right than left-hemisphere cortical excitability.
- Cortical excitability in healthy volunteersis distinct from that in major depressive disorder.

ABSTRACT

Objective: Mood disorders have been associated with lateralized brain dysfunction, on the left-side for depression and right-side for mania. Consistently, asymmetry of cortical excitability, as measured by transcranial magnetic stimulation (TMS) has been reported. Here, we reviewed and summarized work assessing such measures bilaterally in mood disorders.
Methods: We performed a systematic review and extracted data to perform meta-analyses of interhemispheric asymmetry of motor cortex excitability, assessed with TMS, across different mood disorders and in healthy subjects. Additionally, potential predictors of interhemispheric asymmetry were explored.
Results: Asymmetry of resting motor threshold (MT) among healthy volunteers was significant, favoring lower right relative to left-hemisphere excitability. MT was also significantly asymmetric in major depressive disorder (MDD), but with lower excitability of the left -hemisphere, when compared to the right, no longer observed in recovered patients. Findings on intracortical facilitation were similar. The few trials including bipolar depression revealed similar trends for imbalance, but with lower right hemisphere excitability, relative to the left.
Conclusions: There is interhemispheric asymmetry of motor cortical excitability in MDD, with lower excitability on left when compared to right-side. Interhemispheric asymmetry, with lower right relative to left-sided excitability, was found for bipolar depression and was also suggested for healthy volunteers, in a pattern that is clearly distinct from MDD.
Significance: Mood disorders display asymmetric motor cortical excitability that is distinct from that found in healthy volunteers, supporting the presence of lateralized brain dysfunction in these disorders.

1. Introduction

Mood and emotions are key features in human experience (Purves et al. 2008), dysfunction of which is a central impairment in mood disorders, that are some of the most debilitating neuropsychiatric disorders (Braun et al. 2008, World Health Organization 2017). Historically, brain regulation of mood and emotions has been hypothesized to be lateralized, with emotions of negative valence, such as sadness and fear, associated with the right hemisphere, whereas positive emotions, such as happiness and pleasure, are associated with the left hemisphere (Ross et al. 1994, Berridge and Kringelbach 2013). Consistent with this hypothesis, there is evidence to support asymmetric brain impairments in mood disorders. Specifically, depressive disorders

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have been associated with left-sided predominance of brain lesions (Robinson et al. 1988), as well as hypoperfusion (Bench et al. 1995) and dysfunction of limbic circuit hubs (Peluso et al. 2009) and functional networks (Padmanabhan et al. 2019). On the other hand, manic syndromes and bipolar disorder have been associated with right-sided predominance of brain lesions (Barahona-Corrêa et al. 2020) and other structural abnormalities (Blumberg et al. 2003, Bora et al. 2010, Abé et al. 2015), as well as hypoperfusion (Starkstein et al. 1987, Altshuler et al. 2005) and state-dependent dysfunction of functional networks (Blond et al. 2012).

Non-invasive brain stimulation treatments, such as repetitive transcranial magnetic stimulation (rTMS), have also supported mood laterality. High frequency rTMS (HF-rTMS), which increases activity of targeted brain regions (Gangitano et al. 2002, Valero-Cabré et al. 2007), when applied to the left dorsolateral prefrontal cortex (DLPFC) is a safe and approved treatment for major depression (Mutz et al. 2019), and specifically for treatment resistant depression (TRD) (Gaynes et al. 2014), with manic symptoms described as potential side effects (Xia et al. 2008, Ozten et al. 2013). On the other hand, there is also evidence to support improvement of depression with low frequency rTMS (LF-rTMS) of the right DLPFC (Mutz et al. 2019), which reduces brain activity (Gangitano et al. 2002, Mottaghy et al. 2002), whereas HF-rTMS in this area is reported to be beneficial in treatment of mania (Grisaru et al. 1998, Michael and Erfurth 2004, Saba et al. 2004, Praharaj et al. 2009). Transcranial magnetic stimulation (TMS) has also been used as a tool to assess *in vivo* neurophysiology in humans (Anand and Hotson 2002, Groppa et al. 2012), namely motor cortex excitability (Pascual-Leone et al. 1998, Fitzgerald et al. 2004) or plasticity-like measures (Huang et al. 2005, Chung et al. 2016), some of which with promising features for future use as biomarkers (Benussi et al. 2017, Oliveira-Maia et al. 2017). TMS may thus be used to assess lateralization of cortical excitability or plasticity and, in fact, an initial study using TMS found evidence for asymmetric motor cortex excitability in patients with depression, with lower excitability in the left hemisphere, which was absent in healthy subjects (Maeda et al. 2000). Following this work, others have addressed this question using different TMS research protocols, including distinct excitability and plasticity measures, and/or with increased statistical power. Some (Lefaucheur et al. 2008), but not all (Navarro et al. 2009), support the results of the original study. Nonetheless, to the best of our knowledge, a review of the available evidence, specifically testing if cortical excitability and plasticity measures acquired with TMS research protocols are asymmetric in patients diagnosed with mood disorders, is lacking.

Here, our primary goal was to test, using a meta-analytic approach, if cortical excitability or plasticity, measured using TMS, is asymmetric among individuals diagnosed with major depressive disorder (MDD), bipolar depression or mania, when compared to healthy volunteers. As secondary aims, we also planned to test if any of such asymmetries change after treatment, and to specify determinants of cortical excitability asymmetry, in patients with mood disorders. Considering the strong evidence supporting mood laterality across several different methods, we hypothesized that cortical excitability and plasticity measures, while symmetric in healthy individuals, are asymmetric in patients with mood disorders, with lower excitability in the left relative to the right hemisphere in patients with depression, and in the right relative to the left hemisphere in patients with mania.

2. Methods

2.1. Protocol and registration

The protocol was published in the PROSPERO database (CRD42019145239) and can be consulted online (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=145239).

2.2. Information sources and search strategy

Search was performed on PubMed, Web-of-Science, EMBASE and Cochrane Library to include papers published up to February 2021. Search terms reflected diagnoses of interest (affective, mood, depression, depressive, MDD, TRD, mixed episode, manic, mania, bipolar, hypomania), cerebral laterality (interhemispheric, laterality, lateral, lateralized, unilateral, symmetrical, asymmetrical, asymmetry, hemisphere, hemispheric, transhemispheric, bilateral, intercommissural, transcallosal, bihemispheric, contralateral), physiological measures (excitation, excitability, modulation, modulate, control, change, modify, activity, activate, deactivate, facilitate, facilitation, inhibit, improve, impair, inhibition, adjust, adjustment, transform, induce, induced, modulated, decrease, affect) and non-invasive brain stimulation modality (theta burst stimulation, TBS, transcranial magnetic stimulation, TMS, repetitive transcranial magnetic stimulation, rTMS, intermittent theta burst, iTBS, continuous theta burst, cTBS). Filters were applied to restrict search results to adult human subjects and no restrictions were applied to publication year (please see Table S1 for further details).

2.3. Study selection and eligibility criteria

After eliminating duplicates, two researchers (GC and DRS) reviewed the list of articles independently, selecting eligible articles according to PRISMA guidelines (Moher et al. 2009). Articles in English, French, Portuguese or Spanish were considered, regardless of publication date, country of origin or data collection setting (inpatient and outpatient). Eligibility required inclusion of a clinical cohort of individuals aged 18 years or older, diagnosed with major depressive episode or disorder, manic episode, or bipolar disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM; editions III, III-TR, IV-TR or 5) and/or the International Classification of Diseases (ICD; editions 9, 10 or 11). Eligibility further required reporting at least one bilateral measure of motor cortex excitability acquired using TMS protocols paired with electromyography (EMG) from upper limb muscles (i.e., hand and/or fingers), and/or of motor cortex plasticity measures, such as change of motor cortex excitability after rTMS or theta burst stimulation (TBS) modulation. Articles were excluded if the following comorbidities were reported among those included in the cohort: neurodevelopmental disorders, schizophrenia or other psychotic disorders, substance-related disorders, neurocognitive disorders, major central nervous system (CNS) disease (including epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, cancer with CNS involvement), disorders of the peripheral nervous system, neuromuscular system or muscle-skeleton system (including Guillain-Barré syndrome or muscular dystrophias), and other severe medical conditions (including hepatic failure, paraneoplastic syndrome, chronic or acute renal failure, uncontrolled diabetes, heart failure or other severely debilitating cardiovascular conditions). Control cohorts were obtained from the eligible studies extracted from our systematic literature review, with a case-control design and healthy

volunteers as controls. The inclusion and exclusion criteria for the healthy subject cohort were equivalent to the clinical cohort, except for additional exclusions according to the presence of major depressive episode, MDD, manic episode, or bipolar disorder. While case reports, literature reviews and meta-analyses were not considered for the final analyses, they were screened for additional eligible references that may have been missed by the original search strategy, as were the reference lists of all eligible articles.

2.4. Data extraction, data items and risk of bias

Three researchers (GC, DRS and ERL) extracted data separately according to PRISMA guidelines (Moher et al. 2009). For each paper the following information was collected: first author name, title and journal, publication year, study type, total sample size, cohort type i.e., clinical (MDD, bipolar depression, MDD & bipolar depression and/or mania) and healthy (if available), and respective sample size. For each cohort, in each paper, we recorded percentage of right-handedness, percentage of women, mean age, medication, clinical severity (Hamilton Depression Rating Scale, HAMD; Montgomery-Asberg Depression Scale-MADRS; Beck Depression Inventory, BDI; Young Mania Rating Scale, YMRS), bilateral cortical excitability measures (resting Motor Threshold, MT; active Motor Threshold, aMT; Motor Evoked Potential, MEP; Intracortical Inhibition, from 1 to 3 milliseconds (ms), ICI; Intracortical Inhibition-Facilitation, from 5 to 8 ms, ICI/F; Intracortical Facilitation, from 10 to 15 ms, ICF; Cortical Silent Period, CSP; 140/120 ratio, 120/140), and finally the ratio and/or change in the aforementioned measures after a single session of rTMS or TBS (Delta MEP), as a measure of cortical plasticity. When available, post treatment changes in clinical severity scores and cortical excitability measures were also extracted. If necessary, corresponding authors were contacted to acquire additional data or clarify information provided in the articles. Study quality score was defined by consensus between GC, DRS and ERL, according to Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (Wells et al. 2000).

2.5. Statistical analysis

In order to assess our main outcome, and considering the predicted high heterogeneity between studies, we performed random-effects meta-analyses to compare mean cortical excitability or plasticity measures between left and right hemisphere, separately for each clinical cohort and in the healthy subject cohort, when at least 2 studies were available (Valentine et al. 2010). A similar approach was also performed for mean cortical excitability or plasticity measures (CEM) obtained after treatment. To quantify effect sizes for meta-analyses, we computed the interhemispheric difference (IHD) in the mean for each CEM, according to the following formula:

$$MeanCEM_{IHD} = MeanCEM_{Left} - MeanCEM_{Right}$$

The pooled standard deviation for each $MeanCEM_{IHD}$ (SD_{IHD}) was calculated according to Borenstein, using the following formula, where SD_1 and SD_2 are the standard deviations for $MeanCEM_{Left}$ and $MeanCEM_{Right}$, respectively, and r the correlation between $MeanCEM_{Left}$ and $MeanCEM_{Right}$ (Borenstein et al. 2011):

$$SD_{IHD} = \sqrt{({SD_1}^2 + {SD_2}^2 - 2 \times r \times SD_1 \times SD_2)}$$

Interhemispheric effect sizes, Cohen's d, for each cortical excitability or plasticity measure were computed according to Borenstein formulas for correlated data (Borenstein et al. 2011):

$$d_{IHD} = \frac{MeanCEM_{IHD}}{SD_{Within-Subject}}$$

where $SD_{Within-Subject}$ is:

$$SD_{Within-Subject} = \frac{SD_{IHD}}{\sqrt{2(1-r)}}$$

For MT, one of the CEM, r was assumed to be 0.75 (Dunlap et al. 1996), in accordance with the correlation between MT_{Left} and MT_{Right} obtained from healthy individuals in our center ($r = 0.762$, $p < 0.0001$; see Supplementary Methods and Table S2 for details). In the absence of appropriate individual data to estimate the remaining left–right mean CEMs correlations, r of 0.5 was assumed, in accordance with prior literature (Dunlap et al. 1996, Morris and DeShon 2002, Borenstein et al. 2011).

Publication bias or small study effect was formally tested if at least 10 studies were available (Dalton et al. 2016, Higgins et al. 2019), using the Begg's test, Duval and Tweedie's Trim and Fill analysis (Begg and Mazumdar 1994, Duval and Tweedie 2000), visual inspection of different graphical representations (Duval and Tweedie 2000, Crowther et al. 2012) and leave-one-out meta-analyses. Sensitivity analyses were performed for primary meta-analyses including 10 studies or more, if at least 2 studies from the original meta-analysis could be conserved (Valentine et al. 2010), to test the robustness of our findings, further control for potential bias and explore variables of interest. Handedness sensitivity analysis was performed with studies including only individuals with right hand-dominance. Studies only with left hand-dominant individuals were not available. An additional sensitivity analysis was performed specifically for metanalyses including MT: since it was the only cortical excitability measure where r of 0.75 was assumed in the effect-size calculation, we repeated the primary analyses assuming r of 0.5, like the remaining cortical excitability measures, to test if this factor would impact the overall results.

Separately for each CEM in each cohort, we also performed univariate meta-regressions to find determinants of IHD, whenever data was available for 10 or more studies, according to best practice for meta-regression (Higgins et al. 2019). Specifically, we planned to explore demographic (age, gender, handedness), depression-related (duration of the illness, number of episodes, baseline severity scores, use of medication, treatment refractoriness) and TMS-related characteristics (acquisition muscle), as well as study bias score. Finally, for cortical excitability measures where at least 2 case-control studies were available, we additionally performed exploratory meta-analyses directly comparing the $MeanCEM_{IHD}$, a metric for left side bias, between healthy subjects and the clinical populations. All analyses, including meta-analyses and meta-regressions, were performed in Stata Statistical Software: Release 15 (StataCorp LLC, College Station, TX).

3. Results

3.1. Literature review

The initial literature search resulted in 1434 articles. After title, abstract and full-text review (Fig. 1), 16 articles (Maeda et al. 2000, Bajbouj et al. 2003, Fitzgerald et al. 2004, Bajbouj et al. 2005, Chistyakov et al. 2005, Bajbouj et al. 2006, Bajwa et al. 2008, Lefaucheur et al. 2008, Navarro et al. 2009, Pallanti et al. 2012, Concerto et al. 2013, Fitzgerald et al. 2013, Malsert et al. 2013, Spampinato et al. 2013, Veronezi et al. 2016, Cristancho et al. 2019), published between 2000 and 2019, were included in the systematic review (see Table 1 for full details on each study). Over-

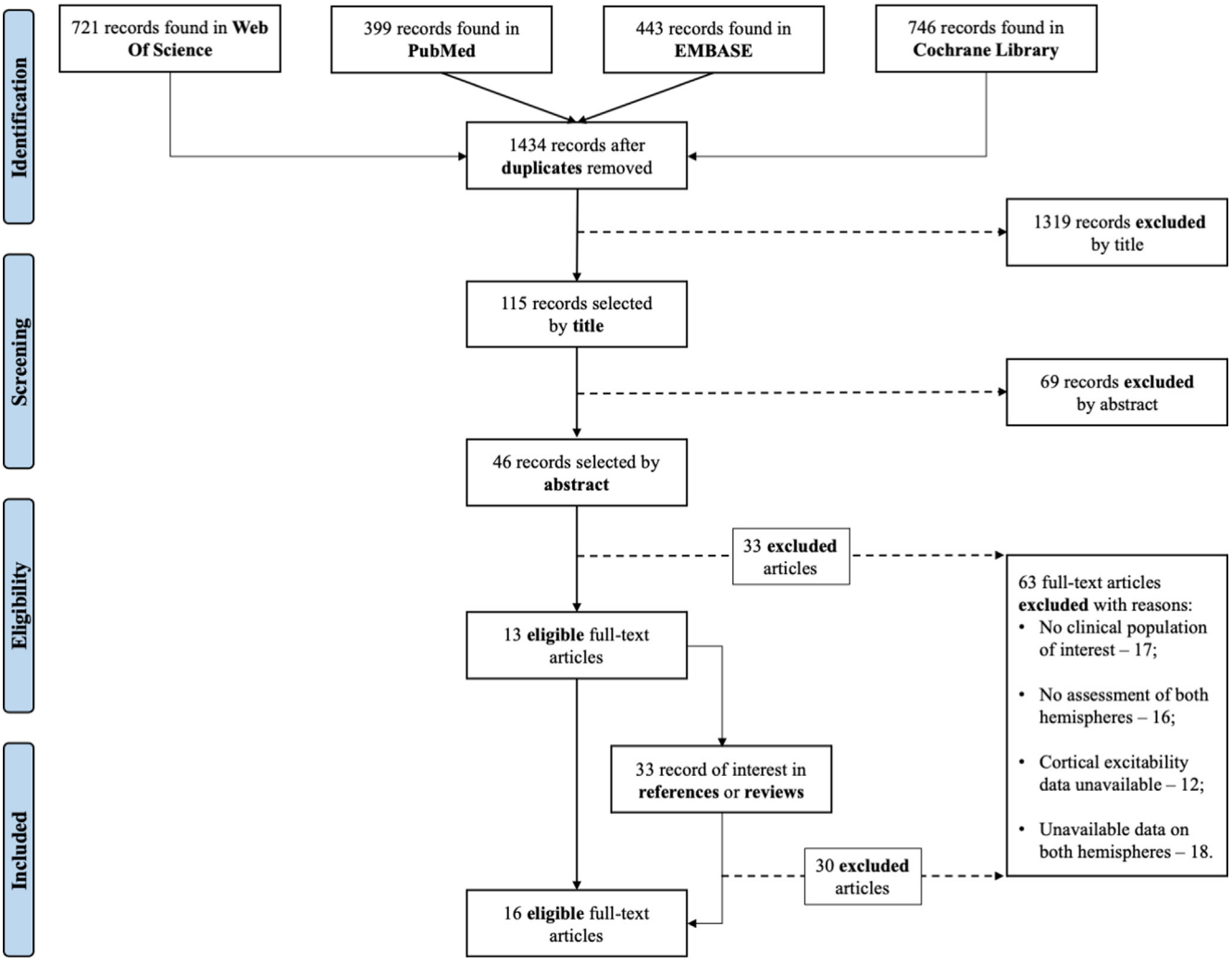

Fig. 1. Article selection flowchart. We performed a systematic review according to PRISMA Guidelines (Moher et al. 2009) and, from an initial pool of 1434 articles, 16 were included (Maeda et al. 2000, Bajbouj et al. 2003, Fitzgerald et al. 2004, Bajbouj et al. 2005, Chistyakov et al. 2005, Bajbouj et al. 2006, Bajwa et al. 2008, Lefaucheur et al. 2008, Navarro et al. 2009, Pallanti et al. 2012, Concerto et al. 2013, Fitzgerald et al. 2013, Malsert et al. 2013, Spampinato et al. 2013, Veronezi et al. 2016, Cristancho et al. 2019).

all study quality was 6 or higher (Table S3), which is considered fair to good quality (Borge et al. 2017). Most studies included medicated patients (Table S4), with only three reporting data from non-medicated patients (Maeda et al. 2000, Chistyakov et al. 2005, Bajbouj et al. 2006). All 16 studies included patients with depression (Maeda et al. 2000, Bajbouj et al. 2003, Fitzgerald et al. 2004, Bajbouj et al. 2005, Chistyakov et al. 2005, Bajbouj et al. 2006, Bajwa et al. 2008, Lefaucheur et al. 2008, Navarro et al. 2009, Pallanti et al. 2012, Concerto et al. 2013, Fitzgerald et al. 2013, Malsert et al. 2013, Spampinato et al. 2013, Veronezi et al. 2016, Cristancho et al. 2019), 12 focusing only on MDD (Maeda et al. 2000, Bajbouj et al. 2003, Bajbouj et al. 2005, Chistyakov et al. 2005, Bajbouj et al. 2006, Bajwa et al. 2008, Lefaucheur et al. 2008, Navarro et al. 2009, Pallanti et al. 2012, Concerto et al. 2013, Spampinato et al. 2013, Veronezi et al. 2016), 4 including both MDD and bipolar depression (Fitzgerald et al. 2004, Fitzgerald et al. 2013, Malsert et al. 2013, Cristancho et al. 2019) and 8 studies including patients with treatment resistant depression (Maeda et al. 2000, Fitzgerald et al. 2004, Navarro et al. 2009, Pallanti et al. 2012, Concerto et al. 2013, Fitzgerald et al. 2013, Spampinato et al. 2013, Cristancho et al. 2019). Only 1 study included a cohort of patients during mania (Malsert et al. 2013). Six studies included a control population (Maeda et al. 2000, Bajwa et al. 2008, Lefaucheur et al. 2008, Concerto et al. 2013, Malsert et al. 2013, Veronezi et al. 2016). The most frequently reported measures of cortical excitability were MT, in 14 studies (Maeda et al. 2000, Bajbouj et al. 2003, Fitzgerald et al. 2004, Bajbouj et al. 2005, Bajbouj et al. 2006, Lefaucheur et al. 2008, Navarro et al. 2009, Pallanti et al. 2012, Concerto et al. 2013, Fitzgerald et al. 2013, Malsert et al. 2013, Spampinato et al. 2013, Veronezi et al. 2016, Cristancho et al. 2019), and paired-pulse measures, namely ICI and ICF, in 9 studies (Maeda et al. 2000, Bajbouj et al. 2003, Fitzgerald et al. 2004, Bajbouj et al. 2005, Bajbouj et al. 2006, Lefaucheur et al. 2008, Concerto et al. 2013, Spampinato et al. 2013, Veronezi et al. 2016). Six studies assessed cortical excitability or plasticity measures before and after treatment (Bajbouj et al. 2003, Bajbouj et al. 2005, Chistyakov et al. 2005, Pallanti et al. 2012, Malsert et al. 2013, Spampinato et al. 2013). Please see Supplementary Material for further details (Tables S5-S9).

Data from the study including patients with mania (Malsert et al. 2013) was excluded from quantitative analysis due to small sample size in the clinical cohort (N = 2 patients). From the remaining cohorts and studies, we extracted data from 608 patients with depression (560 MDD, 48 bipolar depression; 47.4 ± 6.7 years-old; 54.8 ± 16.4% female; 96.7 ± 5.9% right-handed) and 109 healthy

Table 1
Summary table for the eligible studies (Maeda et al. 2000; Bajbouj et al. 2003; Fitzgerald et al. 2004; Bajbouj et al. 2005; Chistyakov et al. 2005; Bajbouj et al. 2006; Bajwa et al. 2008; Lefaucheur et al. 2008; Navarro et al. 2009; Pallanti et al. 2012; Concerto et al. 2013; Fitzgerald et al. 2013; Malsert et al. 2013; Spampinato et al. 2013; Veronezi et al. 2016; Cristancho et al. 2019).

Publication	Control. Study	Total Sample	Treat.	Med.	Study Quality	Cohort Type	Cohort Size	R-Hand. (%)	Age (y)	Fem. (%)	Ep. Dur. (m)	Prev. Ep.	BD	TRD	HAMD	MADRS	BDI	YMRS	Hand Musc.
Maeda et al. 2000	Yes	16	No	No	8	D	8	87.50	46.80	37.50				8	30.50		21.50		APB
						H	8	100.00	44.90	25.00									
Bajbouj et al. 2003	No	12	Yes	Yes	6	D	12	100.00	51.10	58.33	6.70	4.70			32.20				FDI
Fitzgerald et al. 2004	No	60	No	Yes	7	D	60	91.67	45.63	43.33		2.96	6	60		36.50	37.00		APB
Bajbouj et al. 2005	No	30	Yes	Yes	7	D	30	100.00	46.00	36.67	13.60	4.70			25.60		27.70		FDI
Chistyakov et al. 2005	No	22	Yes	No	7	D	22		56.82	68.18					42.96		31.36		APB
Bajbouj et al. 2006	Yes	40	No	No	8	D	20	100.00	42.90	30.00	5.33	2.60			21.10				FDI
						H	20	100.00	44.00	30.00									
Bajwa et al. 2008	Yes	27	No	Yes	8	D	13	100.00	36.30	92.31		1.90					23.00		FDI
						H	14	100.00	33.70	85.71									
Lefaucheur et al. 2008	Yes	70	No		8	D	35	100.00	56.03	60.00					21.23	32.09			APB
						H	35	100.00	43.00	51.43									
Navarro et al. 2009	No	91	No	Yes	7	D	91	84.62	46.13	56.04				91	27.11				APB
Pallanti et al. 2012	No	28	Yes	Yes	7	D	28	100.00	41.30	57.14	5.49			28	23.64				APB
Concerto et al. 2013	Yes	33	No	Yes	8	D	11	100.00	57.18	54.55	4.33			11	20.27				FDI
						H	11		67.36	45.45					4.73				
Fitzgerald et al. 2013	No	179	No	Yes	7	D	179		47.60	69.83			40	179	19.65		37.74		
Malsert et al. 2013	Yes	11	Yes	Yes	7	D	2	100.00	56.50	0.00			2			24.50		0.00	FDI
						M	2	100.00	56.50	0.00						6.00		21.00	
						H	9		34.00	55.56									
Spampinato et al. 2013	No	22	Yes	Yes	8	D	22		52.82	36.36	18.45			22	21.00	27.00			FDI
Veronezi et al. 2016	Yes	81	No	Yes	8	D	60	100.00	37.67	68.33	15.00	5.33			21.67				APB
						H	21	100.00	28.00	47.62									
Cristancho et al. 2019	No	17	No	Yes	8	D	17		48.70	52.94			2	17	13.90				

APB – *Abductor Pollicis Brevis*; BD – Bipolar Depression; BDI – Beck Depression Inventory; Control. – Controlled; D – Depression; Ep. Dur. – Episode duration; FDI – First Digit Interosseus; Fem. – Female; H – Healthy; HAMD – Hamilton Depression Rating Scale; m – months; M – Mania; MADRS – Montgomery–Åsberg Depression Rating Scale; Med. – Medication (studies with or without medicated subjects); Musc. – Muscle; Prev. Ep. – Previous episode; R-Hand. – Right handedness; TRD – Treatment Resistant Depression; Treat. – Treatment: studies with (Yes) or without (No) cortical excitability measures before and after treatment; y – years; YMRS – Young Mania Rating Scale.

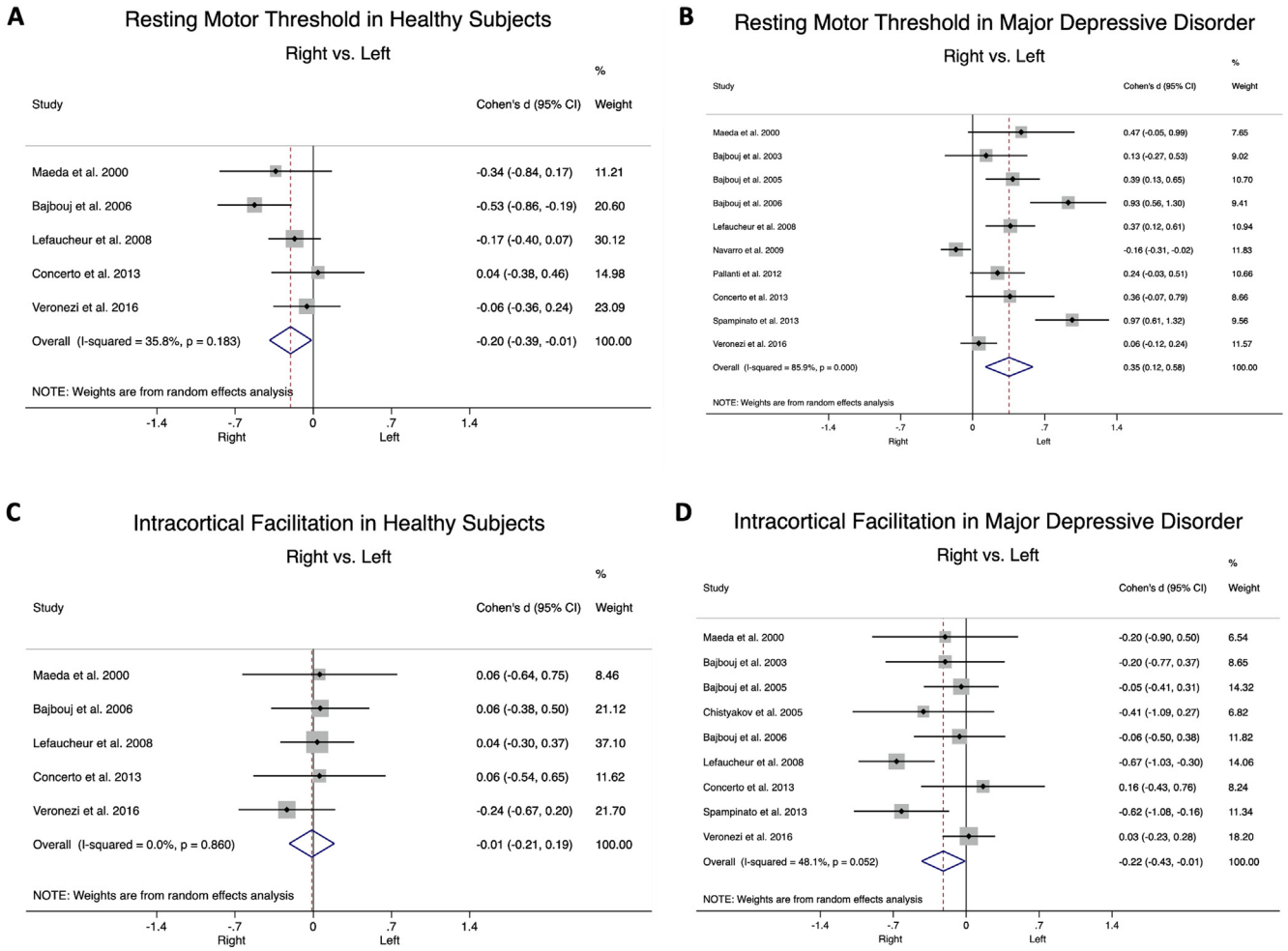

Fig. 2. Cortical excitability random effects meta-analysis in major depressive disorder and healthy subjects. While meta-analysis of resting motor threshold (MT) in healthy subjects showed higher right-sided MT (A), in major depressive disorder (MDD) there was a significant hemispheric asymmetry favoring higher MT (lower cortical excitability) in the left relative to the right hemisphere (B). For intracortical facilitation (ICF), on the other hand, no lateralization was found in healthy subjects (C), whereas lower ICF (lower cortical excitability) was detected on the left relative to the right hemisphere in patients with MDD. CI – Confidence Interval.

individuals (43.5 ± 13.5 years-old; 47.5 ± 21.4% female; all right-handed). Among the depression cohorts, the average duration of current depressive episode was 9.8 ± 5.7 months, average clinical severity was 24.7 ± 7.3 for HAMD, 31.9 ± 4.8 for MADRS and 29.7 ± 6.9 for BDI, and the number of previous episodes was 3.7 ± 1.4.

3.2. Results and synthesis of studies

While MT was significantly asymmetric in healthy subjects (Cohen's d = −0.20, p = 0.03, N = 5) favoring higher MT on the right when compared to the left-hemisphere, among patients with MDD it was significantly asymmetric (Cohen's d = 0.35, p = 0.003, N = 10) but with higher MT, and thus lower cortical excitability, in the left relative to the right-hemisphere (Fig. 2A & B). On the other hand, analyses of ICF supported hemispheric balance of cortical excitability in healthy volunteers (Cohen's d = −0.01, p = 0.90, N = 5), whereas among those with MDD it was significantly asymmetric (Cohen's d = −0.22, p = 0.04, N = 9), with lower ICF, and thus decreased cortical excitability, in left when compared to right-hemisphere (Fig. 2C & D). Asymmetry in both cortical excitability measures was no longer observed in patients with MDD after treatment (MT: Cohen's d = −0.18, p = 0.22, N = 4; ICF: Cohen's d = −0.21, p = 0.23, N = 4; Fig. 3A & B). Interhemispheric asymmetry, but with opposite laterality, was found among the studies of depression including patients with bipolar depression (MT: Cohen's d = −0.21, p = 0.001, N = 3), thus supporting lower cortical excitability in right hemisphere, when compared to the left-side, in the context of bipolar disorder (Fig. S1). Data for the remaining cortical excitability measures, analyzed when at least two studies were available, did not show significant interhemispheric asymmetry in any of the groups of interest, neither in healthy subjects (ICI: Cohen's d = 0.02, p = 0.83, N = 5; ICI at 1 ms: Cohen's d = −0.33, p = 0.16, N = 2; ICI at 3 ms: Cohen's d = −0.12, p = 0.55, N = 2; ICI/F: Cohen's d = −0.11, p = 0.64, N = 2; ICF at 10 ms: Cohen's d = 0.02, p = 0.92, N = 2; ICF at 15 ms: Cohen's d = −0.05, p = 0.80, N = 2; CSP: Cohen's d = −0.01, p = 0.97, N = 4; 120/140: Cohen's d = −0.16, p = 0.23, N = 2) nor patients with MDD (MEP ratio: Cohen's d = 0.03, p = 0.95, N = 2; ICI: Cohen's d = −0.05, p = 0.61, N = 9; ICI at 1 ms: Cohen's d = −0.08, p = 0.66, N = 3; ICI at 2 ms: Cohen's d = −0.17, p = 0.28, N = 2; ICI at 3 ms: Cohen's d = −0.05, p = 0.74, N = 5; ICI/F: Cohen's d = −0.11, p = 0.56, N = 3; ICI/F at 6 ms: Cohen's d = −0.74, p = 0.09, N = 2; ICF at 10 ms: Cohen's d = −0.26, p = 0.19, N = 4; ICF at 15 ms: Cohen's d = −0.08, p = 0.74, N = 3; CSP: Cohen's d = −0.03, p = 0.80, N = 6; 120/140: Cohen's d = −0.21, p = 0.27, N = 2). Due to insufficient number of studies (N < 2), we did not perform metanalyses for aMT, MEP amplitude, ICI/F at 5 ms, ICI/F at 7 ms, ICI/F at 8 ms, ICF at

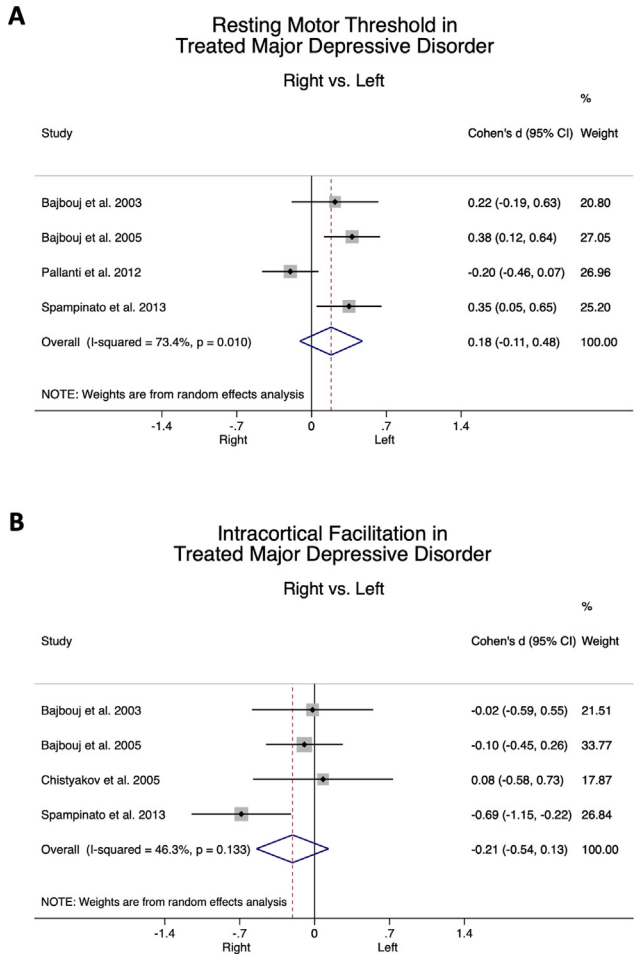

Fig. 3. Cortical excitability random effects meta-analysis after treatment of major depressive disorder. The hemispheric asymmetry in resting motor threshold (A) and intracortical facilitation (B) was no longer observed after treatment for major depressive disorder. CI – Confidence Interval.

11 ms, ICF at 12 ms, ICF at 13 ms, delta MEP amplitude or area under the curve (AUC) in both healthy subjects and patients with MDD, for MEP ratio, ICI at 2 ms and ICI/F at 6 ms in healthy subjects, as well as for any cortical excitability measure, besides MT, in cohorts including patients with bipolar depression.

3.3. Risk of bias across studies

The number of studies available allowed to correctly assess the risk of publication bias for studies with MT in patients with MDD (Dalton et al. 2016). The Begg's test, testing publication bias/small-studies effect, demonstrated insufficient evidence to consider the presence of publication bias (p = 0.28). Moreover, all funnel plots (Fig. S2) were fairly symmetric and, while Duval and Tweedie's Trim and Fill analysis imputed a single study, this study did not change the overall effect (Cohen's d = 0.29, p = 0.01, N = 10 + 1). In the Impact Contours Plot, a graphical augmentation of the funnel plot that illustrates the potential impact of a new study on the meta-analysis, showed that this meta-analysis is robust to the impact of a new study. Moreover, when performing leave-one-out meta-analyses (Fig. S3), the MT in MDD overall effect was not dependent on a single study. For the remaining meta-analyses, evidence for publication bias or small study effect cannot be excluded due to the small number of studies available (Dalton et al. 2016, Higgins et al. 2019).

3.4. Sensitivity analyses

When performing sensitivity analyses, we were able to further explore interhemispheric asymmetry for studies assessing MT in patients with MDD. MT asymmetry in MDD was conserved irrespective of medication status, in studies including only right-handed individuals, in the highest quality studies, in studies including control cohorts, in studies including treatment resistant MDD patients and studies including a before and after treatment assessment (Fig. S4A-G). Regarding the absence of asymmetry after treatment, it was similarly observed when only the sub-cohort with treatment responders was considered (Fig. S4H). Finally, we found a similar MT lateralization effect in MDD when assuming a *r* of 0.5 in effect size calculation, as used for the other cortical excitability measures (Fig. S4I).

3.5. Exploratory analyses of interhemispheric asymmetry

The number of studies available was sufficient to further explore factors associated with interhemispheric asymmetry (MT_{IHD}) for studies with MT in patients with MDD. Such factors were explored using univariate random-effect meta-regressions of MT_{IHD}, namely for age, gender, study quality, baseline clinical severity by HAMD and muscle where EMG was acquired (Table S10). Other factors were not explored due to small number of studies available (N < 10). The percentage of women included in each study was negatively associated with left side MT lateralization in MDD ($ß_1 = -0.02 \pm 0.01$, p = 0.02, N = 10; Fig. S5). The remaining meta-regressions were not significant.

Finally, for studies including control cohorts we directly compared the $MeanCEM_{IHD}$, a metric for left side bias, between healthy subjects and patients with MDD. In MDD there was a left side bias in MT when compared to healthy subjects (Cohen's d = 0.84, p = 0.004, N = 5; Fig. S6), further supporting lower cortical excitability in the left hemisphere when compared to right hemisphere, in patients with MDD. Importantly, such bias was not dependent on specific changes of cortical excitability in neither the left nor the right side of the brain (Fig. S7). Left side bias was not observed for the remaining cortical excitability measures (ICI: Cohen's d = 0.04, p = 0.82, N = 5; ICI at 1 ms: Cohen's d = 0.12, p = 0.72, N = 2; ICI at 3 ms: Cohen's d = 0.25, p = 0.34, N = 2; ICI/F: Cohen's d = 0.09, p = 0.79, N = 2; ICF: Cohen's d = −0.15, p = 0.56, N = 5; ICF at 10 ms: Cohen's d = −0.01, p = 0.98, N = 2; ICF at 15 ms: Cohen's d = 0.22, p = 0.39, N = 2; CSP: Cohen's d = −0.14, p = 0.34, N = 4; 120/140: Cohen's d = −0.21, p = 0.31, N = 2). The number of available case-control studies was insufficient (N < 2) to perform similar analyses for aMT, MEP amplitude or ratio, ICI at 2 ms, ICI/F at 5 ms, ICI/F at 6 ms, ICI/F at 7 ms, ICI/F at 8 ms, ICF at 11 ms, ICF at 12 ms, ICF at 13 ms and delta MEP amplitude or AUC, and in reports including patients with bipolar depression.

4. Discussion

In the current study, we tested if available evidence regarding cortical excitability supports the hypothesis that mood disorders are associated to asymmetric brain dysfunction (Bench et al. 1995, Blond et al. 2012). We have shown that cortical excitability is asymmetric in patients with major depressive disorder, and distinct from what is found in healthy volunteers, bipolar depression, or mania (please see Fig. 4 for a summary of results). To the best of our knowledge, this was the first time this hypothesis was tested formally by a systematic analysis of published evidence, not only in major depressive disorder but also in other mood disorders.

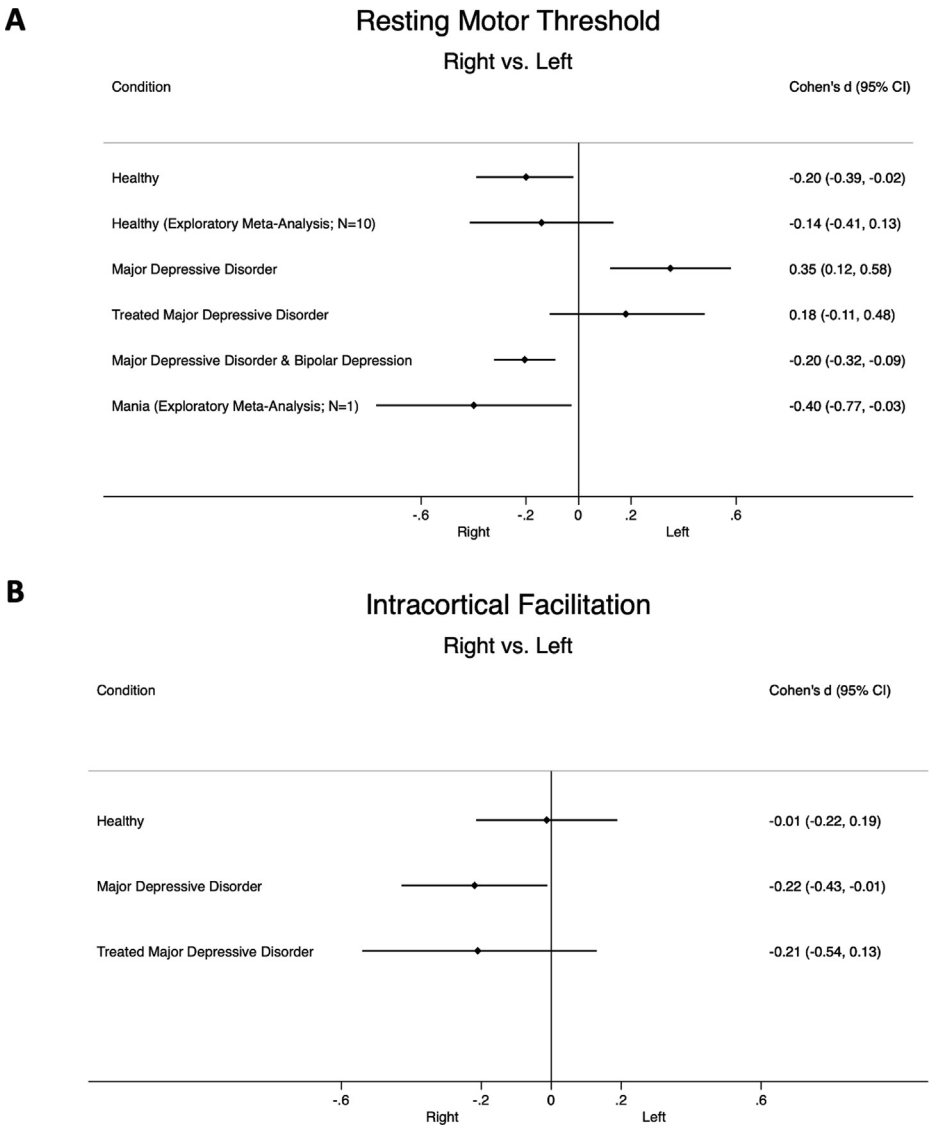

Fig. 4. Cortical excitability hemispheric asymmetry across mood disorders. When cortical excitability is assessed using resting motor threshold (MT; A) or intracortical facilitation (ICF; B), there is a consistent hemispheric asymmetry, favoring lower cortical excitability on the left when compared to the right side for major depressive disorder and on the right when compared to the left side for studies including patients with bipolar depression. In an MT exploratory meta-analysis (N = 1), i.e., considering a single study excluded in the full-text phase, mania showed similar right-sided cortical excitability when compared to the left hemisphere. In healthy subjects, while for ICF there was no evidence for interhemispheric asymmetry, for MT there was lower cortical excitability in the right relative to the left hemisphere. However, in another exploratory meta-analysis (N = 10), i.e., adding five cohorts of healthy subjects from articles excluded in the full-text phase, MT was found to be symmetric. CI – Confidence Interval.

Specifically, we found that MT, a cortical excitability measure which is thought to reflect neuronal membrane excitability (Ziemann et al. 1998), as well as ICF, which may reflect excitatory inputs from glutamatergic pathways (Liepert et al. 1997, Ilić et al. 2002) and/or depression of GABAergic function (Pearce et al. 1995), were significantly asymmetric in major depressive disorder, with higher MT and lower ICF in the left relative to the right motor cortex, favoring lower excitability of the left relative to the right side (Liepert et al. 1997, Ilić et al. 2002, Groppa et al. 2012). Nevertheless, it is also important to consider that these measures, MT in particular, are impacted by age and cortical atrophy (Kozel et al. 2000), which may also contribute to these findings. A distinct pattern was observed in healthy subjects: while there was no evidence of asymmetry for ICF, for MT there was significant asymmetry, but with lower right-sided cortical excitability, when compared to the contralateral side. Interestingly, in an additional exploratory analysis, adding five cohorts of healthy subjects from articles excluded in full-text phase due to characteristics of the clinical populations, MT was found to be symmetric (Cohen's $d = -0.14$, $p = 0.31$, $N = 10$; Fig. 4), supporting the possibility that motor cortical excitability may actually be symmetric in healthy individuals. Furthermore, when directly comparing patients with MDD and healthy subjects from each manuscript using a measure of left-sided MT bias, the evidence was supportive of lower cortical excitability in the left when compared to the right-hemisphere in patients with major depressive disorder. Importantly, such bias was not dependent on specific cortical excitability changes on the left or right-side (Fig. S7). These findings further support our main conclusion, namely that it is the interplay between both hemispheres that is potentially disrupted in patients diagnosed with major depressive disorder, rather than changes in either of the hemispheres.

Importantly, impaired left–right balance of cortical excitability in major depressive disorder, as reflected by MT, was robust even when controlling for different potential sociodemographic or clinical confounding factors, such as medication (Kimiskidis et al.

2006, Navarro et al. 2009) or handedness. Concerning the latter, we restricted the analysis to studies including only right-handed patients, and results were equivalent. While studies including only left-handed patients were not available, future studies in this population would help interpret the impact of handedness in MT laterality in major depressive disorder. Moreover, after treatment with different therapeutic strategies, including medication combined with ECT (Bajbouj et al. 2003) or with rTMS (Bajbouj et al. 2005, Pallanti et al. 2012, Spampinato et al. 2013), MT asymmetry was no longer observed, further supporting that lower left than right-sided cortical excitability assessed with MT may be a promising state marker of major depressive disorder, that should be further explored in future studies. These results also support previous electrophysiologic and neuroimaging evidence for impaired left sided activity across several brain regions in untreated major depressive disorder patients, when compared to controls or to the other side of the brain (Kocmur et al. 1998, Brody et al. 2001, Diego et al. 2001, Knott et al. 2001, Mottaghy et al. 2002). Furthermore, and similarly to what we have found in the current meta-analysis, effective pharmacological and non-pharmacological antidepressant treatments induced functional changes to restore the activity of these regions (Kocmur et al. 1998, Brody et al. 2001, Mottaghy et al. 2002, Bellani et al. 2011). One of the non-pharmacological treatment strategies is rTMS, where treatment of MDD is performed through stimulation of lateralized cortical regions of the brain (Mutz et al. 2019). Specifically, for treatment of depression, either high frequency rTMS, that increases cortical excitability, is applied to the left DLPFC, or low frequency rTMS, that reduces cortical excitability (Gangitano et al. 2002, Mottaghy et al. 2002), is applied to the right DLPFC (Mutz et al. 2019). Our findings support the lateralized impact of these rTMS protocols, suggesting that cortical excitability may need to be increased in the left hemisphere, and/or decreased in the right hemisphere, to normalize asymmetric patterns of brain activity in patients with major depressive disorder. Nevertheless, this hypothesis, which may suggest another potential treatment mechanism of major depressive disorder, needs to be further clarified in future prospective studies, that should include different treatment modalities, not only brain stimulation strategies, but also psychotherapy and medication, in combination or as single treatment modalities.

We also found that studies including more women revealed less MT asymmetry among patients with MDD. Because data was not reported separately according to gender, we cannot conclude that women have decreased cortical excitability asymmetry when compared to men. Nevertheless, we believe this result merits further consideration and should be explored in future studies, particularly since this is not the first time that gender-dependent differences in cortical excitability (Perciavalle et al. 2010) and neuroplasticity (Ridding and Ziemann 2010) have been reported, typically with higher values among women. It is also interesting to speculate to which degree variability in hemispheric asymmetry of cortical excitability may contribute towards antidepressant response to rTMS, given that prior meta-analyses of rTMS efficacy have shown that in studies with more women also there is a higher likelihood of acute (Kedzior et al. 2014) and durable (Senova et al. 2019) antidepressant response.

Regarding findings for other mood disorders, beyond MDD, interpretations must be made with great caution, given the small number of studies that are available. It is nevertheless noteworthy that, in studies of depression including patients diagnosed with bipolar disorder, while hemispheric asymmetry was also found, it had opposite laterality, favoring lower motor cortex excitability in the right hemisphere when compared to the left-side. Furthermore, in one of the studies excluded from our review, due to comorbid substance use disorder (Ruiz-Veguilla et al. 2016), patients with mania had lower right relative to left-sided cortical excitability (Fig. 4). Overall, these results suggest that mood changes associated to bipolar disorder (bipolar depression and mania) may be associated with similar patterns of cortical excitability, with lower right-sided excitability, when compared to the contralateral hemisphere. However, it is also important to underline that a similar pattern of MT lateralization was also observed in our analyses of healthy subjects that, nevertheless, was no longer observed in an exploratory analysis with additional control cohorts, where no evidence of asymmetry was found (Fig. 4). While future studies should be conducted to explicitly address the question of cortical excitability asymmetry in bipolar disorder, the exploratory findings reported here support previous claims of right-sided dysfunction in this disorder (Blond et al. 2012). Furthermore, if these findings are confirmed, asymmetry of cortical excitability may be a relevant diagnostic biomarker for affective disorders, contributing towards efforts to classify and differentiate bipolar depression from MDD according to measures of brain function (Hirschfeld et al. 2003, Manelis et al. 2020). Hence, while this evidence cannot be viewed as definitive, cortical excitability asymmetry assessed with MT should be explored in future studies, not only as a potential state marker of major depressive disorder, as stressed above, but also as a diagnostic biomarker to distinguish major depressive disorder from bipolar depression.

Interestingly, the finding of lower right than left-sided cortical excitability in bipolar depression is somewhat conflicting with the evidence of positive clinical effects of right-sided low frequency rTMS and left-sided high frequency rTMS in bipolar depression (Nguyen et al. 2021). However, it is important to consider that available evidence concerning rTMS efficacy for treatment of bipolar depression is still limited. While some studies have favored its efficacy (Nguyen et al. 2021), others have discouraged its use (McGirr et al. 2021). Uncertainty regarding efficacy of different rTMS protocols for bipolar depression does not allow for a definitive explanation for this potential conflict regarding the evidence presented here. However, it is noteworthy that rTMS may have paradoxical effects according to baseline conditions (Fecteau et al. 2006, Silvanto et al. 2008, Kobayashi 2010). It is thus possible that baseline level of cortical excitability determines the direction of the response to rTMS (Silvanto et al. 2008), with atypical cortical excitability in bipolar depression determining unexpected physiological responses to this form of brain stimulation. Nevertheless, this is a question that will require additional research.

For the remaining cortical excitability measures, we were not able to find significant evidence of lateralization across mood disorders. This could result from several different factors that may have conditioned our findings. First, the small number of eligible studies may have decreased the power to detect statistical significance. In fact, significant findings were restricted to MT and ICF, which were the measures with most eligible studies. Second, the methodologies for acquisition of the less common cortical excitability measures are more heterogeneous, that may have decreased reproducibility within and between studies, leading to more variability. Finally, asymmetry as assessed by these specific cortical excitability measures may in fact be absent, while for MT and ICF it is present, since different mechanisms have been associated to different measures of cortical excitability. As an example, while MT is mainly associated to excitatory cellular machinery such as ionic channels conductivity (Ziemann et al. 1998), ICI has been linked to inhibitory mechanisms such as GABA neurotransmission (Ilić et al. 2002). Accordingly, future studies should be conducted, not only aiming to understand if other TMS cortical excitability measures are also lateralized in the brain, but also clarifying which specific cortical excitability mechanisms are asymmetrically impaired in affective disorders.

In this study we found evidence supporting asymmetry of motor cortex excitability in affective disorders, with distinct

patterns for major depressive disorder and bipolar depression. In fact, while neurophysiology of motor cortex excitability is still poorly understood, interhemispheric asymmetry of motor cortex excitability has been previously associated to neurobiology of emotion (Cicinelli et al. 2000, Cicinelli et al. 2003, Schutter et al. 2008, Koch et al. 2011). Furthermore, current evidence supports the hypothesis that, in affective disorders, there is interhemispheric dysregulation of membrane excitability in pyramidal neurons and of gamma-aminobutyric acid (GABA) and glutamate neurotransmission (Maeda et al. 2000, Lefaucheur et al. 2008, Malsert et al. 2013). This hypothesis is consistent with current theories on the pathophysiology of affective disorders, where the monoamine theory has been replaced by a more complex model including dysregulation of GABAergic and glutamatergic synaptic neurotransmission (Brambilla et al. 2001, Kugaya and Sanacora 2005). In fact, different lines of evidence, including not only TMS studies but also cerebrospinal fluid analysis, positron emission tomography (PET) and magnetic resonance spectroscopy (MRS), have implicated both GABA and glutamate in pathophysiology of affective disorders (Petty and Schlesser 1981, Brambilla et al. 2001, Kugaya and Sanacora 2005, Lefaucheur et al. 2008, Yüksel and Öngür 2010, Malsert et al. 2013, Reddy-Thootkur et al. 2020). Furthermore, successful treatment with psychotropic medication, electroconvulsive therapy (ECT) and rTMS were found to be associated with the normalization of GABA or glutamate dysfunction (Sanacora et al. 2002, Michael et al. 2003, Pfleiderer et al. 2003, Sanacora et al. 2003, Luborzewski et al. 2007), and both neurotransmitter systems have also been explored, with promising results, as potential targets for treatment (Krystal et al. 2002, Mathew et al. 2008).

Potential limitations of this study should be considered. First, we have collected a small number of studies with small size cohorts – especially when considering studies including bipolar depression and/or mania. However, we have conducted a very thorough systematic review, which included a search strategy comprising four literature databases while also reviewing the lists of references from eligible articles and literature reviews included in our search results. Hence, we believe these strategies led us to collect the largest pool of studies assessing bilateral TMS cortical excitability measures among patients with mood disorders. A second limitation results from the heterogeneity between studies. Yet, several strategies were used to control for this potential limitation. In fact, since high levels of heterogeneity were expected, random effect meta-analyses were planned and conducted, as mentioned in the review protocol. Moreover, we have used standardized effect-sizes, decreasing the potential impact of study heterogeneity in the overall results. Also, when appropriate and according to our review protocol, we conducted several sensitivity analyses to confirm the robustness of our findings. A third limitation is the fact that because we have formally tested several TMS cortical excitability measures, false positive results may occur. While this is in fact a possibility, several facts argue to the contrary. First, meta-analyses are performed to clarify false positive results at the individual study level and, when performed according to standard procedures, as was the case here, meta-analytic false positive results are unlikely (Moher et al. 2009). Furthermore, all our significant meta-analyses are consistent with a single main finding: in major depressive disorder, motor cortical excitability is asymmetric, with lower values in the left when compared to the right hemisphere, while in bipolar disorder and in healthy volunteers cortical excitability is lower in the right relative to the left hemisphere, or symmetric. The internal coherence of our findings is confirmed across different cortical excitability measures (MT and ICF) and across sensitivity analyses. Furthermore, our results are consistent with previous data supporting similar lateralization patterns in studies using other research methods, such as electroencephalography and several neuroimaging modalities (Kocmur et al. 1998, Brody et al. 2001, Diego et al. 2001, Knott et al. 2001, Mottaghy et al. 2002, Bellani et al. 2011), supporting the presence of a relevant biological effect. Finally, it is arguable that cortical excitability measures acquired in the motor cortex are relevant for pathophysiology of affective disorders, since they may not reflect brain dysfunction in regions more consistently associated to these conditions, such as the prefrontal cortex (Koenigs and Grafman 2009, Blond et al. 2012). However, it is noteworthy that both major depressive disorder and bipolar depression may impact the motor system, with significant changes in motor function reported in patients diagnosed with both disorders (Caligiuri and Ellwanger 2000, Lohr and Caligiuri 2006). Moreover, it is known that activity in the prefrontal and motor cortices is associated in cognitive tasks, where attention to action, for example, increased the effective connectivity between dorsal prefrontal cortex and the motor system (Rowe et al. 2002, Rowe et al. 2005). Additionally, rTMS modulation of motor cortex excitability has been shown to predict antidepressant response to prefrontal cortex rTMS (Oliveira-Maia et al. 2017, Hinchman et al. 2018), further suggesting associations between motor cortex excitability and prefrontal cortex excitability and/or function. Additional studies using TMS-Electroencephalogram cortical excitability measures, acquired directly in prefrontal regions (Voineskos et al. 2019) may contribute to clarify this hypothesis.

5. Conclusions

In conclusion, we have shown that there is interhemispheric asymmetry of motor cortical excitability in major depressive disorder, with lower excitability in the left when compared to the right-hemisphere. Interhemispheric asymmetry, but with lower excitability on the right when compared to the left hemisphere, was found for bipolar depression and may also be present in mania. The possibility of lower right-sided excitability, relative to the left, was also suggested for healthy volunteers, that was thus clearly distinct from the pattern in major depressive disorder. However, exploratory analyses also suggested the possibility that motor cortical excitability is symmetric in healthy volunteers, further supporting the possibility that lateralized brain dysfunction is a characteristic of patients with mood disorders.

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None of the aforementioned agencies had a role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, in the preparation, review, or approval of the manuscript, nor in the decision to submit the manuscript for publication.

The remaining authors declare that they have no potential conflicts of interest involving this work, including relevant financial activities outside the submitted work and any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written.

Author contributions

GC and AJO-M conceived and designed the work; GC, DRS, ERL and CS acquired the data; GC and AJO-M analyzed and interpreted data; GC and AJO-M drafted the work; DRS, ERL and CS revised the manuscript critically for important intellectual content; all authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.01.137.

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