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ORIGINAL ARTICLE

Repetitive transcranial magnetic stimulation (rTMS) fails to increase serum brain-derived neurotrophic factor (BDNF)

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Brain-derived neurotrophic factor;
Efficacy;
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Serum level

Summary
Objectives. — Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal plasticity and in the pathophysiology of various brain disorders. Repetitive transcranial magnetic stimulation (rTMS) has been widely used in neuropsychiatric disease. It is presumed that BDNF mediates the therapeutic benefits of rTMS, but previous results are contradictory. We therefore conducted a meta-analysis to examine the efficacy of rTMS to increase serum BDNF.
Methods. — We performed a comprehensive literature search for clinical trials evaluating the efficacy of rTMS and addressing serum BDNF level. To pool effect size estimate (Hedges' *g*) of serum BDNF across studies, a meta-analysis was performed according to the Cochrane guideline.
Results. — rTMS failed to increase serum BDNF level with effect size of −0.12 (95% CI: −0.30, 0.06) ($P = 0.193$). Multilevel mixed-effects models analysis showed that overall effect of rTMS on BDNF levels was influenced by group of participants (healthy vs. disease) ($P < 0.001$), stimulation frequency (low-frequency vs. high-frequency) of rTMS ($P = 0.007$), treatment duration ($P < 0.001$) of rTMS, and population age ($P < 0.001$).
Conclusions. — Repetitive rTMS fails to increase serum BDNF, and it seems that serum BDNF level is related to frequency and duration of rTMS, as well as age and health status of population.

Introduction

Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal plasticity and in the pathophysiology of various brain disorders [4,12,13]. Repetitive transcranial magnetic stimulation (rTMS), which is a noninvasive

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technique with minimal side effects, has been widely used in neuropsychiatric disease as a therapeutic tool [17]. It is presumed that BDNF mediates the therapeutic benefits of rTMS [22], and that the observed changes of BDNF in peripheral blood may be due to rTMS-induced modulation of BDNF-TrkB signaling in the brain [5,27]. However, accumulating evidence shows contradictory effects of rTMS on serum level of BDNF [6,19,20,25]. To clarify this confusion, we conducted this meta-analysis.

Methods

The ''preferred reporting items for systematic reviews and meta-analyses'' (PRISMA) statement was followed for this pooled analysis [21]. We searched PubMed, EMBASE, and the Cochrane library for randomized controlled clinical trials that examined the effect of repetitive transcranial magnetic stimulation (rTMS) on serum brain-derived neurotrophic factor (BDNF) through February 28, 2019 by using combinations of ''transcranial magnetic stimulation'' or ''TMS'' and ''brain-derived neurotrophic factor'' or ''BDNF''.

Inclusion and exclusion criteria

We included a study if: (1) clinical cohort study; (2) repetitive transcranial magnetic stimulation (rTMS) used for participants; (3) serum brain-derived neurotrophic factor (BDNF) measured before and after rTMS. Data from animal experiments were excluded.

Data extraction and quality assessment

Two independent raters (B.J. and D.H.) abstracted data using a standardized form, and disagreements were resolved by discussion. We extracted the following data: author, sample size and demographic characteristics of participants, characteristics of rTMS, treatment duration, separate outcome measures before and after rTMS. The frequency of ≤ 1 Hz was defined as low-frequency rTMS, and that of>5 Hz as high-frequency [2]. If the mean and standard deviation (SD) of the change scores were not directly extracted from the text, they were calculated by using the following formula recommended by the Cochrane Handbook for Systematic Reviews of Interventions [14]:

$$\mathrm{Mean}_{\mathrm{change}} = \mathrm{Mean}_{\mathrm{final}} - \mathrm{Mean}_{\mathrm{baseline}}$$

$$\mathrm{SD}_{\mathrm{change}} = \sqrt{SD^2_{baseline} + SD^2_{final} - \left(2 * Corr * SD_{baseline} * SD_{final}\right)}$$

The same two raters (B.J. and D.H.) independently assessed the quality of included studies using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies, which is recommended by the Cochrane Collaborative Group for the assessment of quality of nonrandomized studies [28]. Based on patient selection (4 criteria), study-control group comparability (1 criterion) and outcome assessment (3 criteria), studies meeting ≥ 5 criteria were considered to be of high quality.

Quantitative data synthesis

We calculated the pooled effect size for the continuous variables using Hedges' *g* and its 95% confidence interval (CI). Hedges' *g* is a variation of Cohen's *d* that corrects for bias due to small sample sizes, and its magnitude can be interpreted as small (0.20), medium (0.50) or large (0.80) [8]. Publication bias was assessed by Egger's test.

We used the I^2 and Cochran-Q test to assess the heterogeneity. When significant heterogeneity was identified, subgroup analysis and meta-regressions were considered to investigate the potential sources. Statistical analysis was performed with the Stata software version 15.0 (Stata, College Station, Texas). Two-tailed *P*-value of less than 0.05 was considered to be significant.

Results

We identified 11 studies [1,9–11,15,16,18,23,24,30,31] with 278 participants that met the inclusion and exclusion criteria (Fig. 1). There were 100 healthy participants and 178 patients with major depression, stroke, amyotrophic lateral sclerosis, or myofascial pain syndrome. These studies were rated as being of good quality (Table 1). The publication bias was not significant by Egger's test ($P = 0.508$).

The pooled overall effect size (Hedges' *g*) was −0.12 (95% CI: −0.30, 0.06) ($P = 0.193$) with significant heterogeneity ($I^2 = 91.0\%$, $P < 0.001$). Multilevel mixed-effects models regression analysis showed that overall effect of rTMS on BDNF levels was influenced by group of participants (healthy vs. disease) ($P < 0.001$, Coef. = −5.20), frequency (low vs. high) of rTMS ($P = 0.007$, Coef. = −1.82), treatment duration ($P < 0.001$, Coef. = 1.94), age ($P < 0.001$, Coef. = 0.32), and sample size ($P = 0.021$, Coef. = −0.06), but not by stimulation site of rTMS ($P = 0.123$), intensity of rTMS ($P = 0.312$), or gender ($P = 0.707$).

Subgroup analysis showed that serum BDNF decreased after rTMS in healthy participants with effect size of −0.52 (95% CI: −0.81, −0.23) ($P < 0.001$), but not for patients with effect size of 0.13 (95% CI: −0.10, 0.36) ($P = 0.263$). High-frequency rTMS also decreased serum BDNF with effect size of −0.25 (95% CI: −0.49, −0.01) ($P = 0.045$) (Fig. 2), and not in low-frequency rTMS with effect size of 0.04 (95% CI: −0.23, 0.30) ($P = 0.798$); but the difference of effect sizes between high-frequency and low-frequency was not significant ($P = 0.739$) by Mann-Whitney *U* test. Serum BDNF increased as the increase of treatment duration with coeff. of 1.71 (95% CI: 0.26, 3.16) ($P = 0.025$), as well as age with that of 0.13 (95% CI: 0.002, 0.26) ($P = 0.047$) (Fig. 3). However, the association of serum BDNF and sample size was not identified by linear regression analysis ($P = 0.478$).

Discussion

According to meta-analysis, we found that repetitive transcranial magnetic stimulation (rTMS) failed to increase serum brain-derived neurotrophic factor (BDNF) with pooled overall effect size (Hedges' *g*) of −0.12 (95% CI: −0.30, 0.06). Furthermore, multilevel mixed-effects models meta-regression analysis showed that high-frequency rTMS could decrease serum BDNF, and serum BDNF also decreased by

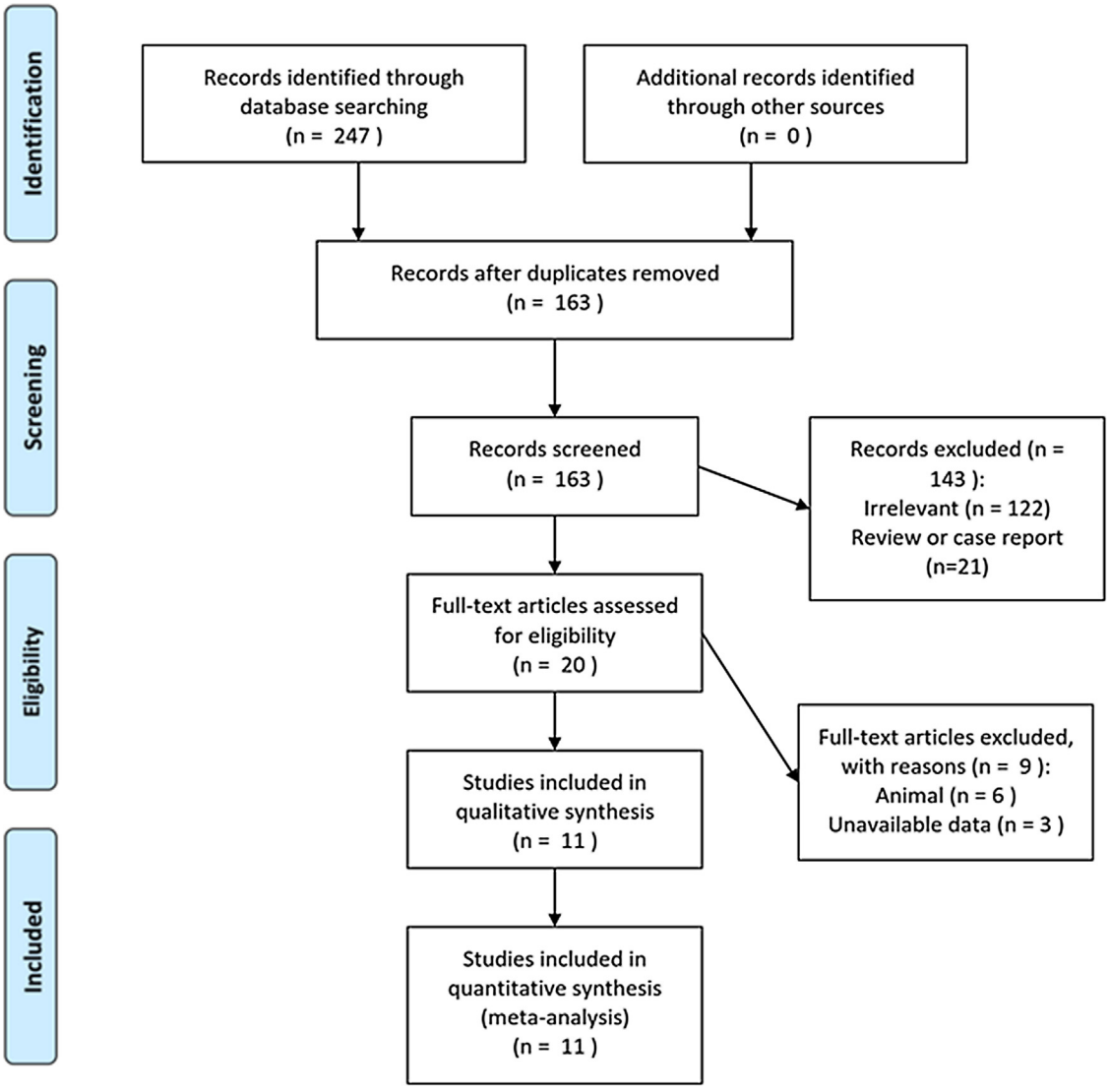

Figure 1 Flow diagram of the reviewing process.

rTMS in the healthy population. Additionally, the serum BDNF slightly increased with the increase of treatment duration of rTMS, as well as age of participants.

The activity-dependent expression of BDNF is primarily mediated by non-NMDA glutamate receptors. Glutamatergic circuits of the human motor cortex can be non-invasively activated using rTMS. Barker et al. [2] originally evaluated motor cortex evoked potentials using rTMS by nerve cell depolarization/hyperpolarization; they found that low-frequency rTMS ($\leq$ 1 Hz) directly hyperpolarizes neural cells via pulsed magnetic field and inhibits the cerebral cortex, while high-frequency rTMS (> 5 Hz) excites the cerebral cortex. Therefore, it is presumed that low-frequency rTMS could reduce cortical excitability and produce long-term depression (LTD) that would decrease serum BDNF, while high-frequency rTMS could stimulate cortical excitability and generate long-term potentiation (LTP)-like effects to increase serum BDNF.

However, our study showed that overall rTMS failed to effectively change serum BDNF level, and in fact high-frequency rTMS might even reduce it. Furthermore, less decreased serum BDNF was related to longer treatment duration of rTMS. We think these conflicting results may be explained by *BDNF* gene polymorphism and impaired brain networks, since BDNF gene polymorphism is known to play a prominent role in the variation of serum BDNF level [3,7]. The overall level of serum BDNF was reduced by gene polymorphism and impaired brain networks. We hypothesize that, due to impaired brain networks, the long-term depression effect of low-frequency rTMS does not necessarily occur, such that serum BDNF level does not significantly vary. In a pathological state, the stimulant effect of high-frequency rTMS may increase dysfunction of already impaired brain networks and thus reduce serum BDNF. With longer treatment duration of rTMS, however, the body equilibrium compensation hypothesis may play a main role in balancing a dysfunctional state.

A similar contradiction also appeared in healthy participants in whom serum BDNF was decreased by rTMS, as well as the increase of serum BDNF seen in older

Table 1 Characteristics of included studies.

Study	Sample size	Spectrum	Stimulation site	Intensity, %	Frequency, Hz	Duration, weeks	Quality
Angelucci-2004 [15]	10	Healthy	Primary motor cortex	110	1	1	3/0/2
	4	Amyotrophic lateral sclerosis	Primary motor cortex	110	1	1	
	4	Amyotrophic lateral sclerosis	Primary motor cortex	110	20	1	
Lang-2006 [16]	14	Depression	Dorsolateral prefrontal cortex	100	20	2	3/0/2
Zanardini-2006 [17]	16	Depression	Dorsolateral prefrontal cortex	—	1—17	1	3/0/2
Lang-2008 [18]	42	Healthy	Dorsolateral prefrontal cortex	70—130	20	2	3/0/2
Gedge-2012 [19]	18	Depression	Dorsolateral prefrontal cortex	80	10	2	3/0/2
Gaede-2014 [20]	13	Healthy	Dorsolateral prefrontal cortex	120	18	1	3/0/2
	13	Healthy	Primary motor cortex	90	5	1	
Schaller-2014 [21]	22	Healthy	Dorsolateral prefrontal cortex	100	25	2	3/0/2
Letizzia-2014 [22]	12	Myofascial pain syndrome	Primary motor cortex	80	10	2	4/0/3
Lu-2015 [23]	19	Stroke	Dorsolateral prefrontal cortex	100	1	4	4/0/2
Niimi-2016 [24]	62	Stroke	Dorsolateral prefrontal cortex	90	1	2	3/0/2
Zhao-2019 [25]	29	Depression	Dorsolateral prefrontal cortex	80	10	4	3/0/2

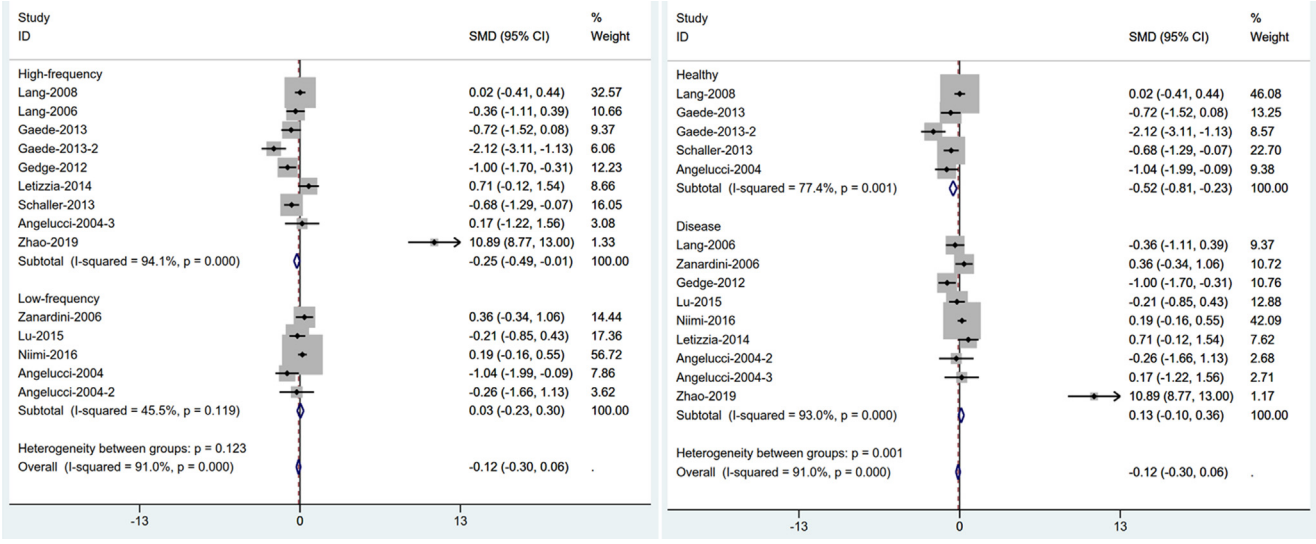

Figure 2 Meta-analysis of effect size (Hedges' *g*) for serum brain-derived neurotrophic factor (BDNF), and subgroup analysis by frequency (high-frequency vs. low-frequency) of repetitive transcranial magnetic stimulation (rTMS) and health status (healthy vs. disease) of population.

people. The effect of BDNF gene polymorphism on serum BDNF has been investigated in previous studies [29]: the BDNF Val66Met polymorphism (rs6265) appears to reduce neural plasticity, and patients have a greater prevalence of heterozygous (A/G) VAL/MET polymorphism than healthy controls. This genetic polymorphism, which impairs BDNF activity, is an important correlate of disease state. Therefore, the lower level of serum BDNF should be more

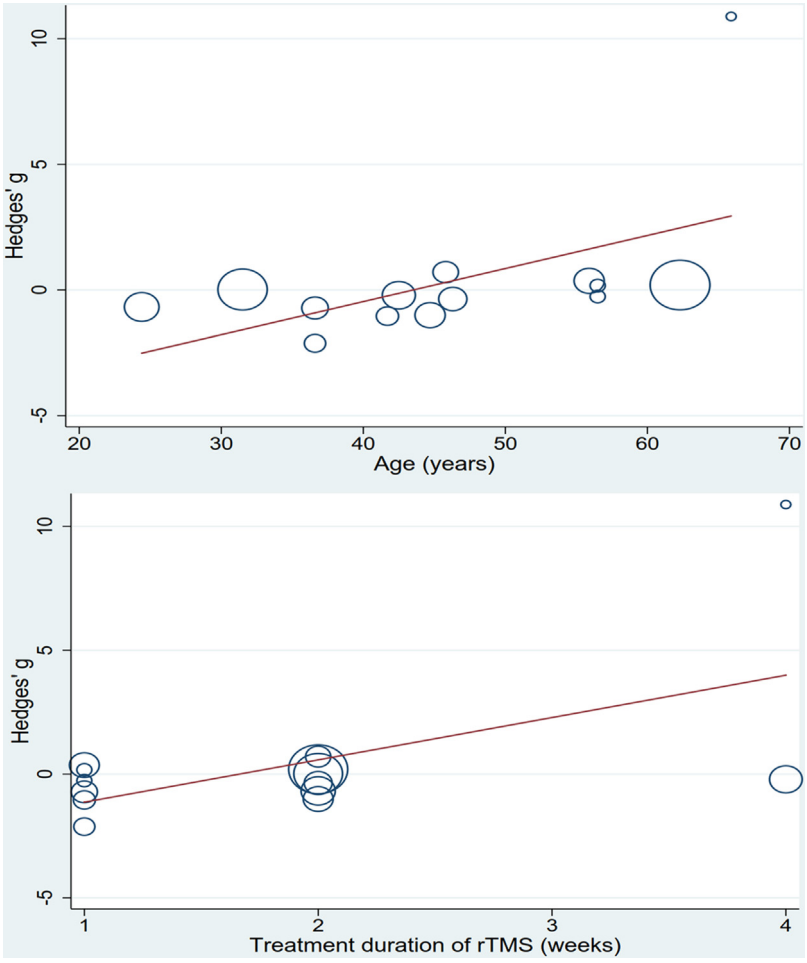

Figure 3 Meta-regression of effect size (Hedges' *g*) for serum brain-derived neurotrophic factor (BDNF) by population age with coef. of 1.71 (95% CI: 0.26, 3.16) ($P = 0.025$) and treatment duration of repetitive transcranial magnetic stimulation (rTMS) with coef. of 0.13 (95% CI: 0.002, 0.26) ($P = 0.047$).

prevalent in patients and older people. In our opinion, the conflicting results may be explained by equilibrium compensation hypothesis. A steady state of serum BDNF exists in healthy people, and the increased BDNF produced by rTMS may be counterbalanced to maintain a steady state of serum BDNF. Due to the neutralizing effect being greater in healthy people than that in patients and old people, as well as superior to the rTMS effect, the overall effect expresses decreased serum BDNF in healthy people and increased BDNF in older people. Furthermore, due to impaired neutralizing effect and greater prevalence of BDNF polymorphism, the overall effect does not show significant variation in patients.

As each disorder presents one specific pattern of brain plasticity reorganization, we have conducted a subgroup analysis with each disorder as a subgroup to explore the impact of rTMS on serum BDNF in each disorder in the current study. However, we did not find any significant result (Supplement). Due to limited data, multicenter and large sample size studies should be conducted in the future.

There are limitations in our study. First, we are unable to analyze the individual serum levels of mature BDNF and pro-BDNF because of the limitation of original studies. Mature BDNF could increase brain excitability, while pro-BDNF seems to reduce brain excitability [26,29]. Therefore, it is clinically and scientifically interesting to measure the individual serum levels of mature BDNF and pro-BDNF. Second, the relatively small sample size weakens our conclusion.

In conclusion, according to our meta-analysis of currently available data, serum BDNF is not increased by using rTMS treatment. Serum BDNF seems to be related to frequency and duration of rTMS, as well as age and health status of population.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neucli.2019.05.068.

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