Individual alpha frequency proximity associated with repetitive transcranial magnetic stimulation outcome: An independent replication study from the ICON-DB consortium

Charlotte L. Roelofsa, Noralie Krepela,b, Juliana Corlierc, Linda L. Carpenterd, Paul B. Fitzgeraldi, Zafiris J. Daskalakisf,g, Indira Tendolkarh, Andrew Wilsonc, Jonathan Downarf, Neil W. Bailey e, Daniel M. Blumberger f,g, Fidel Vila-Rodriguezj, Andrew F. Leuchterc,1, Martijn Arns a,b,k,1,⇑

a Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, the Netherlands
b Dept. of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands
c TMS Clinical and Research Program, Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior at UCLA, Dept. of Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
d Butler Hospital Mood Disorders Research Program and Neuromodulation Research Facility, Dept. of Psychiatry and Human Behavior Alpert Medical School of Brown University, Providence, RI, USA
e Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University and Alfred Hospital, Melbourne, Australia, Epworth Centre for Innovation in Mental Health, Epworth HealthCare, VIC, Australia
f Dept. of Psychiatry, University of Toronto, Toronto, ON, Canada
g Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, ON, Canada
h Donders Institute for Brain, Cognition and Behavior, Dept. of Psychiatry, Radboud University Medical Center, Nijmegen, the Netherlands
i Epworth Centre for Innovation in Mental Health, Epworth HealthCare and Monash University Department of Psychiatry, Camberwell, VIC, Australia
j Non-Invasive Neurostimulation Therapies Laboratory, Dept. Psychiatry, The University of British Columbia, Vancouver, BC, Canada
k Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Location AMC, Amsterdam Neuroscience, Amsterdam, the Netherlands

See Articles, pages 616–617, and 650–659

ARTICLE INFO

Article history:
Accepted 1 October 2020
Available online 10 November 2020

Keywords:
Replication
Alpha frequency
EEG
rTMS
Arnold Tongue
Synchronization
ICON-DB

HIGHLIGHTS

- rTMS treatment outcome is quadratically related to the individual alpha peak frequency (IAF) in depression.
- Absolute distance of IAF to 10 Hz is linearly related to clinical outcome.
- These results strengthen the theory that 10 Hz rTMS entrains brain oscillations.

ABSTRACT

Objective: The aim of the current study was to attempt to replicate the finding that the individual alpha frequency (IAF) as well as the absolute difference between IAF and 10 Hz stimulation frequency (IAF-prox) is related to treatment outcome.
Methods: Correlations were performed to investigate the relationship between IAF-prox and percentage symptom improvement in a sample of 153 patients with major depressive disorder treated with 10 Hz (N = 59) to the left dorsolateral prefrontal cortex (DLPFC) or 1 Hz (N = 94) to the right DLPFC repetitive Transcranial Magnetic Stimulation (rTMS).
Results: There was a significant negative correlation between IAF-prox and the percentage of symptom improvement only for the 10 Hz group. Curve fitting models revealed that there was a quadratic association between IAF and treatment response in the 10 Hz group, with a peak at 10 Hz IAF.
Conclusion: The main result of Corlier and colleagues was replicated, and the findings suggest that the distance between 10 Hz stimulation frequency and the IAF may influence clinical outcome in a nonlinear manner.

⇑ Corresponding author at: Research Institute Brainclinics, Brainclinics Foundation, Bijleveldsingel 32, 6524 AD Nijmegen, The Netherlands.
E-mail address: martijn@brainclinics.com (M. Arns).
1 Indicates shared senior author.

1388-2457/© 2020 International Federation of Clinical Neurophysiology. Published by Elsevier B.V.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
1. Introduction

Currently, antidepressant drugs are often the first treatment option for patients with Major Depressive Disorder (MDD). However, not all patients benefit from this treatment, usually achieving response rates of 30–40% to the first treatment course (Rush et al., 2006). Multiple studies have shown that repetitive transcranial magnetic stimulation (rTMS) applied to the left or right dorsolateral prefrontal cortex (DLPFC) is an efficacious (George et al., 2010; O’Reardon et al., 2007; Brunelin et al., 2014) and effective treatment in MDD (Carpenter et al., 2012; Fitzgerald et al., 2016; Donse et al., 2018), offering a viable alternative for patients that do not respond to antidepressants. Increased mechanistic understanding of both MDD and how rTMS exactly works in the treatment of MDD could lead to optimized selection of treatment for patients as well as individualized stimulation parameters, thereby potentially improving treatment outcome.

The dominant activity in the resting state EEG is the alpha rhythm, with a frequency between 7–13 Hz. Research exploring the Individual Alpha peak Frequency (IAF) has identified intra- and inter-individual differences (Haegens et al., 2014), yet the IAF seems to be heritable and stable over time (Smit et al., 2006). Ever since the first description that the alpha frequency can be entrained by photic stimulation by Adrian and Matthews (Adrian and Matthews, 1934), this phenomenon has been considered a possible mechanism of action of various neuromodulation treatments such as tACS and rTMS (Leuchter et al., 2015). This neural oscillation entrainment also has the property that phase coupling can be more pronounced with increasing stimulation intensity as well as at stimulation frequencies closer to each participants’ intrinsic frequency (Nortbohm et al., 2016).

The primary purpose of this paper is to attempt to replicate the recent findings reported by Corlier and colleagues, where the proximity of IAF to the 10 Hz TMS stimulation frequency was associated with better treatment response (Corlier et al., 2019).

Oscillations in the alpha band are thought to represent a thalamocortical oscillation (Bollimunta et al., 2011). Interference of this rhythm has been hypothesized to reset thalamocortical oscillators that are abnormal in depressed individuals and therefore may be related to the therapeutic mechanisms of rTMS (Leuchter et al., 2013). Applying the concept of entrainment to rTMS, stimulation at 10 Hz will hypothetically result in a stronger entrainment of alpha oscillations in an individual whose IAF is closer to 10 Hz, rather than in an individual whose IAF is further away from 10 Hz (Nortbohm et al., 2016). This effect of rTMS has already been demonstrated in schizophrenia patients. Jin and colleagues delivered rTMS to schizophrenia patients at their IAF, which resulted in better clinical effects relative to stimulation at other frequencies, as well as increased alpha power from pre- to post-treatment (Jin et al., 2005; which was replicated: Jin et al., 2012).

The alpha frequency varies between individuals, and multiple studies have investigated the IAF and its association with treatment response to antidepressant treatments such as rTMS (Arns et al., 2012; Corlier et al., 2019), antidepressant medication (Arns et al., 2015), as well as in other disorders (for review see Olbrich et al., 2015). With respect to rTMS two approaches have been reported. Several studies have reported a linear association between IAF and response to rTMS, where overall a slower IAF is considered a predictor for non-response (Arns et al., 2012; Arns et al., 2010) generally interpreted as reflecting abnormality (Arns et al., 2015). However, more recently the same group failed to replicate the linear association (Krepel et al., 2018). On the other hand, Corlier and colleagues reported an association between the proximity of IAF to the 10 Hz TMS stimulation frequency and treatment response (Corlier et al., 2019). This latter ‘proximity’ approach implicates a quadratic association between IAF and treatment response (higher treatment responses in individuals with an IAF of 10 Hz, and lower response in individuals with an IAF of both higher and lower frequencies). In addition to the relationship between IAF-prox and treatment outcome, Corlier and colleagues also found that the absolute IAF was related to treatment outcome (Corlier et al., 2019). Of interest, Corlier and colleagues used an average reference montage, which is known to reflect more focal cortical activity, whereas Arns and colleagues used a linked-ears montage in their earlier studies. Since the primary purpose of this study was to replicate the study performed by Corlier and colleagues, the primary IAF employed was based on average reference. In addition, a linked-ears montage has also been tested as secondary analysis, and the amount of (dis)agreement between these EEG referencing montages. In this study, the alpha activity as measured below the coil is investigated. This is in line with replication, since Corlier and colleagues used the average reference and therefore focal frontal alpha was studied.

The aim of the current study was to investigate the replicability of the finding of Corlier et al. (2019) using the data from Krepel et al. (2018). It was hypothesized that the proximity of an individual’s alpha frequency to 10 Hz is associated with clinical improvement in MDD after 10 Hz rTMS applied to the left DLPFC. In order to provide a test of the proposed explanation that it is the proximity of IAF to the stimulation frequency that drives this association (rather than simply the proximity of IAF to 10 Hz regardless of stimulation), an additional analysis was performed. In this analysis, the same comparison between proximity to 10 Hz and treatment effect was used, but in a group of participants treated with 1 Hz stimulation to the right DLPFC. It was hypothesized that the association would not be present in the group that had 1 Hz rTMS applied to the right DLPFC. Additionally, it was hypothesized that the absolute IAF is not correlated with treatment outcome, given the previously mentioned non-replication (Krepel et al., 2018). Furthermore, the effect of two different EEG montages was investigated; a linked ears montage (as previously used in Arns et al., 2016; Arns et al., 2012) and an average reference montage (as used in Corlier et al., 2019).

2. Methods

2.1. Study design

An open-label study was conducted with data of patients who were diagnosed with major depressive disorder (MDD) or dysthymia and treated with rTMS in combination with psychotherapy. All subjects signed an informed consent form. Inclusion criteria were: 1) A diagnosis of MDD or dysthymia; 2) BDI-II-NL (Beck Depression Inventory) of 14 or higher at baseline; and 3) Treatment consisting of rTMS (left DLPFC rTMS at 10 Hz or right DLPFC at 1 Hz) combined with psychotherapy for at least 10 sessions.
contrast with Corlier et al. (2019), the choice of the applied rTMS protocol was not based on clinical criteria, but the first few years the standard protocol was 10 Hz, and when it was found that the clinical benefits for 10 Hz and 1 Hz were similar, the standard protocol became 1 Hz. Exclusion criteria were: 1) Previous ECT treatment; 2) Epilepsy; 3) Wearing a cardiac pacemaker; 4) Metal implants in the cranium; and 5) Pregnancy. Assessments including BDI, DASS, and PSQI were taken at baseline, every fifth session, and clinical endpoint (last rTMS session). Patients received an average of 20.8 (SD 7.3) rTMS treatment sessions, which did not differ between the 10 Hz and 1 Hz treatment groups \( t(173) = -0.260 \), \( p = .795 \). Medication usage was not systematically tracked. Further details about treatment and clinical variables can be found in Donse et al. (2018) and Krepel et al. (2019).

### 2.2. EEG procedure

Resting-state EEG recordings were performed using a standardized methodology (Brain Resource Ltd., Australia). EEG data were acquired from 26 channels (NuAmps; 10–20 electrode international system) and were recorded for two minutes with eyes closed (EC), and two minutes with eyes open (EO) with the participant asked to fixate on a red dot on the screen. Participants were instructed to remain relaxed for the duration of the recording. Vertical eye movements were recorded with electrodes above the middle of the left eyebrow and below the middle of the left bottom eyelid. Horizontal eye movements were recorded with electrodes placed lateral to the outer canthus of each eye. Skin impedance was < 10 kOhm for all electrodes (sampling rate = 500 Hz; Low-pass filter of 100 Hz with attenuation of 40 dB per decade and no high-pass filter).

### 2.3. EEG pre-processing and IAF

EEG data were analyzed in Brain Vision Analyzer 2.0 (Brain Products). Data were EEG-corrected using the regression-based Gratton technique (Gratton et al., 1983), re-referenced to the average reference, filtered \((0.3 – 100 \text{ Hz and notch})\), segmented in 4-second epochs, and artifactual epochs were removed using an automated procedure, with a maximal allowed difference of 150 \(\mu\)V within an interval of 100 ms. An average of 29.5 segments (SD = 1.01) were included per subject, resulting in an average of 118 seconds of included data per subject. This implicated 98.3% of usable data. The IAF was extracted from eyes closed resting states and calculated for F3 and F4. In short, calculating the IAF consisted of the following steps: 1) A Fast Fourier Transform applied to EC using 4 sec. segments with 50% overlap to get a power spectrum for each site, with a Hamming window applied to each segment; 2) The IAF for each site was determined by identifying the maximum value within the 7–13 Hz alpha range. If the power of the alpha frequency peak was lower than 1.5 Z-score below the mean, the patient was considered not to have a dominant IAF rhythm and thus was not included in the analysis (these EEGs are also known as low voltage alpha EEG). This 1.5 Z-score cut-off was chosen because a bimodal frequency distribution was visible for IAF (see Supplementary Figure S1), and this cut-off reflected the majority of the people and incorporated the bimodal distribution as well as possible. Secondly, visual inspection of the raw EEG data confirmed that no dominant alpha power was present, and no clear alpha peak could be distinguished from the background EEG. This criterion yielded a similar percentage of subjects having no dominant IAF as reported by Corlier and colleagues. Of the total sample of 175 patients, 12.6% was determined not to have a dominant IAF, which is consistent with the 15.1% reported by Corlier and colleagues (2019). IAF-prox was calculated as the absolute value of the distance from IAF to 10 Hz.

### 2.4. Statistics

Since the primary aim was to replicate the results from the Corlier et al. (2019) study, an a priori defined analysis plan was drafted by the first author (CR) was shared with the ICON-DB consortium and amended/approved by all members. Data analysis was carried out exactly according to this analysis plan and the primary outcome was thus defined as a correlation between continuous symptom improvement (BDI change) and IAF at F3 (for 10 Hz rTMS) quantified using an average reference, covaried for age. Due to the a priori defined primary hypothesis and replication nature, a one-tailed partial correlation was conducted.

Descriptive statistics at pre-treatment, post-treatment and change scores can be found in Table 1. Since TMS protocol specific effects were expected, only data was included from patients that received one rTMS protocol (1 Hz or 10 Hz), hence 21 were excluded from the original sample \((n = 196)\) resulting in a sample of 175. 12.6% had no dominant IAF and thus were excluded, resulting in a sample of 153 MDD patients included in the analyses. The dataset \((n = 153)\) was divided into groups based on rTMS protocol: a group of patients treated with 10 Hz rTMS applied to the left DLPPC and a group of patients treated with 1 Hz rTMS applied to the right DLPPC. For the 10 Hz group the IAF was estimated at F3, while for the 1 Hz group the IAF was estimated at F4 to match the calculation of IAF to the stimulation site. To ensure sample comparability of the two groups, a Chi-square test was performed to compare gender and response ratios and an ANOVA to compare age, baseline depression severity, clinical improvement, and IAF between the two groups.

Due to the a priori defined, directional and replication nature of our primary hypothesis, a one-tailed Spearman correlation was conducted. One-tailed statistical tests are recommended when a result in the opposite direction to our previous research would provide the same rejection of our previous conclusion as no difference between groups (Ruxton and Neuhäuser, 2010). To further investigate whether the relation between IAF and BDI percentage change was linear or quadratic, post-hoc curve fitting was applied using GraphPad Prism (version 6.00 for Macintosh, GraphPad Software, La Jolla California USA, www.graphpad.com). A straight line was statistically compared to a quadratic function, where the quadratic function was constrained to a maximum at 10 Hz, in line with the hypothesis. Using Akaike’s Information Criteria it was determined how well the data supports the straight line fit or the quadratic fit, and additionally an analysis of variance determined how much a line model improves by chance with a quadratic function.

As the study was designed to test the single primary hypothesis, that IAF-prox to 10 Hz is associated with treatment response in the 10 Hz group only (with other statistical tests conducted only to demonstrate the specificity of the replication result to variation in pre-processing steps and treatment parameters), no multiple comparison corrections were necessary.

### Table 1

<table>
<thead>
<tr>
<th>Total sample</th>
<th>10 Hz</th>
<th>1 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 153</td>
<td>10 Hz</td>
<td>1 Hz</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>43.00 (12.95)</td>
<td>40.27 (11.89)</td>
</tr>
<tr>
<td>Sex (n male)</td>
<td>77 (50%)</td>
<td>30 (51%)</td>
</tr>
<tr>
<td>BDI pre</td>
<td>30.99 (9.60)</td>
<td>30.41 (8.90)</td>
</tr>
<tr>
<td>BDI post</td>
<td>13.99 (12.16)</td>
<td>13.71 (11.56)</td>
</tr>
<tr>
<td>IAF</td>
<td>9.47 (1.16)</td>
<td>9.42 (1.16)</td>
</tr>
<tr>
<td>IAF-prox</td>
<td>0.97 (0.82)</td>
<td>0.96 (0.86)</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; IAF: individual alpha frequency.
3. Results

153 MDD patients were included in the analyses. In Table 1, the mean baseline values with standard deviations are reported. No significant differences were found between the groups for sex, age, baseline depression severity (BDI intake), BDI change, or IAF (all $p > 0.086$).

An one-tailed Spearman correlation test demonstrated a significant correlation ($r(59) = -0.250; r^2 = 0.063; p = .028$) between BDI percentage change and IAF-prox in the 10 Hz sample (see Fig. 1). However, repeating this analysis in the 1 Hz group showed no significant correlation ($r(94) = -0.119; r^2 = 0.014; p = .126$). Across the total sample a significant correlation was observed ($r(153) = -0.162; r^2 = 0.026; p = .051$). No significant correlations were found between BDI percentage change and the absolute IAF for both the 10 Hz sample ($r(59) = 0.006; r^2 < 0.001; p = .483$), the 1 Hz sample ($r(94) = 0.024; r^2 = 0.001; p = .410$), as well as the total sample ($r(153) = -0.007; r^2 < 0.001; p = .466$). Additionally, oscillation strength (alpha peak amplitude) and treatment response were not correlated ($r(153) = 0.003; r^2 < 0.001; p = .487$).

3.1. Post-hoc analyses

In the study of Arn et al. (2012) as well as Krepel et al. (2018) a linked ears reference was used, whereas in this replication study an averaged reference EEG montage was used in line with Corlier et al. (2019). To examine a possible influence of referencing, the IAF was recalculated using the linked-ears montage, and the analyses were repeated. These analyses yielded no significant correlations between BDI percentage change and IAF-prox (all $p > .395$). A scatterplot of the comparison of these two IAFs can be found in Supplementary Figure S2. Additional analysis demonstrated that the mean IAF calculated with a linked-ears montage (mean = 8.94; SD = 1.12) was significantly lower than the mean IAF measured with the average reference montage (mean = 9.48; SD = 1.22; $p < .000$).

Since the main hypothesis implies a quadratic association (Notbohm et al., 2016), a Loess fit was plotted for the 10 Hz group (Fig. 2). This plot visualizes that indeed the data is best explained by a quadratic association, with a peak close to 10 Hz. To further test this statistically, curve fitting was applied. It was tested if a quadratic model, constrained to a maximum at 10 Hz, would fit the data better than a linear model. In the 10 Hz group, the quadratic fit was the correct model with 91.4% probability thus favoring the quadratic model over a linear model. Removal of the single outlier at 12.5 Hz did not change the results.

4. Discussion

The aim of this study was to replicate the association between clinical outcome and the proximity of the IAF to 10 Hz rTMS in an MDD sample as was recently published by Corlier et al.
(2019). Our results replicated the earlier reported findings, where an association was observed between the proximity of the IAF to 10 Hz and clinical response to 10 Hz left DLPFC rTMS, which explained 6.3% of the variance. This association was not significant for the 1 Hz right DLPFC rTMS group. Additionally, in contrast with the results of Corlier et al. (2019), no association between absolute IAF and treatment response was found using both the average reference as well as linked ears references, thereby in line with the recent results from Krepel et al. (2018). Curve fitting and a Loess fit – also see Fig. 2 – further confirmed that the association is quadratic, meaning that individuals with an IAF closer to 10 Hz showed most clinical improvement with 10 Hz rTMS. However, it is important to note that these results depend on the choice of EEG montage.

These results are theoretically in line with the properties of oscillation entrainment, which are conceptualized by the Arnold Tongue. The Arnold Tongue predicts that the degree of synchronization (entrainment) of an oscillator coupled to a rhythmic driving force depends on the amplitude of the driving force and the driving frequency (Fröhlich, 2015). With a driving frequency that approaches the intrinsic frequency, entrainment is more likely to occur (Notbohm et al., 2016). For example, tACS has a relatively weak stimulation strength and should therefore be aimed more accurately at the intrinsic stimulation frequency. On the other hand, rTMS has a relatively higher stimulation intensity and therefore requires less precise frequency matching (i.e. a relatively larger mismatch between stimulation frequency and intrinsic frequency is allowed). To summarize, the more closely an externally applied stimulation frequency matches an intrinsic frequency, the more likely it is that entrainment will occur. A higher degree of entrainment might be related to a stronger neuroplasticity effect, that eventually mediates long-term clinical and behavioral changes (Vosskuhl et al., 2018). It is unclear, however, how large a frequency difference can exist and still elicit optimal rTMS entrainment effects.

The current results help resolve the earlier contradictory results (Corlier et al., 2019; Arns et al., 2012) where a linear association between IAF and rTMS response was reported, which was not replicated (Krepel et al., 2018). Firstly, the use of an average reference montage in this study vs. a linked ears montage in these prior studies yielded different results. Secondly, a further inspection of the original data revealed that in the first sample from Arns et al. (2012) there was a relative high proportion of IAFs below 10 Hz (Arns et al sample: 82% of subjects had IAF < 10 Hz vs. Krepel et al., 68.3% of subjects had IAF < 10 Hz), thereby explaining the earlier reported linear finding (i.e. if the majority of IAF are below 10 Hz, the quadratic association with a peak at 10 Hz will be modelled as a linear association). This could also explain why Corlier and colleagues (2019) observed a relationship between absolute IAF and clinical improvement (due to a high proportion of IAFs below 10 Hz), yet in the current study all data point to a quadratic association.

These findings should be interpreted in the context of resonance of brain circuitry. Each brain circuit has one or more preferred resonant frequencies at which its activity can be best modulated (Zaehle et al., 2010). Studies using several different neuromodulation techniques have shown that cortical regions are particularly susceptible to the effects of stimulation at intrinsic peak frequencies in the delta (Schmidt et al., 2014; Marshall et al., 2006), theta (Albouy et al., 2017; Polania et al., 2012), alpha (Klimesch et al., 2003; Thut et al., 2011), beta (Romei et al., 2016; Pogosyan et al., 2009), or gamma (Helfrich et al., 2014) frequency ranges. Specific resonant frequencies vary among brain regions, as well as across individuals. Future rTMS studies should examine such endogenous resonant frequencies across the frequency spectrum, and the clinical outcomes of treatment in relation to resonant frequencies outside of the alpha band.

The findings of this study emphasize the need for replication, not only to confirm or refute previous results but also to sculpt and refine currently existing research. Interestingly, a recent report showed that of 97 attempts to replicate previous research, only 35 were successful (Open Science Collaboration, 2015). The high rate of non-replication is of concern in the context of low rates of replication attempts; the rate of replications published in 100 journals has been studied and it was concluded that 1.07% of all publications were replications (Makel et al., 2012). Insufficient direct replication of previous EEG findings has also characterized the literature describing biomarkers for response prediction when treating depression (Widge et al., 2019). The gap between the low rate of replication attempts and the high rate of non-replication creates a false positive knowledge space, where studies provide evidence for conclusions that are not accurate or generalizable. The need for replication has been reported in multiple papers (Brandt et al., 2014; Makel et al., 2012; Simons et al., 2014), and the current study is an example of how studies may fit into this approach. This was also the primary reason for establishing the ICON-DB consortium at the 2019 Brain Stimulation conference in Vancouver (see acknowledgements for more details) of which this publication is the first result. Not only did the current study verify the results as obtained by Corlier and colleagues, but it also refined the result by considering the stimulation protocol. This builds on the currently existing body of knowledge, and aids in the development of a knowledge base which future research may extend upon and facilitates translation into clinical practice.

With regards to implications for rTMS treatment, the observed association between a patient’s IAF and 10 Hz may imply that the specific frequency at which a patient is treated plays a role in clinical outcome in the treatment of MDD. The result might suggest that DLPFC stimulation with rTMS at the IAF could be more successful at entraining ongoing alpha oscillations in line with the Arnold Tongue model. This has already been demonstrated in schizophrenic patients (Jin et al., 2005; Jin et al., 2012), where individualized rTMS showed a significantly larger therapeutic effect than conditions with stimulation frequencies of 3 Hz or 20 Hz. However, an earlier smaller study where IAF + 1 Hz was applied did not find any advantages (Arns et al., 2010). They did, however, find a trend for reduced response to 9 Hz rTMS, which warrants caution and requires further research before such frequency individualization is implemented in clinical practice.

There were several limitations in this study. First, in this study psychotherapy was combined with rTMS making it difficult to distinguish whether the obtained relation of a marker to treatment outcome reflects a generic relationship for treatment improvement or a relationship for treatment improvement to either rTMS, psychotherapy, or the combination of both. Second, since the 1 Hz stimulation was applied on a different brain area than the 10 Hz stimulation, respectively right DLPFC and left DLPFC, further work is required to find out whether the finding generalizes to other brain areas or other stimulation patterns. Thirdly, most patients used antidepressant medication at the start and during the rTMS treatment (although all patients still met clinical criteria for MDD). Still, it is possible that the interaction between IAF, stimulation frequency, and clinical outcome was influenced by medication status or other uncontrolled factors. For example, benzodiazepines have the most marked effects on the EEG by slowing down the IAF (Sim and Tsoi, 1992). Third, even though the main result of Corlier et al. (2019) was replicated, it cannot be ruled out that somatosensory and auditory aspects of the rTMS mediated the effect, instead of the transcranial magnetic stimulation. Finally, although the curve fitting data confirmed that a model constrained to a 10 Hz peak was the best model, the Loess fit in Fig. 2 suggests the optimal IAF is just below 10 Hz. Although an insufficient sample size prevents from drawing firm conclusions from this, this notion was
confirmed in a recent model simulation by Li and colleagues (2019) where it was demonstrated that stimulation with a frequency slightly higher than the endogenous frequency results in optimal entrainment and enhancement. Future studies should investigate this in more detail, using larger samples.

With respect to the EEG pre-processing parameters, in the current study the common average reference was used, which is in line with Corlier et al. (2019). In earlier studies, a linked ears montage was used. To examine a possible influence of referencing, the IAF was recalculated using the average mastoid-reference, and the analyses were repeated. These analyses did not yield any significant relationship between IAF-prox and BDI percentage change. The IAF values for both montages are shown in Supplementary Figure S2. In general, linked ears is used as a reference if the signal in central areas or along the midline is of interest, as the mastoid electrodes are expected to pick up relatively little cortical activity from the top of the head. Therefore, a linked ears montage shows a more volume conducted alpha, where the average reference montage represents the more focal alpha activity. The linked ears montage is valid under the assumption that the average of the potentials recorded over two mastoids is close to zero or neutral. However, some argue that this is not the case (Hagemann et al., 2001).

Alternatively, the average reference is the average electrical activity measured across all scalp channels. The average reference is useful to delineate focal activity. When using this reference, amplitudes will overall be reduced, but each channel will contribute equally to the new reference (Lei and Liao, 2017). Qin and colleagues reported that average reference is a better choice than linked-ears when applied to both stimulated and real resting-state EEG data (Qin et al., 2010). Therefore, the fact that the association was only found for the average reference, which can be considered to be sensitive to more focal cortical activity, strengthens the main hypothesis that 10 Hz rTMS entrains endogenous EEG activity underneath the coil.

In conclusion, the main result of Corlier et al (2019) was replicated, and the findings suggest that the distance between 10 Hz stimulation frequency and the IAF may influence clinical outcome, suggesting the most optimal rTMS frequency is the one identical to the frontal IAF. Further research should examine a broader range of stimulation frequencies to specifically examine the effect of the magnitude of difference between stimulation frequency and the IAF on clinical outcome, and additionally investigate what would be the optimal stimulation frequency for the 12.6% of patients that were classified as low voltage alpha EEG. Secondly, future studies should investigate changes in IAF over the course of treatment. If present, this would call for changes in rTMS frequency across treatment as well. Finally, in a future study it would be of interest to obtain two separate measures of eyes closed data with recordings separated by a few hours, to investigate the reliability of the IAF.

Acknowledgments

This report forms the first communication of the ‘International Consortium On Neumodulation – Discovery of Biomarkers (ICON-DB)’, which was established during the 3rd International Brain Stimulation Conference held in Vancouver in 2019. A group of EEG and TMS researchers decided to initiate this consortium in order to facilitate direct replication of EEG and TMS-EEG findings by facilitating immediate and independent cross-dataset replication in order to foster robustness of research findings and facilitate translation into clinical practice. Requests for replication studies can be emailed to Andrew Leuchter (afl@ucla.edu) or Martijn Arns (martijn@brainclinics.com).

Disclosures

MA is unpaid chairman of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications related to EEG, neuromodulation and psychophysiology, but receives no royalties related to these patents; Research Institute Brainclinics received research funding from Brain Resource (Sydney, Australia), Urgotech (France) and neuroCare Group (Munich, Germany), and equipment support from Deymed, neuroConn, Brainsway and Magventure.

FVR receives research support from Canadian Institutes of Health Research, Brian Canada, Michael Smith Foundation for Health Research, Vancouver Coastal Health Research Institute, and in-kind equipment support for investigator-initiated trial from MagVenture. He has participated in an advisory board for Janssen.

PBF is supported by a NHMRC Practitioner Fellowship (1078567). PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Neuronetics and Brainsway Ltd and funding for research from Neuronetics. He is on scientific advisory boards for Bioinformatics Ltd and LivaNova and is founder of TMS Clinics Australia.

AFL discloses that he has received research support from NIH, Neuronetics, Breast Cancer Foundation, Department of Defense, CHDI Foundation, and Neurosigma. He has served as a consultant to Ionis Pharmaceuticals, CHDI Foundation, and Neosync. Inc. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA). He has stock options in Neosync, Inc. and equity interest in BBA.

DMB has received research support from the CIHR, NIH, Brain Canada and the Temerty Family Foundation through the CAMH Foundation and the Campbell Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd., and he is the principal site investigator for three sponsor-initiated studies for Brainsway Ltd. He received in-kind equipment support from Magventure for investigator-initiated research. He received medication supplies for an investigator-initiated trial from Indivior. He has participated in an advisory board for Janssen.

LLC discloses research support or in-kind equipment support from Neuronetics, Neosync, Nexstim, AffectNeuro, and Janssen. She has received consulting income for advisory board work from AffectNeuro, Janssen, Neurolief, Sage Therapeutics, Neuronetics, and NeuroniX.

In the last 5 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. His work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the National Institutes of Mental Health (NIMH) and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

JC, NK, NWB, and CR have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.10.017.

References


