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The relationship between individual alpha peak frequency and clinical outcome with repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder (MDD)

Juliana Corlier [a, b, *], Linda L. Carpenter [c], Andrew C. Wilson [a, b], Eric Tirrell [c], A. Polly Gobin [c], Brian Kavanaugh [d], Andrew F. Leuchter [a, b]

[a] TMS Clinical and Research Program, Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, CA, USA
[b] Department of Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[c] Butler Hospital Mood Disorders Research Program and Neuromodulation Research Facility, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA
[d] E. P. Bradley Hospital, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA

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ABSTRACT

Background: The individual α frequency (IAF) has been associated with the outcome of repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder (MDD), but the association has been inconsistent.
Hypothesis: Proximity of IAF to the stimulation frequency, rather than the value of IAF per se, is associated with outcome for patients receiving 10 Hz rTMS.
Methods: We examined the relationships between IAF, rTMS stimulation frequency, and treatment outcome in 147 patients. All patients initially received 10 Hz rTMS unilateral treatment delivered to left dorsolateral prefrontal cortex (DLPFC) (10UL), with subsets of patients changed to unilateral 5 Hz to left DLPFC (5UL) or sequential bilateral (SB) stimulation (10 Hz/1Hz) to left and right DLPFC based upon worsening symptoms with or intolerance of 10UL. Outcome was percent change in total score on the Inventory of Depressive Symptomatology – Self Report (IDS-SR) scale from pre-treatment baseline to the 30th treatment. IAF values and absolute difference between IAF and 10 Hz (|IAF-10Hz|) were examined in relation to outcome for the overall sample and for each stimulation group separately.
Results: There was no correlation between IAF value, or |IAF-10Hz| and outcome in the overall sample. ANCOVA showed a significant interaction between IAF measures and treatment type. Post-hoc analyses revealed that IAF and |IAF-10Hz| were both significantly associated with degree of improvement (IDS-SR % change) for patients who received 10UL ($P < 0.01$) but not 5UL or SB stimulation. There was a trend-level difference in IAF between responders and non-responders only within the 10 Hz group, but not within the other treatment groups (n.s.). For the 10UL group, membership in the highest IAF quartile was associated with significantly greater clinical improvement than membership in the lowest IAF quartile ($p = 0.0034$).
Conclusions: IAF measures were associated with clinical outcome of patients treated with 10UL but not 5UL or SB rTMS treatment. This suggests that interactions between endogenous frequencies and treatment outcome may be related to the selected stimulation parameters and/or physiologic and clinical characteristics of patients who benefit from those parameters.

Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) for treatment of Major Depressive Disorder (MDD) is commonly administered to left dorsolateral prefrontal cortex (DLPFC) at a frequency of 10 Hz [1]. One possible effect of rTMS is the entrainment of

* Corresponding author. Semel Institute for Neuroscience and Human Behavior David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Los Angeles, CA, USA.
E-mail address: corlier@ucla.edu (J. Corlier).

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oscillations in underlying cortex to the frequency of stimulation [2]. This change in oscillations may rapidly spread through brain networks to related brain regions [3,4]. 10 Hz is the center of the alpha (α) frequency band, with oscillations in the α band representing a thalamocortical rhythm [5]. Entrainment of α oscillations has been hypothesized to "reset" thalamocortical oscillators and may be related to the therapeutic mechanism of rTMS [6,7]. In healthy control patients, α oscillations play a key role in organizing the activity, function, and flow of information within resting state networks (RSNs) [8–10]. Fluctuations in the local functional Magnetic Resonance Imaging (fMRI) BOLD signal are strongly related to spontaneous α oscillations that largely explain evoked fMRI response variance [11–14]. A possible role for α rhythms in depression is also suggested by findings demonstrating that α band oscillatory activity is significantly disturbed in MDD [15] and that α-band metrics early in the course of antidepressant medication (but not placebo) are statistical predictors of subsequent response or remission [16].

Each brain network has a preferred resonant frequency [17], which is best defined by its peak frequency [18]. While the range and peak frequency of α oscillations vary across individuals [19], individual alpha frequency (IAF; the single largest oscillatory peak in the α band) is a highly stable neurophysiological trait marker with high reliability observed across multiple measurements for up to six months in healthy adults [20], and stability over a course of standard rTMS treatment confirmed in a clinical sample [21]. It has been hypothesized that the IAF for each person may represent a resonant frequency at which networks are best engaged by neuromodulation treatments [6,7]. This hypothesis is supported by the finding that low intensity transcranial alternating current stimulation (tACS) of a circuit at its IAF upregulates α oscillations and may enhance spike-timing dependent plasticity (STDP) [22]. Applying principles arising from the relationship between stimulus amplitude and resonance frequency as characterized by the "Arnold Tongue" model [23], lower intensities of noninvasive brain stimulation may be able to entrain alpha oscillations when stimulation frequency more closely approximates the subject's IAF. The potential efficacy of this approach was supported by a subsequent multi-site randomized sham-control trial comparing low-field IAF stimulation relative to sham, albeit only in the per-protocol population which were treated at the correct IAF value and completed at least 80% of scheduled treatment sessions [24].

Clinical investigations have yielded conflicting evidence regarding IAF-guided rTMS. One study reported that a single session of rTMS at IAF +1 Hz was associated with greater enhancement of cognitive task performance than with stimulation at slower or faster frequencies [25]. A controlled trial of rTMS to DLPFC regions for treatment of negative schizophrenia symptoms showed that stimulus frequency matched to IAF was superior to sham, 3 Hz, or 20 Hz stimulation [26], and a subsequent schizophrenia trial confirmed IAF stimulation was superior to sham, independent of the stimulation target [27]. However, IAF +1 Hz did not subsequently prove superior for guiding rTMS treatment frequency in depressed patients when compared to outcome previously obtained with standard 10 Hz stimulation [28]. A follow up study observed a relationship between IAF and rTMS treatment outcome [29], although this was not replicated in a larger cohort of 106 patients [30].

We have hypothesized that differing results among prior studies may indicate that the difference between the intrinsic oscillations (IAF) and the stimulation frequency, rather than IAF alone, may be a key factor that determines the outcome of treatment. We thus examined the relationship between the absolute distance between IAF and 10Hz, as well as IAF values, and treatment outcome in 147 patients undergoing clinical rTMS treatment for MDD at two clinics. All patients were initially treated with 10 Hz rTMS stimulation administered to left DLPFC; 68 continued with this protocol (10UL). Subsets of patients were switched to either 5 Hz stimulation to left DLPFC (5UL, N = 39) or to sequential bilateral stimulation (10 Hz at left DLPFC followed by 1 Hz at right DLPFC, SB, N = 40) for the majority of their treatment sessions because of worsening symptoms or inability to tolerate 10UL. We tested the hypothesis that the distance between patients' IAF and 10 Hz would be significantly related to treatment outcome for patients who received 10 Hz stimulation, but not for patients treated with the other stimulation protocols.

Methods

Subjects

Subjects were 147 individuals 19–79 (mean = 47.6, SD = 14.8) years of age with a primary diagnosis of MDD confirmed by the Mini International Neuropsychiatric Interview (MINI) [31], and who were referred for rTMS treatment in the TMS Clinical and Research Service at UCLA, or the TMS Program at Butler Hospital. The research protocol was approved by the UCLA and Butler Hospital IRBs and all patients provided informed consent prior to EEG procedures. There were no study-specific treatment decisions or experimental changes in rTMS parameters related to study participation. Patients presented with at least moderately severe depressive symptoms based upon a 17-item Hamilton Depression Rating Scale Score (Ham-D_{17}) [32] ≥17 or minimal rating of 'moderately ill' on the Patient Global Impression of Severity (PGI-S), and most were receiving concomitant treatment with at least one antidepressant or other psychotropic medication. All patients underwent standard safety screening and medical clearance to receive rTMS therapy [1]. Demographic characteristics of patients are shown in Table 1.

Clinical outcome

Outcome was based upon the percentage change in total score on the 30-item Inventory of Depressive Symptomatology – Self-Report version (IDS-SR) [33] from pretreatment baseline to immediately following the 30th treatment.

EEG recording and pre-processing

Electroencephalographic (EEG) data were recorded using the "eego mylab" TMS-compatible EEG system at a sampling rate of 2000 Hz (Advanced Neuro Technology [ANT]; Enschede, Netherlands). Electrodes were applied using the 64-electrode "WaveGuard" system with sintered Ag/AgCl electrodes mounted in an elastic cap and positioned according to the Extended 10–20 System with EOG electrodes above and below the left eye. Data were recorded using full-band EEG DC amplifiers without filters during data acquisition, and recording was performed using a common average reference with impedance kept below 10 kΩ. A subset of the sample had EEG collected with a sparse montage of 8 dry comb electrodes in a neoprene cap (F3, FP1, FPZ, FP2, FZ, CZ, PZ, OZ) and two reference electrodes applied to the right mastoid bone (StarStim, Neuroelectrics Inc.). In total, 60% of 10UL patient and 100% of SB patients had EEG recorded by the ANT system (same system at UCLA and Butler) and 40% of the 10UL group, 100% of the 5 Hz, and 0% of the SB group were recorded with the StarStim system. Resting-state EEG was recorded during 'eyes closed' condition prior to the first rTMS treatment. At UCLA, 5 min and at Butler/Brown 8 min of data were collected.

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Table 1
Sample characteristics and rTMS treatment outcome. Table shows demographic information, test statistics and p-values.

	Total sample n = 147	10UL n = 68	5UL n = 39	SB n = 40	Test Statistic 10UL vs. 5UL vs. SB	P-value
Age, Mean (±SD)	47.6 (±14.7)	48.0 (±15.0)	47.5 (±13.7)	47.0 (±15.7)	F = 0.1	0.94
Gender (% male)	49.7%	48.5%	66.7%	35.0%	$\chi^2 = 7.2$	0.02
Baseline IDS-SR scores, Mean (±SD)	44.7 (±11.2)	43.4 (±10.1)	48.6 (±10.8)	43.0 (±12.6)	F = 3.4	0.04
6-week IDS-SR, Mean (±SD)	28.0 (±12.7)	24.1 (±11.5)	30.9 (±11.8)	32.2 (±13.4)	F = 6.7	0.002
IAF, Mean (±SD)	9.4 (±1.1)	9.4 (±1.0)	9.2 (±1.0)	9.6 (±1.2)	F = 1.3	0.27

Semi-automated EEG preprocessing for artifact detection was performed using the ICA-based FASTER algorithm [34]. This EEGLAB toolbox resamples the data to 1000 Hz, removes muscle, heart, motion, ocular artifacts, and other noise using a multiple step procedure consisting of a) bandpass filtering [0.5–55 Hz], b) ICA, c) rejection and/or interpolation of bad channels/epochs. After preprocessing, data underwent visual inspection to reject any remaining epochs containing artifact. Even though the FASTER toolbox was tested for 32 + electrodes, we applied this method to both data sets to minimize preprocessing differences not related to rTMS treatment. To ensure good quality of data at both sites, after preprocessing data underwent visual inspection to reject any remaining epochs containing artifact.

Individual α frequency (IAF) determination

Using artifact-free data obtained from EEG preprocessing, the frequency power spectrum recorded at the electrode F3 was calculated using Welch's power spectral density estimate. Based upon 4-s long data segments sampled at 1000 Hz, spectra were computed with a frequency resolution is of 0.25 Hz with relative power estimates for each frequency bin expressed as the percentage of total power in the range 2–20 Hz. Each subject's IAF was determined by identifying the highest peak within the 7–13 Hz alpha range [25] that surpassed a 95% confidence interval of the mean spectral power in the same range derived from a 2000-samples bootstrapped distribution. If no peak surpassed the confidence interval, the patient was considered not to have a dominant IAF rhythm and was not considered in the analysis (15.1% of our original sample of n = 147). Supplementary Fig. 1 shows example spectra and IAF detections for 30 representative patients and the IAF distribution for all groups.

rTMS procedures

All rTMS treatments were performed with either the Magstim Rapid 2 stimulator using a 70 mm coil (Magstim, Whitland, South Wales, UK) or the Neuronetics' Neurostar treatment system (Neuronetics, Malvern, PA, USA). Motor threshold (MT) determination was performed prior to the first treatment, with MT defined as the minimum stimulus intensity necessary to elicit a motor response in the right abductor pollicis brevis (APB) or first dorsal interosseus (FDI) muscles for ≥ 50% of applied stimuli.

Following MT determination, treatments were performed with patients seated in a semi-reclined position using standard safety procedures and ear protection. Treatments initially consisted of 3000 pulses delivered to the left DLPFC target (defined using the Beam F3 method) [35] at a frequency of 10 Hz using 40 pulse bursts, a 26 s intertrain interval (ITI), and an intensity of up to 120% MT (to which patients were accommodated in the first several treatment sessions).

All patients underwent treatment initially with 10 Hz stimulation to left DLPFC at an intensity of at least 80% MT. Clinicians adjusted stimulation intensity, coil angle, and number of pulses administered as needed to manage patient comfort, and % MT was increased as tolerated towards a maximum of 120% MT to maximize therapeutic benefit. At the UCLA site, patients unable to tolerate 10 Hz stimulation by the fifth treatment session because of anxiety, agitation, or pain, or who had worsening depressive symptoms underwent the addition of 1 Hz stimulation to right DLPFC (i.e., sequential bilateral stimulation). At the Butler site, patients who could not tolerate 10 Hz were changed to 5 Hz, continuing with unilateral stimulation over left DLPFC. For analyses, patients were grouped into categories based upon their predominant rTMS treatment protocol: 10 Hz unilateral left DLPFC stimulation (10UL) (N = 68), 5 Hz unilateral left DLPFC stimulation (5UL) (N = 39), and sequential bilateral (SB) (N = 40).

Data analysis

We performed a Kruskall-Wallis test to compare gender ratios and T-tests to compare age, baseline depression severity, clinical improvement, and IAF among the different treatment protocol groups. For all patients, both peak IAF and the absolute value of the numerical difference between peak IAF and 10 Hz (|IAF − 10|) were calculated. Analysis of covariance (ANCOVA) was performed on the pooled data sample (n = 147) to evaluate whether there was a difference in relationships between IAF or |IAF-10 Hz| and clinical outcome that were modulated by treatment protocol type, using the percentage IDS-SR change as the dependent and IAF, |IAF − 10|, and treatment protocol group (10UL, 5UL, or SB) as independent variables. Subsequent post-hoc Pearson's correlations were performed between the percentage change in IDS-SR and IAF or |IAF − 10| for the pooled sample and separate treatment groups as appropriate. T-tests were used to compare mean IAF and |IAF − 10| values for responders and non-responders (defined as ≥ 40% improvement in IDS-SR) and to compare the mean IDS-SR scores for 10 Hz subgroups defined by quartiles of the IAF distribution.

Results

Sample characteristics and rTMS treatment outcome are presented in Table 1. There was no significant difference in age or IAF among the three treatment groups (Fig. 1). There was a significant group difference in gender distribution and mean depression baseline severity, but ANCOVA analyses showed that those two variables did not affect IAF distance to 10Hz (p = 0.71, p = 0.88, respectively). There was also no group significant effect research site (UCLA or Butler, p = 0.66). Examination of mean final IDS-SR across the three treatment protocol groups revealed significantly superior outcome in the 10UL group, followed by 5UL and then SB (Table 1). The ANCOVA of pooled data showed no effect of the IAF value or |IAF − 10| on outcome, but a significant effect of treatment protocol type (p < 0.001) and a significant interaction between IAF and treatment type was observed (p = 0.03). Post-hoc correlations showed no relationship between IAF value or |IAF-10Hz| and clinical outcome for the pooled data sample (n.s). However, significant correlations were found for both IAF variables in the 10UL group (r = 0.314, p = 0.009, $p_{adj} = 0.036$ and r = −0.305, p = 0.011, $p_{adj} = 0.045$), but not in 5UL or SB groups (n.s., Fig. 2). T-tests

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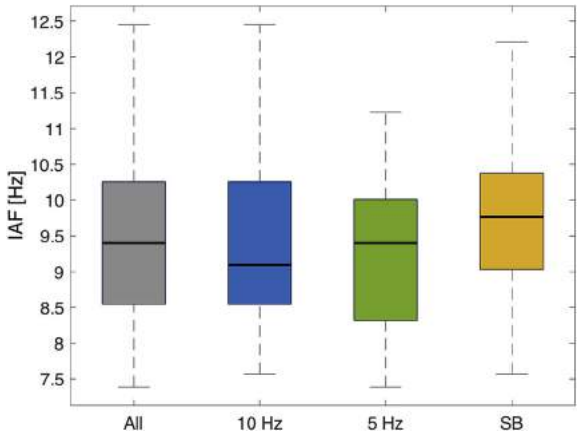

Fig. 1. IAF distributions for all patients. Box and whiskers plots show the IAF distributions for the pooled patient sample ('All'; grey), the 10 Hz unilateral ('10 Hz'; blue), 5 Hz unilateral ('5 Hz'; green) and sequential bilateral ('SB'; yellow) treatment groups. There were no significant differences in IAF among these groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

comparing mean IAF and |IAF − 10| for responders and non-responders showed a statistical trend for |IAF − 10| group difference ($p = 0.065$) within the 10UL group, but not within other treatment groups (n.s. for both IAF measures). A T-test comparing the clinical outcome of 10 Hz patients with an IAF in the top vs bottom quartile IAF distribution showed a significantly better outcome for the patients with high IAF ($p = 0.0034$).

Discussion

We found that there was no association between the IAF and clinical outcome in the overall sample. However, both IAF and the difference between patients' IAF and 10 Hz were significantly correlated with treatment outcome among depressed patients receiving predominantly 10 Hz unilateral rTMS stimulation to the left DLPFC. The post-hoc T-tests comparing IAF between responders and non-responders reached trend level significance only for the 10UL group but not any other group. Patients within the 10UL group with an IAF in the top quartile of the IAF distribution had a significantly better clinical outcome than those from the bottom IAF quartile. Our results suggest that the specific frequency of stimulation in relation to a patient's IAF may play a role in MDD symptom reduction for a subset of patients, identified here as those who tolerated and continued to receive the standard "default" 10 Hz treatment protocol. For this subgroup and not the others, the higher the IAF value and the lower the absolute distance of IAF from the 10 Hz stimulation frequency, the greater the symptom improvement following a six-week course of rTMS.

It is notable that significant relationships with IAF were not found in groups of patients treated with 5 Hz or SB rTMS, even though 10 Hz stimulation over left DLPFC remained a component of treatment for SB group. It is difficult to interpret these findings because assignment to stimulation protocol was neither randomized nor experimentally controlled, but rather made based up on the early clinical effects of 10 Hz unilateral treatment. Those patients with worsening anxiety, insomnia, agitation, or other symptoms were switched on clinical grounds to an alternative (5UL or SB) treatment protocol. It is possible that early clinical worsening with the 10UL protocol corresponds with an underlying biotype that has the unique neurophysiologic characteristic of a relationship between IAF measures and treatment outcome. This possibility would be consistent with the fact that the 10UL patients had better treatment outcome than the 5UL and SB groups, who may have had more treatment resistant illness or differed from the 10UL group on the basis of another clinical or neurophysiological factor. It also is possible that the relationship between IAF measures and outcome only emerges for patients who receive predominantly 10 Hz stimulation for their entire treatment course. Prospective assignment of patients to different treatment protocols based upon neurophysiologic characteristics would be necessary in order to disambiguate these underlying relationships.

While the post-hoc T-test comparing the IAF between responders and non-responders showed only a statistical trend, the significant correlations in the 10UL group suggests that small differences in stimulation frequency may produce significant differences in neurophysiologic effect. Depressed patients with a high IAF at baseline had better clinical outcome than patients with a low IAF. This finding is consistent with prior results showing that small adjustments in stimulation frequency affects which nodes within a single resting state network (RSN) are engaged [36,37], the extent to which rTMS stimulation changes local vs. distant network modules [38], and the degree of engagement between a RSN and an affiliated brain region. For example, different stimulation frequencies applied to a parietal node can change interactions of the frontoparietal control network (FCN) with the default mode network (DMN) from excitatory to inhibitory [39].

Baseline IAF value has previously been evaluated in relation to MDD rTMS treatment outcome, independent of stimulation frequency. A study of 90 MDD patients identified a relationship between peak IAF (recorded from frontal electrode sites) and outcome with rTMS responders showing a higher IAF in a sample treated with either left 10 Hz or right 1 Hz stimulation [29]. However, a subsequent study employing the same methods in a larger sample failed to replicate that initial finding [30]. A large dataset from the sham-controlled OPT-TMS trial ($n = 180$) also did not show a relationship between clinical outcome and any of the α metrics derived from 4-channel EEG recordings (eyes open) at baseline or serially [40], although limitations of the EEG data in that study make the findings difficult to interpret. None of these studies explored a link between IAF distance to stimulation frequency and clinical benefit. The present findings may reconcile prior conflicting evidence by considering separately those patients who predominantly received 10 Hz treatment. We found a significant relationship between both IAF and |IAF-10| and clinical outcome only for those patients who had high tolerability for 10UL, but not for other treatment groups. Differences in peak α frequency calculations described across published reports also make it challenging to compare findings across studies; not all calculated IAF from the rTMS stimulation site (left DLPFC) as in the current study, and peak frequencies such as IAF can differ significantly across brain regions (data not presented, but see Ref. [41] for similar report).

One aspect of the current findings appears to be contradictory. How is it possible for those with greater |IAF-10Hz| distance to have worse treatment outcome when, at the high end of the alpha range, treatment outcome was better? This finding reflects the limited number of patients in this sample having an IAF considerably higher than 10 Hz (only 5/68 had an IAF > 10.5 Hz). Given the substantial inter-subject variability in outcome among our patients, a larger sample would be necessary to reliably determine whether higher IAF is associated with superior outcome in the upper alpha frequency range for patients treated with 10 Hz stimulation.

While preliminary, the present study results reflect a signal that adds to a growing body of work investigating whether noninvasive brain stimulation with rTMS "tuned" to the preferred frequency of the underlying α generator might produce better clinical outcome through entrainment of ongoing α oscillations [6,7]. This hypothesis is compelling because it is consistent with the concept of circuit

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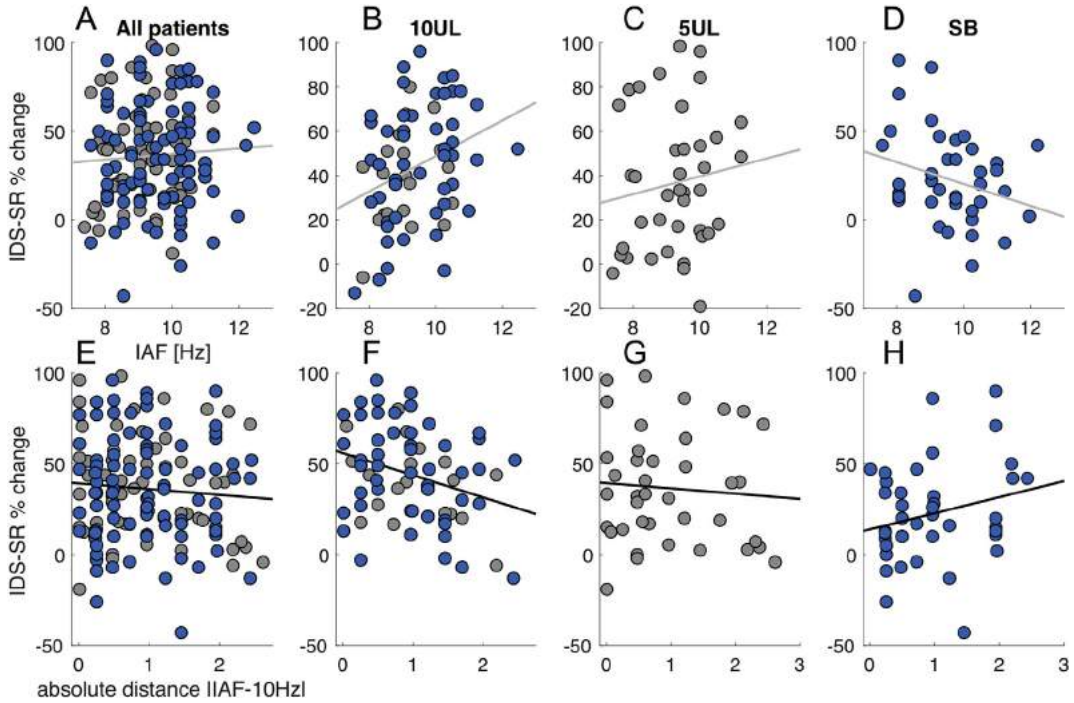

Fig. 2. Relationship between IAF measures and change in IDS-SR score. The upper row shows percent change in IDS-SR as a function of IAF for the pooled sample (A) and separately for those treated with 10UL (B), 5UL (C), and SB (D). Bottom row shows the relationship between the absolute distance between IAF and 10 Hz (|IAF-10Hz|) and the percent change in IDS-SR for the pooled sample (E), those treated with 10UL (F), 5UL (G), and SB (H). Black lines represent the least square fit. Only the 10UL group (B & F) shows a significant relationship for both IAF measures, as marked by the asterisk. Blue and grey markers show patients from UCLA and Butler site, respectively. The corresponding correlation coefficients r and p-values were as following: (A) $r = 0.06$, $p = 0.49$; (B) $r = 0.314$, $p = 0.009$; $p_{adj} = 0.036$; (C) $r = 0.13$, $p = 0.42$; (D) $r = -0.26$, $p = 0.1$; (E) $r = 0.08$, $p = 0.35$; (F) $r = -0.305$, $p = 0.011$, $p_{adj} = 0.045$; (G) $r = -0.08$, $p = 0.65$; (H) $r = 0.23$, $p = 0.15$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

resonance, wherein the tendency of neuronal circuits to oscillate at greater amplitudes at specific frequencies is explained as a function of specific neuronal properties and circuit architecture [17,42]. In the visual system, entrainment of intrinsic ongoing oscillation through sensory stimulation has been shown to act in a similar fashion, occurring at preferred frequencies of 10, 20 and 40 Hz [43]. Stimulation bursts tuned to an endogenous alpha band may be more successful in reproducing a natural oscillatory signature [2,41] and intermittent theta stimulation (iTBS) bursts tailored to patients' individually-defined prominent theta and gamma rhythms produced more robust mood and cortical plasticity enhancement than default iTBS parameters [44]. More rigorous research is needed to inform the field about EEG biomarkers which could ultimately be useful for clinical application [45].

Strengths of this study include the large sample size and the ecological validity of using unselected MDD patient treated in the course of usual practice. However, several limitations are noteworthy. First, it is important to note that the differences in IAF reported here, while statistically significant, are of limited prognostic value: responders and non-responders did not differ in their mean IAF or |IAF-10| values. Second, these patients were treated with both rTMS and one or more psychotropic medications for their depressive symptoms. It is possible that IAF values, clinical outcome, and the relationship between IAF and stimulation frequency was influenced by concurrent medication status or by other uncontrolled factors. Third, the coil angle, number of pulses administered, and other factors commonly adjusted in clinical practice were not systematically controlled. It is possible that these other factors influenced treatment outcomes and the results reported here. Fourth, the decision to treat with predominantly 10UL, 5UL, or SB stimulation was made using a clinical decision-making paradigm rather than experimentally-controlled assignment. It is possible that had all these patients continued to receive 10UL treatment, the results would be different.

Replication studies are needed to determine whether these preliminary findings are sufficiently robust to merit prospective study of IAF as a candidate for a personalized rTMS parameter approach for treating depression. These results do, however, underscore the importance of understanding the relationships among rTMS stimulation frequency, endogenous rhythms, and treatment outcome. Future research should investigate the potential utility of systematically examining the effects of stimulation across a range of pulse frequencies, inclusive of and beyond the α range, to a single neuroanatomic target (such as left DLPFC). Such broad interrogation across the frequency spectrum may generate additional insights about the magnitude of difference between stimulation frequency and naturally occurring brain rhythms on clinical outcomes [46].

Conflicts of interest

Drs. Corlier and Kavanaugh, Mr. Tirrell and Ms. Gobin have no disclosures.

Dr. Carpenter received consulting income from Magstim and Janssen, and clinical trial support from Cervel, Neuronetics, Neosync, Janssen, and Feelmore Labs. Butler Hospital has received research equipment support from Neuronetics, Cervel, and Nexstim.

Mr. Wilson has served as a consultant to HeartCloud, Inc.

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NeuroSigma, Inc. He has served as a consultant to NeoSync, Inc., Ionis Pharmaceuticals, Inc., and ElMindA. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA). Dr. Leuchter owns stock options in NeoSync, Inc. and has equity interest in BBA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.07.018.

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