EEG-based biomarkers predict individual differences in TMS-induced entrainment of intrinsic brain rhythms

Jelena Trajkovic [a,b,*], Alexander T. Sack [a], Vincenzo Romei [b,c,**]

[a] *Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, 6229 ER, the Netherlands*
[b] *Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia, Alma Mater Studiorum – Università di Bologna, Campus di Cesena, Cesena, 47521, Italy*
[c] *Facultad de Lenguas y Educación, Universidad Antonio de Nebrija, Madrid, 28015, Spain*

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ABSTRACT

Background: Entrainment (increase) and modulation (shift) of intrinsic brain oscillations via rhythmic-TMS (rh-TMS) enables to either increase the amplitude of the individual peak oscillatory frequency, or experimentally slowing/accelerating this intrinsic peak oscillatory frequency by slightly shifting it. Both entrainment, and modulation of brain oscillations can lead to different measurable perceptual and cognitive changes. However, there are noticeable between-participant differences in such experimental entrainment outcomes.

Objective/hypothesis: The current study aimed at explaining these inter-individual differences in entrainment/frequency shift success. Here we hypothesize that the width and the height of the Arnold tongue, i.e., the frequency offsets that can still lead to oscillatory change, can be individually modelled via resting-state neural markers, and may explain and predict efficacy and limitation of successful rhythmic-TMS (rh-TMS) manipulation.

Methods: Spectral decomposition of resting-state data was used to extract the spectral curve of alpha activity, serving as a proxy of an individual Arnold tongue. These parameters were then used as predictors of the rh-TMS outcome, when increasing alpha-amplitude (i.e., applying pulse train tuned to the individual alpha frequency, IAF), or modulating the alpha-frequency (i.e., making alpha faster or slower by stimulating at IAF±1Hz frequencies).

Results: Our results showed that the height of the at-rest alpha curve predicted how well the entrainment increased the intrinsic oscillatory peak frequency, with a higher at-rest spectral curve negatively predicting amplitude-enhancement during entrainment selectively during IAF-stimulation. In contrast, the wider the resting-state alpha curve, the higher the modulation effects aiming to shift the intrinsic frequency towards faster or slower rhythms.

Conclusion: These results not only offer a theoretical and experimental model for explaining the variance across different rh-TMS studies reporting heterogenous rh-TMS outcomes, but also introduce a potential biomarker and corresponding evaluative tool to develop most optimal and personalized rh-TMS protocols, both in research and clinical applications.

1. Introduction

Rhythmic Transcranial Magnetic Stimulation (rh-TMS) allows the modulation of ongoing endogenous oscillatory brain rhythms by applying multiple, periodic electromagnetic pulses that drive the intrinsic oscillations to become synchronized to this external, rhythmic pulse train. Several studies have successfully used rh-TMS to entrain (increase) and modulate (shift) brain oscillations [1–6], and/or obtain measurable effects on behavior [2–4,7,8]. However, recent studies have also pointed towards some important methodological considerations regarding the specificity of rhythmic-TMS entrainment protocols [2,8,9].The first consideration is the importance of individually determined stimulation parameters. For instance, when aiming to entrain oscillatory alpha-activity, a possible entrainment protocol may either simply deduce the inter-pulse train interval based on a standard one-size-fits-all

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Abbreviations

EEG -   Electroencephalography
Rh-TMS –   rhythmic Transcranial Magnetic Stimulation
IAF –   Individual Alpha Frequency
NIBS –   Non-invasive brain stimulation

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10 Hz stimulation applied to all participants, or deliver on individually calibrated frequency, calculated based on the individual resting state or task induced individual alpha-frequency (IAF). Previous research indicates that entrainment effects are more robust and also larger if TMS protocols are based on individually tailored and thus personalized protocols [8,10]. In healthy volunteers, for example, brain stimulation entrainment only successfully modulated the attentional bias when applied at the IAF, but not when stimulating with the IAF ± 2 Hz [11]. Interestingly, such a personalized brain stimulation entrainment protocol approach was also demonstrated to be clinically relevant, as deviations between the IAF and the stimulation frequency correlated with NIBS treatment outcome in depressive patients [12,13]. Why would this IAF entrainment be of particular clinical relevance? It has been suggested that the IAF might represent a resonant frequency, which normalizes regulation and facilitates reemergence of intrinsic cerebral rhythms, and through this mechanism restores normal brain function [14]. It could be that the alpha entrainment via rh-TMS is able to "reset" thalamocortical alpha oscillators, that have been previously related as key mechanism of brain network organization, that influence local signal processing, widespread information exchange, and ultimately perception and behavior [15]. Importantly, a recent study from our group demonstrated that the standard 10 Hz stimulation could be inefficient not only because of the lack of precision, but also because stimulating either at the exact IAF versus at a certain distance between the stimulation frequency and the IAF may have differential consequences on brain and behavior. Our group, for example, recently demonstrated that modulating, i.e. shifting the individual alpha-frequency by stimulating at IAF ± 1 Hz selectively changed perceptual acuity, whereas increasing the amplitude of the individual alpha frequency by stimulating at the exact IAF specifically shaped subjective awareness [2]. This indicates that 10-Hz entrainment may have different neural and behavioral effects for participants with near-10Hz IAF versus participants with either higher and/or lower intrinsic IAF. Moreover, various cognitive and clinical impairments haven't only been related to the anomalous alpha synchrony, but also to a slower alpha oscillatory cycling, accounting for cognitive deficits [16–18]. Therefore, shifting alpha towards a faster pace could increase visual perception, attention, and the speed of information processing. In sum, for both basic research and clinical application, personalizing the rhythmic stimulation protocols aimed at entraining alpha activity or shifting the alpha frequency is paramount for obtaining reliable and desired stimulation outcomes.

The main challenge in achieving robust and reliable rh-TMS effects, both on brain and behavior, however, remains the high inter-subject variability in entrainment and modulation outcomes, a variability that also persists even when the stimulation protocols are personalized. Concretely, we showed that individualized rh-TMS at IAF + - 1 Hz induces either speeding-up or slowing-down of the intrinsic alpha activity with a range between 0 and 2Hz across participants. rh-TMS at the exact IAF also led to large differences in the extent by which the alpha-amplitude was entrained (increased) across the different participants. Crucially, this inter-individual variability in rh-TMS-induced effects correlated with the behavioral-cognitive outcomes of brain stimulation, with more successful induced neural entrainment or frequency shifting leading to larger behavioral changes [2]. Hence, rh-TMS is only optimally effective in modulating behavioral-cognitive performances if it has also effectively induced the desired effects in the brain. These neural

entrainment and modulation effects, however, largely vary between participants and so do the behavioral-cognitive outcomes [8,12,19,20]. The crucial question remains how to explain and potentially reduce this inter-subject variability in rh-TMS efficacy? Does successful rh-TMS-induced outcome represent a random between-participants variability, or can we identify a biomarker that allows us to predict successful entrainment/frequency-shifting? The implications of finding such a potential biomarker cannot be overestimated as it may not only allow us to identify before applying the brain stimulation protocol which subjects or patients are more likely to respond in the desired manner, but it may even allow us to personalize the rh-TMS protocol itself to increase individual efficacy and reduce inter-subject variability, both in research and clinical practice. The current study aimed at contributing to this objective by identifying individual resting-state neural markers related to effective rh-TMS outcome.

The current theoretical concept of entrainment is based on the so-called Arnold tongue which predicts the degree of synchronization (entrainment) of an oscillator (here: brain) coupled to a rhythmic driving force (here: rh-TMS), depending on two parameters: the amplitude of the driving force and the driving frequency [21]. This parameter set can be visualized as an area in a plot which exhibits stimulation frequency on the x-axis and stimulation intensity on the y-axis (see Fig. 1). The larger the stimulation intensity, the broader the range of stimulation frequencies at which the oscillator entrains to the stimulation; on the other hand, if we aim the exact frequency of the natural oscillator, we will need less external power to entrain. Accordingly, for the alpha activity, IAF obtained via power spectrum during resting state has been shown to lead to best entrainment effects. The mentioned individual power spectrum gives us information about the level of neural synchronization of a certain neural population at the specific frequencies: not only about where this synchronization is maximal, which would represent the individual peak frequency (in our case, IAF), but also what ratio of this neural population is oscillating at slightly lower or higher frequencies. Given this premise, if the individual spectrum is wider or narrower would mean that off-peak intrinsic frequencies are more present or absent. If we then use the external force (such as TMS) to drive this internal oscillator towards these off-peak frequencies (in our case, IAF ± 1Hz), the wider alpha spectrum will then allow us to more easily do so, since already the natural oscillator is more inclined towards these frequencies. This would mean that Arnold tongue describing the effects of entrainment could be modelled based on the individual power spectrum: not only the frequency where the entrainment outcome will be maximal (IAF), but also the outcomes when we drive the frequency towards lower or higher frequencies: if the stimulation intensity is the same, the rh-TMS outcome (green markers) would depend on the width of the Arnold tongue (see Fig. 1).

As for the alpha amplitude, here we assume a relationship between the stimulation intensity and the baseline oscillator synchronization: the more there is an initial synchronization the harder is to entrain it, as demonstrated previously [22]: thus, the stimulation intensity needs to be higher. Therefore, we could represent the relative stimulation amplitude (defined as the inverse of the baseline alpha synchronization) on the y-axis instead of stimulation intensity (see Fig. 1).

In sum, here we hypothesize that the width and the height of the Arnold tongue, i.e., the frequency offsets that can successfully lead to frequency drifts and the baseline amplitude levels, could be individually modelled for each participant, allowing the prediction of rh-TMS effects on an individual level.

2. Material and methods

Please note that the participants and the TMS-EEG data during the perceptual task are the same as in Di Gregorio et al., 2022 [2]. However, here the focus of analysis is on the eyes-open and eyes-closed resting-state EEG activity (data not previously investigated), in relation to the on-task entrainment outcome, as reported in Di Gregorio et al., 2022 [2].
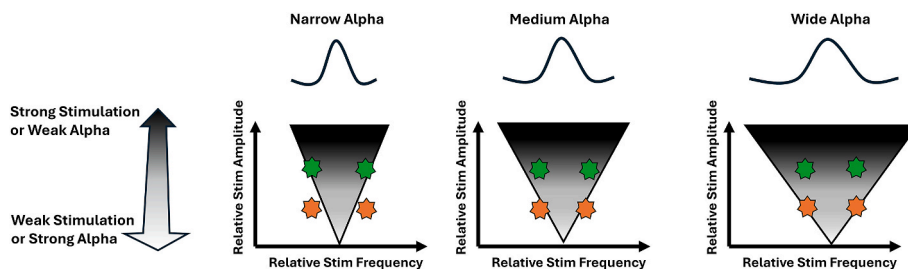
Fig. 1. Schematic representation of the relationship between the stimulation (relative to the natural) frequency, the stimulation (perturbation) intensity, and the occurrence of synchronization (Arnold tongue). The right, middle, and left panel represent a potential different width of the Arnold tongue (narrow, medium and wide alpha, respectively). Green (orange) markers represent different off-peak (IAF-1Hz, IAF + 1 Hz) stimulations of the same intensity. Green vs. orange markers represent different off-peak stimulations of the low (in green) vs high (in orange) relative stimulation amplitude. Markers that fall out of the Arnold tongue (depicted as a triangle surface on the graph) are assumed to not be entrained. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Participants. Sixty-eight healthy volunteers (37 females, 31 males; mean age $\pm$ SE = 22.93 $\pm$ 0.51 years) were recruited for the current study. All of them had a normal or corrected-to-normal vision and met TMS safety criteria by self-report. All participants gave written informed consent before taking part in the study, which was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee at the University of Bologna. Here, participants were assigned to one of three groups with distinct stimulation protocols: IAF-1Hz (N = 17 participants, mean age 22.64 $\pm$ 0.53, nine females), IAF (N = 34 participants, mean age 22.92 $\pm$ 0.61, eighteen females) and IAF+1Hz (N = 17 participants, mean age 23.88 $\pm$ 0.77, eight females). One participant (IAF- 1Hz group) was excluded because the resting-state data was not available.

Stimuli and task procedure. An eyes-open and eyes-closed resting-state data during the EEG recording was obtained from all the participants included in the study. Specifically, participants were comfortably seated in a dimmed-lit room with their eyes closed (eyes-closed resting-state condition) or with a gaze on a fixation cross on a screen, while recording their EEG activity for 3 min per condition. The same participants also conducted a visual discrimination task (see Fig. 2), during a concurrent rh-TMS-EEG measurement. Specifically, prestimulus alpha activity was fine-tuned relative to IAF via five-pulse rh-TMS bursts. Furthermore, we selectively modified the amplitude or frequency of brain rhythms by adjusting the timing between pulses based on participant's individual alpha rhythms (IAF). We used rh-TMS at a 1 Hz slower or faster speed relative to a participant's individual oscillatory

frequency (IAF-1Hz group and IAF+1HZ group) to induce alterations in the oscillatory-frequency cycle length. To selectively modulate oscillatory amplitude, the frequency of the rh-TMS pulse trains was precisely matched to the participant's intrinsic IAF, enhancing neural firing synchronization and phase alignment without modifying the frequency of oscillatory activity (IAF group). The rh-TMS design adhered to current safety standards [23–25].

Stimulation was delivered via a 70 mm figure-of-eight coil connected to a Magstim Rapid Transcranial Magnetic Stimulator (Magstim Company, UK) onto the right occipital site (in correspondence with the O2 electrode), with the coil surface oriented tangentially to the scalp, while the coil handle was oriented perpendicular to the medial plane of the subject's head (latero-medial current direction). The strength of the pulses was held constant at 60% of the maximum stimulator output (MSO), roughly corresponding to previously described phosphene thresholds [26–29]. Non-specific rh-TMS effects were controlled for by using a within-subject sham control stimulation, which was achieved using a modified coil that was placed far enough away from the scalp (by adding a styrofoam cube to the coil itself) to assure the lack of effective stimulation while maintaining coil position, as well as tactile and acoustic sensations. Each subject received three consecutive rh-TMS and sham blocks (900 active rh-TMS pulses) whereas the order of TMS and sham blocks was randomized, corresponding to a total of six blocks with 60 trials per block (N trials = 360). No subject reported phosphenes during the execution of the task.

Psychophysiological recording – acquisition and analysis. EEG data were collected from 64 Ag/AgCl electrodes and from the right mastoid with Brain Vision recorder software (Brain Products, Munich, Germany). The Ground electrode was placed on the right cheek, while the left mastoid served as online reference. The electrooculogram (EOG) was recorded from above and below the left eye and from the outer canthi of both eyes. During the recording, a band-pass filter of 0.01–100 Hz was used, along with a sampling rate of 5000 Hz. The impedance of all electrodes was kept below 10 kΩ. EEG data were pre-processed using custom made routines in MatLab R2013b (The Mathworks, Natick, MA, USA).

Processing of the eyes-open and eyes-closed resting-state data included re-referencing of the signal to the average activity across all electrodes, an offline resampling to 500 Hz, and applying a high-pass (0.5 Hz) and low-pass (50 Hz) filter. Parameters of the alpha activity were then estimated from the posterior, parieto-occipital cluster of the right hemisphere (PO8, PO4 and O2 electrode), in the vicinity of where the rh-TMS was applied (O2 electrode). In order to obtain local power spectrum, power spectrum density has been calculated using Welch's method, with a Hanning windows tapering with 10% overlap and the 0.1 frequency resolution. The spectra were then decomposed into periodic and aperiodic components using the FOOOF algorithm [30]. The obtained flattened spectra (periodic-aperiodic component) in the alpha range (7–14 Hz) was fitted to a Gaussian curve using Matlab fit function. The Gaussian model fits peaks, and is given by:
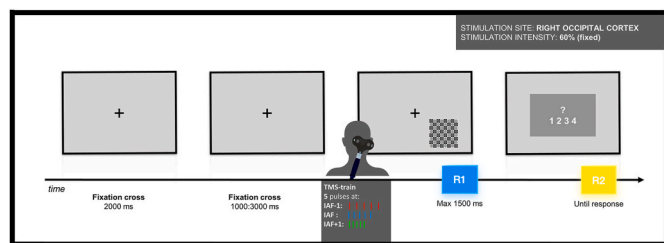
Fig. 2. Experimental design. EEG data were collected during a visual detection task. Each trial started with a fixation cross, after which stimuli could randomly appear in the lower left or right visual field. The primary task was to respond (R1) by pressing a space bar if the checkerboard contained grey circles. After this, participants rated their confidence in their first response (R2) on a Likert scale from 1 (no confidence at all) to 4 (high confidence). In addition, 5 rhythmic-TMS pulses were administered before stimulus presentation. Participants were assigned to 3 different groups. For each group, rhythmic-TMS pulses were set at a certain alpha-frequency: individual alpha-frequency (IAF) group (blues bars), slower pace (IAF-1Hz) group (red bars), and faster pace (IAF+1Hz) group (green bars). ms = milliseconds. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

$$y = a*e\char`\^[\ [\![-((x\text{-}b)/c)]\!]\ \char`\^2\ ]$$

where a is the amplitude, b is the centroid, c is related to the peak width. Here, the amplitude and the width of the curve (defined as the height of the curve's peak and the standard deviation of the Gaussian curve, respectively) were used as a proxy of individuals Arnold tongue, while the centroid has been used as an estimation of the IAF.

Processing of the EEG data during task and, more specifically, during rh-TMS was processed via TMS-EEG signal analyzer (TESA) cleaning protocol, specifically created for removing TMS-induced artifacts from the EEG (for more details, see Ref. [2]). It is an open-source EEGLab extension, specifically designed to tackle the TMS-artifacts. Specifically, it identifies and removes the signal right before and after TMS pulses (−10 ms–10 ms) and it interpolates it, then uses two rounds of ICA (Individual Component Analysis) to first remove rhythmic-TMS-evoked scalp muscle artifacts and then to remove other artifacts, such as blinks, eye movement, persistent muscle activity and electrode noise. This is only one out of several toolboxes that has been proposed to facilitate the TMS-EEG data analysis and has been used extensively in the TMS-EEG research. After the signal cleaning, the rh-TMS outcome was estimated as a difference in the pre-stimulus alpha parameters during rh-TMS (i.e., changes in the alpha-frequency for the IAF-1 Hz and IAF+1 Hz stimulations, and changes in the alpha-amplitude for the IAF entrainment), see Ref. [2] for details on the analysis) between the active TMS and SHAM stimulation.

Additionally, in order to compare alpha synchronization during rest, here defined as the height of the resting-state Gaussian curve of the alpha frequency, with the pre-stimulus alpha-amplitude during the visual detection task, we used alpha-amplitude values during the SHAM condition of the task, as previously obtained.

Statistical Analyses. To assess for consistency of the alpha parameters across different conditions, IAF, curve width and height were compared *between the eyes-open and eyes-closed resting state conditions* via a non-parametric robust correlation estimate (bootstrapped Spearman correlation). The advantage of this correlation coefficient is that it takes into account the presence of bivariate outliers (by excluding them), and thus is not sensitive to the presence of extreme values in the overall structure of the data [31]. As to ensure that these parameters remain stable also during task, we performed the same analysis to compare eyes-open condition and task condition (sham stimulation). Additionally in order to exclude the presence of significant differences between these conditions, a repeated measures ANOVA was performed, with a paired, two-tailed t-tests was conducted. Finally, a linear multiple regression analysis was used to test the regression model where different parameters of alpha activity during eyes open condition (IAF and curve width and height) would predict rh-TMS outcomes (defined as change in frequency or amplitude between the active TMS and SHAM condition). Prior to conducting the analysis, casewise diagnostics, aimed to identify outliers, based on standard residual (<3 std, default value) and Cook's distance (>1, default value) were performed. Afterwards, forward stepwise method was used, starting from the null model and adding each predictor improving the model the most, one at a time, until the stopping criterion, base on p-values, has been met (enter: p = .05; stop: p = .1). Multiple regression analysis and ANOVA have been conducted in JASP statistical program [32]. Finally, we used the non-parametric bootstrapped Spearman correlation to affirm the robustness of the obtained significant predictors of the stimulation outcome.

3. Results

3.1. Inter-condition consistency of resting-state alpha parameters

Results obtained here confirm that IAF is indeed stable across the eyes-closed and eyes-open conditions. Specifically, although IAF is faster during eyes-open respect to eyes-closed condition ($M_{closed} = 10.436$;

$M_{open} = 10.645$; $t(63) = 2.449$, $p = 0.017$; $d = 0.29$), they are highly correlated ($r=.60$, CI = [0.381 0.762]). Likewise, the width of the fitted Gaussian curve showed the same trend, thus yielding highly correlated measures ($r=.365$, CI = [0.130 0.571]), with a wider curve during eyes-closed condition ($M_{closed} = 2.076$; $M_{open} = 1.886$; $t(63) = 3.55$, $p = 0.001$; $d = 0.45$). Additionally, the amplitude of the fitted Gaussian curve was significantly higher for the eyes-closed vs. eyes-open condition ($M_{closed} = 1.125$; $M_{open} = 0.566$; $t(63) = 10.57$, $p < .001$; $d = 1.33$), which is expected due to the higher alpha synchronization in the absence of visual stimulation [33]. Nonetheless, the amplitudes across the two conditions were significantly correlated ($r=.425$, CI = [0.171 0.629]), with higher alpha synchronization during eyes-closed condition related to higher amplitudes during the eyes-open resting state (see Fig. 3).

In sum, parameters of alpha activity, that could serve to individually calibrate and predict rh-TMS outcomes, seem consistent across different resting-state conditions. Therefore, although these parameters differ between individuals, they seem generally stable within participants across different resting-state conditions. For completeness, we also conducted the same analysis between the eyes-open and on-task parameters (sham condition), which resulted to also be highly correlated (see Fig. 1A of Supplementary material).

These results are reassuring, as the increased variability across different conditions would have otherwise questioned the validity of using those parameters when selecting the optimal rh-TMS target frequency, as well as in predicting entrainment outcomes. For simplicity, we decided that our focus of the further analyses will be the resting-state eyes-open condition (but we also tested the model during the eyes-closed condition), given that it was the condition used to determine which stimulation parameters were to be selected during the entrainment protocol.

3.2. The height of the at-rest alpha curve predicts the entrainment effects selectively during an at-peak stimulation (IAF)

Typical entrainment NIBS protocols are focused on increasing alpha-amplitude without inducing changes in alpha-frequency. As previously discussed, and as predicted by the Arnolds' tongue, these effects will be maximum for the stimulation on the exact IAF of the participant [2,8, 34].

However, they seem also to depend on individually modelled parameters of the Arnolds' tongue, approximated via fitting of the Gaussian curve to the alpha power spectrum of the participant. Specifically, the results indicate that the height of the Gaussian curve at IAF at-rest could successfully predict the entrainment outcome ($R = 0.116$, $\beta = -0.34$, $p= .049$), with higher baseline alpha-peak amplitude leading to lower entrainment effects. Results were also confirmed by a robust, non-parametric correlational coefficient ($r = -.300$, CI = [−0.611–0.006], see Fig. 4). These results confirm previous findings of entrainment occurring only when the baseline alpha-amplitude is low [22], thus also speaking in favor of the inverse relationship between the baseline alpha-amplitude and the needed strength of the external oscillator for the entrainment to occur.

The possible explanation behind it is that more synchronized alpha during baseline could lead to ceiling effects, where already highly synchronized activity in the alpha range could not be additionally entrained. If that was the case, this high alpha synchronization should be present also during the task, subsequently disabling the maximal entrainment effect when rh-TMS occurs. This possibility was tested by comparing resting-state alpha synchronization with pre-stimulus alpha-amplitude during the task in trials without the active rh-TMS. Indeed, higher at-rest alpha levels were associated with a higher alpha-amplitude in the pre-stimulus task window ($r=.771$, CI = [0.627 0.871]) even in the absence of stimulation, speaking in favor of a possible ceiling effect preventing further alpha synchronization to occur.

On the other hand, the width of the curve and the IAF did not add
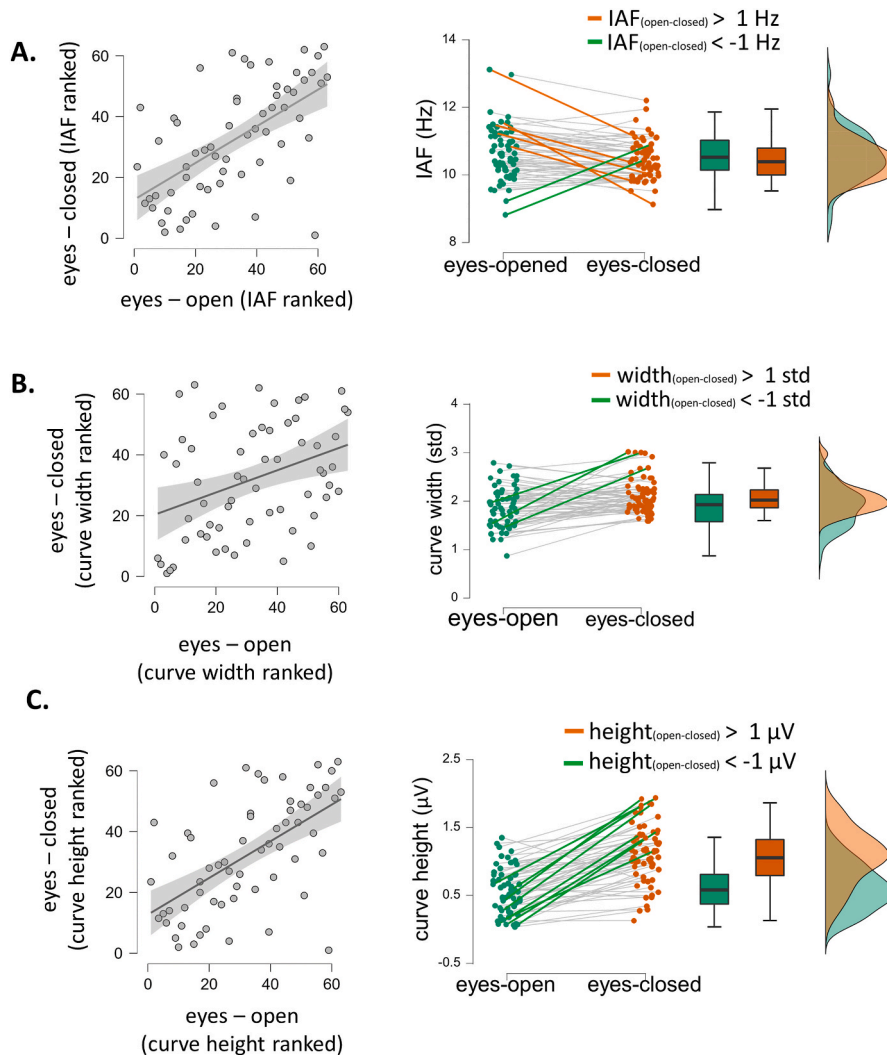
Fig. 3. Consistency of resting state alpha parameters. A. IAF across eyes-open and eyes-closed resting state. Left: Scatter plot of the IAF (measured in Hz, ranked values) across eyes-open (x axis) and eyes-closed (y axis) resting state. Right: Individual variations across the two conditions, and boxplots of the IAF (measured in Hz) along with distributions across eyes-open and eyes-closed resting state. Middle lines present the median values; the box spans the interquartile range (IQR: from the 25th percentile to the 75th percentile); the whiskers cover the 1.5 times the IQR. ***B. Curve width across eyes-open and eyes-closed resting state.*** Left: Scatter plot of the curve width (measured in standard deviations, ranked values) across eyes-open (x axis) and eyes-closed (y axis) resting state. Right: Individual variations across the two conditions, and boxplots of the curve width along with distributions across eyes-open and eyes-closed resting state. Middle lines present the median values; the box spans the IQR); the whiskers cover the 1.5 times the IQR. ***C. Curve height across eyes-open and eyes-closed resting state.*** Left: Scatter plot of the curve height (measured in microvolts, ranked values) across eyes-open (x axis) and eyes-closed (y axis) resting state. Right: Individual variations across the two conditions, and boxplot of the curve height along with distributions across eyes-open and eyes-closed resting state. Middle lines present the median values; the box spans the IQR; the whiskers cover the 1.5 times the IQR. Hz = Hertz. Std = standard deviation. μV = microvolts.

valuable information to the prediction model of the on-task entrainment outcome, which is a result that should be expected given that, in this case, there is no deviation from the optimal stimulation frequency (IAF).

For completeness, we also tested if the same entrainment outcome could be predicted by the parameters obtained during the eyes-closed condition, which did not yield any significant predictors (all $R_s^2 <$ 0.023, all $p_s > 0.407$).

3.3. The width of the at-rest alpha curve predicts the frequency-shift effects during an off-peak stimulation (IAF ± 1 Hz)

Although the at-rest IAF can be, at least partially, considered a stable trait, state-dependent alpha-frequency shifts have been well documented. For instance, differences in IAF can drive aspects of visual and temporal processing [2,8,35,36]. Therefore, tuning alpha-frequency towards a slower or faster pace is possible via rh-TMS and can aid us in understanding the functional role of alpha frequency by testing the

perceptual consequences of such shifts, ultimately leading towards possible therapeutic protocols aimed at enhancing perceptual and temporal sampling in patients.

However, there were significant inter-individual differences in the rh-TMS outcomes, consequently leading to the variability in the behavioral effects [2]. Here, we aimed at affirming if the individual parameters of Arnold tongue could aid us in understanding this variability. Again, as per on-peak entrainment, a significant predictor of the model was the height of the resting state curve (β = 0.556, p < .001), where higher at-rest alpha curve was more difficult to modulate. Crucially, the regression model also identified the width of the at-rest curve as a significant predictor of the at-task shifting outcome towards 1Hz slower or faster pace ($R^2 = 0.542$, β = −0.59, p < .001). Specifically, the wider the individual Arnolds' tongue, as approximated via Gaussian fit to the alpha power spectrum, the higher were the shifting effects towards lower or higher frequencies, confirmed also by a non-parametric robust correlation (r=.367, CI = [0.08 0.704], see
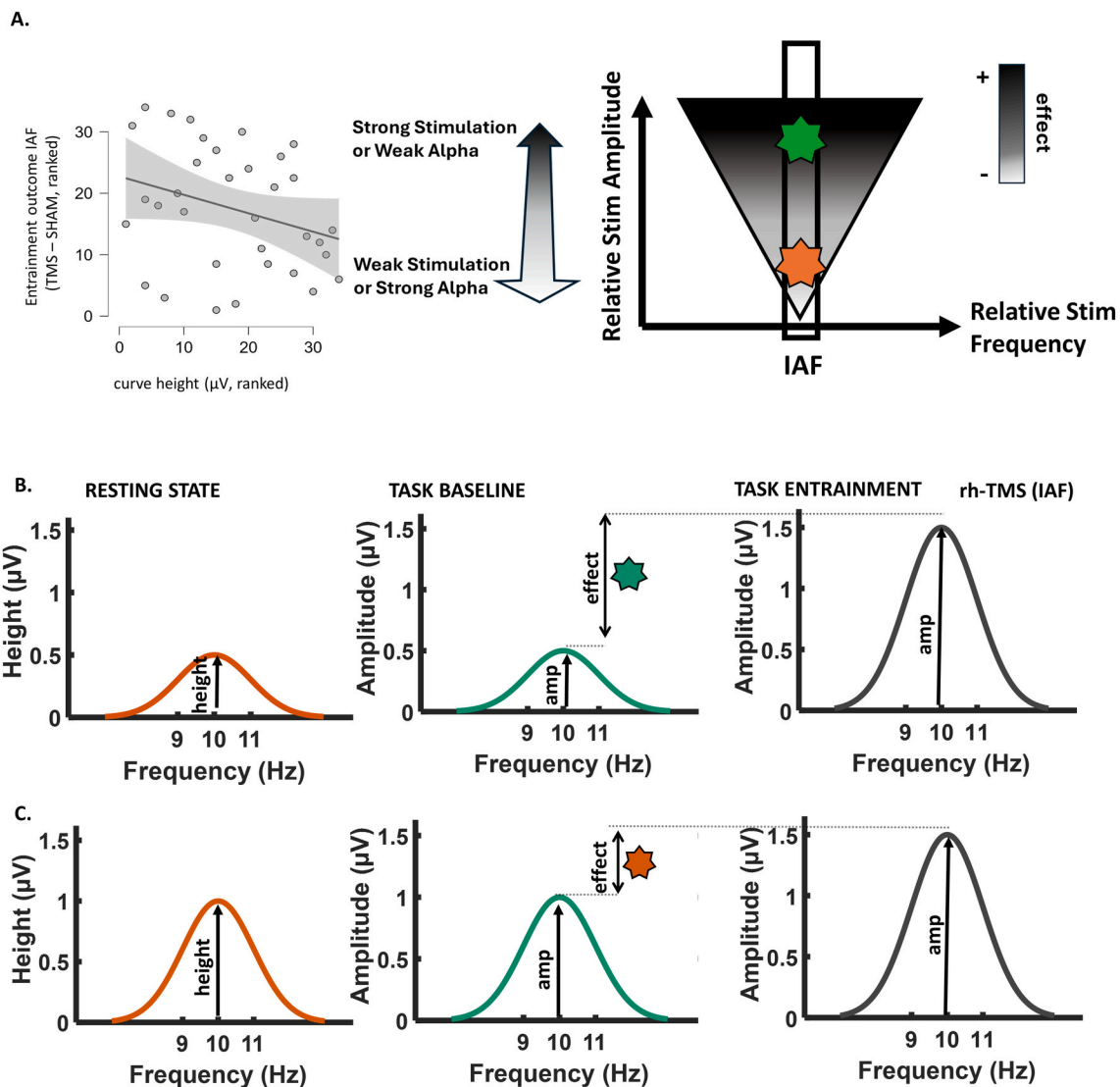
Fig. 4. The height of the at-rest alpha curve predicts the entrainment effects during an at-peak stimulation (IAF). A. *Left:* Scatter plot of the curve height (x axis, ranked values) as a predictor on on-task entrainment outcome, calculated as a difference of pre-stimulus alpha amplitude during active TMS vs SHAM stimulation (y axis, ranked values*). Right:* Schematic representation of the relationship between the stimulation (relative to the natural) frequency, the relative level of the neural synchronization (stimulation amplitude), and the occurrence of synchronization. Green vs. orange markers represent different on-peak stimulations of the low (in green) vs highly (in orange) synchronized oscillator. ***B. Model of a participant with lower Gaussian curve during resting state.*** It is hypothesized that low-amplitude resting state data would translate into desynchronized (low-amplitude) alpha activity during task, more susceptible to entrainment, as shown by higher entrainment effects. ***C. Model of a participant with higher Gaussian curve during resting state.*** It is hypothesized that high-amplitude resting state data would translate into more synchronized (high-amplitude) alpha activity during task. In turn, it is possible that already highly synchronized activity in the alpha range could not be additionally entrained, as shown by lower entrainment effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 5). Finally, IAF could not predict the rh-TMS effects, which is expected since the stimulation parameters (inter-pulse interval) were a priori tuned based on the IAF values.

For completeness, we also tested if the same rh-TMS outcome could be predicted by the parameters obtained during the eyes-closed condition, which did not yield any significant predictors (all $R_s^2 < 0.038$, all $p_s > 0.292$).

4. Discussion

In recent years, we have witnessed a sharp rise in the use of a combined TMS-EEG approach, with a grand part of this research dedicated to increasing or modulating oscillatory activity via rh-TMS protocols [2,3, 8,11,37,38]. At the same time, not much is known about the parameters that determine the efficacy of these neural effects, and that could

potentially explain the between-participant variability that is often observed [34].

According to the concept of the Arnold tongue, entrainment effects should be largest for the stimulation frequencies closely matching the frequency of the intrinsic oscillator [21]. Concerning alpha frequency entrainment, that would mean that the entrainment effects, in terms of the induced increase of the intrinsic alpha-amplitude, should be largest for the stimulation individually calibrated to the participants IAF [9,34, 37]. Previous studies repeatedly demonstrated that there are substantial inter-individual differences in the IAF [9,10], and that these differences could reflect general cognitive abilities [11,12], memory [13] and language processing [14], partially explained by genetic variations [15,16]. Based on these results, it has been proposed that at-rest IAF reflects a stable trait, representing a reasonable reference point of NIBS (non-invasive brain stimulation) parameters. Our recent study confirmed this
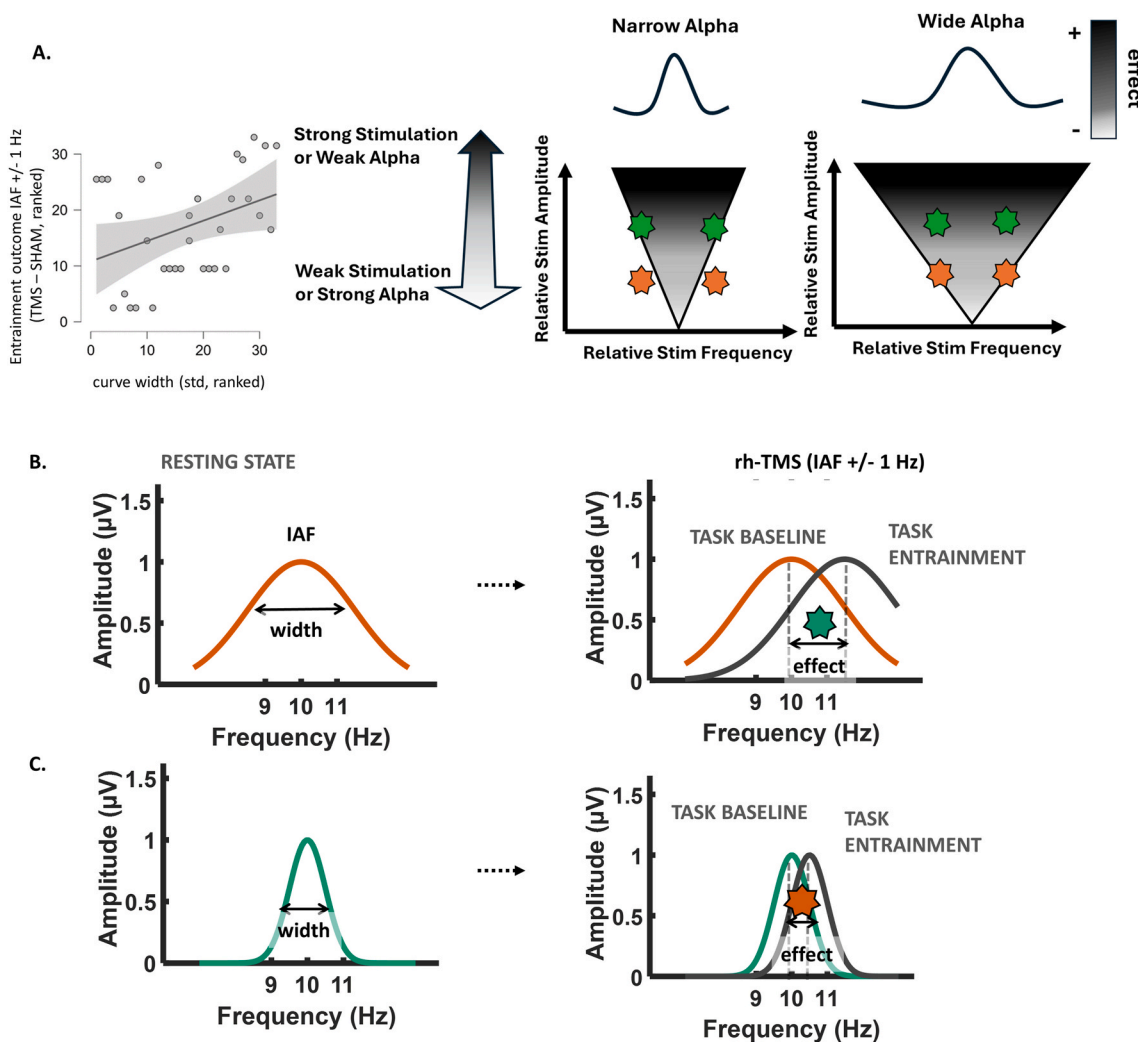
Fig. 5. The width of the at-rest alpha curve predicts the off-peak rh-TMS effects during an off-peak stimulation A. *Left:* Scatter plot of the curve width (x axis, ranked values) as a predictor of on-task off-peak rh-TMS outcome (IAF-1Hz and IAF+1Hz stimulations), calculated as a difference in the IAF during active TMS vs SHAM stimulation (y axis, ranked values). *Middle and Right:* Schematic representation of the relationship between the stimulation (relative to the natural) frequency, the relative level of the neural synchronization (stimulation amplitude), and the occurrence of synchronization (narrow and wide Arnold tongue). Green vs. orange markers represent different off-peak stimulations of the low (in green) vs highly (in orange) synchronized oscillator. Markers that fall out of the Arnold tongue (depicted as a triangle surface on the graph) are assumed to not be entrained. ***B. Model of a participant with wider Gaussian curve during resting state.*** It is hypothesized that a wider resting state curve would mean that the alpha-activity of a participant is more susceptible towards frequency shifts, as shown by higher rh-TMS effects. ***C. Model of a participant with narrower Gaussian curve during resting state.*** It is hypothesized a narrow resting state curve would mean that the alpha-activity of a participant is less susceptible towards frequency shifts, as shown by lower rh-TMS effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

notion, while additionally demonstrating that the 1 Hz offsets of the IAF are capable of driving/shifting the oscillators towards slower or faster rhythms, with distinct behavioral outcomes [2,35,39–42]. Nonetheless, a significant inter-individual variability in effectively increasing the amplitude of the IAF is still observed even when stimulating at the exact IAF in each participant. The aim of the current study was to explain this variability, by hypothesizing that the parameters of the Arnold tongue could be better described on the individual level, via Gaussian fitting of the alpha power spectrum [34,43,44]. In other words, the entrainment of the IAF and frequency shifting could be better predicted by the intrinsic system parameters shaping the height and the width of the individual spectral curve, rather than based on a general simple rule applied across all participants. To this aim, we approximated the individual Arnold tongue via Gaussian fitting of the power spectrum in the alpha range during eyes-closed and eyes-open resting state conditions. We first compared the obtained alpha parameters (IAF, curve width and height) between these two conditions to test their robustness and

variability across different states. Second, we used these parameters to predict the efficacy of rh-TMS-induced effects.

We revealed that both the IAF and the width of the fitted Gaussian were highly correlated across the eyes-closed and eyes-open conditions, even though the IAF was faster and the curve was wider during eyes-open condition. Likewise, although the curve was higher for the eyes-closed condition, due to the expected higher alpha synchronization in the condition without the visual input [33,45,46], the correlation between the two measures remained significant. The here reported resting-state IAF as an adequate approximation of the on-task entrainment parameters has also been found in other studies [34,43]. In addition, our results introduce several other relevant parameters, such as the width and the height of the Gaussian fit, as potential predictors of effective entrainment/frequency shifts. Given their consistency across different experimental conditions, these results encourage their potential as a valid estimator of successful manipulation of brain oscillations using rhythmic brain stimulation. On the other hand, although highly

correlated, please note that the parameters of the eyes-closed condition could not predict on-task rh-TMS outcomes. It might be that the eyes-open condition (vs eyes-closed condition) parameters are more predictive since they are more similar to the on-task activity in terms of all the parameters (alpha amplitude, IAF, curve width). However, we cannot claim this with certainty, because we a priori chose to use the eyes-open parameters to tune the TMS stimulation frequency.

Entrainment outcomes aimed at increasing on-task alpha-amplitude by stimulating at the exact IAF were best predicted by the height of the at-rest Gaussian curve, i.e., the height of the individual Arnold tongue. Specifically, higher at-rest alpha synchronization led to lower entrainment effects, in terms of lower alpha-amplitude increase. The most straightforward interpretation of these results would be that participants who already had highly synchronized alpha activity at baseline could experience a ceiling effect during entrainment, where already highly synchronized activity in the alpha range doesn't have much room for further entrainment. This interpretation was further confirmed by the additional analysis demonstrating that, even without entrainment, participants that have higher at-rest alpha-amplitudes have lower alpha-increase in the pre-stimulus time window during task. The practical implication of these results would be that, to ensure maximal entrainment effects, the alpha activity of the participant should be desynchronized prior to applying entrainment protocols. For instance, a highly repetitive and long task may lead to gradual synchronization of alpha activity [47], potentially causing entrainment to gradually decrease with prolonged task duration, a notion worth considering now when designing entrainment studies.

Intriguingly, along with the baseline alpha-amplitude, the width of the individual Arnold tongue successfully predicted rh-TMS outcomes when stimulating at off-peak frequencies, e.g., when trying to steer alpha activity toward a faster or slower rhythm. Concretely, participants with a wider at-rest alpha power spectrum showed more flexibility in being tuned towards faster or slower frequencies via rh-TMS. Although the focus of the current study was to identify potential predictors of the rh-TMS outcome, alpha frequency shifts during task are present even without rh-TMS, and can be self-regulated and tuned autonomously, in order to adjust to task demands and regulate information processing [36,48,49]. Therefore, the width of the Gaussian fitting of the at-rest alpha power spectrum could not only predict the flexibility of the IAF when faced with off-peak rh-TMS stimulation, but it might also present a more general marker of on-task IAF modulatory flexibility. In other words, it might represent the ability to regulate the alpha frequency to maximize information processing given the task demands.

Apart from predicting the effects of stimulation outcomes based on individual EEG biomarkers, please note that the stimulation effects might be additionally enhanced via other individualization practices. For instance, fMRI-based localization of the stimulation site (instead of using the electrode position as here) or the titration of the TMS intensity based on the individual phosphene threshold (instead of fixed intensity) might maximize the stimulation outcome. Likewise, closed-loop optimization of the TMS online protocols [50] as to time the stimulation during the windows of high-cortical excitability [51,52] should further enhance the induced plastic changes.

5. Conclusions

The current study revealed that the width and the height of the individual alpha power spectrum, here defined as individual Arnold tongue, predicts efficacy of the rhythmic TMS. Whereas the height of the Arnold tongue predicted rh-TMS-induced increases in alpha amplitude (entrainment) when stimulating at IAF, the width of the Arnold tongue predicted the efficacy in shifting the individual alpha frequency (IAF) to slower or faster rhythms. These biomarkers were able to predict and explain individual variability in rh-TMS outcomes on both brain activity and behavioral measures [34,53]. The here-reported findings not only help us understand the conflicting results and small effect sizes obtained

in previous brain stimulation entrainment studies, but also pave the way to optimize entrainment or frequency modulation effects through protocol personalization. From a translational perspective, personalizing rh-TMS protocols based on the individual Arnold tongue parameters described here, could increase effect sizes of clinical brain stimulation therapies across a wide range of applications [34,53].

Data availability

All data reported in this paper have been made publicly available through the Open Science Framework: https://osf.io/hk8nj/.

CRediT authorship contribution statement

Jelena Trajkovic: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Alexander T. Sack:** Writing – review & editing, Writing – original draft. **Vincenzo Romei:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ATS is chief scientific advisor for PlatoScience Medical, scientific advisor for Alpha Brain Technologies, Founder and CEO of Neurowear Medical, director of the International Clinical TMS Certification Course (www.tmscourse.eu), and president of the Academy of Brain Stimulation (www.brainstimulation-academy.com). He also received equipment support from MagVenture, Magstim, and Deymed Diagnostics. The other authors declare no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.02.016.

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