Mindfulness training is associated with changes in alpha-theta cross-frequency dynamics during meditation

Authors: Julio Rodriguez-Larios[1], Kian Foong Wong[2], Julian Lim[2], Kaat Alaerts[1]

[1]University of Leuven, KU Leuven, Belgium, Department of Rehabilitation Sciences, Research Group for Neurorehabilitation

[2]Centre for Sleep and Cognition, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

***Corresponding author:**

Kaat Alaerts

kaat.alaerts@kuleuven.be

Research Group for Neurorehabilitation (eNRGy)

Tervuursevest 101 - box 1501

3001 Leuven (Belgium)

DECLARATIONS

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AUTHOR CONTRIBUTIONS

JL designed the study. KFW prepared the stimuli, collected and pre-process the data. JRL performed the data analysis and wrote the first draft of the manuscript. KA, JL and JRL contributed to the writing of the manuscript (review and editing). All authors commented on previous versions of the manuscript and approved the final version.

Abstract

Objectives. Previous literature suggests that cross-frequency phase synchronization is a mechanism by which information is transmitted and coordinated in the brain. Since cross-frequency phase synchronization is only strictly possible when two oscillators form a harmonic frequency ratio (e.g. 2:1,3:1), a recent theory posited that interactions between brain oscillations at different frequencies are facilitated/hindered by the transient occurrence of harmonic/non-harmonic cross-frequency arrangements. In this line, recent evidence has shown that 2:1 harmonic relationships between alpha (8-14 Hz) and theta (4–8 Hz) rhythms are reduced during meditative states in experienced practitioners. In the present study, we investigated whether mindfulness training in novices is associated with longitudinal changes in alpha-theta cross-frequency dynamics during meditation practice.

Methods. Thirty-six participants (mean age = 30.3; 2 men) underwent an eight-week mindfulness training program based on the mindfulness-based stress reduction (MBSR) syllabus and electroencephalography (EEG) recordings (64 electrodes) were performed during a guided meditation before and after the training.

Results. Mindfulness training compliance (quantified by minutes of attendance and practice at home) was significantly correlated to decreased 3:1 harmonicity and cross-frequency phase synchrony between alpha and theta rhythms during meditation.

Conclusions. Mindfulness training in novices was shown to be associated with a reduction in alpha-theta cross-frequency coupling during meditation. EEG parameters based on alpha-theta cross-frequency dynamics may be adequate for quantifying and/or facilitating mindfulness meditation training.

Keywords: Neural oscillations, Mindfulness, Cross-frequency coupling, Meditation

The practice of mindfulness, which is defined as paying attention to the present moment in a purposeful and non-judgmental way (Kabat-Zinn, 2006), has been shown to have positive effects on mental health (Keng et al., 2011). In particular, different versions of the standardized 8-week Mindfulness Based Stress Reduction (MBSR) training program (Kabat-Zinn, 1982) have been successfully used to reduce depression and anxiety in clinical and non-clinical populations (Deplus et al., 2016; Desrosiers et al., 2013; Hilton et al., 2016; Keng et al., 2011). Concerning its mechanisms of action, several authors have proposed that the ability to be mindful in the present moment reduces unnecessary or excessive mind wandering, which has been linked to rumination and worry, and therefore, poor mental health (Deng et al., 2014; Desrosiers et al., 2013; Killingsworth & Gilbert, 2010; Marchetti et al., 2014; Wang et al., 2017). Mind wandering is generally conceptualized as spontaneous, self-generated thought often reflecting self-referential thinking in terms of memories, future plans or fantasies (Fox et al., 2018; Smallwood & Schooler, 2015). It has been suggested that mind wandering and mindfulness are opposing constructs (Mrazek et al., 2012). In this line, it has been shown that individuals with low trait mindfulness display high self-reported mind wandering, and that mindfulness training reduces mind wandering during different cognitive tasks (Morrison et al., 2014; Mrazek et al., 2012, 2013).

The neural correlates of meditative states have been widely studied through electroencephalography (EEG). EEG allows the measurement of neural oscillations in the brain at different frequency bands (i.e. delta (1-4Hz) , theta (4-8Hz), alpha (8-14Hz), beta (14-30Hz), and gamma (>30Hz)) that have been related to different cognitive functions and states of consciousness (Clayton et al., 2015; Fell et al., 2010; Sauseng et al., 2010).

Meditative states have been most consistently associated to changes in alpha (8-14Hz) and theta (4-8Hz) neural oscillations (Fell et al., 2010; Lee et al., 2018; Lomas et al., 2015). From an experiential perspective, it is commonly anticipated that these EEG changes during meditation relative to rest reflect reduced occurrence of mind wandering episodes (Faber et al., 2015; Hinterberger et al., 2014; Lehmann et al., 2012); which, at least in the context of focused attention meditation, are considered distractors (Dahl et al., 2015; Lutz et al., 2015). In support of this notion, experience sampling paradigms have shown that mind wandering during breath focus meditation is associated with power modulations in alpha and theta neural oscillations (Braboszcz & Delorme, 2011; Brandmeyer & Delorme, 2018; van Son et al., 2019).

A recent study showed that the interaction between alpha and theta rhythms is also affected during meditation practice (Rodriguez-Larios et al., 2020). Information exchange between brain rhythms is thought to be implemented through cross-frequency phase synchronization (Palva & Palva, 2017). Crucially, phase synchronization between two oscillators depends on transient changes in their center frequencies and their influence in the occurrence of different cross-frequency ratios. For example, an acceleration of alpha frequency (from 8Hz to 10Hz) and a deceleration of theta frequency (from 7 Hz to 5Hz) would lead to increased 2:1 phase synchronization if these frequency changes result in an increased incidence of 2:1 cross-frequency ratios (e.g. $alpha_{10Hz}$ / $theta_{5Hz}$ = 2) (i.e. harmonicity) (Rodriguez-Larios & Alaerts, 2019). In this way, it has been shown meditative states (relative to rest) in experienced practitioners are associated with a deceleration of alpha frequency (Mierau et al., 2017; Saggar et al., 2012), an acceleration of theta frequency, and a reduced alpha:theta 2:1 harmonicity (Rodriguez-Larios et al., 2020). Based on these results and previous literature, it has been proposed that mind wandering in the context meditation practice could be characterized by increased harmonicity (and therefore cross-frequency coupling) between alpha and theta rhythms (Rodriguez-Larios et al., 2020).

Considering the important role of EEG alpha-theta cross-frequency dynamics during meditative states in experienced practitioners (Rodriguez-Larios et al., 2020), the current study aimed to address whether meditation training in novices affects alpha-theta cross-frequency dynamics during meditation. We hypothesized meditation training to be associated with a reduction in alpha:theta harmonicity during meditation practice, which is anticipated to be reflective of reduced mind wandering after completion of the mindfulness training (Mrazek et al., 2012, 2013). To test this hypothesis, we analyzed a data set containing EEG recordings of thirty-six novice meditators during a guided meditation before and after an eight-week mindfulness training program. Specifically, we assessed whether participants with a high compliance to the mindfulness training (quantified through minutes of home practice and attendance to the course) displayed stronger pre-to-post reductions in alpha:theta harmonicity.

Methods

Participants

Forty-six nurses from a local government hospital in Singapore were recruited to participate in this study. Of these, ten were excluded from the analysis as they did not return for the post-intervention data collection. The remaining thirty-six nurses (mean age = 30.3 years, SD = 8.52; 2 men) participated in both experimental sessions, which occurred before and after the mindfulness training program (see next section).

Participants were compensated with SGD $40 in each session. The study was approved by the Singhealth Centralized Institutional Review Board and was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. All participants provided written informed consent.

Procedure

Participants underwent the same experimental conditions before and after mindfulness training while electroencephalography (EEG) was recorded. For each participant, EEG data were collected at the same time of day to control for possible circadian effects. Participants were asked to engage in meditation, guided by auditory instructions for a duration of 4 min. These instructions involved directing the attention to the breath, the body and sounds in the outside space whilst keeping the eyes closed. Note that the assessment session also encompassed short sessions of eyes open and eyes closed task-free activity as well as a sustained attention task, but analyses of these conditions are not part of the current report (see Wong et al., 2018).

Mindfulness Course. The Mindfulness course consisted of eight weekly 90-minute sessions conducted by an experienced instructor. The training was based on the mindfulness-based stress reduction (MBSR) program developed by Kabat-Zinn et al. (1982). Both formal (e.g., mindful breathing, body scan) and informal (communication with compassion) exercises were taught as part of this program. Participants were strongly encouraged to practice the techniques taught in class for at least 15 min a day at home.

Measures

Mindfulness training compliance was quantified by summing the minutes of training in each attended session (90 minutes per session) and self-reported meditation at home. In this regard, participants varied significantly in the number of sessions attended (mean = 4.13; SD = 2.33) and the practice at home (mean = 160.45 min; SD = 280 min). Consequently, there was a high variability in mindfulness training compliance between subjects (mean = 532.95 min; SD = 391.93 min).

EEG data was recorded using a BrainProducts MR+ amplifier with a sixty-four-channel actiCAP (standard 10–20 electrode positioning). Sampling rate was 250 Hz and the reference and ground electrodes were FCz and Fpz respectively. All electrode impedances were brought below 10 kΩ before the start of the recording. EEG data were processed in EEGLAB (Delorme & Makeig, 2004). Data were re-referenced offline to the average of mastoids (A1 + A2)/2) and band pass filtered at 1–30 Hz. Infomax ICA was used to identify and remove eye movement components from the data. Noisy channels were interpolated using spherical interpolation as implemented in EEGLAB.

Data Analyses

Cross-Frequency Ratios Estimation. The incidence of different alpha-theta cross-frequency ratios during the two meditation sessions (pre and post mindfulness training) were estimated using two different analytical approaches: i) instantaneous frequency (IF) and ii) find peaks (FP). The IF approach estimates the time varying frequencies of alpha and theta rhythms using the method developed by Cohen (2014). First, the EEG signal was filtered for alpha (8 - 14 Hz) and theta (4 - 8Hz) bands with a FIR plateau-shaped digital filter (transition zones = 15 %). Then, the Hilbert transform was applied to extract the instantaneous phase of alpha and theta rhythms. Next, the instantaneous frequency was computed by multiplying the first temporal derivative of the phase angle by the sampling rate and dividing it by 2pi (Figure 1A first row). An iterative median filter was applied to the instantaneous frequency time series (10 steps between 10 and 400 ms) in order to attenuate frequency jumps caused by noise. Finally, the time-varying alpha:theta ratio (Figure 1A second row) and the incidence of each ratio (from 1 to 3.5 in 0.1 steps) was computed. The FP approach estimates the time varying frequencies of alpha and theta rhythms by defining transient peak frequencies in the frequency spectrum of short time windows (see Rodriguez-Larios & Alaerts, 2019). For this purpose, short time Fourier transform was applied to the pre-processed EEG data using the spectrogram function in MATLAB r2019b (window = 1 second; overlap = 90%) to compute the time varying spectrum between 2 and 15 Hz with frequency resolution of 0.1 Hz. Then, peaks in the alpha (8-14Hz) and theta (4-8Hz) frequency bands were defined using the MATLAB function 'findpeaks'. When two peaks were found within one frequency band, only the one with the highest amplitude was selected. Finally, the time varying cross-frequency ratios and their incidence were computed. Unlike the IF approach, FP cross-frequency ratios were determined within a range between 1.1 and 3.4 in 0.1 steps, since peak frequencies cannot be defined at the edges of the frequency bands.

Cross-Frequency Synchronization Estimation. In order to estimate the degree of cross-frequency synchronization between alpha and theta rhythms, the n:m phase locking value (PLV) was computed using a sliding window of 300ms (Palva et al., 2005; Palva & Palva, 2017; Siebenhühner et al., 2016). PLV quantifies the consistency of the phase relationships between two oscillators of different frequencies. For that purpose, the instantaneous phase of alpha and theta rhythms were obtained after the application of a FIIR filter and Hilbert transform (see previous section). Then, the instantaneous phase difference between alpha and theta rhythms was calculated to create unitary vectors whose mean length is proportional to the level of phase synchronization (Tass et al., 1998). Since, given their frequency range, cross-frequency coupling between alpha (8-14Hz) and theta (4-8Hz) rhythms is only possible for the ratios 1:2 and 1:3, the n:m phase-locking value was estimated with n=1 and m=2-3. In the last row of Figure 1A, we illustrate how, as mathematically predicted, cross-frequency ratios approximating the second and third harmonic maximize transient 1:2 and 1:3 cross-frequency phase synchronization. For a better visualization of the relationship between harmonic ratios and phase synchrony, Figure 1B depicts the mean 1:2 and 1:3 phase synchronization for each cross-frequency ratio in an exemplary subject (across electrodes).

Statistical Analysis. In a first analysis, pre-to-post changes in alpha-theta cross-frequency ratios / synchronization were averaged across electrodes and correlations with mindfulness training compliance were computed using Spearman correlation coefficients with false-discovery-rate (FDR) correction for multiple comparisons (i.e., correcting for number of cross-frequency ratios) (FDR linear step-up procedure as implemented in MATLAB r2019b). Next, a non-parametric cluster permutation approach was adopted (as implemented in Fieldtrip; see Maris & Oostenveld, 2007) to assess the significance of the correlations when ran separately for each electrode and cross-frequency ratio. This statistical method controls for the type I error rate arising from multiple comparisons through a Montecarlo randomization, to identify clusters of significant correlations taking into account both the spatial (electrodes) and ratio proximity dimensions. In short, the data is shuffled (1000 permutations) to estimate a "null" distribution of effect size based on cluster-level statistics (sum of t-values with the same sign across adjacent electrodes and cross-frequency ratios). Finally, the cluster-corrected p-value is defined as the proportion of random partitions in the null distribution whose test statistics exceeded the one obtained for each significant cluster ($p<0.05$) in the original (non-shuffled) data.

Results

Changes in Alpha-Theta Cross-Frequency Dynamics in Relation to Mindfulness Training

Spearman correlations revealed that pre-post changes in alpha-theta cross-frequency dynamics during meditation were significantly associated with inter-individual differences in compliance to the mindfulness training program. A consistent pattern of results emerged across the two analytic approaches (instantaneous frequency (IF) and find peaks (FP)), indicating that participants with a greater compliance to the training displayed a pre-to-post reduction in the incidence of alpha:theta ratios around the 'harmonic' ratio 3.0 (i.e., negative correlations for ratios between 2.2 (2.8) and 3.5 (3.4) based on the IF (FP) approach; all, $p<0.05$; FDR corrected) (Figure 2A). In addition, higher training compliance was also positively associated with a marked pre-to-post increase in the incidence of alpha:theta ratios around the 'non-harmonic' ratio 1.6 (i.e., positive correlations for ratios between 1.5 (1.5) and 1.6 (1.7) based on the IF (FP) approach; all, $p<0.05$; FDR corrected) (Figure 2A). For visualization purposes, Figure 2B depicts - separately for the IF and FP approaches - the positive relationship with ratios between 1.5 and 1.6 ($rho_{IF} = .50$;$p_{IF}=.002$; $rho_{FP} = .55$;$p_{FP}<.001$) and the negative relationship with ratios between 2.8 and 3.4 (rho_{IF} = -.54;p_{IF}=.001; rho_{FP} = -.57;p_{FP}<.001). Finally, Figure 2C depicts the results of the non-parametric cluster permutation approach assessing the significance of the correlations separately for each electrode and ratio incidence. This analysis revealed a significant negative cluster with a widespread spatial distribution (i.e. majority of the electrodes) for ratios around 3.0 for both the IF (ratios = 2.2-3.5; $tcluster_{IF}$ =-1285 ; p_{IF} =.008) and FP analytical approach (ratios = 2.6-3.4; $tcluster_{FP}$ =-780 ; p_{FP}<0.001). In addition, a positive cluster approximating the ratio 1.6 (1.3 – 1.7 for IF and 1.5 to 1.7 for FP) was identified, although here, the test statistic only reached statistical tendency (t_{IF} = 326; p_{IF} = .057; t_{FP} =114 ; p_{FP}=.082).

Changes in Phase Synchrony in Relation to Mindfulness Training

Changes in 3:1 phase synchrony between alpha (8-14 Hz) and theta (4-8 Hz) rhythms during meditation (post – pre) were negatively correlated (Spearman's rho) to mindfulness training when averaged across electrodes (rho = -0.44; p = 0.0072). Similar results were obtained (rho =-0.49; p = 0.0023) when using narrower bandpass filters to isolate theta and alpha rhythms around the third harmonic (i.e. theta = 4-5Hz; alpha =10-13Hz). No significant correlations were identified for changes in 2:1 phase synchrony during meditation and mindfulness training.

Changes in Mean Alpha/Theta Frequency in Relation to Mindfulness Training

In addition to the analysis of cross-frequency dynamics, we explored whether modulations of alpha and theta peak frequencies during meditation were correlated (Spearman's rho) to compliance when analyzed separately. For that purpose, the mean peak frequency of alpha/theta rhythms was calculated by averaging the time varying peak frequencies obtained with both the IF and FP approaches (see methods). At least for the instantaneous frequency (IF) approach, a positive correlation was identified between pre-to-post changes in the mean theta peak frequency and compliance, indicating that participants with high compliance displayed a stronger pre-to-post increase in theta peak frequency (acceleration of the theta rhythm) (rho_{IF}= 0.36;p_{IF} = 0.029). A similar tendency was evident for the find peaks (FP) approach (rho_{FP} = 0.27; p_{FP} = 0.10). No significant relationships were identified however between pre-to-post changes in mean alpha peak frequency and training compliance (rho_{IF}=-0.22; p_{IF} = 0.17; rho_{FP} = -0.20; p_{FP} = 0.23).

Assessing the Contribution of Artifactual Harmonics

Non-sinusoidal properties of a single oscillator can produce artifactual harmonics in the frequency spectra that could be wrongly interpreted as two interacting oscillators (Scheffer-Teixeira & Tort, 2016). If the here reported 3:1 harmonic relationship between alpha and theta rhythms would reflect non-sinusoidal properties of a single oscillator, modulations of alpha and theta power at 3:1 harmonic positions should be highly correlated (see Palva et al., 2005). In order to rule out this possibility, we performed Spearman correlations between the power time series of alpha and theta rhythms at 3:1 harmonic positions (theta= 4-5 Hz; alpha = 12-14Hz) for each electrode, subject and condition. The correlations were generally low (median rho value = 0.033) and negative in ~30% of the cases. Based on these results, we concluded that alpha and theta rhythms at 3:1 positions reflect two different oscillatory components (rather than one component with non-sinusoidal properties).

Discussion

The aim of this study was to assess whether mindfulness training is related to changes in alpha-theta cross-frequency dynamics during meditation. For that purpose, EEG during meditation practice was recorded in thirty-six participants before and after they underwent an eight-week mindfulness training course. In line with previous results with experienced meditation practitioners (Rodriguez-Larios et al., 2020), it is shown that mindfulness training (i.e. minutes of practice at home and attendance to the course) is significantly correlated to reduced harmonicity (and therefore coupling) between alpha (8-14 Hz) and theta (4-8 Hz) rhythms. Based on previous literature showing that meditation training leads to reduced occurrence of mind wandering episodes during meditation (Brandmeyer & Delorme, 2018), we speculate that reduced alpha:theta coupling during meditation is reflective of reduced mind wandering. Together, this study suggests that EEG parameters based on alpha-theta cross-frequency dynamics could be used to quantify the level of mindfulness training and/or facilitate meditation practice.

Previous literature has shown robust modulations in the frequency and power of alpha and theta rhythms during meditative states (Aftanas & Golocheikine, 2001; Jian-Zhou et al., 1988; Lomas et al., 2015; Qin et al., 2009; Saggar et al., 2012; Takahashi et al., 2005; Yamamoto et al., 2006). However, until now, these changes have not been analyzed nor interpreted from a cross-frequency dynamics perspective. In this regard, a recent study suggests that the previously reported modulations in alpha and theta rhythms could reflect changes in cross-frequency dynamics (Rodriguez-Larios et al., 2020). Specifically, it was shown that the frequency of theta (4-18 Hz) and alpha (8-14 Hz) rhythms tended to approximate during meditation thereby reducing the occurrence of harmonic 2:1 cross-frequency relationships. In the same line, this study shows that the degree of mindfulness training in novices is significantly correlated to an approximation of alpha and theta rhythms in the frequency spectrum during meditation (leading in this case to a reduced occurrence of 3:1 cross-frequency ratios). Together, these studies suggest that meditative states could be characterized by reduced cross-frequency interactions (via 2:1/3:1 cross-frequency phase synchrony) between alpha and theta rhythms.

Because the main hypothesis in this study was formulated based on previous results with experienced meditation practitioners (Rodriguez-Larios et al., 2020), it is important to underline two main differences when comparing the results of these two studies. First, whilst meditative states in experienced practitioners were associated with a reduced occurrence of alpha:theta cross-frequency ratios centered around the ratio 2:1 (see Rodriguez-Larios et al., 2020) we here report a significant negative correlation between mindfulness training and the occurrence of cross-frequency ratios centered around the ratio 3:1 during meditation practice (see Figure 2A). Secondly, while in Rodriguez-Larios et al., (2020) showed an increased incidence of ratios between 1 and 1.5 during meditative states (relative to rest), in this study we found that that the incidence of ratios around 1.6 during meditation correlated positively to mindfulness training. We theorize that these differences could reflect different stages of meditation practice. Hence, decreases in 3:1 alpha:theta harmonicity at the expense of an increased incidence of 1.6 ratios could reflect superficial meditative states reached in earlier stages of the practice which are characterized by relaxation, focused attention and reduced mind wandering (Fell, Axmacher, & Haupt, 2010). On the other hand, the deep meditative states reached by long-term practitioners (which have been linked to a wide variety of cognitive, emotional and perceptual changes; see Gifford-May & Thompson,

1994) may be characterized by reduced 2:1 alpha:theta cross-frequency interactions at the expense of the convergence of these two rhythms (increased incidence of cross-frequency ratios approximating 1; see Rodriguez-Larios et al., 2020).

The interplay between alpha and theta rhythms has been shown to be functionally relevant for tasks involving memory and executive control (Dimitriadis et al., 2016; Kawasaki et al., 2010; Popov et al., 2018). In this way, it has been proposed that alpha rhythms subserve the memory component whilst theta rhythms underlie the executive one (de Vries et al., 2020). Given the roles of alpha and theta rhythms in cognitive processing, it can be anticipated that a certain degree of alpha-theta coupling is necessary for the generation of mind wandering episodes, as these would entail both memory and executive components (i.e. retrieval, storage and manipulation of information) (Kam & Handy, 2014; Smallwood & Schooler, 2006). Our results are in line with this notion since we show that alpha-theta cross-frequency coupling during meditation is negatively correlated to mindfulness training (which has been previously shown to reduce mind wandering during meditation and other cognitive tasks; see Brandmeyer & Delorme, 2016; Mrazek et al., 2013, 2012). The suggested association between alpha-theta coupling and mind wandering during meditation practice remains speculative however and hence, future studies using experience sampling paradigms may be warranted (Braboszcz & Delorme, 2011; Brandmeyer & Delorme, 2018; van Son et al., 2019) to delineate the phenomenological counterpart of transient changes in alpha-theta cross-frequency dynamics during meditation practice more formally.

In addition to the negative correlation between mindfulness training and the incidence of 3:1 alpha:theta cross-frequency ratios during meditation, we also reported a positive correlation for cross-frequency ratios around 1.6 (when averaged across electrodes). Interestingly, this ratio approximates to the golden mean (i.e. 1.618), which has been proposed as an optimal cross-frequency ratio to enable 'decoupling' between two neighboring brain rhythms (see Klimesch, 2013, 2018). In this way, it has been mathematically demonstrated that a cross-frequency ratio based on the golden mean provides the most irregular pattern of excitatory phase meetings and therefore reflect a 'maximally desynchronized brain state' which would avoid spurious, unwanted phase synchronizations (Pletzer et al., 2010). In the light of these theoretical accounts, it can be speculated that a greater incidence of ratios around 1.6 during meditation is reflecting a greater decoupling between two neighboring rhythms in the alpha-theta range. In this regard, it is important to highlight that previous studies have largely overlooked the role of non-harmonic cross-frequency ratios because cross-frequency phase synchrony can only be calculated between harmonic frequencies (Palva & Palva, 2017). As illustrated in this study, calculating the incidence of different cross-frequency ratios allows to assess the functional relevance of specific cross-frequency arrangements that would maximize coupling (harmonic) or decoupling (non-harmonic) between different brain rhythms. In this way, further research is necessary to elucidate, whether, as theoretically proposed, the golden mean is the preferred non-harmonic ratio to minimize unwanted interactions (i.e. 'spurious coupling'; see Pletzer et al., 2010) between neighboring rhythms (e.g. alpha and theta) in the brain.

Vettese et al., (2009) reviewed the literature on adherence to mindfulness homework and its relationship to program outcomes. They concluded that the literature is mixed, with only half the identified studies reporting a relationship between practice and change in functioning (Vettese et al., 2009). The authors point to a deficiency in methodological rigor as a potential reason for this. However, we also note that few of these studies reported on objective measures such as changes detectable by electrophysiology or neuroimaging as their outcome measure. Our current results add to the evidence that home mindfulness practice can affect such measures and suggest that more studies could focus on the differential effects of practice compliance on objective and subjective markers (Van Dam et al., 2018).

From a translational perspective, our results could help to envisage EEG-neurofeedback protocols based on cross-frequency dynamics to facilitate meditation practice. EEG-neurofeedback is a brain computer interface methodology that allows users to learn how to self-regulate neural oscillations by the presentation of stimuli that are contingent to the real time EEG signal (Spilker et al., 1969). EEG-Neurofeedback aimed at aiding meditation practice could be of specific interest for those clinical and subclinical populations that would hugely benefit from the beneficial effects of mindfulness (Cachia et al., 2016; Zylowska et al., 2008), but for whom difficulties may arise with complying to the training e.g. due to an inability to understand the training instructions. To the authors' knowledge, there have been few attempts to modulate the center frequency of different brain rhythms via EEG-neurofeedback (Angelakis et al., 2007; Lavy et al., 2018), as training protocols are typically based on up- or down-regulating the power (and not the frequency) of neural oscillations (Enriquez-Geppert et al., 2017; Gruzelier, 2014). Based on the present results and prior evidence (Mierau et al., 2017; Rodriguez-Larios et al., 2020), we propose that the frequency of neural oscillations (and/or their cross-frequency ratio) could form a sensitive target for facilitating meditation practice.

In summary, this study shows that mindfulness training correlates negatively to cross-frequency coupling between alpha (8-14 Hz) and theta (4-8 Hz) rhythms during meditation. These results are in line with previous evidence showing that alpha-theta coupling is maximized during higher order cognitive processing and minimized during meditative states (Kawasaki et al., 2014; Rodriguez-Larios et al., 2020; Rodriguez-Larios & Alaerts, 2019; Schack et al., 2005). Based on our results and previous literature, we conclude that EEG alpha-theta cross-frequency dynamics can be considered an adequate target to quantify and/ or facilitate mindfulness training.

Limitations and Future Research

Our study has a few limitations. First, the study is correlational and retrospective, limiting our ability to make causal claims. Furthermore, as this was a pilot experiment, we did not perform randomization or recruit a control group. In this way, it is important to underline that since we did not systematically vary mindfulness training across subjects, the identified differences in compliance might have been -at least partly-related to pre-existing inter-individual differences. For example, it is possible that participants with a specific personality profile and/or pre-existing mental health issues had a higher motivation to attend and comply with the program instructions and therefore, benefited more from it. In this view, it would have been highly informative to have obtained more in-depth characterizations of the included participant sample, with respect to possible person-dependent factors that may have modulated compliance. In the same line, it is also possible that the experience of participants during the first meditation (pre-training) influenced their future compliance to the training. For example, participants that experienced greater mind wandering frequency and/or engagement during the first meditation (pre-training) might have been more motivated to comply during the training. In this way, exploratory analysis were conducted to assess whether 3:1 alpha:theta harmonicity during the first meditation (pre-training) could predict future training compliance. Although we did not find any significant correlations, there was a tendency for participants with higher compliance to show greater 3:1 alpha:theta harmonicity during the first meditation session (rho_{IF}=0.22; p_{IF} = 0.18; rho_{FP} = -0.24; p_{FP} = 0.15). This exploratory analysis therefore provides tentative indications that participants with already high 3:1 alpha:theta harmonicity during the first meditation session (pre-training) could have displayed an increased motivation to comply with the training and therefore, a more pronounced intervention-induced pre-to-post change in alpha-theta cross-frequency dynamics. Future research is warranted however to further delineate possible neural, behavioral and phenomenological predictors of mindfulness training compliance.

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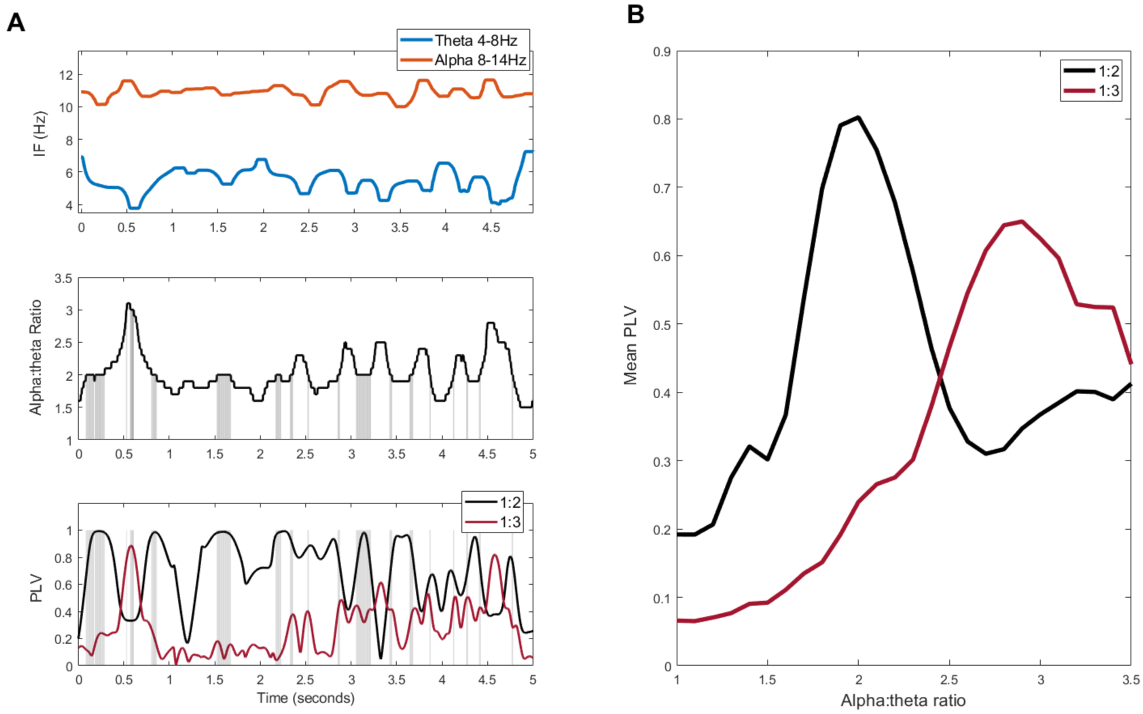

Fig. 1 Estimation of alpha:theta cross-frequency ratios and their relation to phase synchrony. **Panel A** visualizes the instantaneous frequency of alpha (8-14 Hz; in orange) and theta (4-8 Hz; in blue) (first row), their cross-frequency ratio (second row) and phase synchrony (i.e. 1:2 and 1:3 phase-locking values: PLV; third row) for an exemplary subject and electrode. Grey areas indicate time points in which alpha and theta rhythms arrange in harmonic positions and therefore maximize their phase synchrony. **Panel B** visualizes the mean 1:2 and 1:3 PLV for each cross-frequency ratio thereby illustrating that phase synchrony is maximized for the 1:2 and 1:3 'harmonic' cross-frequency relationships

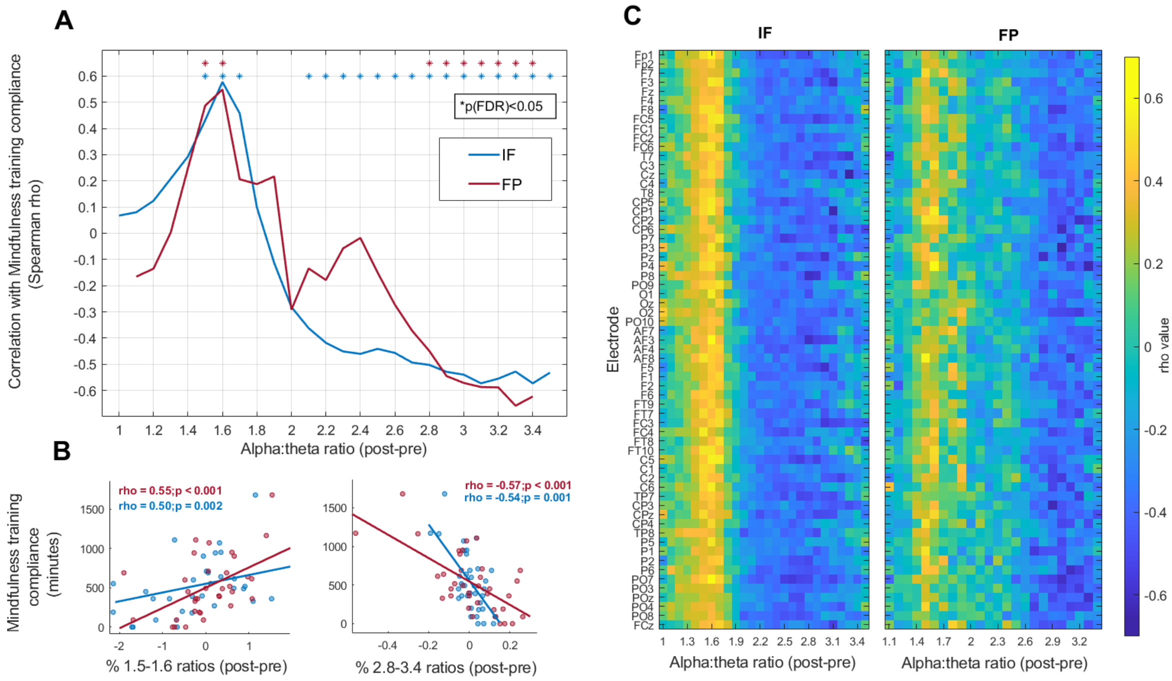

Fig. 2 Relationship between post-pre changes in the incidence of alpha:theta cross-frequency ratios and Mindfulness training compliance. **Panel A** illustrates the Spearman rho correlations between mindfulness training compliance (minutes) and post-pre changes in the incidence of each cross-frequency ratio (averaged across electrodes), separately for the instantaneous frequency (IF; blue) and find peaks (FP; red) analytical approaches. Asterisks mark significant correlations as p<0.05 (FDR corrected). **Panel B** visualizes correlations for those cross-frequency ratios that yielded statistically significant results with both analytical approaches. **Panel C** depicts the correlations between compliance and post-pre changes in the incidence of each cross-frequency ratio, separately for each electrode. Blue/yellow colors refer to negative/positive Spearman rho coefficients.