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Publication Date

2022-11-01

DOI

10.1016/j.ijpsycho.2022.08.006

Peer reviewed

HHS Public Access

Author manuscript

Int J Psychophysiol. Author manuscript; available in PMC 2024 June 24.

Published in final edited form as:

Int J Psychophysiol. 2022 November ; 181: 50–63. doi:10.1016/j.ijpsycho.2022.08.006.

Heart rate variability (HRV) changes and cortical volume changes in a randomized trial of five weeks of daily HRV biofeedback in younger and older adults

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Abstract

Previous studies indicate that the structure and function of medial prefrontal cortex (PFC) and lateral orbitofrontal cortex (OFC) are associated with heart rate variability (HRV). Typically, this association is assumed to reflect the PFC's role in controlling HRV and emotion regulation, with better prefrontal structural integrity supporting greater HRV and better emotion regulation. However, as a control system, the PFC must monitor and respond to heart rate oscillatory activity. Thus, engaging in regulatory feedback during heart rate oscillatory activity may over time help shape PFC structure, as relevant circuits and connections are modified. In the current study with younger and older adults, we tested whether 5 weeks of daily sessions of biofeedback to increase heart rate oscillations (Osc+ condition) vs. to decrease heart rate oscillations (Osc− condition) affected cortical volume in left OFC and right OFC, two regions particularly associated with HRV

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CRediT authorship contribution statement

The authors made the following contributions. Hyun Joo Yoo: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft; Kaoru Nashiro: Conceptualization, Data curation, Investigation, Writing - review & editing, Project administration; Jungwon Min: Conceptualization, Data curation, Investigation; Christine Cho: Conceptualization, Data curation, Investigation, Resources, Project administration; Shelby L. Bachman, Padideh Nasseri, & Shai Porat: Conceptualization, Data curation, Investigation, Writing - review & editing; Shubir Dutt: Investigation, Writing - review & editing; Vardui Grigoryan & Paul Choi: Data curation, Investigation; Julian F. Thayer, Paul Lehrer, & Catie Chang: Conceptualization, Writing - review & editing; Mara Mather: Conceptualization, Funding acquisition, Resources, Project administration, Supervision, Writing - review & editing.

Data/code Availability Statement

The empirical data used for this paper will be available in the public repository, OpenNeuro, "HRV-ER" (https://openneuro.org/datasets/ds003823) before publication. The codes used for cortical volume analysis using Freesurfer 6.0 are freely available online (https://github.com/EmotionCognitionLab/HRV-ER-OFCvolume) and codes for other statistical analyses are available upon request from the corresponding author.

Declaration of Competing Interest

The authors declare no conflicts of interest with respect to authorship or the publication of this article.

in prior studies. The left OFC showed significant differences in volume change across conditions, with Osc+ increasing volume relative to Osc−. The volume changes in left OFC were significantly correlated with changes in mood disturbance. In addition, resting low frequency HRV increased more in the Osc+ than in the Osc− condition. These findings indicate that daily biofeedback sessions regulating heart rate oscillatory activity can shape both resting HRV and the brain circuits that help control HRV and regulate emotion.

Keywords

heart rate variability; biofeedback; orbitofrontal cortex; cortical volume

1. Introduction

Higher heart rate variability (HRV) is associated with more positive emotion and better emotion regulation whereas lower HRV is associated with poorer physiological, emotional, cognitive, behavioral regulation and self-rated health (Alvares et al., 2013; Beauchaine and Thayer, 2015; Chalmers et al., 2014; Clamor et al., 2016; Jarczok et al., 2015; Kemp et al., 2010; Koenig et al., 2016a; Koenig et al., 2016b; Thayer et al., 2012; Thayer et al., 2000; Thayer et al., 2009a; Thayer and Lane, 2000, 2009). Why is HRV so closely linked to emotion regulation? In the neurovisceral integration model, HRV reflects the activity of an integrative neural network regulating physiological, cognitive, and emotional responses (Thayer and Lane, 2000, 2009). Furthermore, according to this model the prefrontal cortex (PFC) exerts inhibitory control over subcortical regions and resting HRV reflects the PFC's ability to inhibit subcortical circuits. Thus, because it reflects more effective PFC regulatory activity, higher resting HRV is associated with better emotion regulation (Williams et al., 2015).

However, recent findings suggest that in addition to *reflecting* the function of brain regions involved in emotion regulation, HRV *influences* brain and emotional function (Mather and Thayer, 2018; Nashiro et al., 2022). One line of evidence suggesting the causal influence of HRV on the brain systems involved in emotion regulation comes from studies of HRV biofeedback. These studies examined the effects of paced breathing at a resonance frequency (around 0.1 Hz frequency) of the baroreflex system (Vaschillo et al., 2006), which induces high oscillations in heart rate (Lehrer et al., 2013). In these studies, participants practice HRV biofeedback for at least 20 min a day for several weeks. A meta-analysis of 24 studies showed that HRV biofeedback using paced breathing at resonance frequency reduced stress and anxiety with a large effect size (Goessl et al., 2017). Another meta-analysis of 58 studies showed HRV biofeedback using paced breathing at resonance frequency had positive effects on a variety of physical, behavioral, and cognitive conditions (Lehrer et al., 2020).

Neuroimaging research provides further evidence for the association between HRV and brain regions involved in emotion regulation (e.g., Matthews et al., 2004; for a review see Thayer et al., 2012). HRV shows associations with brain activity in PFC regions (Ahs et al., 2009; Chang et al., 2013; Critchley et al., 2003; Lane et al., 2009; Smith et al., 2015). Also, individual differences in resting HRV are associated with individual differences in PFC brain

structure. Across two datasets from our lab, greater structural thickness in prefrontal regions was associated with greater HRV in younger and older adults (Yoo et al., 2018). A recent meta-analysis pooled data from 20 research groups (N = 1218, age range:12~87) to examine the relationships between cortical thickness in PFC regions and resting HRV (Koenig et al., 2021). In the PFC, the most robust association was that people with greater left lateral OFC thickness tended to have higher HRV. Also, right lateral OFC and medial OFC showed an association between HRV and cortical thickness. These findings suggest the importance of OFC in regulating the autonomic nervous system (ANS) activity (see also Thayer et al., 2009a; Thayer and Lane, 2000).

The most obvious interpretation of these correlational findings is that decreased structural thickness or volume in the OFC leads to decreases in HRV. In this causal model, changes in structural volume cause changes in HRV. However, HRV may also influence OFC structural volume. In a recent clinical trial, we found that 5 weeks of HRV biofeedback training increased left amygdala-medial PFC connectivity and generally increased functional connectivity within emotion-related resting-state networks in younger adults (ClinicalTrials.gov NCT03458910; Heart Rate Variability and Emotion Regulation or "HRV-ER"; Nashiro et al., 2022). We manipulated HRV using five weeks of daily HRV biofeedback training to increase heart rate oscillations (Osc+ condition) vs. to decrease heart rate oscillations (Osc− condition). Here we examined if this manipulation led to changes in the structural volume of the OFC regions where structural volume has previously been associated with HRV. As an HRV-biofeedback manipulation check, we compared how much heart rate oscillatory activity increased during daily HRV biofeedback training compared with during rest. We also examined if daily HRV biofeedback training affected resting HRV.

To test if daily HRV biofeedback training led to change in structural volume, we took a region-of-interest (ROI) approach targeting the OFC based on past findings reviewed above (Koenig et al., 2021; Kumral et al., 2019; Sakaki et al., 2016; Yoo et al., 2018). Two studies indicated OFC consistently showed a significant association with HRV even when controlling for age and gender variables (Koenig et al., 2021; Yoo et al., 2018). Thus, we selected the left and right OFC (encompassing both medial and lateral subregions) as two prefrontal ROIs associated with resting vagal HRV from previous findings.

Additionally, we examined the age differences in HRV training effects on structural volume in OFC. In a pharmacological blockade study, age-related differences in the cortical control of HRV have been reported (Thayer et al., 2009b). Older adults showed less inhibitory control of heart rate by the frontal cortex than did younger adults. However, the Thayer et al. study did not discriminate between prefrontal subregions. Interestingly, the more ventral regions of the brain seem to be relatively preserved with age whereas more dorsal, lateral, and superior regions show greater decline with age (Fjell and Walhovd, 2010; Mather, 2016). Therefore, it might be possible that HRV biofeedback training has similar effects on structural volume in the OFC across younger and older adults.

Finally, we examined whether the effects of biofeedback condition on structural volume changes and resting HRV changes were mediated by daily high amplitude oscillations during practice. In addition, we were interested in how any changes in structural volume in these

regions might relate to emotional well-being and so tested whether resonance frequency power during practice and volume changes or resting HRV changes would sequentially mediate any associations between condition and mood disturbance change.

2. Methods

2.1. Participants

No prior research had examined how HRV biofeedback affected brain structure, so we did not have prior research to rely on to estimate effect sizes. Thus, we planned to recruit 200 participants to generally have sufficient power to detect small-to-medium effect sizes. G*Power 3.1.9.4 software indicated that with $\alpha = 0.05$; power = 0.8, and effect size f = 0.2, the minimum N needed was 199. But the study was terminated due to the COVID-19 pandemic and it ended with an N of 162 (see below), which provided 80% power at $\alpha = 0.05$ to detect effect sizes f = 0.22 (small-to-medium effects). We recruited 121 younger participants aged between 18 and 35 years and 72 older participants aged between 55 and 80 years via the USC Healthy Minds community subject pool, a USC online bulletin board, Facebook and flyers between January 2018 and March 2020. Participants provided written informed consent approved by the University of Southern California (USC) Institutional Review Board. Participants were assigned to small groups of 3–6 people, with each group meeting at the same time and day each week. After recruitment and scheduling of each wave of groups, the groups were randomized to one of two conditions (see Supplementary Figure S1 for flow diagram): biofeedback training either to increase or decrease HRV. Upon completing the study, participants were paid for their participation and received bonus payments based on their individual and group performances (incentives for training were the same across conditions; see details below under “Rewards for Performance”). Prospective participants were screened and excluded for any medical, neurological, or psychiatric illness (but we included people who were taking antidepressant or anti-anxiety medication and/or attending psychotherapy only if the treatment had been ongoing and unchanged for at least three months and no changes were anticipated). We excluded people who had a disorder that would impede performing the HRV biofeedback procedures (e.g., coronary artery disease, angina, cardiac pacemaker), who were currently trained in relaxation, biofeedback or breathing techniques, or were on any psychoactive drugs other than antidepressants or anti-anxiety medications. For older adults, we also excluded people who scored lower than 16 on the TELE (Gatz et al., 1995) for possible dementia._Gender, education, age, and race were similar in the two conditions.

Out of 193 participants, 25 people (15 younger adults and 10 older adults) dropped out of the study and six older adults did not complete the post-intervention cognitive and HRV assessments due to the COVID pandemic, leaving 162 participants (106 younger adults and 56 older adults) who completed all 7 weeks of the study.

2.2. Procedure

2.2.1. Overview of 7-week Protocol Schedule—The study protocol involved seven weekly lab visits and five weeks of home biofeedback training. The first lab visit involved the non-MRI baseline measurements, including various questionnaires. The second lab visit

involved the baseline MRI session, followed by the first biofeedback calibration and training session. Each of the lab calibration sessions started with a 5-min baseline rest period followed by different strategies to find the best condition. After calibration sessions were completed, participants were notified which strategy was the best and requested to practice the best condition at home for 10 min twice a day for the 1st training week (between the 1st-week visit and the 2nd-week visit), 15 min twice a day for the 2nd training week (between the 2nd week visit and the 3rd week visit), and 20 min twice a day for the last weeks (between the 3rd week visit and the 7th week visit).

The weekly lab visits (except for weeks with MRI sessions) were run in small groups of participants from the same condition in which participants shared their experiences and tips about biofeedback training with other participants, while 1–2 researchers facilitated the discussion. Outside the lab, participants used a customized social app to communicate with other members of their group and researchers about their progress on daily biofeedback training. For instance, participants gave each other ‘thumbs-up’ or smiling face emojis when they completed training for the day, and researchers sent participants a friendly reminder to complete home training when they were falling behind. The week-6 lab visit repeated the assessments from the first lab visit. The final (7th) lab visit first repeated the baseline MRI session scans in the same order.

2.2.2. Biofeedback Training for the Osc+ condition—During all practice sessions, participants wore an ear sensor to measure their pulse. They viewed real-time heart rate biofeedback while breathing in through the nose and out through the mouth in synchrony with the emWave pacer. The emWave software (HeartMath®Institute, 2020) provided a summary ‘coherence’ score for participants that was calculated as peak power/(total power - peak power), with peak power determined by finding the highest peak within the range of .04 - .26 Hz and calculating the integral of the window .015 Hz above and below this highest peak, divided by total power computed for the .0033 - .4 Hz range.

During the second lab visit, we introduced participants to the device and identified the resonance frequency for each participant during five minutes of paced breathing at 6, 6.5, 5.5, 5 and finally 4.5 breaths/min (Lehrer et al., 2013). After all 5-min breathing segments were complete, we computed various aspects of the oscillatory dynamics for each breathing pace using Kubios HRV Premium 3.1 software (Tarvainen et al., 2014) and estimated which breathing pace best approximated the resonance frequency by assessing which one had the most of the following characteristics: highest low frequency (LF) power, the highest maximum LF amplitude peak on the spectral graph, highest peak-to-trough amplitude, cleanest and highest-amplitude LF peak, highest coherence score and highest the root mean squared successive differences (RMSSD). Participants were then instructed to train at home with the pacer set to their identified resonance frequency and to try to maximize their coherence scores.

During the third visit, they were asked to complete three 5-min paced breathing segments: the best condition from the last week’s visit, half breath per minute faster and half breath slower than the best condition. They were then instructed to train the following week at the pace that best approximated the resonance frequency based on the characteristics listed

above. In subsequent weekly visits, during 5-min training segments, they were asked to try out abdominal breathing and inhaling through nose/exhaling through pursed lips as well as other strategies of their choice.

2.2.3. Biofeedback Training for the Osc− condition—The same biofeedback ear sensor was used in this condition. However, we created custom software to display a different set of feedback to the Osc− participants. During each Osc− training session, a 'calmness' score was provided as feedback to the participants instead of the coherence score. The calmness score was calculated by multiplying the coherence score that would have been displayed in the Osc+ condition by −1 adding 10 (an 'anti-coherence' score). Thus, participants got more positive feedback (higher calmness scores) when their heart rate oscillatory activity in the 0.04 – 0.26 Hz range was low.

Participants also received a point adjustment that gave a penalty when heart rate was the lowest it had been in the past 15 s. Specifically, every 5 s, a local maximum IBI was set based on the maximum IBI from the last 15 s. If, at that point, the participant's current IBI was longer than this local maximum, the calmness score displayed for the next 5 s was the anti-coherence score - 2. Naturally, most of the time, current IBI was lower than the local maximum, and in those cases, the calmness score was the anti-coherence score +1. Thus, there was a penalty in their calmness score for moments when their heart rate was slower than it had been in any of the past 15 s. However, the average heart rate during biofeedback sessions did not differ significantly across conditions. Thus, this additional feedback appeared to have had little impact on heart rate.

During the initial calibration session at the end of the second lab visit, each participant was introduced to the device and feedback and was asked to come up with five strategies to lower heart rate and heart rate oscillations. The participant was instructed to wear the ear sensor and view real-time heart rate biofeedback while they tried each strategy for five minutes. We analyzed the data in Kubios and identified the best strategy as the one that had the most of the following characteristics: lowest LF power, the minimum LF amplitude peak on the spectral graph, lowest peak-to-trough amplitude, multiple and lowest-amplitude LF peak, highest calmness score and lowest RMSSD. Participants were then instructed to use this strategy to try to maximize their calmness scores in their home training sessions.

On the third visit, they were asked to select three strategies and try each out in a 5-min session. The strategy identified as best (based on the same characteristics used in the initial calibration session) was selected as the one to focus on during home training. In subsequent weekly visits, during 5-min training segments, they were asked to try out strategies of their choice.

2.2.4. Weekly Emotion Questionnaire—During each lab visit, participants completed the profile of mood states (POMS; Grove and Prapavessis, 1992). We used the 40-item version of POMS. Participants reported how much each item reflected how they felt at the moment using a scale from 1 (not at all) to 5 (extremely). Total mood disturbance was calculated by subtracting positive-item totals from negative-item totals. A constant value

(i.e., 100) was added to the total mood disturbance to eliminate negative scores. Higher scores indicate greater negative affect.

2.2.5. Rewards for Performance—In addition to receiving compensation of $15 per hour for each lab visit, participants were eligible to receive rewards based on individual and group performance. For individual performance rewards, each week participants had the opportunity to earn $2 for each instance (up to a maximum of 10) they exceeded their assigned target score (target scores were assigned each week and were the average of the top 10 scores earned from the previous week's training sessions plus 0.3). Group performance rewards were earned when members of a participant's group completed a minimum of 80% of their assigned biofeedback training minutes. For example, if a participant completed 100% of their training, they received an additional $3 for each group member who also completed 100% of their training. If a participant completed 80% of their training, they received an additional $2 for each group member who also completed at least 80% of their training. Rewards were calculated weekly, and participants received weekly updates on their earnings at their lab visits.

2.3. MRI Scan Parameters

The scans were conducted with a 3T Siemens MAGNETOM Trio scanner with a 32-channel head array coil at the USC Dana and David Dornsife Neuroimaging Center. T1-weighted 3D structural MRI brain scans were acquired pre and post-intervention using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the parameters of TR = 2300 ms, TE = 2.26 ms, slice thickness = 1.0 mm, flip angle = 9°, field of view = 256 mm, and voxel size = 1.0 × 1.0 mm, with 175 volumes collected (4:44 min).

2.4. Data Processing and Analyses

2.4.1. Overview of the planned analyses—We analyzed three types of data; heart rate data during rest and during training, T1 weighted structural image data, and behavioral data to measure emotional disturbance via POMS questionnaire.

First, we computed the autoregressive spectral power for the pre-intervention rest and for each training session and compared the average spectral power from all training sessions with the pre-intervention spectral power. Also, we compared the main HRV indexes across pre and post-intervention rest to examine the HRV intervention effect on resting HRV. Secondly, we applied automatic segmentation on the T1 structural image and extracted the volume data from left and right OFC ROIs. To examine the intervention effect on structural volume of the left and right OFC ROIs, we ran mixed ANCOVAs (time-point × condition × age group) with total grey matter volume as a covariate. Lastly, we examined the relationship between resting HRV change, volume change, and changes in emotional disturbance using correlation analysis and mediation analysis.

2.4.2. Heart Rate Oscillations During Seated Rest—HRV was measured while participants sat in a chair with knees at a 90 degrees angle and both feet flat on the floor for 5 minutes at pre- and post-intervention lab visits (i.e., the second and 7th lab visits, respectively). Participants' pulse was measured using HeartMath emWave pro software

with an infrared pulse plethysmograph (ppg) ear sensor. Pulse wave was recorded with a sampling rate of 370 Hz, and inter-beat interval data was extracted after eliminating ectopic beats or other sources of artifacts through a built-in process in emWave pro software. We used Kubios HRV Premium Version 3.1 (Tarvainen et al., 2014) to compute three standard heart rate variability metrics: RMSSD, a time domain analysis; and high frequency power (HF-power) and low frequency power (LF-power), which are frequency domain analyses. RMSSD is the primary resting HRV time domain metric (Laborde et al., 2017; Shaffer and Ginsberg, 2017), as previous research identified it as an indicator of parasympathetic response (Kleiger et al., 2005; Thayer and Lane, 2000). RMSSD is also less affected by respiratory rate than HF HRV (Hill et al., 2009). In the frequency domain, the low-frequency (LF) band ranges between 0.04 and 0.15 Hz. The LF band reflects a mix between sympathetic and vagal influences that shows an influence of both sympathetic and parasympathetic branches (Berntson et al., 1997; Malik et al., 1996). The HF band ranges between between 0.15 and 0.40 Hz (Malik et al., 1996) and reflects vagal influences.

In the frequency domain analysis, an autoregressive model was applied to the inter-beat interval time series to derive spectral power in the HF range (0.15 to 0.40 Hz) and LF range (0.04–0.15 Hz). HF-power and LF-power were natural log-transformed to normalize the distribution (Ellis et al., 2008; Laborde et al., 2017). Heart rate data from ear sensors failed to save for the first four participants in the Osc− condition because of technical issues with the first version of the Osc− biofeedback software; therefore, we analyzed data from the remaining 102 younger adults and 56 older adults. In younger adults, we excluded outliers who on a box-and-whisker plot were above Q3 + 3 × the interquartile range on total power on pre-intervention rest (N = 3), post-intervention rest (N = 1), or average training (N = 1), leaving an N of 97 for younger adults (N_{Osc+} = 52; N_{Osc-} = 45). In older adults, we excluded outliers who on a box-and-whisker plot were above Q3 + 3 × the interquartile range on total power on pre-intervention rest (N = 1), or post-intervention rest (N = 2), leaving an N of 53 for older adults (N_{Osc+} = 25; N_{Osc-} = 28).

HRV indexes were analyzed using mixed analysis of variance (ANOVA) with condition (Osc+ versus Osc−) and age group (older adults versus younger adults) as between-subject factors and time-point (pre vs post) as a within-subject factor. Cohen's *d* effect size estimates were calculated. The statistical analyses were performed using the software SPSS version 28.

2.4.3. Heart Rate Oscillations During Training—To assess the impact of Osc+ versus Osc− biofeedback during training sessions, we used Kubios HRV Premium 3.1 (Tarvainen et al., 2014) to compute autoregressive spectral power for each training session. We analyzed the same data from the resting HRV, 97 younger adults (5437 sessions) and 53 older adults (4137 sessions). We averaged the autoregressive total spectral power from all training sessions for each participant. In addition, we extracted the summed power within the .063~.125 Hz range for each participant (corresponding to periods of 8–16s, a range encompassing paces used by Osc+ participants for their breathing) to obtain a measure of resonance frequency oscillatory activity during biofeedback.

2.4.4. T1-Weighted Neuroimaging Processing—Among the 106 younger adults and 56 older adults who completed all 7 weeks of the study, 100 younger adults and 51 older adults finished pre-intervention and post-intervention MRI sessions.

Each participant's T1 structural image was preprocessed using Freesurfer image analysis suite version 6.0 (http://surfer.nmr.mgh.harvard.edu/). Cortical reconstruction and volumetric segmentation were performed. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 1999a; Fischl et al., 1999b; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006; Segonne et al., 2004).

Following initial preprocessing, we used the Freesurfer 6.0 image analysis suite longitudinal stream to automatically extract volume estimates (Reuter et al., 2012). This longitudinal stream within FreeSurfer creates an unbiased subject-specific template by co-registering scans from the pre- and post-intervention time-points using a robust and inverse consistent algorithm (Reuter et al., 2010; Reuter et al., 2012), and uses these subject-specific templates for pre-processing the individual scans (e.g., during skull stripping and atlas registration). This approach improves reliability and statistical power while avoiding processing bias favoring the baseline scans that may affect groups unequally (Reuter et al., 2012).

Finally, using a parcellation algorithm, the individual brains were mapped to the Desikan–Killiany probabilistic cortical atlas based on anatomic landmarks and cortical geometry (Desikan et al., 2006). Individual participants' cortical thickness, surface area and volume were then extracted directly from FreeSurfer. Cortical volumes for bilateral lateral and medial OFC were used in the final statistical analysis.

For quality control, we used automated measures computed by FreeSurfer of the contrast-to-noise ratio (the difference in signal intensity between regions of different tissue types and noise signal) and the Euler number (a metric of cortical surface reconstruction) to identify poor quality structural scans (Chalavi et al., 2012; Rosen et al., 2018). For analyses of volumetric change, we excluded outliers (N = 4 for younger adults and N = 2 for older adults) who on a box-and-whisker plot were above Q3 + 3 × the interquartile range on either of these metrics on either pre or post scans, leaving an N of 96 for younger adults (N_{Osc+} = 49; N_{Osc-} = 47) and an N of 49 for older adults (N_{Osc+} = 24; N_{Osc-} = 25).

The final common dataset from HRV and MRI data had an N of 88 for younger adults (N_{Osc+} = 45; N_{Osc-} = 43) and an N of 46 for older adults (N_{Osc+} = 21; N_{Osc-} = 25).

2.4.5. Regions of Interest and Neuroimaging Statistical Analyses—The grey matter cortical volume percent changes were analyzed using mixed analysis of covariance (ANCOVA) with condition (Osc+ versus Osc−) and age group (older adults versus younger adults) as between-subject factors and time-point (pre versus post) as a within-subject factor

and total grey matter volume as a covariate. Cohen's *d* effect size estimates were calculated. Benjamini–Hochberg procedure was applied to control the false discovery rate for multiple comparisons (Hochberg and Benjamini, 1990).

2.4.6. Mediation Analysis—To examine whether the relationships between training condition and either the ROI volume changes or the resting HRV changes were mediated by the resonance frequency power within the .063~.125 Hz range during practice, we conducted a mediation analysis using the PROCESS macro (Hayes, 2017). In each model, the unstandardized regression coefficient (c) reflects the total effect. Coefficient c′ reflects the direct effect of the independent variable on the dependent variable absent the mediator. Coefficients a and b reflect the relationships between the mediator and the independent variable and the dependent variable, respectively. The product of coefficients (a × b) indicates how much the relationship between independent variable and dependent variable is mediated by the mediator (i.e., the indirect effect).

Bootstrapping was used for testing mediation hypotheses, using a resampling procedure of 10,000 bootstrap samples (Preacher and Hayes, 2008). Point estimates and confidence intervals (95%) were estimated for the indirect effect. The point estimate was considered significant when the confidence interval did not contain zero.

3. Results

3.1. Sample Characteristics

Details about the baseline characteristics of the participants can be found in Table 1. As RMSSD, HF-power, and LF-power were not normally distributed, they were transformed using the natural logarithm. HRV characteristics for subgroups based on daily medication reports are shown in Supplementary Table S1.

3.2. HRV Biofeedback Condition Differences in HRV during Training Sessions

To examine how participants in the Osc+ and Osc− conditions performed during HRV biofeedback training, we computed heart rate spectral frequency power during training using an autoregressive approach. As intended, those in the Osc+ condition increased their total spectral frequency power during training, whereas those in the Osc− condition did not significantly influence spectral frequency power compared to their own baseline rest, leading to a significant interaction of session type (baseline vs. training) and condition, $F(1,146) = 28.84$, $p < .001$, effect size Cohen's $d = .889$, 95% CI [0.545, 1.219]; Fig. 1. Both younger adults, $F(1,95) = 37.54$, $p < .001$, $d = 1.257$, 95% CI [0.806, 1.678], and older adults, $F(1,51) = 5.38$, $p = .024$, $d = .648$, 95% CI [0.028, 1.186], independently showed significant interactions. The three-way interaction of age group, condition, and session type was not significant, $F(1,146) = .48$, $p = .491$, $d = .110$, 95% CI [0, 0.372]. We also examined spectral frequency power in the resonance breathing frequency range (8–16s; 0.063 Hz~0.125 Hz). Those in the Osc+ condition increased spectral frequency power during practice sessions, whereas those in the Osc− condition did not significantly influence spectral frequency power in the resonance frequency range compared to their own baseline rest, leading to a significant interaction of session type (baseline vs. training) and condition, $F(1,146) = 28.63$,

$p < .001$, $d = .886$, 95% CI [0.540, 1.216] ; Fig. 1. When separated by age group, younger adults showed a significant interaction, $F(1,95) = 45.33$, $p < .001$, $d = 1.382$, 95% CI [0.921 1.807], and older adults showed a marginally significant interaction, $F(1,51) = 3.85$, $p = .055$, $d = .549$, 95% CI [0.013, 1.085]. The three-way interaction of age group, condition, and session type was not significant, $F(1,146) = 2.18$, $p = .142$, $d = .247$, 95% CI [−0, 0.565].

3.3. HRV Biofeedback Condition Differences in Resting HRV Changes

Next, we examined the effect of HRV biofeedback training on resting HRV. Measures of resting HRV, log RMSSD, log HF power, and log LF power at rest in pre-intervention (week 2) and post-intervention (week 7) were examined. To test whether HRV changed from pre to post time-points, whether this depended on training conditions, and whether the age groups showed differences in the time-point x condition interaction, we performed a series of three-way mixed ANOVAs, one for each measure. In these ANOVAs, time-point was a within-subjects factor (2 levels: pre, post), condition was a between-subjects factor (2 levels: Osc+, Osc−), and age group was another between-subjects factor (2 levels: younger adults, older adults). We found a significant 2-way interaction effect between time-point and condition on log LF power, $F(1, 146) = 6.60$, $p = .014$, $d = .424$, 95% CI [0.093, 0.748]. When separated by age group, younger adults showed a significant interaction, $F(1,95) = 10.30$, $p = .002$, $d = .659$, 95% CI [0.242, 1.059], and older adults showed no significant interaction, $F(1,51) = 0.70$, $p = .407$, $d = .238$, 95% CI [−0.292, 0.768]. We did not find significant interaction effects of time-point and condition on log RMSSD and log HF power. Also, we did not observe significant three-way interaction effects of time-point, condition, and age group on log RMSSD, log HF power or log LF power. Planned comparisons of post-intervention compared to pre-intervention within each subgroup indicated that older adults in the Osc+ condition showed increases in log RMSSD in post-intervention compared to pre-intervention, $t(24) = 2.19$, $p = .029$, $d = .351$, 95% CI [0.003, 0.699], and in log LF power, $t(24) = 2.02$, $p = .054$, $d = .326$, 95% CI [−0.020, 0.673], and Osc+ younger adults showed a significant increase in log LF power in post-intervention compared to pre-intervention, $t(51) = 2.93$, $p = .005$, $d = .437$, 95% CI [0.125, 0.749]; Fig. 2 A, B, C. There were no significant pre-post differences in the Osc− condition.

3.4. ROI analysis: The Effects of HRV Biofeedback Training on Volume Change

To examine our main question of the effect of HRV biofeedback training on cortical volume in left and right OFC ROIs, we performed a three-way mixed ANCOVA (time-point × condition × age group) on the volume of each ROI including time-point (pre vs post) as a within-subject factor and condition (OSC+ vs. OSC−) and age group (younger vs. older) as between-subject factors. Total grey volume was included as a covariate to control for differences among age groups and individual differences. We found a significant time-point × condition interaction effect on left OFC volume, indicating that OSC+ participants showed increases in volume relative to OSC− participants, $F(1,140) = 8.33$, $p = .005$, $d = .487$, 95% CI [0.149, 0.817]; Fig. 3. There was no significant two-way time-point × condition interaction on right OFC volume, $F(1,140) = 1.36$, $p = .246$, $d = .201$, 95% CI [0, 0.525]; Fig. 3.

There was no significant three-way interaction of time-point, condition, and age group on left OFC volume, $F(1,140) = 0.003$, $p = .958$, $d = 0$, 95% CI [0, 0.001], nor on right OFC volume, $F(1,140) = 0.02$, $p = .881$, $d = 0$, 95% CI [0, 0.007]; Fig. 4, indicating that the left OFC interaction of time-point and condition did not differ significantly across age groups. Indeed, when separated by age group, there were significant time-point × condition interaction effects on left OFC volume in both age groups; $F(1,93) = 5.42$, $p = .022$, $d = .483$, 95% CI [0.045, 0.885] for younger adults and $F(1,46) = 5.63$, $p = .022$, $d = .700$, 95% CI [0.063, 1.264] for older adults (Fig. 4). After applying the Benjamini–Hochberg procedure, interaction effects remained significant for both younger and older adults. There were no significant two-way interaction effects on right OFC volume in either age group (Fig. 4). As indicated in Table 1, the between-condition differences in baseline right or left OFC volume were not significant. We note that the size of detectable differences differs for between- vs. within-subjects effects due to differences in variance. In particular, within-subjects pre vs. post OFC volume estimates ($r = .969$, $p < .001$ for left and $r = .964$, $p < .001$ for right OFC) were highly reliable, contributing to our ability to detect within-person structural change in this study.

We also examined another kind of interval estimate for effect size, the null- counternull interval (Rosnow and Rosenthal, 2009). The counternull interval provides the largest nonnull magnitude of the effect size that is supported by the same amount of evidence as the null value of the effect size (in this case, 0). The counternull value for the $\underline{d} = 0.013$ effect size for the interaction of time-point, condition and age group in the left OFC was $d = .026$. Similarly, the value of $d = 0.016$ for the interaction effect of condition and age group in right OFC yields a counternull value of $d = .032$ limits. According to Cohen's conventions, a d of .20 is a small effect size. Thus, the counternull indicates that these interaction effects are equally likely to be null or to be small effects, such that there are unlikely to be large differences between age groups in terms of the effects of condition on left OFC and right OFC.

3.5. The Relationship between HRV Biofeedback Training and Volume Changes in ROIs

We examined the association between power within the resonance frequency band during training, resting HRV changes, and volume changes in two ROIs. Table 2 shows partial correlation coefficients between power within the resonance frequency band during training, resting HRV changes, and volume changes in three ROIs, controlling for resonance frequency power during pre-intervention rest.

To examine whether the resonance frequency power during practice mediated the relationship between training condition and structural volume changes or resting HRV changes, we conducted a mediation analysis using bootstrapping method Model 4 of the PROCESS macro with 10000 bootstrap samples. Mediation analysis diagrams are depicted in Fig. 5. The path estimates (direct, indirect, and total effects) of the proposed model along with 95% confidence intervals generated through the bootstrapping method were presented in Table 3.

First, we examined the mediation model on volume change in left OFC, controlling for resonance frequency power during pre-intervention rest. For this model with volume

change in left OFC as the dependent variable (Fig. 5A and Table 3A), the total effect was statistically significant, c = 1.628, p = .002, 95% CI [0.626, 2.630]. The direct effect was also significant, c′ = 1.849, p = .006, 95% CI [0.528, 3.170], but the indirect effect was not significant, ab = −0.221, 95% CI [−0.945, 0.565]. For the model with volume change in right OFC as the dependent variable, total, direct, and indirect effects were not significant.

Next, we used a mediation model to test whether resonance frequency power during practice sessions mediated resting HRV changes, controlling for resonance frequency power during pre-intervention rest. For log HF-power change as dependent variable in a model (Fig. 5B and Table 3B), the total effect was not significant, c = −0.139, p = .403, 95% CI [−0.467, 0.189], but the direct effect was significant, c′ = −0.503, p = .020, 95% CI [−0.925, −0.081], and the indirect effect was significant, ab = 0.364, 95% CI [0.099, 0.634]. For log LF-power change as dependent variable in a model (Fig. 5C and Table 3C), the total effect was significant, c = 0.581, p = .003, 95% CI [0.206, 0.957], but the direct effect was not significant, c′ = −0.146, p = .528, 95% CI [−0.692, 0.310], and the indirect effect was significant, ab = 0.727, 95% CI [0.422, 1.069]. For RMSSD change as the dependent variable in a model, total, direct, and indirect effects were not significant.

The results of the mediation analyses suggest that the relationships between training condition and volume changes in left OFC are not mediated by resonance frequency power during practice because no indirect effects were significant. Thus, the condition effects on structural volume did not depend on the degree of intensity of the oscillations during practice. In contrast, the relationships between training condition and HRV changes (log HF-power and LF-power), were mediated by resonance frequency power during practice.

3.6. Sequential Mediating Effects on the Relationship between Condition and Mood Disturbance Change

As a subsequent analysis, we extended the simple mediation model to a sequential mediation model to examine mood disturbance change.

First, we examined the mediating effect of resonance frequency power during practice and volume changes in left OFC on the relationship between condition and mood disturbance change. For a model including volume change in left OFC as a second mediator, we found a significant indirect effect of condition on mood disturbance change through volume changes in left OFC, bf = −1.781, 95% CI [−4.602, −0.034]; Fig. 6 and Table 4. The negative relationship indicates that greater increases in left OFC volume led to greater decreases in negative mood. But the indirect effect of condition on mood disturbance change through resonance frequency power during practice was not significant, ae = 1.391, 95% CI [−1.595, 4.742], and the indirect effect of condition on mood disturbance change through both resonance frequency power during practice and volume change in left OFC was not significant, adf = 0.219, 95% CI [−0.549, 1.237].

Next, we examined the mediation effect of resonance frequency power during practice and resting HRV changes on the relationship between condition and mood disturbance change. In both models including log HF power or log LF power as a second mediator, no direct and indirect effects were significant.

Thus, volume changes in left OFC mediated the relationship between condition and mood disturbance change.

4. Discussion

In conclusion, these findings indicate that daily practice of HRV biofeedback can affect the structural volume of prefrontal brain regions that have previously been associated with individual differences in HRV. Participants who showed greater increases in volume in left OFC across the intervention period also tended to show decreases in negative affect during that time, suggesting that these prefrontal structural changes may contribute to the positive emotional outcomes seen in HRV biofeedback intervention studies (Goessl et al., 2017; Lehrer et al., 2020). Previous studies have shown that the structure and function of PFC is related to HRV (Ahs et al., 2009; Chang et al., 2013; Critchley et al., 2003; Koenig et al., 2021; Kumral et al., 2019; Lane et al., 2009; Sakaki et al., 2016; Smith et al., 2015; Yoo et al., 2018). Typically, it is assumed that PFC exerts inhibitory control over subcortical regions and HRV reflects the PFC's ability to inhibit subcortical circuits. However, this relationship may also reflect influences from heart to brain, if HRV itself influences brain and emotional function (Mather and Thayer, 2018). Indeed, studies that manipulated HRV directly using HRV biofeedback have shown that changes in heart rate bring positive changes in physiological, behavioral, and brain level (Goessl et al., 2017; Lehrer et al., 2020; Lehrer et al., 2013; Nashiro et al., 2022).

In the current study, we examined whether HRV biofeedback training affects the structural volume of the OFC, a region of the brain where individual differences in structure have previously been associated with HRV. The Osc+ condition increased left OFC volume relative to the Osc− condition, whereas there were no significant effects of condition on right OFC volume.

Subsequent mediation analyses testing the potential mediating role of the amplitude of heart rate oscillations achieved during practice sessions revealed that training condition affected structural volume in left OFC directly. The performance level, or how high the heart rate oscillation was during training, did not mediate this relationship. This suggests that the critical factor affecting OFC structure was the attempt to regulate heart rate oscillations rather than the magnitude of the oscillatory dynamics that resulted from the regulation attempt. In contrast, mediation analyses on log HF and LF-power showed the relationships between training condition and log HF and LF-power were mediated by power during training within the resonance frequency band. Thus, the amplitude of heart rate oscillations achieved during training appears to play a key role in determining how much participants' resting HRV was affected by the interventions. Further analysis with the sequential model showed volume change in left OFC mediated the relationship between condition and mood disturbance change, whereas the amplitude of oscillations during the practice did not significantly mediate this relationship. This suggests that the OFC regulatory dynamics that were affected by the interventions in turn affected mood. More generally, these findings suggest that the psychological goal of increasing or decreasing heart rate oscillations and the physiological oscillatory dynamics that result from these goals during the training sessions have some independent downstream effects.

We also found while Osc+ younger adults showed a significant increase in LF power in post-intervention compared to pre-intervention, Osc+ older adults showed a significant increase in RMSSD in post-intervention compared to pre-intervention. One possibility is that older adults' vagal HRV can benefit more from interventions due to declining resting vagal HRV (Koenig, 2020). Also, the possibility cannot be ruled out that older adults may have difficulty continuing training at their own resonance frequency resulting in affecting broader frequency range in resting HRV, while young adults can effectively follow training at their own resonance frequency resulting in affecting low frequency range in resting HRV.

In our study, we compared two conditions that had opposite biofeedback goals, with the Osc+ group trying to increase HRV during practice sessions, which they did successfully, while the Osc− group tried to decrease HRV, which they on average did not succeed in doing, compared with their own resting HRV. Our significant group-by-time-point interactions were associated with both increases in volume in the Osc+ group and decreases in volume in the Osc− condition. The Osc+ condition produced a 0.55% increase in left OFC volume. The Osc− condition produced a 0.96% decrease in left OFC volume. A review focusing on structural brain plasticity in adult learning (Lovden et al., 2013) reported that studies using various training protocols like exercise, motor, and cognitive training with acceptable quality had net effects of training on cortical volume that fell within 2 ~ 5% for 5 days to ~ 3-month training (Engvig et al., 2010; Martensson et al., 2012; Takeuchi et al., 2011). Increases in hippocampal volume are in the 2 ~ 4% range for 3 to 12-month training (Erickson et al., 2011; Lovden et al., 2012; Martensson et al., 2012). A video gaming training group that trained for 2 months for at least 30 min per day with a video game showed a significant 1~3% increase in gray matter volume compared to pretest in the right hippocampal formation, right dorsolateral prefrontal cortex, and bilateral cerebellum, whereas a control group did not (Kuhn et al., 2014). Likewise, individuals training fine motor skills of writing and tracing with their non-dominant left hand over a 7-week period displayed a significant (~2%) increase of gray matter volume of both left and right primary motor cortex relative to a control group after 4 weeks (Wenger et al., 2017). Our 5 weeks of HRV biofeedback intervention showed a similar range of effects as these other intervention studies in left OFC. Because we did not have a no-intervention comparison group, we cannot be sure how much of the Osc− declines in volume correspond with normal atrophy. Future studies are needed to investigate potential effects of this active control condition compared with a passive baseline.

Healthy aging is associated with significant changes in both the brain and the heart (Thayer et al., 2021). The decline of HRV from early adulthood to late adulthood is similar to changes in cortical changes in the brain (Koenig, 2020). The PFC is a critical region for emotion regulation and is one of the last regions to fully develop and one of the first to show age-related declines (Raz et al., 2005). It is important that this study revealed a relationship between HRV biofeedback and cortical volume in OFC not only in young adults but also in healthy older adults. This is of potential relevance for mild cognitive impairment (MCI) or neurodegenerative disorders like Alzheimer's disease (AD) and frontotemporal dementia as frontal regions' function in older adults with MCI or several types of dementia decreases. Lower HRV in dementia patients than in healthy individuals has been reported (Alvares et al., 2016; Jensen-Dahm et al., 2015; Kim et al., 2018). However, the results were

not always consistent. For example, a study addressed the relationships between HRV and cortical thickness in AD signature regions in healthy control and older adults with amnesic MCI (Lin et al., 2017). They found higher HF-HRV at rest was significantly related to both more severe AD-associated neurodegeneration and worse cognitive ability and also showed that high anterior cingulate cortex activity significantly mediated relationships between HF-HRV and cortical thickness, suggesting a compensatory process. This result indicates that individuals with amnesic MCI may still have the capacity to rely on frontal regions' compensation, thus maintaining parasympathetic nervous system regardless of AD pathology (Lin et al., 2017). Therefore, future research will be necessary to see HRV biofeedback intervention effects on cortical volume or thickness with participants with MCI or AD.

To examine whether HRV biofeedback training affects brain structure, we used brain volume as our dependent variable. In previous longitudinal research, Freesurfer volume measures were generally more reliable than Freesurfer thickness measures ($p \leq 0.002$; Schwarz et al., 2016). The volume also shows more longitudinal change than cortical thickness or surface area (Storsve et al., 2014). Furthermore, a negative relationship between change in thickness and surface area was found across several regions, where more thinning was associated with less decrease in the area (Storsve et al., 2014). Thus, the volume seemed like the best overall measure of structure for our study that involved longitudinal change.

There are reported sex differences in HRV (Kuo et al., 1999; Thayer et al., 2021; Williams et al., 2019), but unfortunately the current sample was not powered to examine sex differences, especially among the older adults who had an unbalanced sex ratio with more females than males. Future studies are needed to more fully investigate potential sex differences and other individual difference relationships.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by NIH R01AG057184 (PI Mather).

We thank our research assistants for their help with data collection: Michelle Wong, Kathryn Cassutt, Collin Amano, Yong Zhang, Paul Choi, Heekyung Rachael Kim, Seungyeon Lee, Alexandra Haydinger, Lauren Thompson, Gabriel Shih, Divya Suri, Sophia Ling, Akanksha Jain, and Linette Bagtas.

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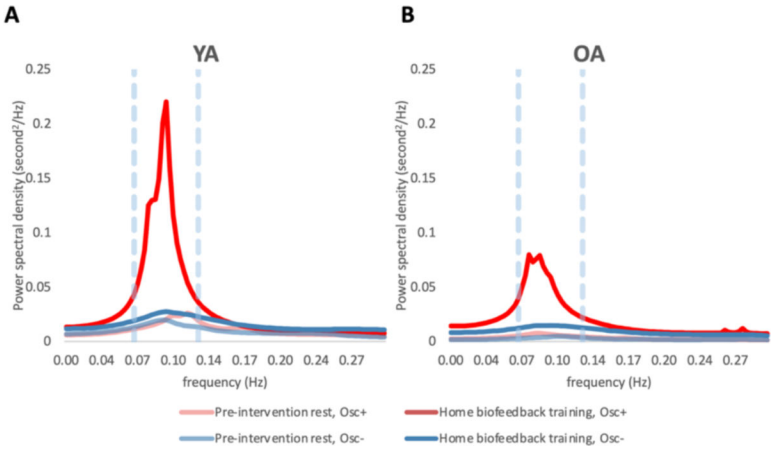

Fig. 1.

Heart rate power spectrum averaged across all practice sessions compared to pre-intervention rest. YA=younger adults, OA=older adults.

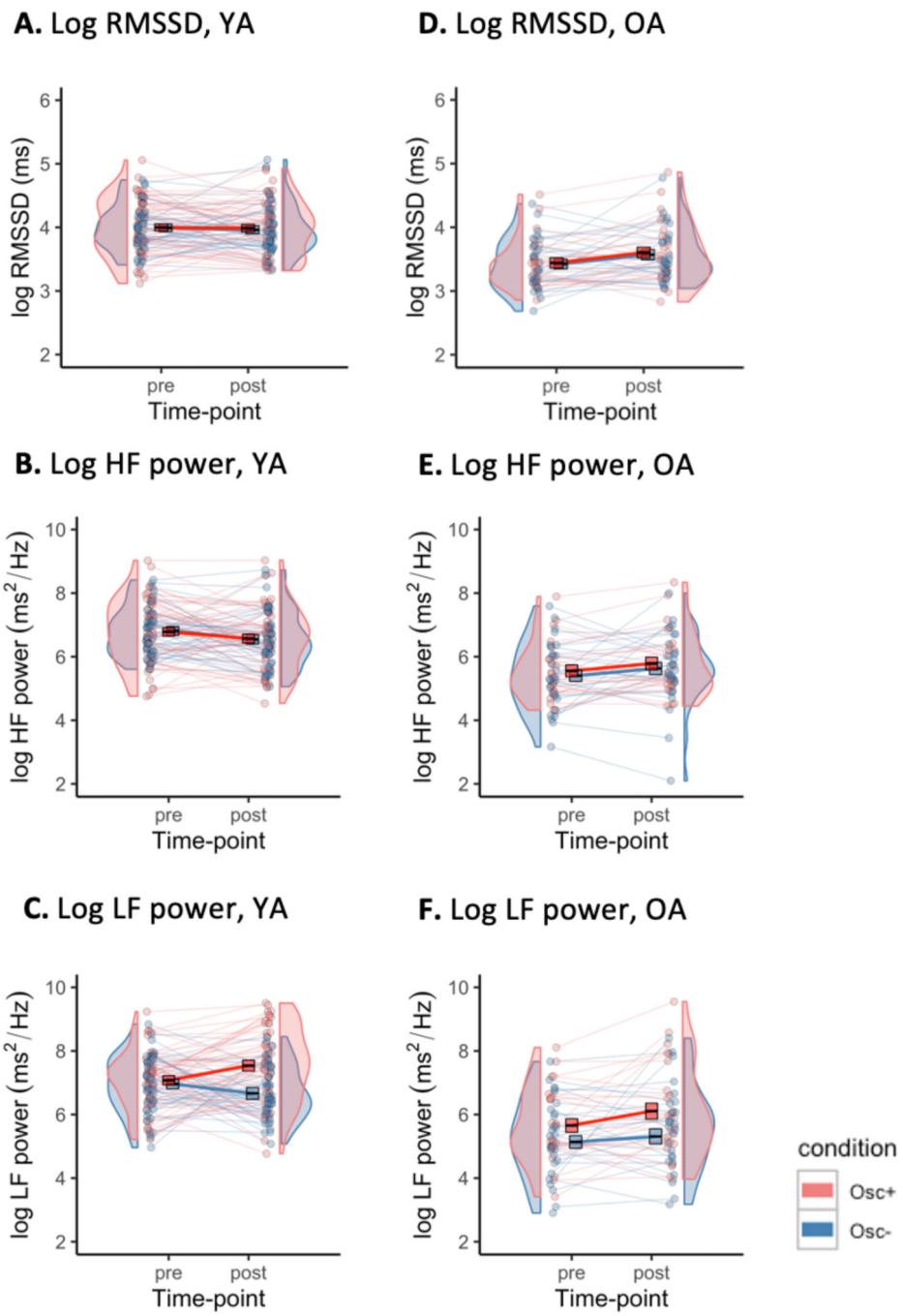

Fig. 2.

Resting HRV changes across the two conditions in each age group. The error bars reflect the standard error. YA=younger adults, OA=older adults.

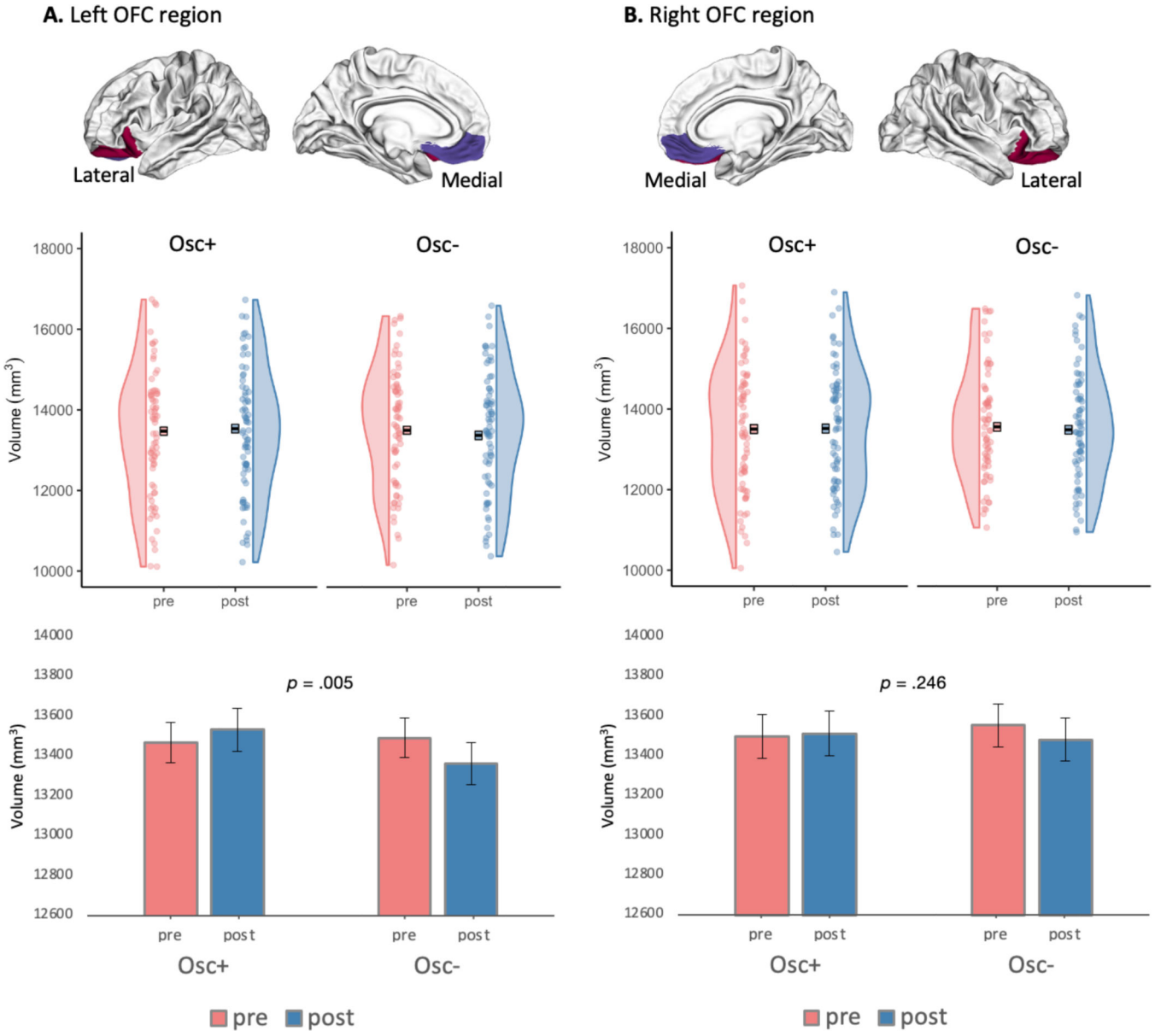

Fig. 3.

Distribution of OFC volume and results of mixed ANCOVAs for left OFC volume (A) and for right OFC volume (B) with total grey volume as a covariate. P values reflect interaction effects of time-point × condition on left OFC volume (in the bottom row in column A) and right OFC volume (in the bottom row in column B). The error bars reflect the standard error.

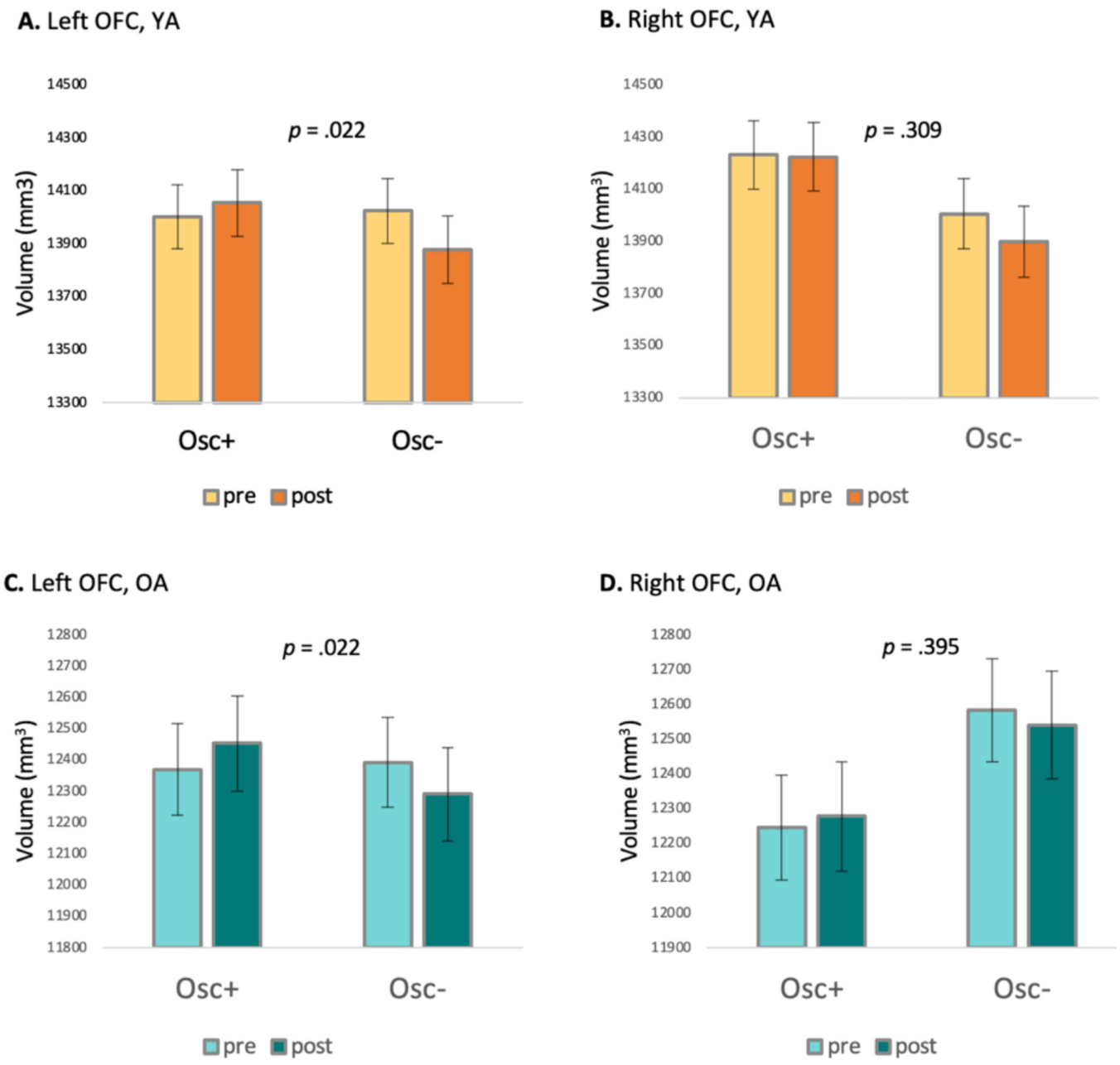

Fig. 4.

Results of mixed ANCOVAs for left OFC volume (A, C) and for right OFC volume (B, D) with total grey volume as a covariate. *P* values reflect two-way interaction effects of time-point × condition on left OFC volume and right OFC volume in younger adults (YA) (A, B panels) and older adults (OA) (C, D panels). The error bars reflect the standard error.

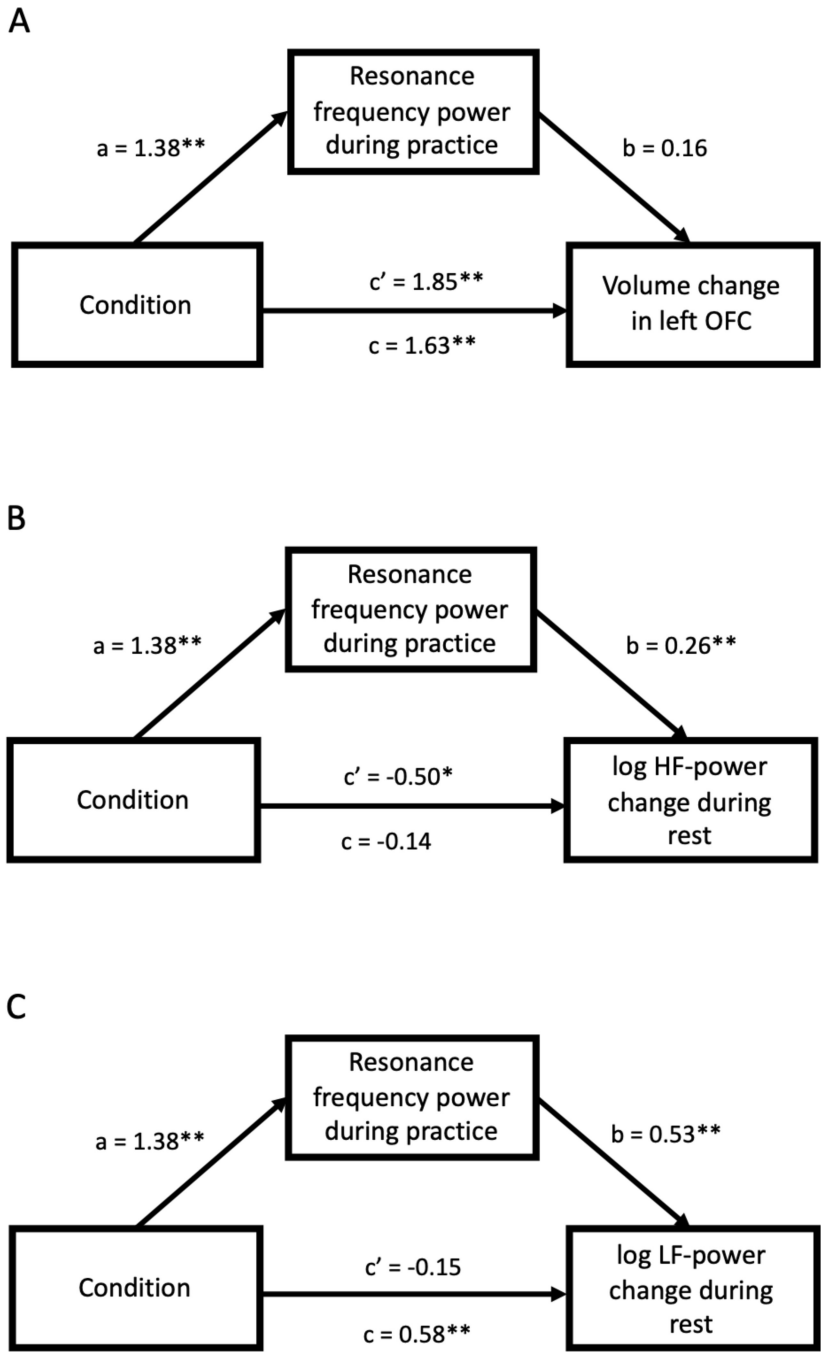

Fig. 5.

Resonance frequency power mediation models of the relationships between training condition and volume changes in left OFC (A), between training condition and HF-power changes during rest (B), and between training condition and LF-power changes during rest (C), controlling for resonance frequency power during pre-intervention rest. a, b, c and c' are expressed as the unstandardized regression coefficient. *$p < .05$; **$p < .01$.

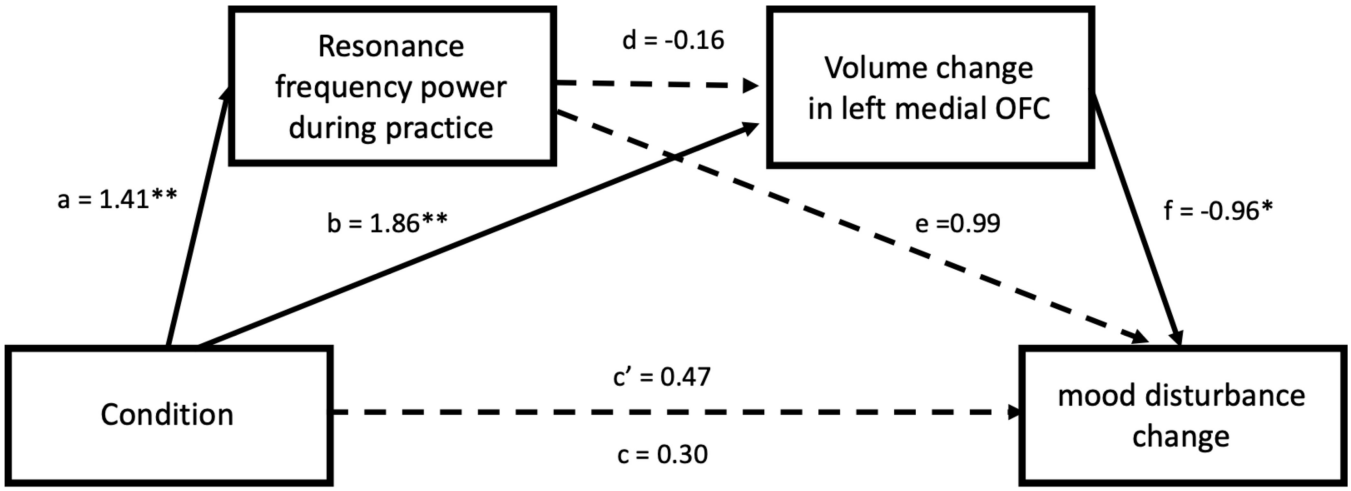

Fig. 6.

Sequential mediation models of resonance frequency power and volume changes in left OFC on the relationships between training condition and mood disturbance change, controlling for resonance frequency power during pre-intervention rest. a, b, c, c', d, e, and f are expressed as the unstandardized regression coefficient. *$p < .05$; **$p < .01$.

Table 1.

Baseline participant characteristics for each condition in each age group (from week 2, before intervention). Means and standard deviations (in parenthesis) are provided. Independent samples t-tests were used to detect condition difference and age group differences.

	Young (18~35 years)			Old (55~80 years)			Age group difference (t)
	Osc+	Osc−	Condition difference (t)	Osc+	Osc−	Condition difference (t)	
Age (years)	22.73 (2.47)	22.69 (3.30)	0.71	64.80 (8.52)	64.93 (5.81)	−0.07	−51.15***
	All: 22.71 (2.87)			All: 64.87 (7.14)			
Sex	25 F/27 M	23 F/ 22 M		17 F / 8 M	20 F / 8 M		
	All: 48 F / 49 M			All: 37 F / 16 M			
Mean HR (beat/min)	72.73 (10.51)	72.73 (9.35)	0.004	68.94 (9.10)	72.38 (10.81)	−1.25	1.15
	All: 72.73 (9.94			All: 70.76 (10.10)			
log RMSSD	4.00 (0.45)	3.99 (0.33)	0.09	3.44 (0.39)	3.42 (0.41)	0.17	8.26***
	All: 4.00 (0.40)			All: 3.43 (0.40)			
log HF-power	6.78 (1.03)	6.81 (0.75)	−0.17	5.56 (0.89)	5.14 (1.39)	0.56	8.27***
	All: 6.80 (0.90)			All: 5.47 (1.00)			
Log LF-power	7.08 (0.89)	6.96 (0.90)	0.63	5.66 (1.19)	5.14 (1.39)	1.45	9.06***
	All: 7.02 (0.89)			All: 5.38 (1.31)			
Left OFC volume (mm^3)	13913.4 (1420.6)	14117.1 (1247.2)	−0.75	12320.2 (1347.0)	12439.2 (1377.3)	−0.31	6.94***
	All: 14013.1 (1335.4)			All: 12380.9 (1349.6)			
Right OFC volume (mm^3)	14147.2 (1433.9)	14093.1 (1273.1)	0.20	12204.3 (1206.4)	12623.1 (1267.2)	−1.18	7.37***
	All: 14120.7 (1350.7)			All: 12418.0 (1243.0)			
Total gray matter volume (mm^3)	700708.4 (57000.6)	709893.9 (49101.1)	−0.84	612543.1 (69611.3)	617571.0 (50089.6)	−0.29	9.24***
	All: 705205.5 (53200.9)			All: 615108.3 (59856.9)			

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$, 2-tailed.

Table 2.

Partial correlation coefficients (*r*) between resonance frequency power during practice, resting HRV changes, and volume changes in ROIs, controlling for resonance frequency power during pre-intervention rest

	Condition	Resonance frequency power	RMSSD change	Log HF-power change	Log LF-power change	Volume change in left OFC	Volume change in right OFC
Resonance frequency power	.649 **†	1					
RMSSD change	−.070	.034	1				
Log HF-power change	−.073	.123	.833 **†	1			
Log LF-power change	.258 **†	.456 **†	.360 **†	.433 **†	1		
Volume change in left OFC	.270 **†	.143	.069	.017	.167	1	
Volume change in right OFC	.108	.040	.070	.097	.091	.626 **†	1
Mood disturbance change	.011	.055	−.186 *	−.136	−.063	−.188 *	−.134

* $p < .05$

** $p < .01$, 2-tailed

† remained significant after multiple comparison correction using Benjamini–Hochberg procedure.

Table 3.

Path coefficients for mediation model (N = 134, bootstrap = 10000).

A: Volume change in left OFC

Effect	Paths	B	SE	t	p	LLCI	ULCI
Total effect (c)	condition→volume change in left LOFC	1.628	0.507	3.214	0.002	0.626	2.630
Direct effect (c′)	condition→volume change in left LOFC	1.849	0.668	2.770	0.006	0.528	3.170
Indirect effect (ab)	condition→resonance frequency power during practice→volume change in left LOFC	−0.221	0.379			−0.945	0.565

B: Log HF-power changes

Effect	Paths	B	SE	t	p	LLCI	ULCI
Total effect (c)	condition→log HF-power change during rest	−0.139	0.166	−0.838	−0.403	−0.467	0.189
Direct effect (c′)	condition→log HF-power change during rest	−0.503	0.213	−2.358	0.020	−0.925	−0.081
Indirect effect (ab)	condition→resonance frequency power during practice→log HF-power change during rest	0.364	0.137			0.099	0.634

C: Log LF-power changes

Effect	Paths	B	SE	t	p	LLCI	ULCI
Total effect (c)	condition→log LF-power change during rest	0.581	0.190	3.060	0.003	0.206	0.957
Direct effect (c′)	condition→log LF-power change during rest	−0.146	0.231	−0.633	0.528	−0.602	0.310
Indirect effect (ab)	condition→resonance frequency power during practice→log LF-power change during rest	0.727	.163			0.422	1.069

SE: standard error; LLCI: Lower Limit of the 95% Confidence Interval; ULCI: Upper Limit of the 95% Confidence Interval

Table 4.

Path coefficients for sequential mediation model of resonance frequency power during practice and volume change in left OFC on the relationship between condition and mood disturbance change (N = 133, bootstrap = 10000).

Effect	Paths	B	SE	t	p	LLCI	ULCI
Total effect (c)	condition→mood disturbance change	0.299	2.507	0.119	0.905	−4.661	5.259
Direct effect (c′)	condition→mood disturbance change	0.470	3.371	0.140	0.889	−6.200	7.140
Indirect effects	Total indirect effect	−0.172	1.739			−3.565	3.253
(ae)	condition→resonance frequency power during practice→mood disturbance change	1.391	1.611			−1.595	4.742
(bf)	condition→volume change in left MOFC→mood disturbance change	−1.781	1.189			−4.602	−0.034
(adf)	condition→resonance frequency power during practice→volume change in left MOFC→mood disturbance change	0.219	0.446			−0.549	1.137

SE: standard error; LLCI: Lower Limit of the 95% Confidence Interval; ULCI: Upper Limit of the 95% Confidence Interval