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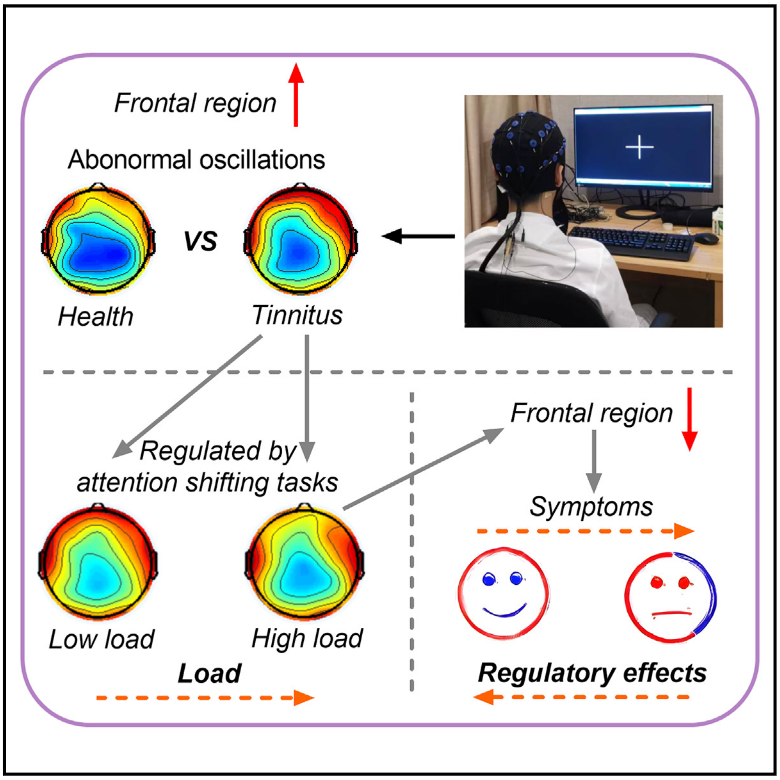
Frontal gamma-alpha ratio reveals neural oscillatory mechanism of attention shifting in tinnitus

Graphical abstract



Highlights

- Abnormal neural oscillations in tinnitus were found in the frontal lobe
- The elevated γ/α ratio can be regulated by multilevel workload attention shifting tasks
- The regulatory effects depend on the level of workload
- The regulatory index correlates with the severity of tinnitus symptoms

Authors

Xueji Feng, Xiaoyu Bao, Haiyun Huang, ..., Yuexin Cai, Qiyun Huang, Yuanqing Li

Correspondence

caiyx25@mail.sysu.edu.cn (Y.C.),
huangqiyun@pazhoulab.cn (Q.H.),
auyqli@scut.edu.cn (Y.L.)

In brief

Neuroscience; Sensory neuroscience

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Article

Frontal gamma-alpha ratio reveals neural oscillatory mechanism of attention shifting in tinnitus

Xueji Feng,[1,3] Xiaoyu Bao,[1,3] Haiyun Huang,[2,3] Zijian Wang,[1,3] Wen Hu,[1] Chenxi Xue,[1] Zhiqing Song,[1] Yuexin Cai,[4,5,*] Qiyun Huang,[3,*] and Yuanqing Li[1,3,6,*]

[1]School of Automation Science and Engineering, South China University of Technology, Guangzhou 510641, China
[2]School of Software, South China Normal University, Foshan 528225, China
[3]Research Center for Brain Machine Intelligence, Pazhou Lab, Guangzhou 510005, China
[4]Department of Otolaryngology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, China
[5]Institute of Hearing and Speech-Language Science, Sun Yat-sen University, Guangzhou 510120, China
[6]Lead contact
*Correspondence: caiyx25@mail.sysu.edu.cn (Y.C.), huangqiyun@pazhoulab.cn (Q.H.), auyqli@scut.edu.cn (Y.L.)
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SUMMARY

In clinical practice, the symptoms of tinnitus patients can be temporarily alleviated by diverting their attention away from disturbing sounds. However, the precise mechanisms through which this alleviation occurs are still not well understood. Here, we aimed to directly evaluate the role of attention in tinnitus alleviation by conducting distraction tasks with multilevel loads and resting-state tests among 52 adults with tinnitus and 52 healthy controls. We demonstrated that the abnormal neural oscillations in tinnitus subjects, reflected in an altered gamma/alpha ratio index in the frontal lobe, could be regulated by attention shifting in a linear manner for which the regulatory effect increased with the load of distraction. Quantitative measures of the regulation significantly correlated with symptom severity. Altogether, our work provides proof-of-concept for the role of attention in tinnitus perception and lays a solid foundation to support evidence-based applications of attention shifting in clinical interventions for tinnitus.

INTRODUCTION

Tinnitus is the perception of sound without an external acoustic source,[1] with a prevalence ranging from 10% to 15%.[2] Not everyone with tinnitus becomes habituated to the sound, and about 1–2% of adults find it to be a major problem that seriously impairs their quality of life.[2] These individuals often experience sleep disorders,[3] lack of concentration,[4] and difficulties with social interaction.[5] To date, the underlying neurological mechanisms of tinnitus are still not fully understood and there are no treatment options available for curing tinnitus.[6] The most common interventions used in clinics, such as cognitive behavioral therapy (CBT),[7,8] tinnitus retraining therapy,[9] sound therapy,[10] and mindfulness-based intervention,[11] are aimed at distracting the individuals' attention from the disturbing sounds (attention shifting) to reduce associated psychological distress.[9,12,13] The alleviation of tinnitus symptoms through attention shifting has been substantiated by subjective patient reports.[14] However, questions remain as to whether and how attention shift can modulate the neurophysiological indices in the brains of tinnitus patients, and particularly how to interpret this phenomenon from the perspective of neuropathological hypotheses of tinnitus.

Although the underlying molecular causes are unclear, tinnitus is believed to be triggered by a hearing loss resulting from dysfunctions or lesions in the ear.[15,16] The deafferentation at certain frequency range deprives auditory input from hair cells to affected neurons in the auditory cortex, which results in a loss of capacity of these neurons to inhibit excitatory input from hair cells located adjacent to the lesion region.[17] This loss of inhibition will lead to a tonotopic map reorganization in the auditory cortex that the affected neurons are tuned to become more responsive to adjacent frequencies rather than the frequency range where hearing loss occurs.[17] This map reorganization process can be accomplished within a very short period and has been proved to be related to the perception of tinnitus.[18,19]

The loss-of-inhibition pathological hypothesis has received support from preclinical studies using anesthetized animal models. For example, it has been shown that after an acoustic trauma, synchronous spiking in spontaneous neural activity, rather than firing rate alone, increases due to a "release of inhibition" in the cat's primary auditory cortex.[20,21] This synchronization in the affected frequency region tends to increase over time.[17] A similar immediate increase in the synchronization of neural firings has also been observed after quinine administration.[22] These findings emphasize the key role of neural synchrony in the pathology of tinnitus.[17,23] To translate preclinical results to humans, Weisz et al. proposed a theoretical model of tinnitus pathology termed the Synchronization-by-Loss-of-Inhibition-Model (SLIM).[23,24] The core hypothesis of the SLIM model is that the underlying neural code of dysfunctional inhibition in

Table 1. Participant demographic data and clinical scores

	Tinnitus	Control	*p*-value
Subjects	52	52	N/A
Age	36.37 ± 11.38	32.48 ± 11.47	0.1245
Sex [male/female]	34/18	40/12	0.1941
Tinnitus handicap inventory [THI]	45.92 ± 21.34	N/A	N/A
Tinnitus laterality [B/L/R]	23/19/10	N/A	N/A
Hearing loss [dB, HL]	32.18 ± 19.86	16.71 ± 2.34	<0.001***
Non-hearing loss (<20 dB)	21	52	N/A
Mild-to-severe (20–65 dB)	31	N/A	N/A
High-frequency hearing loss (25–65 dB)	22	N/A	N/A

Values are shown as means ± SD, where SD denotes the standard deviation. For comparisons of age and hearing loss between groups, nonparametric Wilcoxon-Mann-Whitney tests were employed, while a chi-square test was used for the comparison of the proportion of males and females. B, bilateral; L, left; R, right; dB, decibel; N/A, not applicable. The THI mean value is calculated with the 49 patients, and the other 3 patients did not complete the THI assessment due to the personal privacy issues. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

tinnitus subjects would manifest as alterations in oscillatory synchrony of spontaneous neural activity.[17,23] In subsequent works, Nathan et al. provided marked evidence for a reduced alpha power (8–12 Hz) and enhanced gamma power (50–60 Hz) in resting spontaneous activity, leading to a sharper gamma-alpha slope in the auditory cortex of tinnitus subjects.[25] The reduced alpha power was further interpreted as reduced activation of inhibitory interneurons, which subsequently caused an increase in the firing synchrony of neurons resulting in enhanced gamma power.[23,24,26]

The SLIM model is considered promising because it bridges the gap between preclinical cell-level firings and ensemble neurophysiological synchrony of neuronal assemblies.[23] It is also able to explain several empirical observations and make valuable predictions.[24] For example, the model predicts the subjective perception of tinnitus can be modulated through higher cognitive functions such as emotion and attention.[23] It assumes that this top-down regulation is largely induced via inhibitory mechanisms.[23] This is consistent with neuroimaging findings indicating alterations of spontaneous neural activity in extended brain regions beyond the auditory cortex of tinnitus subjects, such as the prefrontal cortex,[1] parietal cortex,[27] anterior cingulate cortex,[28] hippocampus,[29] and insula.[30] Hence, the exact perception of tinnitus is likely to involve a broader range of brain areas responsible for high-order cognitive functions, which may be a downstream consequence of the loss of inhibition and tonotopic map reorganization in the auditory cortex.[23,24]

Tinnitus percept is reportedly alleviated when individuals perform cognitively demanding tasks that distract their attention from disturbing sounds.[31,32] Despite the effectiveness of attention shifting being repeatedly confirmed in clinical practice,[9,12,13] it is not fully understood whether and how the tinnitus brain physiologically responds to the shifting processes.[14] Following the SLIM model, a reasonable hypothesis for the neural code of tinnitus alleviation through attention shifting is that a potential recovery of inhibition may be induced in brain regions related to tinnitus percept, physiologically reflected as an alpha synchronization and gamma desynchronization.[23,24] However, the current SLIM model, which is primarily grounded in resting spontaneous neural activity,[25] still requires further clarification regarding its applicability to task-related states and the intricacies of its connection with high-order cognitive functions such as attention.[23,24] Therefore, it remains an open question whether ongoing spontaneous oscillations can be regulated by attention shifting in tinnitus subjects. A more effective strategy to address this question would be to set up tasks with varying degrees of attention shifting and observe how concomitant changes occur in neural oscillatory dynamics.

In this study, our primary objective is to directly test the hypotheses that attention shifting can regulate abnormal neural activity, as evidenced by neural oscillatory indicators such as alpha and gamma powers, within the brains of tinnitus patients. We hope that our work can provide supportive evidence for establishing a connection between attention shifting and the pathological mechanisms of tinnitus, thereby extending the applicability of the SLIM model beyond explaining baseline abnormal states to elucidating dynamic changes during clinical interventions. To this end, we designed three attention tasks with different levels of distraction: active listening to tinnitus (no distractions, only for tinnitus participants), an instructed gazing task (mild distraction), and a mental arithmetic task (strong distraction). Eye-open and eye-closed resting states were also implemented to verify the SLIM model and used as baselines for comparisons. EEG power spectral density (PSD) features and PSD ratio were extracted and compared between 52 patients with chronic tinnitus and an equal number of age-matched healthy controls. Demographic information of all participants is provided in Table 1 (see method details). Altogether, we hope our work can help with elucidation of the mechanism of attention shifting in tinnitus regulation and therefore provide a solid foundation to support evidence-based applications of attention shifting in clinical practice and interventions of tinnitus.

RESULTS

Steeper inverse relationship in tinnitus subjects between temporal alpha and gamma power

When examining the eyes-open results for each side separately, the alpha-gamma correlation was significant for tinnitus subjects in both the left ($r = -0.51$, $p < 0.001$***) and right ($r = -0.53$, $p < 0.001$***) temporal regions. However, for control subjects, the results were significant for the right temporal region ($r = -0.31$, $p = 0.031$*) and showed a trend toward significance for the left temporal region ($r = -0.26$, $p = 0.058$). For the average temporal region, it was found that the tinnitus group showed significant results ($r = -0.56$, $p < 0.001$***), while the control group was borderline significant ($r = -0.26$, $p = 0.064$). Furthermore, we compared the steepness of the regression lines (slope of univariate linear fitting) between tinnitus and control subjects to examine differences in the alpha–gamma relationship. We

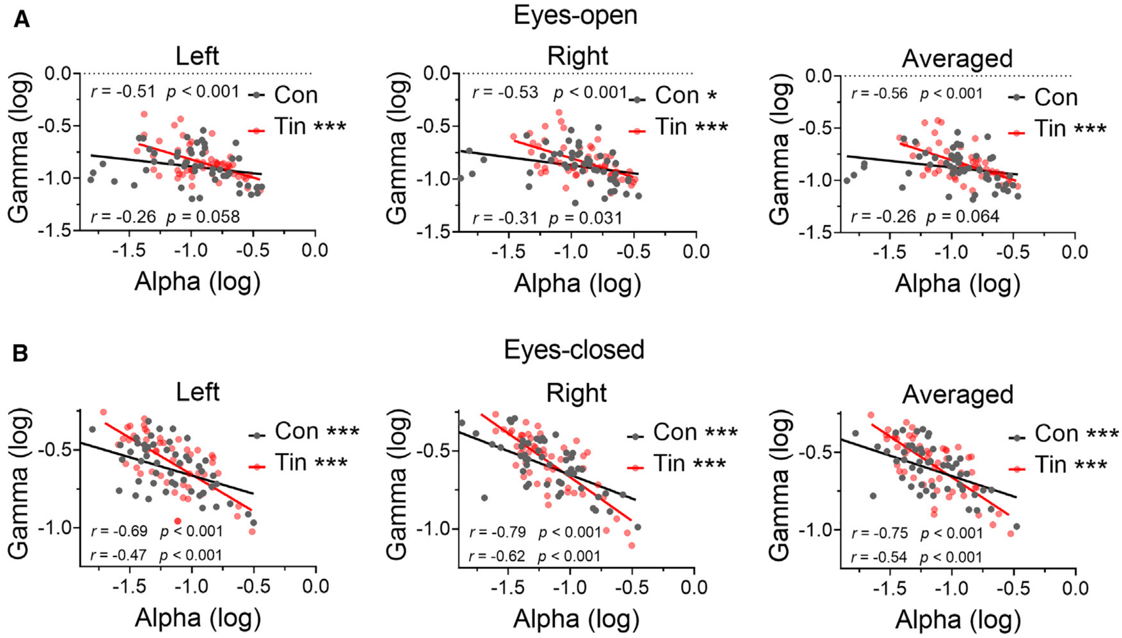

Figure 1. Correlation of temporal gamma and alpha power density in tinnitus vs. control groups

The results have been normalized (as described in the method details), and the logarithmic values are plotted separately for each temporal side and averaged across both sources. For each condition, the gamma-alpha slope was calculated using linear regression. The red slope depicts the linear regression for the tinnitus group, whereas the black slope represents the control group. *r* is the coefficient of slope in linear regression; *p* is statistical significance value. Thus, an asterisk following the tinnitus group or control group signifies statistical significance, while the absence of an asterisk denotes no significance. Lastly, within each condition, the slopes of the tinnitus and control groups were also directly compared using the *F*-test. (A) Under eyes-open condition. (B) Under eyes-closed condition. Left: left temporal region; Right: right temporal regions; Averaged: averaged across both temporal regions. Con: controls ($n = 52$); Tin: tinnitus ($n = 52$). *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

confirmed a significantly steeper slope in tinnitus subjects compared to controls for results averaged across both temporal sources ($F(1,100) = 5.57$, $p = 0.021$*) and for the left temporal region separately ($F(1,100) = 3.96$, $p = 0.040$*). For the right temporal region alone, the significance was at edge ($F(1,100) = 3.81$, $p = 0.054$). This abnormal inverse relationship between gamma and alpha, reflected in the slope, is consistent with previous reports and thus verifies the effectiveness of the SLIM model for tinnitus[25](Figure 1A).

Similar results were observed under the eyes-closed condition as well (Figure 1B). A strong negative alpha-gamma correlation was confirmed for both tinnitus subjects (averaged: $r = -0.75$, $p < 0.001$***; left temporal region: $r = -0.69$, $p < 0.001$***; right temporal region: $r = -0.79$, $p < 0.001$***) and controls (averaged: $r = -0.54$, $p < 0.001$***; left temporal region: $r = -0.47$, $p < 0.001$***; right temporal region: $r = -0.62$, $p < 0.001$***). The slopes of tinnitus subjects exhibited significantly steeper gradients than those of the controls (averaged: $F(1,100) = 8.75$, $p = 0.004$**; left temporal region: $F(1,100) = 6.45$, $p = 0.013$*; right temporal region: $F(1,100) = 9.56$, $p = 0.003$**). The slope during the eyes-closed state seems to be more pronounced than the one during the eyes-open state. However, this requires further confirmation. Nevertheless, our focus was on the abnormal inverse gamma-alpha relationship in tinnitus subjects, which was consistent between the eyes-open and eyes-closed states.

The gamma/alpha ratio of tinnitus subjects was significantly elevated in the frontal region at rest and in the temporal parietal region during attention shifting

To investigate across a wider frequency range, PSDs and PSD ratios for the five frequency bands were calculated and globally averaged across the 30 recording channels (see the method details). The results were then compared between tinnitus subjects and controls under four different states: the eyes-open resting state, the eyes-closed resting state, instructed gazing, and mental arithmetic. No group differences were observed in any PSD or PSD ratio features during the eyes-open or eyes-closed resting states at the global level (Figures 2A and 2B). In contrast, a significant group difference was observed in the globally averaged gamma band PSD and the gamma/alpha ratio when performing attention-shifting tasks (Figures 2C and 2D). Specifically, the gamma/alpha ratio was significantly higher in tinnitus participants compared to controls during instructed gazing ($t(102) = 2.97$, $p = 0.030$*) and mental arithmetic ($t(102) = 2.72$, $p = 0.047$*). The gamma band PSD of the tinnitus subjects was also significantly higher than that of the control group during instructed gazing ($t(102) = 2.65$, $p = 0.041$*) and was at edge when doing mental arithmetic ($t(102) = 2.17$, $p = 0.093$). No group differences were observed in other PSD or PSD ratio features. The SLIM model proposes a strong theoretical hypothesis of an abnormal inverse relationship between gamma and alpha brain activity in tinnitus compared to normal individuals.[23] This

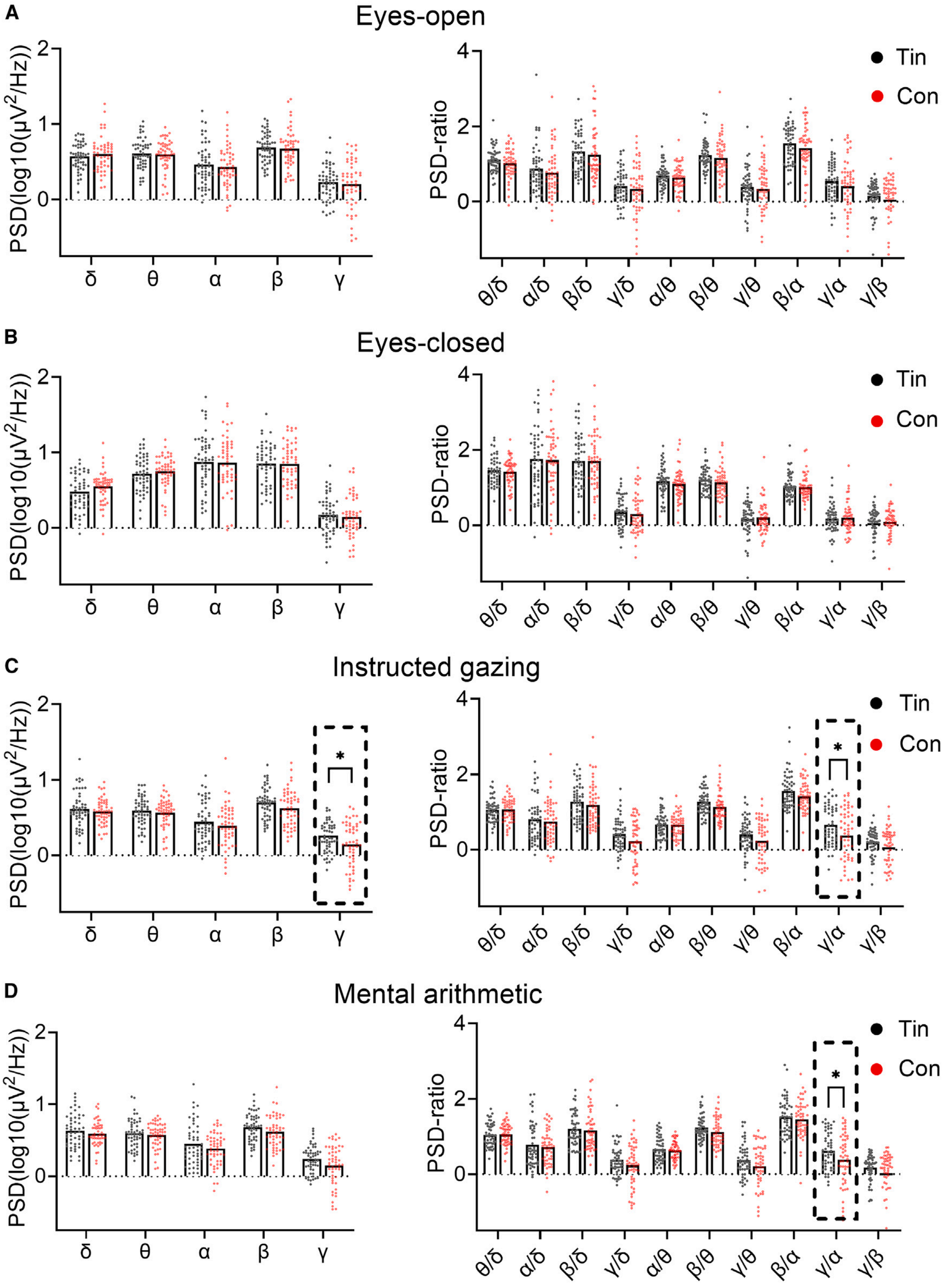

Figure 2. Group comparisons analyzed global PSDs and ratios across five bands

Results are presented separately for comparisons conducted under the following conditions: (A) eyes-open resting state; (B) eyes-closed resting state; (C) instructed gazing; (D) mental arithmetic. Tinnitus subjects exhibited higher global gamma PSD and gamma/alpha ratio than controls during attention shifting tasks, but not during resting states. Con: controls (n = 52); Tin: tinnitus (n = 52). The inter-group comparisons were conducted using two-tailed independent-sample t test; *: $p < 0.05$. The bar graph displays the mean values.

Table 2. Designate the regions of interest (ROIs)

Brain regions	Channels
Frontal	Fp1/Fp2/F7/F3/FZ/F4/F8
Left temporal	FT7/T3/TP7/T5
Right temporal	FT8/T4/TP8/T6
Temporal parietal	FC3/FCZ/FC4/C3/CZ/C4/ CP3/CPZ/CP4/P3/PZ/P4
Occipital	O1/OZ/O2

hypothesis is supported by existing literature and further confirmed by this study.[25] Thus, it is reasonable to propose that the gamma/alpha ratio, as an enhanced measurement indicator, may be more effective in capturing neural oscillatory abnormalities in tinnitus subjects.

Therefore, we further compared the gamma/alpha ratio between the tinnitus subjects and the control group in five functional brain regions: the frontal lobe, temporal parietal lobe, left temporal lobe, right temporal lobe, and occipital lobe (please see the Table 2 in method details). At rest, with eyes open, the gamma/alpha ratio was significantly elevated in the frontal lobe of tinnitus subjects ($t(102) = 2.1$, $p = 0.035$*, Figure 3A), whereas it was comparable to that of controls in other regions and when the eyes were closed (Figure 3B). In contrast, during the instructed gazing or mental arithmetic tasks, the observed difference in the frontal lobe was not statistically significant (IG: $t(102) = 1.45$, $p = 0.152$, Figure 3C; MA: $t(102) = 0.62$, $p = 0.534$, Figure 3D). Instead, a consistent group difference was found in the temporal parietal lobe for both attention tasks (IG: $t(102) = 2.28$, $p = 0.022$*, Figure 3C; MA: $t(102) = 2.09$, $p = 0.031$*, Figure 3D).

To clarify the potential impact of hearing loss on the observed differences in neural oscillation indices, we employed a multiple regression model to assess the potential contributions of these variables (see the method details). The results of our model indicated that hearing loss did not significantly affect the gamma/alpha ratio index of the frontal lobe during the eyes-open state ($t(102) = 0.94$, $p = 0.352$). After controlling for the covariate of hearing loss, the significant group effect revealed that the difference observed in the frontal region between the tinnitus and control groups was primarily attributed to the presence of tinnitus itself ($t(102) = 2.96$, $p = 0.004$**). Furthermore, the level of hearing loss did not significantly impact the measured indicators in the attention task, which mainly reflected in the parietal regions (IG: $t(102) = 1.75$, $p = 0.083$; MA: $t(102) = 1.35$, $p = 0.181$). After controlling for the covariate of hearing loss, the model indicates that the main driver of intergroup differences was whether the subjects had tinnitus (IG: $t(102) = 2.79$, $p = 0.004$**; MA: $t(102) = 3.02$, $p = 0.003$**). These results indicate that the observed abnormal neural oscillation indicators are primarily attributed to the presence of tinnitus and are not affected by confounding variables such as hearing loss.

Shifting attention linearly decreased gamma/alpha ratio in the frontal lobe of tinnitus subjects

To investigate whether and how the potential abnormal oscillation (gamma/alpha ratio) in tinnitus brains is modulated by tasks that involve varying degrees of distraction due to shifting attention, tinnitus subjects performed an additional task to actively listen to their tinnitus sound, simulating the daily scenario where the subjects' attention is confined to the distressing sound (see the method details). Prior research has indicated that numerous tinnitus patients find it challenging to attain the typical "resting state4" due to their involuntary focus on the sound of their tinnitus while at rest.[33] Consequently, the tinnitus state can be ordered in ascending order of distraction load: active listening < eyes-open resting state < instructed gazing < mental arithmetic.

Here, we conducted a one-way ANOVA on three attention states in the five regions respectively, to investigate the gamma/alpha ratio changes in tinnitus attention regulation caused by different attention states. Then, the three attention tasks in these brain regions were subsequently compared with the non-typical "resting state" (eyes-open resting state) respectively as well. As shown in Figure 4, the difference in the gamma/alpha ratio between different states of tinnitus in the brain was predominantly observed in the frontal regions (frontal lobe: ($F(2,153) = 9.15$, $p < 0.001$***; left temporal lobe: $F(2, 153) = 3.21$, $p = 0.06$; right temporal lobe: $F(2, 153) = 0.97$, $p = 0.379$; temporal parietal lobe: $F(2, 153) = 0.51$, $p = 0.549$; occipital lobe: $F(2, 153) = 0.06$, $p = 0.891$). Interestingly, when comparing the non-typical "resting state" with the other three attention tasks, we found that in the frontal region (Figure 4B), there was no difference in the results between the eyes-open resting state and active listening (EO vs. AL: $t(51) = 0.50$, $p = 0.617$), or between the eyes-open resting state and instructed gazing (EO vs. IG: $t(51) = 0.12$, $p = 0.906$). This suggests that tinnitus patients are troubled by tinnitus sounds even during rest or mild distraction. By contrast, the abnormally elevated neural oscillations in frontal region during the eyes-open resting state can be regulated during the performing of high load tasks (EO vs. MA: $t(51) = 2.68$, $p = 0.01$**). However, all three attention tasks induced a significantly larger gamma/alpha ratio compared to the eyes-open resting state in the temporal parietal region (EO vs. AL: $t(51) = 4.04$, $p < 0.001$***; EO vs. IG: $t(51) = 3.42$, $p = 0.001$***; EO vs. MA: $t(51) = 2.34$, $p = 0.023$*, Figure 4D). These temporal parietal changes seem to be linked solely to changes in attention focus, not to the type or load of attention involved. No task differences or shifting effect were observed in other brain regions of subjects with tinnitus (Figures 4C, 4D, and 4F). Therefore, the regulatory effect on tinnitus perception is primarily reflected in the brain's frontal lobe.

For comparison, we evaluated the regulatory effect of attention tasks (i.e., instructed gazing and mental arithmetic) on the baseline resting state (i.e., eyes-open condition) in the control group with respect to the gamma/alpha ratio using the one-way ANOVA method. Indeed, none of the attention task were observed to exert a regulatory effect in any brain region, including the frontal region (EO vs. IG: $t(51) = 0.75$, $p = 0.454$; EO vs. MA: $t(51) = 0.30$, $p = 0.766$, Figure 5B) and the temporo-parietal region (EO vs. IG: $t(51) = 0.04$, $p = 0.787$; EO vs. MA: $t(51) = 0.27$, $p = 0.968$, Figure 5E).

Individual attention shifting regulations correlated with clinical severity

Next, to ensure consistency when comparing states, we established active listening to tinnitus as the baseline, simulating the

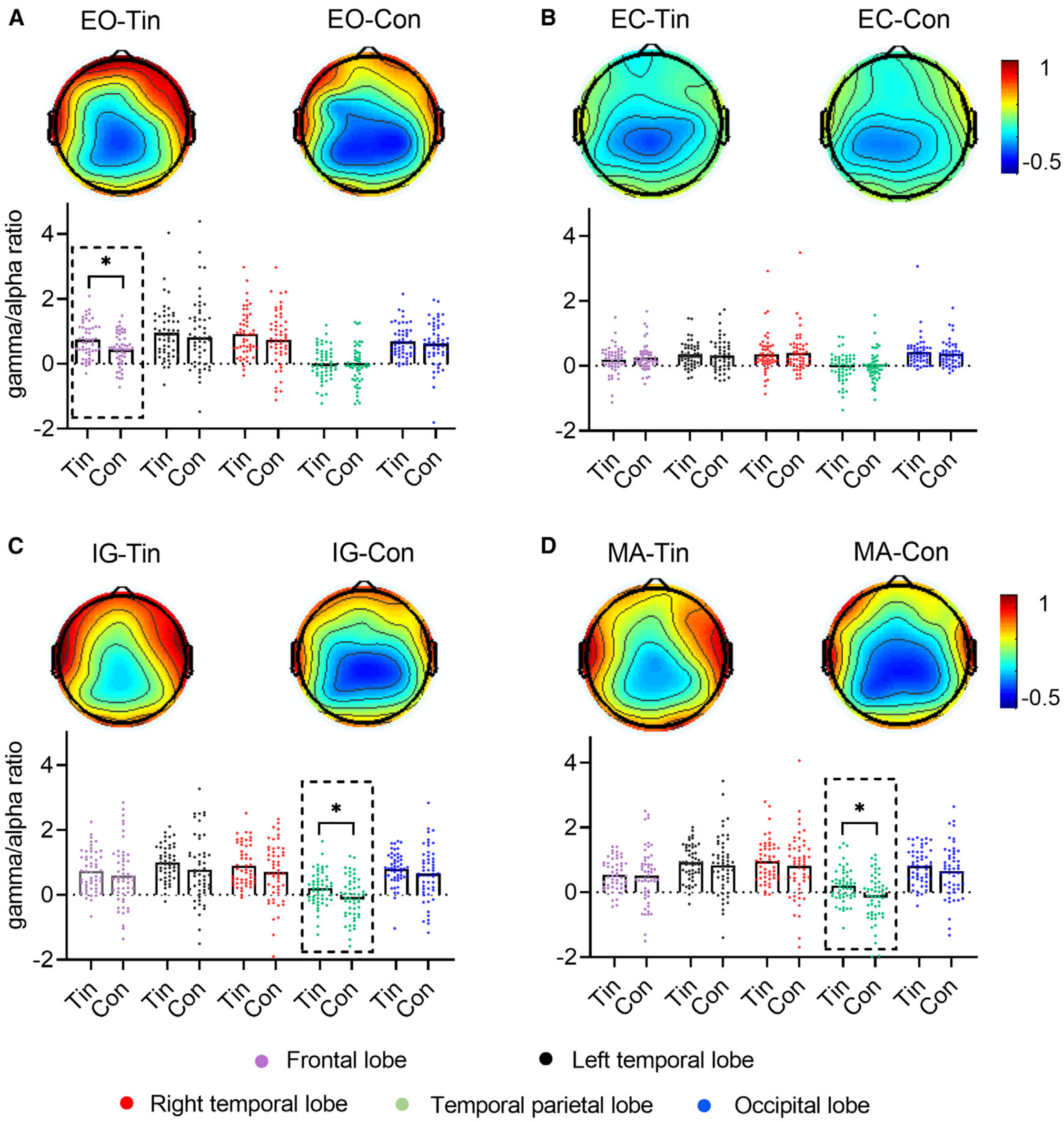

Figure 3. Region-specific group comparisons of the gamma/alpha ratio

Topographies and scatterplots are presented for the gamma/alpha ratios collected under: (A) eyes-open resting state; (B) eyes-closed resting state; (C) instructed gazing; (D) mental arithmetic. Comparisons between tinnitus subjects and controls were conducted separately for the five functional regions, i.e., frontal lobe (purple), left temporal lobe (red), right temporal lobe (black), temporal parietal lobe (green) and occipital lobe (blue). Con, controls (n = 52); Tin, tinnitus subjects (n = 52); EO, eyes-open; EC, eyes-closed; IG, instructed gazing; MA, mental arithmetic. These inter-group comparisons were conducted using two-tailed independent-sample t test, and the results were corrected for multiple comparisons using Benjamini-Hochberg method. *: $p < 0.05$. The bar graph displays the mean values. The scale bar displays the range of the gamma/alpha ratio from −0.5 to 1.

scenario where tinnitus patients are bothered by the annoying sound at rest. Thus, we moved beyond group-level statistics to examine the consistency of attention shifting regulation within the frontal lobe of tinnitus subjects at an individual level. To achieve this, we trained an SVM model for each subject to classify between pairs of tasks of interest, such as active listening/instructed gazing (AL/IG) and active listening/mental arithmetic (AL/MA; see the method details). The classification accuracy served as a channel-level measure of the regulatory effect, which was induced by shifting attention away from tinnitus sounds. Results showed that the mean classification accuracy of AL/MA (73.1 ± 13.1%) was significantly higher than that of AL/IG (68.1 ± 15.7%) ($t(51) = 2.26$, $p = 0.014$*; Figures 6A and 6B). Notably, the mean accuracy of the latter (AL/IG) was also significantly higher than the chance level ($p = 0.039$*, permutation testing for 5000 times). We also drew spaghetti plots to clearly demonstrate the individual-level variations in the frontal gamma/alpha ratio under different task

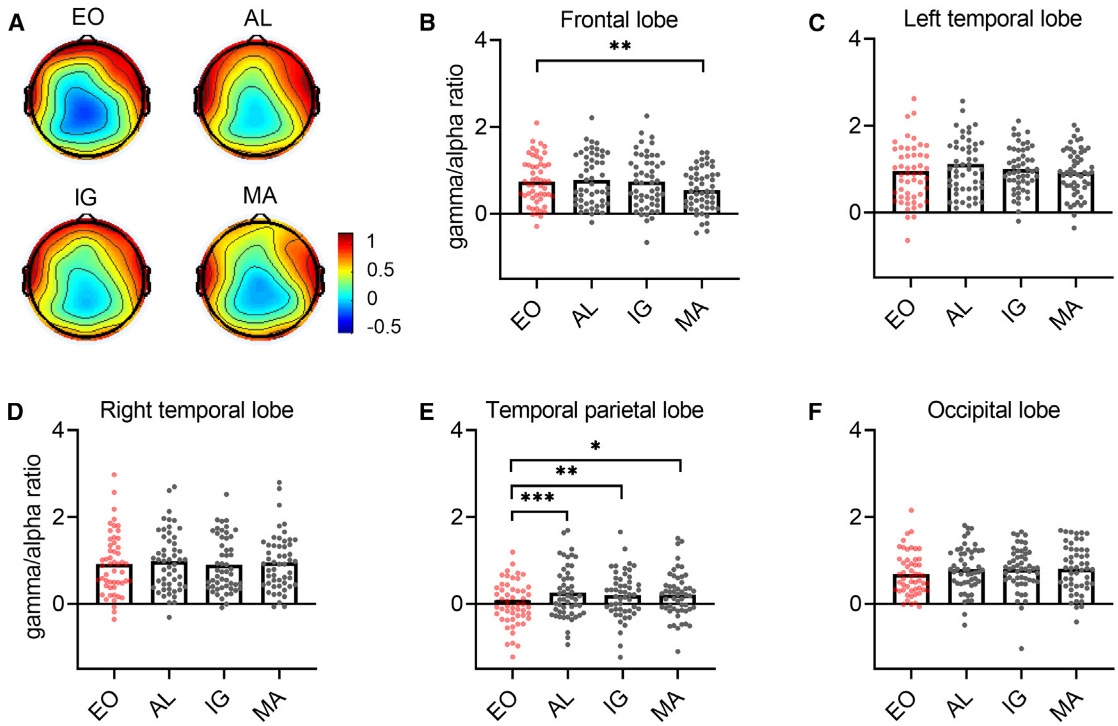

Figure 4. Region-specific regulations induced by attention shifting in tinnitus subjects

(A–F) We conducted a one-way ANOVA on the three attention states in each of the five regions to investigate the changes in the gamma/alpha ratio during tinnitus attention regulation that are attributed to different attention states. Subsequently, a two-tailed paired-sample *t* test was used to compare each of the three attention tasks in these brain regions with the non-typical "resting state" (eyes-open resting state) as well. (A) The topographies of the gamma/alpha ratio in tinnitus subjects ($n = 52$) are presented for the eyes-open resting state, active listening, instructed gazing, and mental arithmetic, respectively. The scale bar displays the range of the gamma/alpha ratio from −0.5 to 1, and scatterplots represent the individual values of the gamma/alpha ratio in: (B) the frontal lobe; (C) the left temporal lobe; (D) the right temporal lobe; (E) the temporal parietal lobe; (F) the occipital lobe. Red dots indicate the values of the eyes-open resting state, black dots indicate the values of the three shifting tasks. EO, eyes-open; AL, active listening; IG, instructed gazing; MA, mental arithmetic. The results were FDR corrected using Benjamini-Hochberg method; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. The bar graph displays the mean values.

conditions (Figures 6C and 6D). Taking the active listening value as a reference, the gamma/alpha ratio decreased in 56% of tinnitus subjects during instructed gazing and in 73% during mental arithmetic. Altogether, our results confirm that the shifting effect on the gamma/alpha ratio was consistent across the majority of tinnitus subjects, and importantly, the strength of this shifting increased with the rise in the distraction load.

We defined a shifting index as the difference between the AL and IG/MA values. We then conducted a correlation analysis to test whether the shift in the gamma/alpha ratio correlated with the clinical severity of tinnitus subjects, measured by clinical scales such as the THI. A strong negative correlation was observed between THI scores and the AL-MA shifting index ($r = -0.39$, $p = 0.007$**; Figure 6F). This indicates that attention shifting is more effective for those with mild symptoms. In other words, it is more difficult for patients with severe symptoms to reverse this indicator. No significant correlation was found between THI scores and the AL-IG shifting index ($r = -0.01$, $p = 0.956$; Figure 6E), potentially due to the weaker shifting effect during the instructed gazing task (low load distraction). Please refer to Figure 7 in method details for further information about the experimental paradigm.

These results indicated that tinnitus severity and cognitive status (which is associated with the load level of attention tasks) may have varying impacts on the shifting effect during the performance of attention-demanding cognitive tasks. In fact, hearing loss, especially high-frequency hearing loss, is closely related to cognitive function and is believed to potentially impact cognitive ability in the context of tinnitus. To clarify the impact of these factors on the shifting effect and their potential interaction, we conducted a 3× 2×2 ANOVA analysis (for details, please see the method details). The results indicated that hearing loss did not exert a significant influence on attention regulation of oscillatory indices ($F(1,86) = 1.44$, $p = 0.233$). The interaction between hearing loss and the levels of tinnitus severity ($F(2,86) = 0.36$, $p = 0.699$), as well as cognitive status ($F(1,86) = 0.13$, $p = 0.909$), also exhibited no notable disparities, suggesting that hearing loss did not affect attention regulation. In contrast, a significant interaction was observed between tinnitus severity and cognitive status factors ($F(2,86) = 3.64$, $p = 0.03$*). Thus, we directly compared the shifting effects between the two cognitive statuses within each of the three severity subgroups using paired-sample *t* tests (two-tailed). The further analyses showed that patients with mild tinnitus ($n = 16$) exhibited a more significant difference between AL-IG state and AL-MA state in shifting their attention away

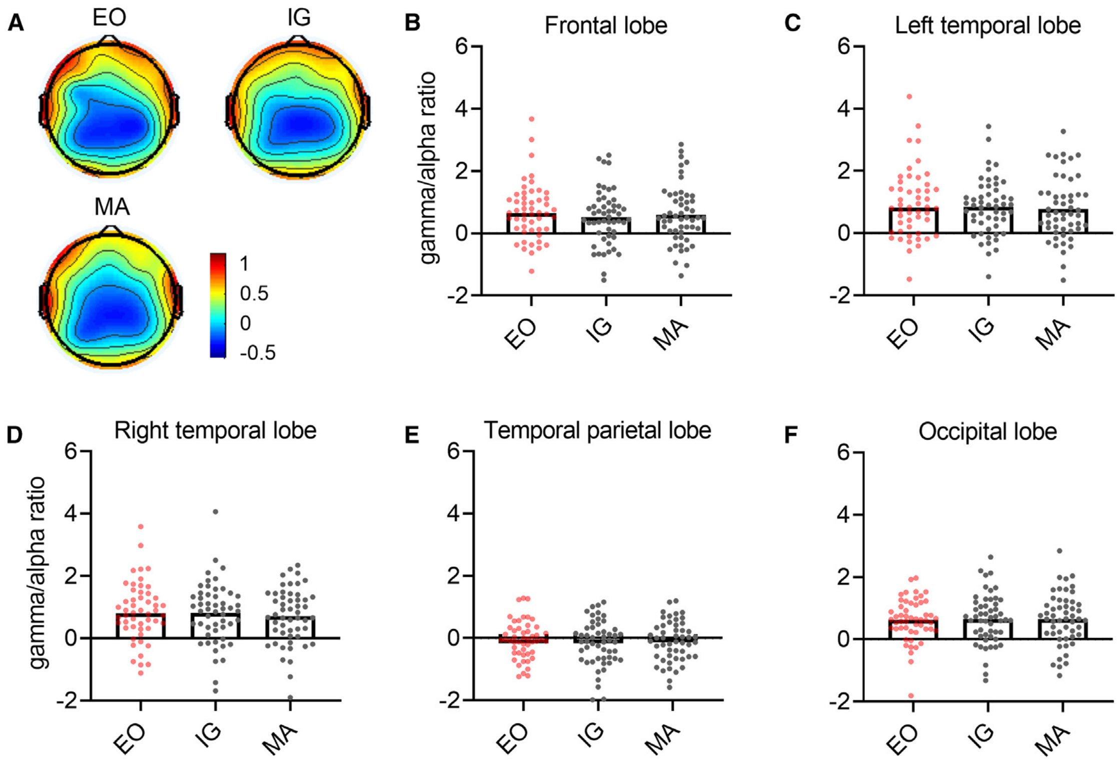

Figure 5. Region-specific regulations induced by attention shifting in control group

(A–F) A one-way ANOVA method was used to evaluate the regulatory effect of attention tasks (i.e., instructed gazing and mental arithmetic) on the gamma/alpha ratio in the control group (n = 52), compared to the baseline resting state (i.e., eyes-open condition). (A) The topographies of the gamma/alpha ratio in control group subjects are presented for the eyes-open resting state, instructed gazing, and mental arithmetic, respectively. The scale bar displays the range of the gamma/alpha ratio from −0.5 to 1, and scatterplots represent the individual values of the gamma/alpha ratio in: (B) the frontal lobe; (C) the left temporal lobe; (D) the right temporal lobe; (E) the temporal parietal lobe; (F) the occipital lobe. Red dots indicate the values of the eyes-open resting state, black dots indicate the values of the two shifting tasks. For comparison with the tinnitus group, in both the frontal region and the temporal parietal region, we compared the baseline (i.e., eyes-open condition) with the two attention tasks in the control group with respect to the gamma/alpha ratio using two-tailed paired-sample t tests, respectively. The results were FDR corrected using Benjamini-Hochberg method. EO, eyes-open; IG, instructed gazing; MA, mental arithmetic. The bar graph displays the mean values.

from tinnitus ($t(15) = 3.23$, $p = 0.0017$**), while those with moderate tinnitus (n = 20) were at edge ($t(19) = 1.91$, $p = 0.059$) and there was no difference in those with severe tinnitus ($t(12) = 0.31$, $p = 0.758$, n = 13). Therefore, compared with severe tinnitus, individuals with mild tinnitus are more likely to regulate the abnormal oscillatory indices of tinnitus by engaging in attention-demanding tasks at a certain level of cognitive load.

DISCUSSION

Tinnitus is a common but pathologically complex symptom,[15] and there is currently no cure for hearing these annoying sounds.[6] In clinical practice, patients can alleviate the symptoms and negative effects by shifting their attention away from the disturbing sounds,[7] ultimately habituating to tinnitus.[34] While the efficacy of attention shifting in tinnitus management is widely acknowledged, the underlying neural mechanisms remain poorly understood.[14,34] Pathological models such as the SLIM imply that tinnitus is more related to a loss of inhibitory function not only in the auditory cortex but also in a broad range of brain regions extending far beyond the location of the auditory lesion.[23,24] However, *in vivo* evidence from patients with tinnitus is lacking. It is therefore of great importance and interest to investigate whether the effectiveness of attention shifting in tinnitus alleviation can be explained under the framework of tinnitus pathological models, such as the SLIM.

The gamma/alpha ratio may serve as a biomarker for tinnitus-related abnormal oscillations

To this end, we first validated the SLIM model by replicating previous findings of a steeper gamma-alpha slope in the auditory regions of tinnitus subjects compared to controls at rest. According to the original SLIM model,[23] the decrease in cortical lateral inhibition leads to alterations in spontaneous synchrony of neuronal assemblies, which is primarily reflected in physiological changes in neural oscillations. A critical assumption of this model is that the normal synchronizing activity regulated by inhibitory interneurons occurs in the alpha range, while the synchronized firing of pyramidal neurons will be reflected as oscillations in the gamma band. Thus, a loss-of-inhibition to external auditory input in tinnitus subjects might cause simultaneously a decrease in the alpha and an increase in the gamma power,

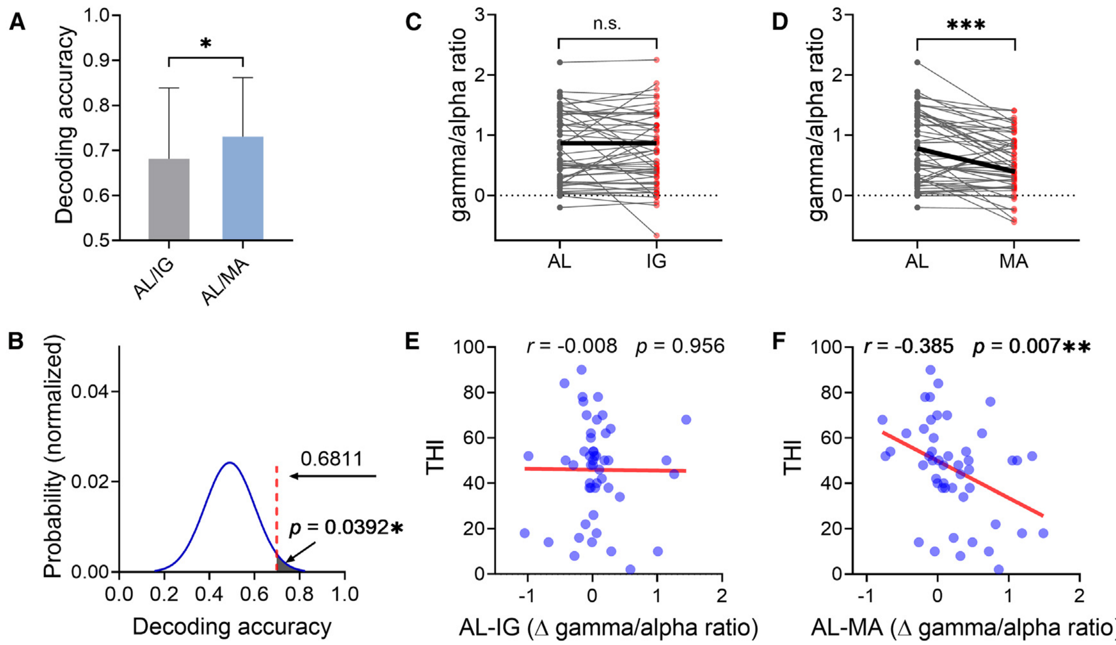

Figure 6. Individual measures of attention shifting regulation and their correlation with clinical severity

(A) The comparison of SVM decoding accuracy between active listening and instructed gazing, as well as between active listening and mental arithmetic tasks, was conducted using paired-sample *t* tests ($n = 52$, one-tailed test). Data are represented as mean ± SD; (B) Random accuracies for active listening and instructed gazing were obtained via permutation testing, where labels of samples were randomly permuted 5000 times; (C) Spaghetti plots illustrate individual shifts in the frontal gamma/alpha ratio between active listening and instructed gazing; (D) Spaghetti plots represent individual shifts in the frontal gamma/alpha ratio between active listening and mental arithmetic; (E and F) Present the correlations between THI scores and the shifting index of AL-IG and AL-MA, respectively ($N = 49$); *t* is Pearson' linear correlation coefficient; *p* is statistical significance value. A paired-sample *t* test was used for the comparison of the gamma/alpha ratio between active listening and instructed gazing in the frontal region, as well as between active listening and mental arithmetic in the same region ($n = 52$, two-tailed test). n.s., not significant; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

ultimately leading to the observed steeper gamma-alpha slope.[25] This theoretical model is in line with the inhibition gating theory, which suggests that information can be rerouted by functionally blocking the task-irrelevant pathways.[35] Specifically, the alpha synchronization of interneurons originally produces a gating effect in a phase-blocking manner, inhibiting gamma responses to inputs from lesion-adjacent regions. Desynchronization of alpha may increase the time window of processing (duty cycle) for gamma activity, leading to an increase in gamma power.[35,36] Therefore, the inverse gamma-alpha relationship is believed to reflect the intrinsic characteristics of abnormal neural activity in tinnitus.[24,26] However, as pointed out by the original authors of SLIM,[25] it was limited to the resting state, and there was a strong overlap between tinnitus subjects and healthy controls in stand-alone alpha and gamma power, which also was confirmed by our results. This overlap hampered further pathological interpretations and clinical practice. In this study, we utilized the gamma/alpha ratio as a single index to quantify and enhance the inverse gamma-alpha relationship. Our results confirm that, only in the resting state, an abnormal elevation of the gamma/alpha ratio was observed in the frontal lobe of tinnitus subjects, and this elevation ceased to be significant between groups during attentional task execution. When performing tasks related to attention, an increase in the gamma/alpha ratio was also observed in the temporal-parietal lobe, which did not show inter-group differences in the resting state and seemed to be related only to attentional task execution. This indicates that the altered gamma-alpha relationship and the underlying loss of inhibition were not restricted to the temporal region. Instead, a broader range of brain regions, such as the frontal and parietal regions, were affected. The gamma/alpha ratio might be a more sensitive biomarker of altered oscillatory behaviors in tinnitus subjects. These results have enriched the understanding of the original SLIM model and greatly expanded its applicability in pathological interpretations of tinnitus.

A potential explanation for the attention shifting effect based on pathological models of tinnitus

Another essential contribution of our work is that we demonstrated that the altered neural oscillations in tinnitus subjects can be regulated by top-down mechanisms through attention shifting. Specifically, the abnormally heightened oscillations, indexed by the gamma/alpha ratio in the frontal region, were reduced in a linear manner as the distraction load increased. The regulatory effect was confirmed by both statistical tests at group level and a machine learning model at individual level. In contrast, this regulatory effect was absent in controls. It is not surprising that the frontal cortex may be involved in the regulatory mechanism of attention shifting in tinnitus. The frontal cortex has been widely acknowledged to have a close relationship with sensory processing,[1] emotional experience,[37] attention networks, and conscious generation,[38,39] thereby serving as a

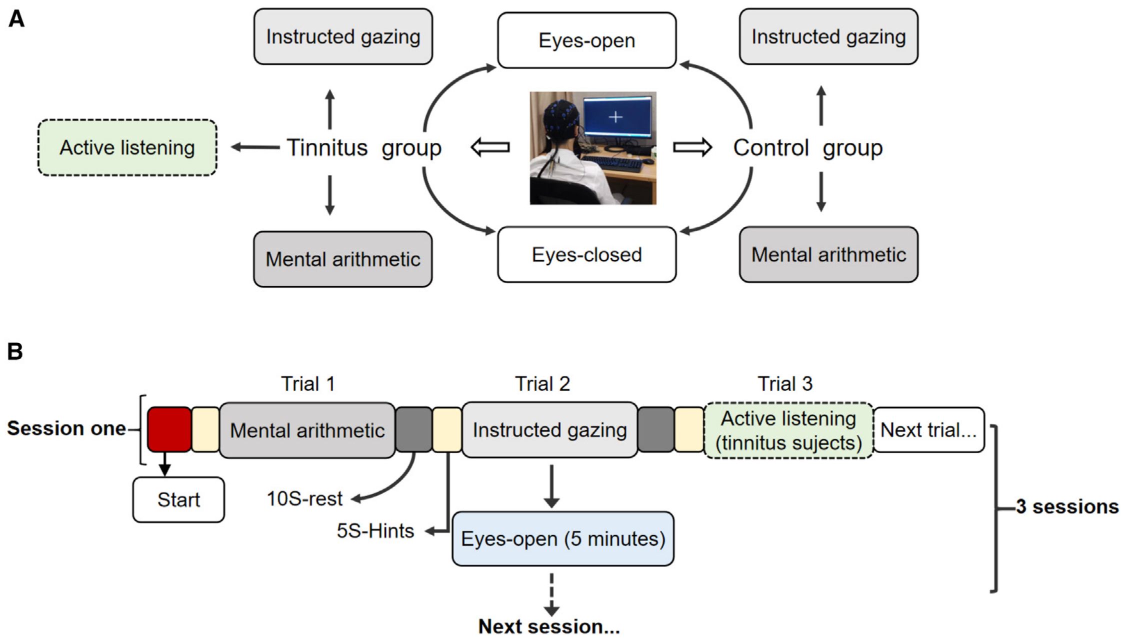

Figure 7. Experimental paradigm and procedure

(A) Both the tinnitus group and control group performed eyes-open and eyes-closed resting state, and the instructed gazing and mental arithmetic task. The tinnitus group completed an additional task by actively listening to their tinnitus sound.

(B) The flowchart of a single session in the experimental procedure. In a session, participants completed five trials under each attention task in a random order. The 5-min eyes-open and eyes-closed resting states were performed in between sessions.

"common endpoint" for diverse incoming information.[40,41] On the one hand, according to the theory of the Global Neuronal Workspace,[42] consciously perceiving of sensory stimuli requires integration of local activities (mainly reflected as gamma oscillations),[43,44] which involves the prefrontal cortex and a broader network linked by long-range functional connections.[45] This global functional integration is realized through slow waves as the carrier, involving mediated attention (alpha waves) and consciousness perception (theta waves).[45] Therefore, the perception of tinnitus is likely to be related to the interaction between alpha and gamma waves in the prefrontal cortex. On the other hand, in everyday life we are confronted with the need to switch attention to external stimuli on a short timescale (transient modulations),[26] which requires dynamically allocating attention resources to specific targets in our environment while other non-relevant aspects are ignored.[46,47] This inhibition process of non-target stimuli, and therefore focusing attention on the target, have been reported to involve alpha oscillations as a filter mechanism.[48–50]

According to the inhibition-timing theory, alpha desynchronization generally facilitates the long-distance synchronization of gamma oscillations, whereas alpha synchronization inhibits gamma propagation.[26] Under the original SLIM model framework, an increase in alpha power at either of the two cortical sites is considered sufficient for disrupting long-range gamma synchronization.[24] Therefore, we infer that an elevation in alpha power in either frontal or temporal regions may interfere with long-range gamma synchronization, potentially resulting in a diminished capacity for sound perception. For tinnitus, under the SLIM framework, the observed increase in alpha power during cognitive tasks may indicate a temporary restoration of inhibitory ability.[23,25] This in turn leads to a reduction in the power of gamma oscillations in frontal and/or temporal regions.[23] It is therefore a reasonable hypothesis that attention-related mechanisms are deeply involved or intertwined with the mechanism of tinnitus perception, and consequently, focusing attention on tinnitus either passively or actively is an indispensable part of tinnitus perception. This hypothesis is supported well by evidence from both subjective reports and objective physiological findings. For example, many tinnitus sufferers report that their attention can be involuntarily drawn to or disturbed by the ringing in their ears.[14] A recent study demonstrated that there was no difference between the EEG features at rest and when actively listening to the tinnitus, indicating an 'invariant' brain in tinnitus subjects.[33] This was also confirmed by our results that showed no significant difference between active listening and the eyes-open state (Figure 4B).

Therefore, a possible explanation for the observed regulations induced by attention shifting on the oscillatory dynamics is that the shifting resolved the entanglement between attention and tinnitus sound, possibly reversed dysfunctional inhibition in the frontal region and eventually led to an alleviation of tinnitus perception. Our findings support the idea that tinnitus can be voluntarily regulated through top-down mechanisms. This is precisely consistent with the SLIM prediction that the inverse relationship between gamma and alpha oscillations is influenced by high-level cognitive functions, such as attention and emotion.[23,24]

It is also worth noting that tinnitus is a hallucinatory auditory sensation that occurs spontaneously in the brain without external stimuli.[1] The attention shifting we focus on also does not require external stimuli and is an autonomous adjustment of the brain's spontaneous activity. Consequently, attention shifting may target similar neural mechanisms to tinnitus perception, which is why it can alleviate tinnitus.

Clinical implications

According to our results, there are at least two key factors that affect the effect of attention shifting of tinnitus in our study: cognitive status (the load level of attention tasks) and the severity of tinnitus. The high-load shifting task (mental arithmetic) demonstrated greater efficacy than the low-load task (instructed gazing) in regulating tinnitus-related oscillatory indices, particularly among patients with mild symptoms. Conversely, patients with more severe symptoms encountered greater challenges in regulating their brain activity through attention shifting tasks. Moreover, our results indicate that hearing loss did not substantially impact the observed effects on attention regulation. These insights could have valuable implications for clinical interventions.

On the one hand, they suggest that engaging in simple or low-demand attention tasks may not be adequate for minimizing or potentially eliminating tinnitus interference. Instead, high-demand attention shifting tasks might be more effective at modulating abnormal oscillations, thereby aiding tinnitus patients in ignoring bothersome sounds. This observation aligns with the load theory, which posits that tasks with higher cognitive loads occupy more attention resources, facilitating task-relevant processing, while tasks with lower cognitive loads require fewer attention resources and leave spare capacity for the perception of task-irrelevant distractions.[51–53] On the other hand, our results imply that severe tinnitus makes it harder to regulate the perception of tinnitus through attention-demanding tasks compared to mild tinnitus. A potential explanation is that the cognitive reserve, a crucial mechanism underlying the brain's capacity in determining the smooth execution of cognitive tasks despite cognitive impairments,[54] is the driver of the response to attention shift paradigm. Individuals with severe tinnitus may have a reduction of cognitive reserve insufficient to allow the working memory to perform the arithmetical calculations able to shift attention.[55] Indeed, individuals with severe tinnitus often grapple with varying degrees of psychological disorders and cognitive decline[56] Their struggles with cognitive tasks likely reflect a certain degree of cognitive impairment, particularly in attention-related areas, which concurs with the notion that tinnitus impairs cognitive function primarily by disrupting executive control of attention.[57] Consequently, patients with severe tinnitus may not benefit well from conventional interventions based on attention shifting, and addressing severe types of tinnitus may pose greater challenges. Potential solutions include integrating more sophisticated and advanced methods, such as brain-computer interfaces based on neurofeedback,[58] to enhance the process of attention shifting. Another potential clinical inspiration is that patients with tinnitus should undergo cognitive screening using tools such as the Montreal Cognitive Assessment (MoCA)[55] before any cognitive interventions are implemented, thereby ensuring that they receive appropriate treatment.

In this study, we investigated the neural oscillatory dynamics associated with attention regulation in tinnitus patients by performing multilevel attention load tasks. We first replicated previous SLIM findings showing an inverse relationship between gamma and alpha activity in the auditory regions of tinnitus subjects. We also validated the SLIM's essential prediction that these abnormal oscillations would be regulated by high-level cognitive mechanisms such as attention. We confirmed an elevated gamma/alpha ratio in tinnitus subjects in a broader range of brain regions, especially in the frontal lobe. Importantly, we showed that altered oscillatory index for tinnitus could be regulated by attention shifting in a linear manner, for which the regulation effect increased with the degree of distraction. Quantifiable indicators of the regulation induced by attention shifting exhibited a strong correlation with clinical severity assessed using the THI score, implying that patients with more severe symptoms require higher load of attention regulations. In summary, our findings provide *in vivo* evidence that consolidate and expand the current pathological model of tinnitus which involves a loss-of-inhibition mechanism. We demonstrate that dynamic changes in neural oscillatory behaviors, reflected by the frontal gamma/alpha ratio index, are the underlying neural code of attention shifting in tinnitus alleviation. This, we hope, will have a knock-on effect on the elucidation of the role of attention in tinnitus perception, thus laying a solid foundation for supporting evidence-based applications of attention shifting in clinical practice and tinnitus interventions.

Limitations of the study

The experimental design lacks clinical-scale evaluation of tinnitus perception before and after those attention tasks. However, in our view, achieving a long-term and effective modulation of the tinnitus severity symptoms may require a prolonged and comprehensive intervention instead of merely shifting attention away from the annoying tinnitus sound. In fact, the cumulative effect of tinnitus on attention shifting at the level of neural oscillations has not been thoroughly explored yet.[14] Nonetheless, this does not undermine the pivotal conclusions of our research. Future investigations may encompass a broader range of distracting tasks and more efficient methods for brain wave regulation, such as neural feedback training, to delve deeper into the neural mechanisms and clinical applications of oscillatory biomarkers of tinnitus.

RESOURCE AVAILABILITY

Lead contact

Requests for further information on software and resources should be directed and will be fulfilled by the lead contact, Yuanqing Li (auyqli@scut.edu.cn).

Materials availability

This study did not generate new unique reagents or materials.

Data and code availability

Data: The data have been deposited at GitHub and are publicly available as of the date of publication. The DOI is GitHub: https://github.com/didi226/Neural_-Mechanism_Tinnitus/tree/main/data and listed in the key resources table.

Code: All original codes are publicly available as of the data of publication. The DOI is GitHub: https://github.com/didi226/Neural_-Mechanism_Tinnitus/tree/main/code and listed in the key resources table.

Additional information: Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Y.L. designed the research; X.F., X.B., H.H., Z.W., W.H., C.X., Y.H., and Z.S. contributed to data collection; Y.C. supported patient data collection; X.F. and Q.H. developed the analysis framework; X.F. analyzed data; X.F. prepared the figures and formatted the manuscript; X.F. and Q.H. wrote the paper; Y.L. and Q.H. edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interest.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Data	Sun Yat-sen Memorial Hospital	https://github.com/didi226/Neural_-Mechanism_Tinnitus/tree/main/data
Software and algorithms		
MATLAB	MathWorks	https://la.mathworks.com/products/matlab.html
EEGLAB	N/A	http://sccn.ucsd.edu/eeglab/index.html
Analysis scripts for data processing	MATLAB	https://github.com/didi226/Neural_-Mechanism_Tinnitus/tree/main/code
Python version 3.9.1	Python Software Foundation	https://www.python.org
Analysis scripts for machine learning	Python 3.9.1	https://github.com/didi226/Neural_-Mechanism_Tinnitus/tree/main/code
GraphPad Prism 8.0.2	GraphPad Software, Inc.	https://www.graphpad.com/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Fifty-two adults with tinnitus (35 males and 17 females; 36.37±11.38 years) and 52 age-matched healthy participants (40 males and 12 females; age, 32.90±11.18 years) participated in this study. All tinnitus subjects were recruited from the Department of Otolaryngology at Sun Yat-sen Memorial Hospital, where had been clinically diagnosed with chronic tinnitus (defined as tinnitus lasting for at least six months). Tinnitus severity and the level of tinnitus handicap were evaluated using the Tinnitus Handicap Inventory (THI). Completed THI questionnaires were returned for 49 out of the 52 tinnitus subjects (THI score, 45.92±21.34). All participants underwent audiometric testing conducted by experienced audiologist, where hearing loss was measured as the average of pure tone measurements at 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz.[59] Additionally, high-frequency hearing loss (with a measurement range of 4-8 kHz average) was recorded for tinnitus participants, requiring low-frequency hearing loss to be below 25 Db.[60] The demographic details of the participants are presented in Table 1. Subjects with pulsatile tinnitus, Ménière's disease, severe hearing loss, central nervous system disorders, or tumors were excluded. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Sun Yat-sen Memorial Hospital (SYSEC-KY-LS-2018-50). All participants provided written informed consent, and the consent process was reviewed and approved by the ethics committee.

METHOD DETAILS

Experimental paradigm

Both the tinnitus subjects and controls completed two resting states (eyes-open and eyes-closed) and two attention tasks (instructed gazing and mental arithmetic). During the instructed gazing task, participants were instructed to gaze and focus their attention on a cross presented on the screen, which was designed to induce mild attention shifting without high-order cognitive involvement. Mental arithmetic is a widely utilized experimental paradigm for studying the mechanisms of attention.[61,62] It has been used to reveal the attention mechanisms involved in tinnitus perception using positron emission tomography, where a backward counting method ('serial sevens test') was employed.[61] Our mental arithmetic paradigm bears similarities but employs continuous subtraction of one to ensure the experiment's continuity and prevent participants from abandoning the task due to its difficulty. During the mental arithmetic task, participants silently performed subtraction operations based on an initial Arabic numeral given. They subtracted one each time and continued to subtract as quickly as possible. When the prompt 'End' appeared on the screen, participants reported the final number they reached. The reported numbers ought to lie within a reasonable range (such as the starting number is 120, the range of the reached number is about: 20-60); excessively large or small values indicate distraction or lack of cooperation and will be excluded from further processing. This task was designed to induce relatively strong shifting of attention through the involvement of high-order cognitive functions, in order to achieve maximum disregard for the perception of tinnitus. In addition, tinnitus subjects performed an extra attention task by actively listening to their tinnitus, to mimic the daily situation that the subject's attention was confined to the annoying sound. Resting states and attention tasks completed by the two groups are summarized in Figure 7A.

Our experiment consisted of three sessions. In each session, participants completed five trials of each attention task in a random order. This resulted in 15 trials per session for the tinnitus subjects and 10 trials per session (no active listening) for the controls.

Before a trial started, a prompt message was displayed on the screen for 5 seconds to remind the subject of the upcoming task. Each trial lasted for 60 s and was ended when the screen displayed "End". The inter-trial interval was 10 seconds. Between the three sessions, participants could take a short break and then completed the 5-min eyes-open and eyes-closed resting state procedure. The experiment was carried out in a quiet, sound-attenuated room, and subjects were instructed to sit comfortably and reduce body movements and eye blinking during the entire test. The experimental procedure is illustrated in Figure 7B.

EEG acquisition and preprocessing

Scalp EEG signals were collected throughout the entire experiment using a 32-channel standard SynAmps2 amplifier (Compumedics Neuroscan, Inc., Australia) with a sampling rate of 250 Hz. Electrode placement followed the international 10-20 system; the right mastoid (M2) was used as the reference, and the ground electrode (GND) was positioned on the forehead. The impedance between the scalp and electrodes was kept below 5 kΩ.

Preprocessing of raw EEG data was conducted using the EEGLAB v13.0.0 toolbox in MATLAB (R2021a, MathWorks, Inc., USA). The steps are briefly described as follows: (1) Raw EEG data collected from 30 channels (excluding M2 and GND) were first filtered with a bandpass filter between 0.1 and 45 Hz. This step aimed to remove the 50-Hz AC line noise and non-physiologically slow drifts. (2) Bad channels were rejected by visual inspection and interpolated via spherical interpolation. (3) The filtered data were re-referenced to the common average from all electrodes. (4) Data epochs from the trials were then segmented. Epochs exceeding a magnitude threshold were considered contaminated and rejected. Subjects with more than 10% bad epochs were discarded. (5) The remaining artifacts were removed using the independent component analysis (ICA) method in the EEGLAB toolbox, and components related to eye blinks, muscle artifacts and ECG artifacts were manually selected and removed based on the decomposed component waveform and topology. (6) The cleaned EEG data were again re-referenced to the common average.

Feature extraction

The preprocessed EEG data for resting state and attention tasks (trial-wise) were first filtered into five frequency bands: delta (δ, 1 to 4 Hz), theta (θ, 4 to 8 Hz), alpha (α, 8 to 13 Hz), beta (β, 13 to 30 Hz), and gamma (γ, 30 to 45 Hz). The data sequence of each channel was then segmented into non-overlapping 5-second epochs. The power spectrum density (PSD) of each epoch was calculated using two-sided autoregressive estimates with the Pyulear function in MATLAB (order set to 10, the number of sampling points is 256, while the sample rate is 250). Inspired by the inverse relationship between gamma and alpha frequency bands in the SLIM model,[23,25] we propose specifically using the ratio of gamma to alpha to amplify and capture this potential neural oscillation. Additionally, for the purpose of comparability, we also consider other frequency band ratios. Consequently, the PSD ratio of each epoch was calculated using the following equation:

$$PSD\,ratio(j,i) = \frac{PSD_{f(j)}}{PSD_{f(i)}}$$

where f denotes the five frequencies (i.e., delta, theta, alpha, beta and gamma), i and j denote the order of the frequency band ($1 \leq i \leq 4, 2 \leq j \leq 5, i < j$). For example, $PSD_{f(1)}$ represents the PSD of the delta frequency band. PSD of each band was divided by PSDs in lower bands, resulting in 10 PSD ratios.

Next, the PSDs and PSD ratios obtained from resting state epochs were averaged for each participant. Any values outside the mean ± 3 standard deviations were rejected. This resulted in a resting-state matrix of PSDs and PSD ratios, respectively, which could be denoted as PSD_{rsEEG} or PSD_{rsEEG} ratio $\in R^{i \times j \times n}$, where i = 52 is the number of subjects, j = 30 denotes the number of channels utilized, n = 5 for PSDs indicating the five frequency bands, and n = 10 for PSD ratios. Similarly, the task-related PSDs and PSD ratios were averaged for each trial, resulting in a PSD matrix and a PSD ratio matrix for each type of attention task, denoted as PSD_{tsEEG} and PSD_{tsEEG} ratio $\in R^{i \times j \times m \times n}$, where i = 52 is the number of subjects, j = 30 denotes the number of channels utilized, m = 15 is the number of trials, n = 5 denotes the five PSDs, and n =10 denotes the 10 PSD ratios.

Region division and slope processing

To investigate region-specific characteristics of tinnitus subjects, we divided the brain topology into five regions of interest based on anatomical structure and physiological function,[63,64] namely the frontal region, parietal and parietal temporal region, left temporal region, right temporal region, and the occipital region. The exact divisions of channels are listed in Table 2. The PSDs and PSD ratios of interest were then compared between tinnitus subjects and controls in each of the five brain regions.

To directly test the SLIM model, we followed the method proposed by Lorenz et al.[25] to calculate the resting-state slope between gamma and alpha band activity in the left, right, and combined left-right temporal regions. Firstly, we normalized the averaged gamma and alpha PSDs by dividing them by the sum of PSDs across all frequency bands, ensuring that the total power across bands was equal to 1. We then took the logarithms (base 10) of the normalized gamma and alpha PSDs to linearize the data and reduce the effects of outliers. Using these values, we fit a linear regression model to the gamma-alpha correlation. The slope of the fitted line was recorded and subsequently compared between tinnitus subjects and controls in the left, right, and combined left-right temporal regions.

Decoding frontal regulation using support vector machines (SVM)

To quantitatively measure the neural oscillatory regulations associated with shifting attention in tinnitus subjects, we applied a binary classification modeling approach using Support Vector Machines (SVM) to train a model based on frontal gamma/alpha ratio characteristics.[65,66] We subsequently utilized this model to distinguish between active listening and instructed gazing, as well as between active listening and mental arithmetic. The decoding accuracy was considered as a quantitative indicator of the degree of attention shifting.

The model was trained and tested using a five-fold cross-validation process. Specifically, we first constructed a feature set $T = \{(x_1, y_1), (x_2, y_2), \ldots, (x_N, y_N)\}$, where the feature vector $x_i \in R^M$ $(M = 7)$ was composed of the gamma/alpha ratios extracted from the seven frontal channels (Fp1, Fp2, F7, F3, FZ, F4, F8), and $y_i \in \{+1, -1\}$ denoted the class (task) label and $i = 1, 2, \ldots, 30$ represented the trial number (15 for each task). The feature set was then fed into the scikit-learn package in Python 3.9.1 for SVM binary classification modeling, which employed a linear kernel function. The model underwent training and validation through a five-fold cross-validation process. Finally, the classification results were recorded for each participant.

QUANTIFICATION AND STATISTICAL ANALYSIS

The gamma-alpha slope was calculated through linear regression, and the results were compared between the tinnitus and control groups using an F-test in GraphPad Prism (Version 8). Direct comparisons of the PSD/PSD ratio features between the tinnitus group and the control group were conducted, using a two-tailed independent-sample *t* test, both at the global level and at the ROI level. To verify the potential confounding effect of hearing loss on the observed intergroup differences in neural indicators, we used a multiple regression model in GraphPad Prism. In this model, we designated group as the independent variable, hearing loss as the covariate, and the measured gamma/alpha ratio as the dependent variable. Additionally, a one-way ANOVA was employed to assess the regulatory effects on the gamma/alpha ratio induced by attention shifting in different brain regions for both the tinnitus and control groups. For both tinnitus and control group, intragroup comparisons between different tasks (resting-state and attention shifting) were performed using a two-tailed paired-sample *t* test. The SVM decoding accuracy of the two pairs of task states of interest was also compared using a one-tailed paired-sample *t* test. The difference between the decoding accuracy of the gaze task and random accuracy was verified using permutation testing. A two-tailed paired-sample *t* test was used to compare the gamma/alpha ratio in the frontal region between active listening and instructed gazing (as well as mental arithmetic) in the tinnitus group, aiming to examine the regulatory effect of attention tasks with different workloads level on tinnitus. To assess the effects of hearing loss (especially high-frequency), tinnitus severity, and cognitive status on attention regulation, we conducted a 3×2×2 ANOVA. Tinnitus subjects were divided into three subgroups based on THI score: mild (0-36 points, 16 subjects, THI = 21.5±12.27), moderate (38-56 points, 20 subjects, THI = 48.8±4.37), and severe (58-100 points, 13 subjects, THI = 71.53±9.13).[67] Cognitive status included AL-IG and AL-MA. Within these, subjects were further divided into those with (HHL = 48.95±15.43, 22 subjects) and without high-frequency hearing loss (HL = 34.96±24.08, 27 subjects). The shifting index (Δ gamma/alpha ratio) was the dependent variable. A two-tailed paired-sample *t* test was directly utilized to compare three distinct tinnitus symptom subtypes with two cognitive statuses, to examine the attention shifting effects at different symptom levels. For group comparisons of demographic information, such as age and hearing loss, non-parametric Wilcoxon-Mann-Whitney tests were employed, while a chi-square test was used for gender. All reported statistics were corrected using the false discovery rate (FDR) method.[68] The significance threshold was set at a P-value < 0.05.

ADDITIONAL RESOURCES

This paper did not create any additional resources.