Resting-state electroencephalography theta predicts neurofeedback treatment 4-month follow-up response in nicotine addiction

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ABSTRACT

Background The high rate of long-term relapse is a major cause of smoking cessation failure. Recently, neurofeedback training has been widely used in the treatment of nicotine addiction; however, approximately 30% of subjects fail to benefit from this intervention. Our previous randomised clinical trial (RCT) examined cognition-guided neurofeedback and demonstrated a significant decrease in daily cigarette consumption at the 4-month follow-up. However, significant individual differences were observed in the 4-month follow-up effects of decreased cigarette consumption. Therefore, it is critical to identify who will benefit from pre-neurofeedback.

Aims We examined whether the resting-state electroencephalography (EEG) characteristics from pre-neurofeedback predicted the 4-month follow-up effects and explored the possible mechanisms.

Methods This was a double-blind RCT. A total of 60 participants with nicotine dependence were randomly assigned to either the real-neurofeedback or yoked-feedback group. They underwent 6 min closed-eye resting EEG recordings both before and after two neurofeedback sessions. A follow-up assessment was conducted after 4 months.

Results The frontal resting-state theta power spectral density (PSD) was significantly altered in the real-feedback group after two neurofeedback visits. Higher theta PSD in the real-feedback group before neurofeedback was the only predictor of decreased cigarette consumption at the 4-month follow-up. Further reliability analysis revealed a significant positive correlation between theta PSD pre-neurofeedback and post-neurofeedback. A leave-one-out cross-validated linear regression of the theta PSD pre-neurofeedback demonstrated a significant correlation between the predicted and observed reductions in cigarette consumption at the 4-month follow-up. Finally, source analysis revealed that the brain mechanisms of the theta PSD predictor were located in the orbital frontal cortex.

Conclusions Our study demonstrated changes in the resting-state theta PSD following neurofeedback training. Moreover, the resting-state theta PSD may serve as a prognostic marker of neurofeedback effects. A higher resting-state theta PSD predicts a better long-term response to neurofeedback treatment, which may facilitate the selection of individualised interventions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neurofeedback is a novel brain modulation method widely used in nicotine addiction treatment. Previous studies have found individual differences in the long-term effects of neurofeedback treatment, and long-term relapse is a major cause of smoking cessation treatment failure. However, being able to predict the long-term effects of neurofeedback treatment in nicotine addicts is lacking.

WHAT THIS STUDY ADDS

⇒ The resting-state theta power spectral density biomarker can predict the daily change in cigarette consumption following neurofeedback in nicotine addicts at the 4-month follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We identified a brain-based biomarker that could predict the 4-month follow-up effects of neurofeedback on nicotine addiction.

Trial registration number ChiCTR-IPR-17011710.

INTRODUCTION

Nicotine addiction, which is a leading cause of induced diseases, is projected to cause approximately 8 million deaths per year worldwide by 2030.1 Despite the widespread use of pharmacological and behavioural approaches for smoking cessation, relapse remains high, even with combination therapies.2 In this context, new smoking cessation strategies and the prediction of the long-term outcomes of smoking cessation are critical for addressing this global health and social challenge.

Neurofeedback is a novel brain modulation technique to train participants to self-regulate their brain signals.3 It has been clinically employed in treating many psychiatric disorders,4 including attention deficit...
hyperactivity disorder, depression, anxiety and drug addiction. However, a few studies have shown that a substantial proportion (approximately 30%) of participants do not completely benefit from neurofeedback.\(^5\) Additionally, one of the main reasons for relapse is that nicotine-related cues evoke nicotine craving.\(^6\) Therefore, we developed a novel cognition-guided neurofeedback protocol based on a cue response model,\(^7\) which showed promising results in reducing cigarette consumption at the 4-month follow-up. However, a few smokers still experienced nicotine craving and did not respond to the intervention.\(^7\) Previous studies have indicated that an outstanding challenge in smoking cessation is the prediction of its long-term effects.\(^8\) Therefore, it is critical to identify who will benefit from the neurofeedback training for nicotine addiction, especially for long-term cigarette consumption effects. Additionally, predicting the response to psychiatric treatment is a goal of clinical psychiatry.\(^9\) As precision medicine suggests, the identification of pretreatment baseline characteristics that predict subsequent symptom improvement, especially long-term, could facilitate optimal treatment selection and inform about timely adjustments.\(^10\) However, this information is currently lacking in neurofeedback training for nicotine addiction.

Nicotine addiction, a brain-related disorder, has been attracting increasing academic interest and recognition.\(^11\) Although clinical and demographic characteristics could help predict treatment effectiveness, they provide limited brain-related information to identify individuals who may experience withdrawal failure or relapse. Therefore, it is necessary to identify brain-based biomarkers to predict treatment outcomes and improve nicotine addiction treatment. Numerous studies have shown that brain-based biomarkers can accurately predict response to addiction treatment, even with long-term improvements in addiction.\(^12\) Moreover, brain-based characteristics often provide better predictions of treatment response than clinical and demographic characteristics, suggesting that brain-based biomarkers may serve as particularly robust predictors of long-term treatment outcomes.\(^2\) Resting-state electroencephalography (EEG) biomarkers have been proposed as a low-cost, task-free method of determining patient response to interventions.\(^13\) This study examined whether resting-state EEG characteristics at pre-neurofeedback could predict long-term cigarette consumption changes through the EEG-neurofeedback treatment.

To our knowledge, few studies have provided a multifaceted and comprehensive assessment of brain-based predictors. We first compared the power spectral density (PSD) of each frequency band between the real-feedback and yoked-feedback groups to identify the significantly altered PSD for each frequency band. Next, we assessed the resting-state EEG predictors from four perspectives: (1) To determine the frequency band of the PSD that predicted the 4-month follow-up effects of neurofeedback, we controlled for all clinical and demographic variables for relevant predictions. (2) To identify pretreatment variables in a treatment-specific manner that could facilitate optimal treatment selection, we examined whether the 4-month follow-up prediction relationship was modulated by the neurofeedback training. (3) To assess the reliability of the resting-state EEG predictors, we re-recorded the resting-state EEG immediately after the neurofeedback training and retested the prediction relationship. (4) To find a clinically useful predictor that could be generalisable for any individual prior to treatment, we implemented the leave-one-out cross-validated linear regression to test whether the predictor could generally predict 4-month follow-up cigarette consumption reduction in new participants. Finally, to further understand the possible mechanism of the predictor, we conducted an EEG network topographical analysis and novel network-based source imaging analysis.

**METHODS**

**Participants**

As the rate of female nicotine addiction in China is low, and given that menstrual cycle phases may affect smoking cue responsiveness and nicotine craving, only male participants were recruited for this study. The participants included 60 nicotine-dependent male smokers (≥10 cigarettes per day and ≥2 smoking years, 18–40 years of age) who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria for nicotine addiction.\(^14\) The participants were recruited through online and poster advertisements. They were excluded if they simultaneously engaged in any other smoking cessation plan; had chronic neurological, psychiatric or medical conditions; had undergone treatment with any drugs during the previous 3 months; or were generally ill-suited to undergo EEG. The participants were randomly assigned to receive two visits for smoking cue reactivity neurofeedback, either from their own brain states (n=30, real-feedback group) or from matched participants in the experimental group (n=30, yoked-feedback group) (figure 1). They signed an informed consent form before and received monetary compensation after completing the experiment. The research protocol was registered with the Chinese Clinical Trial Registry (ChiCTR-IPR-17011710, https://trialsearch.who.int/?TrialID=ChiCTR-IPR-17011710).

**Experimental procedure**

The experiment was a double-blind randomised clinical trial (RCT). The participants were required to abstain from smoking cigarettes 2 hours before every visit. During the baseline visit (visit 1), they completed several trait-related questionnaires, including the Fagerström Test for Nicotine Dependence, Emotion Regulation Questionnaire, Barratt Impulsivity Scale, and Sensitivity to Punishment and Sensitivity to Reward Questionnaire. One day later (visit 2), after arriving at the laboratory, they completed state-related questionnaires, including...
85 males recruited by advertisement for study participation were assessed for eligibility

Inclusion criteria:
- Smoking 10+ cigarettes per day for ≥ 2 years
- Between 18–40 years of age
- Good mental and physical health assessed via the Mini-International Neuropsychiatric Interview

Exclusion criteria:
- Chronic neurological, psychiatric, or medical conditions
- Treatment with any drugs during the previous 3 months
- Declined study participation

60 participants were enrolled
- 30 assigned to the real-feedback group
- 30 assigned to the yoked-feedback group

44 participants completed the 4-month follow-up
- real-feedback group (n = 22)
- yoked-feedback group (n = 22)

Figure 1 Schematic diagram of participants.

the Positive and Negative Affect Scales, Beck Anxiety Inventory, State-Trait Anxiety Inventory, Beck Depression Inventory, Visual Analog Mood Scales and Tobacco Craving Questionnaire. Afterwards, they underwent a 6 min resting EEG recording (pre-neurofeedback). During the resting-state EEG acquisition, they were required to keep their eyes closed throughout and were instructed to relax as much as possible while not thinking of anything specific. Next, the participants underwent the neurofeedback training. Each training visit comprised eight cycles, with 40 trials per cycle. Each trial was updated after every 2 seconds. During the neurofeedback training, the participants were instructed to adjust their cognitive strategies to decrease the feedback curve probabilistic score, representing the extent to which the brain activity pattern matched the pattern of reactivity to the smoking cue (online supplemental figure 1). Details of the neurofeedback procedure can be found in the online supplemental methods. One or 2 days later (visit 3), the participants were administered the same neurofeedback training as in the previous visit. After that, they performed the same resting EEG recording for 6 min as before the first neurofeedback training session (post-neurofeedback). All the participants underwent two neurofeedback training visits. One week, 1 month and 4 months after the neurofeedback training session (post-neurofeedback), the number of cigarettes smoked per day, reflecting cigarette consumption, was assessed (visit 4). The number of cigarettes smoked per day—the primary treatment outcome—refers to the average number of cigarettes smoked per day from the last visit/telephone interview to the current visit (online supplemental figure 2).

**EEG recording**

The EEG data were recorded using a SynAmps RT amplifier (NeuroScan, Charlotte, North Carolina, USA). A total of 64 Ag/AgCl electrodes were placed on the scalp at specific locations, according to the extended international 10–20 system. Additionally, electrical activities were recorded over the right and left mastoids. The vertical electro-oculography (EOG) was performed using bipolar channels placed above and below the left eye. The horizontal EOG was performed using bipolar channels placed lateral to the outer canthi of both eyes. The reference electrode was attached to the tip of the nose, and the ground electrode was attached to the AFz. The impedance between the reference electrode and any recording electrode was kept under 5 kΩ. All signals were digitised at 500 Hz during data collection.

**EEG analysis**

The EEG data computations were performed using the EEGLAB v2013.0 toolbox ([https://sccn.ucsd.edu/eeeglab](https://sccn.ucsd.edu/eeeglab)) in MATLAB (R2019b, MathWorks, Natick, Massachusetts, USA). Obvious technical artefacts were removed after visual inspection, and the EEG data from four participants (real-feedback group: n=2; yoked-feedback group: n=2) were excluded because of excessive artefacts. A high-pass filter with a cut-off of 0.5 Hz was applied to remove the low-frequency noise. Continuous EEG data were segmented into non-overlapping epochs of 1000 ms, and any epochs with amplitudes exceeding ±80 μV were rejected. The resting-state EEG PSD was calculated using the EEGLAB function `spectopo` and divided into five frequency bands: delta (1–4 Hz), theta (5–7 Hz), alpha (8–13 Hz), beta (14–30 Hz) and gamma (31–48 Hz). The PSD values of all the epochs for each band were averaged.

To assess the generalisability of the prediction model, we employed the leave-one-out cross-validated linear regression. We built a model by fitting a linear regression from the N-1 participants between resting EEG PSD and 4-month cigarette consumption change. The resting-state EEG PSD of the remaining one participant was then input into the trained model to generate the predicted 4-month follow-up cigarette consumption change. This process was iterated N times to obtain the predicted 4-month follow-up cigarette consumption for all participants. Thereafter, we evaluated the predictive power of each model by correlating the predicted and observed 4-month follow-up cigarette consumption changes for all participants.

The scalp topography analysis aimed to identify the distribution of the correlation between the resting-state EEG predictor and 4-month follow-up cigarette consumption. The correlation coefficients were calculated at each electrode and transformed into Z values using Fisher's R-to-Z transformation. The brain cortical source of the resting-state EEG predictor was estimated using the Resting-state Cortex Rhythms toolbox ([http://www.leixulab.net/recor.asp](http://www.leixulab.net/recor.asp)). A total of 60 channels were matched to the scalp surface. First, the cortical current density of
EEG rhythms was obtained using a network-based source imaging technique. Second, the overall electrical activity intensity of each large-scale brain network was obtained by averaging the electrical activity intensity of the nodes within each network.

**Statistical analysis**

Statistical analyses were performed using custom scripts in MATLAB. Two-sample t-tests were performed to compare the changes in the resting-state EEG PSD between the real-feedback and yoked-feedback groups. To control for multiple comparisons, we applied a cluster-based permutation correction method using the FieldTrip toolbox. The corrected p values were computed through 500 iterations, and clusters were deemed significant at a threshold of p<0.05. Pearson’s correlation was used to examine the correlation between the resting-state EEG PSD at pre-neurofeedback and altered daily cigarette consumption at 4-month follow-up, resting-state EEG PSD between pre-neurofeedback and post-neurofeedback, and predicted versus observed 4-month follow-up daily cigarette consumption change. Moreover, we employed a permutation-based correction for multiple comparisons in the correlational analyses using the mult_comp_perm_corr function in MATLAB. The corrected p values were obtained by estimating the probability distribution of the correlation coefficients through the randomisation of observations within each variable over 5000 iterations. Fisher’s R-to-Z transformation and z-test statistics were used to compare the correlation coefficients. A two-tailed p value <0.05 was regarded as significant for all tests.

**RESULTS**

**Four-month follow-up effect of neurofeedback for daily cigarette consumption**

In our previous neurofeedback RCT, we evaluated the clinical and demographic measures between the real-feedback and yoked-feedback groups before neurofeedback training and found no significant difference between the two groups (online supplemental table 1). Additionally, our previous study demonstrated a significant reduction in daily cigarette consumption at the 4-month follow-up after neurofeedback training in the real-feedback group compared with the yoked-feedback group (t(42)=−2.07, p=0.044, Cohen’s d=−0.64, figure 2A, online supplemental table 1). Despite the significant 4-month follow-up effect of neurofeedback, we observed considerable interindividual variability in the decline in daily cigarette consumption in the real-feedback group (figure 2B).

**Effects of neurofeedback training on resting EEG**

Two-sample t-tests were used to compare the changes (pre minus post) in the PSD at each frequency band before and after the neurofeedback training between the real-feedback and yoked-feedback groups. There was no significant difference in the PSD at each frequency band between the two groups before the neurofeedback training (online supplemental figure 3 and online supplemental table 2). After two neurofeedback visits, the frontal (F1, Fz, F2, FC1) theta PSD change was significantly higher and the bilateral parietal-occipital (P3, P8, PO7, PO5, PO3, PO6, PO8) alpha PSD change was significantly lower in the real-feedback group compared with the yoked-feedback group (figure 3 and table 1). After cluster-based permutation correction, a frontal cluster (F1, Fz, F2 and FC1) exhibited a significant alteration in the theta PSD (p_correct=0.043). However, no cluster in the parietal-occipital region passed the alpha PSD correction. Additionally, there were no significant differences in the SDs of the alpha PSD among the statistically significant altered channels (t(38)=1.55, p=0.136, Cohen’s d=0.49). We compared the baseline PSD between the real-feedback group and matched non-smoking participants (normal control group, n=21). There was no significant difference in the theta or alpha PSD of the real-feedback group compared with that of the normal control group (online supplemental figure 4).

**Resting-state theta PSD as a predictor of 4-month follow-up treatment effect**

Based on the observed individual differences and changes in the resting-state theta and alpha PSDs, we studied the

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**Figure 2** The effects of neurofeedback on daily cigarette consumption. (A) Daily cigarette consumption at pre-neurofeedback and 4-month follow-up. Error bar (SE). (B) Changes in individual daily cigarette consumption (pre minus 4 months). *p<0.05. SE, standard error.
The effects of neurofeedback on the resting-state electroencephalography (EEG) power spectral density (PSD). PSD changes (ΔPSD, pre-PSD minus post-PSD) in each band in the real-feedback and yoked-feedback groups after two visits of neurofeedback. T value topographies displaying significant ΔPSD of the real-feedback group compared with the yoked-feedback group. White dot: cluster-based permutation-corrected p<0.05.

Each band in the real-feedback and yoked-feedback groups significantly changed with neurofeedback, with the real-feedback group displaying greater change than the yoked-feedback group. This suggests that neurofeedback training can alter the resting-state EEG PSD patterns.

**Treatment-specific predictor**

Identifying pretreatment variables (predictors) in a treatment-specific manner can facilitate optimal treatment selection. To address whether the resting-state theta PSD is a predictor of the neurofeedback treatment, we examined whether the group variable (real-feedback group vs yoked-feedback group) affected the direction and/or strength of the association between the resting-state theta PSD and the treatment outcome. The results showed a significant association between the resting-state theta PSD and treatment outcome in the real-feedback group (r=0.68, p<0.001) but not in the yoked-feedback group (r=0.18, p=0.435). Moreover, the correlation for the real-feedback group was significantly stronger than that for the yoked-feedback group (z=1.88, p=0.030, one-tailed). These findings indicated that the resting-state theta PSD was specific to the treatment group in predicting a reduction in daily cigarette consumption.

**Table 1** Mean ΔPSD values and their SDs of channels with significant differences

<table>
<thead>
<tr>
<th>Band (Hz)</th>
<th>Real-feedback group (mean, SD)</th>
<th>Yoked-feedback group (mean, SD)</th>
<th>Statistic</th>
<th>P value</th>
<th>P correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theta (5–7 Hz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>−0.62 (1.13)</td>
<td>0.26 (1.15)</td>
<td>−2.44</td>
<td>0.019*</td>
<td>0.043*</td>
</tr>
<tr>
<td>Fz</td>
<td>−0.61 (1.11)</td>
<td>0.24 (1.03)</td>
<td>−2.54</td>
<td>0.015*</td>
<td>0.043*</td>
</tr>
<tr>
<td>F2</td>
<td>−0.58 (1.01)</td>
<td>0.14 (1.04)</td>
<td>−2.23</td>
<td>0.032*</td>
<td>0.043*</td>
</tr>
<tr>
<td>FC1</td>
<td>−0.33 (0.99)</td>
<td>0.27 (0.83)</td>
<td>−2.10</td>
<td>0.043*</td>
<td>0.043*</td>
</tr>
<tr>
<td>Alpha (8–13 Hz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>0.23 (1.89)</td>
<td>−0.81 (1.11)</td>
<td>2.12</td>
<td>0.040*</td>
<td>0.074</td>
</tr>
<tr>
<td>PO7</td>
<td>0.43 (2.40)</td>
<td>−0.81 (1.05)</td>
<td>2.12</td>
<td>0.041*</td>
<td>0.074</td>
</tr>
<tr>
<td>PO5</td>
<td>0.31 (2.21)</td>
<td>−0.89 (1.14)</td>
<td>2.17</td>
<td>0.037*</td>
<td>0.074</td>
</tr>
<tr>
<td>PO3</td>
<td>0.24 (1.95)</td>
<td>−0.83 (1.06)</td>
<td>2.16</td>
<td>0.037*</td>
<td>0.074</td>
</tr>
<tr>
<td>P8</td>
<td>0.51 (1.87)</td>
<td>−0.57 (1.21)</td>
<td>2.17</td>
<td>0.036*</td>
<td>0.078</td>
</tr>
<tr>
<td>PO6</td>
<td>0.48 (1.74)</td>
<td>−0.71 (1.17)</td>
<td>2.56</td>
<td>0.015*</td>
<td>0.078</td>
</tr>
<tr>
<td>PO8</td>
<td>0.54 (2.03)</td>
<td>−0.08 (1.23)</td>
<td>2.56</td>
<td>0.015*</td>
<td>0.078</td>
</tr>
</tbody>
</table>

ΔPSD=pre-PSD minus post-PSD. P correct is the cluster-based permutation-corrected p value.

*p<0.05 or P correct<0.05.

PSD, power spectral density; SD, standard deviation.
Figure 4  The resting-state theta PSD predicts daily cigarette consumption at a 4-month follow-up and its brain mechanisms. (A) The correlation between the pre-neurofeedback resting-state mean theta PSD or alpha PSD and the changed daily cigarette consumption after 4 months was calculated for the real-feedback group. (B) The correlation between the pre-neurofeedback resting-state mean theta PSD across the permutation-corrected significant cluster and the decreased daily cigarette consumption after 4 months was calculated for the two groups. (C) The correlation between the observed and predicted 4-month follow-up treatment outcome. (D) The scalp distribution of correlation between the resting-state theta PSD and 4-month follow-up effects. (E) The network-based source imaging of the resting-state theta PSD. Shaded areas indicate 95% CIs. CI, confidence interval; PSD, power spectral density.

Test–retest reliability of predictor
To assess the reliability of the resting-state theta PSD predictor, we correlated the theta PSDs between pre-neurofeedback and post-neurofeedback. The correlation revealed a significant positive correlation between the two phases (r=0.87, p<0.001) in the real-feedback group.

Generalisability of predictor
To determine whether resting-state theta PSD predicted 4-month follow-up treatment outcomes in novel individuals, a leave-one-out cross-validated linear regression was employed. The correlation between the observed and predicted treatment outcomes was highly significant (r=0.58, p=0.007) (figure 4C), with statistical significance confirmed by permutation-based correction (p=0.009). Additionally, there was no significant difference between the observed and predicted outcomes (t(19)=0.01, p=0.990, Cohen’s d=0.005; paired t-test). Altogether, these findings indicated the good generalisability of the resting-state theta PSD predictor.

Brain mechanism of predictor
To further explore the brain mechanism of the resting-state theta PSD, we conducted the EEG scalp topographical and network-based source imaging analyses. The scalp analysis revealed a strong correlation between the resting-state theta PSD and the 4-month follow-up effects in the frontal regions (figure 4D). This is consistent with the brain regions where the theta PSD changes in the resting-state EEG after the neurofeedback training. The source analysis was averaged over the real-feedback group’s pre-neurofeedback EEG data to calculate the current source density in the theta band. Figure 4E shows the current density distribution of theta, which is mainly located in the orbital frontal cortex (OFC), consistent with the scalp analysis.

DISCUSSION
Main findings
This study examined the association between resting-state EEG characteristics and the 4-month follow-up effect of nicotine-guided neurofeedback in patients with nicotine addiction. The primary results were as follows. First, the resting-state theta PSD significantly changed after the neurofeedback training in the real-feedback group compared with the yoked-feedback group. Second, the resting-state theta PSD was a predictor of reduced cigarette consumption at the 4-month follow-up. Third, the
test–retest analysis and machine learning showed that the theta PSD predictor was reliable and general in predicting the 4-month follow-up effects. Finally, the brain mechanism of the theta predictor might be located in the OFC.

Several pre-post EEG studies on behavioural approaches and hypnosis-induced reductions in smoking have identified enhanced theta oscillations. Consistent with these findings, our study observed an increase in the frontal theta PSD in the real-feedback group after two neurofeedback training sessions compared with the yoked-feedback group. Notably, the brain regions and neural processes involved in nicotine addiction extensively overlap with those underpinning cognitive functioning. An increase in the theta power is intimately associated with enhanced cognitive control, and enhanced alpha power is more indicative of reduced attention. The neurofeedback process requires extensive involvement of cognitive control and attention, which has been observed in many studies on neurofeedback interventions for smoking. Furthermore, enhanced theta power has been observed during short-term nicotine withdrawal. Our findings showed an alteration in the alpha power among patients in the yoked-feedback group. This divergence may be attributed to the feedback signals presented to participants in the yoked-feedback group; these were not their own actual signals. Consequently, this mismatch in feedback signals may have caused fatigue effects, leading to further deterioration of attention and elevation of the alpha power in these patients. Therefore, our neurofeedback can further prolong the withdrawal response time in patients with nicotine addiction. This suggests that the novel cognitive-guided neurofeedback system we developed may be a reliable method to quit smoking.

Previous studies on treating nicotine addiction based on the cognitive–behavioural therapy and nicotine replacement therapy have shown that the clinical and demographic measures related to addiction (eg, self-reported intentions, self-efficacy, self-reference, etc) could also predict the long-term effects. However, these measures are subjective and may not be conducive to capturing small changes in the state of individuals with nicotine addiction. The present study found that even after controlling for all scale measures, the resting-state theta PSD remained a significant predictor of the 4-month follow-up decreased cigarette consumption. This suggested that the theta PSD predictor was consistently associated with smoking behaviour change, and that the resting-state neuroimaging predictor may provide a unique prediction of individual differences in long-term behaviour change compared with previous subjective measures. In contrast, the alpha PSD—irrespective of controlling for all variables—did not provide a valid prediction of reduced smoking. This was probably because alpha oscillations depend on an individual’s level of awareness and attention and the alpha PSD change was primarily observed in the yoked-feedback group. Baseline alpha oscillations do not determine an individual’s state after neurofeedback and do not predict smoking. An individual’s cognitive control influences cigarette consumption. Therefore, individuals with stronger baseline cognitive control (higher resting-state theta PSD) are more likely to benefit from neurofeedback and experience reduced nicotine craving. Additionally, neuroimaging predictors help identify individuals at risk of relapse and provide targeted treatment for them.

We observed significant theta PSD prediction in the real-feedback group but not in the yoked-feedback group. This result demonstrates that the theta predictor is a treatment-specific moderator, reflecting changes in cigarette consumption. Many studies have explored interventions on nicotine addiction and have shown that certain neuroimaging biomarkers (eg, medial prefrontal cortex activation, insula activation, etc) could predict long-term changes in smoking behaviour. The theta predictor could provide additional valuable information by identifying smokers who may benefit more from the neurofeedback intervention. Moreover, previous neuroimaging biomarkers were expensive and unsuitable for frequent testing for continuous follow-up. In contrast, the EEG is inexpensive and suitable for continuous testing, allowing appropriate adjustments to treatment plans based on changes in the patient’s brain state. Collectively, the resting-state theta PSD predictor benefits smokers who select appropriate treatment approaches before the intervention, which may improve the treatment success rate.

The theta PSD after two neurofeedback sessions highly correlated with that before neurofeedback. The test–retest findings indicate that the theta PSD predictor is a reliable biomarker for predicting long-term effects. Few previous studies on interventions on nicotine addiction have shown the reliability of potential predictors from the test–retest predictor viewpoint. A few studies have shown that the resting-state EEG biomarkers are reliable traits for predicting outcomes after an intervention. Taken together, the theta PSD may be a trait characteristic for a form of nicotine addiction that is responsive to neurofeedback training.

The leave-one-out cross-validated linear regression approach strongly correlated the predicted long-term decrease in cigarette consumption based on the theta PSD biomarker with the observed decrease in cigarette consumption for each participant, indicating the likely generalisability of the findings. In most previous studies that attempted to predict nicotine addiction treatment outcomes, prediction referred to the correlation between baseline measures and treatment outcomes. However, it is unknown how the prediction findings in a given participant data set would apply to a new participant. Predictors that are useful in clinical practice should have high generalisability and should be applicable to new participants with unknown outcomes. The current cross-validation results were restricted to inter-validation groups. Further studies should include outer validation groups to better validate the generalisability of the predictor.
The retrospective source of the resting-state theta PSD prediction was most significantly concentrated in the OFC, which is consistent with the area of the theta PSD changes in the resting-state EEG, validating our speculation about the brain mechanism of this predictor. Theta oscillations in the frontal midline are associated with cognitive control, which involves the brain control network. Furthermore, the rewarding properties of nicotine tend to weaken one’s self-control over nicotine use, leading to self-control deficits. Numerous studies have shown that neurofeedback training involves a control network—that is, a high degree of self-control is critical for neurofeedback training—and that neurofeedback performance directly affects an individual’s behaviour. Overall, participants with higher resting-state theta might have increased motivation and self-control for neurofeedback training and, thus, improved smoking behaviour. Further studies are required to confirm these hypotheses.

Regarding the clinical implications, the consistent and reliable association in scalp electrodes indicates that a considerably smaller array of electrodes may provide a sufficient biomarker for predicting neurofeedback treatment outcomes. These predictors can be used to screen and identify individuals at a higher risk of relapse, which, in turn, can help assess treatment response outcomes and improve outcomes for individuals with nicotine addiction. Additionally, predicting individual differences in the long-term effects of neurofeedback can facilitate patient stratification and provide targeted treatment for those most likely to benefit from this type of intervention.

Limitations

The current study has a few limitations. First, the generalisability of the novel neurofeedback effects on females is limited. This was because of the low smoking rate (2.7%) among Chinese females and the potential influence of the menstrual cycle phase on nicotine craving and behaviour. Second, participants were followed up only at 1 week, 1 month and 4 months after the final neurofeedback session. Although previous studies on smoking cessation included 6-month follow-ups, the follow-up periods in the current study met the common periods lasting 2–8 weeks in acute treatment trials. Additionally, increasing the sample size would enhance the statistical power of the study.

Implications

This is the first study to establish the resting-state EEG biomarker, theta PSD, as a prognostic marker for 4-month follow-up neurofeedback treatment outcomes. The theta PSD biomarker may be useful in developing personalised treatment programmes for patients with nicotine dependence while providing a potential brain-based biomarker for the clinical identification of individuals at a high risk of relapse.

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Contributors JB and XZ conceived the experiments. JB, QM, YZ and YY performed the experiments. JB and QM analysed the data. GM, YZ and JB wrote the manuscript. JB, YY, LY and JL helped polish the writing. JB is the guarantor of the study.

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Patient consent for publication Not applicable.

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REFERENCES


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Supplementary Information for

Resting-state electroencephalography theta predicts neurofeedback treatment 4-month follow-up response in nicotine addiction

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SUPPLEMENTARY METHODS

Neurofeedback

The neurofeedback includes offline classifier construction and real-time feedback training.

**offline classifier construction**

The offline classifier construction phase was approximately 21.5 min including the smoking cue reactivity task and support vector machine (SVM) classifier training. Smoking cue reactivity task consisted of pseudo-randomized 3 smoking blocks and 3 neutral blocks. Each block consists of 55 trials, among which 50 trials are smoking or neutral cues, another five randomly distributed trials were animal cues (e.g., kangaroo). During the task, participants were asked to follow instructions to view the pictures. When the animal picture was displayed participants were asked to press the button immediately. Electroencephalography (EEG) was recorded simultaneously during the task. A 90s rest between blocks.

A personalized classifier was then trained using the smoking cue task to distinguish the EEG activity patterns corresponding to smoking and neutral cue responses. The raw EEG was fed into the SVM classifier to identify patterns of brain responses to smoking cue.

**real-time EEG neurofeedback training**

The neurofeedback training was approximately 21 minutes and consisted of 8 cycles, with each training cycle containing 40 trials. Each trial was updated every 2 seconds which consisted of 1 second of acquisition and 1 second of computation. During neurofeedback training, participants were asked to repeatedly and
continuously deactivate a real-time EEG activity pattern of smoking cue responsiveness calculated using a previously constructed classifier. Based on the SVM classifier, probability scores (range, 0-1) were returned to characterize the probability of similarity between current brain activity and the pattern of smoking brain activity measured in the smoking cue reactivity task. Probability scores were displayed at the bottom of the screen. Probability scores were also converted to pictures displayed in the upper half of the screen, with lower probability scores resulting in a picture with a lower craving level (Supplementary Fig 1). Participants were asked to keep their scores below 0.5 as much as possible. The real-feedback group reflects the real brain state of the participant. The yoked-feedback group is the brain state of the participants in the real-feedback group that corresponds to it.

Supplementary Fig 1. Screenshot of the feedback during the neurofeedback. This image was created by us. We confirm that we have permission to reuse the image.
### Supplementary Table 1. Baseline Characteristics and long-term treatment outcome in two groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>real-feedback group (n =22)</th>
<th>yoked-feedback group (n =22)</th>
<th>T value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>24.9(3.9)</td>
<td>24.1(4.2)</td>
<td>0.58</td>
<td>0.566</td>
</tr>
<tr>
<td>Education (Years)</td>
<td>13.8(3.4)</td>
<td>14.9(1.6)</td>
<td>-1.27</td>
<td>0.212</td>
</tr>
<tr>
<td>Cigarettes/Day</td>
<td>13.7(4.1)</td>
<td>14.6(3.8)</td>
<td>-0.80</td>
<td>0.429</td>
</tr>
<tr>
<td>Years of cigarette use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTND</td>
<td>4.5(2.1)</td>
<td>4.4(1.5)</td>
<td>0.17</td>
<td>0.869</td>
</tr>
<tr>
<td>Motivation to quit</td>
<td>5.2(2.1)</td>
<td>6.4(2.2)</td>
<td>-1.63</td>
<td>0.111</td>
</tr>
<tr>
<td>BIS</td>
<td>59.8(5.7)</td>
<td>58.8(5.3)</td>
<td>0.63</td>
<td>0.532</td>
</tr>
<tr>
<td>SPSRQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punishment</td>
<td>8.4(3.8)</td>
<td>9.1(4.2)</td>
<td>-0.59</td>
<td>0.556</td>
</tr>
<tr>
<td>Reward</td>
<td>7.5(2.4)</td>
<td>7.2(2.5)</td>
<td>-1.11</td>
<td>0.621</td>
</tr>
<tr>
<td>ERQ</td>
<td>45.7(6.4)</td>
<td>47.8(8.8)</td>
<td>-0.90</td>
<td>0.372</td>
</tr>
<tr>
<td>PANAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16.4(7.6)</td>
<td>15.0(5.4)</td>
<td>0.73</td>
<td>0.467</td>
</tr>
<tr>
<td>Positive</td>
<td>26.4(8.2)</td>
<td>27.0(8.0)</td>
<td>-0.28</td>
<td>0.781</td>
</tr>
<tr>
<td>BAI</td>
<td>29.1(9.3)</td>
<td>27.5(7.9)</td>
<td>0.63</td>
<td>0.527</td>
</tr>
<tr>
<td>BDI</td>
<td>5.5(4.9)</td>
<td>3.7(3.7)</td>
<td>1.27</td>
<td>0.210</td>
</tr>
<tr>
<td>STAI</td>
<td>81.14(12.1)</td>
<td>86.18(7.2)</td>
<td>-1.67</td>
<td>0.102</td>
</tr>
<tr>
<td>Long-term effects on DCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-NF</td>
<td>13.7(4.1)</td>
<td>14.6(3.8)</td>
<td>-0.80</td>
<td>0.429</td>
</tr>
<tr>
<td>1-week</td>
<td>9.8(4.0)</td>
<td>12.6(4.6)</td>
<td>-2.19</td>
<td>0.034*</td>
</tr>
<tr>
<td>1-month</td>
<td>8.8(4.1)</td>
<td>13.0(6.5)</td>
<td>-2.56</td>
<td>0.014*</td>
</tr>
<tr>
<td>4-month</td>
<td>10.3(5.5)</td>
<td>14.2(6.9)</td>
<td>-2.07</td>
<td>0.044*</td>
</tr>
</tbody>
</table>

Values are mean and values in parentheses are 1 standard deviation (SD). FTND, Fagerström Test of Nicotine Dependence; ERQ, Emotion Regulation Questionnaire;
Supplementary Table 2. Overall mean power spectral density (PSD) values with standard deviations of all channels before neurofeedback

<table>
<thead>
<tr>
<th></th>
<th>real-feedback group (mean, SD)</th>
<th>yoked-feedback group (mean, SD)</th>
<th>Statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta (1-4 Hz)</td>
<td>9.44 (1.9)</td>
<td>9.78 (1.5)</td>
<td>-0.62</td>
<td>0.536</td>
</tr>
<tr>
<td>Theta (5-7 Hz)</td>
<td>4.29(1.7)</td>
<td>3.94(1.3)</td>
<td>0.73</td>
<td>0.473</td>
</tr>
<tr>
<td>Alpha (8-13 Hz)</td>
<td>4.71(3.2)</td>
<td>4.06(2.9)</td>
<td>0.68</td>
<td>0.503</td>
</tr>
<tr>
<td>Beta (13-30 Hz)</td>
<td>-2.85(1.6)</td>
<td>-2.58(1.7)</td>
<td>-0.50</td>
<td>0.620</td>
</tr>
<tr>
<td>Gamma (31-48 Hz)</td>
<td>-6.68(2.1)</td>
<td>-6.29(2.1)</td>
<td>-0.58</td>
<td>0.566</td>
</tr>
</tbody>
</table>
Supplementary Fig 2. Experimental protocol. FTND, Fagerström Test of Nicotine Dependence; ERQ, Emotion Regulation Questionnaire; SPRSQ, The Sensitivity to Punishment and Sensitivity to Reward Questionnaire; BIS, Barratt Impulsivity Scale; MQS, Motivation of Quitting Smoking; PANAS, Positive and Negative Affect Scales; BAI, Beck Anxiety Inventory; STAI, State-trait Anxiety Inventory; BDI, Beck Depression Inventory; DCC, daily cigarette consumption; NF, neurofeedback; TCQ, Tobacco Craving Questionnaire; EEG, electroencephalography.
Supplementary Fig 3. Power spectral density (PSD) of each frequency band in the real-feedback and yoked-feedback groups before neurofeedback. Two-sample t-tests were used to compare the PSD of the two groups before neurofeedback, which revealed no significant differences in the two groups.
Supplementary Fig 4. Power spectral density (PSD) of theta and alpha bands in the real-feedback group and normal control group.