RESEARCH ARTICLE

The top-down regulation from the prefrontal cortex to insula via hypnotic aversion suggestions reduces smoking craving

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Funding information

Open Foundation of CAS Key Laboratory of Brain Function and Disease of University of Science and Technology of China, Grant/Award Number: 2013-3; the Anhui Natural Science Foundation, Grant/Award Number: 1808085MH291; the National Natural Science Foundation of China, Grant/Award Number: 31171083, 31771221, 31471071, 81171326; the project of human social science of Anhui province, Grant/Award Number: SK2016A047; University of Science and Technology of China

Abstract

Hypnosis has been shown to have treatment effects on nicotine addiction. However, the neural basis of these effects is poorly understood. This preliminary study investigated the neural mechanisms of hypnosis-based treatment on cigarette smoking, specifically, whether the hypnosis involves a top-down or bottom-up mechanism. Two groups of 45 smokers underwent a smoking aversion suggestion and viewed smoking-related pictures and neutral pictures. One group underwent functional magnetic resonance imaging scanning twice (control and hypnotic states), whereas the other group underwent two electroencephalograph sessions. Our study found that self-reported smoking craving decreased in both groups following hypnosis. Smoking cue-elicited activations in the right dorsal lateral prefrontal cortex (rDLPFC) and left insula (II) and the functional connectivity between the rDLPFC and II were increased in the hypnotic state compared with the control state. The delta band source waveforms indicated the activation from 390 to 862 ms at the rDLPFC and from 490 to 900 ms at the II was significantly different between the smoking and neutral conditions in the hypnotic state, suggesting the activation in the rDLPFC preceded that in the II. These results suggest that the decreased smoking craving via hypnotic aversion suggestions may arise from the top-down regulation of the rDLPFC to the II. Our findings provide novel neurobiological evidence for understanding the therapeutic effects of hypnosis on nicotine addiction, and the prefrontal–insula circuit may serve as an imaging biomarker to monitor the treatment efficacy noninvasively.

KEYWORDS

EEG, fMRI, hypnosis, nicotine addiction, smoking craving

Xiaoming Li and Lijun Chen contributed equally to this study.

1 | INTRODUCTION

Cigarette smoking leads to more than 6 million annual deaths globally and is the leading preventable cause of death worldwide (GBD 2015 Tobacco Collaborators, 2017). Craving has been defined as the strong desire to pursue a substance (Skinner & Aubin, 2010). Smoking craving is a primary symptom of tobacco dependence (Piñeiro et al., 2014) and has been utilized as an important target of smoking cessation treatments (Piasecki, 2006). Specifically, exposure to smoking-related cues elicits robust craving (Saladin et al., 2012).

Despite the availability of treatments for tobacco dependence, only 6% of the more than 1 billion smokers each year are successful in doing so for more than a month (Hughes, 2007; Siu & Tyndale, 2007). Therefore, it is necessary to develop alternatives with greater efficacy for the treatment of tobacco dependence such as hypnotherapy. Hypnosis is a technique that can induce a state of consciousness characterized with the heightened susceptibility to suggestion (Mendelsohn, Chalamish, Solomonovich, & Dudai, 2008). It has been used to help smokers to quit smoking (Green, 1999) and its efficacy has been assessed but with mixed results (Baillie, Mattick, Hall, & Webster, 1994; Barnes et al., 2010; Tahiri, Mottillo, Joseph, Pilote, & Eisenberg, 2012; Viswesvaran & Schmidt, 1992). Previous studies (Barnes et al., 2010) have shown a great variation in the quitting rates (from to 88%) 6 months after the hypnosis treatment. These differences can be explained by the different hypnotherapy regimens, the variation in frequency, the number of treatments (Holroyd, 1980), and the relationship between the therapist and patient (Frankel, 1976) in the previous studies. Meanwhile, the success of hypnotherapy may be due to the hypnotisability (Perry, Gelfand, & Marcovitch, 1979), which varies among individuals. However, most of the previous studies have not considered the hypnotisability as an important factor in the treatment, which might be a reason of the found in the previous studies.

The neural mechanism of hypnosis for the reduction of cigarette smoking may be addressed using the rapidly developing neuroimaging techniques. The present study exploits functional magnetic resonance imaging (fMRI) and electroencephalograph (EEG) to examine the treatment effects of hypnosis on cigarette smoking and investigate the underlying neural mechanism of hypnosis in reducing smoking craving.

According to neurocognitive models of selective attention (Bishop, 2009; Shechner et al., 2012), the deployment of attention in the presence of emotional stimuli is regulated by two major mechanisms: a bottom-up, stimulus-driven mechanism (Davis & Whalen, 2001) and a top-down, goal-oriented control mechanism (MacDonald III, Cohen, Stenger, & Carter, 2000; Wolfe, Butcher, Lee, & Hyle, 2003). Some previous studies suggest that hypnosis is a type of top-down regulation (Dienes & Hutton, 2013; Landry, Appourchaux, & Raz, 2014; Mendelsohn et al., 2008; Raz, Lamar, Buhle, Kane, & Peterson, 2007; Vanhaudenhuyse et al., 2009; Ward, Oakley, Frackowiak, & Halligan, 2003), while the others argue that hypnosis influences processes in a bottom-up way (Kaiser, Barker, Haenschel, Baldeweg, & Gruzelier, 1997; Neufeld, Brown, Lee-Grimm, Newen, & Brüne, 2016).

To date, there is no reliable evidence indicating exact mechanisms (top-down or bottom-up) in hypnosis. For example, Vanhaudenhuyse et al. (2009) demonstrated a hypnosis-related increase in the

functional connectivity between the primary somatosensory cortex and prefrontal cortices in the processing of pain stimuli, which might reflect a top-down modulation. However, findings of functional connectivity alone between brain regions are not sufficient to prove top-down or bottom-up processes. For a causal association, the regulatory brain regions should be activated preceding to other brain regions. With fMRI alone, this evidence may not be obtained due to the low temporal resolution of fMRI.

Compared with fMRI, EEG has a higher temporal resolution and is able to distinguish the temporal order of relevant activation in these brain regions during hypnotic suggestions. The combination of fMRI and EEG data enables the identification of the temporal order of neural activation, as well as the spatial patterns implicated in hypnotic phenomena. This information would help to understand how these brain regions form a network of regulation and how their interactions reduce smoking craving, which would be highly useful for developing more effective treatment strategies for nicotine addiction and other mental illnesses.

The purpose of the present study is, thus, to investigate how hypnotic aversion suggestions reduce craving in cigarette smokers, and particularly whether a top-down or a bottom-up mechanism is involved. Data were obtained from two separate groups of cigarette smokers. One group performed a smoking-related cue task twice during fMRI scanning (in control and hypnotic states, respectively), whereas the other group performed a similar task during EEG data collection. We speculate that there are two candidate brain networks that link hypnotic aversion suggestions to reduction of cigarette craving. One network comprises regulatory brain regions, for example, the prefrontal areas (Dienes & Hutton, 2013; Landry et al., 2014; Raz, 2011), and the other network comprises aversion-generative brain regions, for example, the insula (Grupe, Oathes, & Nitschke, 2013; Hayes & Northoff, 2012). We further predict that the insula would be functionally connected to the prefrontal regions during the experience of hypnotic aversion suggestions. Finally, we predict that activation in the prefrontal regions should antecede activation in the insula, suggesting a top-down control process.

2 | MATERIALS AND METHODS

2.1 | Participants

Two groups of 45 smokers (≥ 10 cigarettes/day for ≥ 2 years, two females) with high hypnotic sensitivity (≥ 9 score), who were interested in quitting with hypnotherapy, screened from 262 volunteers with the Stanford Hypnotic Susceptibility Scale (Weitzenhoffer & Hilgard, 1962), were included in the present study. One group (24 smokers) performed a smoking-related cue task in the MRI scanner (fMRI group), whereas the other group (21 smokers) performed an almost same task during EEG data collection (EEG group). There was no significant difference in gender, age, number of cigarettes smoked per day, or number of years smoked between two groups (Table 1). All participants were told not to smoking for 2 hr before the experiment. No participants had a history of psychiatric or neurological disease. The criteria were based on a semistructured clinical interview, which

assessed the health status of the participants. The study was approved by the Human Ethics Committee of the University of Science and Technology of China and performed according to the Code of Ethics of the World Medical Association and the Helsinki Declaration of 1975. Participants were recruited in Hefei, China by advertising. All participants provided written informed consent, and they were paid 400 Chinese Yuan for attending the fMRI scan or 300 Chinese Yuan for attending the EEG scan.

The present study was not conducted as a repeated measures design. Because it will have serial order carryover effects, which could become confounded with the experimental effects if they are not effectively counterbalanced (Brooks, 2012).

2.2 | Experimental procedure in the fMRI group

The experimental protocol included a control state and a hypnotic state. Both protocols were performed while in the magnet. In the control state, the smokers were scanned in the awake state, whereas in the hypnotic state, the smokers were scanned following the induction of a hypnotic state. After entering the scanner, the smokers were induced into the hypnotic state by the hypnotist using a standard hypnotic procedure (Weitzenhoffer & Hilgard, 1962). The hypnotist subsequently issued the smoking disgust suggestion to the participants in the hypnotic state (see more details in the Supporting Information). Two states were performed on independent days (apart from 2 days to 1 week). To test the effects of single-session hypnosis and to avoid the aftereffect of hypnosis, the scan of the control state was performed first.

Before and after the scan in each state, Tobacco Craving Questionnaire (TCQ, Heishman, Singleton, & Pickworth, 2008) was completed by every participant. The participants performed the self-rating scale of smoking disgust after each state. Fagerström Test for Nicotine Dependence (FTND, Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was used for assessing nicotine dependence. The details of the questionnaires are provided in the Supporting Information. In each state, two scan runs were performed. In each scan run, the participants were presented with two types of pictures: smoking and neutral pictures taken from our previous study (Zhang et al., 2011). Fifty smoking-related pictures and fifty neutral pictures were selected as the stimuli. Each scan consisted of 25 smoking-related pictures and 25 neutral pictures, and each picture was maintained for 2 s. A varying fixation interval between 2 and 12 s (mean: 7 s) randomly occurred between two pictures, and the order of the pictures was pseudorandom and balanced across the participants. The detailed experimental

paradigm is shown in Figure 1. The participants were also scanned via resting-state fMRI in the control and hypnotic state (see Supporting Information).

2.3 | Experimental procedure in the EEG group

Similar to the fMRI group (Figure 1), 90 smoking pictures and 90 neutral pictures (including all those in fMRI group and plus 40 new ones) were employed and repeated twice. An additional 20 animal pictures were presented as irrespective stimuli to make the participants focus their attention on the task. When these animal pictures were shown, the subjects were required to press the space key to react. All stimuli (2,000 ms duration for each stimulus) were presented at random interstimulus intervals between 1,800 and 2,200 ms (mean = 2,000 ms). The rate of pressing button when the animal pictures displayed was 94.61% in the control state and 91.18% in the hypnotic state. The rate did not differ significantly between the two states ($\chi^2 = 0.721, p = .396$).

2.4 | fMRI data acquisition, preprocessing, and analyses

The individual neural activity was estimated using a general linear model that comprised two regressors of interest (smoking pictures and neutral pictures). A whole brain 2×2 ANOVA with state (hypnotic and control) and cue (smoking and neutral pictures) as two within-subject factors was conducted. A psychophysiological interaction (PPI) analysis was conducted to investigate the changes in the functional connectivity between the regulation-related brain regions and the disgust-related brain regions for each state. See details in Supporting Information. In fMRI analysis, seven participants were excluded from the analyses because they were not able to be hypnotized or their head motion exceeded 2 mm or 2° in MRI scanning.

2.5 | EEG source analysis

We used Scan 4.3 (Neuroscan, Charlotte, NC) to calculate the ERPs in the delta (0.1–3.9 Hz), theta (4–7.9 Hz), alpha (8–12.9 Hz), beta (13–29.9 Hz), and gamma (30–49.9 Hz) frequency bands (Egner, Jamieson, & Gruzellier, 2005). We performed a source analysis using BESA Research 6.0 (Megis GmbH, Munich, Germany).

Source models (Figure 2) were created based on grand-averaged ERPs in every frequency band, which were calculated by collapsing smoking-related and neutral cue-induced activities in each state. Using the source model building in the delta band in the hypnotic

TABLE 1 Information for two groups of subjects

	fMRI group	EEG group	<i>t</i>	<i>p</i>
Sex	23/1 (M/F)	20/1 (M/F)		
Age	25.08 ± 3.23	23.81 ± 2.42	1.479	.146
Number of cigarettes smoked per day	17.92 ± 6.83	15.19 ± 6.03	1.410	.166
Number of years smoked	6.96 ± 3.74	5.24 ± 2.98	1.690	.098
SHSS score	10.04 ± 1.12	10.24 ± 1.14	0.582	.563
FTND score	5.29 ± 1.71	4.19 ± 2.62	1.691	.109

EEG = electroencephalograph; fMRI = functional magnetic resonance imaging; FTND = Fagerström Test for Nicotine Dependence.

FIGURE 1 Experimental design in the fMRI and EEG groups. (a) Flowchart of the fMRI group. (b) Single-trial design in the fMRI group. (c) Flowchart of the EEG group. (d) Single-trial design in the EEG group [Color figure can be viewed at wileyonlinelibrary.com]

band as an example, we placed regional sources based on our fMRI results in a source model for the delta band grand averaged ERP data in the hypnotic state. The source locations were fixed, whereas the orientations were free to fit over the whole segment. The source models in every other frequency band in the hypnotic state with the same locations and in every frequency band for the control state were created following the described steps above (more details on source models were described in the Supporting Information).

A cluster-based permutation test was performed with BESA Statistics 1.0 to determine whether there were different source activations to smoking and neutral pictures. In EEG source analysis, one participant was excluded because of excessive artifacts in the EEG signal (>67% of the epochs over $\pm 60 \mu V$). Finally, an individual analysis in the rDLPFC and II and the FTND/TCQ/disgust data were performed. See details in Supporting Information.

3 | RESULTS

3.1 | Behavioral performance

A 2×2 repeated-measure ANOVA on the TCQ scores with time (before/after scan) and state (hypnotic and control) as within-subject factors revealed a significant main effect of time ($F_{(1,85)} = 19.320$, $p < .001$, $\eta_p^2 = 0.185$) and time $\times$ state interaction ($F_{(1,85)} = 13.204$, $p < .001$, $\eta_p^2 = 0.134$), but not the main effect of state ($F_{(1,85)} = 3.315$, $p = .072$, $\eta_p^2 = 0.038$), in the combined (fMRI + EEG) data. The planned t tests (two-tailed) indicated that the TCQ scores were significantly decreased after the scan in the hypnotic state ($t = 5.565$, $df = 43$, $p < .001$, Cohen's $d = 0.839$), but not in the control state

($t = 0.575$, $df = 43$, $p = .569$, Cohen's $d = 0.087$) (Figure 3a). The participants were more disgusted with cigarettes in the hypnotic state compared with the control state ($t = 4.974$, $df = 37$, $p < .001$, Cohen's $d = 0.807$ in the combined data, Figure 3b). The self-report hypnotic depth was positively correlated with the difference of the scores of disgust to cigarettes (control state–hypnotic state) ($r = 0.495$, $p = .002$, Figure 3c); however, it was not related to the TCQ score changes ($p > .1$). The results of individual fMRI and EEG groups were similar to those of the combined group, and are shown in the Supporting Information and Figure S1. In addition, the effects of hypnosis on smoking in participants with different hypnotisability were shown in the Supporting Information.

3.2 | Effects of hypnotic smoking aversion suggestion—fMRI data

A 2×2 repeated-measure ANOVA on the whole brain revealed a significant state (hypnotic and control) $\times$ cue (smoking and neutral pictures) interaction ([hypnotic state (smoking–neutral)]–[control state (smoking–neutral)]) in the right medial frontal cortex (rMFC), right middle frontal gyrus (rMFG), left insula (II), II/left inferior frontal cortex (IIFC), right dorsal lateral prefrontal cortex (rDLPFC), and left dorsal lateral prefrontal cortex (IDLPFC) (Table 2; Figure 4a, family-wise error (FWE) corrected $p < .05$). The planned t tests (two-tailed) indicated that these brain regions had higher activations in the hypnotic state compared with the control state when smokers watched the smoking-related pictures (rMFC: $t = 2.351$, $p = .016$, Cohen's $d = 0.570$; rMFG: $t = 1.907$, $p = .038$, Cohen's $d = 0.463$; II: $t = 2.807$, $p = .007$, Cohen's $d = 0.681$; II/IIFC: $t = 2.837$, $p = .006$, Cohen's $d = 0.688$; rDLPFC: $t = 1.962$, $p = .034$, Cohen's $d = 0.462$; IDLPFC: $t = 2.211$,

FIGURE 2 The final source model in the delta band. (a) Sources at the rMFC and II/IIFC showed almost no activation (peak < 10 nAm) when there were eight regional sources in a source model of the delta band grand averaged ERP data in the hypnotic state. (b) The final source model of delta band grand-average ERP in the hypnotic state. (c) The final source model of grand-average ERP in the control state [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Behavioral results in the control and hypnotic states in the combined data (fMRI + EEG). (a) TCQ score in the combined data. (b) Smoking disgust in the combined data. Lower scores indicated stronger disgusted with cigarettes. (c) Correlation between self-reported hypnotic depth and increased disgust in the combined data. TCQ = Tobacco Craving Questionnaire. *, $p < .05$; **, $p < .01$. Error bars represent SE

$p = .021$, Cohen's $d = 0.536$). However, there was no effect on these brain regions when the smokers watched the neutral pictures (all $ps > 0.1$).

Whole-brain analyses revealed the activations induced by cue (smoking pictures vs. neutral picture) identified in previous nicotine addiction studies (Chen et al., 2018; Courtney, Ghahremani, London, & Ray, 2014; Yalachkov & Naumer, 2011), including left pre-cuneus, rMFG and right inferior parietal lobule (Table 3) in the control state (see Supporting Information). Whole-brain analyses indicated the brain activation by cue (smoking pictures vs. neutral picture) was comprehensive during hypnotic state (Table 3).

3.3 | Psychophysiological interaction

The functional connectivity between the II and rDLPFC increased significantly ($t = 2.854$, $p = .011$, Cohen's $d = 0.596$) in the hypnotic state when smoking pictures were presented, whereas no hypnosis-related functional connectivity alteration was identified ($t = 1.895$, $p = .763$, Cohen's $d = 0.022$) when neutral pictures were presented (Figure 4b). There was no hypnosis-related functional connectivity alteration between the II and other prefrontal ROIs, neither the II/IIFC to all prefrontal ROIs, when neutral or smoking-related pictures were presented (all $ps > 0.05$).

3.4 | EEG source-waveform analysis

Statistical analysis of the delta band source waveforms in the hypnotic state indicated that the source activation in response to smoking pictures and neutral pictures was significantly different at the II and rDLPFC (Figure 4c). The activation from 490 to 900 ms at the II ($p = .012$) and from 390 to 862 ms at the rDLPFC ($p = .006$) was significantly different between the two conditions (smoking and neutral) in the hypnotic state, but not in the control state, suggesting the activation in the rDLPFC preceded that in the II in the hypnotic state. Results of the delta band source waveforms at the other four sources are in Figure S2A (Supporting Information), and results of the theta, alpha, beta, and gamma sources are in Figure S2B–E (Supporting Information).

TABLE 2 State $\times$ cue ANCOVA results

Regions	Talairach coordinates			Volume (mm ³)
	x	y	z	
rMFC	−22.4	−33.7	+26.7	1,350
rMFG	−24.2	−22.3	+35.8	837
II	+32.1	−13.0	+2.7	783
II/IIFC	+29.8	−24.5	+14.0	783
rDLPFC	−25.6	−45.8	+11.4	567
IDL PFC	+27.5	−35.1	+25.8	1,350

IDL PFC = left dorsal lateral prefrontal cortex; IIFC = left inferior frontal cortex; II = left insular; rDLPFC = right dorsal lateral prefrontal cortex; rMFC = right medial frontal cortex; rMFG = right middle frontal gyrus. The x coordinate is the horizontal position (with positive values to the left), the y coordinate is depth (with positive values anterior to the posterior commissure), and the z coordinate is the vertical position (with positive values superior to the anterior commissure). FWE corrected $p < .05$.

3.5 | Correlations of the FTND and EEG/fMRI data

The FTND (Heatherton et al., 1991) scores were correlated significantly with the activation difference between the smoking pictures and neutral pictures in the delta band source waveforms at both the rDLPFC ($r = 0.537$, $p = .015$) and II ($r = 0.677$, $p = .001$) (Figure 5). No significant correlation was identified between the FTND score and fMRI activation induced by hypnotic smoking aversion suggestion in the rDLPFC or II (all $ps > 0.05$). The relationship between the functional connectivity between the II and rDLPFC and the TCQ scores/disgust scores was shown in the Supporting Information.

3.6 | Results of the resting state of two groups

The resting state fMRI data indicated that the connectivity between the left medial frontal gyrus and the left anterior cingulate decreased in the hypnotic resting states compared with the control resting states ($t = 1.935$, $p = .038$, Cohen's $d = 0.451$, see Figure S3), which was consistent with a previous study regarding the neural basis of hypnosis (Friston et al., 1997). In EEG group, we identified increased posterior theta power in the resting EEG following hypnosis ($t = 2.335$, $p = .031$, Cohen's $d = 0.483$). This finding was consistent with the previous hypnosis study (Williams & Gruzelier, 2001). Their studies demonstrated that participants are in a state of hypnosis; therefore, our results also indicated that the participants became hypnotized in the hypnotic state in both the fMRI and EEG environments (resting fMRI and EEG data acquisition, preprocessing and analyses see details in Supporting Information).

4 | DISCUSSION

To the best of our knowledge, this investigation is the first study regarding the neural basis of hypnosis treatment for nicotine addiction and, more generally, for psychiatric/mental disorders. The most important finding in the present study is the reduction of smoking craving via the prefrontal–insula network in a top-down manner following hypnotic aversion suggestion.

4.1 | Prefrontal–insula network is involved in reducing craving following hypnotic aversion suggestion

In the present study, we identified an increased recruitment of prefrontal brain regions, including the rDLPFC, IDLPFC, and rMFG, when smokers were exposed to smoking pictures during the hypnotic state. PFC activation in hypnosis has been demonstrated in previous studies (Mendelsohn et al., 2008; Vanhaudenhuyse et al., 2009). Some studies have found that the prefrontal brain regions involved in attentional control processes in cognitive tasks (Botvinick, Braver, Barch, Carter, & Cohen, 2001; MacDonald III et al., 2000).

In the present study, we found that hypnotic aversion suggestions for smoking trigger brain regions related to aversion, such as the II and II/IIFC. Previous studies have demonstrated that insula activation was associated with feelings of disgust (Grupe et al., 2013; Hayes & Northoff, 2012; Scharmüller, Leutgeb, Schäfer, & Schienle, 2012). Some

FIGURE 4 fMRI and EEG results. (a) Significant differences in the activation elicited by smoking-related pictures (smoking vs. neutral) between the hypnotic and control states. FWE corrected $p < .05$. (b) Functional connectivity between the rDLPFC and II. (c) Grand-average differences (smoking-related pictures minus neutral pictures) in the delta band source waveforms of the II and rDLPFC in the hypnotic state and control state. *, $p < .05$; **, $p < .01$. Error bars represent SE [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5 Correlation of the FTND score and the EEG signal. (a) The activation in the rDLPFC was correlated with the FTND score. (b) The activation in the II was correlated with the FTND score

TABLE 3 Activations induced by cue (smoking pictures vs. neutral picture) in the control and hypnotic state

Active regions	Talairach coordinates			Volume (mm ³)
	x	y	z	
Control state				
Left precuneus	+8.6	+72.1	+36.2	891
rMFG	−34.5	−57.5	+3.3	378
Right inferior parietal lobule	−55.0	+28.4	+33.8	378
Right inferior parietal lobule	−31.6	+48.1	+55.4	351
Right cuneus	−14.7	+84.3	+17.3	297
Hypnotic state				
Left medial frontal gyrus	+2.0	−38.5	+21.6	39,825
Left middle frontal gyrus	+23.6	−39.7	−0.0	945
Left insula	+32.9	−11.0	+4.5	729
Left medial frontal gyrus	+1.9	−9.1	+44.1	729
Left medial frontal gyrus	−0.2	+6.4	+60.1	648
Right superior temporal gyrus	−30.0	−18.4	−32.9	540
Left superior temporal gyrus	+38.2	−6.9	−21.9	486
Left precentral gyrus	+56.1	+2.5	+31.6	432
Right superior frontal gyrus	−12.0	−8.3	+62.1	405
Left uncus	+34.4	−1.8	−27.5	378
Left inferior frontal gyrus	+37.8	−10.4	−10.9	378
Left inferior frontal Gyrus	+29.7	−25.7	−11.0	378
Right superior temporal Gyrus	−32.8	−2.7	−10.3	378
Right medial frontal Gyrus	−7.0	−49.3	−3.3	351
Right superior parietal lobule	−28.7	+54.4	+53.6	324
Left culmen	+35.1	+30.1	−24.3	270
Right insula	−45.0	−9.7	+13.5	270

rMFG = right middle frontal gyrus.

The x coordinate is the horizontal position (with positive values to the left), the y coordinate is depth (with positive values anterior to the posterior commissure), and the z coordinate is the vertical position (with positive values superior to the anterior commissure). FWE corrected $p < .05$.

other studies have suggested that the insula plays a significant role in smoking craving (Naqvi, Rudrauf, Damasio, & Bechara, 2007). We identified an enhanced activation in the II during the hypnotic state. However, the question remains regarding whether insula activation corresponds with aversion processing or smoking craving. Our data in this study demonstrate that the self-reported cravings of current smokers decreased, whereas the subjective experience of aversion to smoking increased, in the hypnotic state. Thus, enhanced activation in the II found in the present study may likely represent a basis for aversive processing, rather than smoking craving. Meanwhile, the II/IIFG, another brain region related with aversion, activated during hypnotic aversion suggestions in the present study, which is consistent with previous neuroimaging findings showing its activation during disgust

stimulation (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Wicker et al., 2003).

Furthermore, the rDLPFC and II activation was positively correlated with the FTND score in the EEG group in the hypnotic state, indicating that the increased nicotine dependence level was associated with the stronger activation in the II and the rDLPFC. This finding suggests that heavy dependent smokers may be more susceptible to smoking disgust suggestion, and therefore more effectual in hypnotherapy. This finding is interesting and may be used to generate a novel hypothesis for individualized hypnotherapy to nicotine addiction, which warrants further investigation.

Moreover, when smokers were exposed to smoking-related pictures, increased functional connectivity between the regulatory regions (e.g., the rDLPFC) and aversion-related areas (e.g., the II) after hypnotic aversion suggestions was identified, suggesting that the prefrontal–insula network is involved in the processing of aversion after hypnotic aversion suggestion. Furthermore, the reduction in craving after hypnotic aversion suggestion may result from an increased aversion emotion. The insula was functionally connected to the PFC in the processing of thermal stimuli (Peltz et al., 2011). Although the contralateral connectivity between the DLPFC and the insula was found in the present study, previous study also found the connectivity between them (Iwabuchi et al., 2017). Other studies have identified reduced prefrontal–insula functional connectivity in anxious participants (Paulus & Stein, 2010). Consistent with these findings, increased prefrontal–insula functional connectivity may reflect an emotion regulation process in the present study.

Hypnosis consists of two components: hypnotic induction and hypnotic suggestions (Oakley & Halligan, 2009). A study (McGeown et al., 2012) indicates that the induction of hypnosis is not necessary for the changes in cortical activity, though hypnotic induction enhances the level of activation in associated cortical areas. That is to say, control state can also induce the changes with hypnotic suggestion. We observed functional connectivity between the rDLPFC and II increased significantly following hypnotic smoking aversion suggestions compared with control state. Although there was no significant correlation between the change of the functional connectivity and the change of scores of disgust to cigarettes, we cannot exclude the possibility smoking aversion suggestion in control state may also increase the alterations of functional connectivity. This is an interesting problem and needs to further study.

4.2 | Prefrontal–insula network functions in a top-down manner

A study (Cojan, Archimi, Cheseaux, Waber, & Vuilleumier, 2013) has identified significantly increased activation in the prefrontal areas during hypnosis, which occurred at approximately 350 ms. The late positive potential (about 500–800 ms) predominantly arose from the insula during emotional processing (not in the hypnotic state) (Scharmüller et al., 2012). However, these findings cannot prove the top-down manner of hypnosis because of the lack of simultaneously high temporal and spatial resolutions. The most interesting result in the present study is that brain activation in the rDLPFC is triggered by smoking pictures that antecede the activation in the II following

FIGURE 6 A model of reduction in smoking craving induced by hypnotic aversion suggestions. Hypnotic aversion suggestions functioned in a top-down manner and recruited the DLPFC, which modulated the activation in the insula. The DLPFC provided a top-down attentional set to modulate the activations of the insula and induce an aversion to smoking, with concomitant reductions in smoking craving

hypnotic aversion suggestions, which indicates a top-down regulation of the rDLPFC on the II. However, studies have suggested that top-down processes from the DLPFC create an attentional “set,” which affects subsequent behavior and are imposed early in the course of activation (Banich et al., 2000). Thus, we speculated that the rDLPFC was initially activated to create and maintain an attentional set, which enables the selection of smoking-related pictures to induce an aversion effect and thereby reflects the psychological process of a top-down regulation of the rDLPFC.

These findings support the top-down regulatory role from hypnotic aversion suggestions via increased prefrontal–insula functional connectivity. Based on findings from the present study, we propose a model that illuminates how the instrumental use of hypnotic suggestions facilitates investigation of the underlying mechanisms of a decrease in smoking craving, in which the prefrontal–insula network may function in a top-down manner to generate an aversion to smoking with concomitant reductions in smoking craving (Figure 6). This model supports a top-down approach in the investigation of the mechanisms of hypnotherapy and associated psychological treatment.

It is interesting that memories could be modulated during hypnotic state (Barnier, 2002; Kihlstrom, 1997; Mendelsohn et al., 2008). And some studies proposed that nicotine and alcohol addiction would be treated using memory-updating protocols (Das, Lawn, & Kamboj, 2015; Germeroth et al., 2017; Xue et al., 2012, 2017). They thought that memory retrieval-extinction procedure is a nonpharmacological method for decreasing drug craving and relapse during abstinence. In the present study, the protocol comprises TCQ measure, hypnotic induction + resting state scanning, and disgusting suggestion, which can be regarded as smoking memories retrieval stage, reconsolidation stage and updating stage, respectively. Thus, it is possible that the inhibited effect of hypnotic suggestion on smoking is due to memory updating.

4.3 | Clinical implications

A top-down mechanism identified in the present study may help to improve our understanding of hypnotherapy. For example, it may explain why in some randomized controlled trials, the hypnosis was not effective in smoking cessation in specific participants and the efficacy of hypnotic treatment had a great variation in quit rates (Barnes et al., 2010). Low suggestible smokers may not be able to recruit top-down mechanism, therefore, it is reasonable to recruit highly hypnotizable smokers in future hypnotherapy. Furthermore, some psychotherapies, such as cognitive reappraisal, also depend on top-down mechanisms (Chiesa, Serretti, & Jakobsen, 2013). For patients with impaired ability of cognitive reappraisal (Keightley et al., 2003), poor treatment outcomes would be expected. Our results suggest that personalized treatments counting for individual differences should be necessary in hypnotherapy and perhaps other psychotherapies.

4.4 | Limitations

There are several limitations in this study. First, because much more trials were usually needed in EEG data compared to fMRI data, therefore, more pictures were included in the EEG group than the fMRI group in our study, which might make potential difference in treatment between groups. Anyway, the arousal and valence and dominant of these pictures were same between groups. Second, in China, one smoking pattern is the disparity between the high prevalence in males and the low prevalence in females (Su et al., 2015), therefore, it is difficult to recruit women smokers in China. In the present study, the sex distribution was highly skewed (only two females), which would be difficult to say to what degree these results would apply to female nicotine addicts. Third, our participants may not have strong smoking craving before hypnosis, due to the relatively short period of abstinence (2 hr), which is regarded as a state of moderate deprivation (Owens et al., 2018). We used such short period of abstinence because we hope to salient the effect of the hypnosis. It would have been more advantageous to assess participants after a longer period of abstinence from smoking (such as 12 hr), because blood levels of norharman are low after 12 hr of smoking abstinence and cue-elicited craving would be stronger (Van Den Eijnden, Spijkerman, & Fekkes, 2003). Finally, this study only examined the short-term effects of hypnotic aversion suggestions on smoking craving. In the future, the long-term effects of hypnotic aversion suggestions and the brain mechanisms involved should be examined.

5 | CONCLUSION

Combined fMRI and EEG with hypnotherapy, our study identified a top-down (prefrontal–insula) mechanism of hypnotic suggestions in reducing smoking craving. Such a mechanism has important implications for the design and optimization of hypnotic treatments of nicotine addiction and other mental disorders, and for the prediction and monitoring of treatment outcomes. Further studies in this direction are warranted to understand the mechanism of other mind–body therapies, where the involvement of a top-down or bottom-up process is unknown.

ACKNOWLEDGMENTS

This work was supported by grants from the National Key Basic Research Program (2016YFA0400900 and 2018YFC0831101), the National Natural Science Foundation of China (31471071, 31771221, 61773360, and 3180070123), and the Fundamental Research Funds for the Central Universities of China, and the Anhui Natural Science Foundation (1808085MH291), and the project of human social science of Anhui province (SK2016A047), and Open Foundation of CAS Key Laboratory of Brain Function and Disease of University of Science and Technology of China (2013-3). The numerical calculations in this study were partly performed with the supercomputing system at the Supercomputing Centre of USTC. Y. Y. was supported by the Intramural Research Program of the National Institute on Drug Abuse. The authors would like to thank Guanbao Cui for his help in organizing recruitment and testing.

CONFLICT OF INTERESTS

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

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How to cite this article: Li X, Chen L, Ma R, et al. The top-down regulation from the prefrontal cortex to insula via hypnotic aversion suggestions reduces smoking craving. *Hum Brain Mapp*. 2019;40:1718–1728. <https://doi.org/10.1002/hbm.24483>