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Increased network centrality as markers of relapse risk in nicotine-dependent individuals treated with varenicline

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Identifying smokers at high risk of relapse could improve the effectiveness of cessation therapies. Although altered regional brain function in smokers has been reported, whether the whole-brain functional organization differs smokers with relapse vulnerability from others remains unclear. Thus, the goal of this study is to investigate the baseline functional connectivity differences between relapsers and quitters. Using resting-state fMRI, we acquired images from 57 smokers prior to quitting attempts. After 12-week treatment with varenicline, smokers were divided into relapsers ($n = 36$) and quitters ($n = 21$) (quitter: continuously abstinent for weeks 9–12). The smoking cessation outcomes were cross-validated by self-reports and expired carbon monoxide. We then used eigenvector centrality (EC) mapping to identify the functional connectivity differences between relapsers and quitters. When compared to quitters, increased EC in the right dorsolateral prefrontal cortex (DLPFC), left middle temporal gyrus (MTG) and cerebellum anterior lobe was observed in relapsers. In addition, a logistic regression analysis of EC data (with DLPFC, MTG and cerebellum included) predicted relapse with 80.7% accuracy. These findings suggest that the DLPFC, MTG and cerebellum may be important substrates of smoking relapse vulnerability. The data also suggest that relapse-vulnerable smokers can be identified before quit attempts, which could enable personalized treatment and improve smoking cessation outcomes.

1. Introduction

Cigarette smoking continues to be a worldwide public health problem. Approximately 22% population smokes currently across the world and 6 million people die from smoking exposure annually. Without effective interventions, the number is expected to reach 2 million in China and 8 million worldwide by 2030 (Chen et al., 2015). Although most smokers desire to quit, the relapse rates remain high. Even with varenicline, a first-line treatment for smoking cessation, the 6-month continuous smoking abstinence rates vary from 14.2% to 46.8% (Cahill et al., 2010). Therefore, identifying relapse-vulnerable smokers before smoking cessation will aid in the development of personalized treatment strategies and possibly reduce smoking relapse.

Chronic smoking, is mainly caused by the addictive component in cigarettes, nicotine; therefore, it is defined as nicotine dependence in DSM-IV. Brain imaging studies have reported brain structural and functional differences between smokers and nonsmokers using magnetic resonance imaging (MRI) (Gallinat et al., 2006; Li et al., 2015; Lin et al., 2014; Shen et al., 2016; Viswanath et al., 2015). Therefore, MRI is a promising tool to identify brain regions and networks underlying relapse vulnerability. Recent functional MRI (fMRI) studies tried to predict smoking cessation outcomes with tasks, and reported different results on different types of cues (Courtney et al., 2016). Smokers who had heightened reactivity to smoking cues were more likely to relapse (Janes et al., 2010), while those had heightened reactivity to smoking-cessation messages were more likely to quit (Chua et al., 2011; Falk et al., 2011; Jasinska et al., 2012). Regarding nondrug-related reward stimuli (i.e., money and pleasant cues), smokers who had weak response were more likely to fail (Sweitzer et al., 2016; Versace et al., 2014;

Abbreviations: BOLD, blood-oxygen level dependent; CO, carbon monoxide; DLPFC, dorsolateral prefrontal cortex; dACC, dorsal anterior cingulated cortex; DMN, default mode network; DSM, Diagnostic and Statistical Manual of Mental Disorders; EC, eigenvector centrality; EPI, echo-planar imaging; FD, framewise displacement; fMRI, functional magnetic resonance imaging; FSPGR, fast spoiled gradient echo; FTND, Fagerström Test for Nicotine Dependence; FOV, field of region; FWHM, full-width half-maximum; GLM, general linear model; MFG, middle frontal gyrus; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; nAChR, nicotinic acetylcholine receptor; rCBF, regional cerebral blood flow; ReHo, regional homogeneity; rsFC, resting-state functional connectivity; SFG, superior frontal gyrus; SPM, Statistical Parametric Mapping; STG, superior temporal gyrus; tDCS, transcranial direct current stimulation; TE, echo time; TMS, transcranial magnetic stimulation; TR, repetition time.

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Wilson et al., 2014). Moreover, two studies (Kronke et al., 2015; Nestor et al., 2011) compared brain reactivity between ex-smokers and current smokers, and found that brain regions involved in top-down control might be important substrates of successful abstinence. All these studies suggested that neural basis of smoking cessation outcomes might be associated with the brain regions just mentioned (e.g., prefrontal cortex, anterior cingulate cortex, amygdala, ventral striatum). Given an increasing number of studies reported neural circuits implicated in this disorder, identifying the specific brain networks that distinguished relapsers form successful quitters should be helpful in improving smoking cessation outcomes.

Recent researches on brain network analyses have investigated the functional changes that are associated with drug abstinence. In cocaine-dependent individuals, amygdala-based network was analyzed between relapsers and non-relapsers, and a model that combined the resting-state functional connectivity (rsFC) and years of education predicted relapse status with 73.3% accuracy (McHugh et al., 2014). Likewise, another study that analyzed regional cerebral blood flow (rCBF) and functional connectivity revealed increased rCBF in hippocampus and strengthened hippocampus-posterior cingulate cortex rsFC in the relapsed group, compared with the early remission and control groups. And the two fMRI features predicted relapse with 75% accuracy following treatment (Adinoff et al., 2015). While in nicotine-dependent individuals, a recent study focused on insula-based network, and found that increased functional connectivity between posterior insula and primary sensorimotor cortices was associated with improved smoking cessation outcomes (Addicott et al., 2015). However, all these studies conducted functional connectivity analyses based on predefined seed regions selected by researchers, although the seed selection depended on a hypothesis, it might result in selection bias.

As a data-driven approach, graph theory-based network analysis has been widely used to quantitatively analyze the complex networks at a whole-brain level. Previous studies (Breckel et al., 2013; Lin et al., 2014) explored brain functional networks in nicotine-dependent individuals using graph theory analysis, however, these studies focused on the neural alterations caused by smoking exposure. Whether the functional organization differs smokers with relapse vulnerability from others remains unclear. To further investigate the nodes of brain network which may potentially involved in relapse risk, we conducted a resting-state fMRI study in a sample of treatment-seeking smokers with a special graph-based method: eigenvector centrality (EC) mapping. This method has been used to investigate brain network centrality in neurodegenerative diseases and mental disorders, such as Alzheimer's disease (Binnewijzend et al., 2014), Parkinson's disease (Lou et al., 2015) and major depression disorder (Song et al., 2016). By attributing a value to each voxel in the brain, EC mapping can simply and objectively detect all the brain areas serving as functional hubs, which have greater connectivity with other parts of the brain. Without having to specify in advance regions of interest, it is independent of researchers' selection and therefore free of selection bias.

2. Materials and methods

2.1. Participants

Sixty-eight smokers, who wanted to quit smoking, participated in this study. Participants were mainly recruited by posted flyers and online advertisements. All participants were male, Han Chinese and right-handed. Smokers were defined as individuals smoked >10 cigarettes per day in the last one year and met the DSM-IV criteria of nicotine dependence. Exclusion criteria were listed as follows: 1) a history of neurological or psychiatric diseases; 2) systemic diseases (i.e., diabetes, hypertension); 3) current use of psychotropic medications or concurrent substance abuse such as alcohol and heroin; 4) MRI contraindications like claustrophobia and metal implants. The screening was done through their medical records and clinical evaluations performed by an experienced psychiatrist. All aspects of the research protocol were reviewed and approved by the Institutional Review Boards of the Second Affiliated Hospital of Zhejiang University School of Medicine. And all subjects provided signed informed consents prior to study participation.

Demographic and baseline smoking data were obtained from all participants by a questionnaire prior to scanning. Nicotine dependence severity was assessed using Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Exhaled carbon monoxide (CO) was measured to confirm participants' smoking status (≥10 ppm). Smokers were allowed to smoke as usual prior to scanning to avoid withdrawal symptoms during scanning. Eleven of 68 smokers were excluded (one with brain tumor, three with excessive head motion and seven without follow-up), resulting in 57 smokers for statistical analysis. A subgroup of these subjects' imaging data has been published previously (Wang et al., in press).

2.2. Image acquisition

Scans were acquired on a 3.0 Tesla GE SIGNA scanner using a birdcage head coil. Conventional T1- and T2-weighted images were performed to rule out structural abnormalities. Resting-state functional scans consisted of 185 echo-planar imaging (EPI) volumes with following parameters: 30 slices (thickness/gap = 4/1 mm), repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, matrix = 64 × 64, field of view (FOV) = 240 × 240 mm^2, flip angle = 80°. During fMRI scanning (370 s), participants were instructed to lie still, keep eyes closed, and not to fall asleep. Ear plugs and foam padding were used to reduce scanner noise and head motion. Additionally, high-resolution anatomical T1-wighted images were obtained using 3D fast spoiled gradient echo (FSPGR) sequence with following parameters: 136 sagittal slices (thickness/gap = 1.2/0 mm), TR = 5.06 ms, TE = 1.12 ms, matrix = 256 × 256, FOV = 240 × 216 mm^2, flip angle = 15°. All magnetic resonance images were visually inspected for image artifacts and anatomical abnormalities by an experienced neuroradiologist (one participant was excluded due to brain tumor).

2.3. Smoking cessation treatment

After prequit imaging and other assessments, all smokers received a 12-week smoking cessation treatment with varenicline (http://www.pfizer.com/products), which is a nicotinic receptor partial agonist. Weekly telephone visits were conducted to know their smoking status and encourage them to make an attempt to quit. Consistent with previous studies, the end point was the 4-week continuous abstinence for the last four weeks of drug treatment (weeks 9–12) (Gonzales et al., 2006; Jorenby et al., 2006). All participants reported quitting smoking for at least 24 h. Following 24 h abstinence, participants who smoked any cigarettes during treatment were considered as relapsers, and those who remained continuously abstinent for the last four weeks of treatment (weeks 9–12) were considered as successful quitters, which was based on weekly self-reports of smoking behavior and cross-validated by an expired CO level (≤6 ppm). Seven participants lost to follow-up during treatment were excluded.

2.4. Resting-state fMRI image preprocessing

Resting BOLD data were preprocessed with the Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSFA, http://www.restfmri.net/forum/DPARSF), which is based on the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first ten volumes were discarded to reduce magnetization disequilibrium, followed by slice-timing correction and head motion correction. Exclusion criteria on head motion was exceeding >2 mm/degree (three participants were excluded). After segmentation of T1 images, resting images were co-registered to T1 images and then