Title: Circuitry-Guided Smoking Cessation in Schizophrenia

Grant number: UG3DA047685

NCT number: NCT03281629

Document date: 02/01/2022

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Study protocol

Background

The prevalence of cigarette smoking in schizophrenia patients (45%-65%) is 3-5 folds higher(Lasser et al., 2000) than the smoking rate (~14%) in the general U.S. population. Although smoking rate has declined in persons with mental illness(Han et al., 2022), the quit rate is low in the schizophrenia population(Lasser et al., 2000; Aubin et al., 2012). Identifying the neurobiological bases responsible for such high smoking vulnerability and continued use is critical to devise better intervention strategies to reduce cigarettes smoking in individuals with schizophrenia.

Many brain regions such as medial/lateral prefrontal cortex, cingulate, insula, ventral striatum, hippocampus, thalamus, and amygdala (Loughead et al., 2010; Franklin et al., 2011; Franklin et al., 2012; Menossi et al., 2013; Funk et al., 2016; Joutsa et al., 2022) and functional connectivity involving anterior cingulate, striatum and insula, medial prefrontal, and temporal cortices regions (Hong et al., 2009; Li et al., 2017; Hsu et al., 2019; Keeley et al., 2020) have been implicated in nicotine addiction. Evidence from animal studies has suggested that the basolateral amygdala, which has bi-directional neural connections with prefrontal cortex and hippocampus, is associated with nicotine addiction(Sharp, 2019). Importantly, many of these structures, especially the amygdala and prefrontal cortex, are also closely associated with schizophrenia(Ho et al., 2019; Zheng et al., 2019; Guimond et al., 2021). Direct comparisons between nicotine addiction and schizophrenia showed shared abnormal functional connectivity between the dorsal anterior cingulate cortex and bilateral subcortical extended amygdala(Moran et al., 2013). The

extended amygdala mainly describes a neuroanatomic region with dense cholinergic neurons, centered at the nucleus basalis and the surrounding structures including the amygdala, substantia innominata, hippocampus, and ventral striatum. It is also the region with the highest nicotine binding in the brain(Shimohama et al., 1985; Cairns et al., 1988; Heimer, 2003). The cholinergic projections from the extended amygdala reach essentially the entire cortex and are important for attention and arousal(Sarter et al., 1999; Heimer, 2003). The extended amygdala may be at the center of the cortical-subcortical reentrant pathways critical for understanding and treating addiction and schizophrenia(Leshner et al., 1999; Heimer, 2000; 2003).

We hypothesized that neuromodulation of the extended amygdala area, a region likely contributing to both nicotine addiction and schizophrenia pathophysiology, may help in correcting the nicotine addiction - schizophrenia comorbidity. However, there is currently no noninvasive method that can specifically target this area, making it difficult to directly test the hypothesis.

Conventional neuromodulation approaches such as repetitive transcranial magnetic stimulation (rTMS) can only stimulate neurons at the scalp surface, while the H-coil method can stimulate deeper but more diffuse brain areas. Previous H-coil neuromodulation was found to be efficacious for short-term smoking cessation(Dinur-Klein et al., 2014; Zangen et al., 2021), although even this approach cannot stimulate deeply enough to reach the extended amygdala. Moreover, rTMS over dorsolateral prefrontal cortex for treating cigarettes use(Eichhammer et al., 2003; Amiaz et al., 2009; Li et al., 2020)and craving(Amiaz et al., 2009; Rose et al., 2011; Hayashi et al., 2013; Li et al., 2013; Trojak et al., 2015; Chang et al., 2018; Li et al.,

2020)resulted in mixed findings(Wing et al., 2012; Prikryl et al., 2014). Identifying alternative circuitry abnormalities that maybe more causally linked to smoking in schizophrenia may be needed in our effort to develop more effective treatment strategy for nicotine addiction in this patient population.

In our pilot study, we identified TMS-targetable cortical brain regions that have robust functional connectivity with the extended amygdala that are related to nicotine addiction. We proposed to use rTMS to test whether modulating this circuit is associated with changes in smoking behaviors in smokers with schizophrenia.

Materials and methods

Participants

We examined whether the nicotine addiction related circuitries thus identified could be modulated by TMS and produce a reduction in nicotine addiction. We used a 20-TMS-session, sham-controlled, parallel-group, participant- and rater-blinded, randomized study design to test this hypothesis. The TMS cortical target that satisfied the pre-defined criteria in our pilot study was the dorsomedial prefrontal cortex (-15, 28, 48 in Talairach space. Details in Results). For this study, 30 SSD smokers (cigarettes per day≥5 over the past 4 weeks) were enrolled. Participants were randomly assigned to receive active or sham TMS at a 2:1 ratio, which allows for more statistical power in the TMS group to explore the association between changes of rsFC and changes of addiction severity. Of the 30 randomized, 26 completed, including 16 in the TMS and 10 in the sham group. The 2:1 ratio of randomization was chosen to assure more statistical power in the TMS group for exploring the association between changes of rsFC and changes of

nicotine addiction severity. Conditions including major medical and neurological illnesses, history of head injury with cognitive sequelae, mental retardation, substance dependence within the past 6 months or current substance abuse (except nicotine), and pregnancy were exclusionary. Subjects were asked not to consume caffeinated drinks prior to scan and be abstinent from alcohol for 24 hours prior to each fMRI and TMS session. No participant vaped or used electronic cigarettes before or during the treatment. Pregnant females were excluded. SSD smokers were not required to be smoking cessation treatment-seeking as the primary purpose here was to assess target engagement, i.e., whether TMS can impact the nicotine addiction severity-related circuitries and such effects, if found, would be related to change in nicotine addiction severity.

TMS

There were 20 TMS sessions over ~4 weeks. Stimulations were 10Hz pulse trains that are considered facilitatory(Wassermann, 1998), delivered as a 4-second stimulation train, followed by a 26-second quiet period, for a total of 30 trains lasting ~15 minutes (1,200 pulses per session). The 10Hz stimulation was selected based on findings from our pilot study that more severe FTND was correlated with lower rsFC (see Results) and accordingly, we hypothesized that facilitatory TMS may induce an increase of the rsFC and reduce nicotine addiction severity. The TMS target was the rsFC-defined dorsomedial prefrontal cortex (details in Results). The Brainsight™ Navigation system (Rogue Research Inc) was used to precisely stimulate the target throughout the treatment. A Magstim Super Rapid^2 Plus1 stimulator and two Magstim air-film, figure-of-eight, 70-mm coils (one active and one sham) were used. The sham coil provided controls for appearance, procedure, and auditory related confounds but not the TMS skin

sensation. Therefore, we combined the sham coil with electric current stimulation (Coulbourn E13-22) and large area electrodes (EPAD, Thymapads) to generate similar skin sensations(Borckardt et al., 2008) at the forehead, triggered by TMS pulses. The pads were also applied to the active TMS condition but without electric stimulation. Participants were asked to guess their group assignment at the end.

We used individualized electric field modeling through SimNIBS(Thielscher et al., 2015) to define both the TMS intensity and coil orientation (Stokes et al., 2007; Deng et al., 2013; Stokes et al., 2013). The individualized TMS intensity was determined to induce electric field strength of 100 V/m or above to ensure effective and comparable stimulations across participants. The TMS coil was positioned so the induced currents ran perpendicular to the gyral orientation of the dorsomedial prefrontal site (Opitz et al., 2011).

Clinical and smoking related assessments

Cigarettes per day and urine cotinine were the primary tobacco consumption indices and the FTND was used to represent severity of nicotine addiction. Previous factor analyses showed that the primary factor of the FTND was loaded with item 1, 3, and 5 of the six FTND questions, which asked time to first cigarette in the morning, whether the first cigarette in the morning or the rest of the cigarettes is most preferred, and whether one smokes more frequently in the first hour of the morning. These are symptoms representing severity of morning withdrawal symptoms or difficulty to maintain abstinence after overnight nonsmoking(Radzius et al., 2003). We used the sum of these items to refer to 'morning smoking severity' of the FTND. FTND score and cigarettes per day were obtained at baseline, session 5 (treatment week 1), 10 (week 2),

15 (week 3), and 20 (week 4). Imaging was performed at baseline, session 5, 10, and 20. The Brief Psychiatric Rating Scale (BPRS) measured the overall psychiatric symptoms(Hedlund et al., 1980). BPRS and urine cotinine were measured at baseline and session 20. All participants (whether receiving active or sham TMS) were encouraged to quit smoking using a standard psychoeducational clinical procedure. Staff conducting these procedures and assessments were blinded to group assignment.

Imaging data acquisition and analysis

Resting-state fMRI scans were obtained using a 3T Siemens Prisma scanner equipped with a 64-channel head coil. The Human Connectome Project multi-band sequences were used: echo-planar pulse sequence with 2mm isotropic, TR=720ms, MB=8, AP/PA encoding, 4 runs×5.4 min each=24minutes). High-resolution ($0.8\times0.8\times0.8mm^3$) T1-weighted MPRAGE images were acquired. Data were processed using Analysis of Functional NeuroImages (AFNI)(Cox, 1996) software. The preprocessed data were spatially smoothed to a FWHM of 6 mm. The linear trend, 6 motion parameters, their 6 temporal derivatives and time courses from the white matter and cerebral spinal fluid were removed as regressors of no interest. Time points with excessive motion (>0.3mm) and their neighboring time points were censored. Images were spatially normalized to the Talairach space(Talairach et al., 1988). Individual statistical maps were then calculated using a seed-based correlation analysis using dorsomedial prefrontal cortex as seed. The mean time-series within each seed ROI was correlated with the time course of each voxel in the brain to obtain resting-state functional connectivity (rsFC). Pearson's correlation coefficients were converted to z values using Fisher's r-to-z transform.

Statistical Analysis Plan

Demographics were compared using ANOVA or $\chi 2$ tests. Target engagement was evaluated by extracting dorsomedial prefrontal cortex seeded rsFC with the extended amygdala regions, including bilateral hippocampus, amygdala, and substantia innominate. The linear mixed effect model was used to evaluate the group by time interaction of rsFC on FTND, cigarettes per day, and urine cotinine, although statistical significance using this full model was not expected as this was a proof-of-concept study. Exploratory analyses were conducted comparing TMS vs. sham at different time points using independent-sample t-test and comparing baseline vs. post-TMS measurements using paired-sample t-tests at $p<0.05$. Effect sizes were calculated for nominally significant measures using Cohen's *d*. The primary analyses assessed the strength of the associations between changes of rsFC and changes in the smoking measures, using Spearman's correlation to account for non-normal distributions. All tests were two-tailed.

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