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Exploring the Relationship Between Smoking and Brain Functional Connectivity in Schizophrenia

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ABSTRACT

Schizophrenia is a chronic psychiatric condition affecting around 1% of the global population ((Rizvi., 2024)). Individuals with schizophrenia exhibit higher levels of smoking (80%) than the general population (15-20%) ((Leonard et al., 2007)). Given that schizophrenia is associated with disrupted functional connectivity, this study will determine the relationship between smoking and functional connectivity in schizophrenic individuals. We used an open dataset of a total of 81 participants who were categorized into four groups: non-schizophrenic smokers (n=22), non-schizophrenic non-smokers (n=22), schizophrenic smokers (n=12), and schizophrenic non-smokers (n=25). Resting-state functional magnetic resonance imaging (fMRI) was available. The CONN toolbox was used to analyze the fMRI data to assess for differences in connectivity using ROI-to-ROI and graph theoretic methods in both the whole brain and a subset of ROIs chosen based on prior literature. Functional connectivity analysis controlling for age and sex revealed a significant difference in degree when comparing all groups with an ANOVA, and a followup pairwise comparison showed reduced average degree for the smoking control group compared to nonsmoking schizophrenia group. In the subset of ROIs, we found a statistically significant group difference for global efficiency and degree, and pairwise comparisons revealed reduced global efficiency for the smoking SCZ group compared to the nonsmoking SCZ group when controlling for age and sex. These findings suggest that smoking is associated with differences in brain network function in individuals with schizophrenia.

INTRODUCTION

Schizophrenia (SCZ) is a mental disorder that impacts how people behave, identified by a combination of positive and negative symptoms. Positive symptoms are psychotic symptoms not typically seen in health patients, and negative symptoms are an absence of normal function. Positive symptoms include hallucinations and delusions, and negative symptoms include disorganized speech, unorganized behavior, and avolition ((Tandon et al., 2013)). Schizophrenia affects about 1% of the global population, and treatment can be difficult to manage due to the challenges of accessing mental health care ((Luvsannyam et al., 2022)). Treatment plans include medication like antipsychotics, cognitive behavioral therapy, and family therapy. These treatment plans, while effective, are costly, with the mean monthly cost for people with schizophrenia being $1806, four times more than the demographic national average of $419 for people without schizophrenia ((Fitch et al., 2014)). Healthcare systems often struggle to treat schizophrenia because of its high cost and chronic nature. One health-related behavior that people

diagnosed with schizophrenia are more probable to engage in is smoking; these individuals have a high usage of smoking of 80%, compared to the national average of 15-20% ((Caponnetto et al., 2022)). This research is critical to understanding the mechanisms of schizophrenia. Given the 80% prevalence of smoking in people with schizophrenia, it is important to clarify what mechanisms may underlie this disparity, particularly in functional connectivity.

The progression of schizophrenia is shaped by a complex interplay of genetic, epigenetic, and external influences, each contributing to the disorder's progression. Several factors are contributory to the progression of schizophrenia, with genetics being a vital contributor to the development of the mental disorder. Neuroimaging studies suggest that genetic threat variants for schizophrenia are associated with altered brain anatomy, particularly in the hippocampus and prefrontal cortex ((Modinos et al., 2017)). Additionally, epigenetic mechanisms like DNA methylation and histone modifications, may mediate how environmental stressors interact with genetics to influence the progression of schizophrenia ((Doyle et al., 2019)). Some environmental factors that influence schizophrenia include family trauma, stress, pregnancy complications, substance abuse, and migration ((Stilo & Murray, 2019)). As it emerges during late adolescence, along with its chronic symptoms, schizophrenia is challenging for recovery, suggesting a potential impairment in both social and psychological functioning.

The hypothalamus acts as a control center and regulates emotions, heart rate, and circadian rhythm, and plays a role in coordinating neural signaling ((Goel et al., 2025)). The hypothalamus is functionally connected to a wide range of brain regions, such as the amygdala, hippocampus, and prefrontal cortex ((Giustina et al., 2022)). People with schizophrenia exhibit decreased functional connectivity with the hypothalamus and other regions of the brain, such as the amygdala, prefrontal cortex, and hippocampus ((Lynall et al., 2010)). The hypothalamus is part of the ventral part of the diencephalon that is connected with the rest of the brain, and as schizophrenic patients tend to have an enlargement of the third ventricle, an impaired diencephalon impacts a range of brain regions, including the cerebral cortex, medulla, and pons ((Jasim, 2021)). Functional connectivity changes in these regions, specifically the hypothalamus, have been correlated with negative symptoms of schizophrenia. Similarly, the hypothalamus influences cognition through stress regulation and sleep performance. To have optimal sleep, the suprachiasmatic nuclei in the hypothalamus help regulate the circadian rhythm of the body ((Ma & Morrison, 2024)). The hypothalamus also governs the hypothalamic-pituitary-adrenal (HPA) axis, a primary regulator for stress responses, eliciting emotional output like mood. The HPA is heavily affected in schizophrenia due to abnormal cortisol levels. This deregulation leads to elevated cortisol levels and poor feedback loops ((Mikulska et al., 2021)). As a result, there is heavy exposure to stress hormones that damage the brain, specifically the prefrontal cortex and hypothalamus.

Large-scale neural systems, namely the salience, frontoparietal, and default mode network (DMN), influence complex cognitive processes, and their dysregulation has been increasingly revealed in the deficits related to schizophrenia. Previous research on the salience network in schizophrenia shows consistent structural and functional abnormalities, indicative of disrupted engagement with stimuli ((Palaniyappan 2010)). Smoking has been suggested to be a significant influence on the misattribution of the salience network, amplifying the network's dysfunction and contributing to symptoms ((Janes et al.,

2018)). Earlier studies on the frontoparietal control network in schizophrenia suggested that disruptions occur in both within-network and cross-network functional connectivity in this disorder, which are marked by cortico-subcortical disconnection ((Tu et al., 2013)). Smoking further promotes control-network dysconnectivity ((Tu et al., 2013)). Previous research on the DMN in schizophrenia shows disrupted functional and anatomical connectivity that demonstrate increased intrinsic activity and structural abnormalities in core DMN regions like the posterior cingulate cortices and the medial prefrontal ((Galindo et al., 2018)). Smoking then contributes to DMN dysregulation, which is linked to differences in task-related suppression ((Hu 2017)). Studies have been associated with decreased gray volume matter in the temporal and frontal lobes, and disruptions in neurotransmitters such as glutamate, dopamine, and GABA ((Luvsannyam et al., n.d.)).

Glutamate functions as a central excitatory signal in the brain and is involved in regulating learning, memory, and mood regulation. In schizophrenia, abnormal glutamatergic signaling has been repeatedly observed, correlating with changes in cognitive impairments and negative symptoms ((Javitt & Zukin, 1991))((Moghaddam & Javitt, 2012)). Glutamate dysregulation may also be tied to oxidative stress and neuroinflammation in the brain, both of which are implicated in the schizophrenic brain ((Nayak., 2025)). Smoking has also been seen to further influence glutamate signaling. Nicotine exposure has been associated with a modulation in glutamate release, which may be why some individuals with schizophrenia report feeling calmer after smoking ((Kumari., 2005)). This may aid in explaining the extremely high prevalence of smoking in people with schizophrenia. Smoking provides a temporary relief in cognitive deficits, but may add to glutamate dysregulation in the long term.

Researchers have turned to graph theory to understand how schizophrenia affects brain connectivity. Graph theory allows scientists to model the brain as a system made up of edges and nodes. Prior studies using fMRI data have revealed that individuals with schizophrenia show reduced global efficiency in the DMN and Salience network ((Lynall et al., 2010)). The changes reflect a brain that is less efficient at integrating information, potentially leading to disorganized thinking. Smoking similarly is associated with alterations in network topology, increasing local clustering in reward-related areas ((Cheng., 2019)). These changes could further be related to variations in emotional regulation in people with schizophrenia who smoke. It may be that smoking interacts with glutamate dysfunction in a cycle. Smoking may initially help glutamate levels, but chronic exposure can disturb neurotransmitter homeostasis and shift connectivity patterns ((Duan., 2015)).

In this paper, we will investigate the relationship between smoking and functional connectivity in schizophrenia. The previous paper that used the same dataset found that smoking was associated with preserved salience-to-default mode network dynamics and increased DMN interactions in individuals with schizophrenia, whereas these dynamics were reduced in healthy controls. We took a different approach and looked at the hypothalamus and its interaction with similar networks and other regions of interests (ROIs). We hypothesize to observe sequences of altered connectivity between our ROIs, including the hypothalamus, the DMN, salience, and fronto-parietal networks, in addition to subcortical regions – the cerebellum, thalamus, and basal ganglia, in schizophrenics who smoke compared to schizophrenics who do not smoke. We also will investigate if the functional connectivity

between the hypothalamus and other regions is affected. We expect to observe lower hypothalamic functional connectivity in schizophrenia smokers compared to schizophrenic nonsmokers. In terms of graph theory results, we expect that schizophrenic smokers will show differences in network organization relative to schizophrenic nonsmokers. If graph theory analyses show that smokers with schizophrenia have further disruptions in the whole brain and subset of regions closely related to key regulatory networks, namely the DMN, salience, and fronto-parietal networks, and subcortical regions – the thalamus, cerebellum, and basal ganglia, it may aid in explaining brain mechanisms related to how nicotine dependence may worsen functional impairments ((Hall., 2015)). However, schizophrenic smokers may also smoke because it helps relieve stress ((Morgan., 2024)). It may also inform interventions, such as behavioral therapies focused on reducing smoking. By exploring this question, we aim to expand understanding of the connection between smoking status and schizophrenia.

METHODS

Subjects

This study used an open dataset (Liao et al., 2020; OpenNeuro: ds001461/versions/1.0.3). The original investigators recruited 43 healthy controls (HCs) and 56 individuals with schizophrenia patients (SPs), all of whom completed informed consent procedures, following ethical approval from the First Affiliated Hospital of Chongqing Medical University. Schizophrenia was diagnosed using the SCID (DSM-IV) and confirmed after a 1-year check in, while HCs and their relatives were screened to ensure no history of schizophrenia. Exclusion criteria included age <16, neurological or psychiatric disorders, recent substance use disorder (except cigarettes), MRI anomalies, or metal implants. After exclusions for incomplete data and excessive head motion, 49 SPs remained (first-episode, 44 chronic), with 39 on stable atypical antipsychotic medication and 10 medication-free. Medication exposure was standardized to chlorpromazine dose-years, with no prolonged use of other drugs. Age, sex, diagnosis, and smoking status were collected and available as part of the open dataset (see Table 1).

MRI Preprocessing

Preprocessing, analysis, and visualization was performed using the standalone version of CONN toolbox (CONN 21a; https://web.conn-toolbox.org/). The CONN toolbox is a software used to display and analyze the functional connectivity of the brain. The Methods used in this study have been generated by the CONN toolbox.

We preprocessed the functional and anatomical data using a flexible pipeline ((Henson., 1999)) that included realignment with correction for susceptibility distortion interactions, slice-timing correction, outlier detection, direct segmentation and normalization to MNI space, and spatial smoothing. We realigned functional data using the SPM realign & unwarp procedure ((Nieto-Castanon., 2011)), where all scans were coregistered to a reference image (the first scan of the first session) using a least-squares approach and a six-parameter (rigid body) transformation ((Power., 2014)). We then resampled the data using b-spline interpolation to correct for motion and susceptibility-induced

distortions. To address temporal misalignment due to interleaved slice acquisition (Siemens order), we applied SPM's slice-timing correction (STC) ((Ashburner., 2005))‘ ((Friston., 1995)), using sinc interpolation to resample each slice's BOLD time series to a common mid-acquisition time. We identified potential outlier scans using the ART toolbox ((Friston 1995)), flagging acquisitions with framewise displacement greater than 0.5 mm or global BOLD signal changes exceeding 3 standard deviations ((Sladky., 2011))‘ ((Calhoun., 2017)). We then computed a reference BOLD image for each subject by averaging all scans that were not identified as outliers. We normalized both functional and anatomical data to MNI space and segmented them into gray matter, white matter, and CSF tissue classes. Resampling was done at 2 mm isotropic resolution using a direct normalization approach ((Calhoun., 2017))‘ ((Ashburner., 2007)), implemented via SPM's unified segmentation and normalization algorithm ((Ashburner., 1997))‘ ((Studholme., 1998)) with the default IXI-549 tissue probability map template. Finally, we smoothed the functional data using spatial convolution with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel of 8 mm.

MRI Denoising

We denoised the functional data using a standard pipeline ((Friston., 1996)) that included regression of potential confounding effects. These confounds consisted of white matter time series (5 CompCor noise components), CSF time series (5 CompCor noise components), motion parameters and their first-order derivatives (12 factors) ((Power., 2014)), outlier scans (up to 30 factors) ((Behzadi., 2007)), session effects and their first-order derivatives (2 factors), and linear trends (2 factors) within each functional run. After regression, we applied bandpass filtering to the BOLD time series, retaining frequencies between 0.008 Hz and 0.09 Hz ((Nieto-Castanon., n.d.)). We estimated the CompCor ((Hallquist., 2013)) noise components within white matter and CSF by calculating the average BOLD signal and the largest principal components that were orthogonal to the BOLD average, motion parameters, and outlier scans, using each subject's eroded segmentation masks. Hypothalamic seeds were defined for each hemisphere for the lateral (MNI coordinates $x = \pm 6$, $y = -9$, -10) and medial (MNI coordinates $x = \pm 4$, $y = -2$, $z = -12$) hypothalamus based on the coordinates from Voigt et al. (2022) which based their coordinates on an atlas of this region ((Baroncini et al., 2012)).

MRI Processing, 1st level

We estimated ROI-to-ROI connectivity (RRC) matrices to characterize patterns of functional connectivity across 91 Harvard-Oxford atlas cortical ROIs, 15 Harvard-Oxford subcortical ROIs, 26 cerebellar ROIs from the AAL atlas, 32 HPC-ICA network ROIs ((Desikan., 2006)), and 4 units of the hypothalamus, totaling 168 ROIs. A subnetwork of ROIs of interest was defined as 45 ROIs comprising the HPC-ICA DMN, salience, and fronto-parietal networks as well as bilateral subcortical regions – the cerebellum, thalamus, basal ganglia, and hypothalamus. We represented functional connectivity strength using Fisher-transformed bivariate correlation coefficients derived from a weighted general linear model (weighted GLM; Friston., 1997). These coefficients were defined separately for each pair of ROIs, modeling the association between their BOLD signal time series ((Nieto-Castanon., 2020)).

MRI Processing, 2nd level

We performed group-level analyses using a General Linear Model (GLM). In our study, four groups underwent resting-state functional magnetic resonance imaging (fMRI): non-smoking individuals with schizophrenia (n = 25), smoking individuals with schizophrenia (n = 22), non-smoking healthy controls (n = 12), and smoking healthy controls (n = 22) (see Table 1). We defined smokers as individuals who used tobacco daily for at least one year. To minimize withdrawal effects, smokers were asked to smoke before arrival but refrained from smoking for 30 minutes prior to scanning to avoid nicotine peaks. We also considered age and sex as covariates in a two-way analysis of covariance (ANCOVA) to assess the interaction between schizophrenia and smoking. Similarly, we used connection-based inference implemented in CONN, which allowed us to make inferences about individual connections, rather than focusing on groups of connections. In order to control family-wise error rates, we used the standard Benjamini and Hochberg's FDR algorithm to compute for each individual connection (between all pairs of ROIs) a connection-level FDR-corrected p-value, which we defined as the expected proportion of false discoveries among all connections with effects larger than this one across the entire ROI-to-ROI matrix. Our default criterion used a connection-level FDR-corrected $p<0.05$ threshold to select among all connections those deemed significant (with larger effects than what we could reasonably expect under the null hypothesis) ((Nieto-Castañon et al., 2020)).

MRI Graph Measures

All ROI-level graph measures below are based on our user-defined non directional graphs with nodes = ROIs, and edges = supra-threshold connections. For each subject (and condition) a graph adjacency matrix A is computed by thresholding the associated ROI-to-ROI Correlation (RRC) matrix r by an absolute (e.g. $z>0.5$) or relative (e.g. highest 10%) threshold. The cost threshold was 0.15, which signifies the proportion of connections that were preserved based on connection strength. The analysis threshold for significance for an FDR-corrected, two-sided, p-value was 0.05. Then, from the resulting graphs, a number of measures can be computed addressing topological properties of each ROI within the graph as well as of the entire network of ROIs (see Latora and Marchiori, 2001, and Achard and Bullmore, 2007, for further details about these and other graph theoretical measures).

Degree & Cost: Degree and Cost are defined, respectively, at each node as the number (degree) or proportion (cost) of edges from/to each node. Degree and Cost at each node/ROI represent measures of network centrality, characterizing the degree of local connectedness of each ROI within a graph.

Average path distance: Average path distance at each node is defined as the average path-distance between this node and all other nodes in the subgraph of connected nodes. Average path distance represents a measure of node centrality within a network, characterizing the degree of global connectedness of each ROI within a graph.

Clustering Coefficient: Clustering Coefficient is defined as the proportion of connected edges in the local neighboring sub-graph for each node/ROI: Clustering coefficient represents a measure of local integration, characterizing the degree of inter-connectedness among all nodes within a node neighboring sub-graph.

Global Efficiency: Global Efficiency at a node is defined as the average of inverse-distances between this node and all other nodes in the same graph. Global efficiency at a node represents a measure of this node centrality within the network, characterizing the degree of global connectedness of each ROI.

Local Efficiency: Local Efficiency at each node is defined as the Global efficiency of the neighboring sub-graph of this node. Local efficiency represents a measure of local integration or coherence, characterizing the degree of inter-connectedness among all nodes within a node neighboring sub-graph.

Betweenness Centrality: Betweenness centrality represents an alternative measure of node centrality within a graph. It is defined as the proportion of times that a node is part of a shortest-path between any two pairs of nodes within a graph.

Statistical Analysis

Statistical analyses were conducted using JASP (Version 0.19.1.0) (JASP Team, 2025). Mean and standard deviation for demographic variables was calculated using this software. To assess for statistical differences in demographic variables between groups, chi-square and ANOVA were used.

Table 1

Description of Participants

	Non-Smoking SCZ	Smoking SCZ	Non-Smoking Controls	Smoking Controls	p
Age, Mean (SD)	31.16(8.82)	35.67(9.06)	29.54(9.72)	34.54(9.82)	0.0231
Gender, M(F)	9(16)	6(6)	19(3)	19(3)	0.00023
N	25	22	12	22	

Note. SCZ = schizophrenia

RESULTS

In the whole brain network, the 2x2 between-subjects ANOVA interaction with diagnosis status and SCZ status, controlling for age and sex, revealed a statistically significant group difference for cost (dof=75, p=0.000792; t=-3.50) and degree (dof=75, p=0.000923; t=-3.45). In the follow up pairwise comparisons for the hypothalamus, there were statistically significantly lower cost and degree for smoking controls when comparing the smoking controls and nonsmoking SCZ groups when controlling for age and sex (t=-3.32, dof=77, p=0.001360; see Figure 1). Specifically, among the pre-selected ROIs (refer to Supplementary Data Table 2 for all values), the right cerebellar lobule 6 (t=-4.77, p=0.000008), the right cerebellar lobule 1 (t=-4.60, p=0.000016), the posterior lobe of the cerebellum (t=-3.98, p=0.000156), the left cerebellar lobule 6 (t=-3.77, p=0.000314), the left cerebellar lobule 1 (t=-3.74, p=0.000347), the right cerebellar lobule 2 (t=-3.51, p=0.000752), the left cerebellar lobule 2 (t=-3.04, p=0.003197), the right lateral prefrontal cortex of the frontoparietal network (t=-3.07, p=0.002993), the left posterior parietal cortex of the frontoparietal network (t=-3.03, p=0.003354), and the left supramarginal gyrus within the salience network (t=-2.93, p=0.004463) showed statistically significant differences between groups.

In the subnetwork, the 2x2 between-subjects ANOVA interaction with diagnosis status and SCZ status, controlling for age and sex, revealed a statistically significant group difference for global efficiency (dof=75, p=0.045308; t=-2.04), cost (dof=75, p=0.000991; t=-3.43), and degree (dof=75, p=0.000916; t=-3.45). In the follow up pairwise comparisons for the subnetwork, there was a statistically significant result showing lower global efficiency for the smoking SCZ group when comparing the smoking SCZ and nonsmoking SCZ groups when controlling for age and sex (t=-2.02, dof=77, p=0.046665).

In the whole network 2x2 between-subjects ANOVA interaction with diagnosis status and SCZ status using ROI-to-ROI connection-based analysis of the full network of 168 ROIs, there were no statistically significant differences in functional connectivity both when correcting for and not correcting for age and sex. In exploratory pairwise analyses, the ROI-to-ROI connection-based analysis of the full network of 168 ROIs for the pairwise comparison of the nonsmoking SCZ group versus nonsmoking control group when controlling for age and sex revealed that the connection between the right posterior inferior temporal gyrus (pITG) and the left cerebellum crus 1 (CC1) was statistically significantly stronger for the nonsmoking SCZ group (dof=77, p=0.011485, t = 5.37). The subnetwork analysis did not reveal statistically significant connections.

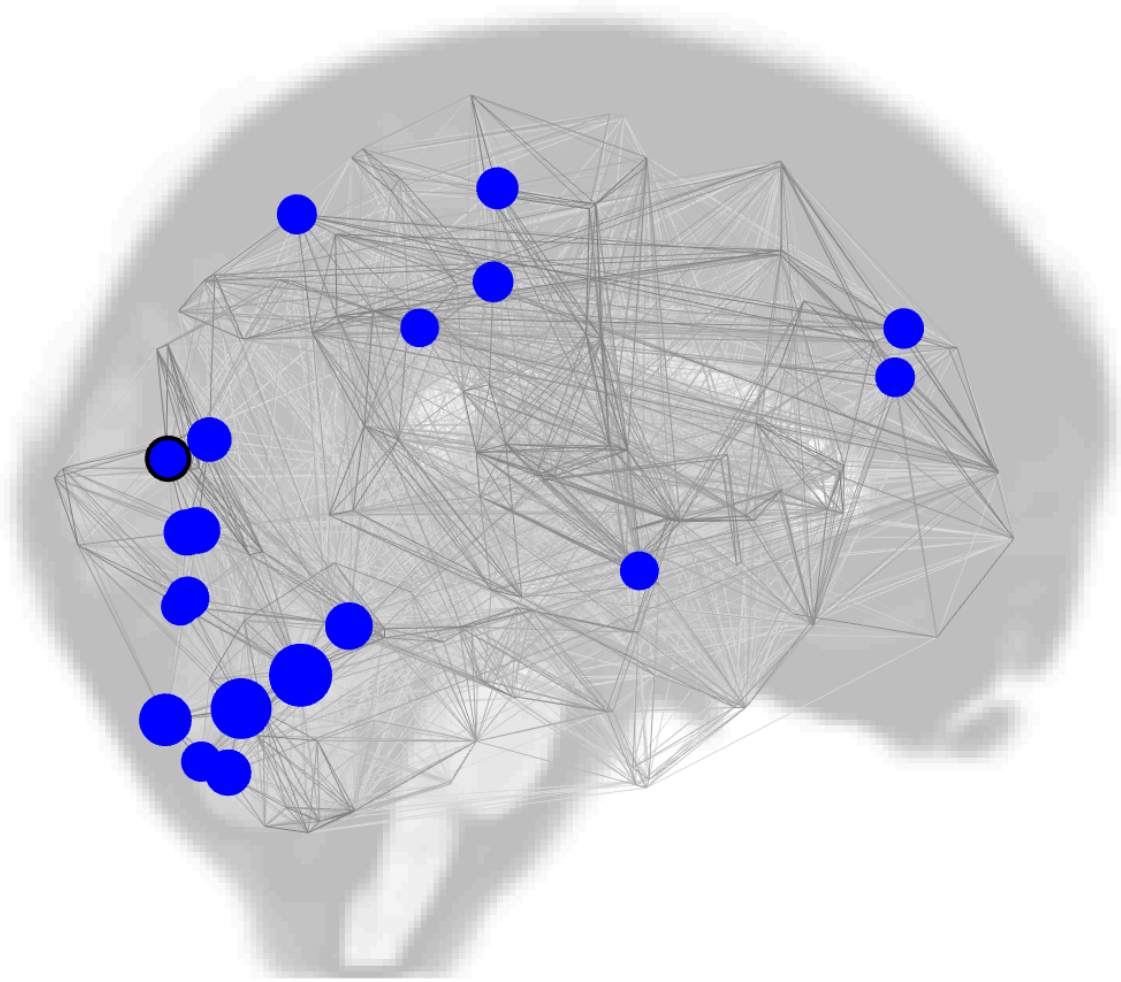

Figure 1. *Whole-brain network visualization and statistical results from a pairwise comparison showing significant difference in cost between the smoking control and nonsmoking SCZ groups (t = -3.32, p = 0.001360, dof = 77). Blue nodes indicate ROIs with significant effects, which is thresholded at p-FDR < 0.05.*

DISCUSSION

This study's purpose was to advance understanding of how smoking modulates functional connectivity in individuals with schizophrenia. When investigating the impact of diagnosis status and SCZ status on whole brain connectivity, controlling for age and sex, we found a statistically significant group difference for cost and degree. In the follow up pairwise comparisons, there were statistically significant results for cost and degree when comparing the smoking controls and nonsmoking SCZ groups. Previous research shows that schizophrenia is associated with lower network connectivity, including reductions in degree, which correlates to cognitive deficits ((Lynall et al., 2010)). Smoking has been associated with additional disruptions in brain structure and connectivity even when people try to self medicate with it ((Kutlu et al., 2015)). Some studies propose that long-term smoking can blunt typical patterns of brain connectivity, especially in attention and reward processing circuits ((Yuan 2015)). A meta-analysis examining seed-based resting-state functional connectivity in individuals with schizophrenia and revealed a lower connectivity between seed regions, such as the right superior temporal cortex, left insula, right medial prefrontal cortex, the DMN, and the right precentral gyrus. ((Li et al., 2019)). No hyperconnectivity was found between seeds and any other network areas in patients. The study concluded that decreased functional connectivity results in the malfunction of information processing ((Li et al., 2019)). In this same analysis of the subnetwork, we found a statistically significant group difference for global efficiency and degree, suggesting that there is a difference in the efficiency of information processing and average number of connections between ROIs in this network. Previous research shows that both schizophrenia and chronic nicotine use impact brain topology, with schizophrenia being associated with reduced global efficiency, and nicotine shown to modulate connectivity in attention, suggesting that their interaction may produce distinct adaptations ((Smucny 2013))' ((Ward 2022)). Another study conducted a meta-analysis of seed-based fMRI studies and found widespread hypoconnectivity in schizophrenia, particularly within networks and regions included in our subnetwork analysis like the default mode network, salience, affective, and thalamic systems ((Dong et al., 2018)). The study's findings show that schizophrenic patients may struggle to differentiate their own perspective from the significance of external stimuli, which is a core symptom of schizophrenia ((Dong et al., 2018)).

In the follow up pairwise comparisons for the subnetwork in the hypothalamus, there was a statistically significant result indicating lower global efficiency for the smoking SCZ group when comparing the nonsmoking SCZ and smoking SCZ groups when controlling for age and sex. These results suggest that smoking status is associated with reduced global efficiency in brain network organization among individuals with schizophrenia. This association may reflect differences in how information is exchanged across networks among smokers with schizophrenia. Previous research shows that smoking is prevalent among people with schizophrenia, often linked at attempts to self medicate ((Potvin et al., 2014)). However, both schizophrenia and chronic smoking are associated with reduced global efficiency and altered connectivity in brain regions such as the DMN and salience networks ((Smucny et al., 2017)). While nicotine may offer short-term cognitive relief, long-term smoking is associated with a worsened overall brain network functioning ((Valentine et al., 2018)). This pattern of results is consistent with the claim that the nicotine in smoking modulates functional connectivity in specific brain regions implicated

in schizophrenia, particularly through its impact on neurotransmitter systems, like the glutamate and dopamine systems ((Moghaddam & Javitt, 2012)) ((Leonard et al., 2007)). Our findings highlight the potential influence of smoking in modulating brain circuits tied to stress regulation and reward processing.

In an exploratory comparison of nonsmoking SCZ versus nonsmoking control groups, there was a statistically significant difference in functional connectivity between the right pITG and left CC1. Since the overall ANOVA was not significant, this exploratory pairwise analysis should be viewed as limited evidence and requires further investigation before being accepted as strong support for these findings since it risks inflating the occurrence of a type 1 error. The pITG has been implicated in processing visual and semantic information, while the CC1 has been shown to influence the regulation in cognitive control and emotional responses ((Jackson 2021)). The significant difference in functional connectivity between the pITG and the CC1 may reflect diagnosis-related differences in circuits involved in attention and social perception, though this should be interpreted cautiously given that it is an exploratory analysis ((Smucny et al., 2017)). These functions are often disrupted in schizophrenia. The plausible altered connectivity may reflect a neural adaptation tied to smoking's effects on dopamine and acetylcholine systems ((Jacobsen et al., 2004)). Because this study is cross-sectional, these associations cannot determine whether smoking influences hypothalamic connectivity or whether pre-existing connectivity differences contribute to smoking behavior in schizophrenia.

One notable limitation of our study is that there were age and gender differences between groups, which may have confounded the connectivity findings. Ages ranged from 17 to 60, introducing variability in brain structure and function that could impact our study. The study also has a small sample size of schizophrenic smokers' group. This might lead to false positives and lack of reproducibility. Although we attempted to control for these variables, it is possible that developmental neurobiological differences influenced the observed connectivity patterns. Another limitation in our study were lifestyle habits such as alcohol consumption, sleep, and stress, which may influence functional connectivity and glutamate levels since they were not accounted for in our dataset. Subsequent studies may expand upon the current results by examining how connectivity patterns change depending on treatment history. Future research on similar topics should also repeat this study with bigger sample sizes. There is also a need for research that explores how smoking might change glutamate levels in the brain and how this affects people with schizophrenia. Even with its limitations, this study contributes valuable insight into how smoking relates to functional connectivity in schizophrenia.

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