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The Association Between Smoking and Major Depression: a Neural Network Analysis

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Abstract: Background and Aim: There is a strong relationship between MDD (major depressive disorder) and smoking. However, the underlying neural mechanisms between MDD and smoking are not clean yet. Although several neuroimaging studies include brain volumes, PET studies for smoked and depressive individuals, fMRI (functional magnetic resonance imaging) analyses have been waiting to fill this gap. We have aimed to investigate the brain network differences between smoking and non-smoking MDD subjects with fMRI analyses. **Method:** Fourteen female (aged 20-38) and six male subjects (aged 21-37) with MDD were recruited in this cross-sectional study. Smoker (n = 10) and non-smoker (n = 10) individuals with MDD were compared with HAM-D (Hamilton Depression Rating Scale) and fMRI. **Results:** In fMRI analyses, smokers exhibited increased brain activations in the precentral gyrus, supplementary motor area, and frontal gyrus in smokers than non-smokers with MDD ($p<0.05$). Clinically, the HAM-D score was higher in smokers than non-smokers (p = 0.046). Smoker and non-smoker groups were similar in age, gender, and duration of MDD. **Conclusion:** In conclusion, increased severity of depression requires different network interactions in smoker depressive patients from non-smokers. Further controlled cases with long-term studies are needed to solve the confusion and clarify cause and effects relationships in this area of cognitive neuroscience.

Key words: Depression, smoking, fMRI.

1. Introduction

Widespread decreases in cerebral volume have been documented in MRI (magnetic resonance imaging) studies of patients with Major Depressive Disorder (MDD) [1-5]. However, demographic factors, such as cigarette smoking, medication use, alcohol, and lifestyle factors, as well as genetic risk factors, may also lead to subtle alterations in brain structure [5-9]. For instance, cigarette smoking is highly prevalent among patients with mental illness, including MDD [10, 11]. Despite that smoking has been associated with decreased volumes in several regions (the posterior and ACC (anterior cingulate cortices), the INS (insular cortex), the dorsolateral prefrontal cortex, and the orbitofrontal cortex in MDD samples, similar analyses of non-psychiatric individuals have revealed increased age-related occipital and striatal volumes, in contrast to numerous regions exhibiting decreases, overlapping with smokers with MDD [12, 13]. It should also be mentioned that in contrast to other structures, the striatum is the only exceptional area exhibiting increased volumes in smokers. Nicotine is a well-known neurotransmitter involved in a wide range of cognitive and motor processes related to the unique distribution of its receptors throughout the CNS (central nervous system) [14-18]. Although numerous animal studies have reported significant changes at the anatomical and neurochemical levels after nicotine exposure [19-22], human studies remain relatively rudimentary [23]. Brody et al. [24] have interestingly reported that nicotine-induced striatal activation was associated with significant alterations in grey matter volumes. It is difficult to explain why patients with MDD and healthy individuals should differ in terms of striatal volumes. However, it is plausible that depression-free smokers express a rich repertoire of

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β-nAChR (*β*-nicotinic acetylcholine receptor), most densely localized in the thalamus, substantia nigra, striatum, and cerebral cortex, leading to increased volumes in this population [25, 26].

In addition to the different distribution of nicotinic receptors in healthy individuals described above, it is also possible that patients with MDD may have additional neurotoxic and traumatic conditions related to depressive status, capable of leading to decreased volumes and hence reversing the beneficial effects of nicotine seen in healthy groups [27-29]. Despite these promising data, there has still been no investigation of the presence of an underlying network hyperactivation, particularly involving the striatum, leading to volume alterations [30, 31]. To the best of our knowledge, no previous studies have examined associations between functional network alterations and smoking in patients with depression. This study explores the relationship between smoking and dynamic brain network alterations in a sample of individuals with MDD aged between 40 and 60 years.

2. Materials and Methods

2.1 Participants

Twenty individuals with MDD were recruited for the study in Neurology and Psychiatry Department, Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital. The local ethics committee approved the study of scientific researches of the Faculty of Medicine, Alanya Alaaddin Keykubat University. All participants gave written informed consent to be included in this project. Subjects were taken to the study after exclusions for cognitive impairments, chronic or acute neurological disease history, and systemic illness. Patients met the *Diagnostic and Statistical Manual of MDD*, Fourth Edition (DSM-IV). Diagnoses were confirmed by two experienced psychiatrists using the mini-international neuropsychiatric interview [32]. The patients were then referred to the radiology department for fMRI (functional magnetic resonance imaging).

2.2 Neuroimaging

fMRI of the patients was performed with the Signa Explorer MR device (General Electric Company, United States). After the patient was positioned in the MR device and the calibration was completed, the resting state activity was recorded for functional imaging. During this recording, patients were asked to keep their eyes open and to stand without a move. fMRI recording lasted approximately 12.5 min, 255 volumes were displayed (TR 3,000 ms, TE 30 ms, FA 90°) (TR/TE: 3,000/30 ms), FOV 256×256×156 mm (FH×AP×RL), voxel size 4×4×4 mm, flip angle 90° and slices 39. The recording parameters for the anatomical T1 image of the sagittal section were 156 slices; (TR/TE: 1/3.7), FOV 256×256×156 mm (FH×AP×RL), voxel size was determined as 1×1×1 mm. For the fMRI analysis, we used the FMRIB FSL software tools on the Linux Mint 18.3 Sylvia operating system (ver.5.0.10, https://www.fmrib.ox.ac.uk/fsl). The raw data were obtained from the MR device as DICOM single slice images and converted to NIFTI format with dcm2niix (ver. V1.0.20170724) command-line tool for the subsequent processing steps. The FSL "fsl_anat" script was used for brain extraction. The preprocessing steps with the FSL FEAT tool were performed collectively for all subjects. In the preprocessing stages, functional images were aligned to the center image and motion correction was applied. A high pass filter was applied with a time constant of 150 s which is well below the 0.01-0.1 Hz range where the resting state networks were observed. The smoothing kernel FWHM was determined as 5 mm. ICA (independent component analysis) was performed with FSL "melodic" tool. In order to clean functional data from the artifacts, due to general body/head movement, respiratory and cardiovascular origin and device-dependent slow signal fluctuations, ICA components depending on their time course, frequency content and spatial distribution are manually labeled. The ICA components labeled as artifacts are removed from the functional data by using the FSL "fsl_regflit" tool. Following the preprocessing step cleaned

functional data anatomical images of individuals were registered to the MNI152 standard brain using the FSL "applywarp" tool. Group level ICA was run on the standard brain images to obtain ICA components. The individual time series and spatial maps of ICA components were calculated by applying two-stage regression with the FSL "dual_regression" tool. The distribution of the data was calculated by the permutation method (5,000 times) and the data from the two groups were compared with design matrix of two-sample unpaired *t*-test. Corrected *p*-values were calculated for multiple comparisons; $p < 0.05$ was considered significant. In addition to a comparison of group-level ICA components, an ROI (region of interest) analysis was performed with maks defining thalamus, globus pallidus, amygdala, insula, cingulate cortex, and right-left superior frontal regions. The final stage of the analysis was repeated with these ROIs and group-level differences were compared for each ROI.

Each patient was positioned in the Signa Explorer MR device (General Electric Company, United States), the resting state activity was recorded for functional imaging after the calibration was completed. For the dual regression process, we used a DMN (default mood network) map [33]. By using this map which includes ten components of DMN, we gained different time series for each component between smokers and non-smokers groups (MDD-S and MDD-NS).

2.3 Statistical Analysis

All statistical analyses were conducted using SPSS 21 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Means and standard deviations were computed for all continuous variables of interest. Comparisons between "non-smoker with MDD" and "smoker with MDD" categories were performed using Student's *t*-test and Mann-Whitney *U* test.

The frequencies of categorical variables were compared using Pearson χ^2 or Fisher's exact test, when appropriate. A value of $p < 0.05$ was considered significant.

3. Results

We have found that there were no differences in age, sex distribution, and duration of MDD between nonsmokers and smokers ($p > 0.5$, Table 1). However, the HAM-D score was significantly higher in smokers ($p = 0.046$).

In evaluating the DMN-lateral occipital cortex component connectivity (shown as green), we observed increased activity in smokers group in the left precentralgyrus, left postcentralgyrus, left insular cortex, left opercular cortex, left superior frontal gyrus, left frontal pole, right precentralgyrus, bilateral supplementary motor area, and bilateral anterior cingulate gyrus (shown as red-yellow) (Figs. 1 and 2; Table 2). A similar high connectivity pattern was also observed for the DMN- hippocampus (shown as green) and left precentral gyrus, left posterior cingulate gyrus, right frontal pole, right anterior supramarginal gyrus, right insular cortex, right precentral gyrus, right postcentral gyrus, right superior frontal gyrus, and right anterior cingulate gyrus (Figs. 3-5; Table 3).

Table 1 Demographic and clinical characteristics of smokers and non-smokers with MDD (mean ± SD for continuous variables).

	Smokers ($n = 12$)	Non-smokers ($n = 12$)	p
Sex			
Male	2	4	0.32
Female	8	6	
HAM-D score	20.75 ± 3.3	17.42 ± 4.3	**0.046***
Duration of MDD (month)	11.83 ± 1.5	11.17 ± 0.7	0.291
Age (years)	29 ± 7.1	27.58 ± 7.8	0.198

t-test and Man-Whitney *U* test were performed for continuous variables and Fisher's Exact Test for categorical variables. * $p < 0.05$

shown in bold. HAM-D: Hamilton Depression Rating Scale, MDD: Major Depressive Disorder, *n* = number of patients.

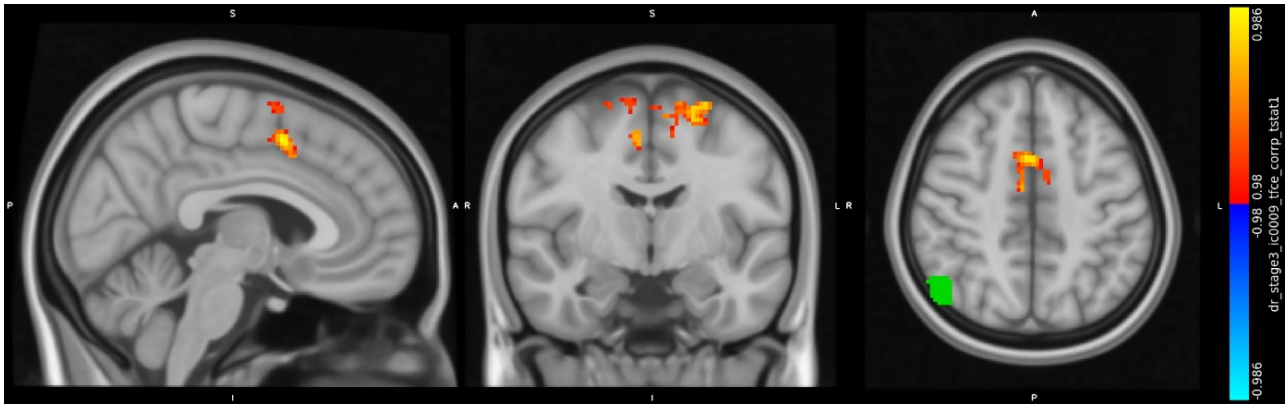

Fig. 1 Smokers showed increased activity in the precentralgyrus and supplementary motor area, shown as red-yellow, while high connectivity patterns between the DMN- lateral occipital cortex component are shown as green.

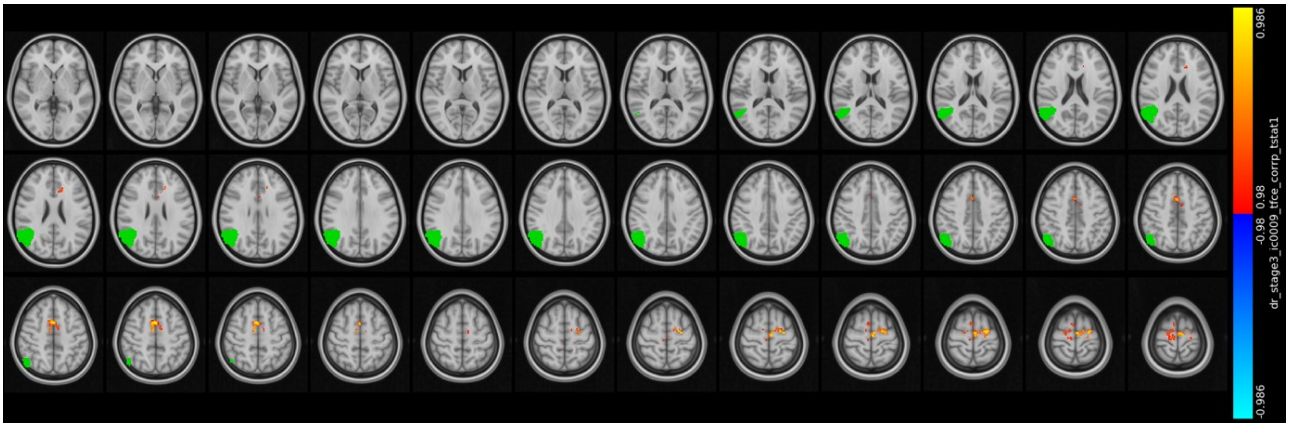

Fig. 2 Detailed mapping of smokers showing increased activity in the left precentralgyrus, left postcentralgyrus, left insular cortex, left opercular cortex, left superior frontal gyrus, left frontal pole, right precentralgyrus, bilateral supplementary motor area, and bilateral anterior cingulate gyrus, shown as red-yellow while high connectivity patterns between the DMN-lateral occipital cortex component are shown as green.

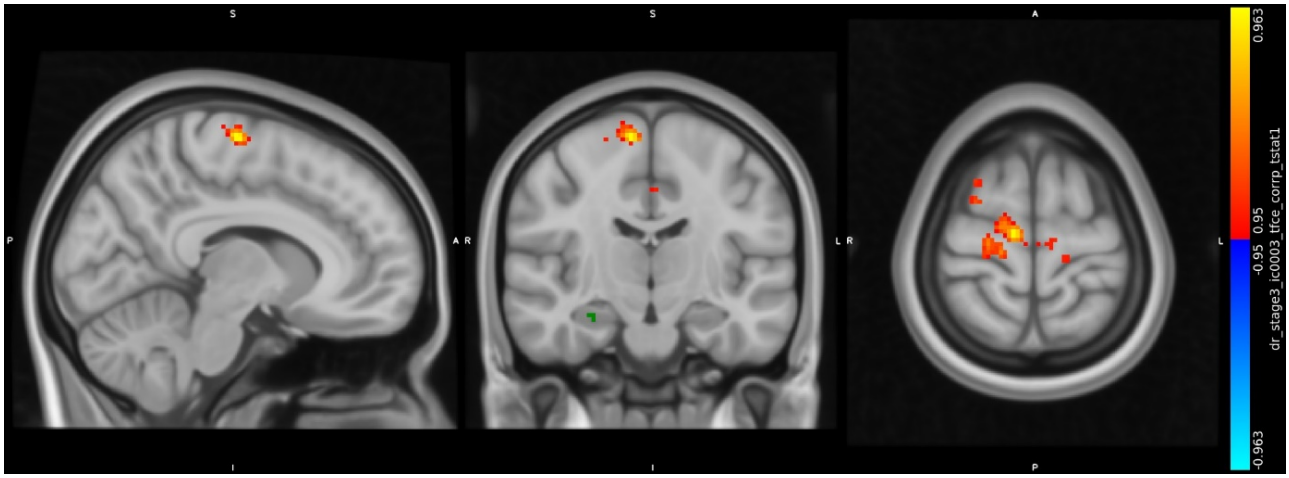

Fig. 3 Smokers showed increased activity in precentralgyrus shown as red yellow while there was a high connectivity between DMN- hippocampus component and the right hippocampus shown as green.

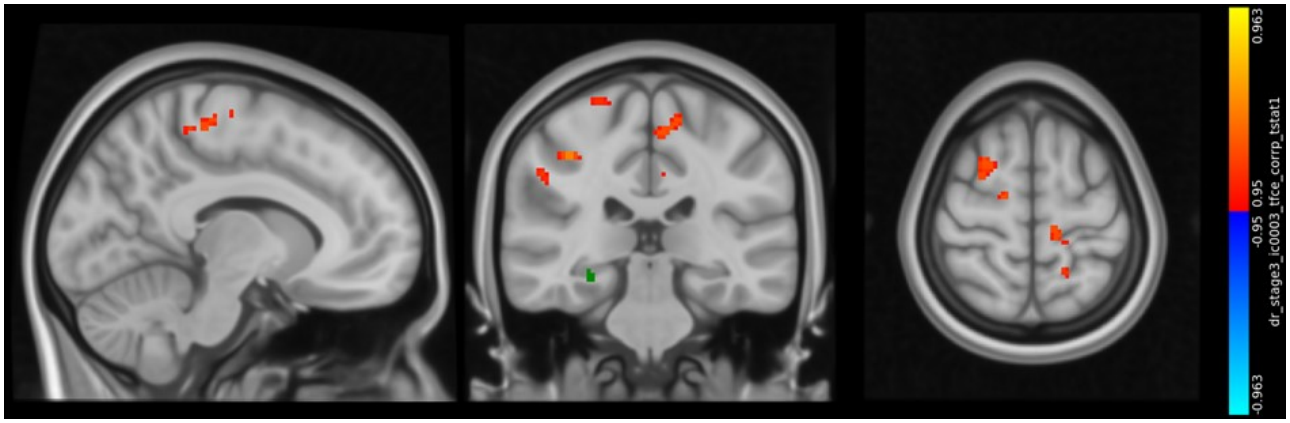

Fig. 4 Smokers showed increased activity in superior frontal gyrus, shown as red yellow while there was a high connectivity between DMN- hippocampus component and the superior frontal gyrus shown as green.

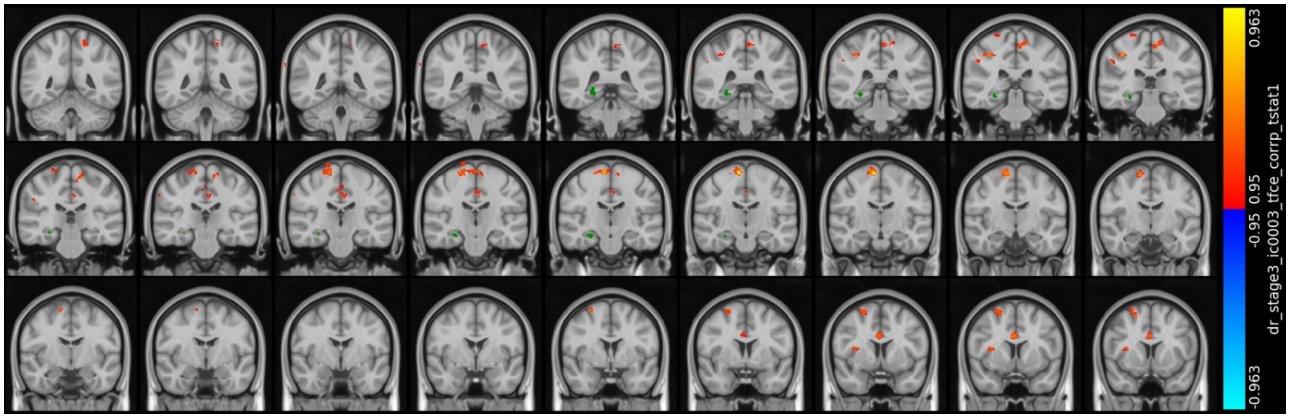

Fig. 5 Detailed mapping of smokers showing increased activity in the left precentralgyrus, left posterior cingulate gyrus, right frontal pole, right anterior supramarginalgyrus, right insular cortex, right precentralgyrus, right postcentralgyrus, right superior frontal gyrus, right anterior cingulate gyrus.

Table 2 Voxel analysis revealed 1-p-MAX values as 0.98 for the precentral gyrus and supplementary motor area (Figs. 1 and 2).

Cluster index	Voxels	1-p-MAX	1-p-MAX X (vox)	1-p-MAX Y (vox)	1-p-MAX Z (vox)	1-p-COG X (vox)	1-p-COG Y (vox)	1-p-COG Z (vox)	COPE-MAX	COPE-MAX X (vox)	COPE-MAX Y (vox)	COPE-MAX Z (vox)	COPE-MEAN
Left anterior cingulate gyrus	10	0.981	46	69	49	45.8	68.6	49.6	4.51	47	69	49	4.16
Right supplementary motor cortex	30	0.982	43	65	68	42.5	64.5	69.7	4.41	44	64	69	4.1
Left paracingulate gyrus	32	0.983	52	75	48	51.7	75.4	48.3	4.96	53	77	49	4.18
Right precentral gyrus	113	0.983	38	52	71	38.9	55.3	70	5.45	38	52	71	3.94
Bilateral supplementary motor area	556	0.986	43	66	61	48.5	60.2	65	4.98	44	66	61	3.9

Table 3 Voxel analysis revealed 1-p-MAX values as 0.95 for the precentral gyrus (Figs. 3 and 4).

Cluster Index	Voxels	1-p-MAX	1-p-MAX X (vox)	1-p-MAX Y (vox)	1-p-MAX Z (vox)	1-p-COG X (vox)	1-p-COG Y (vox)	1-p-COG Z (vox)	COPE-MAX	COPE-MAX X (vox)	COPE-MAX Y (vox)	COPE-MAX Z (vox)	COPE-MEAN
Right frontal pole	1	951	30	82	56	30	82	56	4.44	30	82	56	4.44
Right anterior supramarginal gyrus	3	951	13	51	55	13	50.3	54.7	3.74	13	51	55	3.63
Left precentral gyrus	12	951	44	51	61	45.1	51.3	60.7	3.49	45	51	61	3.32
Right anterior supramarginal gyrus	23	953	19	47	54	19.2	47.4	53.7	4.21	19	47	54	3.68
Right insular cortex	36	955	29	67	42	28	67.4	41.7	4.93	29	67	42	4.11
Right postcentral gyrus	44	956	26	48	58	26.8	46.7	58.5	4.69	26	48	59	3.91
Left posterior cingulate gyrus	54	954	47	50	54	45.9	51.6	55.7	4.15	47	51	54	3.31
Right superior frontal gyrus	81	954	32	67	67	32.6	66	67	4.15	31	63	68	3.56
Right anterior cingulate gyrus	94	956	43	67	50	43.7	68.7	51.2	4.34	43	67	50	3.49
Left precentral gyrus	145	954	48	48	64	51	44.1	65.6	3.86	49	48	65	3.25
Right precentral gyrus	279	963	40	55	70	37.9	53.4	70.6	5.56	40	55	70	3.36

4. Discussion

Based on the current literature, it is difficult to conclude why healthy individuals and those with MDD respond differently to nicotine exposure. In order to resolve this question, we evaluated the underlying functional resting-state fMRI correlates in two different groups (MDD-S and MDD-NS). Comparison of smoking and non-smoking MDD patients revealed that those with smoking habits exhibited increased regional activity in areas such as the precentral gyrus, supplementary motor area, and superior frontal gyrus compared to nicotine-free patients. This finding is partly consistent with previous healthy human data showing increased striatal volumes in smokers [6]. Janes et al. [34] have recently shown that nicotine addiction leads to a significant increase in striatal volumes and fronto-striatal connections. Additionally, the cingulate and insular cortices, regions reported as enriched with nicotinic acetylcholine receptors [25], have previously been implicated in smoking addiction among healthy smokers in resting state fMRI studies [35]. To the best of our knowledge, only a few studies have examined associations between functional/metabolic imaging and smoking in patients with MDD [23]. Busto et al. [36] observed lower striatal binding than depressed non-smokers and controls in their PET study. This finding is consistent with an investigation by Brody et al. [37] showing decreased binding activity in striatal regions, compatible with decreased serotonin transporter (SERT) availability in diencephalic, midbrain regions in depressed smokers [38].

Although the general vascular effects of smoking on the superior frontal gyrus and left precentral gyrus could not be excluded entirely [39], it should be remembered that regions involved in cognitive control (including the superior frontal gyrus) can be activated after smoking, consistent with its previously reported procognitive effects [39]. In this study, these effects can be attributed to smoking rather than depression. Another recent study showed that β-nAChR availability was significantly higher in regions such as the striatum, while no significant correlation was found between depression severity and Ach receptor availability [40]. In contrast, in a recent

SPECT study, smoking depressive patients exhibited increased GABA (gama amino bütirik asit) availability, positively correlated with anxiety and depression scores, compared with non-smokers [41]. However, the samples were relatively small in most of these studies, and potential confounders could not be ruled out.

We observed increased depression severity in the MDD-S group than MDD-NS, consistent with many previous MDD studies [13, 42, 43]. However, the underlying correlates of depression severity in smokers have not been fully investigated. There are few fMRI studies [23] showing a similar direct correlation between depression severity, the activity of cingulate cortex [44], as well as the white-matter lesion load in the postcentral gyrus [39]. Interestingly, insular and supramarginal gyrus activity has also been shown to be involved in the severity of nicotine withdrawal-induced adverse effects in healthy persons [45, 46].

However, that research compared depressed and non-depressed smokers and differed in some respects from our study design. Our findings regarding the underlying correlates of increased depression severity in smokers may be particularly valuable since no previous resting-state fMRI study has been undertaken in this population. In contrast, many other studies have suggested the reverse pattern, indicating an inverse correlation between the activity of the cingulate gyrus and precentral gyrus and the severity of depression [47, 48]. However, it should not be forgotten that these studies were conducted without specifically focusing on smokers vs. non-smokers, thus raising the question of whether smoking might reverse the well-known pathophysiological process (i.e., cortico-limbic interaction) that determines the severity of depression.

There are a number of limitations to this study. First, the sample was small and limited data were available, and further studies with large samples are needed. Second, due to its cross-sectional nature, the study was not primarily designed to examine the effects of smoking. A mechanistic link between cigarette smoking and the severity of MDD was not conclusively established. A more detailed analysis of smoking severity and history may help elucidate the differences observed between the patients and controls.

5. Conclusion

In conclusion, although it has been suggested that smoking produces some benefits, such as on cognition, in addition to its well-known adverse vascular effects, it also seems to exacerbate the severity of depression which might be associated with different network interactions than those from non-smokers. Further controlled long-term studies are now required to resolve this confusion and to clarify the cause and effect relationship in this area of cognitive neuroscience.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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