

[Abstract:0501] Neuroimaging in psychiatry**Effects of smoking on gray matter volume reductions in major depressive disorder**Nabi Zorlu¹, Pelin Kurtgoz Zorlu², Dursun Hakan Delibas², Zehra Hilal Adibelli³, Emel Pasa Baskin², Fatma Gul Imamoglu³¹Department of Psychiatry, Izmir Katip Celebi University, Atatürk Training and Research Hospital, Izmir-Turkey²Department of Psychiatry, Izmir Bozyaka Training and Research Hospital, Izmir-Turkey³Department of Radiology, Izmir Bozyaka Training and Research Hospital, Izmir-Turkey

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INTRODUCTION: Major depressive disorder (MDD) is a potentially debilitating psychiatric disorder characterized by feelings of guilt, anhedonia, and sadness, and may involve dysfunction in cognition, sleep, appetite, and energy. In particular, magnetic resonance imaging (MRI) has been widely applied to identify the key brain regions implicated in the pathophysiology of MDD. Several meta-analyses of region-of-interest and voxel-based morphometry structural MRI studies in MDD have been reported, providing evidence of volume reductions in the hippocampus, amygdala, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) as well as caudate and putamen¹. However, there have been a number of non-replications and contrasting results across studies. A number of explanations for the great variability in findings have been proposed including age of the sample examined, medication status, illness severity, sex, and age of MDD onset.

One important confounding variable may be smoking behavior, since smoking has been associated with a range of mental disorders including schizophrenia, anxiety disorders and depression. Studies in healthy controls have found associations between cigarette smoking and a variety of adverse central nervous system effects, such as global brain atrophy, and structural abnormalities in prefrontal regions as well as reduced gray matter (GM) volumes in the anterior cingulate, occipital and temporal cortices including the parahippocampal structures and hippocampal substructures². Thus, smoking status might impact gray matter volumes in studies with psychiatric populations. In line with this, a recent study found that a proportion of the volume reduction seen in the hippocampus and dorsolateral prefrontal cortex in schizophrenia is associated with smoking rather than with the diagnosis of schizophrenia². To the best of our knowledge, there is no study that has specifically evaluated the underlying brain structural changes that may mediate the impact of smoking status in MDD.

The purpose of this study is to evaluate the effect of smoking status on gray matter volumes in MDD patients. As most previous studies found smaller gray-matter volumes in smokers than nonsmokers, we hypothesized that MDD participants who smoke cigarettes would exhibit lower gray-matter volume in ACC, OFC and subcortical structures compared with non-smoker MDD patients.

METHODS:

Participants: Forty MDD participants (20 smokers and 20 non-smokers) were recruited from outpatients at the Department of Psychiatry, Bozyaka Education and Research Hospital. All MDD participants were diagnosed by two trained psychiatrists individually using the Structured Clinical Interview for DSM-4 and met the following inclusion criteria: fulfilling DSM-4 criteria for major depressive disorder; aged 18 to 65; no comorbid other Axis I psychiatric disorders; currently experiencing an episode of depression with a score of at least 20 on the 17-item Hamilton Depression Rating Scale (HDRS-17) and medication-free for at least 2 months.

Exclusion criteria for all participants were: less than 18 years of age; any MRI contraindications; pregnancy; history of head injury or neurological disorder and any concomitant medical disorder. All participants were right-handed, underwent baseline clinical assessment and MRI scan within 48 hours of initial contact. Nicotine dependence levels were assessed with the Fagerström Test for Nicotine Dependence (FTND). All participants gave written informed consent to participate in the study. The study was approved by local research and ethics committees.

Image Data Acquisition: All MRI scans were performed on a 1.5T Achieva MR imager (Philips Medical Systems, Eindhoven, Netherlands) with a standard quadrature head coil. All subjects were scanned with a 3D T1-weighted turbo gradient echo sequence with SENSE using the following parameters: coronal orientation, matrix 256 x 256, 1 x 1 mm² in-plane resolution, slice thickness 1 mm, TE/TR=5.6/12ms, flip angle $\alpha=19^\circ$.

Statistical Analysis: Demographic and clinical characteristics were analyzed using an independent-samples t-test with significance set at $p<0.05$. If data did not meet the assumptions required to perform parametric analysis, the non-parametric Mann-Whitney U-test was performed.

For the MRI data, the structural data was analyzed with FSL-VBM³ (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>), an optimized VBM protocol carried out with FSL tools. Briefly, structural images were skull-stripped and then tissue-segmented into gray matter, white matter, and CSF. The resulting gray matter partial volume images were aligned to MNI152 standard space using an affine followed by a nonlinear registration with the Image Registration Toolkit. The resulting images were averaged to create a study-specific template, to which the native gray matter images were then non-linearly re-registered. The registered partial volume-segmented images were modulated (to correct for local expansion or contraction) by the Jacobian of the warp field and smoothed with an isotropic Gaussian kernel with

FWHM=7mm. The Harvard–Oxford Cortical and Subcortical Structural Atlases implemented in FSL were used to create masks for our regions of interest (ROIs): the left and right hippocampus, left and right amygdala, left and right caudate, left and right putamen, ACC and OFC. Probability range was set to 50 % for all 10 structures. Finally, to compare groups, a voxel-wise general linear model was applied using permutation-based (5000 permutations) non-parametric testing, correcting for multiple comparisons across space. First, volumes were compared in our ROIs, using the created masks. Second, an exploratory whole-brain analysis was done, using the gray matter image from the study-specific template to investigate whether any not predicted differences existed between groups.

RESULTS:

Demographic and Clinical Characteristics: We did not find any significant differences in age, years of education, number of depressive episodes, age at first episode, duration of current depressive episode, HDRS-17 scores and body mass index scores between the groups.

VBM Results: The VBM ROI analyses showed that left hippocampus ($p=0.009$), right caudate ($p=0.015$), left amygdala ($p=0.020$) and right amygdala ($p=0.024$) volumes were smaller in smokers with MDD compared to non-smokers with MDD. We found no group differences for the volumes in the ROIs for the right hippocampus, left caudate, left and right putamen, ACC and orbitofrontal cortex.

The exploratory whole-brain analysis did not reveal any gray matter volume differences between smokers with MDD and non-smokers with MDD.

DISCUSSION: To our knowledge, this is the first study to specifically examine the impact of smoking status on gray matter volumes in patients with MDD. We hypothesized that differences in smoking behavior in MDD might explain the variability of GM volume reductions reported in the literature. We found that compared to non-smoker MDD patients, smoker MDD patients showed significantly lower volumes in the left hippocampus, right and left amygdala and the right caudate. It is important to consider that the two patient groups did not differ in their disease severity.

The results of our study are in line with previous investigations in healthy controls suggesting that smoking may impact GM volumes of hippocampus, amygdala and caudate⁴; however, other studies have found more widespread differences in the cortex between smokers and non-smokers⁵. Discrepancies may be attributable to the small sample sizes or to the differential patterns of smoking behavior assessed across studies. One possible interpretation of our results is that volume differences in the hippocampus, amygdala and caudate in smoker MDD patients vs. non-smoker MDD patients may be more related to adverse effects of cigarette smoke or to an interaction between smoking and a primary pathological process that affects neurons of the hippocampus and other brain regions. Also, the possibility that MDD patients who smoke carry genetic variants that increase the susceptibility for MDD and addictive behavior cannot be excluded. Due to the cross-sectional design of our study, we were not able to measure causal relationships. Thus, it is conceivable that MDD patients with more pronounced structural brain changes are more prone to smoking.

Our findings need to be viewed in light of some limitations. Firstly, the study sample is small and the findings need to be replicated in other populations and in a larger sample. Secondly, this is a cross-sectional study and the longitudinal follow-up of these subjects would proffer further insights into the complex interaction between smoking status, illness factors and changes in brain gray matter volumes. A third limitation is the lack of a control group, and at this time we are reporting preliminary results based on only 40 patients, 20 in each group.

In conclusion, our preliminary data suggest that volumetric reductions previously reported in MDD may be partially attributable to smoking, especially in subcortical structures. Therefore, we recommend an assessment of smoking status in future MRI studies in samples including psychiatric patients.

Keywords: depression, gray matter volume, smoking

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