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Original Research

Functional MRI Correlates of Stroop N-Back Test Underpin the Diagnosis of Major Depression

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Abstract

Introduction: In the current study, we used the Stroop Color and Word Test (SCWT) combined with an n-back component in functional magnetic resonance imaging (fMRI) in order to activate the working memory and cognitive interference in patients with Major Depressive Disorder (MDD) as compared to healthy controls. Our hypothesis was that there would be significant alterations in the selective visual attention processing regions of the brain which may identify mechanisms underlying major depression. **Materials and Methods**: Fifty participants, of which 24 were patients with depression and 26 healthy controls were recruited. **Results**: The first major finding of the current study was hypoactivation in the lingual gyrus during the condition with instructions to track the sequence of the words (word>color) of the Stroop n-back task and hyperactivation of the same structure in the opposite (color>word) condition where subjects had to focus on the order of the word color in depressed patients as compared to healthy controls. **Conclusions**: Changes in these regions have been consistently reported across studies with different fMRI techniques in both adolescent and adult patients with MDD reinforcing the role of the region in the pathophysiology of depression. Further studies are needed to examine possible longitudinal changes in the region and its activity in remission.

Keywords: functional magnetic resonance imaging; Stroop test; major depressive disorder

1. Introduction

Major depressive disorder (MDD) is a highly prevalent, debilitating disorder, affecting every sixth person of the population, and is also a leading cause of disability worldwide.

Despite its prevalence and tremendous socio-economic burden, there is still a lack of understanding of the exact causes, pathophysiology, and treatment of the disease. Similar to other mental illnesses, currently, there is no biomarker for the diagnosis of depression and the clinician relies on subjective evaluation for the diagnostic process and treatment plan [1–3].

This is not only moving psychiatry away from other medical specialties, but also creates practical difficulties in distinguishing between overlapping disorders with similar manifestations and disease patterns [4,5].

A great scientific effort in recent years has been dedicated to the search for reliable biomarkers for mental illnesses. A promising amount of research deploys neuroimaging as a tool to deepen the understanding of the underlying mechanisms in MDD. Studies with Magnetic Resonance Imaging (MRI) and functional MRI show structural and functional alterations in MDD patients, especially in regions governing emotion processing and mood [6].

MDD is a very heterogeneous disease with several subtypes and clinical specifiers, and this might be one of the reasons why the search for neuroimaging biomarkers has yielded divergent results [7]. Activations in regions related to mood and emotions are commonly reported, and the majority of studies are designed with emotionally charged paradigms, but it is yet to be confirmed if these are consistent in-between MDD diagnoses of different subtypes.

Common across all subtypes of MDD are deficits in working memory presenting with deficits in attention and concentration and diminished cognitive control, which manifests as rumination of negative thoughts [8–10].

A widely used tool to examine the working memory is the n-back task—patients are asked to monitor a series of verbal or nonverbal stimuli and to point out when the currently presented stimulus is the same as the one presented n-times before the current.

In depression, a neuroimaging study with the n-back test showed that patients presented with cortical and cingulate hyperactivation during task performance, which persisted even in remission following antidepressant treatment [11]. These findings demonstrated that when using working memory, patients employed more processing resources. Another fMRI study on verbal working memory of young healthy individuals with increased familial risk for depression reported that while maintaining comparable working memory capacity and response accuracy, they have greater activation in the lateral occipital cortex, superior temporal cortex, and superior parietal cortex [12].

These findings suggest that changes in neural circuitry supporting working memory are present regardless of a depressive state and further studying might bring promising results in the search for MDD biomarkers. Moreover, the neuroimaging alterations in subjects with familial risk of depression suggest that white matter changes may be a possible substrate for the predisposition for MDD [12].

Another extensively used tool for evaluation of cognitive functions is the Stroop Color and Word Test (SCWT). It is used to assess the ability to block cognitive interference—the participants are asked to ignore a feature of one stimulus while processing a second stimulus congruent or incongruent to the first one known as the Stroop Effect [13].

There have been mixed results in the literature on the Stroop effect in depression. One meta-analysis showed that only 50% of MDD patients are expected to show clinically relevant deficits on tasks such as the Stroop task [14]. A more recent quantitative meta-analysis of Stroop task in depression revealed considerable depression-related Stroop effects [15]. However, the studies exploring the Stroop effect in depressed patients have not provided an explanation on the underlying mechanisms leading to these differences. Thus, researching the differences in brain activity during such a task may provide valuable insights into the pathophysiology of the cognitive deficits in depression. An fMRI study combining the Stroop task and event-related fMRI paradigm showed that patients with depression exhibited hyperactivity in the rostral anterior cingulate gyrus and the left dorsolateral prefrontal cortex, strongly correlating with the Stroop interference, while no behavioral differences in performance were observed, either in reaction time, or in the number of correct answers compared to controls [16].

In the current study, we used the Stroop Color and Word Test combined with an n-back component in fMRI in order to activate the working memory and cognitive interference in patients with MDD as compared to healthy controls. We aimed to investigate potential neuroimaging differences across the groups and our hypothesis was that there would be significant alterations in the selective visual attention processing regions of the brain which may identify mechanisms underlying major depression.

2. Subjects and Methods

2.1 Subjects

Fifty participants were enrolled in the study, of which 24 were patients with depression (9 males, mean age 37.7 years) and 26 were healthy controls (8 males, mean age 39 years). All patients with diagnosis MDD were outpatients recruited at several psychiatry clinics in Bulgaria. Healthy volunteers were recruited amongst the personnel of the lab, and friends, colleagues and family members of the authors or patients.

We used DSM-V criteria for the diagnosis of MDD and the severity of depression was scaled using the Hamilton Depression Rating Scale (HAM-D). Patients were excluded if they had a high suicidal risk or if they had a previous or current psychiatric diagnosis from DSM-V other than depression or anxiety. We introduced the Hamilton Anxiety Rating Scale (HAM-A) as an addition.

Healthy controls were interviewed to exclude an existing psychiatric disorder. Further exclusion criteria for both patients and healthy controls were neuroimmune and neuroinflammatory disorders such as irritable bowel syndrome, systemic autoimmune diseases, chronic obstructive pulmonary disease, neurodegenerative diseases, type 1 and type 2 diabetes, dementia, stroke, and current and/or recent infectious diseases.

2.2 Methods

2.2.1 MR Scanning

The MR scanning procedure was performed on a 3T MRI system (Discovery 750w, General Electric, Boston MA, USA). The protocol included a high-resolution structural scan (Sag 3D T1) with a slice thickness of 1mm, matrix 256 $\times$ 256, TR (relaxation time) 7.2 ms, TE (echo time) 2.3, and flip angle 12. A functional series (2D EPI sequence) was also performed with the following parameters—slice thickness 3 mm, matrix 64 $\times$ 64, TR 2000 msec, TE 30 msec, and flip angle 90. Before each functional scan, 5 dummy time series were acquired.

2.2.2 Stroop N-Back Paradigm

The Stroop Color and Word test is widely used in clinical and experimental practice. In this study we decided to use this instrument in order to assess the ability to inhibit cognitive interference when two types of stimuli are coming at once (words that are the names of colors appearing in the same or different color). Thus we have congruent stimuli (the word “red” in red) and incongruent stimuli (the word “red” in yellow). In addition, an n-back component was added, and in the first part of the task, subjects were instructed to press a button every time the word was the same as the one two screens back (word condition). In the second part, the subjects had to press a button every time the color of the word was the same as the one two screens back (color condition). There were four consecutive 60 second blocks of each active condition (word and color) alternating with an off block (fixation cross) with a duration of 20 s.

2.2.3 Image Processing

We used SPM 12 software (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/, UCL, London, UK) running on MATLAB R2021 for Windows, in order to process functional data. During the preprocessing stage the images were realigned, co-registered with the high-resolution anatomical image, normalized to MNI (Montreal Neuroimaging Institute) space, and spatially smoothed with 8 mm FWHM (full-wide-half-maximum) Gaussian kernel. In the postprocessing stage General Linear Model (GLM) was applied to the time series, convolved

Table 1. Demographic and Clinical Characteristics of the sample.

	Healthy controls (n = 26)	Depressed patients (n = 24)	Statistical significance
Age (mean ± SD)	39 ± 12.4	37.7 ± 14	0.722[a]
Sex (M/F)	8/18	9/15	0.616[b]
Education (years)	14.6 ± 2	12.8 ± 3.3	0.031[a]
HAM-D	2.7 ± 3	23.2 ± 5.0	<0.001[a]
HAM-A	4.8 ± 4.7	24.5 ± 7.6	<0.001[a]
Age at onset (years)		29.6 ± 11	
Illness duration (months)		44.6 ± 57.5	
Episode duration (weeks)		34.6 ± 55.6	

SD, Standart Deviation; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale.
[a] Independent Samples *t*-test. [b] χ^2 test.

with a canonical hemodynamic response function (HRF). The design matrix included the six rigid body motion correction parameters as covariates of no interest. Individual T-contrasts were defined for the active and passive conditions, as follows—word>off (1), color>off (2), word>color (3), color>word (4). The individual contrast maps were included in a second-level analysis to test the differences between the two groups by means of independent sample *t*-test (Controls vs. Patients = C>P, Patients vs. Controls = P>C). A cluster-forming threshold of $p < 0.001$ uncorrected was used with a peak level threshold of $p < 0.05$ FWE corrected.

2.3 Statistical Analysis

The demographic and clinical characteristics of the sample as well as the behavioral measures were subjected to Descriptive statistics, Independent samples t-test and Chi-square (χ^2 test) analysis implemented in IBM SPSS Statistics, Version 28 (Chicago, IL, USA). For continuous variables such as age, education, illness duration and similar mean values and standard deviations were calculated and subsequently independent sample *t*-test was used to define significant differences. Categorical variables such as sex were described as ratio and chi-statistics was used to test for significant discrepancies between the groups studied. For all statistical analysis a significance threshold of $p > 0.05$ was chosen.

3. Results

3.1 Demographic and Clinical Characteristics

There were no statistically significant differences in age and sex between the depressed patients and the control group (Table 1). The educational level in the control group (M = 14.6, SD = 2; $p = 0.031$) was significantly higher. Expectedly, depressed patients had a higher score on the Hamilton Depression Rating Scale (HAM-D) as well as the Hamilton Anxiety Rating Scale (HAM-A).

Patients were treated with selective serotonin reuptake inhibitors (n = 9), serotonine and noradrenalin reuptake inhibitors (n = 6), augmentation with benzodiazepine derivates (n = 6) and/or other medication (n = 9). All patients have been on stable dosage for the last 14 days prior to the scanning procedure.

3.2 Stroop N-Back Performance

There were no statistically significant differences in terms of task execution between controls (M = 0.77, SD = 0.21; $p = 0.731$) and patients (M = 0.74, SD = 0.27; $p = 0.731$) in the first part (word condition) of SCWT. The performance of the controls in the second part of the task (color condition) is significantly better (M = 0.77, SD = 0.22; $p = 0.041$). There were no statistically significant differences between controls (M = 1.55, SD = 0.39; $p = 0.147$) and depressed patients (M = 1.34, SD = 0.50; $p = 0.147$) in the overall performance on both tasks.

3.3 Functional MRI Differences between Depressed Patients and Healthy Controls

We performed a two-sample *t*-test across our two groups (Depression and Healthy Controls) on each of the four first level contrasts. Moreover, as a covariate we added the individual performance from the task of each subject. This led to reduction of the initial cluster sizes which however kept the same localization of the peak activity. For the first two contrasts, where each condition from the task is weighed up the off condition (word>off, color>off), we did not find any significant between group differences. However, for the third and fourth contrast (word>color, color>word) the analysis yielded significant clusters of residual activations with peaks in the Lingual Gyrus (LiG) and Fusiform Gyrus (FuG). The clusters had the following size and peak MNI coordinates respectively (28, –62, –2) and a voxel size of 289. In the word>color contrast, the healthy control group demonstrated higher activations in the above-mentioned regions. For the color>word contrast, expectedly, the results were a "mirror" image of the word>color contrast with patients showing significantly higher activations in the same two regions (Fig. 1).

4. Discussion

The first major finding of the current study was that patients with depression showed hypoactivation in the lingual gyrus during the word>color condition of the Stroop

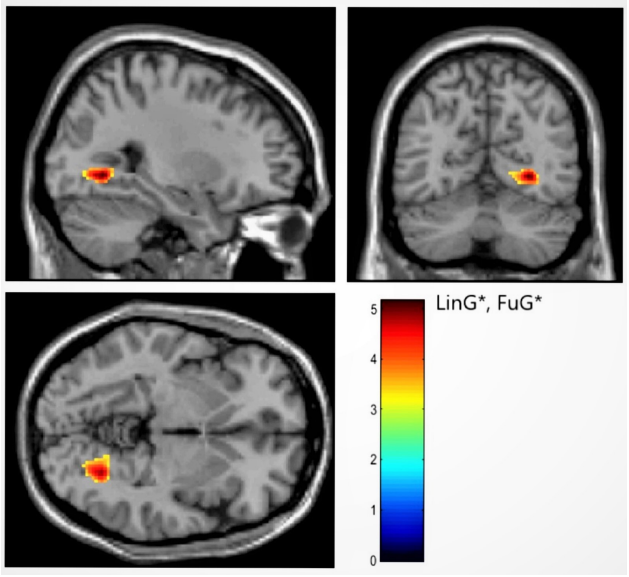

Fig. 1. Cluster of higher activation of the word>color contrast in healthy controls during the Stroop Color and Word Test (SCWT) task with Montreal Neurological Institute (MNI) coordinates (28, –62, –2) and a voxel size of 289.

n-back task and hyperactivation of the same structure in the color>word condition in comparison to healthy controls.

The lingual gyrus is a part of the visual recognition network and has a role in word processing and face perception [17]. While, due to the nature of the presented stimuli, the involvement of the visual cortex is expected, the alternations in lingual gyrus activations in depressed patients could provide important insights for the pathophysiological mechanisms of depression.

There is a growing amount of data on the role of the lingual gyrus in social functioning and emotion [18,19]. A study reported an association of the lingual gyrus in the recognition of masked fearful faces or the "fear" network [20]. Another study investigating neural markers for self-criticism revealed activation of the lingual gyrus during self-criticism as a marker of visual mental imagery [21]. This suggests that abnormalities in the visual cognitive circuit observed in MDD, may be a result of a negative bias in emotion recognition and processing [22]. Indeed, aberrant activations of the lingual gyrus and the visual network in patients with MDD compared to healthy controls have been reported in a number of fMRI studies [23,24].

Resting-state fMRI (rs-fMRI) studies on MDD have also revealed changes in the connectivity patterns of the lingual gyrus region. One study investigating resting-state brain function showed increased regional homogeneity in the lingual gyrus in adolescent patients with MDD compared to healthy controls [25]. Another rs-fMRI study found aberrations in the visual recognition circuit associated with a disjoining between the right lingual gyrus and right fusiform gyrus in depression [26]. Wang reported decreased voxel-mirrored homotopic connectivity values in the lingual and fusiform gyri in patients with bipolar disorder and MDD in a depressive episode as compared to healthy individuals, which suggests bilateral aberrant functional connectivity of both structures in mood disorders [27]. Overall, these findings support the hypothesis that the activations of the lingual gyrus in patients with depression may be a sign of functional impairment in emotion processing. The majority of studies implementing the Stroop task in major depression employ the emotional version, where the presented words have emotional valence. We chose the classic color-word Stroop task in order to minimize the individual differences in perception and thus avoid possible additional bias in the determined brain activations. For example, the word "car" in the Emotional Stroop task is considered neutral, however, it does not exclude the chance that a patient had a recent negative experience with frequent and costly car maintenance problems.

The activations observed in the current study are the result of the performance in a neutral task. Further investigation is needed to see if these changes are present outside of a depressive episode.

The second major finding of the study is the established difference in activity in the fusiform gyrus between patients and healthy controls during the two task conditions.

The fusiform gyrus is a part of the visual cortex and has an important role in face recognition and registering emotion in face stimuli [28,29]. A subregion of the fusiform gyrus has also been reported as responsible for processing words in written form "Zevin, *et al.* [30]". Therefore, this structure may be a hub allowing the integration of emotional and cognitive processing via the modulation of visual stimulation [31]. Additionally, the role of the fusiform gyrus in synaesthesia studies suggests it has a role in the experience of color [32]. As previously mentioned, activations related to word and color processing were to be expected due to the presented Stroop task but the differences in activations between MDD patients and controls are indicative of disease-related aberrations in the region.

Several studies report functional and structural changes in the fusiform gyrus in depression. A meta-analysis of fMRI studies in MDD with emotional valence showed hypoactivation for positive stimuli and hyperactivation for negative stimuli in this brain structure [33]. A study combining gyrification and resting-state functional connectivity showed that patients with MDD have hypogyrification in the right fusiform gyrus compared to HCs, as well as decreased functional connectivity between the right fusiform gyrus and the precentral and postcentral gyrus and right superior temporal gyrus [34]. The Fusiform/lingual gyri are not commonly reported as markers in depression. However, structural and functional changes in those gyri are documented. The largest fMRI analysis in MDD patients done by ENIGMA-MDD showed a significant reduction in surface area in bilateral lingual

gyrus in adolescents with depression compared to controls. In adults, there was a significant cortical thinning in the fusiform gyrus [35]. Another study employing voxel-based morphometry showed that the volume of the lingual gyrus was associated with responsiveness to antidepressive treatment in MDD patients. The nonresponsive patients had a decreased gray matter volume in the right lingual gyrus, which was not observed in the treatment-responsive group [36].

Apart from structural and functional changes, it is interesting to note potential neurochemical alternations in this brain region. Previous studies on autism spectrum disorders showed a significant reduction in the density of gamma-aminobutyric acid B ($GABA_B$) receptors in the anterior and posterior cingulate cortex and the fusiform gyrus, areas known for socio-emotional processing and identification of faces and facial expressions [37]. Studies using magnetic resonance spectroscopy (MRS) in depression consistently showed reduction in occipital GABA [38–40] pointing out occipital GABA as a candidate biomarker for acute depressed state. A recent study investigated further on the potential of occipital GABA as a biomarker in acute depression by combining MRS measurement of GABA in middle temporal visual area and a paradigm of visual motion processing [41]. The results from the visual paradigm show that acute MDD patients show specific deficits in visual surround motion suppression, correlating with the symptoms severity. A smaller sample of MDD participants in this study replicated these results and additionally were tested with MRS, showing lower GABA concentration in higher-order occipital cortex, correlating with the deficits in visual perception.

Additionally, a study on the effect of electroconvulsive therapy (ECT) on brain 5-HT(2) receptors in major depression reported a reduction of these receptors in all cortical areas, which corelated with the reduction in the right parahippocampal gyrus, right lingual gyrus, and right medial frontal gyrus and the improvement of the symptoms [42]. Another study demonstrated the cortical thickness of the fusiform gyrus was significantly higher in HCs than in patients with treatment-resistant depression but after performing several procedures of ECT this between-group inference was no longer present [43]. These findings suggest that structural aberrations as well as altered activations in the lingual/fusiform gyri could not only be potential markers for the diagnosis of MDD, but they may provide a promising target for further research on the treatment of depression.

There are two potential lines of interpretation of the current findings. One would be that these results represent mere biological markers of disease, in other words that SWCT served as diagnostically irrelevant, however robust stimulus to capture underlying mechanism of depression, more specifically of the cognitive deficits in depression.

The other possible interpretation is that the current study should be rather seen as incremental validation of SCWT in terms of clinical measure. In that case the test is cross-validated with functional MRI, in line with our previous reports with other clinically relevant tests [40–42].

Although the latter is declared as definitive goal of our research program [44,45], it is still out of reach. Independent study replication in increased samples is required to support such a claim. Further analyses of the clinical performance on SWCT in correlation with the functional MRI data are necessary as well.

5. Limitations

This study included a small sample size which may present a potential confound. Furthermore, all patients were on stable medication and most of them received very heterogenous co-medication including mood stabilizers antipsychotics, and treatment for somatic disorders. These two factors combined made it difficult to group patients according to specific pharmacological agents or report any defined daily doses or imipramine equivalents. Notwithstanding, this is a frequent constraint in neuroscientific research [27,46,47]. Overall antidepressants are supposed to normalize brain function. Since we compare healthy controls and individuals with a major depressive episode, the factor of antidepressant treatment may per se diminish the difference between groups without being added as a specific co-variate [48–50]. Yet these limitations are common for the entire field of translational psychiatry [51]. We selected a relatively neutral paradigm to avoid superposition and interference with emotional activations in depressed patients. However, the effect of color on emotions as an additional confounding factor cannot be eliminated in general. The higher educational level of the control group is another possible limitation.

6. Conclusions

Our previous research has delivered evidence that different clinical psychological diagnostic tests have specific functional neural correlates [52–54].

There have been identified neural correlates of impairment in working memory by means of administration of clinically relevant diagnostic tool (SWCT) simultaneously with functional MRI series in patients with MDD. We observed altered activations in the lingual and fusiform gyri between depressed patients and healthy controls. Changes in these regions were consistently reported across studies with different fMRI techniques in both adolescent and adult patients with MDD reinforcing the role of the region in the pathophysiology of depression. Further studies are needed to examine possible longitudinal changes in the region and its activity in remission.

Author Contributions

DSim delivered project proposal, ethics committee approval; experimental design, recruitment of the patients and their clinical evaluation; and wrote the paper in its introduction; RP performed statistical data analysis and visualization of the results; KS participated in the collection of the control sample; and the data processing; AT delivered the discussion and language editing; SK provided data quality control and supervision; DSto provided overall supervision and management of the project.

Ethics Approval and Consent to Participate

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Medical University of Plovdiv Ethical Committee (2/19.04.2018) as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All subjects gave written informed consent before their enrolment into the study.

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Conflict of Interest

DSto is serving as the Guest Editor for this special issue named "Advances in Depression Research". We declare that DSto had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to YN. The authors declare no conflict of interest.

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