ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2021; 13(3); 192-200
Original Research Article

Executive Functions and Glutamate Levels in the Prefrontal Cortex in Major Depressive Disorder

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Received: 01-07-2021 / Revised: 04-08-2021 / Accepted: 20-09-2021
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Conflict of interest: Nil

Abstract

Background: Executive functions are most commonly impaired cognitive functions in Major depressive Disorder. The executive dysfunction can lead to impairment in judgement, organization, planning and decision-making. The prefrontal cortex has been found to be the primary site for these functions. Glutamatergic theory of depression postulates that depression may result due to disruption in the glutamatergic neurotransmission in the brain. Magnetic Resonance Spectroscopy (MRS) has provided opportunity to study these neurotransmitters to find out the etiopathogenesis of major depressive disorder and associated cognitive impairment. Trail Making test is one of the most widely used assessment tool to study the executive functions. This study was planned to study association of executive dysfunctions as assessed on trail making test (TMT-A and B) and glutamate levels in the prefrontal cortex. **Method:** This cross-sectional observational study was carried out in the Department of Psychiatry, PGIMER and Dr. RML Hospital, New Delhi and NMR Research Centre, INMAS, DRDO, Ministry of Defence, Government of India between November 2014 to February 2016. 25 adult patients with major depressive disorder without treatment from last 6 weeks and 24 healthy controls were included in the study. The patients and controls were interviewed using the Hindi version of diagnostic interview for genetic studies for diagnosis. Patients were further assessed on Hamilton depression rating scale and Hamilton anxiety rating scale to measure the severity of depressive and anxiety symptoms. Trail Making test part A and part B were administered to both patients and controls to assess the executive functions. Neuro-metabolites of glutamate in the prefrontal cortex of both the groups were measured on Magnetic Resonance Spectroscopy. **Results:** The analysis also showed that the mean age at onset of the depressive

episode was 32.56 years and mean total lifetime duration was 25.8 months for the cases. Controls performed significantly better than cases on Trail Making Test Part A and part B (p - value < 0.0001). After adjusting for age and sex as covariates for analysis of glutamate and other metabolites in cases and controls, no significant difference was found. The severity of depression as measured by HAM-D scores was not correlated to either the TMT scores or glutamate levels as measured by MRS in the prefrontal cortex. **Conclusion:** Though the cases and control were not matched on education, but the executive dysfunction did not significantly correlate with glutamate and it's neuro-metabolites level in prefrontal cortex.

Keywords: Major Depressive disorder, executive functions, magnetic resonance spectroscopy, glutamate, prefrontal cortex

Introduction

Major depressive Disorder (MDD) causes a number of impairments in cognitive functions primarily executive functions (EFs) which refer to a family of top-down mental processes needed to concentrate and pay attention [1]. There are three core EFs-inhibition, working memory (WM), and cognitive flexibility [2,3]. These core EFs build the base for higher-order EFs such as reasoning, problem solving, and planning. Executive functions are carried out by the prefrontal cortex and it's damage can lead to impairment in judgement, organization, planning and decision-making[4].

Many theories like glucocorticoid theory[5], theory of neuronal plasticity[6,7], neurotrophic hypothesis of depression[8], inflammatory hypothesis[9] and glutamatergic theory of depression have been postulated to explain etiopathogenesis of depression.

Glutamatergic theory of depression postulates that depression may result due to disruption in the glutamatergic neurotransmission in the brain. Glutamate constitutes 50-60% of all neurotransmission in the brain (remaining 40-50% is GABAergic)[10]. Therefore, 90-99% of neurons are GABAergic or glutamatergic, and only less than 10% is for all the others monoamines, neuropeptides and neuroendocrine neuromodulators. Thus, proper CNS functioning depends upon keeping the excitatory/inhibitory physiological balance[11]. Studies supporting this theory have seen that a single dose of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine produced rapid and large antidepressant effects in patients with treatment-resistant MDD[12].

Neuroimaging studies especially Magnetic Resonance Spectroscopy (MRS) have been carried out to study the concentrations of Glutamate and GABA, which have consistently showed reductions in total gamma-amino butyric acid (GABA) concentrations in the prefrontal and occipital cortex in acute depression [13]. Magnetic Resonance Spectroscopy (MRS) is a non-invasive radio diagnostic tool, which has extensively been used to study molecular pathophysiology of different neuropsychiatric disorders. It has also been used to find relation between cognitive deficits and brain damage especially frontal lobe.

Various assessment tools have been used to assess executive functions in patients with Major Depressive Disorder. Trail Making test is one of the assessment tool, which has been hypothesized to reflect a wide variety of cognitive processes including attention, visual search and scanning, sequencing and shifting, psychomotor speed, abstraction, flexibility, ability to execute and modify a plan of action, and ability to maintain two trains of thought simultaneously[14].

Based on these findings, we hypothesize that depression is associated with impairment of executive functions as assessed by trail making test [15] (TMT-A and B) and reduced levels of glutamate in the prefrontal cortex.

Methodology

The study was carried out in the Department of Psychiatry, PGIMER and Dr. RML Hospital, New Delhi and NMR Research Centre, INMAS, DRDO, Ministry of Defence, Government of India. Ethical clearance was taken from institutional ethics committee for the study. The study duration was from November 2014 to February 2016. It was a cross sectional observational study and a sample size of 25 patients and controls were initially planned as sample size in previous studies had ranged from 13 to 39. During the course of the study, 33 patients and 26 controls were recruited. Data of 8 patients could not be included as 4 patients could not undergo MRS due to claustrophobia and there was post processing loss of data of 4 patients. 2 controls could not be included in the study as there was post processing loss of their data as well. Inclusion criteria for patients was as follows: Written informed consent from patient and caregivers, both genders, aged 18-50 years, patients diagnosed with Major Depressive Disorder as per DSM IV-TR [16] and not taking any psychotropic medication including anti-depressants from last 6 weeks. Patients with comorbid anxiety disorder, substance dependence except nicotine in past 6 months, history of medical/ neurological illnesses interfering with executive functions, pregnancy, intellectual disability and any contraindication to Magnetic Resonance spectroscopy were excluded from the study. Healthy controls were primarily students from both the institutes.

The patients and controls were interviewed using the Hindi version of diagnostic interview for genetic studies [17] for diagnosis. Patients with depression were further assessed on Hamilton depression rating scale [18] and Hamilton anxiety rating scale [19] to measure the severity of depressive and anxiety symptoms. Trail Making test [15] part A and part B were administered to both patients and controls to assess the executive functions.

MRS was carried out using 3 Tesla whole-body MRI system (Magnetom Skyra, Siemens, Germany) with a 32-channel head coil. Expandable ear cushions were used to immobilize the subject's head. Anatomical imaging was done in all the three orthogonal planes for adjusting the MRS voxels. T2 weighted multi-slice images (TR=5600ms, TE= 100ms, NEX= 1312 X 512 matrix & FOV = 180 X 220 mm, 25 slices, slice thickness = 4 mm, distance factor= 1.2 mm) covering the entire brain was obtained. For our region of interest i.e. Ventromedial prefrontal cortex (VMPFC), 10 X 10 X 10 mm3 voxel was positioned. MRS was obtained using PRESS (Point resolved spectroscopy) sequence with the following parameters: TR/TE = 2000ms/33ms; 2048 spectral points; 1200 Hz spectral bandwidth and 256 averages. Automated global shimming was used to minimize the BO in homogeneities and localized shimming was done to further minimize BO field variations over the voxel of interest. Unsuppressed water (with 10 averages) spectra were also acquired prior to the water suppressed metabolic acquisition and was used for spectral quantifications. MRS data processing was done using the LC model software. Only the metabolites with Cramer Rao Lower Bounds less than 20% were analyzed, relative peaks of Glutamate, Myoinositol, N- Acetyl aspartate, combined peak of glutamate and glutamine (Glu + Gln) relative to total creatine were measured. tCr values were used as reference because the total amount of creatine is a measure of general brain metabolism and appears to be stable in psychotropic medication naïve subjects [20].

Statistical analyses

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. If normality of data was rejected on

Kolmogorov-Smirnov test then non-parametric test was used on the rejected data.

Statistical tests were applied as follows-

1.Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups and ANCOVA test was used to compare after adjusting for age and gender.

2.Qualitative variables were correlated using Chi-Square test.

3. Spearman rank correlation coefficient was used to assess the association of HAMD total with various parameters.

A p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

The results showed that cases and controls were significantly different in terms of years of formal education (p value <0.0001). They did not differ in terms of their age and gender. (Table-1)

The analysis also showed that the mean age at onset of the depressive episode was 32.56 years and mean total lifetime duration was 25.8 months for the cases. The mean number of episodes was 1.24 with maximum of 3 episodes and the mean duration of current episode was 6.76 months. (Table-1)

3 patients presented with psychotic symptoms and suicidal attempt. As expected the cases and the controls were significantly different when their HAM-D scores and HAM-A scores were compared.(Table-1)

Table 1: Demographic and Clinical Variables of Cases and Controls

	Cases	Controls	Statistics (p-value)
Age (in years)	34.68 ± 8.76	31.46 ± 3.22	0.095
Gender (male/female)	Male = 13 Female = 12	Male = 9 Female = 15	0.308
Education (years of formal education)	12.2 ± 3.29	15.88 ± 1.08	<0.0001
Age at onset (years)	32.56 ± 7.52		
duration of current episode (in months)	6.76 ± 2.57		
number of episodes	1.24 ± 0.52		
total lifetime duration (in months)	25.8 ± 41.57		
Psychotic symptoms	Absent- 22 Present – 3		
Suicidal attempt	Absent – 22 Present -3		
HAMD total	16.32 ± 3.33	2.75 ± 1.42	<0.0001
HAMA total	10.08 ± 2.29	4.08 ± 2	<0.0001

In terms of performance in the trail making test part A and part B, the cases and the controls differed significantly. (p - value < 0.0001) with controls performing much better than patients.

Table 2: Trail making test scores of cases and controls

	Cases	Controls	Statistics p-value
TMT A (in seconds)	70.8 ± 26.16	27.33 ± 5.14	<0.0001
TMT B (in seconds)	235.12 ± 44.11	47.92 ± 6.85	<0.0001

After adjusting for age and sex as covariates for analysis of glutamate and other metabolites in cases and controls, no significant difference was found in all the metabolites measured between the cases and the controls.

Table 3: Neurometabolite levels of cases and controls

	Cases	Controls	Statistics p- value (after adjusting for age and sex)
Cr	14.5 ± 43.63	5.32 ± 0.61	0.36
Glu	29.41 ± 72.31	9.34 ± 3.14	0.231
Ins	28.93 ± 72.49	9.66 ± 2.44	0.252
NAA	16.87 ± 46.07	7.24 ± 1.07	0.362
Glu + Gln (Glx)	43.72 ± 97.13	14.55 ± 6.84	0.17

The severity of depression as measured by HAM-D scores was not correlated to either the TMT scores or glutamate levels as measured by MRS in the prefrontal cortex.

Table 4: Correlation of HAM-D scores with TMT scores and glutamate levels

		HAMDTOTAL
Glu	Correlation Coefficient	0.104
	P value	0.6194
TMT A time	Correlation Coefficient	0.122
	P value	0.5603
TMT B time	Correlation Coefficient	0.371
	P value	0.0676

Discussion

In spite of great advances made in the field of understanding the etiology of Major Depressive disorder, its cause still remains as elusive as ever closing the doors for a unified hypothesis of depression[21]. Among the numerous theories, the Glutamatergic Theory of Major Depressive disorder holds considerable promise and has given way to various imaging studies in patients with Depression, among which, Magnetic Resonance Spectroscopy which directly measures concentration of glutamate and other neuro-metabolites in specific regions of the brain offers significant advantage.

In present study, we used MRS to assess the levels of various neuro-metabolites, particularly glutamate in the prefrontal cortex. We also use the trail making test, an executive function test to see the functioning of the prefrontal cortex. The Trail making test, which consists of 2 parts, A and B is hypothesized to reflect a number of cognitive processes including attention, visual search and scanning, psychomotor speed, sequencing and shifting, flexibility, abstraction, ability to execute and modify a plan of action, and ability to maintain two trains of thought simultaneously [14]. Various studies have used trail making test in patients with Depression [22-26]

In the present study, data of 25 patients of Major Depressive disorder and 24 healthy controls was analyzed. There was statistically significant difference between the education levels of cases and controls. This is a limitation of our study as studies have reported effect of education on performance on TMT A and B scores [27-29].

We recruited treatment naïve subjects (at least 6 weeks) as some evidence suggests that long-term or repeated use of some antidepressant medications may impair cognitive function (30-31]. We also

recruited patients from both the inpatient units and OPD, but the majority of our patients (22) were recruited from the OPD. Jarvis and Barth [32] have noted that, in general, patients who are hospitalized perform poorer on neurocognitive measures despite any reason for hospitalization.

Some evidence exists to show that trait anxiety and anxiety disorders are associated with impairments on neuropsychological measures of EF [33] Hence, some deficits attributed to MDD could be due to a comorbid anxiety disorder or it may be possible that the co-occurring disorders may contribute additively or interactively to EF impairments. Studies have found that only depressed patients with comorbid anxiety had more impairment in EF [34]. Comorbid anxiety may also mask the effect of depression [35]. Few studies have excluded participants with comorbid Axis I disorders (including anxiety disorders). We used the Hamilton Anxiety rating scale to note the severity of anxiety symptoms and excluded those with severe anxiety symptoms or those suffering from a anxiety disorder. Our subjects had a mean HAM-A score of 10.08 which suggests that all our patients had only mild anxiety symptoms.

Evidence also suggests that EF impairment is greater in patients with more severe depressive symptoms [35] but there are studies which do not support this finding [37-39]**.** In our study, there was no statistically significant correlation between executive functions and severity of depression as measured by HDRS and TMT A or B scores.

Studies have been undertaken to assess glutamate related abnormalities in patients with Major Depressive disorder. These studies have assesses the levels of Glutamate, Glutamine and Glx (Glutamate + Glutamine) in various regions of the brain including prefrontal cortex [13]. Field strengths ranged from 1.5 Tesla (T) to 4T. Single voxel spectroscopy was used in all studies with PRESS being the most commonly used MRS sequence, followed by STEAM; J-editing, L-COSY. Approaches to quantification of metabolites included internal reference to Cr or water concentration, normalization to an external standard (e.g. phantom), and reporting in institutional units or arbitrary units. As age and gender can affect glutamate concentrations [40], in our study, we used ANCOVA with age and gender as covariates to compare glutamate levels.

In our study, we looked specifically at the prefrontal cortex as we were also looking for executive function deficits associated with prefrontal cortex.

In the studies that looked specifically at the prefrontal cortex, Michael et al [41] and Hasler et al [42] found that depressed patients had reduced glutamate/glutamine (Glx) concentrations. In addition, Michael et al found that Glx concentrations correlated negatively with severity of depression. After successful ECT treatment, Glx increased significantly and levels no longer differed from those of age-matched controls. In our study, we found no reduction of Glu or Glx levels and no correlation with severity of depressive symptoms.

Despite the plethora of MRS studies done in patients with MDD, the exact meaning and significance of the findings is still not clear. As glutamate has both metabolic as well as neurotransmitter role, the exact meaning of glutamate levels as assessed by MRS is an area of interest [43]. Further studies are needed to confirm these findings.

Conclusion

Our study is a step towards validating the glutamatergic theory of depression and offers the additional advantage of assessing the executive function deficits in patients with depression. To our knowledge, this is the first study to assess both these parameters. But lack of an education matched control group significantly limits the validity of our findings. Nonetheless,

we hope that in future, such studies are conducted to expand our knowledge base further.

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