NEURO-COGNITIVE FUNCTIONS IN PATIENTS OF MAJOR DEPRESSION

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Abstract : Earlier studies have shown conflicting results regarding impairment of executive functions in patients of major depression. In the present study, subjects were divided into following groups-Group 1 (19 Males & 11 females, age 18–45 years) consisting of patients of major depression diagnosed on the basis of DSM IV criteria and Group 2 (20 Males & 10 females, age 18–45 years) consisting of healthy subjects who had been screened for any sub-psychiatric illness by standardized hindi version of Goldberg's General Health Questionnaire (G.H.Q.). All the Group 1 & Group 2 subjects were rated on Hamilton Rating Scale for Depression (HAM-D) and then administered Neuro-cognitive test battery consisting of Letter Cancellation test, Trail Making test 'A' & 'B', Ruff Figural Fluency test, Forward & Reverse Digit Span test for assessing following cognitive domains : Attention span, visuo-motor scanning, short term memory and executive functions like working memory, information manipulation, set-shifting strategy analysis etc. Results showed significant impairment on all the studied neuro-cognitive parameters in Group 1 subjects as compared to Group 2 subjects, which demonstrate significant impairment of attention, visuomotor speed, immediate verbal memory, short-term retentive capacity and executive functions (strategic planning, attentional set shifting and working memory) in patients of major depression. It may probably be due to the disruption of dorso-lateral prefrontal cortex (dlpfc) and orbito-frontal networks in patients of major depression

Key words : major depression   DSM-IV criteria   executive functions

INTRODUCTION

Depressive disorders afflict about 10–25% of women and 5–12% of men and is considered as the most common mood disorder, which may manifest as single or

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recurrent episodes (1). Depression is known to affect mood, movement and cognition and cognitive deficits are considered as the epiphenomenona of the disorder (2). It is important to understand the pattern of cognitive impairments as it may directly affect the capacity of the patients to participate in occupational and social activities. It is commonly accepted that depression affects learning and episodic memory including both explicit verbal and visual memory (3, 4) while implicit memory is spared (5, 6). However, there have been conflicting results in the pattern of executive functions that are impaired in the depression. Many studies suggest the impairment of attentional set shifting, working memory (4, 7) and increased perseverative responses (8), while other studies contradict many of these findings (9). There is also paucity of data on neuro-cognitive functions in depressive disorders in Indian scenario. Therefore, present study has been conducted to evaluate the neuro-cognitive functions including executive functions in patients of major depression.

METHODS

The present study was carried out in the Department of Physiology and Department of Psychiatry, Lady Hardinge Medical College and Smt. Sucheta Knplani Hospital, New Delhi.

Study design : Prior permission for the present project was taken from the institutional ethics committee and then thirty patients suffering from Major Depression (19 Males and 11 Females) in the age group of 18–45 years were recruited from out patient services of the Department of

Psychiatry, S.S.K.R Two Psychiatrists using DSM-IV criteria confirmed the diagnosis independently.

Thirty healthy non-smoker volunteers (Age : 18–45 years) (20 Males and 10 Females) were part of this study. There was no history of previous chronic illness or drug abuse in these subjects.

All the participants signed a declaration of written informed consent and they were free to withdraw from the study at any stage.

Major depression group :

Inclusion criteria :

(i) Patients in the age group of 18 to 45 years utilizing the services of the Department of Psychiatry, Lady Hardinge Medical College with the diagnosis of Major Depression according to DSM-IV criteria.

(ii) At least *six* years of formal education.

(iii) Had not been treated for the current episode of Depression.

Exclusion criteria :

(i) Patients with history of previous or current organic disease.

(ii) Patients with past history or current evidence of substance dependence.

(iii) Patients with epilepsy or mental retardation.

(iv) Patients who were unwilling or unable to participate.

The subjects were divided into following groups :

GROUP 1   (n=30) (19 Males and 11 Females) 30 diagnosed patients suffering from Major depression.

GROUP 2   (n=30) (20 Males and 10 Females) Control group of 30 Healthy subjects.

Subjects were asked to report in the Department of Physiology at 9 A.M. for the recording of parameters. At the start of the study (Pre test value), semi-structured performa for socio-demographic details was filled in by all the subjects. All the subjects were then rated on Hamilton Rating Scale for Depression (HAM-D). Group 2 subjects were also screened for any sub-psychiatric illness by standardized Hindi version of Goldberg's General Health Questionnaire. All group 1 and Group 2 subjects were then assessed on Neuro-Cognitive Test Battery.

In the Neurocognitive Battery, the tests were presented to all the subjects in the same order as has been mentioned here :

• Letter Cancellation test.

• Trail making Test 'A'

• Trail making Test 'B'

• Ruff Figural Fluency Test.

• Digit Span Forward and Reverse Test.

The entire assessment took about 2-3 hours. Also, the subjects were not allowed more than two breaks in the entire session if so desired.

Instruments of the study :

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (10). It is the official psychiatric coding system used in the United States of America and it provides specified diagnostic criteria provided for each mental disorder. These criteria include a list of features that must be present for a diagnosis to be made. These criteria increase the reliability of clinicians' process of diagnosis. It was due to this reason of high specificity that this instrument was used to confirm the diagnosis of major depression in this study.

Hamilton Rating Scale for Depression (HAM-D) (11).

This scale consists of 17 variables with ratings from 0 to 4 for certain variables such as depressed mood, guilt, suicidal tendencies, work and interests whilst other variables like insomnia, agitation, and general somatic symptoms are rated from 0 to 2. The individual scores for each variable are to be added to provide for a cumulative score for the patient. It is used for quantifying the results of an interview. Reliability is good to excellent, including internal consistency and inter-rater assessments. Validity appears good on correlation with other symptom measures. Thus, it was included in this study to rate the depressive component in the patients suffering from major depressive disorder.

Standardized Hindi Version of Goldberg's' General Health Questionnaire (12) Goldberg's' GHQ is considered as one of the best screening devices available so far for identifying minor psychiatric illnesses in

general population and it also serves as a screening device for epidemiologists. It has been translated in Hindi by translation-retranslating method and split-half method. The tool is considered sensitive and reliable. Each question is rated on a score of 0 to 1. Individuals having score of 7 and below can be taken as 'probable normals', scores from 8 to 15 as 'probable cases' and more than 15 as 'definite cases'. It was used in the study to select normal control subjects free from any form of psychiatric illness.

Neurocognitive Test Battery :

In order to facilitate replication, only tests available and frequently documented in the neuro-psychological literature were employed (13).

Letter Cancellation Test : This test assesses visual scanning, response speed and sustained attention. The subject is presented with letters of English alphabet, and is instructed to cancel out specific letters. The score is the time taken by subject to actually perform this task. In addition, the numbers of different errors (omissions and commissions) done by the subject are also counted.

Trail Making Test :

Part A : assesses visuo-motor speed and attention. The subject is instructed to draw a straight line to connect 25 consecutive circles. The score is the time taken by the subject to complete the task.

Part B : In addition to visuo-motor speed and attention, it requires the patient to shift strategy and hence, is a sensitive measure

of executive function as well. In this the subject is instructed to connect 25 numbered and lettered circles by alternating between the two sequences. The score is the total time taken by the patient to complete the task.

Ruff Figural Fluency Test : This test permits us to study the non-verbal fluency of a subject, which is an indirect measure of subject's ability to form a strategy to complete a given task. The subject is presented with a sheet of paper on which 40 boxes are present. The objective is to draw dissimilar patterns in these boxes by joining dots present in these boxes in a specified period of time. The score is based on total number of dissimilar patterns, and number of perseverations. The rotations were also noted in this test along with patterns and perseverations as rotations are considered to be the hallmark in the strategic approach (A measure of executive function).

Digit Span :

Digits Forward : assesses immediate verbal memory span. In the test, subjects must repeat back sequences of digits of increasing length read out by the examiner. The score is maximum number of digits that the patient can recall.

Digits Backward : In addition to auditory attention and short-term retentive capacity this test also assesses the ability to manipulate information in the verbal working memory (and hence is sensitive measure of executive function). The subject has to repeat the sequences of numbers of increasing digit length in reverse order to what was said by the examiner. The score is

the maximum number of such digits that the patient is able to reverse.

Statistical analysis

For each group, Mean and Standard Deviation of the scores were calculated. Inter-group mean differences in Age, Hamilton Rating Scale for Depression and neuro-cognitive test parameters were tested for significance by using Mann-Whitney U test. Chi-square test was used to compare the sex-distribution and modified Kuppuswami socio-economic scale. The interpretation of 'P' values was as follows :

$P>0.05$ – Not significant. $P<0.05$ – Significant. $P<0.01$ – Highly significant. $P<0.001$ Very highly significant.

RESULTS

The subjects' characteristics and their relevant clinical data are shown in Table I.

Table I demonstrates that patients in both Group 1 and Group 2 had no statistically significant differences in the age and sex distribution. Revised Kuppuswami's scale was used for determining socio-economic status of the two groups. Both the groups had the majority of patients from middle socio-economic group and no significant difference was found in socio-economic status of the two groups. There was highly significant difference in the base-line (Pre-test) HAM-D scores in the patients of Group 1 and Group 2. So, the two Groups were comparable for the study.

Table II shows comparison of neuro-cognitive parameters between patients of

TABLE I : Characteristics of subjects.

Parameters	Group 1 (n=30)	Group 2 (n=30)
Age (yrs) (Mean±S.D.)	31.77±8.47	31.47±8.72
Gender		
• Females	11	10
• Males	19	20
Marital status		
• Married	19	21
• Unmarried	10	9
• Divorced, separated or widowed	1	0
Socio-economic status		
• Upper	0	0
• Middle (upper & lower)	23	22
• Lower	7	8
HAM-D (Mean±S.D.)	20.37±4.20	01.87±0.97***
No. of previous episodes of MDD		
0	3	4
1	11	9
2	10	9
3 or more	6	8

***$P<0.001$ MDD : Major Depressive Disorder. HAM-D : Hamilton Rating Scale for Depression

TABLE II : Showing comparison in the base-line neuro-cognitive test parameters between Group 1 and Group 2 subjects. (Mean±S.D.)

Parameters	Group 1 (n=30)	Group 2 (n=30)
Letter cancellation test		
• Time (sec)	150.17±5.84	129.87±5.54*
• Omissions	8.13±0.95	5.33±0.78*
• Commissions	0.27±0.14	0.27±0.12
Trail making test 'A'	118.43±7.62	82.93±6.62***
Trail making test 'B'	194.37±9.89	132.45±8.18***
Ruff figural fluency test		
• Patterns	12.27±1.53	15.57±1.11
• Rotations	02.97±0.50	5.57±0.74**
• Perseverations	24.87±1.83	18.87±1.36*
Forward digit span test	4.80±0.89	5.67±0.24*
Reverse digit span test	3.23±0.14	4.17±0.30*

*$P<0.05$, **$P<0.01$, ***$P<0.001$

major depression and healthy subjects. It demonstrates that there was statistically significant impairment on all the tested neuro-cognitive parameters in the Group 1 subjects as compared to Group 2 subjects.

DISCUSSION

Two groups were well matched for age, sex, and socio-economic status. So, they were comparable for the study. In the present study, patients of Major depression (Group 1) showed a significant impairment on Letter Cancellation Test compared to normal subjects (P<0.01). Further, they also made more errors of omissions on this test (P<0.05) thereby, demonstrating an impairment of visual scanning, response speed and attention span in depressed subjects.

The depressed patients also showed a significant impairment on Trail Making Test 'A' (P<0.01) and Trail Making Test 'B' (P<0.001) when compared to normal subjects hence, depicting an impairment of visuo-motor speed and attention span and ability for set shifting (executive function).

In the Ruff figural fluency test, no significant differences were observed in the total scores for new patterns generated, but significant impairment was seen on number of rotations (P<0.01) and preseverations (P<0.05) in depressed subjects, again demonstrating an impairment of non-verbal fluency and deficit in executive functioning.

The depressed patients also showed a significant impairment on Digit Forward Span Test (FDS) (P<0.05) and Reverse Digit Span (RDS) (P<0.05), hence, showing impairment of immediate verbal memory, auditory attention, short term retentive capacity and ability to manipulate information in the verbal working memory, which again demonstrates an impairment of executive function.

Therefore, from the results of the present study, it is concluded that there is significant impairment of attention, visuomotor speed, immediate verbal memory, short- term retentive capacity and executive functions (strategic planning, attentional set shifting and working memory) in patients of depression when compared with normal subjects.

Our results are in agreement with previous studies, which suggest that executive functions and attentional mechanisms are selectively affected by depression (14). Dorso-lateral prefrontal cortex (dlpfc) and anterior cingulate cortex are the key structures that play a uniquely critical role in orchestrating working memory and attention (14). Dlpfc is also involved in attentional set-shifting strategies. Neuro-imaging studies have implicated left dlpfc and orbito-fronto-ventral region as major sites of functional and structural abnormalities in major depression with marked decrease in neuronal and glial density in these regions (15, 16). There is significant evidence suggesting the existence of distinct, parallel functional networks (17, 18) or loops linking pre-frontal and sub-cortical regions and disruption of these functional networks is implicated in the pathogenesis of a number of psychiatric disorders including major depression (19), with its effect on affective, vegetative and autonomic domains (18). So, our findings also

support the above hypothesis of disruption of dlpfc and orbito-frontal networks in patients of major depression. To conclude, there was significant impairment on all the studied neuro-psychological tasks including executive functions in patients of major depression. Future studies should be supported with more comprehensive test batteries and should also include event related potential studies (ERP) such as P 300 wave.

ACKNOWLEDGEMENTS

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