Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Research

Analysis of HAM-D Scores on Cognitive Functions and Heart Rate Variability in Patients with Major Depressive Disorder

Sunidhi Sharma[1], Sudhanshu Kacker[1], *Neha Saboo[1]

[1]Department of Physiology, RUHS College of Medical Sciences, India.

Abstract

Background: Previous research has shown that Major Depressive Disorder (MDD) is accompanied by severe impairments in cognitive and autonomic processes, which may linger even when mood symptoms recover. This study aimed to analyse the relationship between depression severity, as measured by the Hamilton Depression Rating Scale (HAM-D), and how it affects heart rate variability (HRV) and cognitive function in patients with Major Depressive Disorder (MDD).

Methodology: The cross-sectional study was conducted at RUHS College of Medical Sciences and Associated Hospitals, Jaipur, from July 2022 to January 2023 on 90 subjects having major depressive disorder (MDD) of either sex in the 20-40 age group using the Hamilton score for depression (HAM D), Heart Rate Variability (HRV) measurements, and a battery of cognitive tests. Regression analyses were conducted to examine the associations between HAM-D scores with both HRV parameters and cognitive functions.

Results: Results indicated a significant negative correlation between HAM-D scores and HRV measures with $p<0.001$, suggesting that increased depression severity is associated with reduced HRV. Additionally, higher HAM-D scores predicted poorer performance on cognitive tasks, particularly in the domains of executive function and working memory. The coefficient of determination $r2=0.724$ suggests that approximately 72.4% of the variance in the dependent variable (Hamilton rating score for depression) could be explained by the combined cognitive function and heart rate variability parameters.

Conclusion: These findings highlight the potential utility of, emphasizing the importance of comprehensive assessment and treatment approaches that address both the affective and cognitive aspects of depression.

Keywords: *HAM-D; Autonomic Function; Cognitive Function; Heart Rate Variability; Major Depressive Disorders.*

***Correspondence:** Professor Neha Saboo, Department of Physiology, RUHS College of Medical Sciences, Partap Nagar, Jaipur, Rajasthan 302033. **Email:** nehasaboo8@gmail.com

How to cite: Sharma S, Kacker S, Saboo N. Analysis of HAM-D Scores on Cognitive Functions and Heart Rate Variability in Patients with Major Depressive Disorder**.** Niger Med J 2024;65(6):973-983.https://doi.org/10.60787/nmj.v65i6.587.

Quick Response Code:

Introduction:

Major Depressive Disorder (MDD) is a prevalent and debilitating mental health condition affecting millions of people worldwide. It is characterized by persistent feelings of sadness, loss of interest or pleasure in activities, and a range of emotional, cognitive, and physical symptoms that significantly impair daily functioning.[1-2]While the main symptoms of MDD are well-established, there is growing acknowledgement that the disorder's impact extends beyond mood abnormalities to disrupt different physiological and cognitive functions.[3] According to the National Mental Health Survey of India (2019) the weighted prevalence of lifetime and current depressive disorder was 5.25% and 2.68%.[4]

The Hamilton Depression Rating Scale (HAM-D) is one of the most widely used clinician-administered depression assessment tools in both clinical practice and research settings. Developed by Max Hamilton in 1960, the HAM-D provides a quantitative measure of depression severity, allowing for standardized assessment and monitoring of depressive symptoms over time. However, the full extent of the HAM-D's predictive value for physiological and cognitive alterations in MDD remains an area of active investigation.[5]

Heart Rate Variability (HRV) has been identified as a useful indicator of autonomic nervous system function and a possible biomarker for several kinds of mental and physical health issues.[6] HRV is the fluctuation in time intervals between consecutive heartbeats, which is assumed to reflect the balance of sympathetic and parasympathetic nervous system activity. Reduced HRV has been linked to an increased cardiovascular risk in those with MDD.[7] However the association between depression severity, cognitive functions, and heart Rate Variability has to be further investigated.

Cognitive dysfunction is increasingly recognized as a core feature of MDD, with deficits observed across multiple domains including attention, memory, executive function, and processing speed.[8] These cognitive impairments can persist even after remission of mood symptoms and contribute significantly to functional disability in MDD patients.[9] Understanding the relationship between depression severity and specific cognitive deficits is crucial for developing targeted interventions and improving overall treatment outcomes.

The intricate links between depression severity, autonomic nervous system function, and cognitive performance in MDD are a complex and clinically relevant field of study. While earlier research discussed above has looked at these factors separately, few studies have looked at the interaction of all three using a standardised measure of depression severity, such as the HAM-D.

Consequently, there is the need to further explore these relationships, with the hope of providing more insights into the broader physiological and cognitive implications of depression severity. This knowledge will contribute to more comprehensive assessment strategies for informing decisions towards the development of integrated treatment approaches that address not only the affective symptoms of MDD but also its autonomic and cognitive manifestations.

The findings from this study would have the potential to enhance our understanding of MDD as a multifaceted disorder, emphasizing the need for holistic assessment and treatment approaches. Moreover, by elucidating the relationships between standardized depression measures, and objective physiological and cognitive markers, this research may contribute to the development of more personalized and effective interventions for individuals suffering from MDD.

Material and Methods

This cross-sectional study with correlational analysis is designed to investigate the relationships between depression severity, heart rate variability (HRV), and cognitive function in patients with Major Depressive Disorder (MDD).

The calculated sample size for the study was 77 with a confidence level of 95%. Due to the 10% dropout rate of non-response subjects, the considerable sample size for the study was 85 with a round off to 90. $n = \frac{z^2 \text{ x } p \text{ x } q}{e^2}$ (Whereas n Sample size, z= the value f standard variate at a given confidence level i.e. 95%, p = sample proportion, q = 1 – p, e = Margin of error). A total of 1745 subjects were screened out of which 90 adults (aged 20-40 years) diagnosed with MDD according to ICD-10 criteria[10] were recruited from outpatient psychiatric clinics. Exclusion criteria included subjects having Psychotic illness like Schizophrenia or schizoaffective disorder, bipolar disorder, organic disorders such as Dementia, Epilepsy or Cerebrovascular disease, history of Electroconvulsive therapy in the last three months, musculoskeletal disorders like Kyphosis, Scoliosis, chronic diseases like Hypertension, Diabetes, and Chronic renal disease. The study was approved by the Institutional Ethics Committee (RUHS-CMS/Ethics/Comm./2022-23/63) and all participants provided a written informed consent form, and a participation information sheet was given to them.

Data collection tools:

Sociodemographic details (according to the modified Kupuswamy scale)[11] data like socioeconomic status, geographical area, marital status, sex, and age were gathered on a detailed proforma.

Depression Severity: For assessing the major depressive disorders, the Hamilton Rating Scale for Depression was used. This scale is the "gold standard" scale for assessing the severity of depression. In addition, this scale is the most sensitive of the commonly used scales for depression in detecting any change in the clinical condition of the patient. It evaluates various symptoms, including mood, anxiety, and physical signs like sleep disturbances, across 17 to 21 items. The HAM-D is known for strong reliability and sensitivity to changes in symptoms, making it valuable for monitoring treatment outcomes.[5]

Autonomic functions: Heart rate variability indices[12] i.e. **Root Mean Square of Successive Differences (RMSSD)**: RMSSD quantifies the short-term beat-to-beat variability in heart rate. It is calculated by first determining the differences between successive R-R intervals (the time between consecutive heartbeats), then squaring these differences, averaging the result, and finally taking the square root. RMSSD primarily reflects parasympathetic nervous system activity and is considered a reliable index of vagal tone; **High Frequency power (HF)**: High Frequency refers to the power in the high frequency band (typically 0.15-0.40 Hz) of the HRV power spectrum. This frequency range corresponds to the respiratory cycle and is mainly influenced by parasympathetic nervous system activity, particularly vagal tone. HF is often referred to as the respiratory band because it corresponds to HR variations related to respiratory sinus arrhythmia. Both of these time domain parameters were recorded by using a Digital Physiograph (MLT004/ST) by AD instruments. The electrocardiogram, or ECG, was recorded for five minutes to determine HRV.

Cognitive Function: Cognitive function was assessed using a battery of neuropsychological tests: including subjective assessment through the Mini-mental state examination (MMSE) which consists of 30 questions assessing various cognitive domains including orientation, registration, attention and calculation, recall, language, and visual construction. The test is scored out of 30 points, with higher scores indicating better cognitive function. Typically administered in 10-15 minutes, the MMSE provides a quick assessment of overall cognitive status. The Montreal cognitive protocol A & B is another

subjective test used in this study. It assesses various cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation. The test consists of 30 items and takes approximately 10-15 minutes to administer. Scoring is out of 30 points, with a score of 26 or above generally considered normal.[13,14] An objective assessment of cognitive function called the auditory Event-Related Potential P300 was also used. It is a positive deflection in the electroencephalogram (EEG) that occurs approximately 300 milliseconds after the onset of a task-relevant auditory stimulus. It is typically elicited using an "oddball" paradigm, where infrequent target stimuli are presented among frequent standard stimuli. The P300 reflects cognitive processes related to attention, stimulus evaluation, and context updating in working memory.[15] An Octopus NCV/EMG/EP- 4 Ch. Machine (model- CMEMG 01) was used in the recording.

Statistical analysis: All the data pertaining to the research (including the sociodemographic details, and cognitive and heart rate variability parameters) were entered into Microsoft Excel 2019 and were analyzed with the help of SPSS 21 software, and the Shapiro-Wilktest was used to determine the results. Linear regression models employed to determine the relationships between HAM-D scores, cognitive performance, and HRV indices, and regression coefficient beta (β) were obtained and $p < 0.05$ was considered as statistical significance.

Results

Figure 1: Distribution of Sociodemographic variables among study participants.

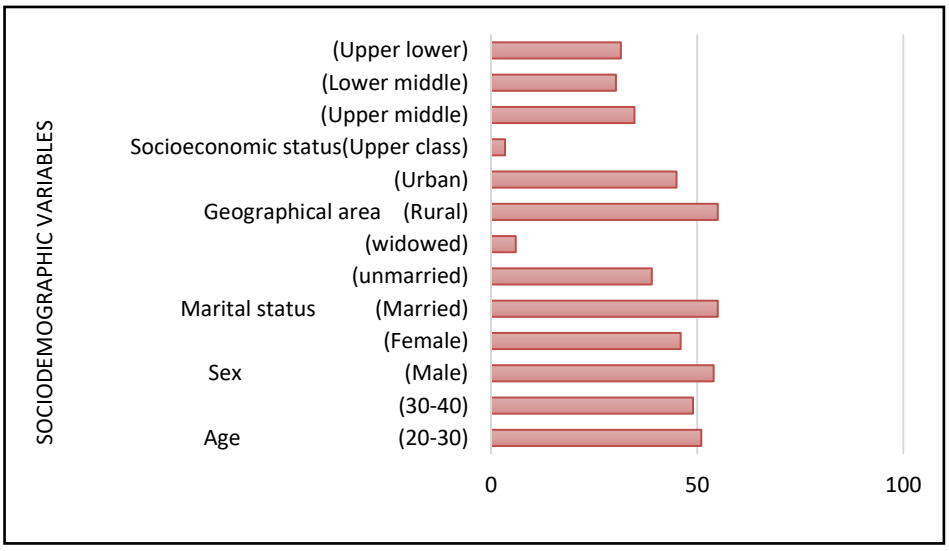

Figure 1 depicts the distribution of participants by sociodemographic variable. It demonstrates that most participants were from rural areas, with 48 (53.3%), as opposed to metropolitan areas, which had approximately 42 (46.7%) participants. In terms of marital status, married people are the most common, accounting for 48 (53.3%) participants, followed by single people at 27 and widowed people at 5. For the socioeconomic level, the upper-middle-class category had the most participants 35 subjects, while the upper class has the lowest (around 3). The age distribution shows that people aged 20-30 are slightly more widespread, with about 46 subjects, than those aged 30-40, who number around 44. Finally, in terms of gender, males were slightly more represented, with 47 participants, than females, who were 43.

Table 1: Regression Analysis of HAM-D Scores on Cognitive Function and Heart Rate Variability Parameters

	Study participants (n=90)		
Dependent Variable: **HAM D Score**	**Regression coefficient(β)**	**Confidence Interval (CI)**	***p-value***
Cognitive function parameters			
MMSE	−0.75	(−0.087,−0.032)	<0.0001**
MoCA&B	-0.43	(-0.626, -0.234)	<0.0001**
P300 (L)	–0.84	(-1.104, -0.57)	<0.0001**
Heart rate variability parameters			
RMSSD	-0.2	(-0.396, -0.004)	0.0573
HF	-0.071	(-0.267, 0.125)	0.5036

HAM D: Hamilton rating scale for depression, **MMSE:** Mini-mental status examination, **MoCA & B:** Montreal cognitive assessment A& B, **P300 (L):** P300 Latency, **RMSSD:** Root means square standard deviation**, HF:** High frequency.

Table 1 depicts the regression coefficient with confidence interval for cognitive and heart rate variability parameters in study participants. In this study, cognitive function parameters (MMSE, MoCA&B, and P300 latency) demonstrated significant inverse relationships with HAM-D scores, indicating that better cognitive function is strongly associated with lower depression severity. Among heart rate variability measures, RMSSD showed a trend towards significance with a potential inverse relationship to depression severity, but this did not reach normal significance levels (p = 0.0573). Overall, cognitive function appears to have a stronger connection to depression severity than heart rate variability in this sample.

Figure 2a depicts that HAM D and better cognitive function are associated with lower depression severity; As MMSE scores improve, indicating greater cognitive function, HAM-D values, which measure the severity of depression, tend to decline. The red regression line emphasizes this inverse association, with a shaded confidence interval indicating greater uncertainty in predictions at the extremes of MMSE scores. The data points clustered around the regression line support the link between enhanced cognitive performance and less depressive symptoms, while the wider confidence interval at higher MMSE scores indicates that the strength of this relationship varies.

Figure 2b shows a negative correlation between HAM-D and MoCA scores, implying that as cognitive function (MoCA) improves, depression intensity (HAM-D) declines. The red regression line emphasises this inverse link, with the shaded area reflecting the confidence interval, which widens near the extremes of MoCA scores, indicating increased variability in those places.

Figure 2a: Relationship between Hamilton Depression Rating Scale (HAM D scores) and Mini-Mental State Examination score (MMSE).

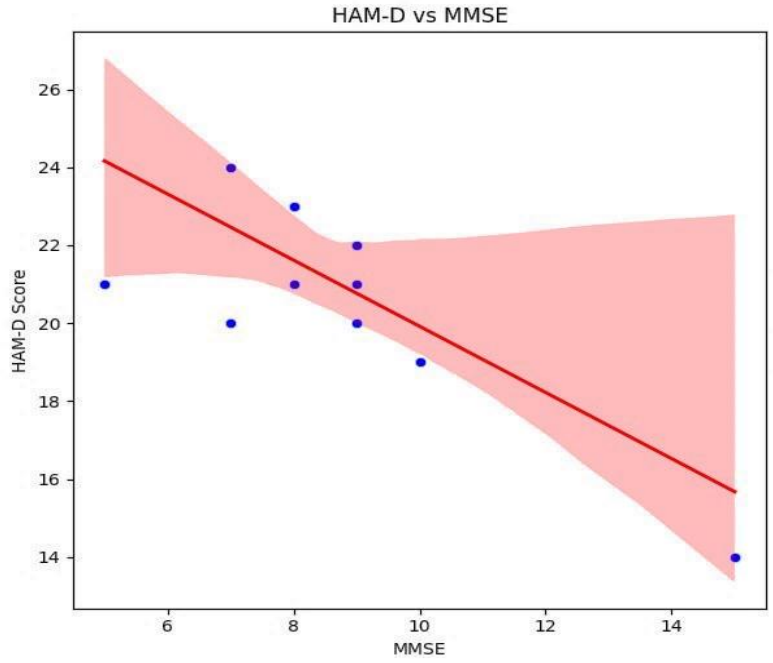

Figure 2b: Relationship between Hamilton Depression Rating Scale (HAM-D scores) and Montreal Cognitive Assessment scores (MoCA).

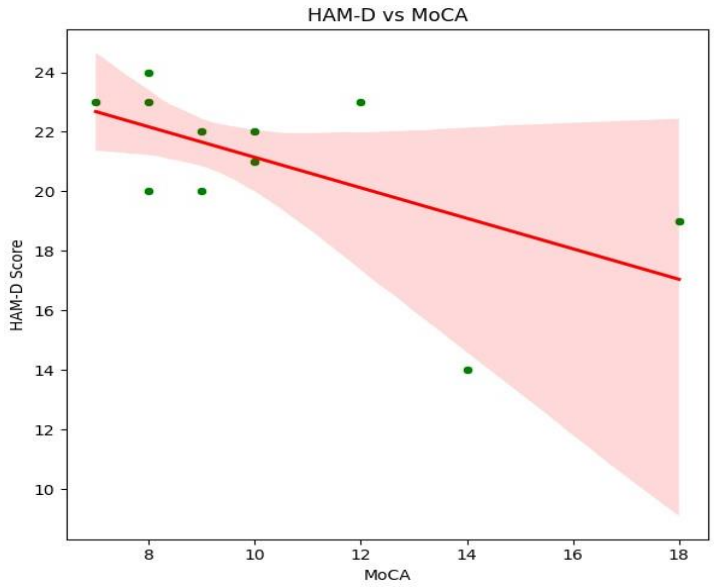

Figure 2c scatter plot shows a positive relationship between P300 latency and HAM-D scores, implying that longer P300 latencies, which represent slower cognitive processing, are related to greater depression severity. The red regression line depicts the rising trend, while the shaded confidence interval reflects higher uncertainty at the lower and upper limits of the P300 delay.

Figure 2c shows the relationships between Hamilton Depression Rating Scale (HAM-D scores) scores and P300 latency (an event-related potential component).

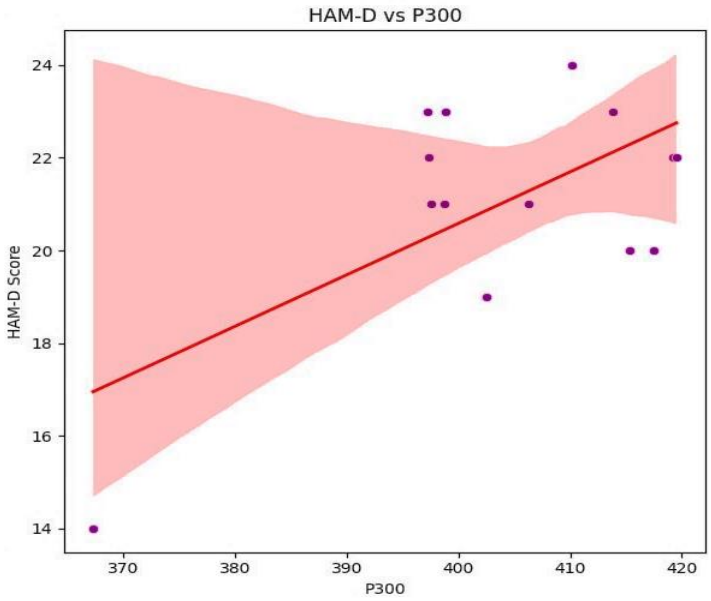

Figure3a: Relationships between Hamilton Depression Rating Scale (HAM-D scores and root mean square standard deviation (RMSSD).

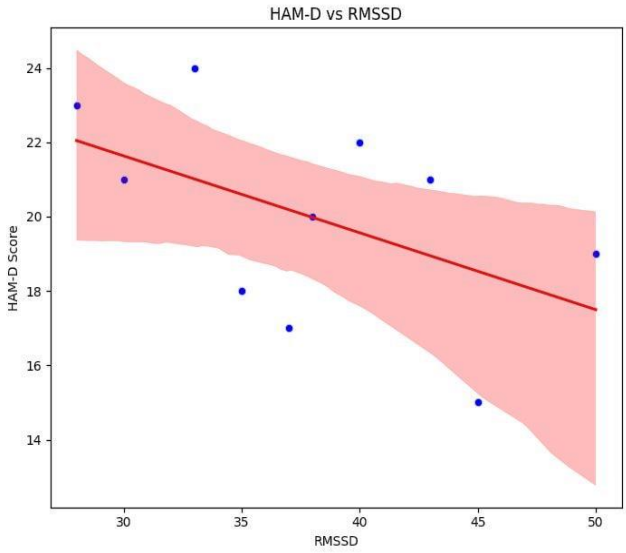

Figure 3a shows the comparison between HAM-D and RMSSD, showing a definite negative correlation, with HAM-D scores declining as RMSSD increases. The data points in the graph, represented by blue dots demonstrate this inverse relationship. This link is shown by the downward-sloping red trend line and the shaded confidence interval, which narrows and drops with increasing RMSSD.

Figure3b: Relationships between Hamilton Depression Rating Scale (HAM-D scores) and High frequency (HF).

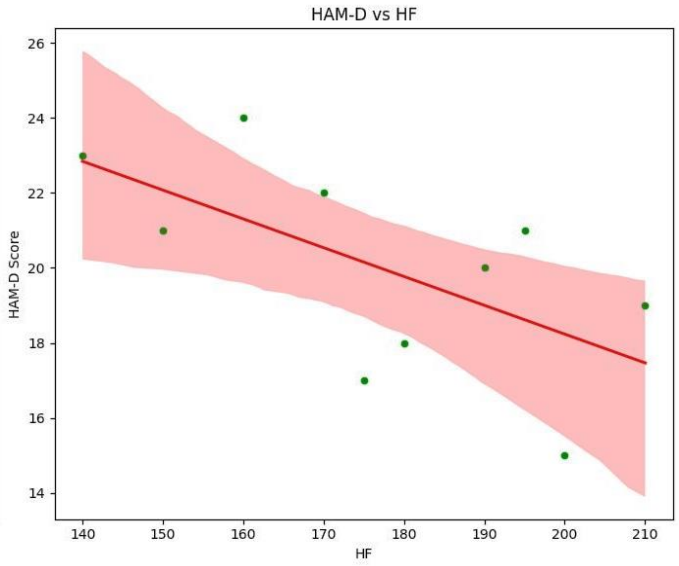

Figure 3b shows a negative correlation. Higher HF values correlate with lower HAM-D scores, as shown by the downward-sloping red trend line and confidence interval. The data points in the graph, represented by green dots demonstrate this inverse relationship.

Overall, the graphs show that higher heart rate variability, whether evaluated by RMSSD or HF, is associated with lower HAM-D scores, indicating less severe depressive symptoms.

Discussion:

This study aimed to investigate how depression severity (as measured by HAM-D scores) related to cognitive functions and heart rate variability in patients with major depressive disorder. Our findings suggest a significant association of HAM-D scores with poorer cognitive functions and heart rate variability. Consistent with the hypotheses and previous research, indicating that increased severity of depression is often accompanied by cognitive impairments and changes in heart rate variability parameters.[16] This study's main findings are summarised as follows.

The strong negative association (estimated -0.75) indicates that higher depression scores are linked to lower cognitive performance as measured by the MMSE. This is consistent with prior findings suggesting that depression can impair cognitive performance. Koenig et al[17] in 2015 reported significant cognitive impairments in patients with severe depressive disorder across multiple areas measured using the MMSE and they proposed that persistent depression causes cognitive deterioration via releasing adrenocorticotrophic hormone, which leads to the secretion of glucocorticoids and prolonged secretion of glucocorticoids may have detrimental effects, leading to hippocampus shrinkage.[17-18]

The moderate negative correlation (estimated -0.43) strengthens the link between depression severity and cognitive function, though not as significantly as the MMSE. This discrepancy could be attributed to the MoCA's greater sensitivity to moderate cognitive impairment. Nasreddine et al[14], in 2005 indicated that the MoCA is effective at detecting small cognitive changes, which could explain the more nuanced association reported here.[14] A similar study done by Blair et al[19], in 2016 found that depressive symptomatology had a negative impact on the MoCA, and these observed executive/attention deficits are consistent with mood dysfunction theories (biological, psychodynamic, cognitive, behavioural, social,

and environmental) that suggest dysregulation in prefrontal regions and cortico-striatal-pallidal-thalamic circuits.[19]

The moderate positive association (estimated 0.5-0.6) between depression levels and P300 latency delay is particularly fascinating. P300 is an event-related potential component involved in cognitive processing. This positive correlation shows that higher depression intensity may be associated with delayed cognitive processing. Bruder et al[20], in 2002 found similar results, with altered P300 responses in people with depression, which they interpreted as evidence of disturbed cognitive resource allocation. This cognitive decline is linked to reduced activity in the prefrontal cortex, which is crucial for regulating mood and cognitive control. Research reveals reduced activity and structural changes in the prefrontal cortex, a brain region critical for these cognitive functions. Additionally, elevated cortisol levels, due to HPA axis dysregulation, contribute to hippocampal atrophy, further impairing memory. Neuroinflammation and disrupted white matter integrity have also been observed, both of which affect brain connectivity and cognitive processing.[20-21]

The negative correlations observed between HAM-D scores and heart rate variability measures (RMSSD and HF) align with research on the relationship between depression and autonomic nervous system function. Kemp et al[7], conducted a meta-analysis in 2010, showing reduced heart rate variability in depression, supporting the idea that depression is associated with autonomic dysfunction. This supports the hypothesis that depression severity is linked to reduced vagal tone, which may contribute to the increased cardiovascular risk observed in MDD patients.[7] One of the studies done by Aimaier et al[22]. in 2022 performed comparisons of HRV parameters between groups and found significant decreases of time- and nonlinear domain measures, reflecting a shift toward sympathetic dominance.[22] Studies done by Oncu et al[23], in 2020 concluded that HRV abnormalities were statistically correlated with the severity of depressive symptoms.[23]

This association could be explained by disruption of the hypothalamic-pituitary-adrenal (HPA) axis, a critical component of the stress response system. Chronic HPA axis activation in MDD may cause autonomic imbalance, favoring sympathetic over parasympathetic activity and resulting in lower HRV.[24] This autonomic imbalance may partially explain the higher risk of cardiovascular disease in MDD patients. MDD has been linked to changes in white matter integrity and a decrease in hippocampus volume, which may influence cognitive function and HRV.[25] Often associated with MDD, sleep issues might impair cognitive and autonomic functioning.[26]

Strength and Limitations:

This study's key strength is its comprehensive methodology, which considers both cognitive and physiological results in relation to depression severity. The inclusion of standardised measures (HAM-D, cognitive tests, and HRV parameters) improves dependability and comparability to previous research. The regression analysis enables the control of any confounding variables, resulting in a more sophisticated understanding of the relationships. However, the study has a few shortcomings. Its cross-sectional approach prevents causal inferences since data does not demonstrate temporal correlations between depression intensity and outcomes. The use of a single time point assessment may fail to convey depression's dynamic nature and impact. Concerns about sample size and representativeness may arise, limiting generalisability. The use of multiple comparisons in regression analysis raises the likelihood of Type I errors, necessitating cautious interpretation of results.

Conclusion:

The observed correlations between HAM-D scores and cognitive impairments suggest that depression severity can significantly impact cognitive processing. This includes slower cognitive functions (P300 latency) and diminished capacity for tasks requiring executive control (MoCA and MMSE Scores). Depression severity, as measured by HAM-D scores, is closely linked to cognitive dysfunction and heart rate variability, reflecting the intertwined nature of emotional and physiological dysregulation in MDD. These findings support the need for treatment strategies that go beyond managing mood symptoms alone, incorporating interventions aimed at improving cognitive function and autonomic balance, such as cognitive remediation therapies and HRV-enhancing techniques like mindfulness and biofeedback.

Acknowledgements: We would like to thank all the participants who have given consent to participate in this study. We also want to acknowledge the faculty of the Department of Physiology, all hospital staff, and colleagues.

Funding: Nil

Conflict of interest: There are no conflicts of interest.

References:

1. Bains N, Abdijadid S. Major Depressive Disorder [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2023 Apr 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559078/.
2. Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. Indian J Psychiatry. 2013;55(3):220-3. doi: 10.4103/0019-5545.117131.
3. McIntyre RS, Lee Y. Cognition in major depressive disorder: A "systemically important functional index" (SIFI). J Clin Psychiatry. 2016;77(6):813-9. doi: 10.4088/JCP.15com10385.
4. Arvind BA, Gururaj G, Loganathan S, Amudhan S, Varghese M, Benegal V, et al. Prevalence and socioeconomic impact of depressive disorders in India: multisite population-based cross-sectional study. BMJ Open 2019; 9(6): e027250.doi:10.1136/bmjopen-2018-027250.
5. Hamilton M. A rating scale for depression. J NeurolNeurosurgPsychiatry. 1960;23(1):56-62. doi: 10.1136/jnnp.23.1.56.
6. Thayer JF, Ahs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. NeurosciBiobehav Rev. 2012;36(2):747-56. doi: 10.1016/j.neubiorev.2011.11.009.
7. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. Biol Psychiatry. 2010;67(11):1067-74. doi: 10.1016/j.biopsych.2009.12.012.
8. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med.2014;44(10):2029-40. doi: 10.1017/S0033291713002535.
9. Bora E, Harrison BJ, Yücel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. Psychol Med.2013;43(10):2017-26. doi: 10.1017/S0033291712002085.
10. *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research.* Geneva: World Health Organization, 1993.
11. Majumder S. Socioeconomic status scales: Revised Kuppuswamy, BG Prasad, and Udai Pareekh's scale updated for 2021. J Family Med Prim Care.2021;10(11):3964-3967. doi: 10.4103/jfmpc.jfmpc_600_21.

12. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation.1996;93(5):1043-65.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res.1975;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6.
14. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221. x.
15. Misra UK, Kalita J. Clinical neurophysiology: nerve conduction, electromyography, evoked potentials. 4th ed. New York, NY: Elsevier Health Sciences; 2019.377-380.
16. Hack LM, Tozzi L, Zenteno S, et al. A Cognitive Biotype of Depression Linking Symptoms, Behavior Measures, Neural Circuits, and Differential Treatment Outcomes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(6): e2318411. doi:10.1001/jamanetworkopen.2023.18411
17. Koenig AM, DeLozier IJ, Zmuda MD, Marron MM, Begley AE, Anderson SJ, et al. Neuropsychological functioning in the acute and remitted States of late-life depression. J Alzheimers Dis. 2015;45(1):175-85. doi: 10.3233/JAD-148006.
18. Delardas O, Giannos P. Cognitive Performance Deficits Are Associated with Clinically Significant Depression Symptoms in Older US Adults. Int J Environ Res Public Health. 2023 Mar 28;20(7):5290. doi: 10.3390/ijerph20075290.
19. Blair M, Coleman K, Jesso S, Desbeaumes Jodoin V, Smolewska K, Warriner E, et al. Depressive Symptoms Negatively Impact Montreal Cognitive Assessment Performance: A Memory Clinic Experience. Can J Neurol Sci. 2016;43(4):513-7. doi: 10.1017/cjn.2015.399.
20. Bruder GE, Kayser J, Tenke CE, Leite P, Schneier FR, Stewart JW, et al. Cognitive ERPs in depressive and anxiety disorders during tonal and phonetic oddball tasks. Clin Electroencephalogr. 2002;33(3):119-24. doi: 10.1177/155005940203300308.
21. MacQueen GM, Campbell S, McEwen BS, et al. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci U S A.2003;100(3): 1387–1392. 26.
22. Aimaier G, Qian K, Zheng Z, Peng W, Zhang Z, Ding J, et al. Interictal Heart Rate Variability as a Biomarker for Comorbid Depressive Disorders among People with Epilepsy. Brain Sci. 2022 May 20;12(5):671. doi: 10.3390/brainsci12050671.
23. Oncu GC, Tudoran C, Enatescu VR, Tudoran M, Pop GN, Bredicean C. Evolution of Heart Rate Variability and Heart Rate Turbulence in Patients with Depressive Illness Treated with Selective Serotonin Reuptake Inhibitors. Medicina (Kaunas) 2020;56(11): 590.doi:10.3390/medicina56110590.
24. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, et al. Depression, heart rate variability, and acute myocardial infarction. Circulation. 2001;104(17):2024-8. doi: 10.1161/hc4201.097834.
25. Schmaal L, Veltman DJ, van ETG, Sämann PG, Frodl T, Jahanshad N, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Mol Psychiatry. 2016;21(6):806-12. doi: 10.1038/mp.2015.69.
26. Riemann D, Krone LB, Wulff K, Nissen C. Sleep, insomnia, and depression. Neuropsychopharmacology. 2020;45(1):74-89. doi: 10.1038/s41386-019-0411-y.