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# Event-related potential and neuropsychological function in depressed older adults with cognitive impairment: A correlational study

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## Abstract

**Background:** Increased depression severity has been linked to cognitive functioning impairment, such as deficits in episodic memory and executive function, causing difficulties in planning strategies, which ultimately lead to impaired decision-making functions. There are number of ways to assess cognitive functions, two most important and routinely done tests are neuropsychological test battery (NBT) and event-related potentials (ERPs).

**Objective:** This study examines the relationship between conventional neuropsychological tests assessing various cognitive domains and an ERP-P300 in depressed older adults.

**Methods:** Forty-six depressed elderly subjects participated in the study. NBT (Pennsylvania's Penn Computerized Neurocognitive Battery [Penn CNP]) assessing attention, episodic memory, working memory, social cognition, complex cognition, and sensorimotor speed and ERP-P300 (amplitude  $\mu$ V and latency ms) was recorded using an auditory oddball paradigm.

**Results:** Correlation test was run and Pearson's analysis and revealed that there was a negative statistically significant linear correlation between working memory on NBT and P300 wave amplitude on ERP-P300 (r = -0.34, P = 0.021) and between complex cognition on NBT and P300 wave latency on ERP-P300 (r = -0.47, P < 0.001). No correlation was found between other tests on NBT and ERP-P300 wave characteristics. Further, the regression analysis ( $R^2$ ) revealed that P300 amplitude was found to significantly predict the working memory ( $R^2 = 0.116$ ) and P300 latency was found to significantly predict the complex cognition ( $R^2 = 0.224$ ).

**Conclusion:** Therefore, we conclude that neurophysiological measurements cannot be substituted by neuropsychological tests or vice versa; rather, higher brain functions should be estimated by both of the methods.

Clinical trial registration: This clinical trial has been prospectively registered on Clinical Trial Registry India (CTRI) with the number CTRI/2021/09/036539.

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## KEYWORDS

depression, event-related potentials, mild cognitive impairment, neuropsychological battery tests, older adults

# 1 | INTRODUCTION

A fundamental human activity, cognition, refers to the action or faculty of knowing. In Darkness Visible; "A Memoir of Madness," William Styron calls depression "a wimp of a word," referring to his own experience.<sup>1</sup> We might also be overly accustomed to the notion that depression is merely a collection of symptoms rather than a serious impairment of cognition. At its simplest, it equals the thinking.<sup>1</sup> According to Hartog and colleagues, depressed patients exhibit deficits across a range of cognitive domains, including automatic attention processing, memory scanning, and memory span, which together point to a slower rate of information processing in automatic subtasks and consequently issues with decision-making abilities.<sup>2</sup>

Various methods can be used to evaluate cognitive abilities. The two most popular techniques are event-related potentials (ERPs; ERP-P300) and neuropsychological tests.<sup>3</sup> The purpose of neuropsychological testing is to examine a psychological function that is known to be correlated with a specific brain structure or neural pathway.<sup>4</sup> These tests often entail the methodical execution of a set of clearly specified steps in a formal setting.<sup>5</sup> Testing prefrontal cognition most precisely consists of a battery of examinations that gauge recall and analytical thinking skills.<sup>6</sup> Visual memory retains a track of attributes of the visual stimulus that the individual sees<sup>7</sup> and working memory is used to manipulate and temporarily store the data needed to carry out difficult cognitive activities.<sup>8</sup> Verbal reasoning is a sophisticated, multicomponential cognitive activity that calls for the use of many different cognitive talents,<sup>9</sup> all of which helps to make conclusions from given information.<sup>10</sup> Logical reasoning measures the capacity to formulate concepts and apply reasoning to a variety of presented stimuli.<sup>11</sup> Assessment of these cognitive abilities is done for research and in therapeutic settings to identify any impairments.<sup>12</sup>

Pennsylvania's Penn Computerized Neurocognitive Battery (PennCNP) is a web-based computerized neuropsychological test battery (NBT), which evaluates a variety of cognitive skills through assessments that measure performance accuracy and speed on key neurobehavioral domains.<sup>13</sup> The psychometric properties of PennCNP are well established,<sup>14</sup> therefore it is regarded as a reliable and valid method to assess several aspects of cognition and variations in the same, if any. The validity of an NBT for detecting mild cognitive impairment (MCI) is reported to be unaffected by depression, and it has also been reported that the computerized NBT for MCI is robust to depressive symptoms, supporting its clinical utility in identifying cognitive impairments and neurodegenerative disease even in elderly patients with depression.<sup>15</sup>

One more way to objectively assess prefrontal cognition is by means of its electrophysiological correlates via electroencephalography. ERPs, which provide a low cost, noninvasive, and repeatable method for assessing brain function linked in psychopathology, have been used in psychophysiological research to explore neurocognitive abnormalities in depressive disorders.<sup>16</sup> In particular, the P300 is a popular ERP measure that is used to look at brain activity in depression.<sup>17</sup> Additionally, studies have shown that the P300 has consistent psychometric features in both normative and clinically depressed populations,<sup>18</sup> giving it an appropriate neural test to examine individual variations in how depression affects neurocognitive functioning.<sup>19</sup>

As both these measures evaluate cognition, a few researchers have also focused on determining the relationship between ERPs and NBT.<sup>20</sup> However, there is a scarcity of information defining the connection between P300 wave features and NBT performance, with only few studies being published on the subject. As a result, in the current investigation, we compared the characteristics of ERP-P300 in depressed older adults with MCI to the results of traditional NBT.

# 2 | MATERIALS AND METHODS

# 2.1 | Methods

The institutional ethical committee of the university, gave its approval for this investigation. This clinical trial has been prospectively registered on Clinical Trial Registry India (CTRI) with the number CTRI/2021/09/036539. Participants were informed about the study during the initial contact, and, after a preliminary diagnostic interview and assessment of the admission requirements, their written informed permission was obtained. The Declaration of Helsinki, 1964 and its updates, were followed when conducting the research for this study. Following a Structure Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders (SCID)-I/NP to determine the DSM-IV diagnosis,<sup>21</sup> qualified consenting individuals had a thorough mental clinical interview and physical examination with the assistance of a clinical neurologist. To confirm the severity of depressive symptoms, the observer rated the Patient Health Questionnaire (PHQ)<sup>22</sup> scoring that was done for the depressed patients, as it has 61% sensitivity and 94% specificity in older adults and takes less time to administer.<sup>23</sup> The good psychometric performance of the PHQ-9, along with its ease of use and relative brevity, makes it attractive compared with the longer Geriatric Depression Scale 15 (GDS-15) and other tools for use in older adults.<sup>24</sup> Further, recent studies have found that the PHQ-9 is more authentic for screening depression in psychiatric clinics.<sup>25</sup> The PHQ-9 is available in over 30 languages,<sup>26</sup> therefore valid for use in different ethnicities, and it is accessed for free.<sup>27</sup> After that, the Mini Mental Status Examination (MMSE)<sup>28</sup> was used to test

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people who had been diagnosed with depression for MCI symptoms. Then, the evaluation of the neurophysiological and neuropsychological function characteristics were carried out. The administration of each test was standardized, and the order in which each test was given to each person was maintained.

# 2.2 | Subjects

Forty-six unmedicated depressed older adults, including both men and women, were recruited for the study from Jamia Nagar in Delhi, India. The following inclusion criteria were used to include the subjects: (i) age 60; (ii) DSM-IV criteria for unipolar major depression based on the non-patient version of the SCID-I/NP<sup>21</sup>; (iii) patients had PHQ scores of 10 or above at the time of  $enrollment^{22}$ ; (iv) participants with MCI with MMSE scores ranging from 18 to 24<sup>28</sup>; (v) participants who are physically sound (stable); and (vi) subjects having basic command of the English language and capacity to give permission after being fully informed. Exclusion criteria were: (i) febrile and medical illness; (ii) medicines that may have an impact on cytokine levels; (iii) vaccines within the past 4 weeks; (iv) usage of psychotropic medications in the 6 weeks prior to the study; (v) fulfilling the DSM-IV criteria for post-traumatic stress disorder, bipolar disorder, or psychosis; and (vi) participants with a diagnosis of any other psychological disorder, recent substance abuse/dependence, and an active suicide plan.

#### 2.3 | Outcome measures

## 2.3.1 | Neurophysiological measures

#### **Event-Related Potential-P300**

Pre and post-training measures for cognitive functions were tested by ERP-P300 including both P300-amplitude (Amp) in micro-volt ( $\mu$ V) and P300 latency (Lat) in milliseconds (ms) during wakefulness for 10 minutes at the same time of the day for all participants to avoid circadian variations on the P300 wave. Environmental factors which influence ERP, such as temperature or noise, was controlled during each recording. Instructions for the last 24 hours were given to the participants to refrain from consuming caffeinated products and excessive adverse events, as these can also contribute to changes in ERP-P300 wave.<sup>29</sup> The subject was made to sit in a relaxed position for the ERP-P300 recording and electrode placement and other procedures were done according to previous studies.<sup>30</sup>

# 2.3.2 | Neuropsychological measures

After a familiarization session, computerized cognitive testing was conducted under observation in a distraction free, calm atmosphere. The PennCNP was used to assess performance on the following neuropsychological domains<sup>14</sup>:

#### Attention

The Continuous Performance Test (CPT) is a well-established paradigm for the measurements of attention and vigilance. When the lines were set up as complete numbers (first half of task) or entire letters, the participants were asked to press the spacebar. Vertical and horizontal lines in seven-segment displays emerge on the screen (at a rate of 1 second each, during the second half of the task). Each half lasts for 1.5 minutes, and the stimulus is only visible for 300ms of each 1-second response window (leaving 700ms of blank screen).<sup>14</sup>

#### Working memory

The Penn letter n-back test (LNB) measures the working memory and executive control. Participants were asked to hit the spacebar while paying attention to a continuous stream of letters flashing on the screen. In the 0-back condition, when the letter on the screen matches the preceding letter during the 1-back condition, the user was asked to press the spacebar. When the letter on the screen is the same as letter before the previous letter during the 2-back condition, they were asked to press the spacebar.<sup>14</sup>

#### Episodic memory

Participants in the Face Memory Test (CPF) were first shown 20 faces before being asked to name them afterward. Twenty faces that participants were instructed to memorize are mixed with 20 novel faces that were distinct from the distracters shown during the immediate recall during the delayed recall. Participants were asked to select one of four buttons ("absolutely yes," "possibly yes," "possibly no," or "certainly no") for each face on both the immediate and delayed recall.<sup>14</sup>

#### Complex cognition

The Verbal Reasoning Test (VRT) measures the language reasoning. Participants must select the correct solution from eight verbal analogy issues. No time limit applies. A practice session is conducted before the test. Speed is based on the median reaction time for the correct responses, whereas accuracy is based on the percentage of accurate responses.<sup>14</sup>

#### Social cognition

The Emotion Differencing Test (EDT) assesses the capacity to recognize the intensity of emotions. Two faces are displayed to the subject. Participants have to identify which face is displaying a stronger or more intense emotion. No time limit applies. There are 36 trials in total; four of them show no emotional difference, whereas the other 32 indicate emotional differences ranging from 10% to 60%.<sup>14</sup>

#### Sensorimotor speed

The Finger Tapping Test (TAP) evaluates manual dexterity and motor speed. Participants are instructed to use their index finger to push the spacebar as frequently as they can. Their dominant and non-dominant hands are used alternately in six trials of 10 seconds each. A practice session for each hand is conducted before the test. The total number of taps on the six trials is used to calculate speed.<sup>14</sup>

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# 2.4 | Statistical analysis

Statistical analysis was performed using SPSS version 28.0. The Shapiro-Wilk test, skewness, and histogram were used to confirm that the distribution of all outcome measures was normal. Before moving on to inferential analysis, the result variables that exhibit non-normal distribution were examined using a nonparametric test or log-transformed. Using the Pearson correlation coefficient, the relationships between neurophysiological and neuropsychological functions were calculated. *R* values of 0.10 or less are often considered to have a little impact, 0.10–0.50 have a moderate impact, and 0.50 or more have a significant impact.<sup>31</sup> To determine if neurophysiological functions significantly predicted neuropsychological functions, the stepwise method of multiple linear regression was applied. Age, gender, and body mass index (BMI) were all entered to the regression analysis along with the neurophysiological measures to examine their predictive role to neuropsychological measures.

# 3 | RESULTS

Samples of 46 depressed older adults with MCI with demographic characteristics mean (age =  $62.47 \pm 2.08$  years, height =  $163.87 \pm 7.56$  cm, weight =  $73.78 \pm 6.2$  kg, BMI =  $27.75 \pm 3.93$ , PHQ =  $14.86 \pm 1.32$ , and MMSE =  $23.17 \pm 1.11$ ) were assessed for both neurophysiological functions (measured by ERP-P300) and neuropsychological functions (measured by NBT) characteristics (Table 1).

To evaluate the association between several areas of neurophysiological functions (Amp) and neuropsychological functions (attention CPT, working memory LNB, episodic memory CPF, complex cognition VRT, social cognition EDT, and sensorimotor speed TAP), we computed Pearson's correlation (Table 2). The relationship

TABLE 1Mean and SD scores for event-relatedpotentials correlates (P300 amplitude and P300 latency) andneuropsychological battery test performance (Continuousperformance test, Letter-n-back test, Face memory test, Verbalreasoning test, Emotion differentiation test, and Finger tappingtest)

SD
0.40
14.63
3.59
5.66
6.10
6.65
4.48
4.03

Note: Data are presented as mean and SD.

Abbreviations: Amp, P300 amplitude; CPF, Face memory test; CPT, Continuous performance test; EDT, Emotion differentiation test; Lat, P300 latency; LNB, Letter-*n*-back test; SD, standard deviation; TAP, Finger tapping test; VRT, Verbal reasoning test. \*P < 0.05 is significant. between Amp and CPF was computed but it did not show any association (r = -0.140, p = 0.352). Similar correlation analyses were performed for Amp and CPT (r = 0.199, p = 0.184), Amp and EDT (r = -0.124, p = 0.411), Amp and VRT (r = -0.008, p = 0.957), and Amp and TAP (r = -0.138, p = 0.359), but no association was found in any of these analyses. Intriguingly, a negative linear correlation between Amp and LNB was found (r = -0.340,  $P = 0.021^*$ ; Figure 1), demonstrating that participants who took lesser time on the LNB showed an optimum amplitude values for the P300 wave, and those who took a longer time to perform the LNB, had their amplitude values decreased when analyzed for the P300 wave.

We next conducted a Pearson's correlation for neurophysiological function (Lat) and neuropsychological functions (attention CPT, working memory LNB, episodic memory CPF, complex cognition VRT, social cognition EDT, and sensorimotor speed TAP; Table 2). Lat and CPF were correlated, and there was no evidence of a link (r = -0.110, P = 0.466). Similarly, a correlation analysis was also done for Lat and CPT (r = -0.102, P = 0.499), Lat and EDT (r = 0.105, P = 0.487), Lat and TAP (r = -0.213, P = 0.155), and Lat and LNB (r = -0.019, P = 0.901), but no relation was found in any of these analyses. Importantly, a negative linear correlation was found between Lat and VRT (r = -0.474,  $P < 0.001^*$ ; Figure 2), demonstrating that participants who scored more on the VRT showed decreased latency values for the P300 wave, and those who scored less on the VRT, had their latency values increased when analyzed for the P300 wave.

Multiple stepwise linear regression analysis ( $R^2$ ) was carried out for Amp and LNB (Table 3). The regression analysis ( $R^2$ ) revealed that Amp was found to significantly predict the working memory using LNB (F(1, 44) = 5.749, P = 0.021, with an  $R^2$  of 0.116). Similarly, regression analysis ( $R^2$ ) was carried out for Lat and VRT. The value of  $R^2$  revealed that Lat was found to significantly predict the complex cognition using VRT (F(1, 44) = 12.717,  $P < 0.001^*$ , with an  $R^2$  of 0.224).

# 4 | DISCUSSION

There are several methods for testing cognition, including straightforward pen-and-paper tests,<sup>32</sup> the NBT,<sup>33</sup> electrophysiological techniques like ERPs,<sup>34</sup> and imaging techniques like functional magnetic resonance imaging (fMRI).<sup>35</sup> Although fMRI is more precise, however, frequent clinical use of it is not possible due to its high cost. The NBT and ERP-P300 are the two most prevalent and distinct biomarkers to evaluate cognition, and both can be performed often in clinics.<sup>36</sup> These tests have attained a level of uniformity that makes them the gold standard for evaluating higher mental function.

In this study, we evaluated the relationship between neurophysiological functions (using ERP-P300) and neuropsychological functions (using PennCNP-NBT) in depressed older adults with MCI. Our findings not only confirmed the increased deterioration in neurophysiological and neuropsychological functions abilities but also established the negative statistically significant association between 178

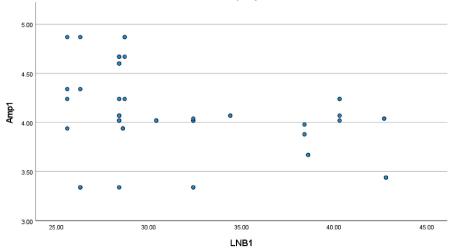
P300 amplitude measured on ERP-P300and working memory (LNB) measured on NBT in depressed older adults with MCI. The results of the current study are consistent with that of an earlier study in which they show a negative correlation between working memory and P300 wave amplitude.<sup>37</sup> Our findings concur with research by other researchers<sup>38</sup> that found links between working memory and P300 amplitude. This demonstrates that participants with greater wave amplitudes outperformed those with smaller P300 amplitude in the working memory challenge. It has been discovered that working memory necessitates the simultaneous storage and processing of information which is essential for the acquisition of both native and second-language vocabulary. Thus, this evaluates the ability to temporarily store and manipulate the data required for such challenging cognitive activities.<sup>8</sup> However, the intensity of neuronal processes that appear to represent the information from the target

TABLE 2 Correlation analysis between event-relatedpotentials correlates (P300 amplitude and P300 latency) and neuropsychological battery test performance (Continuous performance test, Letter-*n*-back test, Face memory test, Verbal reasoning test, Emotion differentiation test, and Finger tapping test; *r* and *P* values are presented)

	Neuroph	functions		
Neuropsychological	Amp		Lat	
functions	r	P value	r	P value
CPF	-0.140	0.352	-0.110	0.466
СРТ	0.199	0.184	-0.102	0.499
EDT	-0.124	0.411	0.105	0.487
LNB	-0.340	0.021*	-0.019	0.901
VRT	-0.008	0.957	-0.474	<0.001*
ТАР	-0.138	0.359	-0.213	0.155

Abbreviations: Amp, P300 amplitude; CPF, Face memory test; CPT, Continuous performance test; EDT, Emotion differentiation test; Lat, P300 latency; LNB, Letter-*n*-back test; TAP, Finger tapping test; VRT, Verbal reasoning test.

\*P < 0.05 is significant.



Scatter Plot of Amp1 by LNB1

stimulus is thought to be reflected in the amplitude of the P300 wave, so that increased attention results in bigger amplitude of P300 waves.<sup>39</sup> Both of these activities evaluate the same underlying brain component in physiological terms.

Second findings of our result in relation to latency showed the negative statistically significant correlations between the latency of P300 wave on ERP-P300 and complex cognition (verbal fluency and total language performance) on NBT (VRT). The finding of the present study shares similarities with a previous study, demonstrating that there is a negative relationship between complex cognition on NBT and P300 wave latency on (ERP-P300).<sup>40</sup> This demonstrates that participants with appropriate wave latency do better on VRT and have more sophisticated cognitive abilities, whereas those with prolonged P300 latency perform worse. Like conferred before, verbal reasoning is a composite, multicomponential cognitive process that implies contribution of various cognitive skills,<sup>9</sup> which helps to make conclusions from the given information.<sup>10</sup> Conversely, it is believed that the latency of the P300 wave reflects the rate of brain activities underpinning the perception and discrimination of a target stimulus.<sup>41</sup> Therefore, we can conclude that participants with shorter wave latency would have superior attention, working memory, language processing, or the complex of all, whereas those with longer P300 latency would react to a particular stimulus on a complex cognition task more slowly. Interesting correlations between ERPs and NBT, like matrices, block designs, and digit span, have been reported by several studies which have worked with various neuropsychological patients.<sup>42</sup> Whereas P300 amplitude and P300 latency have been linked to neuropsychological test performance in the literature, but it is unclear which aspects of cognitive function are reflected in the observed associations.<sup>42</sup>

We correspondingly tested for association between P300 wave amplitude and other neuropsychological function domains. No correlation was found between P300 wave amplitude and other domains of neuropsychological functions (attention, episodic memory, complex cognition, social cognition, and sensorimotor speed). Likewise, no association between P300 wave latency and other neuropsychological functions domains (attention, working memory,

**FIGURE 1** Pearson correlation coefficients showing a significant association between the P300-amplitude (Amp1) and Letter *n* back test (LNB1; r = -0.340,  $P = 0.021^*$ )

FIGURE 2 Pearson correlation coefficients showing a significant association between the P300-latency (Lat 1) and Verbal reasoning test (VRT1)  $(r = -0.474, P < 0.001^*)$ 

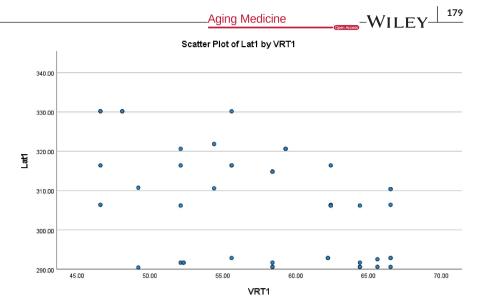


TABLE 3 Regression analysis for (P300 amplitude and Letterback test) and for (P300 latency and Verbal reasoning test;  $R^2$  and beta coefficients values are presented)

Regression weights	Beta coefficients	R <sup>2</sup>	F	P values
$Amp {\rightarrow} LNB$	-4.416	0.116	5.749	0.021*
$Lat \mathop{\rightarrow} VRT$	-0.228	0.224	12.717	<0.001*

Abbreviations: Amp, P300 amplitude; Lat, P300 latency; LNB, Letterback test; VRT, Verbal reasoning test.

\*P < 0.05 is significant.

episodic memory, social cognition, and sensorimotor speed) were found. Similar findings were made in the study by Maeshima and colleagues,<sup>43</sup> in which healthy subjects underwent both the neuropsychological testing and ERP-P300 recording, with no association identified between the measurements of the two.

Most importantly in our study, P300 amplitude was found to significantly predict the working memory, which is in line with another study,<sup>44</sup> and P300 latency was found to significantly predict the complex cognition which is again supported by a previous study,<sup>45</sup> even after accounting for confounding factors, including BMI, age, and gender of the participants. This suggests that the participant's capacity for executing memory tasks in daily life declined as the P300 wave amplitude decreased. Similar to this, the participants' capacity for undertaking challenging cognitive activities in daily life declined as the P300 wave latency grew.

# 5 | CONCLUSION

Overall, the findings of this study indicate that combining the analysis of the ERP-P300 with the use of sensitive computerized NBT may provide a very useful method for determining the neurophysiological and neuropsychological function status of depressed older adults, particularly those with MCI. Clinically, both the test (NBT and ERP-P300 are easy to apply and inexpensive methods). Both methods proved sufficient and would allow adequate recording and later comparison with other neuropsychological variables in any clinical research settings. Further, the number of channels and sensory cues used can be different in the clinical settings or future studies. In addition, the study implies that ERP P300 and computerized NBT probably reflect and assess different processes involved in cognitive functions. Aseemand and colleagues also suggested that combined use of neuropsychological tasks and the analysis of the P300 may offer a very useful method for the assessment of cognitive functions.<sup>29</sup> Further, many studies incorporated both the method of testing in their studies<sup>46,47</sup> in a variety of populations. Considering all these facts, the present study implies that, although ERPs and neuropsychological tests are considered specific for cognitive testing, but the standardized testing procedure should make use of both the measures, as one measure cannot be replaced by the other.

However, the potential limitation of our study is the sample size of convenience. Furthermore, even though high-density arrays are currently available, we only used two recording sites for this work (Cz and Fpz). Future research may also use different numbers of channels and sensory cues. Upcoming studies can include questionnairebased psychological assessments, additional tasks from a battery of neuropsychological tests that measure various cognitive domains and link them with ERPs, for a deeper understanding.

#### AUTHOR CONTRIBUTIONS

ZK conceived the study, executed the analysis and drafted the manuscript; NC helps in comprehensive mental clinical examination and screening of the subjects for this study. AS and AP assisted in interpreting the results and critically appraised the manuscript. All authors have read and approved the final manuscript, and agree with the order of the presentation of the authors.

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## CONFLICT OF INTEREST

Authors disclose no conflict of interest.

# ETHICAL APPROVAL

The Institutional Ethical Committee (IEC), Jamia Millia Islamia (A Central University), gave its approval for this investigation.

## PATIENT CONSENT STATEMENT

Participants were informed about the study during the initial contact, and after a preliminary diagnostic interview and assessment of the admission requirements, their written informed permission was obtained.

# PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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