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Original Article

Assessing BDNF correlations with non-invasive indicators of neurological decline in different age groups.

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Abstract

Background: Health is the prime concern of the modern world, and with the increasing life span, both the physical and mental health of human being decline, eventually affecting the cognitive abilities of a person, which may be due to normal aging processes or neuropathological reasons. A cross-sectional study investigated the relationship between BDNF level, neurological disturbance, and aging.
Methodology: Cognitive assessment is done through verbal fluency test (FAS, DSST, and 6CIT) and BDNF level in blood found through HPLC utilizing the ALIZA kit method.
Results: Descriptive statistics were applied for continuous variables. Hence, one-way ANOVA was performed to show the relationship between cognitive parameters and aging.
Conclusion: Our study reports that verbal fluency disturbs as lifetime increases, although sex, education, obesity, or lifestyle does not affect cognition.

Keywords

Aging, Brain Derive Neurotrophic Factor, Verbal Fluency Test, Cognitive Impairment/Cognitive Decline

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Introduction

A healthy lifestyle increases the life expectancy of an individual and hence the elderly population of the world. According to statistics, in 2050, older adults occupied 20% of the world population, and most lived in developing countries[1]. Aging is a natural phenomenon, despite the world population aging rapidly, and mental health problems are one of those reasons. Persistent pressure or stress disturb the normal functioning of the brain and body and eventually causes processing psychophysiological disturbance, which is one of the cause of earlier cognitive impairment observed in the different aged group of the world population[2].

Brain-derived neurotrophic factor (BDNF), a secretory growth factor involved in the neuronal plasticity process of learning and memory and also provides neuroprotective effects by regulating the neuron's survival, differentiations, and repair and thus provides a shield in different adverse conditions such as glutamatergic stimulation, cerebral ischemia, hypoglycemia, and neurotoxicity[3,4]. It is highly expressed in the hippocampus and cortex region while produced and secreted by the peripheral tissues as BDNF and pro-BDNF. Pro-BDNF binds to low-affinity p75 neurotrophin receptors and induces long-term depression, promotes neuronal cell death, and facilitates the resculpting of neuronal circuits. In contrast, mature BDNF binds with higher-affinity tropomyosin-related kinase family (Trk) receptors, increasing cell survival and differentiation, long-term potentiation (LTP), dendritic spine complexity, and synaptic plasticity [5,6]. Changes in BDNF level are associated with healthy and pathological aging; besides this, its expression also varies in different pathological conditions, i.e., depression, eating disorders, schizophrenia, dementia, Huntington's disease, and Parkinson's disease[7].

The brain-derived neurotrophic factor is a potential marker of cognitive decline. Hence, to observe any impairment in a person's cognition, a verbal fluency test is one of the most common non-invasive neuropsychological assessment tools utilized in clinical and research settings8. It is also utilized to measure verbal ability, including lexical knowledge and retrieval ability[9], and as a test of executive control ability[10] in a non-clinical group. Since verbal fluency requires selective attention, selective inhibition, internal response generation, and mental shifting to generate words from memory, the VF task assesses language functions like vocabulary size or naming, speed of response, mental organization, search strategies, and long-term memory.

Cognitive factors are necessary for good performance on the verbal fluency task. These factors include cognitive speed, which refers to the rate of verbal retrieval and the ability to formulate effective recall strategies[11]; cognitive flexibility, which refers to switching strategies[12] rapidly; and semantic memory[13]. Phonological fluency is helpful in the detection of cognitive deficits in pathologies with frontal involvement14. Research has shown that a healthy human can speak 12 words in a minute, starting with a specific letter15. Hence, poor performance on VF tasks links to cognitive decline, which would be a sign of frontal and temporal lobe impairment[16,17]; even though gender and age both influence verbal fluency task performance18, i.e., females pronounced more words than males, and older people have low verbal fluency than youngers[19,20,21].

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Methodology

Research Design

To evaluate the correlation of circulating BDNF levels with phonemic verbal fluency and cognitive impairment in healthy subjects, a cross-sectional study was conducted from 8th June 2021 to 4th December 2022. The study participants are healthy males and females aged between 19 to 69 years with at least twelve years of education. Subjects with neurological, hematological, or motor disorders were excluded from the study. Study parameters are divided into an invasive and non-invasive categories. Consent forms along with demographic variables were enlisted initially, and with the convenience of participants, cognitive assessments were performed individually in a quiet, peaceful environment. Evaluation is done through three non-invasive verbal tests, including FAS for phonemic word fluency assessment, the Digit symbol substitution test (DSST) to evaluate human associate learning, and The Cognitive Impairment Test (6CIT) for any cognitive disability. For invasive parameters, BDNF detection in blood serum was done thru RayBio® Human BDNF ELISA (Enzyme-Linked Immunosorbent Assay) kit, an in-vitro method in which immobilized BDNF antibodies, HRP conjugated streptavidin, and TMB substrate solutions were used while the results observed at 450 nm wavelength.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 was used for statistical analysis. The variables are demonstrated by using descriptive statistics where mean and standard deviation were used to present all the continuous variables like age, BMI, and aging indicators. On the other hand, categorical variables such as gender, marital status, obesity, socioeconomic status (SES,) and education represent frequency and percentages. One-way analysis of variance (ANOVA) was used to determine the age-wise alterations in the aging indicators invasive like BDNF and non-invasive, including DSST Time (sec), FAS Score, and 6CIT Score. Pearson correlation was used to correlate age with the indicators of aging. Chi-square (X2) test for the stratification of the aging parameters concerning the demographic characteristics of the study population and the Box and whisker plot for graphical presentation. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 412 subjects were enrolled, males were 218, and females were 194 with a mean age of 32.65±12.62 years and a mean BMI of 22.69±5.70 kg/m2. Concerning obesity, 58.5% of subjects were average, 19.9% were underweight, and 21.6% were overweight or obese. BDNF was 22.88±3.77 ng/ml.

Table 1: Mean and Standard Deviation of Neuropsychological Assessment of Population.

Parameters	Mean± Standard deviation
6CIT score	6.24±4.831
DSST Time	131.05±78.634

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FAS Score	26.03±17.071

It was found that the mean serum BDNF level declined with age, i.e., 23.84±3.53 ng/ml (20 to 36 years) to 19.62±1.68 ng/ml among subjects aged 54 to 70 years ($p<0.05$).

Table 2: Brain-derived Neurotrophic Factor analysis in different age groups.

Invasive Indicator	Age Groups			p-value
	20 to 36 years	37 to 53 years	54 to 70 years	
BDNF (ng/ml)	23.84±3.53	21.25±3.98	19.62±1.68	.000

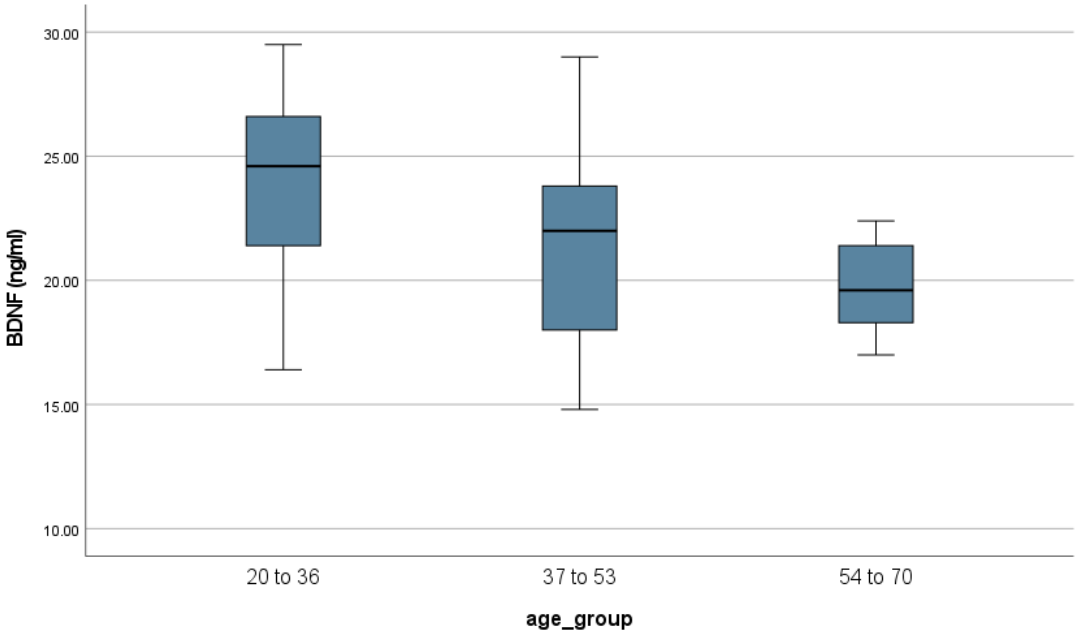

Figure 1: Whisker Plot showing the age-wise decline in the serum brain-derived neurotrophic factor.

Figure 1 shows a Box and whisker plot comparing the serum BDNF level in three different tertiles of age, i.e., 20 to 36 years, 37 to 53 years, and 54 to 70 years. The serum BDNF concentration was significantly high (median; 25th–75th percentiles) among the age group 20 to 36 years (24.6; 24.60-26.60 ng/dl) as compared to those with 54 to 70 years (19.6; 18.30-21.4 ng/dl) of age.

We have also estimated the association of study characteristics with BDNF level. A significant relationship was observed between characteristics including gender, education, marital status, obesity (BMI), age group, longevity, 6CIT score (cognitive abilities), and BDNF level ($p<0.05$). The results cannot be generalized as most of the study participants had normal BDNF levels.

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Table 3: Representation of cognitive impairment in study participants.

Variable		BDNF		
		Low (N=10)	Normal (N=402)	
6CIT	Normal	-	251(62.4)	.000
	Mild Cognitive Impairment	-	36(9.0)	
	Significant Cognitive Impairment	10(100)	115(28.6)	

*P value 0.000

Table 4: Representation of Non-Invasive Indicators in study participants.

Non-Invasive Indicators	Age Groups			p-value
	20 to 36 years	37 to 53 years	54 to 70 years	
DSST Time (sec)	118.47±53.20	125.60±109.28	208.85±104.25	.000
FAS Score	28.38±17.50	23.71±17.03	15.85±8.61	.000
6CIT Score	5.96±4.83	7.19±4.94	6.54±4.59	.148

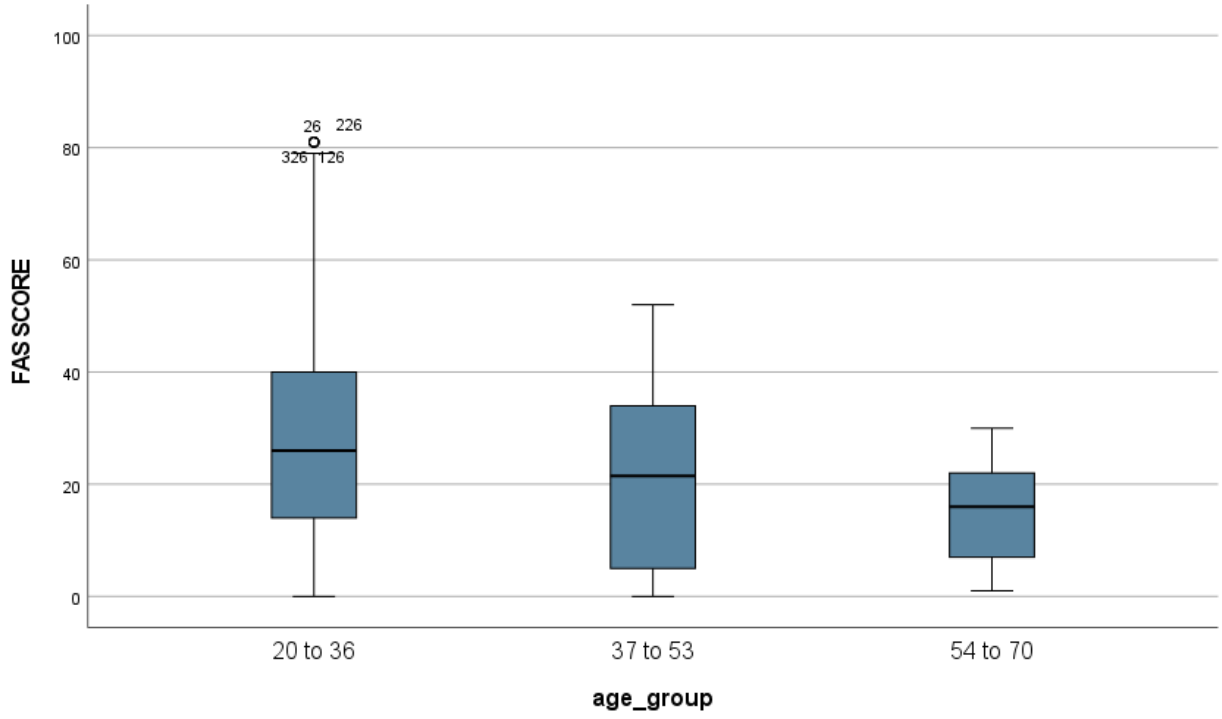

Figure 2: Whisker Plot showing the FAS score (Verbal Fluency) stratified by age.

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The FAS score was significantly high (median; 25th–75th percentiles) among the age group 20 to 36 years (26.0; 14.0-40.0) as compared to those with 54 to 70 years (16.0; 7.0-22.0) of age as shown in Figure 02.

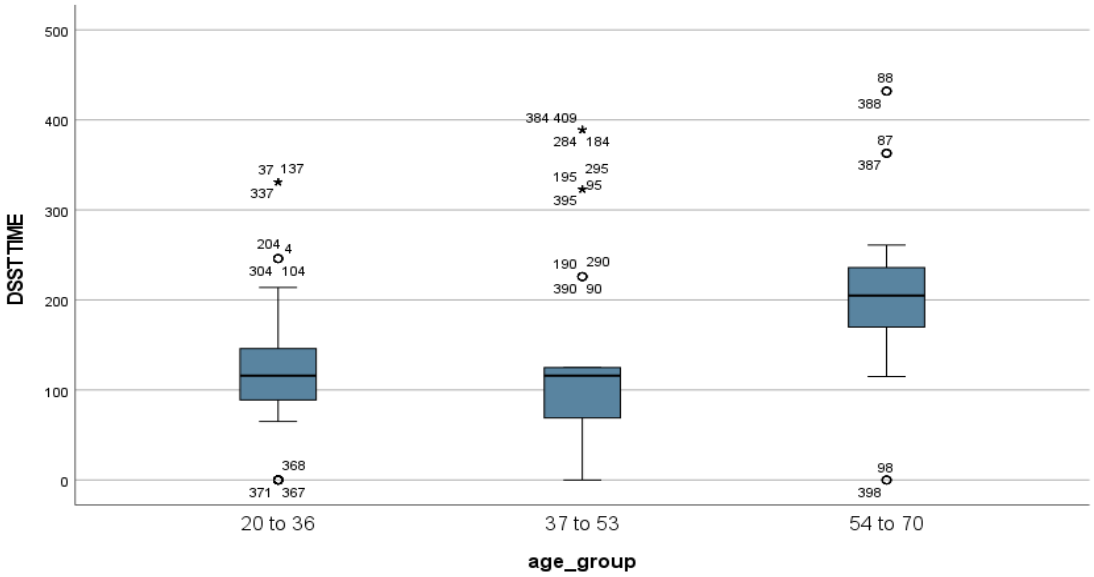

Figure 3: Whisker Plot showing the Digit Symbol Substitution Test (DSST) time stratified by age.

Figure 3 shows how DSST time gradually increased with age, i.e., 116; 89-146 seconds (20 to 36 years) compared to 205; 170-236 seconds (54 to 70 years).

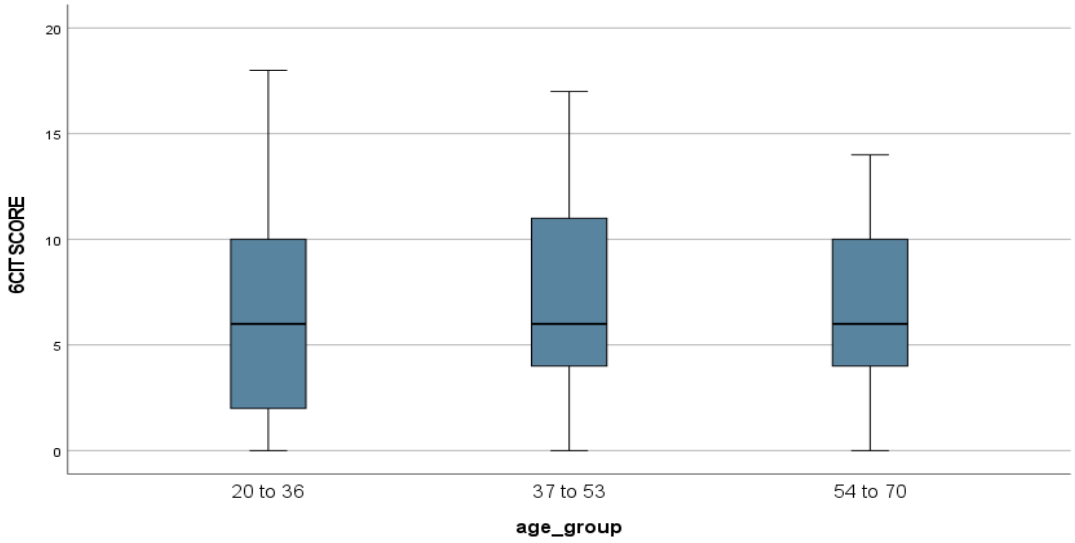

Figure 4: Whisker Plot showing the 6CIT scores stratified by age.

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There were no significant changes in the 6CIT score in the studied age groups, i.e., the median was six among 20 to 36 years, and the same was for those in the 37 to 53 years and 54 to 70 years age groups, as shown in figure 4.

Table 5 illustrates the correlation between age, BDNF, and non-invasive evaluative constraints.

Correlation of Parameters	Age	BDNF
Age	1	
BDNF	-0.438**	1
FAS Score	-0.318**	0.027
DSST Time	0.341**	-0.095
6CIT Score	0.021	-0.013

** Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Discussion

The mean FAS scores of the participating individuals support the evidence that with increasing age, the verbal fluency of an individual decrease ($p<0.05$) (Figure 02). A longitudinal study on the German population reported a similar result, which states that verbal fluency defect is the prominent indicator of cognitive impairment[22]. However, our study found no significant correlation between verbal fluency and sex, education, obesity, or lifestyle. Studies have also suggested that the brain area, mainly the hippocampus is sensitive to stress and can cause verbal declarative memory[23]. Gaillard conducted a study of verbal fluency tests and observed that younger individuals and children tend to have an active cortex compared to adults and suggested that the pattern of verbal fluency mainly developed in early childhood. Moreover, the results of his study propose that the verbal fluency test can be used in determining the brain regions with language dominance[24].

With another non-invasive constant, it was observed that the DSST time increased as the age increased ($p<0.05$) (Figure 03). It is the only neuropsychology test with a low impact on the language, culture, and education of an individual's task performance[25]. It was considered that during World War 2, the DSST test was the only clinical measure used to distinguish the patients according to brain damage compared to the controls[26]. Previous Studies suggest that DSST is more useful clinically since it is sensitive to individuals' cognitive defects and is associated with brain disorders. Better results on DSST can be achieved with intact motor speed, visuoperceptual functions, and individual ability to draw/write. DSST results are

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affected by the individual's performance which is associated with their learning ability. That is why it is also known as the "measure of complex attention" in an individual[25]

Our results showed that the median 6CIT score in all studied age groups was six, and the effects of cognitive decline were not prominent (Figure 26). It measured that the mean score of 6CIT was less in younger individuals (5.96±4.83) as compared to elder individuals (6.54±4.59) in the study ($p>0.05$) (Table 04). Studies suggest that any injury to neurons of the hippocampus CA3 region due to any stress, decreases in BDNF, increased glutamate level, or elevation of inflammatory cytokines can induce inhibition of neurogenesis[28], which causes defects in new learning that are also associated with increased levels of glucocorticoids due to stress[29,30]. Wide-ranging cognitive domains with compromised functions include verbal learning and memory, attention working memory, executive functions, and information processing speed[31].

Similarly, evidence suggests that increased inflammation causes detrimental effects on the brain and cognitive levels, called neuroinflammation, which has a significant role in peripheral pro-inflammatory cytokines that play its role through several pathways. Among the cytokines playing an essential role in neuroinflammation is IL-6[32]. As suggested by the evidence from the studies, the ability of BDNF to induce functional synaptic plasticity and changes in synaptic morphology has been considered an attractive candidate as a molecular mediator of learning and memory[33]. Studies have shown that individuals with cognitive decline-related conditions and diseases, including any traumatic event or mild cognitive impairment, tend to have significantly low BDNF levels[34]. Moreover, recent studies suggested that BDNF is the circulating biomarker for cognitive and memory functions in healthy individuals[35,36].

Conclusion

It is concluded that increased inflammation causes detrimental effects on the brain and cognitive levels. With increased age, serum BDNF levels decline, along with the verbal fluency of an individual, and our results show an increase in the DSST time with aging. Moreover, it is suggested that individuals with cognitive decline-related conditions and diseases, including any traumatic event or mild cognitive impairment, tend to have significantly low BDNF levels, with decreased verbal fluency and DSST time. Based on the data collected, BDNF was in the normal range & the non-existence of a relationship between psychological parameters and BDNF cannot be ruled out.

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