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Full length Research Article

Age-Related Changes in Cognition, Plasma Levels of Brain-Derived Neurotrophic Factor and Selected Indices of Inflammation in Adults at Different Decades of Life

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Summary: Ageing is associated with neurological disorders that are characterized by cognitive impairment. Reports have shown that brain-derived neurotrophic factor (BDNF) is involved in neurogenesis and neuroplasticity. Additionally, chronic inflammation-associated with ageing plays important roles in immunosenescence. However, there is a dearth of information on the interplay between BDNF and inflammation in the context of cognitive decline in the elderly. Thus, this study was designed to determine cognition, plasma levels of BDNF and selected indices of inflammation in human adults at different decades of life. Eighty-eight human adults sub-divided into 4 groups: group I (30 – 39 years), group II (40 – 49 years), group III (50 – 59 years) and group IV (≥60 years) were enrolled into this cross-sectional study. Cognitive function was assessed using the Mini-mental state examination (MMSE). Plasma levels of BDNF and nitric oxide (NO) were determined using ELISA and spectrophotometry. White blood cell count and differentials were done using standard methods and neutrophil-lymphocyte ratio (NLR) was calculated appropriately. There was significant reduction in cognitive score and plasma levels of BDNF as decades of life increased. The cognitive scores were significantly higher in groups I ($p = 0.000$), II ($p = 0.000$), and III ($p = 0.000$) compared with group IV. Similarly, the median plasma level of BDNF was higher in group I compared with groups III ($p = 0.007$) and IV ($p = 0.002$). The mean mixed count (monocytes, basophils and eosinophils) was significantly higher in group IV compared with group I ($p = 0.003$), while mean plasma level of NO was higher in group III compared with group I ($p = 0.003$). Age was a significant predictor of cognition ($B = -0.325$, $SE = 0.033$, $p = 0.000$) and BDNF level ($B = -107.660$, $SE = 35.825$, $p = 0.003$). Furthermore, BDNF levels had significant positive correlation with the cognitive score in group I. Conclusively, there was progressive reduction in cognitive score and plasma BDNF level with increasing decades of human life. This may indicate that plasma BDNF level could predict susceptibility to cognitive dysfunction as ageing progresses.

Keywords*: Aging, Brain-derived neurotrophic factor, Immunosenescence, Inflammation, Cognition.*

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INTRODUCTION

Ageing is a complex process that is associated with changes in biological, physiological, immunological, psychological, behavioural, and social processes. It is characterized by a progressive and irreversible decline in physical functions resulting from the gradual loss of certain bioprotective and regenerative capabilities (Hernandez-Segura *et al*., 2018). As ageing progresses, vital organs begin to lose some functions, and all cells change, becoming larger and less able to divide and multiply (Dulken *et al*., 2019).

Genetic and epigenetic factors play multifaceted roles in the process of ageing and usually result in a reduction in endocrine, immunological, and cognitive functions, among others. It has been reported that gradual loss of cognitive capacity in elderly individuals is linked to changes in the cortex or hippocampal regions of the brain that are involved in learning and memory (Crook *et al*., 1987; Kwok, 2010; O'Shea *et al*., 2016).

Some neuronal loss also occur during normal ageing but usually does not exceed 10% (Morrison and Baxter, 2012). Morphological changes in neurons, especially dendrites and axons, are involved in cognitive decline and behavioural changes (Dickstein *et al*., 2013). With increasing age, the dendritic trees undergo regression, while the dendritic shafts decrease in number, become shorter and less branched, and have fewer spines (Dickstein *et al*., 2013).

Several proteins, including brain-derived neurotrophic factor (BDNF), are involved in regulating the growth, survival, and differentiation of neurons. The BDNF is a neuropeptide of the neurotrophin family that can bind to a

specific receptor known as tropomyosin kinase receptor B, activating intracellular signaling pathways that result in the regulation of the growth, survival, and differentiation of neurons (Webster *et al*., 2006). It is involved in the modulation of synaptic plasticity, including the induction or enhancement of long-term potentiation (Dong *et al*., 2022), through the promotion of neurogenesis and/or dendritic outgrowth (Pizzorusso *et al*., 2000). The BDNF is highly expressed in the hippocampus, amygdala, cerebellum and cerebral cortex in both rodents and humans, with the highest levels found in the hippocampus, an area that is involved in learning and memory (Hofer *et al*., 1990; Miranda *et al*., 2019). Reports abound indicating that BDNF plays a critical role in maintaining hippocampal volume in adults (Teixeira *et al*., 2010). It is hypothesized that BDNF influences age-related changes in hippocampal volume through several age-related alterations within the hippocampus. In the central nervous system, BDNF and downstream prosurvival pathways have been demonstrated to protect neurons from damage and enhance neuronal network reorganization after injury (Numakawa *et al*., 2010). It has also been reported that BDNF treatment can reduce the degree of microglial activation in certain brain injury models, although these responses are considered a consequence of reduced neuronal injury and death elicited by BDNF (Jiang *et al*., 2011). Additionally, Mizoguchi *et al*. (2020) reported that BDNF hypofunction is associated with age-related memory impairment.

The aging process is accompanied by a state of low-grade non-resolving activation of inflammatory pathways, a phenomenon known as inflammaging (Bowirrat, 2022). This stage is usually associated with an increased number of inflammatory cells in the central nervous system (CNS), thus contributing to a greater degree of neuroinflammation (Stichel and Luebbert, 2007).

Inflammatory pathways can be activated by self-debris and self-molecules that result from unhealthy or dead cells produced at a relatively high rate in aged tissues, the accumulation of senescent cells and their associated proinflammatory secretome (Garthwaite *et al*., 1988; Sama and Norris, 2013). Several age-related synaptic alterations in Ca2+ homeostasis may be responsible for the elevation of intracellular Ca2+ and neuroinflammation, as indicated by the production of proinflammatory cytokines, including interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) (Lourenço *et al*., 2017). Cellular markers of inflammation, such as the neutrophil-lymphocyte ratio (NLR), positively correlate with age. Older people have been observed to have elevated NLRs compared with young adults (Li *et al*., 2015).

Nitric oxide (NO) plays important roles in several neurobiological processes, ranging from the regulation of endothelium-dependent vasodilation to neurotransmission, and participates in host defence mechanisms (Boje, 2004). Because it has been described to be both neuroprotective and neurotoxic, it has been referred to as a Janus-faced molecule (Toledo and Augusto, 2012). It is a crucial component of the signal transduction pathways used for memory formation, sensory processing, and the regulation of cerebral blood flow (Bernard-Gauthier *et al*., 2013). NO signalling in the ageing brain revealed that a small decrease in neuronal-derived NO in the aged hippocampus was accompanied by a more robust decrease in the cerebrovascular response produced upon stimulation of neuronal activity. It has been shown that there is decreased nitric oxide synthase (NOS) expression with age, both as constitutive and inducible isoforms (Lourenço *et al*., 2017). An increase in mediators of inflammation reduces BDNF expression, and BDNF may play an important negative regulatory role in inflammation within the brain (Schramm *et al*., 2002). Currently, there is a dearth of information on age-related changes in BDNF levels and inflammation in Nigerian adults. Thus, this study was designed to determine the relationship between cognition, plasma BDNF levels and selected indices of inflammation in adults of different decades of life to provide information that could be of therapeutic importance to age-related neurological status in health and disease conditions.

MATERIALS AND METHODS

Human ethics and consent to participate: This study was carried out in accordance with the Declaration of Helsinki and approved by the University of Ibadan/University College Hospital Joint Ethics Committee (UI/EC/21/0698). Additionally, written informed consent was obtained from each study participant.

Study participants and location: A total of 88 apparently healthy adults (39 males, 49 females) were enrolled in this cross-sectional study. The participants consisted of 20, 22, 22 and 24 adults within the age ranges of 30–39 years (Group I), 40–49 years (Group II), 50–59 years (Group III), and 60 years and above (Group IV), respectively. The participants were enrolled using a convenient sampling method from the metropolis of Ibadan city, Nigeria.

Assessment of neurocognition: Neurocognition was assessed using the Mini-Mental State Examination (MMSE), a neuropsychological screening test used to assess the speed of information processing, executive function, learning, memory, motor function, and verbal function. The test yields a single composite score that reflects disease severity. Scores <10, 10–20, 21–24 and ≥25 indicate severe impairment, moderate impairment, mild impairment and no impairment, respectively (Folstein *et al*., 1975).

Inclusion and exclusion criteria: Apparently healthy adults within the age range of 30 years and above with no history of stroke, posttraumatic stress disorder, learning disability, mental illness, substance abuse and/or dependence, metabolic and cardiovascular diseases or autoimmunity were enrolled into this study. Patients with HIV or CNS opportunistic infections such as toxoplasmosis and meningitis were excluded from the study. Additionally, patients with a history of previous or present smoking and alcohol consumption and patients who recently used anti-inflammatory drugs and steroids were excluded from the study.

Blood sample collection: Venous blood (5 ml) was collected from the antecubital fossa of each participant, using needle and syringe, after at least 10 minutes of rest and dispensed into heparin-containing sample bottles. Twenty-five microliters (25 µL) of whole blood was taken for the nitroblue tetrazolium (NBT) assay. The remaining

blood sample was centrifuged at 3000 rpm for 15 minutes, and the obtained plasma samples were stored at -20°C until analysis.

Laboratory analysis: The plasma BDNF level was determined using a Sandwich ELISA following the manufacturer's instructions (ElabScience Biotechnology, Inc., USA). The plasma level of NO was determined using the Griess reagent as described by Green *et al*. (1982), while the neutrophil phagocytic activity was determined using the modified semiquantitative NBT procedure as described by Edem and Arinola (2015). Complete blood analysis was performed using a 3-parameter Hematology Autoanalyzer (Mindray BC-5390, Shenzhen Mindray Bio-Medical Electronics Co., China). Thereafter, the neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of the neutrophil count (%) to the lymphocyte count (%) (Li *et al*., 2015).

Data analysis: The Statistical Package for Social Sciences (SPSS), version 23.0, was used for data analysis. The data were assessed for a Gaussian distribution; thereafter, an appropriate statistical tool was applied. The Gaussian distribution of the data was assessed using a histogram with a normal curve. Mean differences between the groups (for variables with Gaussian distributions) were determined using ANOVA followed by LSD post hoc tests. However, the Kruskal–Wallis and Mann–Whitney U tests were used to determine differences in median values between the groups (for variables with a non-Gaussian distribution). Correlations between the variables were determined using the Spearman rho correlation. Linear regression analysis was used to predict the relationship between the age (as an independent variable) and cognitive score (dependent variable) as well as age and plasma BDNF level (dependent variable). P values less than 0.05 were considered to indicate statistical significance. Results are presented as mean ± standard deviation or median (interquartile range), as appropriate.

RESULTS

The age of the study participants ranged between 31 and 82 years, with a mean of 52.28 ± 13.63 years. As shown in Figures 1 and 2, there was a significant reduction in the neurocognitive score (p-value = 0.000) and plasma BDNF level (p-value = 0.009) as the age increased. The neurocognitive scores were significantly higher in Group I (29.35 ± 0.67), Group II (28.00 ± 1.72), and Group III (26.68 ± 2.32) than in Group IV (19.17 ± 8.48). Similarly, the median plasma BDNF level was significantly higher in Group I [8561.65 (5895-10310.90)] than in Groups III [5082.72 (3154.31-5360.06), p-value = 0.007] and IV [4630.59 (1758.43-4630.59), p-value = 0.002].

In Table 1, there were significant differences in the mean plasma levels of NO and mixed count among the four groups. The mean mixed count (monocytes, basophils and eosinophils) was significantly higher in Group IV than in Group I (p -value = 0.003), while the mean plasma NO level was significantly higher in Group III than in Group I (p value = 0.003).

In Table 2, correlations between the neurocognitive score and other parameters are presented. The median plasma level of BDNF level had significant positive correlation with the neurocognitive score in Group I. None of the other parameters were significantly correlated with the neurocognitive score.

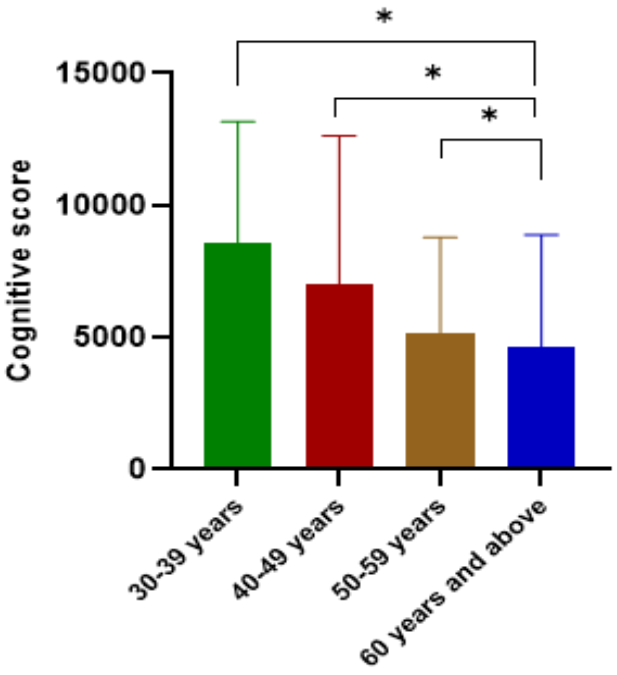

Figure 1:
Cognitive score in adults at different decades of human life
*Significant at p<0.05

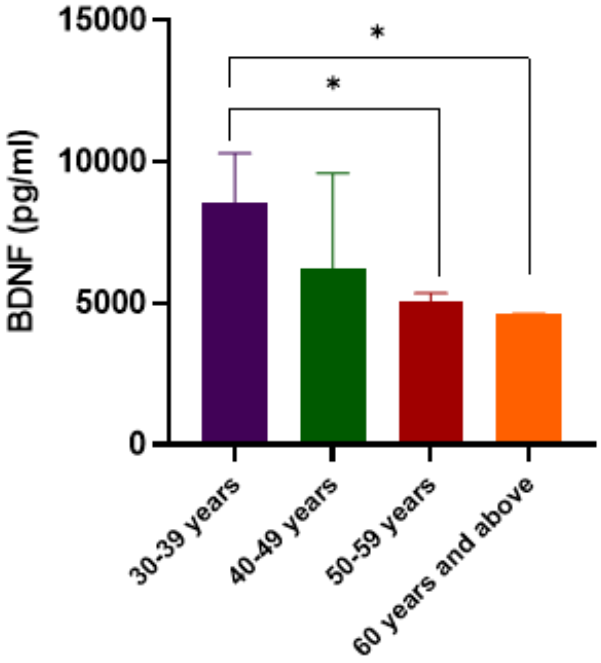

Figure 2:
Plasma BDNF levels in adults at different decades of human life

Table 1:
White blood cell count, neutrophil-to-lymphocyte ratio and plasma nitric oxide level in adults in different decades

Parameters	Group I (n = 20)	Group II (n = 22)	Group III (n = 22)	Group IV (n = 24)	p-value
WBC count (cmm)	6267 ± 2414	7547 ± 3501	819 5± 3465	6727 ± 1622	0.200
Neutrophil count (%)	44.42 ± 13.70	53.45 ± 13.87	53.31 ± 12.21	46.90 ± 11.85	0.088
Lymphocytes count (%)	40.26 ± 11.07	39.07 ± 14.29	37.28 ± 18.24	40.39 ± 9.38	0.898
Mixed count (%)	5.75 (3.63-9.78)[a]	8.35 (2.73 - 10.08)	8.60 (5.30 - 11.20)	12.10 (9.40 - 15.40)	0.021*
NLR	1.11 (0.63 - 1.92)[a]	1.54 (0.97 - 1.86)	1.35 (0.81 - 2.19)	1.02 (0.81 - 1.60)	0.231
NO (µM)	0.85 (0.83-0.89)[b]	0.92 (0.84-1.09)	0.93 (0.88-0.98)	0.87 (0.85 - 0.92)	0.011*

**Significant at P<0.05, WBC = white blood cell, cmms = cubic millimeter, Mixed = other leucocytes, NLR = neutrophil–to-lymphocyte ratio, NO = nitric oxide. [a]Compared with Group IV, [b]Compared with Group III, Group I = 30-39 years, Group II = 40-49 years, Group III = 50-59 years, Group IV = 60 years and above*

Table 2:
Correlations between the neurocognitive score, neutrophil-to-lymphocyte ratio and plasma BDNF level concentration

Parameters	Group I (n = 20)		Group II (n = 22)		Group III (n = 22)		Group IV (n = 24)	
	MMSE							
	r	p	r	p	r	p	r	p
BDNF (pg/ml)	0.604	0.013*	0.402	0.098	0.233	0.368	0.315	0.294
NO (µM)	-0.237	0.315	0.166	0.460	-0.399	0.066	0.033	0.878
NLR	0.318	0.198	-0.094	0.701	-0.121	0.613	-0.226	0.417

**Significant at P<0.05; MMSE = Mini-Mental State Examination; NLR = neutrophil–to–lymphocyte ratio; BDNF = brain-derived neurotrophic factor; NO = nitric oxide, r = correlation coefficient; Group I = 30-39 years, Group II = 40-49 years, Group III = 50-59 years, Group IV = 60 years and above.*

Table 3:
Linear regression analysis of age and cognition in the study participants

Predictor	Unstandardized Coefficients		Standardized Coefficient	t-value	p-value
	B	Standard error	Beta		
Constant	42.545	1.808	—	23.531	0.000*
Age (years)	-0.325	0.033	-0.723	-9.700	0.000*
R²					0.522
F					94.093
P					0.000*
Regression equation: Cognitive score = 42.545 + [-0.325 (Age)]					

*Significant at *P*<0.05, Dependent variable- Cognitive score, Predictor variable- Age

Table 4:
Linear regression analysis of age and BDNF level in the study participants

Predictor	Unstandardized Coefficients		Standardized Coefficient	t-value	p-value
	B	Standard error	Beta		
Constant	11875.107	1935.022	—	6.137	0.000*
Age (years)	-107.660	35.825	-0.308	-3.005	0.003*
R²					0.095
F					9.031
P					0.003*
Regression equation: Plasma BDNF level = 11875.107 + [-107.66 (Age)]					

*Significant at *P*<0.05, Dependent variable- BDNF (pg/ml), Predictor variable- Age, BDNF = Brain-derived neurotrophic factor

As presented in Tables 3 and 4, age was a significant predictor of cognition (B = -0.325, SE = 0.033, p = 0.000) and BDNF level (B = -107.660, SE = 35.825, p = 0.003). This indicates that, for every year increase in the age of the study participants, cognition decreased by 0.325, while BDNF level decreased by 107.66 pg/ml. The proportion of variance in cognitive score that could be explained by age was 52.2%, while the proportion of variance in plasma BDNF levels that could be explained by age was 9.5%.

DISCUSSION

It is well established that cognitive function is affected by ageing, as approximately 40% of individuals aged 65 years and older suffer from some form of memory loss (Aigbogun *et al*., 2017; Brito *et al*., 2023). Although several factors have been identified, the mechanisms through which the identified factors result in cognitive dysfunction are poorly understood.

This study observed a significant decrease in cognitive score as the duration of life increased. The regression analysis further supported this, showing that age was negatively related to cognition. These observations corroborate the findings of Park *et al*. (2002), who showed that there are gradual age-related declines in the cognitive mechanisms of speed, working memory, and long-term memory beginning in young adulthood. The observations from this study could be due to a decrease in neuronal activation and alterations in several regions of the brain as ageing progresses. Brain activity in regions such as the cortex, hippocampus and cerebellum is altered during ageing (Calautti *et al*., 2001; Brito *et al*., 2020). This results in a decrease in the speed of processing, working memory, inhibitory function, and long-term memory (Park and Reuter-Lorenz, 2009; Randhawa and Varghese, 2024).

The BDNF is involved in plasticity, neuronal survival, formation of new synapses, dendritic branching, and modulation of excitatory and inhibitory neurotransmitter profiles (Edelmann *et al*., 2014). A decrease in its level has been associated with age-related memory impairment (Panja *et al*., 2014). In this study, there was a progressive decrease in the plasma BDNF concentration as the subjects aged. The plasma BDNF levels were significantly lower in participants aged 50 years and older than in those who were younger. Additionally, a negative relationship was observed between age and BDNF level. These observations are in line with the findings of Mizoguchi *et al*. (2020), who showed that low serum BDNF levels are associated with age-related memory impairment in elderly individuals. Although a reduction in BDNF expression has been associated with chronic inflammation, which is a common feature in elderly individuals (2011), the findings of this study might not be inflammation related, as no significant difference in the NLR was observed when all the groups were compared. The observed reduced plasma BDNF could, therefore, be due to decreased physical activity, which is common in elderly people. BDNF levels are activity-dependent (Gorgoulis *et al*., 2019). Exercise is an inducer of neuronal plasticity, neurogenesis and survival (Huang *et al*., 2014). Furthermore, the observed low level of BDNF in aged individuals could be diet-dependent, as poor appetite is a common problem in older people (Pilgrim *et al*., 2015). A study by Gorgoulis *et al*. (2019) showed that diet can provoke changes in BDNF levels under physiological conditions. Low BDNF levels have been reported in adults consuming high sugar and fat-containing diets (Mizoguchi *et al*. (2020), while diets rich in omega-3 fatty acids have been shown to induce an increase in BDNF levels and a reduction in cognitive impairment (Wu *et al*., 2004; Mizoguchi *et al*., 2020).

The observed significant positive correlation between BDNF level and cognitive score indicated that an increase in BDNF level may be associated with improved cognition. This observation is not surprising, as the interplay between BDNF and cognition is well established. BDNF could therefore be considered a potential therapy for brain pathologies because it can directly or indirectly modulate changes within the brain (Nagahara and Tuszynski, 2011; Gorgoulis *et al*., 2019). Nagahara and Tuszynski (2011) reported that BDNF has a potential role in the pathogenesis and treatment of both neurological and psychiatric disorders.

Chronic inflammation is a common feature of ageing. Cellular markers of inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), have been shown to correlate positively with age. In this study, no significant difference in the NLR was observed between the groups. This observation contradicts the findings of Li *et al*. (Li *et al*., 2015), who showed that older people have a higher NLR than young adults. These differences could be due to variations in the selection of study participants, as participants in this study were grouped according to decade of life, and age-associated chronic inflammation might not be linear.

Nitric oxide is a mediator and regulator of inflammatory responses (Sharma *et al*., 2007). The function of NO in the hypothalamus has largely been implicated in learning processes and memory formation. In this study, the mean plasma NO concentration was significantly higher in participants aged 40–49 years (Group II) and 50–59 years (Group III) than in participants aged 30–39 years (Group I). This contradicts the findings of Van der Loo *et al*. (2000), who showed that the bioavailability or generation of NOS-derived NO decreases with age. However, Siervo *et al*. (2018) reported that age-related changes in serum NO levels peaked between 50 and 59 years in both sexes and declined thereafter. This finding is similar to what was observed in this study, in which the NO concentration decreased in participants aged 60 years and older. Although this observation could not be fully explained at present, it might indicate that the serum NO concentration reflects the well-established immunosenescence pattern.

The small sample size was a limitation in this study. Additionally, the use of only the MMSE to assess cognitive function was a limitation. The MMSE has been reported to have low sensitivity for detecting mild cognitive disorders, and it is largely a screening tool

It could be concluded from this study that there is a progressive reduction in the plasma BDNF concentration and cognitive score with increasing decades of life. This may indicate that the plasma BDNF concentration could predict susceptibility to cognitive impairment as aging progresses and could be further explored as a potential neuroprotective and functional restorative factor in patients with cognitive dysfunction. However, large population studies are suggested to confirm the findings of this study. Similarly, a randomized blinded clinical trial is suggested to evaluate the therapeutic effect of BDNF administration on improving cognition and preventing dementia in elderly people.

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