DOI: 10.7860/JCDR/2022/58565.17207

Original Article

Physiology Section

Cognitive Evoked Potentials in Anaemic Women: A Cross-sectional Study

UMME KULSOOM SHEEMA[1], ALKA RAWEKAR[2]

ABSTRACT

Introduction: Iron Deficiency Anaemia (IDA) is a globally prevalent nutritional disorder and an important risk factor for the development of Mild Cognitive Impairment (MCI). A manifestation of IDA is altered electrogenesis in the central nervous system. As women of reproductive age are more susceptible to this form of anaemia, it is important to assess their cognitive function. Auditory cognitive evoked potentials/P300 are sensitive in detecting MCI which is indicated by prolonged latency and reduced amplitude.

Aim: To investigate the effect of IDA on cognitive function using cognitive evoked potentials/P300 in neurologically intact women.

Materials and Methods: A cross-sectional study was conducted at the Central Neurophysiology Laboratory, Acharya Vinobha Bhave Rural hospital (AVBRH) attached to Jawaharlal Nehru Medical College (JNMC), Wardha, Maharashtra, India, from January 2018 to February 2022. A total of 260 women were recruited for the study. Based on their blood haemoglobin and serum ferritin levels, 130 women were grouped as anaemic and 130 as non anaemic. The P300 was used as an objective tool to assess cognitive function. Haematological parameters like blood haemoglobin and serum ferritin levels were compared ('t'-test) and correlated (Spearman's correlation) with the latency and amplitude of the P300 wave in the two groups.

Results: The mean age (years) and Body Mass Index (BMI) (kg/m^2) of anaemic women were 23.88±3.67 and 20.98±1.45, respectively; and that of non anaemic women were 24.09±3.41, and 21.25±1.27 ($p>0.05$) respectively. The blood haemoglobin (mg/dL) and serum ferritin (ng/mL) were significantly ($p<0.001$) lower in anaemic group (10.37±0.95, 8.55±3.78) compared to non anaemic group (13.02±0.70, 27.61±10.52). The latency of P300 wave (ms) was significantly prolonged ($p<0.001$) in anaemic women (317.75±7.34) in comparison to non anaemic women (311.71±9.02), while the P300 amplitude did not differ between the two groups ($p>0.05$). A highly significant low negative correlation of P300 latency with haemoglobin ($r=-0.48$, $p<0.001$) and highly significant moderate negative correlation with serum ferritin ($r=-0.55$, $p<0.001$) was observed. And a negligible positive correlation of P300 amplitude with haemoglobin ($r=0.26$, $p<0.05$) and serum ferritin ($r=0.24$, $p<0.05$) was observed.

Conclusion: Cognitive evoked potential is an objective method that aids in the early detection of cognitive impairment. Evaluating the cognitive function in anaemic women and ensuring adequate iron treatment can prevent MCI from progressing to severe forms like dementia and other neuropsychological disorders.

Keywords: Event related potentials, Iron deficiency anaemia, Microcytic hypochromic anaemia, Nutritional anaemia

INTRODUCTION

Anaemia affects approximately one third of the world's population and the most affected population lies in developing countries. Iron deficiency is the major contributing factor for the development of anaemia. Women in developing countries are more susceptible to this deficiency due to low dietary intake, menstrual blood loss, and increased demand during pregnancy and lactation [1]. National Family Health Survey (NFHS)- 5 carried out by the Union Ministry of Health and Family Welfare, India during the year 2019-2021 shows prevalence of anaemia to be 57% in non pregnant women belonging to the age group of 15-49 years [2].

According to WHO, IDA in non pregnant adult females is blood haemoglobin <12 g/dL and serum ferritin <15 ng/mL [1]. Iron is required for myelogenesis, synaptogenesis and neurotransmitter synthesis and their regulation in the Central Nervous System (CNS) and hence, its deficiency alters these physiological processes [3]. An increase in the severity of ID hampers erythropoiesis leading to iron deficiency anaemia. Reduced haemoglobin levels in IDA are associated with inadequate oxygen supply to the brain. The chronic low oxygen supply may affect the brain energy metabolism, intellectual functioning, and cerebral integrity [4]. The IDA has a significant impact on the attention domain of cognition compared to iron deficient and iron replete individuals, aggravating the cognitive dysfunction [5]. Evidence from various prospective and cross-sectional studies demonstrated a significant association between anaemia, cognitive decline, and risk of development of dementia [6-9].

Evoked potentials are electrophysiological signals that are recorded in response to a particular stimulus like a light flash (visual) or a pure tone (auditory) [10]. The auditory evoked potential is also known as Cognitive Evoked Potential (CEP) or P300. They are long latency evoked potentials and are helpful to measure the electrophysiological signals that are generated by neuronal activities in multiple regions of the brain. The auditory CEP is an index to measure the attention and working memory domains of cognition [11]. P300 was first reported 50 years ago and is recorded as a large positive wave with a peak latency approximately 300 ms after the stimulus onset, therefore, the term P300 [12]. The P300 amplitude measures the brain's processing action to the change in the environmental stimulus. Hence, it is hypothesised as an index of attentional resources and working memory [13]. An increase in P300 amplitude reflects increased activation of neural circuits and is proportionate to the attention and memory resources allocated, with larger amplitudes indicating higher cognitive capability [14]. It's latency is related to cognitive efficacy. It is proportional to the time required to detect and evaluate the stimulus and assesses, how rapidly the attentional and memory resources are recruited, indicating the processing time required before a response is generated. While cognitive disorders record prolonged latencies, shorter latencies are related to superior cognitive performance [12].

Systematic review and meta-analysis reported anaemia increases the risk of developing cognitive impairment by 1.39 times and dementia by 34% [15,16]. The CEP evaluation is beneficial in detecting early MCI, assessing the severity of cognitive decline and risk of progression to dementia [17,18]. A clinical trial in anaemic adults observed impaired P300 waves which improved following iron therapy [19]. Literature search reveals only few studies utilising these potentials to measure the cognitive function in adult population with IDA [4,19,20]. As the prevalence of IDA is higher in women, they may be at a greater risk of developing cognitive impairment compared to men. Hence, the present study aimed to investigate whether iron deficiency anaemia impairs the cognitive evoked potentials in neurologically intact women. The objective of the study was, to compare and correlate the cognitive evoked potentials in anaemic and healthy women. Null hypothesis of the study proposes that the cognitive evoked potentials are not altered in women with iron deficiency anaemia.

MATERIALS AND METHODS

The present cross-sectional study was carried out at the Central Neurophysiology Laboratory, Acharya Vinobha Bhave Rural Hospital (AVBRH) attached to Jawaharlal Nehru Medical College (JNMC), Wardha, Maharashtra, India, from January 2018 to February 2022. Women aged 18-30 years from the Department of General Medicine and Obstetrics and Gynaecology, and community volunteers were recruited for the study. Ethical clearance was obtained from the Institutional Ethics Committee, DMIMS (DU) (Reference no. - DMIMS (DU)/IEC/2017-18/6569). An informed consent was taken from the participants before commencing the study.

Sample size calculation: It was calculated as 130 anaemic subjects and 130 non anaemic healthy subjects using the formula "Comparison of means (two groups)" with a Confidence Interval (CI) 95%, power 80% [21].

$$n \geq \frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2 (\sigma_1^2+\sigma_2^2/r)}{(\mu_1-\mu_2)^2}$$

The participants between the age 18-30 years and normal BMI (>18.5 or <23 kg/m^2) underwent haematological evaluation for anaemia [22]. Participants were grouped as anaemic and non anaemic based on their haemoglobin and serum ferritin levels [1].

Inclusion criteria: For anaemic group (women with IDA)- women whose haemoglobin level was <12 g/dL and serum ferritin <15 ng/mL. For non anaemic group (healthy women without IDA)- women with haemoglobin levels ≥12 g/dL and serum ferritin ≥15 ng/mL.

Exclusion criteria: BMI <18.5 or >23 kg/m^2, current pregnancy or pregnancy within the previous year, currently lactating, on hormonal contraceptives, irregular menstrual cycles, recent blood donation, pre-existing ear diseases with clinical deafness, known cases of endocrine disorders (e.g., diabetes mellitus, thyroid dysfunction) and neurological diseases, use of medications-like iron supplements, major or minor tranquilizer that may alter cognitive and neurophysiological measures.

Study Procedure

Blood samples of the enrolled participants were evaluated for a complete haemogram by Coulter and serum ferritin by Electrochemiluminescence Immuno Assay (ECLIA) method according to the "Standard Operating Procedure" (SOP) [23,24]. Based on blood haemoglobin and serum ferritin levels the participants were grouped as women with IDA and healthy women without IDA.

The cognitive evoked potentials/P300 were then recorded using Neurosoft Spectrum-5 [25]. The participants were instructed to lie down and close their eyes. Silver disc electrodes were placed at both the mastoids (reference), vertex (active) and forehead (ground) for recording the auditory evoked potentials. The "oddball paradigm" was used to elicit the P300 waves. Each participant was presented with two types of auditory stimuli, such that infrequent target stimuli were given in a background of frequent standard/non target stimuli. Binaural stimuli at 70 dB with target stimuli of 2000 Hz and standard stimuli of 1000 Hz were presented. The participants were instructed to respond by pressing the button to the target stimuli and not to the standard stimuli. A response to the target stimulus elicited a large positive potential with a peak latency at approximately 300 ms, i.e., P300. A total of 100 stimuli were presented and the probability of target stimuli was 30%. Latency (ms) was marked as the time from the stimulus onset to the peak of the positive wave. The amplitude (μV) is measured as a difference between the pre-stimulus baseline and the peak of the positive large wave appearing in a time window of 250-500 ms [26].

STATISTICAL ANALYSIS

Data was analysed using R statistical software (version 4.1.3). The values were expressed as mean and Standard Deviation (SD). The Independent 't'-test was applied for comparing the P300 parameters in anaemic and healthy women and the Spearman's correlation test was applied to find the correlation between haemoglobin and serum ferritin with P300 parameters. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 260 women (130-anaemic, 130-non anaemic) were included in the study, and the mean age of anaemic women was 23.88±3.67 years and 24.09±3.41 years for non anaemic women (p>0.05). Blood haemoglobin levels (mg/dL) were significantly lower in anaemic women (10.37±0.95) than in non anaemic (13.02±0.70) (p <0.001). Serum ferritin (ng/mL) was significantly lower in anaemics (8.55±3.78) compared to non anaemic women (27.61±10.52) (p<0.001) [Table/Fig-1]. The P300 wave parameters were compared between the study groups, and it was observed that the P300 latency (ms) was significantly prolonged in anaemic women (317.75±7.34) compared to non anaemic women (311.71±9.02) (p<0.001) [Table/Fig-2,3]. The P300 amplitude (μV) was reduced in anaemic women compared to non anaemic women, though this difference was not statistically significant (p>0.05) [Table/Fig-2,4].

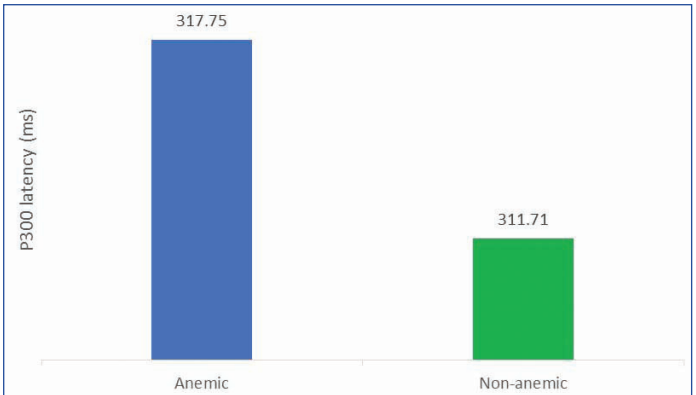
Variables	Anaemic women (mean±SD)	Non anaemic women (mean±SD)
Age (years)	23.88±3.67	24.09±3.41
BMI (kg/m^2)	20.98±1.45	21.25±1.27
Haemoglobin (g/dL)	10.37±0.95**	13.02±0.70**
Serum ferritin (ng/mL)	8.55±3.78**	27.61±10.52**

[Table/Fig-1]: Baseline characteristics of participants.
Independent 't'-test, **p value <0.001; highly significant

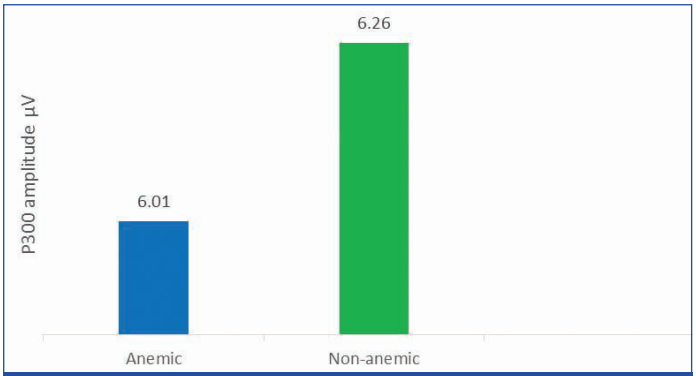
P300 wave	Anaemic women (mean±SD)	Non anaemic women (mean±SD)
Latency (ms)	317.75±7.34**	311.71±9.02**
Amplitude (μV)	6.01±1.81	6.26±1.84

[Table/Fig-2]: Comparison of cognitive evoked potentials/ P300 in anaemic and non anaemic women.
Independent t-test, **p<0.001; highly significant

P300 wave parameters were correlated with haemoglobin and serum ferritin levels [Table/Fig-5]. The correlation between P300 latency and haemoglobin was observed as a low negative correlation (r=-0.481, p<0.001) [Table/Fig-6]. And the correlation between P300 latency and serum ferritin was a moderate negative correlation (r=-0.552, p<0.001) [Table/Fig-7]. The P300 amplitude showed negligible correlation with haemoglobin (r=0.26, p<0.05) [Table/Fig-8] and serum ferritin (r=0.24, p<0.05) [Table/Fig-9].



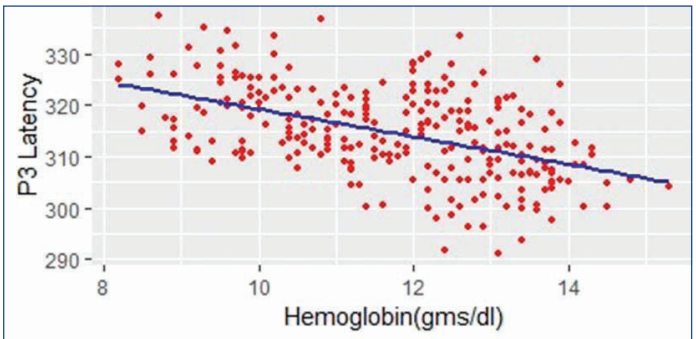
[Table/Fig-3]: Bar graph depicting the comparison of P300 latency (ms) between the anaemic and non anaemic women.



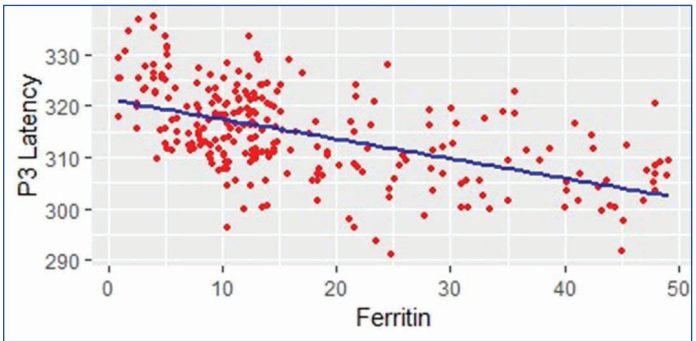
[Table/Fig-4]: Bar graph showing the comparison of P300 amplitude (µV) between the anaemic and non anaemic women.

P300 wave (260 N)	Haemoglobin (mg/dL) r-value	Ferritin (ng/mL) r-value
Latency (ms)	-0.481**	-0.552**
Amplitude (µV)	0.26*	0.24*

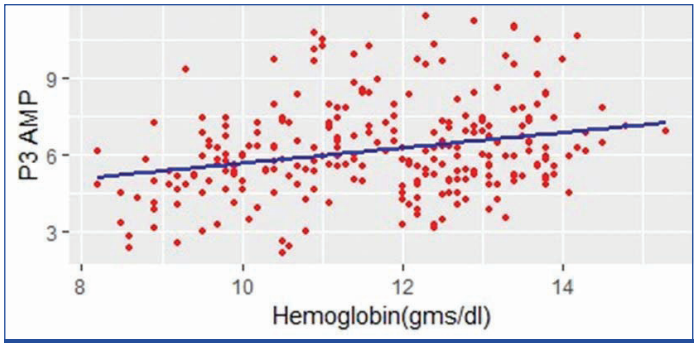
[Table/Fig-5]: Statistical correlation between cognitive evoked potential/P300 with haemoglobin levels and serum ferritin levels in the participants.
Spearman's correlation test, **p<0.001; highly significant, *p<0.05; significant



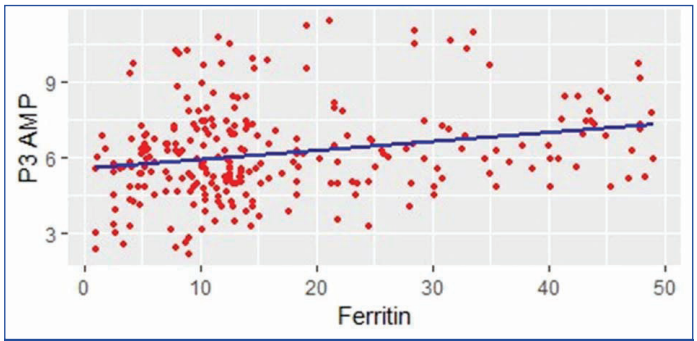
[Table/Fig-6]: Scatter plot of P300 latency (ms) across haemoglobin (mg/dL).



[Table/Fig-7]: Scatterplot of P300 latency (ms) across serum ferritin (ng/mL).



[Table/Fig-8]: Scatterplot of P300 latency (ms) across serum ferritin (ng/mL).



[Table/Fig-9]: Scatter plot of P300 amplitude (µV) across serum ferritin (ng/mL).

DISCUSSION

Iron Deficiency Anaemia is a potential risk factor for cognitive decline conceivably due to chronic brain hypo-oxygenation [4]. In adulthood, iron is essential for the synthesis of brain neurotransmitters and their regulation (e.g., dopamine, Norepinephrine [NE], serotonin) [3,27]. Inadequate brain iron availability affects neurotransmission and signalling, myelination, neurometabolism, and gene profiles [3,28]. Because of its requirement in the maintenance of these functions, iron deficiency may lead to impaired impulse transmission in the brain [29]. Hence, the present study results rejects the null hypothesis that, the cognitive evoked potentials are not altered in women with IDA.

When Electroencephalogram (EEG) signals were correlated with blood haemoglobin and serum ferritin levels, slowed power spectrum in EEG was noted, indicating that systemic iron status affects normal brain functioning [19,30,31]. The cortical impulses triggered by neurotransmitters released in response to an external stimulus can be recorded non invasively using evoked potentials [11]. The auditory evoked potentials like the P300 helps to measure the electrophysiological signals, which are generated by neuronal activities in multiple regions in the brain in response to an auditory stimulus evaluation [10].

The P300 documented in patients with Chronic Kidney Disorders (CKD) after administration of erythropoietin to increase the haematocrit revealed shortened latencies and amplified P300 wave, suggesting that correction of anaemia improves the P300 and hence, neurocognitive functions [32,33].

Present study findings were consistent with the results from previous studies in adults [4,19,20]. Khedr et al., observed significantly reduced amplitude and prolonged latencies in anaemics compared to controls. Following iron therapy in cases though amplitudes increased, no change in latencies was observed. The study also found a negative correlation between haemoglobin and P300 latency, and a positive correlation between serum ferritin and amplitude [19]. Kececi H and Degirmenci Y also observed improvement in P300 latencies and amplitudes after an improvement in haematological parameters with iron therapy, suggesting that anaemia decreases cognitive performance [4]. A case-control study by Kharat P and Waghmare P, in 32 anaemic women and 42 controls showed significantly prolonged latency and reduced amplitude in their cases compared to controls [20].

The hypothesis for neural generators of P300 proposes that during auditory tasks the discrimination between the target and the standard stimuli initiates activity in the frontal lobe which is involved in the attentional function. This is followed by activation of memory operations in the temporoparietal regions, requiring intact integrity at this junctional area. This cascade of activation was evident by neuroimaging techniques like functional Magnetic Resonance Imaging (fMRI) with simultaneous Event Related Potential (ERP) recording revealing frontal to temporoparietal lobe activation [12]. According to the dual transmitter P300 hypothesis, the attention domain which is a function of the frontal area is mediated by dopaminergic activity, while the working memory involving the temporoparietal junction is associated with NE activity [13]. Rat models indicate that adequate serum iron maintains brain iron [32] and that iron deficiency leads to diminished central dopaminergic transmission and receptor trafficking, with the D2 receptor particularly affected [34-36]. Iron deficiency and hypoxia in IDA are thus implicated in impairing the P300 wave, due to their possible effect on neurotransmitter and brain energy metabolism [14].

As cognition is a fundamental factor for maintaining the quality of life, the impaired cognitive function is correlated with poor quality of life and poor life outlook [37]. Anaemic individuals are vulnerable to lack of attentiveness, diminished working memory, delayed decision making, that eventually impairs their cognitive ability [20]. Mild cognitive impairment is asymptomatic; however there is a possibility to progress to dementia and Alzheimer's disease. So, improving the haemoglobin levels with timely treatment has a beneficial effect in reducing the risk of progression to cognitive impairment [38]. In future, similar studies reporting the utilisation of P300 for the diagnosis of cognitive impairment in women with anaemia must be encouraged. Further research in a large population, at the community level, for screening cognitive dysfunction using P300 and reporting whether correction of anaemia restores it, is required to support the present findings.

Limitation(s)

Follow-up of anaemic subjects for P300 evaluation after the administration of iron supplements to improve haemoglobin and ferritin levels were not performed. The changes in cognitive evoked potentials post iron supplementation, if at all, will help draw definite conclusions.

CONCLUSION(S)

Cognitive evoked potential is a sensitive and objective tool for screening cognition. Since anaemia due to iron deficiency impairs these potentials, CEP can be utilised for early detection of MCI associated with IDA. As MCI is a transition phase towards dementia, it is important to screen anaemic women in reproductive age, so as to prevent the clinical and social adverse effects of cognitive decline, in later stages of their life.

REFERENCES

[1] Nutritional anemia: Tools for effective prevention and control. Geneva: World Health Organization; 2017. https://www.who.int/publications/i/item/9789241513067.

[2] National Family Health Survey (NFHS) 5 (2019 21), National and State Fact Sheets. Available from: http://rchiips.org/nfhs/ factsheet_NFHS 5.shtml. [Last accessed on 2022 Feb 28].

[3] Beard JL, Connar JR. Iron status and neural functioning. Annu Rev Nutr. 2003;23:41-58.

[4] Kececi H, Degirmenci Y. Quantitative EEG and cognitive evoked potentials in anemia. Neurophysiol Clin. 2008;38(2):137 43.

[5] Cook R, O' Dwyer N, Parker H, Donges C, Cheng H, Steinbeck K, et al. Iron deficiency anemia, not iron deficiency, is associated with reduced attention in healthy young women. Nutrients. 2017;9(11):1216 28.

[6] Atti AR, Palmer K, Volpato S, Zuliani G, Winblad B, Fratiglioni L. Anaemia increases the risk of dementia in cognitively intact elderly. Neurobiol Aging. 2006;27(2):278 84.

[7] Shah RC, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Hemoglobin level in older persons and incident alzheimer disease: Prospective cohort analysis. Neurology. 2011;77(33):219 26.

[8] Jaleel I, Saikumar P, Devak P. Effect of Hb% on cognitive skills in UG medical students. J Clin Diagn Res. 2013;7(7):1325-27.

[9] Agrawal S, Kumar S, Ingole V, Acharya S, Wanjari A, Bawankule S, et al. Does anemia affects cognitive functions in neurologically intact adult patients: Two-year cross-sectional study at rural tertiary care hospital. J Family Med Prim Care. 2019;8(9):3005 8.

[10] Vanden Bos, Gary R. Evoked potential. APA Dictionary of Psychology. 2nd ed. Washington, DC: American Psychological Association; 2015. p. 390.

[11] Oken BS. Endogenous event-related potentials. In: Chiappa KH, editor. Evoked Potentials in Clinical Medicine. Philadelphia: JB Lippincott Company; 1999. p. 529-63.

[12] Polich J. Updating P300: An integrative theory of P3a and P3b. Clin Neurophysiol. 2007;118(10):2128 48.

[13] Polich J, Criado JR. Neuropsychology and neuropharmacology of P3a and P3b. Int J Psychophysiol. 2006;60(2):172 85.

[14] Algarín C, Nelson CA, Peirano P, Westerlund A, Reyes S, Lozoff B. Iron deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years. Dev Med Child Neurol. 2013;55(5):453 58.

[15] Kung WM, Yuan SP, Lin MS, Wu CC, Islam MM, Atique S, et al. Anemia and the risk of cognitive impairment: An updated systematic review and meta-analysis. Brain Sci. 2021;11(6):777.

[16] Gattas BS, Ibetoh CN, Stratulat E, Liu F, Wuni GY, Bahuva R, et al. The impact of low hemoglobin levels on cognitive brain functions. Cureus. 2020;12(11):e11378.

[17] Egerházi A, Glaub T, Balla P, Berecz R, Degrell I. P300 in mild cognitive impairment and in dementia. Psychiatr Hung. 2008;23(5):349-57.

[18] Gualbetro Cintra MT, Silva Tavares MC, Gomes SA, de Oliveira Gonçalves T, Mantos da Cunha LC, Gonçalves DU, et al. P300 evoked potential and risk of mild cognitive impairment progression to Alzheimer's dementia: A literature review. J Neurol Neurophysiol. 2015;6(5):322.

[19] Khedr E, Hamed SA, Elbeih E, El Shereef H, Ahmad Y, Ahmed S. Iron states and cognitive abilities in young adults: Neuropsychological and neurophysiological assessment. Eur Arch Psychiatry Clin Neurosci. 2008;258(8):489 96.

[20] Kharat P, Waghmare P. Could anemia be the reason for dysfunctional cognition? Int J Res Med Sci. 2015;3(3):663-69.

[21] Gupta S, Sharma G, Atri SK, Sharma P. Reversible alteration of brainstem auditory evoked potential in iron deficient anemic patients in response to treatment. Int J Community Med Public Health. 2021;8(4):1877-79.

[22] WHO expert consultation appropriate body mass index for Asia populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63.

[23] Complete Blood Count with 5 Part Differential in Whole Blood NHANES 2013-2014. https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/CBC_H_MET_COMPLETE_BLOOD_COUNT.pdf.

[24] National Institute for Biological Standards and Control (NIBSC), Blanche Lane, South Mimms, Potters Bar, Herts, EN6 3QG. http://www.nibsc.ac.uk/documents/ifu/94-572.pdf.

[25] Neuron-Spectrum-5. https://neurosoft.com/en/catalog/eeg/neuron-spectrum-5. [Last accessed on 2022 Sept. 28].

[26] Mishra UK, Kalita J. Clinical neurophysiology: Nerve conduction, electromyography, evoked potentials. 2nd ed. N. Delhi: Reed Elsevier India Private Ltd; 2006. P. 1-9, 329-45, 423-34.

[27] Beard J. Iron deficiency alters brain development and functioning. J Nutr. 2003;133(5 Suppl 1):1468S-72S.

[28] Lozoff B. Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction. J. Nutr. 2011;141(4):740S-46S.

[29] Ferreira A, Neves P, Gozzelino R. Multilevel impacts of iron in the brain: The cross talk between neurophysiological mechanisms, cognition, and social behavior. Pharmaceuticals (Basel). 2019;12(3):126.

[30] Wenger MJ, Rhoten SE, Murray-Kolb LE, Scott SP, Boy E, Gahutu JB, et al. Changes in iron status are related to changes in brain activity and behavior in Rwandan female university students: Results from a randomized controlled efficacy trial involving iron biofortified Beans. J Nutr. 2019;149(4):687 97.

[31] Otero GA, Aguirre DM, Porcayo R, Fernandez T. Psychological and Electroencephalographic study in school children with iron deficiency. Int J Neurosci. 1999;99(1-4):113 21.

[32] Pickett JL, Theberge DC, Brown WS, Schweitzer SU, Nissenson AR. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis. 1999;33(6):1122 30.

[33] Singh NP, Sahni V, Wadhwa A, Garg S, Bajaj SK, Kohli R, et al. Effect of improvement in anemia on electro neurophysiological markers (P300) of cognitive dysfunction in chronic kidney disease. Hemodial Int. 2006;10(3):267-73.

[34] Youdim MB, Ben-Shachar D, Yehuda S. Putative biological mechanisms of the effect of iron deficiency on brain biochemistry and behavior. Am J Clin Nutr. 1989;50(3 Suppl):607-15.

[35] Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine d 1 and d 2 receptors in rat brain. Pharmacol. Biochem Behav. 2001;69(3-4):409-18.

[36] Unger EL, Wiesinger JA, Hao L, Beard JL. Dopamine D2 receptor expression is altered by changes in cellular iron levels in PC12 cells and rat brain tissue. J Nutr. 2008;138(12):2487-94.
[37] Kwa VIH, Limburg M, de Haan RJ. The role of cognitive impairment in the quality of life after ischaemic stroke. J Neurol. 1996;243(8):599-04.
[38] Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia, and Alzheimer's disease. Nat Rev Neurol. 2018;14(11):653-66.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Physiology, Mahadevappa Rampure Medical College (RGUHS, Bangalore), Kalaburagi, Karnataka, India.
2. Professor, Department of Physiology, Jawaharlal Nehru Medical College (DMIMS), Nagpur, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Umme Kulsoom Sheema,
4-601/74/7, Banda Nawaz Colony, MB Nagar Extension, Ring Road,
Kalaburagi, Karnataka, India.
E-mail: ummekulsoom22@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 29, 2022
- Manual Googling: Nov 04, 2022
- iThenticate Software: Nov 09, 2022 (23%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 21, 2022**
Date of Peer Review: **Aug 06, 2022**
Date of Acceptance: **Nov 10, 2022**
Date of Publishing: **Dec 01, 2022**