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Interhemispheric Comparison of Alpha Frequency of EEG in Premenopausal Women taking Oral Contraceptives

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ABSTRACT

Introduction: Sex hormones influence many aspects of neuronal functioning as well as behavior. Though the female brain is more homogenously organized as compared with the male brain, there are certain functional aspects which seem to be lateralized in female brain. Hence it was hypothesized that probably the sex hormones affect the female brain differentially on the two sides of the cerebral hemispheres.

Methods and Materials: The study was performed in 55 volunteer females attending the family planning clinic. The alpha wave frequency was measured before and after prescribing oral contraceptive pills to the same group. Interhemispheric comparisons were made in the follicular and luteal phases of the menstrual cycle both before and after the usage of oral contraceptive pills.

Result: Alpha wave frequencies were found to be significantly higher in the luteal phase (p value 0.0043) and on the right hemisphere (p values 0.01 and 0.04) in the normally menstruating females. Oral contraceptive pill intake abolished the interphase (P value 0.88) and interhemispheric (P values 0.23 and 0.31) differences in the alpha wave frequencies. The luteal phase alpha wave frequency was significantly decreased during luteal phase in the pill taking phase (P value 0.005 and 0.023).

Conclusion: The present study not only reconfirms the effect of cyclic hormone fluctuations on neuronal functioning but also proves the differential effect of sex hormones on the two cerebral hemispheres in naturally menstruating women. These interhemispheric differences were abolished by the oral contraceptives.

KEYWORDS:EEG, Alpha wave frequency, Oral contraceptives.

INTRODUCTION

The reproductive system of the female unlike that of male is characterized by cyclic and pulsatile release of gonadotropins. These hormones are responsible for corresponding changes in ovaries and other sex organs. Although the influence of ovarian hormones is not restricted to the endocrine control, but it extends to many different regions of the central nervous system. Sex hormones affect both morphological and functional properties of the brain regions, which are not directly involved in the control of reproductive behavior. Estrogen has been held responsible for increase in volume of temporal lobe and associated regions of the brain.[1-3] The changes in sex steroids not only affect the neuronal architecture but also its excitability and cognitive ability.[4] Estrogen increases and progesterone seems to decrease neuronal excitability in general.[5] It is not surprising therefore, sex steroids can influence the electrical activity including Electro Encephalo Gram.

Electro Encephalogram (EEG) is the record of background electrical activity of the brain recorded with scalp electrodes. In an adult at rest with mind wandering and eyes closed, the most prominent component of the EEG is a fairly regular pattern of waves at a frequency of 8-12/sec and amplitude of 50 micro volts; these are called as alpha oscillations or waves.[6] They are most marked in the occipital and parietal area. As the eyes open attention is focused upon something the alpha waves are replaced by beta waves. This is known as alpha block and is thought to be due to event related desynchronization. In addition to mark physiological

inhibition[6] alpha frequency has been positively correlated with general intelligence of the individual.[7,8]
The activity recorded in the EEG arises mostly form the synchronous activity of the glutamatergic synapses in the superficial layers of the cortex.[9] Usually 90% of the neurons in the superficial cortical layers are glutamatergic.[10] Due the majority of such neurons largest share of total energy expenditure is probably done by the glutamatergic synapses of the cortex.[11,12] The normal energy expenditure of the brain is mainly due to this continuous background activity of the neurons and increase in mental work, while performing some mental task, adds very little to this background energy expenditure. This was probably known to Hans Berger himself far back in 1929[12,13] Fluctuations in female sex hormones have been shown to affect the energy balance during menstrual cycle. The energy expenditure and intake is more in luteal phase in comparison to that in follicular phase of menstrual cycle.[14] Many animal and human studies have shown a negative correlation of food intake with estradiol which predominates in the follicular phase of the menstrual cycle. As fluctuations in female sex hormones influence the energy balance, keeping in mind that EEG is largely due to the synchronous activity of the glutamatergic neurons which consumes majority of the energy in the brain, it can be concluded that the alpha oscillations could be related to the cyclic changes in the levels of sex hormones.
Effect of oral contraceptives on neuronal functioning has been extensively studied. It has been described that oral contraceptives and endogenous hormones are associated with a decrease in connectivity in the resting neuronal network of central nervous system.[15] Functional magnetic resonance imaging, has been used to measure the hemodynamic response of the brain to the neuronal activities.[16] With the increase in the physiological activity in any part of the brain there is associated change in the local blood flow. The most common functional imaging signal is Blood Oxygenation Level Dependent signal (BOLD).[17] When normally menstruating women were compared with those who are taking oral contraceptive pills, the pill users showed a stronger BOLD response to faces in the right fusiform face area[18], but they showed smaller BOLD responses to erotic stimuli in left precentral gyrus.[19] Oral contraceptives impart masculinizing changes in numerical task performance on functional MRI scans.[20]
Women on contraceptive pills have larger areas in frontal and temporal lobes in vortex based morphometric studies, as compared to normally menstruating ones.[2,3]
The female brain seems to be more homogeneously organized, while that of male is more heterogeneously or focally organized.[21,22] Men show stronger lateralization of cognitive functions, whereas women have greater bilateral representation on them and EEG power shows greater hemispheric asymmetry in men than in women. In normally menstruating women estrogen dominant phases correlate positively with performance in verbal memory tasks, working memory, and learning but negatively with performance in spatial tasks.[23-28] As right hemisphere of the brain is considered to be primarily responsible for spatial processing rather than the left one, estrogen might be influencing the two hemispheres differently.[29]

AIMS AND OBJECTIVES

The aim of the present prospective study was to compare resting alpha wave frequency between the two cerebral hemispheres across the normal menstrual cycle and see the effect of oral contraceptives on it.

Table-1: Clinical Characteristics of the Subjects.

Number of Subjects (n)	55	
Variables	Mean	**SD**
Mean Age	2 years	**± 4.7**
Body Weight	55.35 kilograms	**± 5.23**
BMI (Kg/m^2)	23.4	**± 1.2**
Menstrual cycle duration	29.2	**± 3.4**

Table 2: Alpha wave frequencies during follicular and luteal phases in normally menstruating women.

No. of Subjects	Alpha wave frequency (Hz)		SD		P value
	Follicular Phase	Luteal Phase	Follicular Phase	Luteal Phase	
55	10.239	10.355	± 0.027	± 0.024	0.0001

Table 3: Interhemispheric comparison of Alpha wave frequencies in normally menstruating women.

No. of Subjects	Phase of cycle	Alpha freq. on Right hemisphere	Alpha freq. on Left hemisphere	P Value
55	Follicular Phase	10.275 ± 0.0075	10.221 ± 0.018	0.01
	Luteal Phase	10.375 ± 0.009	10.335 ± 0.01	0.04

Table 4: Alpha wave frequencies during follicular and luteal phases in women taking OCP's.

No. of Subjects	Alpha wave frequency (Hz)		SD		P value
	Follicular Phase	Luteal Phase	Follicular Phase	Luteal Phase	
55	10.239	10.242	± 0.026	± 0.025	0.88

Table 5: Interhemispheric comparison of Alpha wave frequencies in women taking OCP's.

No. of Subjects	Phase of cycle	Alpha freq. on Right hemisphere	Alpha freq. on Left hemisphere	P Value
55	Follicular Phase	10.257 ± 0.020	10.22 ± 0.018	0.23
	Luteal Phase	10.257 ± 0.019	10227 ± 0.022	0.31

Table 6: Comparison of mean alpha frequencies before and after taking OCP's.

No of Subjects	Phase of menstrual cycle	Alpha frequency before oral contraceptives	Alpha frequency after oral contraceptives	P value
55	Follicular Right Hemisphere	10.258 ± 0.022	10.257 ± 0.0200	0.38
	Follicular Left Hemisphere	10.22 1± 0.018	10.222 ± 0.01	0.22
	Luteal Right Hemisphere	10.375 ± 0.009	10.257 ± 0.019	0.0056
	Luteal Left Hemisphere	10.335±.013	10.227 ± 0.022	0.0232

MATERIALS &METHODS

The study was performed in the department of Obstetrics and Gynecology, KGMU, Lucknow, UP, India. After taking ethical clearance the study group was selected from the females attending the family planning clinic of the department. A total of 55 candidates who volunteered and gave written consent to participate in the study were selected. The following inclusion criteria were adopted for the study:

1. No history of oral contraceptive intake or use of hormone in any other form.
2. Regular and spontaneous menstrual cycle of 26-33 days (29.2 $\pm$ 3.4 days).
3. A normal gynecological examination.
4. Normal BMI (23.4 $\pm$ 1.2)
5. Absence of any personal or family history of seizures.
6. Absence of any substance/drug abuse.
7. All subjects underwent a clinical examination and brief psychological interview.

The clinical characteristics of the subjects are given in the table 1.

Just before the recording of EEG the subjects were given a brief health checkup, with special attention to the body temperature (to exclude febrile status) and pulse rate. To avoid circadian variations, the EEG was recorded preferably between 12.00 to 2.00 pm.

In the present study Neurofax Electroencephalograph machine was used. The electrodes were placed according to 10-20 system (Montreal method).[30] EEG was recorded while the subject was lying on a couch in a sound proof room with eyes closed. The recordings were made twice during the menstrual cycle, first during follicular phase (5-8 day) and during luteal phase (18-23 day). After recordings the EEG in both the phases of menstrual cycle, the subjects were given oral contraceptive pills containing 0.03 mg of ethinyl estradiol and 0.15 mg levonorgestrel. On 4th month of oral contraceptive use the EEG was recorded again in the two phases of the menstrual cycle, at 7th and 21st days of pill intake.

RESULTS

The alpha frequency was significantly higher (p value 0.0043) in luteal phase than during follicular phase of normally menstruating women (table 2). On interhemispheric comparison the alpha frequencies were found to be significantly higher on the right hemisphere as compared to the left side in normally menstruating women (p values 0.01 and 0.04) (table 3). After 4 months of oral contraceptive intake the alpha frequencies were measured again. The difference in mean alpha frequencies between follicular and luteal phases were made insignificant by oral contraceptive pills (P value 0.88) (table 4). The differences in alpha frequency between two hemispheres were also rendered insignificant in the pill taking group (P values 0.23 and 0.31) (table 5). On making gross phase wise comparison between pre and post oral contraceptive pill usage it was discovered that the frequencies were insignificantly different between follicular phases (P values 0.38 and 0.22) but during luteal phase the frequencies were significantly decreased in the pill taking phase (P values 0.005 and 0.023) (Table 6).

DISCUSSION

Our study has reconfirmed the profound effect of fluctuation of female hormones during menstrual cycle on the alpha rhythm of EEG.[31,32] Our study has not only underlined the negative correlation of alpha rhythm frequency with the estradiol predominant follicular phase of the menstrual cycle but has also highlighted the influence of oral contraceptives in making alpha frequency similar to that seen during follicular phase of the menstrual cycle. The results of our study are in unison with that of some workers who found no association between estradiol and alpha frequency in women taking oral contraceptive pills.

Brain has been found to be tonically active in a base line level all the time irrespective of the task, in many functional MRI and PET studies.[12] The intrinsic base line activity of the brain is largely responsible for the alpha rhythm of the EEG. This ongoing resting alpha frequency has been correlated with the cognitive ability of the individual.[8] This indirectly hints that fluctuation in alpha frequency during menstrual cycle may affect individual's performance.

The changes in the frequency of the EEG waves along the menstrual cycle might be due to the neuromodulatory role the estrogen and progesterone have on the synaptic transmission. The alpha rhythm depends more on the ratio of estrogen and progesterone than any one of them. The frequency being low in the follicular phase, which has high estrogen but low progesterone levels and it is high in the luteal phase which has high levels of the both of them. The fluctuation in the sex hormones has been shown to affect the gene expression in the rats. Elevated estrogen increases the expression of GABA A receptors.[33] Estradiol is also expected to affect the formation of glutamate decarboxylase enzyme which is involved in the synthesis of GABA through its effect on *gad2* promotor gene.[34] Hence it is logical to assume that estrogen affects both the formation of GABA receptors and the GABA itself. Similar effect is expected in human beings too.

Negative correlation of estrogen levels with the alpha rhythm frequency as shown in our study has also been linked to the cyclic changes in food intake during the menstrual cycle.[35,14] Studies show that the food intake decreases in the follicular phase than during the luteal phase. As discussed earlier most of the cortical neurons which are considered to generate alpha rhythm are gluamatergic.[10] These neurons are supposed to consume most of the energy used by the whole brain. Hence the level of energy intake in the form of food can directly affect the level of activity in these cortical neurons. This explains the correlation of low food intake due to estrogen during follicular phase with lower frequencies of the alpha rhythm. The increase in body temperature due to increased progesterone levels during luteal phase has been independently held responsible to affect the alpha wave frequency.

Oral contraceptive pills are expected to grossly affect the structure and functioning of the female brain.[2,3,20] In the present study it was seen that oral contraceptives have blunted the natural differences in alpha frequency between the follicular and the luteal phases in naturally menstruating women. The interhemispheric differences were also abolished. The alpha frequency after oral contraceptive intake was seen closer to that seen during the follicular phase of the natural cycle.

The interhemispheric difference in the alpha frequency indicated a differential influence of sex hormones on the two cerebral hemispheres. Keeping in the mind the different specialties of the two hemispheres discussed above,[23-28] the differential impact of sex hormones on the two hemispheres may explain the negative correlation of spatial task performance with the levels of estrogen.

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