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Comparison of attention in females before and after puberty and during menopause

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ABSTRACT

Objective: Due to the presence of estrogen and progesterone receptors in the brain this study is to evaluate the hypothesis that sexuality changes during the menstrual cycle and accompanied with aging in females have some effects on attention.
Materials and methods: 17 immature-girls, 15 young-adult women with regular menstrual cycles and 17 postmenopausal-women were studied here. Cognitive tests of Stroop and ANT performed three times for young-adults at early follicular, ovulation and mid-luteal phases respectively and for both the immature-girls and postmenopausal-women only in one session. Serum levels of sex-related hormones were measured after each session.
Results: Interference scores of postmenopausal-women and immature-girls in the Stroop test were significantly higher than the young-adults in different phases. Function of alerting-network was significantly weaker for immature-girls than the other groups, however, in orienting-network; there weren't significant difference between the groups. Function of executive control network was significantly poorer in immature-girls and it was significantly better in mid-luteal phase of young-adults than in the others. The serum levels of progesterone, LH and FSH were significantly higher in the postmenopausal-women than the other groups. Serum levels of estradiol were significantly less in the immature-girls than the other groups.
Conclusions: Low levels of estrogen in immature-girls maybe associated with reduced attention in the Stroop test and decreased performance of executive control network in the attentional network tests. Also, low levels of estrogen and high levels of LH and FSH in the post-menopausal women seems to have effects on the attention performance in the Stroop test.

1. Introduction

Extensive studies on sexuality differences in cognitive abilities suggest that women perform consistently better than men on tasks of verbal-related ability such as memory recall and fluency, whereas men perform better than women on spatial ability related tasks (Hatta & Nagaya, 2009). The research has shown that there are differences in performance between male and female brains, which can lead to differences in the functions of Neuropsychology (Casey, 1996). In this regard, Kimura (1996) proposed a model that explains why there is a sex difference in cognitive abilities. Kimura's model is sometimes called the "sex-related hormone theory" and the main points are that most of the sexually differentiated functions are strongly influenced by the amount of hormonal secretion, while the role of estrogen is critical in verbal ability and perceptual speed (Hatta & Nagaya, 2009). Many researchers who are interested in cerebral functional asymmetry have reported findings that cognitive performance in women appears to be modulated by the fluctuation of sex related hormone levels over the menstrual cycle (Hausmann & Gunturkun, 2000; Heister, Landis, Regard, & Schroeder-Heister, 1989). In part from the studies on the relation between sex-related hormones and functional cerebral asymmetry, researchers examined sex-related developmental changes in cognitive abilities that relate to prefrontal cortex function in middle-aged and elderly people (Munro et al., 2012). The findings showed that the sex difference in cognitive abilities does not remain stable throughout human life, especially in women, and strongly suggest that biological factors, such as sex-related hormones that contribute to prefrontal cortex function, seem to be related to age-related sex differences (Taketani & Maehara, 2001). The findings also indicate that sex-related hormones might have different effects depending on the

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type of cognitive abilities such as attention, memory, and verbal fluency (Hatta & Nagaya, 2009). Physiological fluctuations in sex hormone levels during the menstrual cycle can serve as a valuable tool for non-invasive studies of the cognitive effects of sex hormones, particularly estrogen (Pompili, Arnone, & Gasbarri, 2012). According to the fluctuation of ovarian hormone at different phases of the menstrual cycle, and changes in the secretion of these hormones with aging, especially after menopause, it prompts us to present a hypothesis in which changes in sexual performance have effects on the attention throughout women life and aging, seems that it is possible to examine this hypothesis in which aging especially in the menopausal period has negative effects on the different levels of attention.

2. Methods

In this study, 42 people in three groups were participated. The first group consisted of 17 healthy immature girls ranging from 9 to 11 years old (9.4 ± 0.87) whose menstrual cycles are not observed, volunteered to participate in this experiment.

The second group consisted of 15 healthy women ranging from 20 to 25 years old (21.8 ± 1.6), with regular menstrual cycles (26–30 days), volunteered to participate in this experiment.

The third group consisted of 17 healthy postmenopausal women ranging from 45 to 55 years old (52.3 ± 1.6), volunteered to participate in this experiment. All persons were none used oral contraceptives, hormonal replacement, or any other medication that could influence the central nervous system.

2.1. Stroop test

The Stroop test is employed to evaluate the attention and information processing speed (Macleod, 1991; Macleod & Macdonald, 2000). In this test, participant are required to name the color of words (red, yellow, blue and green) that are shown in colors incongruent to the name of the color.

In this study, the computer classic Stroop test is presented by Salehi Fadardi and Ziaei (2010) for Persian users (Salehi Fadardi & Ziaei, 2010).

2.2. Attention network test

The original Attention Network Test (ANT) was presented by Fan et al. (2002) (Fan, Mccandliss, Sommer, Raz, & Posner, 2002; Ishigami & Klein, 2010). ANT is a suitable behavioural test in neuropsychology researches and it is designed to evaluate the different levels of attention network including alerting, orienting and executive control within a single 30-min testing session (Hahn et al., 2011). ANT is a combination of "Cued Reaction Time" and Flanker task (Fan et al., 2002). The ANT involves viewing a sequence of visual cues, arrows and responding to the direction of a central arrow (Brunye, Mahoney, Lieberman, & Taylor, 2010).

At the beginning of session 1, the participants were given the instructions for the two cognitive tests. The second group of participants (young adult women with regular menstrual cycles) were tested three times: the early follicular phase (cycle day 2–3), ovulatory phase (cycle day 14) and mid-luteal phase (cycle day 21–22). All three testing sessions were conducted at the same time between 10 am to 2 pm to possibly decrease the potential effects of circadian rhythm upon brain function. Directly after every session, 5 ml of blood from each participant was collected for hormonal testing. The first group of participants (immature girls) and third (postmenopausal women) were tested in a single session, and directly 5 ml of blood from each participant was collected for hormonal testing. Subsequently, the serum levels of estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone were measured by ELISA test in blood samples.

2.3. Statistical analysis

The results are presented as mean ± SEM. One-way ANOVA was used and the post hoc Tukey test was used to compare means. $p < 0.05$ was considered as the minimum level of significance. All statistical analyses were performed using GraphPad Prism 5 software (GraphPad Software Inc., USA), and the graphs were drawn using Microsoft Excel 2010 software.

3. Results

3.1. Stroop test

The results of Stroop test showed that the interference score-was calculated by subtracting the mean reaction time (s) for incongruent stimuli from mean reaction time (s) for congruent stimuli shows significant changes according to different groups of females [$F(4,69) = 7.683$, $p < 0.001$]. These results indicated that the interference score is significantly higher in immature girls and menopausal women than in young adults in the different phases of the menstrual cycle ($p < 0.001$), (Fig. 1).

3.2. ANT results

3.2.1. Alerting network

The results revealed that the difference score in the alerting network – was calculated by subtracting mean RTs of the conditions with no cue from the mean RTs of the conditions with double cues- changes according to different groups of females [$F(4,78) = 4.789$, $p < 0.001$]. The Fig. 2 shows that, this index is significantly higher in immature girls than in the other groups ($p < 0.001$). In addition, difference score in the alerting network showed no significant difference in the different phases of the menstrual cycle (Fig. 2).

3.2.2. Orienting network

The comparison of orienting network between the different groups showed that the difference score in orienting network – was calculated by subtracting the mean RTs of the conditions with center cues from the mean RTs of the conditions with spatial cues-there was no significant change according to different groups of females [$F(4,78) = 0.7354$, $p < 0.57$], (Fig. 3).

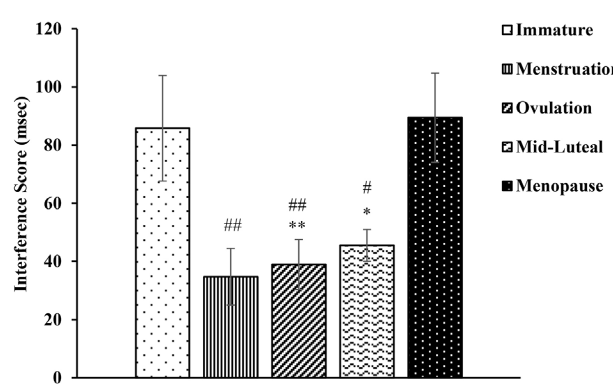

Fig. 1. The Comparison of the interference score in different stages of immature to menopause. Interference score was significantly increased in immature girls and postmenopausal women than in young adults in the different phases of the menstrual cycle. The results are presented as mean ± SEM. (*$p < 0.05$ and **$p < 0.01$ compared to immature and #$p < 0.05$ and ##$p < 0.01$ compared to postmenopausal women).

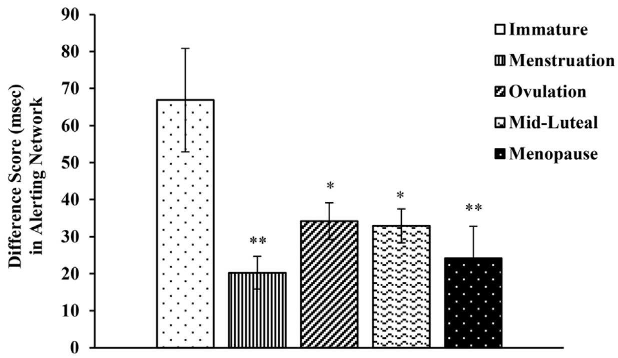

Fig. 2. The comparison of alerting network in different stages of immature to menopause. The difference score in the alerting network was increased significantly in immature girls than the other groups. The results are presented as mean ± SEM. (*p < 0.05 and **p < 0.01 compared to immature girls).

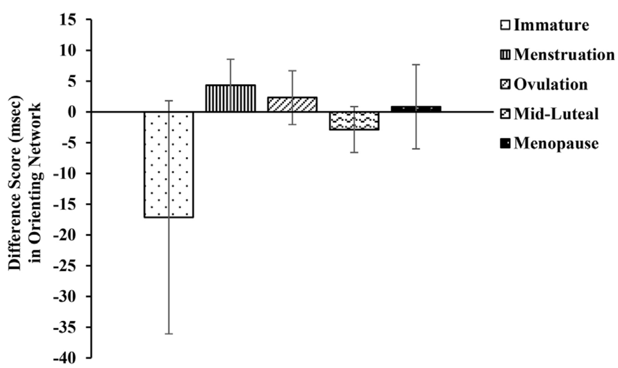

Fig. 3. The comparison of orienting network in different stages of immature to menopause. Comparison of the difference score in orienting network showed no significant difference between the different groups. The results are presented as mean ± SEM.

3.2.3. Executive control network

The comparison of executive control network showed that the difference scores in the executive control network –was calculated by subtracting the mean RTs of the conditions with incongruent flankers from the mean RTs of the conditions with congruent flankers- changes according to the different groups of females [F (4.78) = 14.149, p < 0.001]. According to Fig. 4, this index is significantly higher in immature girls than in other groups (p < 0.001). In addition, the different score in the executive control network is lower in mid-luteal than in immature girls, postmenopausal women and the other phases of the menstrual cycle (p < 0.001), (Fig. 4).

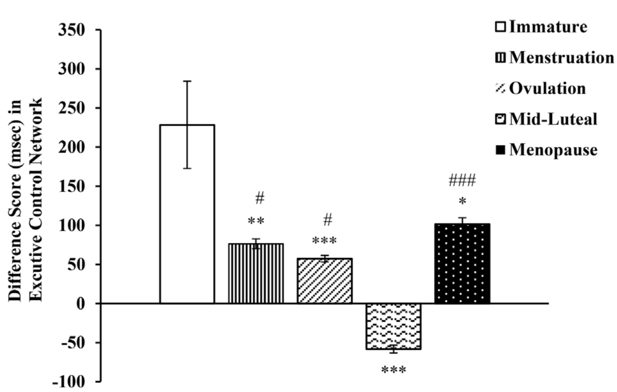

Fig. 4. The comparison of executive control network in different stages of immature to menopause. The difference score in the executive control was significantly higher in immature girls than the other groups, and it was significantly lower in mid-luteal phase than the others. The results are presented as mean ± SEM. (*p < 0.05, **p < 0.01 and ***p < 0.001 compared to immature girls and #p < 0.05 and ###p < 0.001 compared to mid-luteal phase of menstrual cycle in young adults).

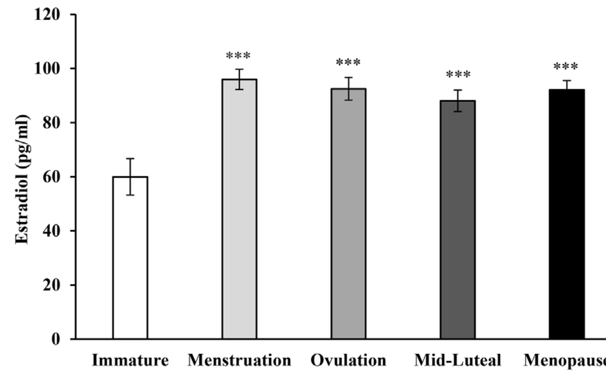

Fig. 5. The estradiol level in different stages of immature to menopause. The results are presented as mean ± SEM. (***p < 0.001 compared to immature girls).

3.3. Results of hormonal assessments

Comparison of plasma estradiol levels indicated that, the levels of the hormone changes according to the different groups of females [F (4,78) = 10.486, p < 0.001]. Fig. 5 shows that estradiol levels are significantly less in the immature girls than in the other groups (p < 0.001), (Fig. 5). Also, comparison of plasma levels of progesterone shows that level of this hormone is affected by different states of women [F (4,78) = 13.477, p < 0.001]. Fig. 6 reveals that the progesterone levels are significantly higher in the postmenopausal women than in the other groups (p < 0.001), (Fig. 6).

Comparison of plasma levels of LH showed that, LH levels change according to different groups of females [F (4,78) = 48.712, p < 0.001]. Plasma levels of LH were significantly higher in postmenopausal women than in other groups, and it was significantly less in the immature girls than in the other groups (p < 0.001). LH levels were significantly higher in the ovulatory phase than in the other phases of the menstrual cycle (p < 0.01), (Fig. 7).

The comparison of FSH levels in blood plasma shows that this hormone changes according to different states of women [F (4,78) = 81.857, p < 0.001]. Fig. 8 suggests that the FSH levels are significantly higher in postmenopausal women than in other groups (p < 0.001). In addition, the results of hormonal assays shows that the FSH levels are significantly lower in the mid-luteal

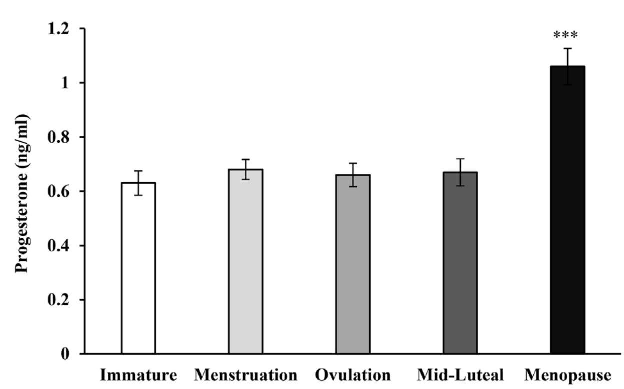

Fig. 6. The levels of progesterone in different stages of immature to menopause. The result are presented as mean ± SEM. (***p < 0.001 compared to immature girls).

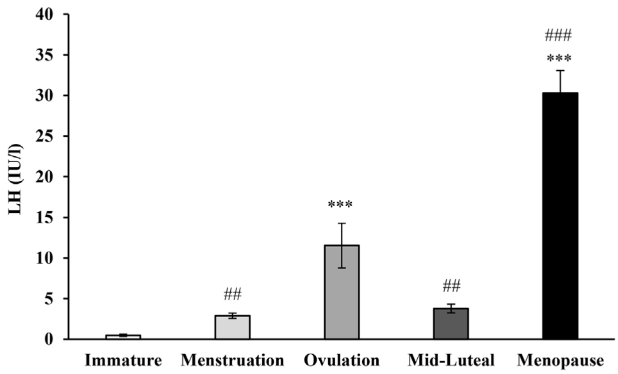

Fig. 7. LH level in different stages of immature to menopause. The results are presented as mean ± SEM. (***$p < 0.001$ compared to immature girls and ##$p < 0.01$ and ###$p < 0.001$ compared to ovulation phase in young adults).

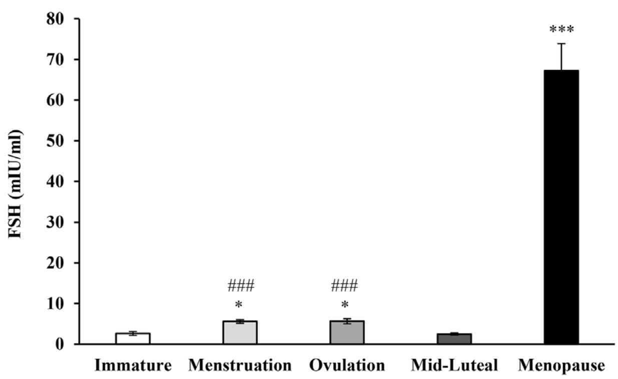

Fig. 8. FSH level in different stages of immature to menopause. The results are presented as mean ± SEM. (*$p < 0.05$ and ***$p < 0.001$ compared to immature girls and ###$p < 0.001$ compared to postmenopausal women).

phase than in other phases of the menstrual cycle ($p < 0.05$), (Fig. 8).

4. Discussion

The evidence suggests that the sexual steroid hormones such as estrogen would be effective in some non-reproductive behaviors such as learning and memory (Pike, Carroll, Rosario, & Barron, 2009). They play a key role in female neurobiology, and due to the presence of estrogen and progesterone receptors in many regions of the central nervous system, it is possible to call the brain as an important organ for sex hormones (Pompili et al., 2012). In addition, the role and effect of sex steroids is dramatically different in lifespan and between male and female (Mccarthy, 2011). In this study, the relationship between attention cognitive function and its different levels with female sex change at different ages before puberty, after puberty at different phases of the menstrual cycle and after the menopause was analyzed. Since these changes were accompanied by hormonal changes, it appeared that it would better to measure the levels of estrogen, progesterone, LH and FSH of blood in each of the above stages in order to possibly discussion their relation with different levels of attention network.

The results of the Stroop test in this study showed that the attention cognitive function is significantly poorer in immature children and postmenopausal women compared to young adults in different phases of the menstrual cycle. Although, in this survey, there was no significant difference in attention performance in different phases of the menstrual cycle, the other findings have emphasized that physiological fluctuations in sex hormone levels across the menstrual cycle allow for non-invasive studies of the cognitive effects of sex hormone in young women and underlie a reliable pattern of cognitive modification across the menstrual cycle (Pompili et al., 2012). According to the changes in across the menstrual cycle, the previous findings showed a significant difference in Stroop task performance between low (the menses) and high (mid-luteal phase) levels of estradiol and progesterone during the menstrual cycle. The authors suggest that sex-related hormone modulation selectively affects cognitive functions depending on the type of task and low level secretion of estradiol appears to contribute to reducing the level of attention that relates to the prefrontal cortex (Hatta & Nagaya, 2009). The other study was supported by the fact that in those tasks which required fine motor skills the highest efficiency would be seen in the late follicular or mid-luteal phases in female, therefore in Stroop test, during postovulatory phase had higher accuracy rates while they read color interference than males. This might have been caused by the effect of hormone progesterone which was probably responsible for the modulating the female executive at this phase of the cycle (Upadhayay & Guragain, 2014).

Menopause is starting a new period in women, in which the menstrual cycle is arrested and the ovarian hormones decreases the least. In the absence of inhibitory effects of estrogen and progesterone, LH and FSH levels for year's remains at a very high level, after menopause, women experience a 3–4 fold and a 4–18 fold increase in serum concentration of LH and FSH, respectively (Meethal, Smith, Bowen, & Atwood, 2005). The results of hormonal measurement in this study proved this funding too.

Now the question may arise as to why we did not use of older women in this study? We were supposed to that if we had included older women, we could not have studied them in the same group because of their different stages in cerebral aging.

During the menopause, however, estrogen deficiency leads to neuroendocrine changes in different areas of the brain and many women reported a decrease in cognitive performance specially dealing with memory (Genazzani, Spinetti, Gallo, & Bernardi, 1999). However, one aspect that has been mostly ignored is whether other hormones of the hypothalamus-pituitary-gonadal axis such as LH and FSH hormone have a role in menopause-associated cognitive dysfunction? In the other words, estrogen is the sole modulator of cognitive function or rather does estrogen act as part of a feedback loop, similar to its role in reproductive function (Bryan et al., 2010).

To support the role of LH, as opposed to estrogen, in cognitive decline after menopause, studies demonstrate that cognitive decline can be restored with estrogen therapy initiated immediately after ovariectomy; estrogen replacement after a long interval is ineffective (Casadesus et al., 2007). Several studies have suggested that estradiol modulates cognitive functions. However, there is generally an inverse relationship between estradiol and Luteinizing hormones, and high LH levels can impede memory. According to the above evidences, this study also showed that there is a significant difference in LH and FSH levels in postmenopausal women compared to immature girls and young adults at different phases of the menstrual cycle. Although, in this study the LH surge in ovulation phase does not show any relevance to the attention function, a long-term study on female chimpanzees showed that the attention and motivation is decreased during ovulation (Inoue & Matsuzawa, 2011).

Although there is little available information dealing with the mechanisms of actions of LH in the brain and also it is not known whether estradiol and LH are acting on the same neural pathway to affect cognitive performances such as spatial memory or attention (Ziegler & Thornton, 2010). Overall, these findings suggest that the gonadotropins such as LH may play an important role in hippocampal related cognitive performance and therefore when examining declines in cognitive performance after menopause, we should be careful to examine all the players involved in the experiment rather than focusing on a single hormone, Because by solely focusing on estrogen we may be overlooking an ignored but very important partner, namely LH (Casadesus et al., 2007).

Neuroimaging studies have shown that cognitive function of attention in the Stroop test is associated with activation of the prefrontal cortex (Hatta & Nagaya, 2009), and since the structure and function of the prefrontal cortex is particularly sensitive to age-related changes in humans and monkeys (Konrad et al., 2005), therefore the Stroop test is affected significantly by age (Comalli et al., 1962). So that older adults in several studies have consistently demonstrated slower color naming on the interference condition, implying a larger Stroop effect (Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000).

Development of executive control functions is associated with the maturation of the prefrontal cortex (Konrad et al., 2005), so that was found that the degree of interference of color-words on color naming is greatest with young children, decreases with increasing age to adulthood and increases again with older ages (Comalli et al., 1962).

The puberty is considered as a remarkable period in brain development and cognitive functions. During this period, there is a marked increase in sex steroid such as estradiol and testosterone. However, during prenatal development, sex steroid hormones act on the nervous system to organize neural circuits in the brain, these neural circuits remains relatively dormant until hormonal stimulation received in adolescence effects on the central nervous system to active adult reproductive physiology, behaviour and cognition (Romeo, 2003). Studies also have shown that the complex cognitive functions such as interference inhibition and cognitive flexibility evolve in adolescence and adulthood and simpler abilities such as selective attention and visuospatial attention corrected during this period (Rubia, Hyde, Halari, Giampietro, & Smith, 2010). According to the mentioned evidences, this study shows that estradiol levels are significantly lower in the immature children than in other groups, and the performance of this group on Stroop test and executive control network in ANT is significantly weaker than in the others.

In the present study, to evaluate attention network performance, the Attention Network Test (ANT) was used. Although, so far, any researches dealing with direct correlation related to the sex hormones estrogen and progesterone hormones, LH and FSH or considering network performance has not been studied, some studies has shown that the alerting effect decreases with age (Zhou, Fan, Lee, Wang, & Wang, 2011). In a study reported that older adults and middle-aged show significantly less alerting than younger adults in response to a warning cue (Jennings, Dagenbach, Engle, & Funke, 2007).

In this study, there was no significant correlation between different groups in orienting network; however, the studies show that unlike alertness, process of orienting was found to be unaffected in the older participants, and the older adults benefit as much as younger adults from physical or symbolic cues that direct attention to the likely location (Zhou et al., 2011). Other study indicated that orienting of attention remained intact with aging by using a central cue (Hartley, 1993), and also the other one showed that there was no age difference in orienting (Fernandez-Duque & Black, 2006).

In the present study, the results showed that executive control function was significantly weaker in the immature girls than in the other groups, and it was significantly better in young adults in mid-luteal phase of the menstrual cycle than in the others.

The executive effect was significantly decreased with age. The results of different tasks have indicated that aging exerts a major effect on cognitive response speed (Zhou et al., 2011).

We conclude that it is likely that the sexual changes associated with aging in extent of secretion of ovarian hormones especially estrogen, during the lifespan of women and also increased levels of LH and FSH after menopause have effects on attention brain networks and finally on attention cognitive performance.

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