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The resting frontal alpha asymmetry across the menstrual cycle: A magnetoencephalographic study ☆

Ren-Jen Hwang [a,b,e], Li-Fen Chen [b,c,d], Tzu-Chen Yeh [b,c,d], Pei-Chi Tu [a], Chung-Haow Tu [a,b], Jen-Chuen Hsieh [a,b,c,d,*]

[a] Institute of Neuroscience, School of Life Science, National Yang-Ming University, Taipei, Taiwan
[b] Laboratory of Integrated Brain Research, Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Brain Research Center, University System of Taiwan
[d] Institute of Brain Science, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Chang Gung Institute of Technology, Tao-Yuan, Taiwan

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Abstract

Gonadotropic hormones play an important role in the regulation of emotion. Previous studies have demonstrated that estrogen can modulate appetitive (approach/positive) and aversive (avoidance/negative) affective behaviors during the menstrual cycle. Frontal alpha asymmetry (a measure of relative difference of the alpha power between the two anterior hemispheres) has been associated with the trait and state reactivity of different affective styles. We studied the pattern change of frontal alpha asymmetry across the menstrual cycle. 16 healthy women participated in this resting magneto-encephalographic (MEG) study during the peri-ovulatory (OV) and menstrual (MC) phases. Our results showed significant interaction of resting MEG alpha activity between hemispheric side and menstrual phases. Difference in spontaneous frontal alpha asymmetry pattern across the menstrual cycle was also noted. Relatively higher right frontal activity was found during the OV phase; relatively higher left frontal activity was noted during the MC phase. The alteration of frontal alpha asymmetry might serve a sub-clinical correlate for hormonal modulation effect on dynamic brain organization for the predisposition and conceptualization of different affective styles across the menstrual cycle.

Keywords: Emotion; Menstrual cycle; Frontal alpha asymmetry; Brain; Magnetoencephalography

Introduction

Recent research exploring the influence of estrogen on human affective processing has implicated the gonadotropic hormone in the female emotional and behavioral regulation. Some experimental evidence suggests that estrogen can enhance approach behaviors or positive emotion in women. The incidence of extra-pair copulation (Slob et al., 1996), number of sexual fantasies (Gangestad et al., 2002) and preference for masculine men (Penton-Voak et al., 1999) were increased in healthy females during the high-estrogen phases of the menstrual cycle. Furthermore, an event-related potential study has demonstrated that women during the ovulatory phase, showed a larger peak in the late-positive component for sexual stimulus (i.e., nude men), which implies an increased sexual desire and deeper emotional processing (Krug et al., 2000). In addition to the aroused response to stimuli of higher sexual valence, clinical studies on menopausal women receiving estrogen-hormone replacement therapy (HRT) have shown that estrogen may represent a potentially critical variable associated with better mood and cognitive performance (Soares et al., 2001).

In addition to the enhanced effect of estrogen on appetitive (approach/positive) behaviors, it has also been reported that estrogen can also modulate the aversive (avoidance/negative) system of affective processing. Studies of ovariectomized mice have shown that the mice have increased fear, vigilance and

☆ MEG study of frontal alpha asymmetry across the menstrual cycle.

* Corresponding author. Brain Research Center and Institute of Brain Science, School of Medicine, National Yang-Ming University, No. 155, Sect. 2, Linong St. Taipei 112, Taiwan. Fax: +886 2 28757480.
E-mail addresses: rjhwang2@vghtpe.gov.tw (R.-J. Hwang), jchsieh@ym.edu.tw (J.-C. Hsieh).

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reactivity to a potentially dangerous environment after estrogen treatment (Morgan and Pfaff, 2001; Morgan et al., 2004). In female adolescents, investigators have found that negative affect and increased anxiety can be significantly related to a rapid increases in estradiol secretion (Warren and Brooks-Gunn, 1989). Furthermore, fear recognition is enhanced in healthy subjects during the high estrogen phase of the menstrual cycle (Pearson and Lewis, 2005). Notwithstanding, young females with Turner's syndrome, lacking estrogen due to genetic deficit, have a specific compromised function for fear recognition (Lawrence et al., 2003a, b). The aforementioned reports on estrogen's modulational effects studied the event-related state responses and the modulation was demonstrated to be context-dependent (Morgan et al., 2004).

It has been shown that baseline electroencephalographic (EEG) asymmetry in the anterior frontal region serves as a reliable measure of individual affective style (positive vs. negative) (Davidson, 2004; Davidson et al., 2002; Henriques and Davidson, 1991; Tomarken et al., 1990, 1992a,b; Wheeler et al., 1993). The resting frontal EEG asymmetry may reflect an implicit conceptualization of affective style with a response predisposition to general approach or withdrawal tendencies (Coan et al., 2006). Left prominence connotes approach-related while right dominance indicates withdrawal-related emotional behaviors, respectively (Davidson, 1995; Sutton and Davidson, 2000). Among different EEG frequencies, the alpha band has been mostly studied. In general, the alpha power, indexing a cortical idling status, is negatively related to the functional magnetic resonance imaging (fMRI) neuronal activity (BOLD activity, *B*lood-*O*xygen-*L*evel-*D*ependent activity) of the corresponding neuronal region (Laufs et al., 2003). It is suggested that the regional alpha power fluctuations operationally correspond to regional neuronal activities in an inverse fashion, i.e., an increased regional alpha power connotes a decreased regional neuronal activity while a decreased regional alpha power reflects an increased neuronal activity (Laufs et al., 2003). The alpha asymmetry score can be deduced by subtracting the left frontal alpha power from the right homologue: the lower the score, the greater the right hemispheric frontal activation. It has been reported that a greater right resting frontal activity (lower asymmetry score) corresponds to a personality trait tendency for withdrawal and/or greater responsiveness to negative affective stimuli, whereas a greater left resting frontal activity (higher asymmetry score) corresponds to a trait tendency to approach or a stronger responsiveness to affectively positive stimuli (Sutton and Davidson, 2000; Sutton and Davidson, 1997; Tomarken et al., 1990; Wheeler et al., 1993).

The frontal EEG asymmetry has been suggested to concur with the concept of behavioral activation and inhibition system (BAS vs. BIS) (Sutton and Davidson, 1997). The BAS/BIS model was proposed by Gray (1982). Activation of the BAS is associated with feelings of hope and approach behaviors (reward responsiveness, drive, and fun-seeking dimensions), whereas the activation of BIS is associated with feelings of anxiety and avoidance behaviors (Gray, 1982; Gray and McNaughton, 2000). The relative greater left and right baseline frontal activity in respect to BAS and BIS engagement has also been reported (Sutton and Davidson, 1997). It is conceivable that BAS/BIS sensitivities are comparable to approach/withdraw affective dimensions on general affective styles. The BAS/BIS inventory has been used for basic and clinical settings to detect and measure the functional manifestations of the BAS/BIS (Carver and White, 1994). The BIS questionnaire has been specifically exploited to detect negative emotion, e.g., depression and anxiety (Harmon-Jones and Allen, 1997).

Based on the aforementioned evidence of estrogen's modulatory effect on approach and withdrawal style, we hypothesized that there might be an alteration of resting frontal alpha asymmetry across the menstrual cycle in accordance with the cyclic variation of gonodatropic hormone. Serum estradiol surges significantly during the ovulatory phase (Krug et al., 2000; O'Reilly et al., 2004; Pearson and Lewis, 2005). We exploited magnetoencephalography (MEG) to measure the frontal alpha asymmetry of neuromagnetic brain activities between the menstruation and periovulatory phases (low vs. high estrogen level). BAS/BIS ratings were also analyzed.

Methods

Participants

Sixteen healthy righted-handed women with regular menstrual cycles were recruited. Mean sample age was 23.96 years (SD = 6.19; range: 19–29). Written informed consent was obtained from each subject prior to the experiment. Inclusion criteria included consistent menstrual cycles of 26–32 days for the preceding 6 months, no pregnancy during experiment, and no usage of oral/hormonal contraceptive agent. The subject should not have history of any neurological/psychiatric disorder or premenstrual syndrome (PMS). The PMS was ruled out by the DSM-IV criteria for the diagnosis of premenstrual dysphoric disorder (American Psychiatric Association, 2000). The subject was restrained from alcohol for at least 48 h and caffeine/tobacco for 12 h before the experiment.

Procedure

A 306-channel MEG system (Vectoview@, Neuromag, Finland) was exploited to measure brain activity at two phases across the menstrual cycle during a 6-min resting period (subjects relaxed and stayed awake). Each subject underwent two MEG sessions: the menstrual phase (MC, during the 2nd to 4th days after menstrual onset) and the periovulatory phase (OV, during 12th to 16th days after menstrual onset) as confirmed by the urinary luteinizing hormone (LH) test. The two sessions were completed within two cycles of each individual. A counterbalanced, repeated-measurement design was used to avoid order effect; 50% of the subjects were studied first with MC-phase and another 50% were studied first with OV-phase measurement, respectively. Behavioral assessment was studied after each MEG recording.

MEG recording

The subject seated comfortably in a magnetically shielded room (Euroshield, Eura, Finland). Spontaneous neuromagnetic activity was recorded continuously for 6 min while the subjects relaxed and stayed awake with their eyes closed. Data were recorded at a sampling rate of 1024 Hz and band-pass filtered at 0.03–330 Hz. Four head-position-indicator (HPI) coils were attached onto the subjects' head and were used to ensure no large head movement throughout the measurement period by comparing the positions of these HPI coils before and after the recordings. The device coordinates of the HPI coils were registered and transformed into the head-device coordinate system. Positions of three defined anatomical landmarks (the nasion and bilateral preauricular points) were additionally taken. These data were used to position subject's head inside the MEG helmet in order to ensure coverage of the same cortical regions under each sensor across the two sessions. The mean translation and rotation of head between the two experimental sessions of every subject was around 5 mm and 3 degrees, respectively. The translation extent was much smaller than the sensor distance (3.4 cm).

Behavioral assessment

Each participant completed self-reported assessments after every MEG session. The State-Trait Anxiety Inventory was used to exam the state anxiety (SAI) as an index of negative mood, reflecting a "transitory emotional state or condition of the human organism" (Spielberger et al., 1983). Each of the 20 SAI items was given a weighted score of 1–4, with a rating of 4 indicating the highest level of anxiety; total score ranged from 20 to 80.

Participants also completed the BAS/BIS scale (Carver and White, 1994). The BIS instrument consists of a unidimensional inventory of seven items reflecting the degree of felt anxiety when confronted with some punishment cues. The BAS instrument consists of 13 items constituting three dimensions: reward responsiveness, drive and fun seeking. Total BAS score is calculated from these 13 items. High internal consistency/reliability (Cronba á value) of the BIS scale, the BAS-reward responsiveness, BAS-drive and BAS-fun seeking subscales has been confirmed to be 0.74, 0.73, 0.76 and 0.66, respectively (Carver and White, 1994).

Analysis

Off-line rejection of eye movement artifact (amplitudes over 3 pT/cm) was performed for every 2-s MEG epoch. Only the measurements of 204 gradiometers were subjected to analysis. An average of 134 (121–150) epochs for each participant was subjected to spectral analysis using Fourier transformation. The right and the left frontal brain areas were the two regions-of-interest in the current study. Each region encompassed 30 channels of coverage (Fig. 1). The mean alpha power (MAP, fT^2/Hz) of brain activity (8–13 Hz) of each hemisphere (left MAP, LMAP; right MAP, RMAP) was calculated by averaging the survived epochs from all the channels. A two-way, repeated-measurements of analysis of variance (ANOVA) on MAP was conducted for the effects of side (left and right hemisphere) and phase (MC vs. OV) as well as interaction, using SPSS-12 (SPSS, Inc, USA). The MAP of each frontal region (LMAP and RMAP) was used for subsequent calculation of alpha-asymmetry score (AAS; AAS=RMAP–LMAP) (Davidson, 1995) to further elucidate the interaction effect, if any. The correlation

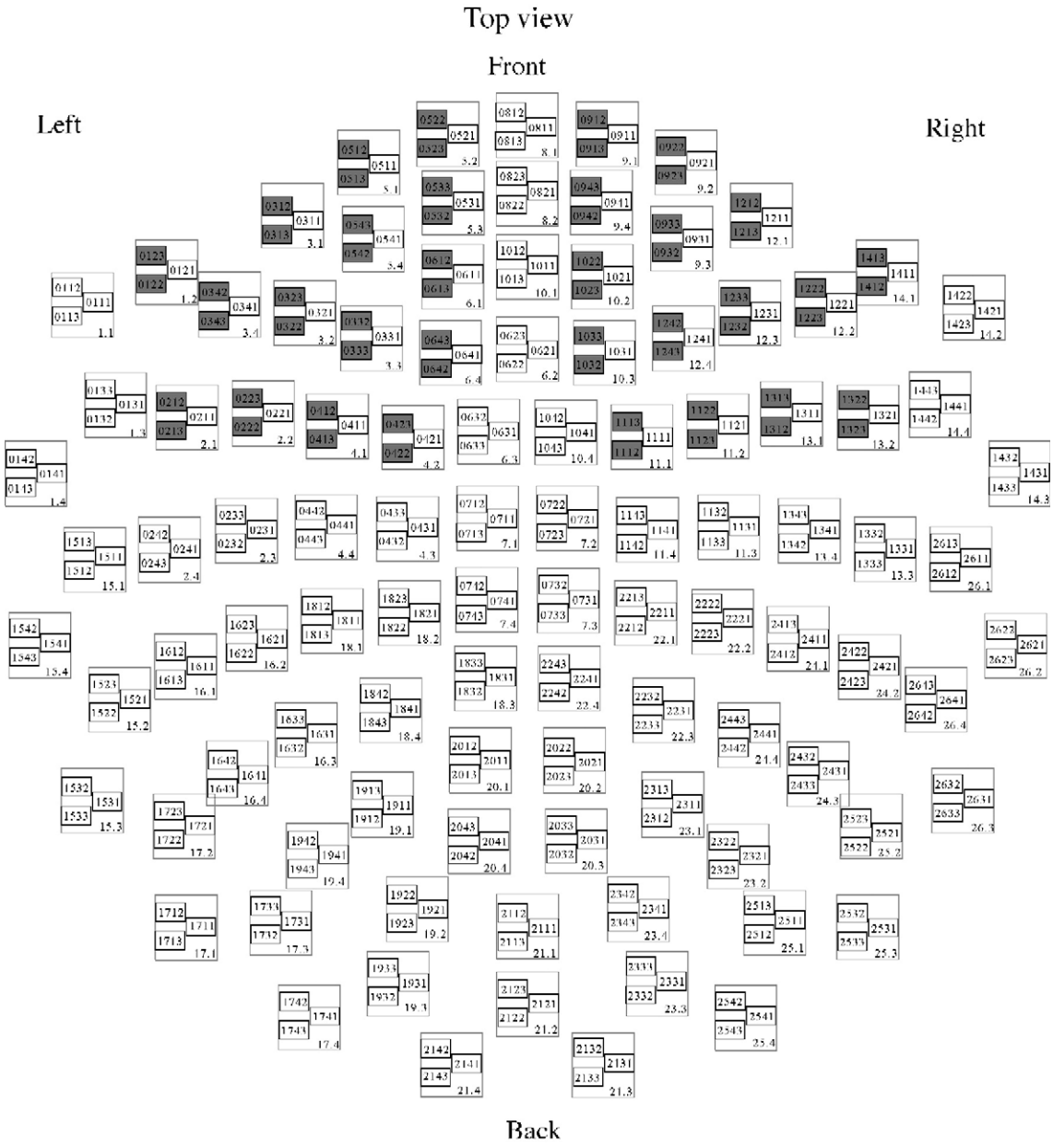

Fig. 1. Frontal regions studied. The MEG channels (paired gradiometers) selected are blacken. MEG, magnetoencephalography.

between the MAP of each frontal area and neuropsychological assessment (SAI, BAS/BIS scale) was examined. MAP of each test session (two per subject) was used as one individual data point for the Pearson correlation analysis.

Results

MEG alpha asymmetry

The mean±standard deviation (±SD) for LAMP was 5.32 (±2.5) (fT^{2}/Hz) and 4.79 (±2.5) for MC and OV, respectively. The mean±standard deviation (±SD) for RMAP was 5.97 (±3.3) and 4.61 (±2.23) for MC and OV, respectively. No significant main effects were found on hemispheric side [$F(1, 15)=0.511$, $p=0.486$] and phase [$F(1, 15)=2.41$, $p=0.141$] on MAP. However, significant interaction between phase and hemisphere was noted [$F(1,15)=11.933$, $p=0.004$] (Geiser–Greenhouse corrected) (Fig. 2). The mean AAS for the MC and OV phases were 0.66±1.52 and −0.19±1.25, respectively. Using Wilcoxon rank-sum test, significant difference of AAS between the MC and OV phase was noted (χ^2 (1)=12.11, $p<0.01$) (Fig. 3). Significantly lower AAS was found in OV women. Note that MEG alpha power is inversely related to cortical activity (see Introduction), thus, lower AAS indicated relatively greater right-hemispheric activity. The data herein denoted relatively higher right frontal activation in the OV phase.

Behavioral data

Neuropsychological assessments of SAI and BAS/BIS did not reveal any significant difference between the menstrual phases ($p>0.05$). SAI score (mean ±SD) for the MC and OV phase was 36.4±8.3 and 35.7±6.8, respectively. The BIS score for the MC and OV phase was 28.9±3.7 and 28.8±4.7, respectively. The BAS score was 49.8±5.0 and 50.3±5.0, respectively. SAI and BIS showed significant positive correlation ($r=0.36$, $p<0.05$).

Correlation between frontal alpha power and behavioral measurement

No significant correlation was detected between either RMAP or AAS with the corresponding BAS, BIS, and SAI scores. Significant correlation was found only between LMAP and the BAS rating ($r=0.354$, $p=0.047<0.05$, $n=32$).

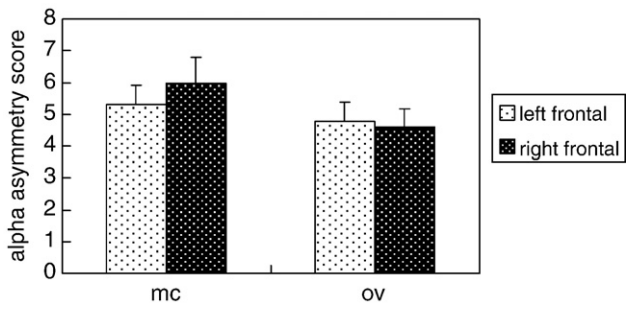

Fig. 2. The mean alpha power in the frontal regions at MC and OV phase. No major effect of hemispheric side and menstrual phase was noted ($df=15$, $p=0.486$ and $p=0.141$, respectively). The phase by side analysis reveals a significant interaction ($F(1,15)=11.933$, $p<0.005$). Error bar represents the standard error of the mean. MEG alpha power is negatively related to the system activity.

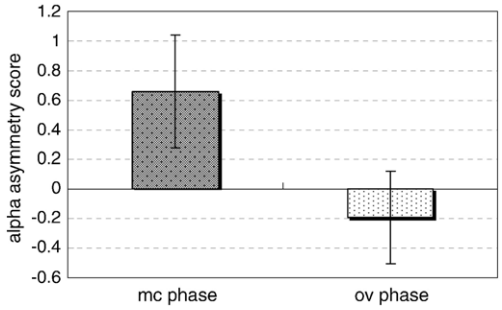

Fig. 3. Frontal AAS across menstrual cycle. The AAS showed significant difference between OV phase and MC phase ($n=16$, $p<0.05$). AAS, alpha asymmetry score. Error bar represents the standard error of the mean.

Discussion

We examined the interrelationship of resting frontal alpha asymmetry and human menstrual cycle. Contrary to previous reports addressing the evoked brain responses in association with active behavioral performance that emphasize the state manifestations of the cognitive or affective systems under challenges, we set out to investigate possible innate cerebral correlate(s) reflecting the biological trait conforming to hormonal modulation with possible psychological correlations. Albeit the fact that there was no major effect of side and phase, respectively, there existed a significant interaction between cerebral hemispheric sides and menstrual phases (Fig. 2). The interaction could be termed as AAS alteration in our study across the menstrual cycle (Fig. 3). Sub-significant trend of a lowered bilateral frontal activity during OV phase as compared with MC one was also noted, which implicated an augmented bilateral frontal activity during OV phase, reflecting a possible heightened sensitivity of both approach/withdrawal or BAS/BIS systems.

The regulatory influences on specific brain regions by estrogen can be mediated in multiple ways (McEwen and Alves, 1999; Rubinow et al., 1998; Rupprecht and Holsboer, 1999). Our results demonstrated that young females can express relatively greater resting right frontal activity (lower AAS) during the OV as compared to MC phase. The high estrogen level could be associated with a higher right frontal activity. It has been demonstrated that the estrogen can modulate the activity of the right anterior hemisphere. An EEG study has shown that the right hemispheric vigilance system can be enhanced by HRT in women with postmenopausal syndrome (Saletu et al., 2005). Estrogenic effects on fear and arousal status are mostly envisaged to occur in the limbic-amygdala structures (Morgan et al., 2004), which serve critically the elaboration of avoidance-related behaviours, which in turn can harbor synergestic modulation on higher perseverance for positive reward (Molto et al., 2007; Newman et al., 1987) during OV phase. Estrogen has also been proposed to modulate the ‘arousal crescent’ of neurons in the female brain, improving assessment of the environment, threat anticipation, and preparing the organism for the stressful but ultimate goal of reproduction (Pfaff et al., 2002).

It is contentious to speculate that higher right frontal activity could be a central correlate for achieving a higher readiness for fertility window.

In our study, MC phase demonstrated relatively greater left baseline frontal activity. In normal subjects, a greater left-sided prefrontal metabolism is associated with lower metabolic activity in the amygdala (Davidson et al., 2000) that plays a key role in the elaboration/appreciation of negative emotion. It has been suggested that baseline prefrontal cortex activity accounts for emotion regulation and the relatively higher left-sided baseline frontal activity is associated with the ability to voluntarily suppress negative emotion (Jackson et al., 2000, 2003). Furthermore, the left prefrontal cortex is crucial in regulating emotional responding, and is particularly indispensable in processing/coping negative stimuli, which is an important protective factor against mood and anxiety disorders.(Jackson et al., 2003; Tomarken and Davidson, 1994). Hence, the relatively higher left frontal resting activity during MC phase, may reverberate the cyclic demand of the organism that commands a better emotional adaptation during the menstruation period.

The BAS/BIS scores did not show significant differences between the OV and MC phases during the menstrual cycle. The BAS/BIS did not show significant correlation with AAS, either. The resting frontal alpha asymmetry has been proposed to reflect a trait-dependent index of the individual's predisposition to respond efficiently in terms of approach and withdrawal-related motivation (Kalin et al., 1998; Tomarken et al., 1990). BAS/BIS sensitivities have also been correlated with resting frontal activities (Sutton and Davidson, 1997). We did not study the state-related withdrawal/approach predisposed resting and evoked brain activity. One explanation is that BAS/BIS sensitivities may differ from the approach/withdrawal responsiveness. Approach/withdrawal responding is usually demonstrated under active and passive challenges of emotional stimuli, while BAS/BIS measurement is usually taken as a trait measurement of one's behavioral tendency. The self-report or baseline mood measures maybe inadequate to uncover subtle individual core differences in subcomponents of emotional reactivity (Davidson, 1998). Notwithstanding, recent studies do not coherently yield the correlation between the lateralized frontal cortical activity and the corresponding BAS/BIS sensitivity (Coan and Allen, 2003; Hagemann et al., 1999; Hewig et al., 2006). Hence, it is tempting to state that the alteration of frontal alpha asymmetry might serve a sub-clinical correlate (or signature) for hormonal modulation effect on dynamic brain organization for the predisposition and conceptualization of different affective styles across the menstrual cycle. This is in congruence to the findings of brain imaging and mapping reports that brain activation patterns can be more sensitive than behavioral measurements in certain conditions (Shaywitz et al., 1999).

It is noteworthy that there existed a positive correlation between the LMAP (a marker for inversed left frontal activity) and BAS ($r=0.354$, $p<0.05$, $n=32$, Fig. 4). The left-frontal activity was inversely correlated with BAS sensitivity. Left prefrontal cortex serves a key role in emotion regulation, i.e., facilitating positive reactivity and inhibiting negative reactivity (Jackson et al., 2003). The left frontal activity imparts the inhibition to the amygdala in an inverse manner (Davidson et al., 2000), which in turn tunes the function of the amygdale for the valence and responsiveness to negative stimulus. The modulation can also simultaneously exert its general arousal effect on the rewarding stimulus (Dreher et al., 2007; Schneider et al., 1995). Such reciprocity between the left frontal activity and BAS might pinpoint possible compensatory mechanisms in the healthy young female for automatic emotional regulation, accounting in part for the lack of difference in behavioral measurements on the group level between menstrual phases in our study. This view might gain indirect support from the studies showing that anxiety does not change significantly across menstrual cycle in healthy young women (Lahmeyer et al., 1982). Similar findings were found in our study that even though SAI and BIS showed significant positive correlation ($r=0.36$, $p<0.05$), (implicating the consistency of both inventories for anxiety assessment), neither measurement revealed significant difference of anxiety observed across the menstrual phases.

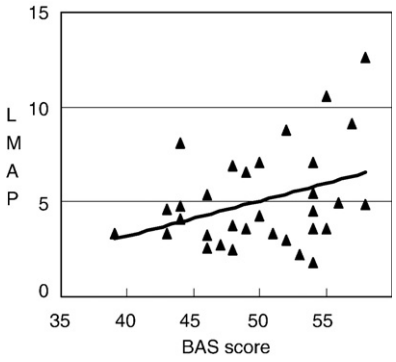

Fig. 4. Relationship between LMAP and BAS score. LMAP, left mean alpha power. BAS, behavior activation system. Significantly positive correlation between LMAP and the BAS rating ($r=0.354$, $p=<0.05$, $n=32$).

In conclusion, our preliminary and exploratory study demonstrated that the baseline frontal alpha asymmetry changed in concomitance with the menstrual cycle. Relatively higher right frontal activity was found during the OV phase; relatively higher left frontal activity was noted during the MC phase. The alteration of frontal alpha asymmetry pattern might serve a sub-clinical correlate (or signature) for hormonal modulation effect on dynamic brain organization across the menstrual cycle.

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