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Effects of the menstrual cycle on auditory event-related potentials

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Abstract

Gonadal steroids (estradiol and progesterone) can alter neuronal functioning, but electrophysiological evidence in women is still sparse. Therefore, the present study investigated event-related potentials (ERPs) to neutral stimuli over the course of the menstrual cycle. In addition, associations between ERPs and salivary estradiol and progesterone concentrations were investigated. Eighteen young healthy women were tested at three different phases of their menstrual cycle (menses, and follicular and luteal phases). ERPs (i.e., the N1 and P2 components, reflecting cortical arousal and the orienting response, the N2, P3, and the Slow Wave (SW), reflecting controlled processing) were measured using two different paradigms. In the luteal phase, early ERPs reflecting the cortical arousal response were diminished in the first stimulus block indicating an attenuated orienting response. These changes were significantly correlated with estradiol as well as progesterone levels. As to the later ERP components, the N2 latency was shorter during menses compared to the other two phases. No menstrual cycle-associated changes were apparent in other late ERP components. In sum, this study documents changes in auditory ERPs across the menstrual cycle with the most prominent changes occurring during the luteal phase. Future ERP studies therefore need to be more attentive to the issue of menstrual phase when studying female subjects or female patients.

Keywords: Estradiol; Progesterone; Event-related potentials; Vertex potential; Menstrual cycle; Orienting response

Introduction

Gonadal steroids not only have reproductive functions but also display neuroactive effects. These are thought to be responsible for changes in mood and cognition over the course of the menstrual cycle, during pregnancy, and after menopause (McEwen and Alves, 1999; Rupprecht et al., 2001; Sherwin, 2003). During menses, levels of estradiol and progesterone are low, the follicular phase is characterized by high estradiol levels, while during the luteal phase, concentrations of both hormones are high (Franz, 1988).

Measuring cognitive performance of women during the menstrual cycle, it has been reported that gonadal steroids enhance those skills for which females typically show better results than males such as verbal fluency, articulation, and manual speed. In contrast, estradiol and progesterone appear to diminish those skills for which male subjects usually show a better performance such as spatial ability, mental rotation, and deductive reasoning (Hampson, 1990a,b; Hausmann et al., 2000; Kimura, 1996; Maki et al., 2002; Postma et al., 1999). Most of these studies observed these improved "female skills" during the luteal phase, indicating that women are most different from men during this phase of the menstrual cycle. In addition, there is also evidence that basic sensory skills vary during the menstrual cycle. For example, hearing sensitivity in women is poorest during menses, which again indicates a shift towards the male pattern (for a review, see McFadden, 1998). It has to be mentioned that several of the experiments mentioned above

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studied their subjects only during the midluteal phase and during menses. Possible changes occurring during the follicular (preovulatory) phase have often been neglected.

Cognitive tests measure effects of sex hormones on the brain only indirectly. Another way to assess brain activity can be achieved by recording the electrical activity on the skull following external stimulation (evoked potentials, EPs). Auditory EPs can be divided into auditory brainstem responses (ABR; generated in the peripheral auditory system), middle latency EPs (generated in the primary auditory cortex), and auditory event-related potentials (ERPs; generated in higher cortical areas). ERPs can be further divided into early and late components reflecting different cognitive functions such as orienting or memory, respectively (see for a review Näätänen, 1988).

Several studies have examined the effect of gonadal steroids on ABRs and reported significant although inconsistent changes across the menstrual cycle. Some studies found no changes across the menstrual cycle (Fagan and Church, 1986; Howard et al., 1992), and some reported longer wave III or wave V peak latencies at ovulation (Caruso et al., 2003; Elkind-Hirsch et al., 1992, 1994) or during the midluteal phase (Tasman et al., 1999).

Considering ERPs, the N1 (negative peak about 100 ms poststimulus) and P2 components (positive peak about 200 ms poststimulus) are thought to indicate automatic stimulus processing. They are influenced by early aspects of attention and orientation (Näätänen and Picton, 1987; Pashler, 1998). Furthermore, the vertex potential (amplitude difference between the N1 and P2 components) is taken as an indicator for the cortical arousal response (Näätänen, 1992). The N2 component (negative peak about 250 ms poststimulus) most likely reflects the classification of deviant stimuli (Näätänen and Gaillard, 1983), whereas the P3 component (positive peak about 300 ms poststimulus) is assumed to be an indicator of controlled (i.e., conscious) processing (Donchin and Coles, 1988). The Slow Wave (SW) reflects further processing invoked by increased task demands (Ruchkin et al., 1988).

Previous studies investigating effects of the menstrual cycle on ERPs have again led to inconsistent results. Although there was a tendency for an enhanced P3 amplitude in the midluteal phase in one study using visual stimuli (Kluck et al., 1992), ERP amplitudes to neutral stimuli did not consistently change over the course of the menstrual cycle in three additional studies using visual (Tasman et al., 1999) or auditory stimuli (Fleck and Polich, 1988; Waldo et al., 1987). Two studies used visual stimuli with reproductive significance and observed an enhanced P3 amplitude in response to male models during the ovulatory phase (Krug et al., 2000) or an enhanced P3 amplitude for male models as well as babies during the luteal phase (Johnston and Wang, 1991).

Therefore, the present study was conducted to measure changes in the ERPs to neutral stimuli during three different phases of the menstrual cycle (menses, and follicular and luteal phases). Two experimental paradigms were used: a habituation paradigm served to measure changes in the early stages of information processing (e.g., orienting and habituation) as reflected in the N1 and P2 and an oddball paradigm served to measure changes in the later stages of information processing (e.g., working memory) as reflected in the N2, P3, and Slow Wave. On the basis of previous studies (outlined above), the most prominent effects were expected to occur in the luteal phase, when both estradiol and progesterone levels are high.

Material and methods

Subjects

Eighteen young (age: 18–35 years, mean: 26.5, SEM: 5.7) normally cycling (24–35 days) women participated in this study. The following inclusion criteria were required: no hormonal contraceptives, no lactation and no pregnancy during the last year, constant menstrual cycle (between 24 and 35 days), no diagnosed premenstrual syndrome, no intake of neuroactive substances, no chronic illnesses (with the exception of allergies), no neurological, psychiatric or endocrinological illnesses, nonsmokers, no subjective hearing problems, normal body weight (body mass index between 18 and 25 kg/m^2). The study was approved by the local ethics committee, and all subjects provided written informed consent.

Design

The study is based on a 3 (menstrual phases) × 3 (electrode position) design with repeated measures. In addition, endocrine, behavioral, and mood measures were taken. Three electroencephalogram (EEG) sessions lasting about 2 h were assigned to the subjects in a randomized way with a permuted sequence determining which menstrual cycle phase was tested first. The following three phases were investigated: menses (second to fourth day of bleeding), follicular phase (15 to 22 days before the onset of the new menstrual cycle), and luteal phase (3 to 9 days before the onset of the new menstrual cycle); the day of onset of the subsequent menstrual period was used retrospectively to confirm the menstrual phases. Although the duration of the menstrual cycle varies across women, this variance is almost exclusively confined to the follicular phase with the onset of the new menses beginning about 14 days after ovulation (Lein, 1979). Therefore, the interval in which the different phases were examined was counted backwards from the first day of the expected onset of the next menses. The study took place at the University of Düsseldorf, in an acoustically and electrically shielded chamber (Industrial Acoustics Company).

Biochemical analysis

On each test day, subjects filled a small tube with saliva. Cotton swab-based sampling was avoided because it might lead to incorrect results for some sex steroids (Shirtcliff et al., 2001). Estradiol and progesterone concentrations were analyzed by an independent laboratory using commercially available radioimmunoassay kits adopted for the analysis of salivary samples (DSL, Sinsheim, Germany). The sensitivity of the progesterone assay is 10 ng/dl (Groschl et al., 2001), and the sensitivity of the estradiol assay is 0.25 pg/ml (Shirtcliff et al., 2000). Inter and intra assay variance was below 12% for both assays.

Psychological measures

Depression and mood were measured with the German short version of the Centre for Epidemiological Studies Depression Scale ("Allgemeine Despressions-Skala"; ADS-K, Hautzinger and Bailer, 1993) and a multidimensional mood questionnaire "Mehrdimensionaler Befindlichkeitsfragebogen" (MDBF; Steyer et al., 1994), respectively. Because neither the depression nor the mood data exhibited differences across the menstrual cycle, they will not be mentioned further.

Paradigms for ERP recordings

Two different paradigms were applied to measure electrophysiological correlates of the cortical arousal response and orienting (N1, P2) and controlled processing of auditory stimulation (N2, P3, SW). The N1 and P2 components were obtained in a habituation task, in which 200 identical stimuli consisting of 1 kHz tones of 75-dB SPL intensity and a duration of 60 ms were presented binaurally via headphones, and the subjects had to mentally count the number of tones heard. To measure the overall attention to these stimuli, the components were analyzed using the averaged ERPs of the 200 tones. Additionally, the course of habituation was investigated dividing the whole trial into four blocks consisting of 50 stimuli each. An oddball paradigm was used to measure the N2 and the P3 components and the Slow Wave. Here, subjects heard standard and target tones binaurally via headphones. Standards consisted of 1-kHz tones with an intensity of 75-dB SPL and a duration of 60 ms, whereas targets had a frequency of 1200 Hz with an intensity of 75-dB SPL and also a duration of 60 ms. In each of the two blocks, there were 200 tones with 80% standards and 20% targets. Subjects had to react to targets as fast as possible by pressing a button.

In both paradigms, a randomized interstimulus interval of 1, 2, or 3 s was used. The order of the paradigms was permuted and randomized between but not within subjects.

Behavioral measures

Reaction times to target stimuli as well as incorrect responses as summation of missed targets and false alarms were recorded in the oddball paradigm.

EEG recording

For ERP determination, the electroencephalogram (EEG) was recorded from Ag/AgCl electrodes (diameter 8 mm, Falk Minow Services, Germany) attached at the midline positions (Fz, Cz, Pz) according to the 10–20 system. The reference electrodes were placed at each mastoid, and the ground electrode at the forehead. Additionally, a vertical electrooculogram and a horizontal electrooculogram were obtained by placing two electrodes sub- and supraorbitally and at the temples, respectively. The subjects were instructed to refrain from blinking as much as possible and to keep their eyes on a fixation mark during the main trials. The electrode positions were cleaned with an abrasive paste "Graspaste," and the electrodes filled with the electrode paste "Elefix" (Nihon Khoden Europe). The skin impedance was kept below 5 kOhm for each electrode and each subject.

A SynAmps amplifier (NEUROSCAN, USA) was used to amplify EEG and occular potentials. The recordings were digitalized with a sampling rate of 250 Hz and were continuously recorded. The low-pass filter was set to 30 Hz, and as a high-pass filter, a DC correction was used. The recordings were stored for later analysis.

ERP analysis

ERP data analysis was undertaken with the "Brainvision" software (Brain Products GmbH). The off-line analysis consisted of a segmentation for each tone (100-ms prestimulus until 900-ms poststimulus), an occular correction, a baseline correction (100-ms prestimulus until the onset of the stimulus), and an artifact rejection ($\pm$ 50 μV). Afterwards, each trial and each electrode position were averaged separately. The peaks of the different components were defined as the maximal negativity or positivity in an a priori defined time interval (N1 peak amplitude: negative peak within 90- to 190-ms poststimulus; P2 peak amplitude: positive peak within 190- to 90-ms poststimulus; N2 peak amplitude: negative peak within 230- to 370-ms poststimulus; P3 peak amplitude: positive peak within 270- to 600-ms poststimulus). The vertex potential was determined as peak-to-peak amplitude between the N1 and the P2 peak amplitudes. The Slow Wave was determined as the area under the curve between 430- and 900-ms poststimulus. Additionally, the latencies for the N1, P2, N2, and P3 peak amplitudes were determined.

After the automatic peak detection, the individual averaged curves were manually inspected and rejected if the peaks were not clearly visible. This resulted in different

numbers of subjects for the different paradigms. Data of 17 women from the oddball paradigm and of 15 women from the habituation paradigm could be used.

Results

Hormonal data

Estradiol and progesterone data were analyzed with analysis of variance (ANOVA) with the within-factor "Phase." Follow-up tests of significant findings were performed using Bonferroni-corrected ($P < 0.017$) Student's t tests. The ANOVA revealed a main effect of Phase for estradiol [$F(2,32) = 7.44$, $P < 0.01$, $\varepsilon = 0.685$] and for progesterone [$F(2,32) = 10.88$, $P < 0.01$, $\varepsilon = 0.668$; see Table 1]. Student's t tests confirmed a significant estradiol increase in the follicular phase compared to the menses [$t(16) = -3.28$, $P < 0.01$] and in the luteal phase compared to the menses [$t(16) = -3.26$, $P < 0.01$]. Student's t tests also revealed a significant progesterone increase in the luteal phase in comparison to the concentration during menses and follicular phase [menses: $t(16) = -3.78$, $P < 0.01$; follicular phase: $t(16) = -3.37$, $P < 0.01$].

ERP data

Fig. 1 shows grand average ERPs to the stimuli in the first block of the habituation task at Cz (top panel) and to the targets in the oddball task at Fz (bottom panel), respectively, since significant effects of the menstrual cycle were detected here (see below).

Habituation paradigm: Early ERPs

Vertex potential: An ANOVA with the repeated-measures factors "Phase" and "Electrode position" was performed for each ERP component to determine the electrode site where each ERP component had its maximum. Afterwards, a one-way ANOVA with the repeated-measures "Phase" was performed for amplitude and latency measures of each ERP component at the electrode position where the respective amplitude was maximal. Greenhouse-Geisser corrected F and P values and the ε are reported.

An ANOVA confirmed Cz as the electrode position with the highest vertex potential amplitude [main effect for "Electrode position": $F(2,28) = 37.33$, $P < 0.001$, $\varepsilon = 0.765$]. Next, ERP components in the habituation paradigm were analyzed with an ANOVA with the repeated factors "Phase" and "Block." Here, a nonsignificant trend was observed for a Block * Phase interaction [$F(6,84) = 1.97$, $P = 0.105$, $\varepsilon = 0.728$]. Further Bonferroni-corrected ANOVAs ($P < 0.0125$) of each of the four blocks separately showed a significant main effect of Phase for the first block [$F(2,28) = 5.89$, $P < 0.01$, $\varepsilon = 0.893$; Fig. 1, top panel]. Bonferroni-corrected ($P < 0.017$) Student t tests revealed a significantly smaller vertex potential in the luteal phase as compared to menses and to follicular phase [menses: $t(14) = -2.86$, $P < 0.05$; follicular phase: $t(14) = -3.41$, $P < 0.01$; see Fig. 2, top panel]. Descriptively, 11 out of 15 subjects showed

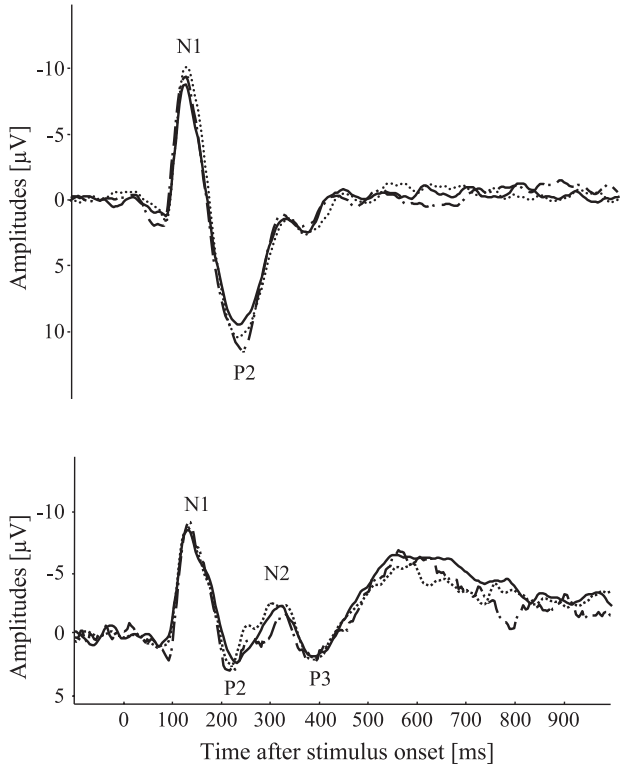

Fig. 1. Grand averages of ERPs during menses (dotted line), follicular phase (dashed line), and luteal phase (solid line) in the first block of the habituation task at electrode position Cz (top panel, $n = 15$) and of the targets in the oddball task at electrode position Fz (bottom panel, $n = 17$). Note the significantly diminished vertex potential during the luteal phase (N1–P2-amplitude difference; top panel) and the shortened N2 peak latency during menses (bottom panel).

Table 1
Hormone concentrations (pg/ml) across the menstrual cycle ($n = 17$)

Hormone concentrations	Menses (M)	Follicular phase (F)	Luteal phase (L)	Significance
Estradiol (pg/ml) (mean ± SEM)	0.74 ± 0.27	1.60 ± 0.27	2.51 ± 0.72	M–F: $P < 0.01$ M–L: $P < 0.01$ F–L: P = n.s.
Progesterone (pg/ml) (mean ± SEM)	44.60 ± 22.24	29.99 ± 7.96	134.61 ± 36.13	M–F: P = n.s. M–L: $P < 0.01$ F–L: $P < 0.01$

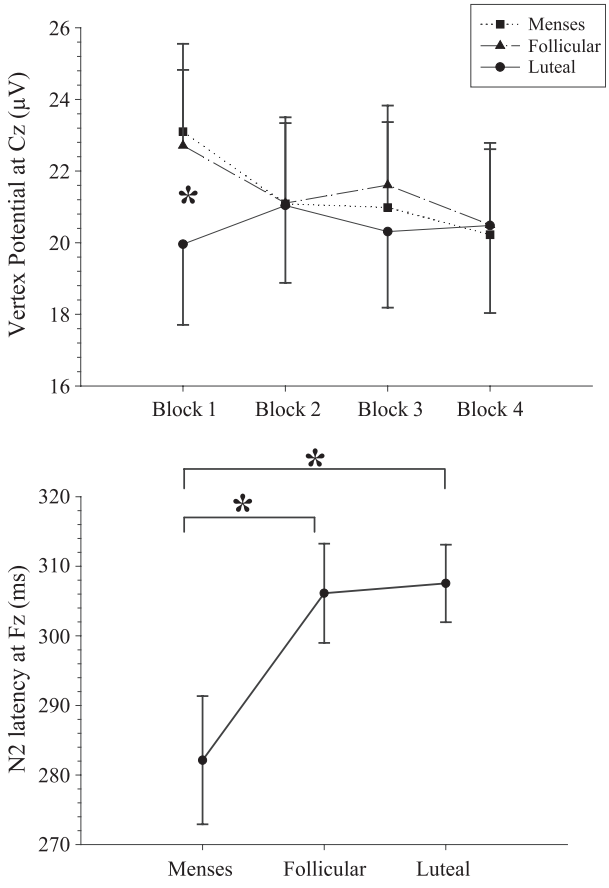

Fig. 2. Peak-to-peak amplitude of the vertex potentials at Cz across the four blocks of habituation and across the menstrual cycle (top panel, $n = 15$) and N2 latency (bottom panel, $n = 17$) at Fz across the menstrual cycle. Bars represent the standard error. *Significant difference in Bonferroni-adjusted Student's t tests.

a smaller vertex potential at Cz during the first block of habituation in the luteal phase in comparison to menses and the follicular phase.

No significant effects of the menstrual cycle were detected for latency or amplitude of N1 or P2.

Oddball paradigm: Late ERPs

N2: An overall ANOVA with the repeated-measures factors "Phase" and "Electrode position" was performed to determine the electrode site where each ERP component had its maximum. Afterwards, a one-way ANOVA with the repeated-measures "Phase" was performed for amplitude and latency measures of each ERP component at the electrode position where the respective amplitude was maximal.

An ANOVA revealed a main effect for "Electrode position" [$F(2,32) = 12.10$, $P < 0.001$, $\varepsilon = 0.816$] with Fz as the electrode position with the highest amplitude. Further ANOVAs at this electrode position detected a significant effect for "Phase" for the N2 latency [$F(2,32) = 6.61$, $P < 0.01$, $\varepsilon = 0.745$; s. Fig. 1, bottom panel]. Bonferroni-corrected Student t tests ($P < 0.017$) revealed significantly longer N2 latencies during the follicular and luteal phase as compared to menses [follicular phase: $t(16) = 3.10$, $P < 0.05$; luteal phase: $t(16) = 2.62$, $P < 0.05$, s. Fig. 2, bottom panel]. Descriptively, 7 of 17 subjects showed a shortened N2 peak latency in menses in comparison to follicular and luteal phases.

No significant effects of the menstrual cycle could be detected on the P3 or the Slow Wave. In addition, no significant effects were apparent for reaction time or errors (data not shown).

Correlation between gonadal steroids and ERPs

A correlational analysis was conducted between the hormonal and electrophysiological measures. For this analysis, each test session (three per subject) was used as one individual data point in a Pearson correlation analysis. The correlation between estradiol as well as progesterone and the vertex potential in the first block of habituation reached statistical significance (estradiol/vertex potential: $r = -0.463$, $P < 0.001$, $n = 45$; progesterone/vertex potential: $r = -0.404$, $P < 0.01$, $n = 45$). No additional significant correlations were detected.

Discussion

We observed changes in early as well as late components of the ERPs representing automatic and controlled processing of stimulus information in different phases of the menstrual cycle. In the luteal phase, the vertex potential was significantly diminished compared to menses and to the follicular phase in the first of four blocks. This result indicates a diminished orienting response in the luteal phase. This suggests that, during high estradiol and progesterone levels, the involuntary cortical arousal response to incoming stimuli is reduced.

The orienting response (Sokolov, 1963, 1990), which appears to be blunted during the luteal phase, is described as a complex of physiological and behavioral changes. The orienting response facilitates stimulus input and processing, conditioning, cortical activity, and gross motor action and is therefore of importance for perception and learning. Consequently, women should display difficulties in these kinds of tasks during the luteal phase. Because there is no difference between the vertex potential in menses and the follicular phase, this effect seems to be caused by progesterone, which also increases in concentration solely during the luteal phase. Indeed statistical analyses revealed a negative correlation between progesterone concentration and the vertex potential in the first block of the habituation paradigm. However, a similar negative correlation was observed for estradiol. Thus, both hormones, estradiol and progesterone, might reduce the vertex potential. Alternatively, these negative correlations could also imply that low levels of estradiol and progesterone are responsible for a large vertex potential.

The second finding of the current study is that, at times of low sex hormone concentrations (during menses), the mental classification of deviant stimuli appears to be faster (shorter N2 latency), whereas it was slower during the follicular and luteal phases. However, no significant correlation with either estradiol or progesterone was detected. In addition, no performance differences (reaction time or errors) were observed across the menstrual cycle, but this task might have been too easy. While this finding fits to the known inhibitory actions of progesterone, it appears to be in contrast to the reported neuroexcitatory effects of estradiol as demonstrated in humans with EMG (Smith et al., 1999, 2002) and therefore needs experimental replication. At least the observation by Tasman et al. (1999) of a prolonged P3 latency during the ovulatory phase appears to be in line with the current findings.

We, of course, cannot exclude the possibility that the menstrual cycle-dependent alterations in basic hearing parameters (see introduction) could have indirectly caused the ERP effects observed in the present study. However hearing sensitivity is worse during menses than during the luteal phase (McFadden, 1998), while the orienting response in the current study was blunted during the luteal phase compared to menses and follicular phase. Future auditory ERP studies should include tests of hearing sensitivity in their experimental paradigms (see McFadden, 1998).

As to previous ERP studies, there is no experiment known to us which examined changes in habituation of the vertex potential over the menstrual cycle. Usually, only the oddball paradigm was used to investigate changes in ERPs, and no significant effect on the P3 amplitude was detected when neutral stimuli were used (Fleck and Polich, 1988; Kluck et al., 1992; Tasman et al., 1999). These previous nonsignificant findings are further supported by the present study.

In sum, the current study observed effects on early and late ERPs over the course of the menstrual cycle. While previous studies had suggested that only ERPs to sexually relevant stimuli change across the menstrual cycle, the present study documents that also some ERPs to neutral stimuli are influenced. Future ERP studies therefore need to be attentive to the issue of menstrual phase when comparing different groups of women or when studying women in a repeated measurement design. The interesting observation of a missing orienting response in the habituation paradigm during the luteal phase should be further investigated using electrophysiological as well as behavioral measures. Moreover, these findings should be extended to women using oral contraceptives.

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