Indian J Physiol Pharmacol 2013; 57(3) : 261–269

NO DIFFERENCE IN THE OMITTED STIMULUS REACTION TIME TASK DURING THE MENSTRUAL CYCLE : A MULTISENSORY STUDY

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(Received on June 11, 2012)

Abstract : Pharmacological studies are currently performed in men and not in women due to the absence of methodological or conceptual information concerning the effects of the menstrual cycle. This is the first study in which three different sensory stimuli were applied to females in an omitted stimulus reaction time (OSRT) task during three phases of the menstrual cycle. Eleven college volunteers with regular menstrual cycles responded to lateralized trains of visual, auditory, and somatosensory stimuli. A participant's OSRT was recorded for each trial performed during the menstrual (day 2-3), follicular (day 7-8), and luteal (day 21-22) phases. The results showed that the ovarian cycle has no effects on the OSRT task in any of the sensory modalities, but the reaction to the missing auditory stimuli was found to be systematically faster than the reactions to the visual and somatosensory stimuli ($P<0.002$). Thus the OSRT is affected by sensory modality but not by the normal menstrual cycle.

Key words : menstrual, reaction time, omitted stimulus, multisensory

INTRODUCTION

An increased awareness of the inclusion of the female in drug abuse research has brought increased scientific interest in the potential influence of the menstrual cycle phase on the responses to neuroactive drugs (1, 2). Many studies have used reaction time (RT) tasks to test the effects of sex hormones or the menstrual cycle (3, 4). Some evidence supports the hypothesis that a simple auditory RT is influenced by the fluctuating levels of sexual hormones across the normal menstrual cycle, which is highest during the premenstrual phase and lowest during the mid-secretory phase (5). Nevertheless, many

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papers report no differences in performance between the different phases of the menstrual cycle (6, 7, 8, 9, 10, 11, 12).

An omitted stimulus task presents a recurrent stimulus that requires an immediate response to the omission of the stimulus. Unlike the reaction to the presentation of a stimulus, the reaction to an omitted stimulus is generated by an endogenous process and is considered to require additional cognitive processes (13, 14). To date, no studies have analyzed the effect of the menstrual cycle on an omitted stimulus reaction time (OSRT) task through the application of three sensory modalities to the same person (14). Multisensory experiments are important because these could provide valuable new information on the possible differences in the sensitivity to steroids that fluctuate during the menstrual cycle between different sensory modalities. Studies that utilize reaction time tasks have showed that auditory stimuli produce faster responses than visual or tactile stimuli (14, 15, 16, 17, 18, 19, 20).

Previous research in males indicates that moderately increasing blood alcohol concentrations can impair the visual and auditory OSRTs without affecting the somatosensory OSRT (18). These interesting results are missing in females because, in part, we do not know how the OSRT task could be influenced by the menstrual cycle. Although previous research has reported that hormonal fluctuations have important impacts on the functional cerebral asymmetries (21, 22, 23), other studies have not observed this laterality (24, 25). To date, no research study has applied lateralized sensory stimuli in the OSRT task.

The aim of the present research study was to determine whether there is any alteration of OSRT task across the normal menstrual cycle when trains of lateralized visual, auditory, and somatosensory stimuli are applied. According to previous research (11, 12, 14, 18, 19, 24, 25), we hypothesize that the auditory stimuli will produce a shorter OSRT than the visual and the somatosensory stimuli and that no changes or asymmetries will be observed between the phases of the menstrual cycle. This study will thus test the OSRT in response to the administration of acute doses of alcohol in women.

METHODS

Participants

Eleven healthy college students with regular menstrual cycles participated in the study (5). The right-handedness was assessed using the Shimizu and Endo (26) questionnaire. All of the participants were aged between 18 and 25 years (mean of 21.8±2), and none had any history of nervous system diseases or motor disability. Subjects with well-defined PMS, any gynecological problems, irregular cycles, or any drug consumption (e.g., hormonal treatment and psychotropic drugs) were excluded from the study. The subjects were instructed to abstain from the consumption of any stimulant drink or alcohol for at least 24 hours before their arrival at the lab and participation. All of the participants volunteered for the study and were informed of the procedures before completing an informed consent form and reporting their age and health history. The protocol was reviewed and approved by the Ethics

Committee of the University of Campeche.

Apparatus and materials

The OSRT task used in this study was similar to that used in prior research (14). In this task, trains of visual, auditory, and somatosensory stimuli were applied at 2-s intervals (0.5 Hz). Only few differences in the visual stimuli must be observed. Briefly, the visual stimuli consisted of light flashes (white light, 10 μs, 1.5×10^{-3} lumen/sec/cm^2) delivered by an optic fiber connected to a photic stimulator (GRASS PS33Plus). The center of the optic fiber tip (4 mm in diameter) was placed 30 cm in front and 30 cm lateral (left or right) from the participant's eyes to ensure the use of the peripheral visual field of each eye (as binocular vision). An electrical stimulator (GRASS S48) triggered the auditory stimuli, which were presented as 10-ms "clicks" to one of the ears through headphones. The auditory thresholds of each ear were determined and then set at 20 times the threshold to ensure that the clicks would be clearly heard. The somatosensory stimuli were administered by two disc electrodes (GRASS F-E5SH) that were placed on the medial finger of the left or the right hand and were connected to the electrical stimulator through a stimulus isolation unit (GRASS SIU5). The somatosensory thresholds were determined for each hand and then set at 1.2 times the threshold, which was well below the pain threshold.

The responses to the termination of a train of stimuli in each sensory modality were also measured. At the outset of a trial, a response key was depressed with the ipsilateral thumb to the side of the stimuli until the train of stimuli ceased, at which point the key was released. The response key was connected to an AC amplifier (GRASS P511). Each stimulus and the release of the response key generated clear changes in the voltage compared with the baseline, and these changes were collected online using a computer fitted with an analog-to digital converter and analyzed using the ACQKNOWLEDGE software (BIOPAC Inc.).

The OSRT was measured as the time between the occurrence of the first missing stimulus and the release of the key. A participant's OSRT was recorded during each visual, auditory, and somatosensory task that was performed during three phases of the menstrual cycle: the menstrual (day 2-3), follicular (day 7-8), and luteal (day 21-22) phases.

Procedure

The subjects who met the inclusion criteria were subjected to reaction time testing during three occasions within one month. The phase during which the first test occurred (menstrual, follicular, or luteal phase) was counterbalanced. After an individual was subjected to the first test, she was scheduled to return to the lab for the next test according to her cycle. The thresholds and intensities were then determined, and the participant was seated in front of a table, where the response key was within easy reach. The task instructions were identical for each sensory modality. The participants were told to hold down the key at the beginning of each trial until they realized that the train of stimuli had ceased, at which point they were to immediately release it.

The participants wore headphones during all of the tests and rested their heads on a chin support that fixed their sight on a blue spot, which was 6.5 cm in diameter, on the wall 79 cm in front of the head. The participants were instructed to maintain their gaze on the central fixation point at all times. Each trial was preceded by a verbal "ready" signal. The number of stimuli (visual, auditory, or somatosensory) in a train during a given trial varied between 5 and 20 in a predetermined pseudorandom fashion. A test of a sensory task included the administration of five trials on each side (left and right; for a total of 10), and the relationship between the side of the stimuli and the response hand was found to be always ipsilateral. The test was completed in approximately 10 minutes and was immediately followed by the next test, which presented a different sensory stimulus. Thus, the test of all three sensory tasks was completed in approximately 30 minutes. The administration of additional trials would extend the duration of a test and possibly introduce boredom and fatigue effects. The starting sensory modality and the side of the stimuli were counterbalanced across the entire sample.

Data analyses

The scores of any trial in which the response occurred before or coincided with the first missing stimulus in a train were discarded. In total, 2.6% of the trial scores were rejected. For each test of a sensory task, a participant's OSRT was averaged over the trials presented on each side. The SPSS software (SPSS, 2001) was used to analyze the OSRT measures using a 3 (cycle, i.e., menstrual, follicular, and luteal) × 3 (sensory, i.e., visual, auditory, and somatosensory) × 2 (sides, i.e., left and right) repeated measures analysis of variance (ANOVA). To correct for the chance occurrence of a result with $P<0.05$ when tests are repeated, a Bonferroni correction was used to adjust the alpha level.

RESULTS

All data were transformed to the log to meet assumptions of normality (Kolmogorov Smirnov test) and equal variance (Levene test). A 3 (cycle) × 3 (sensory) × 2 (side) ANOVA of the OSRT showed that the main effect was obtained through the sensory factors ($F_{2,20} = 18.81$, $P<0.0001$, $\eta^2 = 0.653$). No main effects were detected for cycle ($F_{2,20} = 3.44$, $P>0.052$, $\eta^2 = 0.256$) or the side of the presentation ($F_{1,10} = 0.151$, $P>0.706$, $\eta^2 = 0.015$), and no interactions were significant ($P>0.086$). The paired comparisons with the Bonferroni correction showed that the response to the auditory task was faster than those obtained with the visual task ($P<0.001$) and the somatosensory task ($P<0.002$). No difference was found between the visual and the somatosensory tasks ($P>0.551$). The non-significant cycle and side effects obtained through ANOVA showed that the mean (SD) OSRT to the tasks were 939.5 ms (278) during the menstrual phase, 959.1 ms (272.7) during the follicular phase, and 814.5 ms (218.8) during the luteal phase. The left and right side presentations were 903.1 ms (221.2) and 905.7 ms (238.5), respectively. Table I shows the mean (SD) of each of the measures.

DISCUSSION

The present research is an extension of

TABLE I: Mean (SD) measures in milliseconds of the omitted stimulus reaction time (OSRT) to different sensory stimuli in the three phases of the menstrual cycle and the two sides. N=11

Sensory Modality	*Side*	*Menstrual M (SD)*	*Follicular M (SD)*	*Luteal M (SD)*
Visual	Left	937.3 (270.0)	1,012.7 (307.6)	784.5 (237.3)
Visual	Right	991.8 (308.9)	980.9 (362.9)	879.1 (244.5)
Auditory	Left	851.8 (310.8)	910.0 (292.2)	714.5 (244.9)
Auditory	Right	819.1 (352.9)	833.6 (324.9)	743.6 (242.8)
Somatosensory	Left	1,034.5 (314.5)	1,030.9 (390.3)	851.8 (291.2)
Somatosensory	Right	1,002.7 (328.6)	986.4 (320.1)	913.6 (238.3)

M = mean; SD = standard deviation.

our previous studies on the OSRT task under drug-free and acute doses of alcohol in college volunteers using trains of sensory stimuli (14, 18, 19, 27, 28, 29). To understand the impact of alcohol or other drugs on the sensory motor system of the female, it is necessary to first determine whether the menstrual cycle is able to affect the performance of the subjects under drug-free conditions.

Although the OSRT paradigm is somewhat uncommon, it bears a resemblance to some real-life situations, such as those that require a reaction to the cessation of a flashing stoplight or to a missing beep on a heart monitor. The omitted stimulus task is considered to require additional cognitive functions, such as sustained attention and the discrimination of the cessation of a temporal stimulus sequence, that are not involved in simple or choice reaction time tasks (14). In this study, we tested whether the OSRT task is altered when trains of lateralized visual, auditory, or somatosensory stimuli are applied across the menstrual cycle. The results clearly showed that the ovarian cycle had no effects on the OSRT task in any of the three sensory systems used, but the sensory modality affected the OSRT. In support of the hypothesis, the auditory stimuli produced faster responses than the visual or the somatosensory stimuli with no hemispheric asymmetries (14, 18, 19, 20, 24).

An important challenge in neuroscience is the identification of how information from the external world, which is perceived through the different senses and processes in the sensory-specific cortical modules, is compared, integrated, and evaluated to obtain an accurate, meaningful, and coherent perception of the external events (17) and how this perception is disturbed by the presence of steroid hormones or drugs. To understand the exact role of the sensory processes on behavior, it is necessary to study the nervous system´s capacity to integrate information across the normal menstrual cycle. The brain integrates and converge signals of many sensory modalities at the brainstem and cortical sites, where individual neurons respond through specific patterns of activation that depend on the nature of the stimulus complex and the intrinsic properties of the neuron (30). The within-subject design in the OSRT paradigm with three sensory modalities during the menstrual cycle phases provided valuable information on the sensitivity of the sensory systems to female steroid fluctuations. This

information is important because the responses were evaluated under the same experimental conditions in each subject, which provided the opportunity to establish comparisons and/or hierarchies among the sensory modalities during the menstrual cycle phases. In addition, such data will be useful in future alcohol and neuroactive drug studies performed in females. The faster processing of auditory signals is in agreement with the results obtained by Rousseau and Rousseau (15), Naito et al. (16), Thesen et al. (17), and our previous work (14, 18, 19). It is hypothesized that this faster response time depends on differences in the timing operations of the sensory-specific modules that are required to reach a time criterion and ultimately trigger a behavioral response (15).

Nene and Pazare (5) found that the simple reaction time to auditory stimuli is highest during the pre-menstrual phase and lowest during the mild secretory phase. Other studies have also found faster RTs during the luteal phase of the cycle (9, 10). The present research does not support these findings but is in agreement with other studies that have shown that the menstrual cycle has no effects on behavior (6, 7, 8, 9, 10, 11, 12). The scientific reasons for this discrepancy in the effects of the menstrual cycle on performance or cognitive processing have not been fully established (31). As in the study conducted by Nene and Pazare (5), this research study did not measure the hormonal levels during the cycle, but, based on existing knowledge, it is possible that the OSRT task might be affected by the normal menstrual cycle. The absence of such effects supports the continuation of OSRT studies of alcohol and other drugs in female subjects.

It is known that ovarian hormones interact with neurotransmitters (dopamine and gamma-aminobutyric acid) to modulate the effects of ethanol (32), and previous studies have shown that the effects of acute alcohol in women are controversial and depend on the variable under study, e.g., Linnoila et al. (33) studied the psychomotor performance and reported that the dose-response relationships of alcohol differ between the different menstrual cycle phases. In contrast, no cyclic differences were observed in the pharmacokinetics (34), consumption (32), and absorption of alcohol (35), or in mood and behavior under intoxication (34, 35). At present, many toxicological research studies are performed only in males due to the absence of reports on the effects of the ovarian cycle on the biochemical, psychological, or physiological variables (36), although some authors argue that that female must not be excluded from studies on the effects of alcohol on behavior because certain behaviors affected by alcohol are not affected by the menstrual cycle phase (34). Studies on male subjects in our lab have shown that the impairment of the acute doses of alcohol on the OSRT is dependent on the sensory stimulus involved in the task (18).

The results obtained in the present research are in agreement with the findings reported by Brick et al. (34) and others (9, 10, 11, 12) because no menstrual effects were obtained in the omitted stimulus task performance. Thus, it will be interesting to perform alcohol experiments in female subjects through the application of multiple sensory stimuli in the OSRT task (36).

In this study, lateralized stimuli were applied because it is known that the

fluctuating levels of hormones during the menstrual cycle are able to affect the timing responses of the right and the left hemispheres (37, 38). It is widely accepted that the left hemisphere (right hand) exhibits greater expertise in both the production and perception of language and in motor control, whereas the right hemisphere (left hand) has a greater degree of engagement in non-verbal, spatial processing, attention, movement planning, and time estimation (39). In the present research study, no lateralized responses were observed, and this finding is in agreement with the results reported by Hausmann et al. (23). This finding is most likely because the greater motor speed performed by the right hand was balanced with the greater attention, time estimation, and movement planning from the right hemisphere to the left hand. However, the absence of asymmetry is not in agreement with the results obtained by Whitehead (40), who found faster responses to targets presented directly to the right hemisphere compared with targets presented to the left hemisphere when the subjects were required to maintain attention continuously for longer than 10 seconds, and the results obtained by Pardo et al. (41), who reported an increased cerebral blood flow in the right frontal lobe after the subjects maintained attention for long periods. Our OSRT task is highly demanding of all of these processes. Thus, additional experiments will be necessary to firmly establish the role of the asymmetric functions on the omitted stimulus tasks with different sensory stimuli in male and female subjects.

The participation of Blanca Alicia Gonzalez Castillo in this study as part of her Psychology Degree Thesis, is gratefully acknowledged.

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