Psychoneuroendocrinology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection

Annett Schirmer[a,*], Nicolas Escoffier[a], Qing Yang Li[b], Hui Li[c], Jennifer Strafford-Wilson[d], Wan-I Li[e]

[a]*Faculty of Arts and Social Sciences, Department of Psychology, National University of Singapore, 9 Arts Link, Block AS4, Level 2, Singapore 117570, Singapore*
[b]*Faculty of Arts and Sciences, Department of Psychology, University of Georgia, USA*
[c]*The Children's Hospital, Zhejiang University of Medicine, China*
[d]*Department of Psychology, Emory University, USA*
[e]*Department of Physiology and Pharmacology, University of Georgia, College of Veterinary Medicine, USA*

Received 12 October 2007; received in revised form 17 February 2008; accepted 20 February 2008

KEYWORDS
Attention;
Estrogen;
Frontal cortex;
Prosody;
Sex differences;
Emotion;
Mismatch negativity

Summary
Prior research revealed sex differences in the processing of unattended changes in speaker prosody. The present study aimed at investigating the role of estrogen in mediating these effects. To this end, the electroencephalogram (EEG) was recorded while participants watched a silent movie with subtitles and passively listened to a syllable sequence that contained occasional changes in speaker prosody. In one block, these changes were neutral, whereas in another block they were emotional. Estrogen values were obtained for each participant and correlated with the mismatch negativity (MMN) amplitude elicited in the EEG. As predicted, female listeners had higher estrogen values than male listeners and showed reduced MMN amplitudes to neutral as compared to emotional change in speaker prosody. Moreover, in both, male and female listeners, MMN amplitudes were negatively correlated with estrogen when the change in speaker prosody was neutral, but not when it was emotional. This suggests that estrogen is associated with reduced distractibility by neutral, but not emotional, events. Emotional events are spared from this reduction in distractibility and more likely to penetrate voluntary attention directed elsewhere. Taken together, the present findings provide evidence for a role of estrogen in human cognition and emotion.

*Corresponding author. Tel.: +65 65168703; fax: +65 67731843.
E-mail address: schirmer@nus.edu.sg (A. Schirmer).

0306-4530/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2008.02.010

1. Introduction

Across past millennia, it has been an accepted fact in many cultures and religions that men and women differ in the way they think and feel. Moreover, philosophers, priests, and scientists have speculated that the mental qualities of the female sex are inferior to that of the male, thereby justifying female oppression (Walford, 1871). These views have been slowly changing with greater need for female employment, particularly after major wars, as well as the efforts of feminist movements (Kimura, 1999). Additionally, psychological investigations revealed that for most cognitive abilities, variability within a sex is greater than variability between the sexes. Hence, the idea that men and women differ fundamentally has been overturned and some now propagate the view that men and women are equivalent in their cognitive and emotional "make-up" (Fausto-Sterling, 1992; Favreau, 1993; Kimmel, 2003).

While this latter, egalitarian view has helped women gain independence and status in society, it turns a blind eye to sex specific specializations of certain mental functions that have been discovered over the past decades. For example, there are sex differences in a number of cognitive processes. Electroencephalography (EEG) research revealed that the N400, a negative deflection elicited in response to semantic incongruity, is larger in women than in men, suggesting deeper semantic analysis (Wirth et al., 2007). In line with this, women typically show enhanced memory for verbal information (Stumpf and Jackson, 1994). Females also excel in the memory for objects and object positions, whereas males perform better at tasks that involve the mental rotation of objects in space or that test mathematical aptitude (Campbell, 1991; Watson and Kimura, 1991; Galea and Kimura, 1993; Eals and Silverman, 1994; Stumpf and Jackson, 1994).

In addition to these cognitive effects, men and women differ in emotional processes. They differ in the engagement of emotion circuits in the brain (for a review see Hamann and Canli, 2004). Greater right amygdala activation to emotional material has been observed in women, whereas greater left amygdala activation has been observed in men (Canli et al., 2002; Cahill, 2003). Furthermore, women show greater physiological reactivity than men to emotional material, in particular if the material is of negative valence (Bradley et al., 2001; Chentsova-Dutton and Tsai, 2007), of social relevance (Schirmer et al., 2007) or presented outside the focus of attention (Schirmer et al., 2005).

Among the potential biological mechanisms that could contribute to sex differences in human cognition and emotion, the action of sex steroids has received most attention. In particular, estrogen plays an important role (for review see Sherwin, 2003; Genazzani et al., 2007). Although synthesized in peripheral systems such as the gonads, liver or adrenal gland, through blood circulation, estrogen passes the blood-brain-barrier and binds to receptors in various parts of the brain, including frontal and medial temporal lobe structures (Goldstein et al., 2001; Ostlund et al., 2003). Effects in the nervous system have been associated with two signaling mechanisms. One induces slow but long-term changes and involves gene transcription via interaction with nuclear receptors. The other, non-genomic, mechanism appears to be mediated by receptors in the plasma membrane and triggers faster and more dynamic changes in brain function (Genazzani et al., 2007). Both mechanisms affect a wide range of neuropeptide and neurotransmitter systems such as the serotonergic, adrenergic and the opiate systems (Fink and Sumner, 1996; Craft et al., 2004). Additionally, changes in cytoarchitecture, including increased spine density of hippocampal neurons, have been reported after estrogen treatment (Gould et al., 1990).

In line with these neurochemical and cytoarchitectural changes, a number of animal studies provided evidence for estrogen effects on cognition and emotion. For example, the injection of estrogen in female rats right after birth induces sexual defeminization (McEwen, 1987). As adults, these rats perform better than untreated female rats in tasks that typically elicit a male advantage (e.g., spatial; Williams et al., 1990). Later in the life, estrogen administration or cycle dependent increases in estrogen do not defeminize. In contrast, they may impair memory for spatial information (Sutcliffe et al., 2007) while enhancing aspects of learning and memory that are typically better in females than in males (Leuner et al., 2003). An enhancing effect of estrogen has also been demonstrated for emotional reactions such as fear (Jasnow et al., 2006).

Research in humans investigated the effects of menstrual cycle or hormone replacement therapy (HRT). Research on menstrual cycle revealed varied results most likely due to differences in the definition of the menstrual cycle phases and the co-variation of other hormones (e.g., progesterone; for a review see Kimura, 1999; Sherwin, 2003). Nevertheless, there is some suggestion that women perform better during high- as compared to low estrogen phases on tasks that normally elicit a female advantage (e.g., verbal memory; Rosenberg and Park, 2002). The reverse seems true for tasks that normally elicit a male advantage (Hampson, 1990a, b; but see Gordon and Lee, 1993; Rosenberg and Park, 2002). Furthermore, there is some suggestion that emotional processes, such as the recognition of fear, are enhanced during high estrogen phases (Pearson and Lewis, 2005). Researchers tackling the effects of estrogen via HRT in post-menopausal women observed better performance under estrogen treatment for a wide range of cognitive skills including attention and concentration, distractibility, inhibition of inappropriate responses, and verbal memory (Resnick et al., 1997; Jacobs et al., 1998; Steffens et al., 1999; Henderson, 2000; Keenan et al., 2001). However, not all studies could replicate these effects and none have looked at the role of HRT in emotional responses (for a review see LeBlanc et al., 2001).

Taken together, the above findings suggest that estrogen may play a role in shaping the way humans think and feel. However, conclusions are still premature due to inconsistent results and methodological problems. Findings from HRT research apply to a changed hormonal environment and may be specific to the aging brain. Existing studies on cycle dependent changes in younger women are based primarily on verbal reports rather than on actual estrogen measurements and hence lack in accuracy. To address these issues, the present study measured estrogen levels in young human adults and correlated the obtained values with an electrophysiological measure of auditory change detection. The measure used here is an event-related potential (ERP)

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

component termed mismatch negativity (MMN). Paradigms that elicit an MMN typically engage participants in reading a self-selected book or watching a silent, subtitled movie while an auditory sequence is presented over headphones (for a discussion on subsidiary tasks see Muller-Gass et al., 2005). The unattended auditory sequence consists of standard sounds that are rarely and unpredictably interrupted by deviant sounds differing from standards in one or more acoustic properties (e.g., pitch, amplitude). Subtracting the ERP of standards from that of deviants reveals a negativity that peaks around 200 ms following stimulus onset and that has a fronto-central scalp distribution (Näätänen et al., 1978; Sams et al., 1985). This negativity, termed MMN, is larger the more salient or perceptible the difference is between standard and deviant events. It has been proposed to reflect the updating of a sensory memory trace and thus a mechanism by which individuals notice change in their environment (for a review see Näätänen et al., 2005). Additionally, MMN studies revealed a link between the MMN and attentional shift towards the change (Näätänen and Michie, 1979; Tse et al., 2006). However, as not every detection of change triggers an attentional shift, it has been proposed that the link between the MMN and attention maybe only indirect. Specifically, only MMN amplitudes that pass a critical threshold and hence reflect the detection of a salient change may be linked to attentional reorientation (Näätänen, 1992; Kujala et al., 2007; Shalgi and Deouell, 2007).

The MMN has found wide experimental and clinical applications. For example, it has been used to study musical processing in musicians and non-musicians (Koelsch et al., 1999) or speech perception in native and non-native listeners (Näätänen et al., 1997), in children and preborn infants (Novitski et al., 2007). Recently, it has also been employed in the study of vocal processing in men and women (Schirmer et al., 2005, 2007). In this line of research, participants listened passively to a sequence of non-meaningful syllables that contained rare changes in speaker tone of voice—also referred to as prosody. Specifically, a neutrally spoken syllable sequence was occasionally interrupted by an emotionally spoken syllable, whereas an emotionally spoken syllable sequence was occasionally interrupted by a neutrally spoken syllable. Subtracting emotional standards from emotional deviants and neutral standards from neutral deviants revealed an MMN for emotional and neutral vocal change, respectively. In women, the MMN to emotional vocal change was larger than the MMN to neutral vocal change indicating that women discriminate emotional and neutral vocalizations presented outside the focus of attention and that emotional vocalizations are more likely than neutral vocalizations to cross the threshold needed for attention capture. In contrast, the MMN in male listeners was comparable for emotional and neutral vocal change suggesting that both events are equally salient (Schirmer et al., 2005, 2007). Moreover, a direct comparison of MMN amplitudes between men and women revealed enhanced responses to emotional vocalizations as well as reduced responses to neutral vocalizations in women relative to men (Schirmer et al., 2005, 2007). Thus, two potential mechanisms may be implicated in the observed sex effect. First, in line with other emotion research (Bradley et al., 2001; Chentsova-Dutton and Tsai, 2007), the detection of emotionally relevant change in the environment may be enhanced in women relative to men. If estrogen contributes to this enhancement, one would expect a positive correlation between estrogen and the MMN amplitude elicited by emotional change. A second mechanism can be inferred from the fact that the MMN amplitude elicited by neutral change tended to be smaller in women than in men. This suggests that women are less likely than men to detect neutral change in the environment which may have a positive effect on their distractibility. Based on evidence from HRT (e.g., Henderson, 2000), also this latter effect could be a function of estrogen. However, if true, this should be reflected in a negative correlation between estrogen and MMN amplitude.

In sum, the present study aimed at elucidating the relationship between estrogen and the detection of emotional and neutral change in speaker tone of voice. Based on previously observed sex differences in vocal processing and research on the effect of estrogen on emotion and cognition we predicted a significant correlation between estrogen values and the MMN elicited to vocal change. For emotionally relevant change, this correlation should be positive indexing enhanced sensitivity to emotional information with increasing levels of estrogen. In contrast, neutral change in tone of voice was expected to elicit a negative correlation between estrogen and the MMN indexing reduced sensitivity to neutral, irrelevant information.

2. Methods

2.1. Subjects

Sixty-six students of the University of Georgia were invited to this study and received course credit for participation. Three participants were excluded due to technical problems during data acquisition. Two more participants were excluded because more than one-third of the EEG recording was artifactual. A standard lab questionnaire was used to record variables of interest such as participant sex, age, medical problems and use of oral contraceptives (OCs). Of the participants included in the study, 37 were female (mean age = 18.61, SD 1.07) and 24 were male (mean age = 19.15, SD 1.42). Only 10 of the female participants indicated that they were not currently using OCs. All participants had normal or corrected to normal vision and were without any known hearing impairments.

2.2. Materials

A female speaker produced the syllables ‘‘dada’’ several times with angry and neutral prosody. Among the available emotional intonations, anger was selected because its processing is well documented in the literature (e.g., Grandjean et al., 2005) and it is known to elicit sex differences (Schirmer et al., 2005, 2007). A group of six listeners (three males) classified each stimulus as very angry, angry, neutral, or emotional (with the emotion not being anger). Two stimuli that had been unanimously identified as ‘‘very angry’’ and ‘‘neutral’’ were selected for the study. The angry and neutral stimuli were equally long (i.e., 557 ms) and loud (i.e., 67 dB max, 56 dB mean), but differed

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

with respect to other acoustic parameters (e.g., F_0, spectral energy). Equal stimulus length was achieved by sampling several vocalizations for each category and by instructing the speaker to keep an equal rhythm. Minor differences in stimulus duration were then edited using the CoolEdit 2000 Software from Syntrillium. Equal stimulus amplitude was achieved by employing the CoolEdit 2000 Normalization algorithm. Maximum and mean amplitude were determined with Praat (Boersma, 2001).

Stimuli were presented in two blocks with 1050 standards ($p = 0.875$) and 150 deviants ($p = 0.125$) in each block. There was a minimum of three and a maximum of 11 standards between deviants. The emotional and the neutral stimuli served as standards and deviants in two separate blocks. In one block, neutral syllables were presented as standards and emotional syllables as deviants. In the other block, emotional syllables were presented as standards and neutral syllables as deviants. Presenting the same syllables as both standards and deviants allowed us to investigate the MMN by comparing physically identical stimuli, thereby reducing the influence of acoustic differences between the neutral and the emotional conditions on MMN amplitude. Block order was counterbalanced across participants. The syllable onset to syllable onset interval in each block was 1200 ms.

2.3. Procedure

The procedure of this study was approved by the Institutional Review Board at the University of Georgia. Prior to the EEG experiment, participants were asked to provide between 10 and 20 ml of saliva using a straw and a plastic test tube. The test tube was subsequently sealed and stored in a −80 °C freezer. Participants were then seated in a comfortable chair facing a computer monitor at a distance of 1.15 m. They were told that they would hear a sequence of spoken syllables but that these syllables were unimportant and should be ignored. Participants were asked to attend to a silent, subtitled movie that they selected from a collection of movies available in the lab. The movie was played on a computer screen in front of the subject for the entire duration of the experiment. During the experiment, auditory stimuli were delivered over ear-insert headphones, which were connected to the sound card of the stimulus presentation computer. The sound volume of the sound card output was set at a comfortable level and kept constant for the duration of the experiment. Thus, each participant was exposed to the same set of stimuli presented under the same conditions.

The EEG was recorded from 64 electrodes mounted in an elastic cap according to the modified 10–20 system. The electro-oculogram (EOG) was recorded using four electrodes, which were attached above and below the right eye and at the outer canthus of each eye. Additionally, one recording electrode was placed on the nose tip. The data were recorded reference free using the ActiveTwo system from Biosemi with a 256 Hz sampling rate.

2.4. Data analysis

Estrogen: After collection, saliva samples were stored in a −80 °C freezer. For analysis, the samples were brought to room temperature, centrifuged at 1200 × *g* for 20 min and the clear top phase of the sample was pipetted into an appropriate test tube. Saliva samples were analyzed with high sensitivity, salivary estrodial enzyme immunoassay kits from Salimetrics Laboratories (www.salimetrics.com), using the procedure recommended by the company without any modifications. A standard curve was developed from a non-linear fit of hormone standards, using version 4.0 of Prism™ from Graph Pad (San Diego, CA, USA). The levels of estradiol were computed by fitting the optical density reading of each saliva sample to the obtained standard curve.

EEG: EEG data were processed with EEGlab (Delorme and Makeig, 2004). The scalp recordings were referenced against the recording from the nose and a 0.5–20 Hz bandpass filter was applied. The continuous data were epoched and baseline corrected using a 200 ms pre-stimulus baseline and an 800 ms time window starting from stimulus onset. Non-typical artifactual epochs caused by drifts or muscle movements were rejected via visual inspection of the data. Infomax, an independent component algorithm implemented in EEGlab, was applied to the remaining data and components reflecting typical artifacts (i.e., horizontal and vertical eye movements) were removed. Back-projected single trials were again screened for residual artifacts. Two difference waves were computed by subtracting neutral standards from neutral deviants and emotional standards from emotional deviants. Both difference waves revealed an MMN that peaked between 100 and 300 ms following stimulus onset. Accordingly, a 100–300 ms time interval was selected and peak latency of the MMN was determined for each electrode and participant. The resulting mean peak latency was 204 ms (SD 51 ms). A 40 ms time window centered around the peak of the MMN was used to obtain mean amplitudes. Mean amplitudes during this time window were subjected to an ANOVA with *Condition* (emotional/neutral), *Region* (anterior/posterior), and *Laterality* (left, center, right) as repeated measure factors and *Sex* and *OC use* as a between subject factor. The factors *Region* and *Laterality* comprised the following subgroups of electrodes: anterior-left: AF7 F5 FC5 C5, anterior-middle: AFZ FZ FCZ CZ, anterior-right: AF8 F6 FC6 C6, posterior-left: CP5 P5 PO7 O1, posterior-middle: CPZ PZ POZ OZ, posterior-right: CP6 P6 PO8 O2. This selection of electrodes insured that the tested subgroups contained equal number of electrodes while providing a broad scalp coverage that enabled us to assess laterally and centrally distributed effects. A linear regression model was used to assess the relationship between estrogen and MMN amplitudes. Correlation analyses were used for follow-up comparisons in males and females, respectively. For planned and post hoc comparisons that exceeded the number of degrees of freedom associated with the treatment source of variance a corrected *p*-value was used according to the modified Bonferroni procedure (see Keppel, 1991).

3. Results

ERP results are presented in Figures 1 and 2. To demonstrate that we could replicate previously reported sex differences in MMN amplitude (Schirmer et al., 2005, 2007) we

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

conducted an ANOVA with *Condition* (emotional/neutral), *Region* (anterior/posterior), and *Laterality* (left, center, right) as repeated measures factor and *Sex* and *OC use* [1] as a between subject factor. This analysis revealed a main effect of *Condition* ($F(1,59) = 4.93$, $p < 0.05$; $\eta_p^2 = 0.08$) and an interaction of *Condition* and *Sex* ($F(1,59) = 4.13$, $p < 0.05$; $\eta_p^2 = 0.07$). Additionally, the *Condition* × *Region* ($F(1,59) = 15.89$, $p < 0.01$; $\eta_p^2 = 0.17$) and the *Condition* × *Region* × *Sex* ($F(1,59) = 6.22$, $p < 0.05$; $\eta_p^2 = 0.1$) interactions were significant. Follow-up analyses of the 3-way interaction were conducted for each sex separately. A significant *Condition* × *Region* interaction ($F(1,35) = 15.92$, $p < 0.001$; $\eta_p^2 = 0.31$) in women indicated that the *Condition* effect was significant over anterior ($F(1,35) = 17.91$, $p < 0.001$; $\eta_p^2 = 0.34$) but not posterior sites ($p > 0.2$). In men, both the *Condition* × *Region* interaction and the *Condition* main effect were non-significant (all $ps > 0.2$). Neither the *Sex* main effect nor any interactions with *Sex* were modified by *OC use* (all $ps > 0.2$).

As expected, estrogen in women (20.13 pg/ml, SD 11.2) was higher than in men (7.8 pg/ml, SD 8.4). A linear regression model, regressing *Estrogen* against the anterior *MMN for Neutral* and *Emotional Change*, was used to assess the relationship between estrogen and the MMN. To control for potential effects of *OC use* and *Sex*, both variables were included in the model. No significant effects of *Estrogen* were observed for the *MMN for Emotional Change* ($p > 0.2$). However, the model with the *MMN for Neutral Change* as the dependent variable revealed a significant effect of *Estrogen* ($t = 3.93$, $p < 0.05$, $f^2 = 0.32$). Individual Pearson correlation analyses for each sex, partialing out *OC use* in females, indicated that both male ($r = 0.45$, $p < 0.05$) and female participants ($r = 0.47$, $p < 0.01$) demonstrated a significant negative correlation between the *MMN for Neutral Change* and *Estrogen* (see Figure 3). In contrast, the correlation between the *MMN for Emotional Change* and *Estrogen* was non-significant in male participants ($p > 0.2$) and merely approached significance in female participants ($p = 0.17$; see Figure 4).

4. Discussion

Over the past decades, researchers have accumulated substantial evidence for sex differences in cognition and emotion. While the majority of this evidence was derived from behavioral measures indicating quantitative differences between men and women (i.e., speed, accuracy; e.g., Galea and Kimura, 1993; Eals and Silverman, 1994), more recent application of neuroimaging measures additionally revealed qualitative differences. That is, men and women differ in the brain structures and processes they engage in a given task (Canli et al., 2002; Cahill, 2003; Federmeier et al., 2001; Schirmer et al., 2005, 2007; Wirth et al., 2007). The present study adds to this evidence. In accord with prior research (Schirmer et al., 2005, 2007), we found sex differences in the electrophysiological correlates of vocal change detection. Female but not male listeners showed a smaller MMN to neutral as compared to emotional vocal change.

While there may be a number of mechanisms contributing to the sex differences observed here, estrogen is particularly interesting because it has been previously implicated in cognition and emotion. Additionally, its effects on the nervous system are relatively well established suggesting both slow and fast changes in brain function (Genazzani et al., 2007). Given these reports, it is not surprising that estrogen should modulate performance in cognitive and emotional tasks. In line with this, we demonstrate here that estrogen is linked to listener sensitivity to unattended and unexpected change in speaker prosody. Implications of these findings for the role of estrogen in cognition and emotion are discussed below.

4.1. Estrogen and cognition

HRT, initially prescribed to protect health and feminity in aging women (Wilson, 1966), has been shown to also protect cognitive function. The discovery of this positive "side effect" has fostered interest in the role of estrogen for cognition. Subsequent studies comparing women on and off estrogen treatment revealed memory enhancements and a lower incidence of dementia (for a review see LeBlanc et al., 2001). Besides affecting memory, HRT studies also indicated an effect of estrogen on attention. For example, Henderson (2000) reported faster responses in a choice reaction time task and decreased distractibility under estrogen treatment. However, as many HRT studies have serious methodological limitations and some failed to observe the above effects (for a review see LeBlanc et al., 2001), the findings from this line of research are inconclusive. Thus, converging evidence from other research approaches is needed.

The present study aimed at providing such evidence by measuring the MMN in response to task-irrelevant auditory change and by correlating MMN amplitudes with individual estrogen values. The MMN is a well-established ERP component that is consistently elicited by unexpected auditory events (for a review see Näätänen et al., 2005). It has been shown to comprise two generators—one in the frontal lobe and one in the temporal lobe—which may serve different functions during change detection (Opitz et al., 2002; Tse et al., 2006). While the temporal generator is believed to reflect a sensory memory process that updates a stored representation of prior auditory input with new information (Näätänen, 1990), the role of the frontal generator is less clear (for a discussion see Opitz et al., 2002; Shalgi and Deouell, 2007). Some have associated the strength of the frontal generator with the reorientation of attention in response to change (Näätänen and Michie, 1979; Tse et al., 2006), whereas others have linked it to change detection difficulty and the need for additional processing resources (Opitz et al., 2002).

In line with the presumed role of the MMN for change detection and the HRT findings on attention (e.g., Keenan et al., 2001), we observed a negative correlation between estrogen and MMN amplitude to neutral deviants. Specifically, when engaged in watching a silent movie with

[1] Please note that some participants failed to disclose the use of OCs in the questionnaire. To nevertheless allow for these participants to be included in the statistical analysis, they were classified as OC users.

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

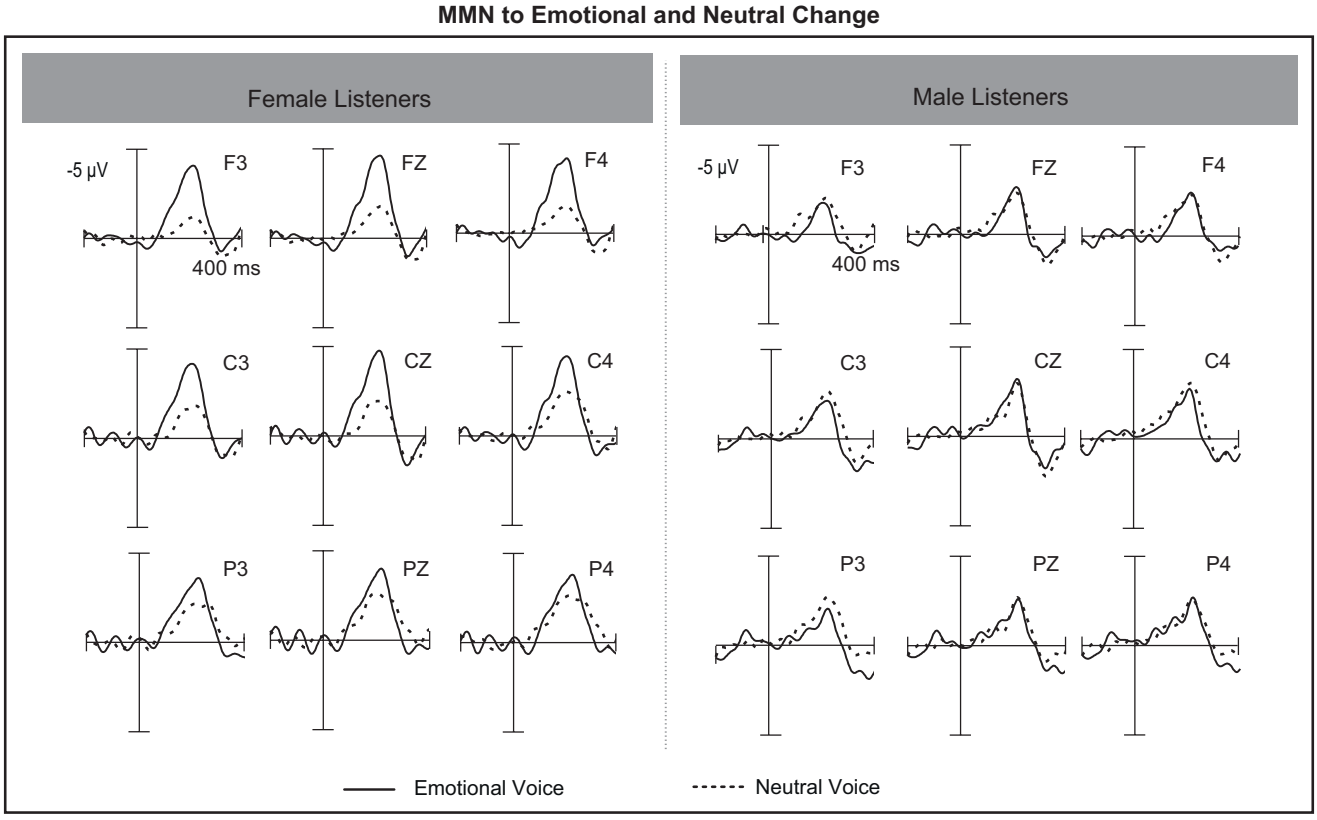

Figure 1 ERP difference waves time locked to stimulus onset. Difference waves were generated by subtracting neutral standards from neutral deviants (dotted line) and emotional standards from emotional deviants (solid line). The MMN is visible in both difference waves as a negative deflection peaking at around 200 ms.

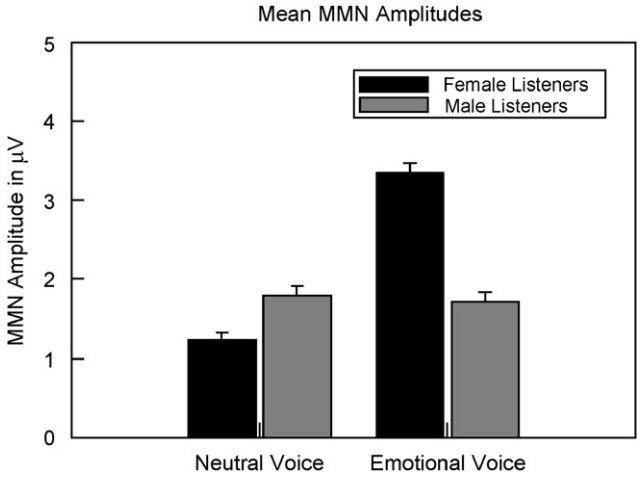

Figure 2 Mean MMN amplitudes and standard error for the neutral and emotional condition, respectively.

subtitles, participants with high estrogen showed a smaller MMN to task-irrelevant, neutral auditory deviants than did participants with low estrogen. This effect was localized over the frontal cortex, which is a major site of estrogen receptors in the brain (Perlman et al., 2005) and has been proposed to be the main modulator of estrogen effects on cognition (Keenan et al., 2001). Based on this and on what is known about the relationship between the MMN, sensitivity to environmental change and attention, one can conclude that estrogen—directly or indirectly—reduces the sensitivity to neutral, task-irrelevant information and thus the likelihood that this information attracts attention.

Interestingly, our data suggest that the effect of estrogen on the MMN is comparable in male and female listeners. However, because females have, on average, higher estrogen values than males, our results suggest that females are less sensitive than males to unattended neutral change. As a consequence their MMN may be smaller and less likely to cross the threshold for attention capture which may make them less distractible than males. Although sex differences in attentional function are less well studied than sex differences in other areas of cognition, some findings support this interpretation. For example, Osorio and colleagues (2003) found faster responses to visual targets in the presence of auditory distractors in women as compared to men. Likewise, girls before and around puberty outperform boys in tasks that require behavioral inhibition and selective attention (Klenberg et al., 2001). Moreover, females are less likely to suffer from attention deficit disorder than males (Stefanatos and Baron, 2007).

Besides attention, research on stimulus encoding and memory appears to be relevant for the present findings. Specifically, reduced distractibility mediated by estrogen could translate into deeper stimulus encoding and better memory. Evidence for this comes from a recent EEG study

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

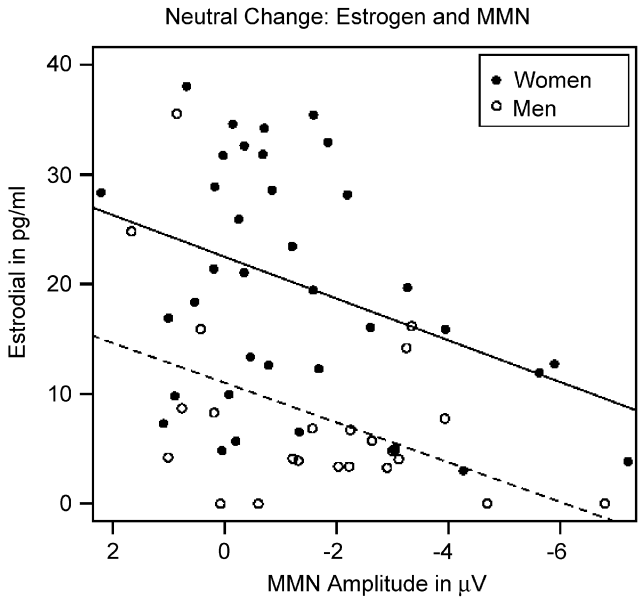

Figure 3 Scatterplot illustrating the relationship between estrogen measures and MMN amplitude in the neutral condition. Filled circles represent female listeners, open circles represent male listeners. Regression lines for females (solid) and males (dashed) are superimposed.

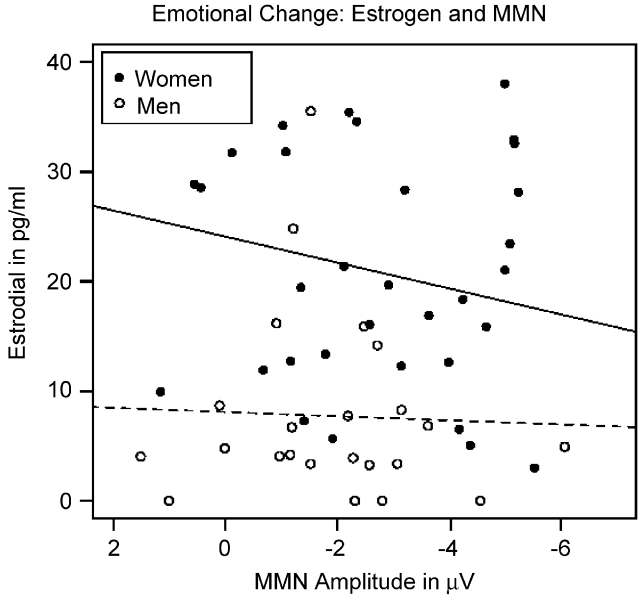

Figure 4 Scatterplot illustrating the relationship between estrogen measures and MMN amplitude in the emotion condition. Filled circles represent female listeners, open circles represent male listeners. Regression lines for females (solid) and males (dashed) are superimposed.

showing increased N400 amplitudes and hence deeper semantic analysis in women as compared to men (Wirth et al., 2007). Furthermore, a large number of behavioral studies found better verbal memory in women than in men (for a review see Kimura, 1999). Interestingly, the female memory advantage appears to be specific to intentional stimulus encoding, but does not show up if men and women are tested for incidental encoding (Chipman and Kimura, 1998). In line with the present results, this suggests that maintenance of attentional focus on the primary task is driving the observed sex effects.

4.2. Estrogen and emotion

Although for a long time considered to be opposites, emotion and cognition are closely intertwined. Given the limitations in processing capacity, not all the information available to humans can be encoded and stored in memory. Emotions serve the important function of moderating the selection of critical information for further processing. Accordingly, facial and vocal auditory expressions elicit greater activation in sensory processing areas when they are emotional as compared to neutral (Grandjean et al., 2005; Vuilleumier et al., 2001, 2004). Emotionally significant stimuli are more likely than neutral stimuli to escape the attentional blink (Anderson and Phelps, 2001) and to be permanently stored in memory (Cahill et al., 1994). While these effects can be observed in both men and women, a closer look suggests that they may be subject to sex differences. Specifically, if the emotional information is of social relevance, enhanced processing is more likely to occur in women than in men (Schirmer et al, 2007). In accord with this, we found that women, but not men, showed a larger MMN to emotional as compared to neutral vocalizations in the present study. Based on the finding that high estrogen during menstrual cycle is associated with enhanced recognition of facial expressions of fear (Pearson and Lewis, 2005), we hypothesized that estrogen would be positively correlated with the MMN amplitude to emotional deviants. However, we failed to observe such a positive correlation in both men and women.

When interpreting these results, one has to consider the intriguing fact that—unlike for neutral stimuli—for emotional stimuli there was also no significant negative correlation in men and only a weak tendency towards a negative correlation in women. This indicates that the estrogen-related attenuation of brain responses to unattended changes in the environment is stronger for neutral than emotional information. Two mechanisms could account for this observation. First, neutral and emotional events may be processed by different systems and only the system that deals with neutral events is sensitive to estrogen. Second, it is possible that the same systems are engaged in the processing of neutral and emotional events, but that the output of these systems triggers effects which are differentially sensitive to estrogen such that they may cancel each other out. Evidence for the first proposition comes from studies indicating that certain structures such as the amygdala or the orbitofrontal cortex have a specific role in emotion (Vuilleumier et al., 2004; Rolls, 2004). However, these structures are rich in estrogen receptors and elimination of these structures impacts estrogen-related emotional responses in animals (Thompson and Moss, 1997). In light of these and related findings in humans (Pearson and Lewis, 2005), it is highly unlikely that the system that processes emotional information is unaffected by estrogen. Evidence for the second proposition can be derived from research

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

revealing processing streams that engage in stimulus processing regardless of valence (Belin et al., 2004; Kanwisher and Yovel, 2006; Schirmer and Kotz, 2006). For example in the case of vocal processing, a stream from primary auditory cortex along the superior temporal sulcus has been implicated for all vocal stimuli. As for the visual system, this stream projects to areas implicated in cognition and emotion and feedback from these areas may inhibit or enhance further stimulus processing (for a review see Schirmer and Kotz, 2006). As estrogen plays a role in both the cognitive and the emotional systems that feedback to stimulus processing it is conceivable that estrogen effects on both would be additive. Accordingly, the estrogen-associated attenuation of responses to unattended vocal change observed in the present study may reflect an influence of estrogen on the cognitive system independently of stimulus valence. Specifically, estrogen may serve to decrease the MMN to unattended changes in the environment regardless of whether they are neutral or emotional. However, because estrogen also serves to enhance emotional sensitivity, the processing of emotional, but not neutral, vocal change is up-regulated and thus negates the effects of estrogen on the MMN. Moreover, if the estrogen-associated up- and down regulation of unattended stimulus processing via the emotional and the cognitive systems are comparable in strength one would expect an attenuated response to neutral environmental change, whereas there should be no attenuation for emotional change. This is what we observed in the present study.

4.3. Limitations and conclusions

Both behavioral and neuroimaging research suggests sex differences in various aspects of cognition and emotion. Among the biological factors that potentially contribute to these differences, findings from animals and humans have highlighted the role of estrogen. However, methodological constraints limit the generalizability of the observed effects. Moreover, conflicting results emerged from HRT and menstrual cycle research in humans, which is likely due to the fact that both failed to directly measure estrogen and to control for other hormonal changes. The present study aimed at overcoming these methodological constraints. Nevertheless, some issues remain and should be taken into consideration when interpreting the observed results.

For example, the present study included female participants regardless of whether they used OCs. The motivation for this was our interest in absolute estrogen values rather than cycle dependent changes thereof. However, one may argue that the inclusion of OC users nevertheless represents a problem as synthetically supplemented and natural estrogen may have differential effects on brain function. To account for this possibility, we included OC use as a variable in our statistical analysis but failed to observe a modulation of the sex and estrogen effects. Although this discounts the idea of differential effects of synthetic and natural estrogen in the context of the present study, the observed null result does not exclude the possibility for a role of OCs. Thus, future inquiries into the modulation of cognition and emotion by estrogen should consider OC use as an important variable and take greater pains to control its effects.

A further factor that should be considered in future studies is the task used to assess estrogen function. Here, we employed an MMN paradigm that has been widely tested in prior research (Muller-Gass et al., 2005). In this paradigm, participants typically read a self-selected book or watch a silent subtitled movie. While this does not allow researchers to ascertain the attentional focus of the participant, it represents a procedure that can be easily applied to various clinical populations as well as infants and young children. In order to comply with current standards and to increase our chances of replicating previous results, we adopted the above paradigm. Moreover, given the nature of the correlation observed between estrogen and the MMN in male and female listeners, we feel that it is unlikely that the present results are attributable to a differential subjective interest in the subsidiary task (i.e., watching a movie). However, due to the implication of the present results for the relationship between estrogen and change detection as well as attention, it will be necessary in future research to employ a more controlled subsidiary task and to record task performance in addition to neurophysiological measures of auditory change detection.

Despite these limitations, the present study advances our understanding of the role of estrogen for emotion and cognition. Unlike previous work, we directly measured estrogen levels in our participants and correlated the obtained values with the MMN, a neurophysiological correlate of change detection. We found that high estrogen is associated with a reduced MMN indicating attenuated sensitivity to unattended changes in speaker prosody. Given the frontal distribution of this effect and the high density of estrogen receptors in the frontal lobe, one may assume that—directly or indirectly—estrogen reduces distractibility and enhances voluntary attention mediated by frontal cortex. Interestingly, emotional events are spared from this reduction in distractibility, suggesting that estrogen facilitates emotional processing such that unattended emotional events may penetrate voluntary attention directed elsewhere. Together, the present results strongly implicate estrogen in cognition and emotion, thereby demonstrating that direct estrogen measurements for investigations in humans are a fruitful approach that should be integrated in future research.

Role of the funding source

This work was partially funded by the National University of Singapore Young Investigator Award conferred to Annett Schirmer (R-581-000-066-123).

Conflict of interest statement

There are no conflicts of interest associated with this manuscript.

Acknowledgments

We would like to thank Trevor Penney and three anonymous reviewers for helpful comments on earlier versions of this manuscript.

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

References

Anderson, A.K., Phelps, E.A., 2001. Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature 411, 305–309.

Belin, P., Fecteau, S., Bedard, C., 2004. Thinking the voice: neural correlates of voice perception. Trends Cogn. Sci. 8, 129–135.

Boersma, P., 2001. Praat, a system for doing phonetics by computer. Glot Int. 5, 341–345.

Bradley, M.M., Codispoti, M., Sabatinelli, D., Lang, P.J., 2001. Emotion and motivation II: sex differences in picture processing. Emotion 1, 300–319.

Cahill, L., 2003. Sex-related influences on the neurobiology of emotionally influenced memory. Ann. N. Y. Acad. Sci. 985, 163–173.

Cahill, L., Prins, B., Weber, M., McGaugh, J.L., 1994. Beta-adrenergic activation and memory for emotional events. Nature 371, 702–704.

Campbell, J.R., 1991. The roots of gender inequity in technical areas. J. Res. Sci. Teach. 28, 251–264.

Canli, T., Desmond, J.E., Zhao, Z., Gabrieli, J.D.E., 2002. Sex differences in the neural basis of emotional memories. Proc. Natl. Acad. Sci. 99, 10789–10794.

Chentsova-Dutton, Y.E., Tsai, J.L., 2007. Gender differences in emotional response among European Americans and among Americans. Cogn. Emot. 21, 162–181.

Chipman, K., Kimura, D., 1998. An investigation of sex differences in incidental memory for verbal and pictorial material. Learn. Individ. Diff. 10, 259–272.

Craft, R.M., Mogil, J.S., Aloisi, A.M., 2004. Sex differences in pain and analgesia: the role of gonadal hormones. Eur. J. Pain 8, 397–411.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134, 9–21.

Eals, M., Silverman, I., 1994. The hunter-gatherer theory of spatial sex differences: proximate factors mediating the female advantage in recall of object arrays. Ethol. Sociobiol. 15, 95–105.

Fausto-Sterling, A., 1992. Myths of Gender. Basic Books, New York.

Favreau, O.E., 1993. Do the Ns justify the means? Null hypothesis testing applied to sex and other differences. Can. Psychol. 34, 64–77.

Federmeier, K.D., Kiston, D.A., Moreno, E.M., Kutas, M., 2001. Effects of transient, mild mood states on semantic memory organization and use: an event-related potential investigation in humans. Neurosci. Lett. 15, 149–152.

Fink, G., Sumner, B.E., 1996. Oestrogen and mental state. Nature 383, 306.

Galea, L.A.M., Kimura, D., 1993. Sex differences in route learning. Pers. Individ. Diff. 14, 53–65.

Genazzani, A.R., Pluchino, N., Luisi, S., Luisi, M., 2007. Estrogen, cognition and female ageing. Hum. Reprod. Update 13, 175–187.

Goldstein, J.M., Seidman, L.J., Horton, N.J., Makris, N., Kennedey, D.N., Caviness, V.S., Faraone, S.V., Tsuang, M.T., 2001. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb. Cortex 11, 490–497.

Gordon, H.W., Lee, P.A., 1993. No difference in cognitive performance between phases of the menstrual cycle. Psychoneuroendocrinology 18, 521–531.

Gould, E., Woolley, C., Frankfurt, M., McEwen, B.S., 1990. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. J. Neurosci. 10, 1286–1291.

Grandjean, D., Sander, D., Pourtois, G., Schwartz, S., Seghier, M.L., Scherer, K.R., Vuilleumier, P., 2005. The voices of wrath: brain responses to angry prosody in meaningless speech. Nat. Neurosci. 8, 145–146.

Hamann, S., Canli, T., 2004. Individual differences in emotion processing. Curr. Opin. Neurobiol. 14, 233–238.

Hampson, E., 1990a. Estrogen-related variations in human spatial and articulatory-motor skills. Psychoneuroendocrinology 15, 97–111.

Hampson, E., 1990b. Variations in sex-related cognitive abilities across the menstrual cylce. Brain Cogn. 14, 26–43.

Henderson, V.W., 2000. Hormone Therapy and the Brain: A Clinical Perspective on the Role of Estrogen. The Parthenon Publishing Group, London.

Jacobs, D.M., Tang, M.-X., Stern, Y., Sano, M., Marder, K., Bell, K.L., Schofield, P., Dooneief, G., Gurland, B., Mayeux, R., 1998. Cognitive function in nondemented older women who took estrogen after menopause. Neurology 50, 368–373.

Jasnow, A.M., Schulkin, J., Pfaff, D.W., 2006. Estrogen facilitates fear conditioning and increases corticotropin releasing hormone mRNA expression in the central amygdala of female mice. Horm. Behav. 49, 197–205.

Kanwisher, N., Yovel, G., 2006. The fusiform face area: a cortical region specialized for the perception of faces. Philos. Trans. R. Soc. B 361, 2109–2128.

Keenan, P.A., Ezzat, W.H., Ginsburg, K., Moore, G.J., 2001. Prefrontal cortex as the site of estrogen's effect on cognition. Psychoneuroendocrinology 26, 577–590.

Keppel, G., 1991. Design and Analysis: A Researchers Handbook. Prentice-Hall, Englewood Cliffs, NJ.

Kimmel, M.S., 2003. The Gendered Society. Oxford University Press, New York.

Kimura, D., 1999. Sex and Cognition. MIT Press, Cambridge, MA.

Klenberg, L., Korkman, M., Lahti-Nuuttila, P., 2001. Differential development of attention and executive functions in 3- to 12-year-old Finnish children. Dev. Neuropsychol. 20, 407–428.

Koelsch, S., Schröger, E., Tervaniemi, M., 1999. Superior attentive and pre-attentive auditory processing in musicians. Neuroreport 10, 1309–1313.

Kujala, T., Tervaniemi, M., Schröger, E., 2007. The mismatch negativity in cognitive and clinical neuroscience: theoretical and methodological considerations. Biol. Psychol. 74, 1–19.

LeBlanc, E.S., Janowsky, J., Chan, B.K., Nelson, H.D., 2001. Hormone replacement therapy and cognition: systematic review and meta-analysis. J. Am. Math. Assoc. 285, 1489–1499.

Leuner, B., Mendolia-Loffredo, S., Shors, T.J., 2003. High levels of estrogen enhance associative memory formation in ovariectomized females. Psychoneuroendocrinology 29, 883–890.

McEwen, B.S., 1987. Observations on brain sexual differentiation: a biochemist's view. In: Reinisch, J.M., Rosenblum, L.A., Sanders, S.A. (Eds.), Masculinity/Femininity. Oxford University Press, New York, pp. 68–79.

Muller-Gass, A., Stelmack, R.M., Campbell, K.B., 2005. "…and were instructed to read a self-selected book while ignoring the auditory stimuli": the effects of task demands on the mismatch negativity. Clin. Neurophysiol. 116, 2142–2152.

Näätänen, R., 1990. The role of attention in auditory information-processing as revealed by event-related potentials and other brain measures of cognitive function. Behav. Brain Sci. 13, 201–232.

Näätänen, R., 1992. Attention and Brain Function. Erlbaum, Hillsdale.

Näätänen, R., Michie, P.T., 1979. Early selective-attention effects on the evoked potential: a critical review and reinterpretation. Biol. Psychol. 8, 81–136.

Näätänen, R., Gaillard, A.W., Mäntysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol. 42, 313–329.

Näätänen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., Vainio, M., Alku, P., Ilmoniemi, R.J., Luuk, A., Allik., J., Sinkkonen, J., Alho, K., 1997. Language-specific phoneme

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010

representations revealed by electric and magnetic brain responses. Nature 385, 432–434.

Näätänen, R., Jacobsen, T., Winkler, I., 2005. Memory based of afferent processes in mismatch negativity (MMN): a review of evidence. Psychophysiology 42, 25–32.

Novitski, N., Huotilainen, M., Tervaniemi, M., Näätänen, R., Fellman, V., 2007. Neonatal frequency discrimination in 250–4000-Hz range: electrophysiological evidence. Clin. Neurophysiol. 118, 412–419.

Opitz, B., Rinne, T., Mecklinger, A., von Cramon, D.Y., Schroger, E., 2002. Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. NeuroImage 15, 167–174.

Osorio, L.C., Cohen, M., Escobar, S.E., Salkowski-Bartlett, A., Compton, R.J., 2003. Selective attention to stressful distracters: effects of neuroticism and gender. Pers. Individ. Diff. 34, 831–844.

Ostlund, H., Keller, E., Hurd, Y.L., 2003. Estrogen receptor gene expression in relation to neuropsychiatric disorders. Ann. N. Y. Acad. Sci. 1007, 54–63.

Pearson, R., Lewis, M.B., 2005. Fear recognition across the menstrual cycle. Horm. Behav. 47, 267–271.

Perlman, W.R., Matsumoto, M., Beltaifa, S., Hyde, T.M., Saunders, R.C., Webster, M.J., Rubinow, D.R., Kleinman, J.E., Weickert, C.S., 2005. Expression of estrogen receptor alpha exon-deleted mRNA variants in the human and non-human primate frontal cortex. Neuroscience 134, 81–95.

Resnick, S.M., Metter, E.J., Zonderman, A.B., 1997. Estrogen replacement therapy and longitudinal decline in visual memory: a possible protective effect? Neurology 49, 1491–1497.

Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain Cogn. 55, 11–29.

Rosenberg, L., Park, S., 2002. Verbal and spatial function across the menstrual cycle in healthy young women. Psychoneuroendocrinology 27, 835–841.

Sams, M., Paavilainen, P., Alho, K., Näätänen, R., 1985. Auditory frequency discrimination and event-related potentials. Electroencephalogr. Clin. Neurophysiol. 62, 437–448.

Schirmer, A., Kotz, S.A., 2006. Beyond the right hemisphere: brain mechanisms mediating vocal emotional processing. Trends Cogn. Sci. 10, 24–30.

Schirmer, A., Striano, T., Friederici, A.D., 2005. Sex differences in the pre-attentive processing of vocal emotional expressions. Neuroreport 16, 635–639.

Schirmer, A., Simpson, E., Escoffier, N., 2007. Listen up! Processing of intensity change differs for vocal and nonvocal sounds. Brain Res. 1176, 103–112.

Shalgi, S., Deouell, L.Y., 2007. Direct evidence for differential roles of temporal and frontal components of auditory change detection. Neuropsychologia 45, 1878–1888.

Sherwin, B.B., 2003. Estrogen and cognitive functioning in women. Endocr. Rev. 24, 133–151.

Stefanatos, G.A., Baron, I.S., 2007. Attention-deficit/hyperactivity disorder: a neuropsychological perspective towards DSM-V. Neuropsychol. Rev. 17, 5–38.

Steffens, D.C., Nroton, M.C., Plassman, B.L., Tschanz, J.T., Wyse, B.W., Welsh-Bohmer, K.A., Anthony, J.C., Breitner, J.C., 1999. Enhanced cognitive performance with estrogen use in nondemented community dwelling older women. J. Am. Geriatr. Soc. 47, 1171–1175.

Stumpf, H., Jackson, D.N., 1994. Gender-related differences in cognitive abilities: evidence from a medical school admissions program. Pers. Individ. Diff. 17, 335–344.

Sutcliffe, J.S., Marshall, K.M., Neill, J.C., 2007. Influence of gender on working and spatial memory in the novel object recognition task in the rat. Behav. Brain Res. 177, 117–125.

Tse, C.Y., Tien, K.R., Penney, T.B., 2006. Event-related optical imaging reveals the temporal dynamics of right temporal and frontal cortex activation in pre-attentive change detection. NeuroImage 29, 314–320.

Thompson, T.L., Moss, R.L., 1997. Modulation of mesolimbic dopaminergic activity over the rat estrous cycle. Neurosci. Lett. 229, 145–148.

Vuilleumier, P., Armony, J.L., Driver, J., Dolan, R.J., 2001. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 30, 829–841.

Vuilleumier, P., Richardson, J., Armony, J.L., Driver, Dolan, R.J., 2004. Distinct spatial frequency sensitivities for processing faces and emotional expressions. Nat. Neurosci. 6, 624–631.

Walford, E., 1871. The Politics & Economics of Aristotle. Bell & Daldy, London.

Watson, N.V., Kimura, D., 1991. Nontrivial sex differences in throwing and intercepting: relation to psychometrically-defined spatial function. Pers. Individ. Diff. 12, 375–385.

Williams, C.L., Barnett, A.M., Meck, W.H., 1990. Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. Behav. Neurosci. 104, 84–97.

Wilson, R., 1966. Feminine Forever—the Amazing New Breakthrough in the Sex Life of Women. Evans, New York.

Wirth, M., Horn, H., Koenig, T., Stein, M., Federspiel, A., Meier, B., Michel, C.M., Strik, W., 2007. Sex differences in semantic processing: event-related brain potentials distinguish between lower and higher order semantic analysis during word reading. Cereb. Cortex 17, 1987–1997.

Please cite this article as: Schirmer, A., et al., What grabs his attention but not hers? Estrogen correlates with neurophysiological measures of vocal change detection. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.02.010