

# Gender Impact on Electrophysiological Activity of the Brain

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## Summary

Gender is presumed to be one of the factors causing interindividual variability in the brain's electrophysiological parameters. Our aim was to characterize the role of gender in visual evoked potentials (VEPs), event-related potentials (ERPs), visual mismatch negativity (vMMN) and the spectral characteristics of the EEG. We examined 42 healthy volunteers (21 women and 21 men, aged 20-29 years). We measured VEPs in response to pattern-reversal and motion-onset stimulation, ERPs in an oddball paradigm and vMMN in response to a combination of motion directions presented in the visual periphery. P100 peak latency for 40' reversal VEPs was significantly shorter in women than in men as determined using a non-parametric Wilcoxon signed-rank test. In addition, women showed higher relative EEG spectral power in the alpha band ( $p=0.023$ ) and lower power in the theta band ( $p=0.004$ ). Our results in this small but homogeneous group of subjects confirm previously reported gender influences on pattern-reversal VEPs and the EEG frequency spectrum. Gender should be taken into consideration in establishing norms on these measures. We found no statistically significant differences between women and men for any of the other stimuli presented.

## Key words

Gender • Pattern-reversal VEPs • Motion VEPs • Event related potentials • Visual mismatch negativity

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## Introduction

Visual evoked potentials (VEPs) are used to interrogate the visual pathway from the retina up through high-level visual cortices. These responses can be measured noninvasively and at low cost. The stimulus most commonly used in VEP acquisition is a luminance-reversing high contrast checkerboard, which predominantly activates the primary visual cortex (V1) (Seki *et al.* 1996, Brecelj *et al.* 1998). Pattern-reversal VEPs (P-VEPs) P100 peak latency and amplitude depend heavily on the pattern's contrast and the visual acuity of the tested subjects (Kubova *et al.* 1995). Onset of motion in the visual field activates the dorsal visual stream and evokes motion-onset VEPs (M-VEPs), which are relatively independent of contrast and visual acuity (Kubova *et al.* 1995). Detection of event-related potentials (ERPs) such as the visual mismatch negativity (vMMN) or the oddball P300 is an important step toward obtaining insight into higher-order cognitive functions. Combining information from these various types of visual evoked potentials can extend our understanding of brain function and elucidate the causes of many diseases that affect the central nervous system (CNS).

Gender is presumed to be one of the factors causing interindividual variation in the electrophysiological parameters of the human brain. Many studies have examined gender effects on P-VEPs (e.g., Fenwick *et al.* 1981, Allison *et al.* 1984, Cohn *et al.* 1985, Malcolm *et al.* 2002, Gregori *et al.* 2006) and, more recently, on ERPs (Polich and Kok 1995, Hoffman and Polich 1999, Sangal and Sangal 1996, Steffensen *et al.* 2008).

The effect of gender on P-VEP parameters is inconsistent across studies. While some studies have

found the dominant P100 peak to be larger in girls than boys (Snyder *et al.* 1981, Allison *et al.* 1984, Cohn *et al.* 1985, Emmerson-Hanover *et al.* 1994), and many believe that this gender difference continues into adulthood (Allison *et al.* 1984, Celesia *et al.* 1987, Emmerson-Hanover *et al.* 1994), other authors have found that P-VEP peak amplitude does not differ across gender (Snyder *et al.* 1981, Cohn *et al.* 1985). An analogous effect has also been reported for P100 peak latency, with some authors reporting shorter latencies in women (Fenwick *et al.* 1981, Emmerson-Hanover *et al.* 1994, Malcolm *et al.* 2002, Gregori *et al.* 2006) and others reporting no gender difference (Cohn *et al.* 1985, Mitchell *et al.* 1987). Celesia *et al.* (1987) found that the effect of gender on P100 latencies depends on the size of the pattern displayed. Although the effect of gender was obvious for smaller checks (15' of visual angle), no difference between males and females was observed for larger checks (30').

A similar gender difference has also been shown in ERPs. Hoffman and Polich (1999) reported that the P300 peak showed larger amplitude and shorter latency in women than in men. However, Steffensen *et al.* (2008) only found a smaller P300 peak amplitude in men, and Sangal and Sangal (1996) reported no gender difference in P300 latency or amplitude.

The distribution of EEG power across the lifespan also differs across genders. The markers of EEG maturation are decreases in slow wave activity (theta, delta) and increases in faster activity (alpha, beta) (Somsen *et al.* 1997, Martinović *et al.* 1998, Clarke *et al.* 2001, Segalowitz *et al.* 2010, Cragg *et al.* 2011). Clarke *et al.* (2001) found that girls' EEG matured more slowly than boys' during childhood, but during adolescence the difference was eliminated. However, Gasser *et al.* (1988) found no gender differences in the EEG power spectrum, likely because of high interindividual variability. The alpha rhythm does not mature until at least age 16 (Marcuse *et al.* 2008).

If men's and women's electrophysiological responses differ, pooling these data inflates the variability of the parameter estimates, thus negatively influencing the sensitivity of clinical examinations.

With this study, we sought to contribute to the estimation of the gender effect on visual information processing at different levels and on spontaneous brain activity and to assess the importance of that effect for clinical examinations of individual subjects.

## Methods

### Subjects

We examined 21 pairs of age-matched healthy individuals (university students) aged 20-29 years. Our subjects had no ophthalmological or neurological disease. Informed consent was obtained from each subject after the test procedure had been explained to him or her. The study was approved by the Ethics Committee, University Hospital Hradec Králové.

### VEPs

#### Pattern-reversal VEPs (P-VEPs)

We used a checkerboard with high luminance contrast (96 % according to Michelson's formula), reversing at 2 Hz, with check sizes of 10', 20' and 40'.

#### Motion-onset VEPs (M-VEPs)

Two types of moving stimuli were used:

a) Translational linear motion of isolated checks (M-VEPs L) (check size 40', check-to-check distance 120' on both vertical and horizontal axes, moving at velocity 10 deg/s) with direction of motion randomly ordered to reduce adaptation of direction-specific cortical neurons.

b) Radial motion of sine-wave modulated concentric circles, contracting and expanding at random, with decreasing spatial frequency (1-0.2 c/deg) toward the periphery of the visual field to account for cortical magnification and with increasing motion velocity (5-25 deg/s) toward the periphery to account for different motion sensitivities in the center versus the periphery of the visual field. We recorded three types of VEPs to radial motion-onset:

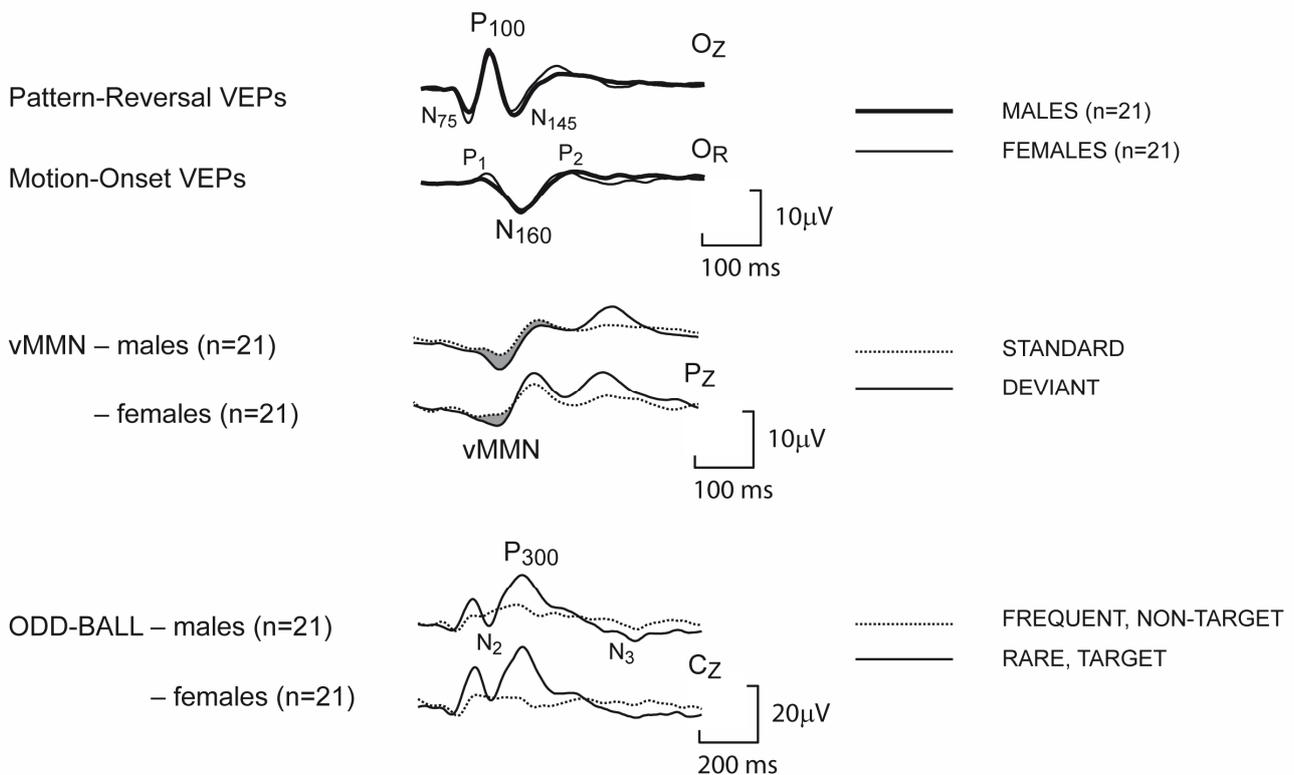
- M-VEPs to full field stimulus subtending 37x28 deg (M-VEPs FF),
- M-VEPs to central 8 deg of the visual field (M-VEPs c8°),
- M-VEPs to periphery of the stimulus field outside the central 20 deg (M-VEPs m20°).

All moving stimuli were moved for 200 ms followed by a stationary period of 1000 ms.

VEPs to binocularly observed stimuli were computed by averaging 40 single responses, each of which consisted of a 440-ms epoch sampled at 500 Hz. In P-VEPs we measured peak latency and absolute mean inter-peak amplitude  $(P100 - (N75 + N145)/2)$  of the main P100 peak. For M-VEPs, we measured peak latency and the absolute mean inter-peak amplitude

((P1+P2)/2-N160) of the N160 peak, which has been shown to represent the main motion-specific component of this VEP type (Kuba and Kubova 1992, Heinrich

2007, Kuba *et al.* 2007). The variables represent absolute peak amplitudes of the respective VEPs as they are shown in the Figure 1.



**Fig. 1.** Obtained VEPs/ERPs. The first row shows P-VEPs. The longer latency of the P100 peak (see Table 1a) in men (thick line) compared to women (thin line) is statistically significant but barely observable. The N160 peak, characteristic of the response to motion-onset stimuli, did not show any statistically significant gender difference, as depicted in the second row. Each group's responses to the vMMN paradigm (standard ERP – dotted line; deviant ERP – solid line) overlap in the middle of the figure. The grey color represents AUC, which did not differ between groups. The bottom part of the figure depicts ERPs recorded during the visual odd-ball paradigm. These responses show similar overlap to the vMMN responses. Responses to frequent non-target stimuli are plotted with a dotted line; responses to rare targets are plotted with a solid line. The groups did not differ in latency or amplitude of the characteristic peak P300. All plotted VEPs and ERPs are total averages over the specified group.

We used the  $O_z$  derivation (the derivation with maximum response and the lowest variability) to evaluate P-VEP parameters. Because the generation of M-VEPs is known to differ across individuals (Holliday *et al.* 1998, Kremlacek *et al.* 1998), we selected the optimal derivation for each subject. The optimal derivation was the one with the shortest N160 peak latency, unless the latencies were not significantly different, in which case it was the derivation with largest amplitude. For each subject, we chose an optimal derivation from the  $O_L$ ,  $O_R$ ,  $O_z$  and  $P_z$  derivations.

Each VEP was acquired twice, and mean values for each subject were submitted to the following statistical analysis.

#### Event related potentials – ERPs

Binocular ERPs were recorded during an oddball

test, in which the letter X (a frequent non-target stimulus appearing with 75 % probability) and Arabic digits 1-9 (rare target stimuli appearing with 25 % probability) appeared in a pseudorandomly intermixed sequence. Both X and the Arabic digits were presented in white at the center of the black stimulus field (average luminance of entire field  $1 \text{ cd/m}^2$ ) and subtended  $5.7 \times 6.3 \text{ deg}$  of the visual angle. Each stimulus was displayed for 500 ms and followed by a black screen with a fixation point for 500 ms. To calculate ERPs, 20 epochs to target stimuli and 20 randomly selected epochs to non-target stimuli (both of 1000 ms duration with sampling frequency of 250 Hz) were averaged for each condition. Before averaging, the epochs with artifacts (primarily blinks) were manually rejected. In the ERPs to frequent and rare stimuli, the absolute mean inter-peak amplitudes ( $(P300 - (N2 + N3)/2)$ ) and peak latencies of the P300 were

measured using the central ( $C_z$ ) derivation.

#### *Visual mismatch negativity – vMMN*

The test paradigm was specifically designed to elicit the vMMN and was based on the three-stimulus design used by from Tales *et al.* (1999). There were three motion-onset events:

- *standard condition* (88 %) – upward motion of a horizontal sinusoidal grating with low (10 %) contrast, spatial frequency of 0.1 c/deg and velocity of 50 deg/s, presented outside the central 15 deg of the visual field;
- *deviant condition* (6 %) – downward motion otherwise identical to the standard condition; and
- *rare condition* (6 %) – a horizontal sinusoidal grating with low (10 %) contrast, spatial frequency of 1 c/deg and velocity of 5 deg/s, presented inside the central 5 deg of the visual field. The motion duration was 200 ms, and the stationary pattern was presented for 600 ms.

The vMMN was evaluated using area under the curve (AUC), computed as the integral of the difference between ERPs to standard versus deviant stimuli. The AUC approached zero for similar ERP responses to standard and deviant stimuli and had negative values when ERPs to deviant stimuli were relatively more negative.

All stimuli were presented on a 21 inch computer monitor (Vision Master Pro 510, Iiyama, Japan) subtending a 37x28 deg of visual angle at 0.6 m viewing distance. The monitor was driven using the Visual Stimulus Generator 2/5 (CRS Ltd., UK) at a vertical refresh frequency of 105 Hz. A mean luminance of 17 cd/m<sup>2</sup> was used for all VEP, ERP and vMMN stimuli. Electrophysiological acquisition was performed in a darkened, sound-attenuated, electromagnetically shielded room with a background luminance of 0.1 cd/m<sup>2</sup>. During the experiment, the subjects sat in a comfortable dental chair with a neck support to reduce muscle artifacts. Correct fixation on the center of the stimulus field was monitored *via* infrared charge-coupled device camera.

Detailed stimulus parameters have been previously described for the radial motion stimuli (Kremlacek 2004 *et al.*) and for the mismatch negativity stimuli (Kremlacek 2006 *et al.*).

#### *Spontaneous electroencephalographic activity – EEG*

For the EEG spectral analysis, we recorded 64 s

of resting EEG with subjects' eyes closed. To estimate the power spectral density of the recording, we averaged 16 periodograms computed using a Fourier Transformation in 4-s EEG segments using a rectangular window. To estimate of the relative power of the EEG spectrum, the following parameters were calculated: the delta (1.75-4 Hz), theta (4.25-8 Hz), alpha (8.25-12 Hz), beta1 (12.25-20 Hz), and beta2 (20.25-30 Hz) bands; the theta/alpha relative power ratio; and the frequency of the dominant peak.

#### *Recordings*

Pseudo-unipolar recordings were acquired from the midline ( $O_z$ ,  $P_z$ ,  $C_z$  and  $F_z$ ) and lateral occipital ( $O_L$  ( $O_R$ ) 5 cm to the left (right) from the  $O_z$  position) derivations with the right earlobe reference.

The signal was amplified by a factor of 20,000 (Contact Precision Instruments, PSYLAB, System 5, UK) in the frequency band of 0.3-100 Hz at -3 dB with a roll-off of 6 and 12 dB per octave. After amplification, the signal was sampled at 500 Hz for VEPs, 250 Hz for ERPs and 100 Hz for spontaneous EEG. The VEP/ERP recordings were synchronized with the backward trace of the monitor's electron beam immediately before the first video frame of a given stimulus.

#### *Analysis*

Because the measured values were not normally distributed, a non-parametric Wilcoxon signed-rank test was applied to assess significant differences.

## **Results**

In a previous study, we found that subject age substantially influenced VEP parameters (Langrova *et al.* 2006). In this study, we tried to minimize this effect by examining healthy volunteers within a narrow age range.

We found that the latency of the main component (P100) for P-VEPs with element size 40' was shorter in women than in men ( $p=0.012$ ). The P100 peak amplitude was not affected by gender. We found no significant differences in P-VEPs to patterns with other element sizes (P-VEPs 20', 10'). We also found no gender differences in peak latency or amplitude of the main component (N160) evoked by motion-onset stimulation. Table 1 summarizes the median, 25<sup>th</sup> and 75<sup>th</sup> percentiles of latencies (a) and amplitudes (b) of P100 peaks of P-VEPs, N160 peak of M-VEPs, and statistical results from the corresponding derivation.

**Table 1.** The effects of gender on the latency [ms] and amplitude [ $\mu$ V] of all tested VEPs obtained at the optimal derivation. Values are expressed as median, 25<sup>th</sup> and 75<sup>th</sup> percentiles. Asterisks represent significance level (\*  $p < 0.05$ ).

## a) VEPs latency [ms]

	Evaluated parameter	Males	Females	p-level	Significance level
<i>P-VEPs 40'</i>	P100	109 (107:114)	108 (104:110)	0.012	*
<i>P-VEPs 20'</i>	P100	110 (107:113)	108 (107:109)	0.365	n.s.
<i>P-VEPs 10'</i>	P100	119 (112:120)	117 (114:118)	0.748	n.s.
<i>M-VEPs L</i>	N160	157 (148:162)	151 (148:161)	0.487	n.s.
<i>M-VEPs FF</i>	N160	148 (143:154)	156 (136:161)	0.664	n.s.
<i>M-VEPs m20°</i>	N160	152(146:162)	154 (150:158)	0.768	n.s.
<i>M-VEPs c8°</i>	N160	152 (148:158)	153 (136:159)	0.465	n.s.
<i>ERP target</i>	P300	368 (336:376)	372 (364:380)	0.087	n.s.

b) VEPs amplitude [ $\mu$ V]

	Evaluated parameter	Males	Females	p-level	Significance level
<i>P-VEPs 40'</i>	P100	11.5 (10.3:14.6)	15.0 (11.2:16.1)	0.305	n.s.
<i>P-VEPs 20'</i>	P100	10.7 (9.1:14.6)	14.2 (12.0:16.6)	0.067	n.s.
<i>P-VEPs 10'</i>	P100	13.1 (10.3:16.1)	16.0 (11.8:19.1)	0.181	n.s.
<i>M-VEPs L</i>	N160	6.8 (5.1:8.3)	7.7 (5.4:10.2)	0.322	n.s.
<i>M-VEPs FF</i>	N160	10.4 (9.0:11.4)	10.4 (7.7:12.4)	0.958	n.s.
<i>M-VEPs m20°</i>	N160	9.8 (7.5:10.9)	9.2 (7.6:10.6)	0.614	n.s.
<i>M-VEPs c8°</i>	N160	9.5 (8.3:11.8)	10.3 (8.9:12.0)	0.889	n.s.
<i>vMMN 120-240 ms [<math>\mu</math>V*ms]</i>	AUC	8.9 (-53.8:24.6)	-30.2 (-53.6:78.8)	0.217	n.s.
<i>ERP target</i>	P300	17.0 (14.5:22.6)	17.8 (13.2:23.2)	0.852	n.s.

**Table 2.** Effects of gender on relative spectral EEG power [%] and frequency of the EEG spectrum dominant peak [Hz]. Values are expressed as median, 25<sup>th</sup> and 75<sup>th</sup> percentiles. Asterisks represent significance level (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ).

	Males	Females	p-level	Significance level
<i>Dominant peak frequency [Hz]</i>	9.5 (9.0:10.3)	10.3 (9.8:10.8)	0.093	n.s.
<i>delta</i>	12.0 (10.1:16.6)	9.5 (8.0:10.9)	0.073	n.s.
<i>theta</i>	16.4 (13.6:22.2)	11.9 (9.6:16.2)	0.004	**
<i>alpha</i>	51.6 (39.1:61.4)	60.7 (54.6:67.3)	0.023	*
<i>beta1</i>	9.4 (6.7:12.8)	9.3 (7.7:14.5)	0.872	n.s.
<i>beta2</i>	4.7 (3.1:6.3)	6.1 (3.8:7.5)	0.538	n.s.
<i>theta/alpha coefficient</i>	0.30 (0.23:0.51)	0.21 (0.15:0.29)	0.007	**

There was no difference between males and females in the P300 component of ERPs to the rare condition. Table 1a and 1b contain the P300 latencies and

amplitudes, respectively that were determined using the C<sub>z</sub> derivation.

We visually inspected the total average, pooling

across genders, of the vMMN to find the interval of maximal difference between responses to the standard and deviant conditions. This interval appeared at 120-240 ms, analogous to the same interval for the auditory MMN. There were no gender differences in AUC over this interval, as assessed by a Wilcoxon test for paired measures (Figure 1).

Significant gender differences were found in the frequency spectrum of the EEG, with a greater power in the alpha band for women ( $p=0.023$ ) and in theta band for men ( $p=0.004$ ). Additionally, the theta/alpha ratio was significantly lower for women than for men ( $p=0.007$ ); see Table 2. We did not find any difference in the frequency of the dominant peak in alpha power ( $p=0.093$ ). Our quantitative analysis of EEG power is summarized in Table 2.

Figure 1 shows the total averages for the VEPs and ERPs, which reflect different levels of visual information processing. The total of the averages were not used in statistical comparisons, as they obscure the paired structure of the experiment; however, these values are shown for demonstration purposes.

## Discussion

In this study, we investigated whether gender must be taken into account in calculating norms for VEPs (an index of low-level sensory processing), ERPs and vMMN (indices of the cognitive level of visual processing) and spectral characteristics of the EEG.

Most studies have found shorter VEP peak latencies (Fenwick *et al.* 1981, Malcolm *et al.* 2002) and larger peak amplitudes (Allison *et al.* 1984, Kaneda *et al.* 1996) in women, and various explanations of these findings have been proposed. Physical characteristics, such as head size (Guthkelch *et al.* 1987, Malcolm *et al.* 2002, Gregori *et al.* 2006) and body temperature (Kaneda *et al.* 1996), are often suggested as sources of gender differences on these measures. It is plausible that head size could affect the latency of the P100 wave. The slight gender difference in P100 latencies corresponds to the slightly smaller average head size in women. Indeed, Gregori *et al.* (2006) examined men and women with the same skull size and found no statistically significant differences in VEP peak latency. Unfortunately, we did not measure skull size in this study and therefore cannot verify its impact on our results.

In addition to physical considerations, neuroendocrinological and neurological factors, including

gonadal steroids, cortisol, thyroxine and  $\gamma$ -aminobutyric acid (Kaneda *et al.* 1996, Sannita 2006), may also be relevant. Many studies have found that estrogens, especially  $17\beta$ -estradiol, affect brain function throughout the lifespan, ranging from early developmental stages to the aging processes in older adults (Hutchison *et al.* 1995). Much work has shown positive effects not only on brain perfusion and metabolism but also on neuronal protection (McCullough *et al.* 2003, Krause *et al.* 2006, Irwin *et al.* 2008). However, we have found no reports linking estrogen to the development of visual perception.

In our study, we evaluated a homogeneous group of 42 healthy subjects. We observed very small gender differences, approximately 1 ms, in P-VEP peak latencies, and only P-VEPs 40' showed a statistically significant gender difference in the P100 peak latency. Although we did not measure any of the aforementioned factors confounding gender differences in VEPs, it seems that gender plays a negligible role in early sensory processing of visual information.

Unlike other studies (Fenwick *et al.* 1981, Malcolm *et al.* 2002), we found very small sex differences in P100 peak latency. These differences could be caused by the age of our volunteers, as the gender differences for this measure seem to change across the lifespan (Emmerson-Hanover *et al.* 1994). Although the authors found distinct P100 latency differences in subjects aged 6-20 and 50-80 years, the differences were smaller in the 20-50-year-old age group.

The previously published findings are inconsistent with respect to gender differences in cognitive ERPs. A study by Sangal and Sangal (1996) found no gender difference in the P300 wave, but a more recent study by Hoffman and Polich (1999) reported larger P300 peak amplitudes in women than men. Our result indicating the absence of a gender difference in the ERP to the rare response (i.e., the P300 wave) supports the previous finding. This inconsistency in the investigations of gender differences in cognitive ERPs might be partially explainable by differences in the stimulus design and the experimental procedure.

Our most striking gender differences appeared in the spectral characteristics of spontaneous EEG. This result is consistent with the results reviewed by Sannita (2006) and might be attributable to testosterone levels, which correlate positively with theta EEG activity. In both men and women, only a small proportion of the EEG power appeared in the lower frequencies (delta, theta); most of the EEG power was present at higher

frequencies (alpha). This finding represents a marker of maturation in the EEG (Somsen *et al.* 1997, Clarke *et al.* 2001, Segalowitz *et al.* 2010, Cragg *et al.* 2011). Kaneda *et al.* (1996) found significantly larger theta and smaller alpha2 powers in women, which is the opposite of our findings. Possible reasons for this discrepancy might be the substantially larger age range and a different method of EEG recording.

The aforementioned relationship between the degree of maturity and distribution of the EEG power spectrum may explain the sex difference we observed in the alpha and theta activity. Matousek (1968) found that the best indicator of maturity is the ratio of theta and alpha activity. In our sample, women showed a higher level of maturity as quantified by this ratio.

In a large sample (almost 1,500 subjects), Chiang *et al.* (2011) showed statistically significant nonlinear changes in alpha power across the lifespan that differed between men and women. Men showed higher alpha power that decreased steeply until age 20. In women, a smaller, consistent decrease in alpha power was observed throughout the lifespan. The ages of our subjects fall in the period in which Chiang *et al.* (2011) found a higher alpha power in women compared to men, and this result was recapitulated in our data.

Our results demonstrate various gender differences in the electrophysiological parameters of human brain function. Although there are negligible gender differences for motion-onset VEPs, ERPs or vMMN, obviating the need to calculate separate norms for men and women, P-VEPs and the EEG frequency spectrum seem to be more influenced by gender, and separate gender-dependent norms should be constructed for these measures.

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A limitation of this study should be mentioned in the context of our negative results. If gender represents a factor with strong impact on some electrophysiological marker (as in P-VEPs 40', where we find a 1 ms difference between groups and a narrow interquartile range), then we can make valid conclusions about gender differences in that marker using a sample of 42 subjects. However, a null result for an electrophysiological marker with a higher variability, such as cognitive ERPs, indicates merely that any gender difference in these parameters was not strong enough to be detected in our sample. To explore a small effect of size approximately 0.2 (Cohen 1992), such as the implicit latency of the P300 peak (estimate based on our intergroup difference and variability), we require a sample size of approximately 200 subjects to ensure the statistical significance of the results. Among studies exploring gender effects on electrophysiological parameters, our sample is larger than some and smaller than others (Fenwick *et al.* 1981 – 48 subjects; Celesia *et al.* 1987 – 112 subjects; Guthkelch *et al.* 1987 – 16 subjects; Emmerson-Hanover *et al.* 1994 – 406 subjects; Kaneda *et al.* 1996 – 200 subjects; Gregori *et al.* 2006 – 54 subjects; Malcolm *et al.* 2002 – 52 subjects; Steffensen *et al.* 2008 – 30 subjects; Cragg *et al.* 2011 – 56 subjects).

## Conflict of Interest

There is no conflict of interest.

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