Response Execution in Lexical Decision Tasks Obscures Sex-specific Lateralization Effects in Language Processing: Evidence from Event-related Potential Measures during Word Reading

A common hypothesis about sex differences in language processing attributes these differences to a bilateral contribution of language-related brain areas in females and a left-hemispheric dominated activation in males. However, most imaging studies failed to find such a generalized lateralization effect and reported a left-lateralized activation in both sexes instead. In a previous semantic priming study, we found a sustained (~190–640 ms) bilateral positivity in the ERP waveforms, which was larger for the female group. Word reading and lexical decision were confounded in that study. In the present study we used a delayed response to separate semantic processing from response selection and execution. The modification of the task design, together with a dense sensor array, showed that females developed a bilateral sustaining posterior positivity/frontal negativity during reading/semantic processing. In contrast, males showed an attenuated positivity at left posterior sites and an attenuated negativity at right frontal sites. This sex-specific lateralization effect disappeared during response processing, evoking a bilaterally distributed activation for both sexes (frontal negative and posterior positive), which was larger for the female subjects. We conclude that, at least under specific conditions, language processing evokes a bilateral activation in females and a lateralization effect in males. However, the processing of the response, which is dominated by a 'P300-like' component evoked by this process, evokes a larger activation in both sexes which obscures the sex-specific lateralization effect when semantic processing and response processing are not separated.

**Keywords:** evoked potentials, gender, language lateralization, language processing, semantic priming, sex difference

**Introduction**

Sex differences in language processing are well known from everyday life, as well as from the scientific literature. For instance, women outperform men in verbal fluency and episodic memory tasks (Herlitz et al., 1997), and in the use of prosodic information (Schirmer et al., 2002; Schirmer and Kotz, 2003). Based on human lesion studies and brain morphometry, the most common hypothesis attributes sex differences to a left-hemispheric dominance in men but a more bilateral activation of language-related brain areas in females (for a review, see Josse and Tzourio-Mazoyer, 2004). Using functional magnetic resonance imaging (fMRI), Shaywitz et al. (1995) were the first to confirm this hypothesis with a noninvasive neurophysiological technique in healthy subjects. They observed a left-lateralized activation in the inferior frontal gyrus (IFG) in men and a bilateral activation in women during a phonological rhyming task. In a semantic task requiring a decision about whether two words come from the same category or not, they found no sex differences in the investigated brain regions (IFG, extrastriate cortex). Since then, several imaging studies have investigated sex differences in language processing. The different methods and language tasks used may account for the reported inconsistent results concerning sex differences. The results of different imaging studies were recently summarized by Josse and Tzourio-Mazoyer (2004) and a meta-analysis by Sommer et al. (2004). Sommer et al. summarized: 'This meta-analysis found no significant sex difference in functional language lateralization in a large sample of 377 men and 442 women. Thus, the hypothesis that language functions are generally presented more bilaterally in women than in men is not supported.' Sommer et al. also found that the studies reporting a sex difference were of smaller sample size than those reporting no difference. Of most relevance to the present study, in ten of the studies included in the meta-analysis subjects had to perform a semantic decision. However, only two of these ten studies reported a sex difference in lateralization, and this bias was not dependent on modality (auditory versus visual).

Compared with studies that used fMRI or positron emission tomography (PET), only a few studies used event-related potentials (ERP) or magnetoencephalography (MEG) to investigate sex differences in language processing. For instance, Skrandies et al. (1999), using ERP measures, reported a higher global field power (from 70 to 1200 ms) in females than in men during word reading and in an anagram detection task. Walla et al. (2001) found a significantly larger left centroparietal MEG activity in men at ~200–400 ms in a visual word recognition task.

In a previous semantic priming study (H. Hill et al., submitted for publication), we found an enlarged positivity in the ERPs of the female group compared with the male group at most electrode sites, with a central maximum. This difference started at ~190 ms after onset of the first stimulus (prime word) and continued until ~640 ms after the second word (target) was displayed. The stimulus onset asynchrony (SOA) was 250 ms. Only a non-significant sex-dependent lateralization effect was found, showing a larger left compared with right sex difference at parietal sites only (electrode sites P3, P4). No sex differences were found for the behavioral and ERP priming effects (this means a facilitated processing of the target when it is semantically related to the prime). The origin of this sustaining positivity, which was larger for the female group, was not clear. Because an immediate lexical decision on the target was required, it could be related to the processing of word meaning or to the lexical decision, as both processes interfered in this task.

The present study was conducted for two reasons: first, to further investigate previously found SOA-dependent semantic priming effects (Hill et al., 2002; these results are reported in Hill et al., 2005); and secondly, to replicate the larger positive
activation in females and differentiate it by experimental manipulations. Therefore a delayed response was used to separate word reading/semantic processing from response selection and execution, and to avoid the overlay of the ERP components (N400, P300) related to these processes (see Hill et al., 2002). In addition, we recorded a 61-channel EEG to increase the spatial resolution and accuracy of localization. In the previous study (H. Hill et al., submitted for publication), 20 electrode sites, in a 10–20 array and referenced to linked mastoids, were used. Such a setup does not provide a sufficient spatial resolution, and a bilateral activation may show up as a unilateral central activity. Thus, we expected a spatially differentiated pattern of this previously found generalized positivity, modulated by task as well as by sex.

Materials and Methods

Subjects
Data were obtained from 31 (15 females) right-handed subjects (students or postgraduates; three additional datasets were excluded due to excessive artifacts). The average age was 23.7 years (females 23.4 years, range 21–26; males 24.1 years, range 23–28). Handedness was assessed using a German version of the Edinburgh Inventory (Oldfield, 1977). The two groups did not differ significantly in age, years of education, or the verbal intelligence score as measured using the MWT-B (Lehrl, 1977). All subjects were healthy native German speakers with normal or corrected-to-normal vision. Participation in the experiment was voluntary and not paid. All subjects gave signed informed consent in accordance with the declaration of Helsinki before participating in the experiment.

Materials and Procedure
ERPs were recorded while subjects performed a lexical decision task. Two letter strings (prime and target) forming either a word or a pseudoword were presented sequentially, separated by an SOA of 150 or 700 ms. Subjects did not respond to the target immediately but to a probe presented 1.2 s after target onset. The semantic distance between prime and target was varied by using directly related, indirectly related and non-related word pairs. Stimuli were taken from previous studies (Weiland et al., 2000; Hill et al., 2002) and consisted of 452 pairs of letter strings (primes and targets) which were divided into two lists. Stimuli were either real German words or legally spelled pseudowords. Pseudowords were derived from real words by replacing one or two letters. The main target relatedness factor was manipulated by using directly related, indirectly related, and non-related word pairs. Stimuli could be presented sequentially, separated by an SOA of 150 or 700 ms. Subjects did not respond to the target immediately but to a probe presented 1.2 s after target onset. The semantic distance between prime and target was varied by using directly related, indirectly related and non-related word pairs. Stimuli were taken from previous studies (Weiland et al., 2000; Hill et al., 2002) and consisted of 452 pairs of letter strings (primes and targets) which were divided into two lists. Stimuli were either real German words or legally spelled pseudowords. Pseudowords were derived from real words by replacing one or two letters. The 216 prime-target combinations of each list consisted of 36 non-related pairs (e.g. leaf–car), 36 indirectly related pairs (e.g. lemon–sweat), 36 directly related associated pairs (e.g. hen–egg), 54 word-pseudoword pairs (e.g. picture–gerba), and 54 pseudoword-word pairs. The prime–target pairs were not phonologically related and did not show any orthographic similarity. The pseudowords were not similar to words related to the real word of the pair. The stimulus material is described in detail in Weisbrod et al. (1999). Both lists were used in an SOA150 version as well as in an SOA700 version. Half of the subjects started with the SOA150 condition, the other half with the SOA700 condition, counterbalanced between female and male subjects. In addition, from each of the four lists, two versions with a different pseudorandomized order were constructed, resulting in a total of eight lists with different randomization. To avoid repetition effects, words and pseudowords were presented only once.

Subjects had to read the prime and target silently and respond to the probe which appeared after presentation of the target as quickly and accurately as possible. The probe was either the question ‘word-word?’ or ‘pseudoword’. Two forms of the probe question were used to avoid that subjects could respond before probe onset. If ‘word-word?’ appeared, subjects had to press the left mouse button with their index finger when prime and target were both real words. Otherwise they had to press the right mouse button with their middle finger. If the question ‘pseudoword?’ appeared, subjects had to press the left button if either prime or target was a pseudoword or the right button if both stimuli were real words (Table 1). All subjects responded with their right hand.

Stimuli were presented on a computer screen synchronously with the refresh cycle of the monitor. Given a viewing distance of ~1 m, each word encircled a visual angle of up to 8° in width and 3° in height. Both primes and targets were presented in the center of the screen. Stimulus presentation and data collection were controlled by the software STIM (Neuroscan, Sterling, VA). Each trial was initiated by the subject pressing one of the mouse buttons. Trials started with a fixation point, displayed in the center of the screen for 700 ms, followed by the prime, which was presented for 150 ms. After an interstimulus interval of 0 or 550 ms, the target was displayed for 1 s. After a delay of 200 ms, the probe was displayed until the subject had responded; it disappeared after 3 s if no response was made. Both the reaction time (RT) and accuracy of the response were recorded. Following the subject’s response, three stars were displayed, which prompted the subject to initiate the subsequent trial. A practice experiment consisting of 10 trials similar to those of the actual experiment was set up with no data sampled. The experiment was performed in an electrically shielded dimly lit room. Subjects were seated in an upright position in front of the computer screen on which the stimuli were presented. Subjects were instructed to perform necessary blinks or movements during the intertrial intervals only.

ERP Recording
A 62-channel EEG was recorded continuously using Synamps DC-amplifiers (NeuroScan, Sterling, VA; USA; sample rate 250 Hz, resolution 0.084 μV/bit, input-impedance 10 MΩ) using an equidistant EasyCap (www.easycap.de) with sintered Ag/AgCl electrodes. Eye movements were monitored using supra- and infra-orbital electrodes and electrodes on the external canthi. The vertex electrode was used as reference. Electrode impedance was maintained below 10 kΩ. The EEG was segmented from 200 ms before stimulus onset to 1000 ms after stimulus onset.

ERP Data Analysis
The EEG was analyzed using Vision Analyzer software (www.brainproducts.com). EEG data were digitally filtered with a 16 Hz zero-phase low pass and segmented into epochs of 1000 ms (SOA700) or 1150 ms (SOA150) duration for each trial, starting 100 ms (SOA700) or 250 ms (SOA150) before onset of the target stimulus. As in the previous study (Hill et al., 2002), two different methods were applied for baseline correction because absolute ERP voltages of the SOA150 and the SOA700 data are not comparable for two reasons: first, in the SOA150 condition, ERP components evoked by the prime (e.g. P300, N400) superimposed the target waveform which did not happen in the SOA700 condition; and secondly, in the SOA700 condition, the prime stimulus evoked a CNV. Therefore, the SOA150 data were aligned to a 100 ms prestimulus baseline before onset of the prime and the SOA700 data to the 100 ms prestimulus interval of the target stimulus.

To investigate the ERPs evoked by the prime (SOA700 only) and the probes, the EEG was segmented from −100 to +700 ms (prime) and from −200 to +1000 ms (probe) around stimulus onset. Segments containing eye movements were removed. Segments containing eye blinks were

Table 1

<table>
<thead>
<tr>
<th>Prime, 150 ms</th>
<th>IS1 Target, 1000 ms</th>
<th>n</th>
<th>IS1, 200 ms</th>
<th>Probe (question), 3000 ms</th>
<th>Response (mouse button)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word</td>
<td>Word (dir.)</td>
<td>18</td>
<td>Word-word?</td>
<td>Left (yes)</td>
<td></td>
</tr>
<tr>
<td>Pseudoword</td>
<td>Word (indir.)</td>
<td>18</td>
<td>Word-word?</td>
<td>Right (no)</td>
<td></td>
</tr>
<tr>
<td>Word</td>
<td>Word (non-rel.)</td>
<td>18</td>
<td>Pseudoword?</td>
<td>Right (no)</td>
<td></td>
</tr>
<tr>
<td>Pseudoword</td>
<td>Word (indir.)</td>
<td>18</td>
<td>Pseudoword?</td>
<td>Left (yes)</td>
<td></td>
</tr>
<tr>
<td>Pseudoword</td>
<td>Pseudoword</td>
<td>27</td>
<td>Word-word?</td>
<td>Right (no)</td>
<td></td>
</tr>
<tr>
<td>Word</td>
<td>Pseudoword</td>
<td>27</td>
<td>Pseudoword?</td>
<td>Left (yes)</td>
<td></td>
</tr>
</tbody>
</table>

The first IS1 was 0 ms (SOA150) or 550 ms (SOA700); dir.: directly related, indir.: indirectly related, non-rel.: non-related.
Results

Behavioral Data

Because a delayed response was used no behavioral data related to semantic priming were obtained. RTs and error rates to the probe were investigated in two separate MANOVAs, with the independent factor sex, and the repeated-measures factors response type (yes–no), SOA (150 ms–700 ms) and condition (pseudoword–word, word–pseudoword, nonrelated, directly related, indirectly related).

For RTs, no main effect for sex ($P > 0.53$) or significant interactions with sex were found. Mean values ($\pm$ SD) were $832 \pm 167$ ms for the female group and $794 \pm 173$ ms for the male group. RTs showed main effects for condition [$F(4,116) = 8.3, P < 0.001$] and for response type [$F(1, 29) = 91.8, P < 0.001$], as well as interactions for SOA $\times$ condition [$F(4,116) = 3.8, P < 0.01$] and for response $\times$ condition [$F(4,116) = 56.2, P < 0.001$]. The shortest RTs were found for yes-responses in the three word–word conditions, while the longest RTs were shown for no-responses in the word–word conditions. RTs for the pseudoword conditions were in-between (Fig. 1). For all conditions, the post-hoc test revealed significant differences between yes- and no-responses. In addition, response type differed significantly between the conditions containing pseudowords and the conditions containing words only. Furthermore, the RTs for the directly related word pairs were significantly shorter than the nonrelated and the indirectly related condition. The interaction SOA $\times$ condition showed a uninterpretable, unsystematic pattern.

For error rates, no significant main effect ($P > 0.12$) or interaction with sex was found. The error rates (mean $= 4.77\%$) showed main effects for SOA [$F(1,29) = 16.8$, $P < 0.001$; mean values for SOA150 = 6%, for SOA700 = 3.47%] and for condition [$F(4,116) = 20.4, P < 0.001$]. The interaction response $\times$ condition [$F(4,116) = 9.3, P < 0.001$; Fig. 2] showed significantly higher error rates for the pseudoword–word condition compared with the remaining conditions and for the word–pseudoword condition compared with the three real-word conditions (yes-responses only). The interaction SOA $\times$ condition [$F(4,116) = 9.3, P < 0.01$] was mainly due to an outlying large error ($13.92\%$) for SOA150 in the pseudoword–word condition. Errorneous (i.e. premature) responses to the target were only found for the SOA700 condition (absolute values, mean 0.29, range 0–1).

Semantic Priming Effects

The target words evoked a centroparietal N400 which was considerably larger in the SOA700 condition than in the SOA150 condition. In both SOAs, the N400 increased with semantic distance, hence showing the typical semantic priming effect. In the SOA150 condition only, directly related target words evoked an early ‘P300-like’ positivity peaking at ~480 ms. A similar but smaller positivity was evoked by indirectly related targets. The N400 and ‘P300’ priming effects showed no obvious sex differences (Fig. 3a–d). The SOA differences for the N400 and
the early ‘P300’ are presented and discussed in detail in Hill et al. (2005).

For both SOAs, two separate MANOVAs were computed comparing the mean activity around the N400 peak (time window 350–450 ms). MANOVAs included the independent variable sex and the repeated measures factors electrode site (centroparietal sites Cz, CP1, CP2, CPz) and semantic distance (nonrelated, indirectly related, directly related). A comparison between SOAs was not performed because of the differences in baselines and component overlay effects.

SOA150 revealed a main effect for semantic distance \[ F(2,58) = 16.6, P < 0.001 \]. Post-hoc analysis revealed significantly more pronounced positive amplitudes for the directly related condition (3.33 µV) and the indirectly related condition (3.14 µV) compared with the nonrelated condition (2.16 µV). Thus, SOA150 showed a direct as well as an indirect semantic priming effect. Neither a main effect for sex \( (P > 0.73) \) nor for the interaction sex \( \times \) condition \( (P > 0.82) \) was found in this analysis.

SOA700 revealed a main effect for semantic distance as well \[ F(2,58) = 12.2, P < 0.001 \]. Post-hoc analysis showed significant differences between all three conditions with the smallest N400 amplitude for the directly related condition (–0.38 µV), followed by the indirectly related condition (–0.97 µV) and the nonrelated condition (–1.35 µV). Thus, like in SOA150, a direct and an indirect semantic priming effect were found. In addition, the directly and indirectly related conditions differed significantly in SOA700. Like in SOA150, neither a main effect for sex \( (P > 0.78) \) nor the sex \( \times \) condition interaction was found \( (P > 0.66) \).

**Sex Differences**

The ERPs evoked by all types of stimuli (primes, targets, probes) were analyzed for sex differences. In general, the visual P100 evoked by the stimulus onset, and in most cases the following N170, were significantly larger (sample-by-sample t-test, \( t > 2.04 \)) at occipital sites (O9, O10, P9, P10) for the female subjects.

For later time intervals, the ERP waveforms showed sex differences for several hundred milliseconds. The topographical pattern of the effects reported below remained mainly constant. In general, the following patterns were found (Figs 4–7).

1. The ERP waveforms were positive at posterior sites and inverted (negative) at frontal sites.
2. Compared with the male subjects, the ERP waveforms of the female subjects were more positive at posterior sites and more negative at frontal sites.

3. This sex difference was lateralized for primes and targets (except for the target words preceded by pseudoword primes in SOA700). The ERPs of the male subjects showed an attenuated positivity over the left posterior scalp region (cf. Fig. 8a, b) and an attenuated negativity at right frontal sites.

4. The probe-related ERPs did not show this sex-specific lateralization effect: the ERP-differences in the positive and the negative amplitude ranges showed a slightly left-lateralized, central pattern (cf. Fig. 9).

5. The target words preceded by pseudoword primes in SOA700 revealed a very different pattern compared with the other conditions, showing only some significant spots: there was a left frontal negative peak at ~510 ms (centered around site F5) for females, which was not found at the contralateral hemisphere or for the male subjects, and a right occipital positivity from 400 to 900 ms for the female subjects only.

The topographical distribution of the sex difference for the different stimulus types is displayed in the t-maps (Fig. 7). The statistical analysis with sample-by-sample t-tests revealed that the sex-differences reported above were significantly different. For the 100 ms intervals (Fig. 7), as well as for the 400 ms intervals (equivalent to the time-window analysis, see below), the t-values were >2.04 for the positive amplitude range and <2.04 for the negative amplitude range of the ERPs. Confirming the sex-specific lateralization effect for primes and targets, no significant t-values were found for the contralateral sites (right posterior and left frontal).

**Onset and Duration of Waveform Differences**

Onset and duration of these differences were explored by t-tests. For the primes in SOA700, the difference started at 160 ms (words) and 200 ms (pseudowords) at the left central site C3. At the left centroparietal electrode site CP5, where mostly the largest effects could be observed, the difference started at ~350 ms and lasted until nearly the end of the recorded epoch. For the targets in SOA700, the waveforms started to deviate at ~160–210 ms (C3) and 310–390 ms (CP5), and lasted until 620–730 ms. Targets preceded by pseudoword primes deviated firstly at the left frontal site F5 at 490 ms.

For SOA150, the waveforms started to differ significantly ($t > 2.04$) ~12–20 ms after target onset (= 162–170 ms after
prime onset). At electrode site CP5, the difference started at ~120–190 ms (different between the five prime-target combinations) and lasted until 660–750 ms.

For the response conditions, the waveforms were significantly different from ~150 ms (left centroparietal site CP3) after probe onset until the end of the recorded epoch (1000 ms at centroparietal site Pz).

The onset latencies of the sex-differences reported above for the posterior effects (positive amplitude range) were comparable (not preceding) to the negative amplitude range at frontal electrode sites.

**Time Window Analysis (MANOVAs)**

For this analysis the mean activities of the time windows from 300 to 700 ms were computed (for SOA150 this time window was related to prime onset). These time windows were centered around the peak of the activity difference in the grand-average waveforms. The duration of the interval was set to find the best match between the different conditions. For analysis, the left posterior electrode sites CP1, CP3, CP5, P1, P3, PO3 were chosen. At this region the sex-differences were largest and could be observed in all conditions. For the interhemispheric comparison, the corresponding sites of the right hemisphere were included (CP2, CP4, CP6, P2, P4, PO4) in the analysis.

For the SOA700 primes a MANOVA with sex as the independent factor and the dependent variables electrode position (six), hemisphere (two) and condition (word, pseudoword) was computed. This analysis revealed main effects for sex \( F(1, 29) = 4.7, P < 0.039 \) and electrode position \( F(5, 145) = 3.3, P < 0.01 \). No further significant main effects or interactions with sex were found (all \( P > 0.14 \)). The mean amplitudes (across all 12 sites) were 1.24 µV for the female group and 0.53 µV for the males.

Two separate MANOVAs were computed for the targets of SOA150 and SOA700 with the factors sex (two), electrode position (six), hemisphere (two), and condition (five: pseudoword–word, word–pseudoword, nonrelated, directly related, indirectly related).

The MANOVA for SOA700 targets revealed main effects for electrode position \( F(5, 145) = 17.9, P < 0.001 \) and for condition \( F(4, 116) = 11.3, P < 0.001 \), but no main effect for sex \( (P < 0.26) \). The interaction sex × hemisphere was not significant \( (P < 0.079) \). A significant interaction for sex × hemisphere × condition was found \( F(4, 116) = 2.5, P = 0.045 \). Post-hoc tests revealed the following results (compare Fig. 8a): (i) the word targets preceded by pseudoword primes showed the smallest amplitudes, independent of sex and hemisphere. The amplitudes were significantly smaller compared with the remaining...
four conditions for the female group over both hemispheres, and for the male group over the right hemisphere. The left hemispheric electrode sites of the male group showed significantly smaller amplitudes compared with the indirectly and the directly related word pairs. (ii) For the female group, the directly related word pairs showed significantly larger amplitudes compared with the other conditions, independent of hemisphere. At least in part, this larger positivity can be attributed to the smaller N400. (iii) The female group showed no hemispherical differences within conditions, that is, females showed a bilateral activation pattern. (iv) The males showed significantly higher amplitudes over their right hemisphere compared with the left hemisphere within the four target stimuli preceded by word primes. (v) The males showed a significantly smaller amplitude over their left hemisphere compared with the left hemisphere of the female group, except for the pseudoword-word pairs. In summary: first, in both groups targets preceded by pseudowords were not processed like targets preceded by words; and secondly, males showed a smaller amplitude at left-hemispheric electrode sites.

The MANOVA for SOA150 targets revealed a main effect for sex \( F(1,29) = 4.3, P < 0.048 \). The mean amplitudes (across all 12 sites) were 2.82 μV for the female group and 1.93 μV for the males. Further main effects were found for electrode position \( F(5,145) = 6.1, P < 0.001 \) and for condition \( F(4,116) = 9.6, P < 0.001 \). The interaction sex × hemisphere failed to reach the significance level \( (P = 0.117) \). Numerically, the mean amplitudes were larger for the female group. Comparable to the SOA700 targets, a bilateral distribution was shown by the female group and a smaller amplitude at left-hemispheric electrode sites by the male group (Fig. 8b).

For the probes, a MANOVA with sex as independent factor and the dependent variables electrode position (six), hemisphere (two), SOA (two) and response condition (four) was computed. This analysis revealed main effects for sex \( F(1,29) = 10.6, P = 0.0024 \) (females: 3.5 μV, males: 1.98 μV), electrode position \( F(5,145) = 6, P < 0.001 \), hemisphere \( F(1,29) = 29.7, P < 0.001 \) (right: 3.3 μV, left: 2.18 μV) and response condition \( F(3,87) = 15, P < 0.001 \). All interactions including the factor sex had \( P \)-values >0.092. No sex-specific lateralization effect was found (Fig. 9).

Because the probe disappeared when response was made, probe-offset effects may affect the time window analysis, although this possibility is unlikely because mean RTs exceeded...
the chosen time window. A correlational analysis confirmed this assumption. Pearson’s $r$ was $-0.03$ for Cz $\times$ RT and $0.03$ for Pz $\times$ RT (all response conditions collapsed).

**Discussion**

**Semantic Priming Effects**

Typically, ERP amplitudes showed a direct and, replicating previous findings, an indirect semantic priming effect. In addition, in SOA150 only, directly related and indirectly related target words evoked an early (~480 ms) ‘recognition-P300’ because subjects may have detected the semantic relationship between word pairs implicitly. This early SOA $\times$ semantic-distance modulated ‘P300-effect’ points clearly to a different functionality as the later (peaking ~750 ms) and smaller ‘P300’ evoked by pseudoword targets in both SOAs (note: probabilities were 25% for pseudoword targets and 75% for word targets). Comparable to this late ‘P300’, pseudoword primes in SOA700 evoked a
centroparietal positivity (for details, see Hill et al., 2005). As in the previous study (H. Hill et al., submitted for publication), the priming effects were independent of sex. This may point to a similarity in priming mechanisms in both sexes, at least for this task design, which used isolated visual stimuli in a typical artificial laboratory setting. More naturalistic language tasks (with associated word pairs included), such as reading a text, hearing a story or talking with a partner, may lead to different results.

**Sex Differences**

This study replicated our general finding of a sex-related difference found in the previous study (H. Hill et al., submitted for publication), which is a larger sustained positive activation in the female group. In contrast to the previous design, we used a delayed response to separately explore sex differences during semantic processing and response execution. The modification in the experimental design and the dense sensor array aimed at a better differentiation of the effects. For the female group, the sustained positivity showed a bilateral distribution over posterior scalp regions and an inverted (negative) frontal pattern related to the presentation of words and pseudowords, and also to the response processing. Male subjects, in contrast, showed an amplitude reduction over the left posterior and right frontal regions related to the word/pseudoword presentation. This sex-specific lateralization effect disappeared when the response on the probe was required.

The sex-specific ERP effect raises the question of its functional (cognitive) significance. The task we used did not delay the lexical decision as effectively as the delayed-probe tasks of Kutas and Hillyard (1989; letter-search task) and of Deacon et al. (1995, 1999; semantic-judgement task). In our task, the prime–target sequence could already be preanalyzed if only words or a pseudoword were used before the probe-question was presented. When the prime was a pseudoword in SOA700, this preanalysis could be finished before the target was presented in all the other conditions, this preanalysis could be performed after presentation of the target (because of the fast stimulus presentation for the pseudoword–word condition in SOA150 as well). The late ‘P300-effects’ related to pseudoword

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**Figure 8.** (a) Mean amplitudes (averaged across six electrode sites) for target words in SOA700. In summary, this interaction reveals the following: first, in both groups targets preceded by pseudowords were not processed like targets preceded by words; and secondly, males showed a smaller amplitude at left-hemispheric electrodes (compare text for details). Prime–target pairs: pw-w = pseudoword-word, w-pw = word-pseudoword, nr = nonrelated, ir = indirectly related, dr = directly related. (b) Mean amplitudes (averaged across six electrode sites) for target words in SOA150. Although males showed a smaller amplitude than females at both hemispheres, this difference was larger at left-hemispheric electrodes, comparable to SOA700. In contrast to SOA700, the pseudoword-word condition also showed a sex-difference (see text for details).
targets (both SOAs) and pseudoword primes (SOA700) support this possibility. Thus (citing one of the reviewers), it seems likely that subjects make the lexical decision (word/ pseudoword judgment) as soon as the stimuli appear, and then wait for the probe to encode and execute the response. Therefore, the ERP response to the prime and target do not reflect lexical and semantic processes that are unencumbered by task-related (categorization- and decision-related) components. This in turn implies that sex-related differences could be related to reading (i.e. linguistic processing of the prime and target), or to the word-pseudoword decision.

Despite this unanswered question, the data provide the following indications about their functionality. The onset of this sex difference at ~150–200 ms after stimulus onset fits with the begin of semantic processing (early visual word processing, e.g. Posner and Abdullaev, 1999; Frishkoff et al., 2004; differentiation between use generation and reading, Abdullaev and Posner, 1998), as well as with non-linguistic semantic processing like, for example, the recognition of facial expressions (e.g. Balconi and Pozzoli, 2003; Balconi and Lucchiarì, 2005). A considerably earlier onset of the effect would make a relation to semantics rather unlikely. Furthermore, the real-word targets preceded by pseudoword primes in SOA700 evoked a very different ERP pattern (cf. Fig. 7) compared with the other conditions and showed no sex difference in the mean activity (cf. Fig. B2). The target could be ignored because the word-pseudoword judgement could already be made to the prime. On the other hand, the pseudoword-preceded target in SOA700 evoked a large N400, comparable to the nonrelated target (cf. Hill et al., 2005), which implies that subjects did not ignore this target. Therefore it may be possible that the sustaining positive-negative activation pattern evoked by primes and targets is related to a categorization process (is the letter string a word or a pseudoword?). However, this argument is weak insofar as a decision about the prime (prior to the target) could evoke processes which may confound the processing of the target. Therefore the question about the functionality (decision-related versus linguistic) of the sex-specific lateralization effect needs further investigation. A suitable methodical approach would be to compare and contrast the different delayed-probe designs (Kutas and Hillyard, 1989; Deacon et al., 1995; the present one). In addition, a passive reading condition (Brown et al., 2000) should be included, especially because an fMRI study of Kansaku et al. (2000) reported a sex-specific lateralization effect during passive story listening.

The larger ERP amplitudes (posterior positivity and frontal negativity for primes, targets and probes independent of lateralization effects) found for female subjects raises questions about the physiological nature of this effect. Positive and negative ERP amplitudes cannot be simply attributed to the decreased or increased activation of the neuronal generators if their location, cytoarchiteconic structure and functionality (inhibitory/excitatory) and the orientation of the cortical layers are not precisely known (cf. Niedermeyer, 1996, 1998). Therefore, polarity does not answer whether females require more or less effort for language processing in general, nor whether the involved brain structures differ with respect to these processing demands. A second question addresses the localization of the neuronal generators (sources) of the ERP effects evoked by primes and targets. Assuming bilateral sources are active in females, and sources in the left hemisphere are the only ones active or at least dominating in males, the topographical distribution of the ERP effects can be explained with the following source-sink pattern: inferior frontal sources may generate the observed negative frontal ERP pattern and their sum-dipoles may project to the posterior region of the contralateral hemisphere. Because no right frontal generators are active in male subjects, an attenuated right frontal negativity and an attenuated left posterior positivity compared with the contralateral hemisphere and compared with the female subjects can be observed.

In the MANOVA-based statistical analysis the posterior left-lateralized sex difference was largest for the SOA700 targets (preceded by word primes), although this effect was attenuated due to the 100 ms pretarget baseline, which removed the influence of the sex difference shown by the primes. For the SOA150 targets and the SOA700 primes, this lateralization effect was visible in the data too and confirmed by the t-test analysis, although it failed to reach the significance level in the MANOVA. In contrast to the prime and target ERPs, the probe-evoked sex difference showed a more bilateral pattern for both sexes with larger amplitudes for the female group, and the ERP itself was dominated by a large centroparietal ‘P300-like’ component evoked by the response processing. Furthermore, in SOA150 directly related and indirectly related targets evoked the earlier (~480 ms), centroparietal ‘recognition P300’ (Hill et al., 2005; see above). These ‘P300-like’ positivities evoked by probes and targets occurred in the same time range as the sex-specific difference effects. Especially for the primed targets in SOA150, the ‘recognition-P300’ with their centroparietal topography has obscured the sex-specific lateralization effect. In contrast, pseudoword targets evoked an additional ‘P300’ in both SOAs (see Hill et al., 2005). However, this component was too late (peaking at ~750 ms) to distort the lateralization effect significantly.

**Methodological Implications**

Despite the unanswered questions about functionality and neuronal sources of the ERP effects, the high temporal
resolution of ERP measures and the chosen design allowed to distinguish a sex difference during visual word processing (and possibly categorization) at the right frontal and left posterior electrode sites and a more bilateral — ‘P300’-dominated — activation related to response processing. Without the experimental separation of the different processing steps, the bilateral activation would obscure the lateralization effect and the advantage of the high temporal resolution of ERP measures would be lost. This may be why ERP studies usually do not report any sex-specific lateralization effects, but what conclusion can be drawn for a comparison with studies using metabolism-based imaging methods like fMRI and PET? In a comment on the meta-analysis of Sommer et al. (2004), Ortigue et al. (2005) reasoned that most imaging studies may have failed to detect sex differences in language lateralization because the temporal resolution of their methods is insufficient. They provided evidence for their point of view by a reanalysis of ERP data using a distributed EEG source analysis procedure, which revealed a sex-specific lateralization effect between at ~180 to 380 ms in a go/no-go paradigm, using word and non-word stimuli. This critical time window for language processing should be too short to develop a detectable increase of blood flow. In their reply to Ortigue et al., Sommer et al. (2005) provided evidence that fMRI should be able to detect subtle differences in language processing nevertheless, but reasoned that there are no sex differences in language processing at the population level. In principle, imaging methods with their high spatial resolution should be able to detect a sex-specific lateralization effect and, in contrast to the surface ERP, separate it from e.g. response-related effects, even if both processes interfere temporally. However, this requires that the chosen baseline be adequate and that the signal intensity be sufficient. Sheth et al. (2004) showed in rat somatosensory cortex that brain metabolism — in contrast to the electrical fields — can only be measured when the stimulation exceeds a certain intensity threshold. Huettel et al. (2004) compared fMRI and intracranial recorded ERPs in humans with visual stimulation, using a static checkerboard with different presentation times (100, 500, 1500 ms). This stimulation evoked a large visual N100 ERP followed by a smaller sustained activation, maintained during the presentation of the checkerboard. FMRI, however, revealed only an activation correlated with the sustained activation. Using a 4 T machine, the maximal blood oxygenation level-dependent (BOLD) response was 1.2% compared with baseline. The interval was 16 s. It can be concluded that it is necessary to increase the stimulus presentation rate to increase metabolism and, as a result, the BOLD response in the neuronal structures generating transient ERPs, and hence make ERP and fMRI measures more comparable. Transferring this comparison of methods implies that imaging methods primarily measure the activity of sources generating sustaining activations and less the generation of distinct ERP components like the N400. These methodical problems have to be considered when the results of metabolism-based imaging studies are related to the results of ERP/MEG measures, not only in language research. Although source analysis techniques can be applied to localize the brain structures generating surface ERP/MEG patterns (e.g. Scherg, 1990; Pascual-Marqui et al., 1994; Michel et al., 2004), these mathematical solutions do not necessarily detect the physiological sources (the ‘inverse problem’). One method of choice to solve this problem is to constrain the potential sources to the activations measured in comparable fMRI/MEG experiments (‘seeding technique’). However, this implies that fMRI and ERP/MEG measure the same activity of the same brain regions, which is not necessarily the case, even if the experiments are identical (cf. Huettel et al., 2004; Michel et al., 2004, p. 2201).

Considering the limitations and advantages of the chosen research method, the heterogeneity of the language tasks used may reach the focus of interest and may be helpful to clarify the controversy about sex-specific lateralization effects. Thus, Kitazawa and Kansaku (2005) concluded in a comment on Sommer et al. (2004), based on an earlier review paper about imaging studies (Kansaku and Kitazawa, 2001), that sex differences in lateralization may not be a general feature of language processing but may be related to the specific condition. Therefore a better separation of the processing steps and the integration of different methods like event-related fMRI, ERP and MEG should help to disentangle this heterogeneity between studies.

Notes
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References