Memory Traces for Spoken Words in the Brain as Revealed by the Hemodynamic Correlate of the Mismatch Negativity

The mismatch negativity response, considered a brain correlate of automatic preattentive auditory processing, is enhanced for word stimuli as compared with acoustically matched pseudowords. This lexical enhancement, taken as a signature of activation of language-specific long-term memory traces, was investigated here using functional magnetic resonance imaging to complement the previous electrophysiological studies. In passive oddball paradigm, word stimuli were randomly presented as rare deviants among frequent pseudowords; the reverse conditions employed infrequent pseudowords among word stimuli. Random-effect analysis indicated clearly distinct patterns for the different lexical types. Whereas the hemodynamic mismatch response was significant for the word deviants, it did not reach significance for the pseudoword conditions. This difference, more pronounced in the left than right hemisphere, was also assessed by analyzing average parameter estimates in regions of interests within both temporal lobes. A significant hemisphere-by-lexicality interaction confirmed stronger blood oxygenation level-dependent mismatch responses to words than pseudowords in the left but not in the right superior temporal cortex. The increased left superior temporal activation and the laterality of cortical sources elicited by spoken words compared with pseudowords may indicate the activation of cortical circuits for lexical material even in passive oddball conditions and suggest involvement of the left superior temporal areas in housing such word-processing neuronal circuits.

Keywords: brain, event-related potential, fMRI (BOLD), language, memory trace

Introduction

Mismatch negativity (MMN), a unique indicator of automatic cerebral processing of acoustic stimuli, has been increasingly utilized for investigating the neural processing of speech and language (Naätänen 2001; Pulvermüller and Shtyrov 2006). MMN, with its major source of activity in the superior temporal auditory cortex, is an evoked brain response elicited by rare (so-called deviant) acoustic stimuli occasionally presented in a sequence of frequent (standard) stimuli (Alho 1995; Naätänen 1995). Importantly, MMN can be elicited in the absence of the subject’s attention to the auditory input (Tiitinen et al. 1994; Schröger 1996). It is therefore considered to reflect the brain’s automatic reaction to any change in the auditory sensory input. More recently, increased MMN amplitudes in response to native language phonemes and syllables and left-hemispheric lateralization of such activations led to a conclusion that preexisting long-term memory traces for speech sounds may be activated in passive oddball paradigm producing this specific MMN increase (Dehaene-Lambertz 1997; Naätänen et al. 1997; Alho et al. 1998; Shtyrov et al. 2000). Strikingly, it was found that the MMN amplitude increases substantially in the process of training as the subjects become more familiar with the experimental stimuli thus developing memory traces for previously unknown items (Naätänen et al. 1993; Winkler et al. 1999). Further still, we found that MMN in response to individual words was greater than for comparable meaningless word-like (i.e., obeying phonological rules of the language) stimuli (Pulvermüller et al. 2001). In a series of studies on this topic, we presented subjects with sets of acoustically matched word and pseudoword stimuli and found an increased MMN response whenever the deviant stimulus was a meaningful word (Pulvermüller et al. 2001, 2004; Shtyrov and Pulvermüller 2002b; Shtyrov et al. 2005). This enhancement, typically peaking at 100–200 ms, is best explained by the activation of cortical memory traces for words realized as distributed strongly connected populations of neurons (Pulvermüller and Shtyrov 2006). The lexical enhancement of the MMN, repeatedly confirmed by our group, was also demonstrated by other groups using various stimulus setups and languages (Korpilahti et al. 2001; Kujala et al. 2002; Sittiprapaporn et al. 2003; Endrass et al. 2004; Pettigrew et al. 2004), leading to a conclusion that, all acoustic factors being equal, lexical (and possibly semantic) status of the deviant may lead to greater neural activation that happens in addition to the change-detection MMN. Wunderlich and Cone-Wesson (2001) did not find larger MMNs to consonant-vowel-consonant words (e.g., bad) than to consonant-vowel pseudowords (ba), but physical stimulus properties were obviously not fully matched; the study focused on psychoacoustic issues instead. Our own studies indicated that the lexical status of the deviant stimulus was relevant for eliciting the MMN, but the lexical status of the standard stimulus did not significantly affect MMN amplitude (Shtyrov and Pulvermüller 2002b). However, others have reported that the event-related brain response evoked by the speech standard stimulus is also affected by its lexicality/familiarity (Diesch et al. 1998; Jacobsen et al. 2004, 2005), the most likely reasons for this discrepancy between different studies being probably of methodological nature.

As a result of such growing body of evidence, the pattern of MMN response to individual word deviants has been considered as indicating a word’s lexicosemantic “signature,” its memory trace activated in the brain, which offers a unique opportunity to investigate neural processing of language in nonattention demanding and task-free fashion. Indeed, investigations of language function using MMN that followed were able to provide a great level of detail on the spatiotemporal patterns of activation involved in early automatic lexical access, semantic category-specific processing, and even in syntactic processes (Shtyrov and Pulvermüller 2002a; Pulvermüller and Shtyrov 2003; Pulvermüller et al. 2003, 2004, 2005; Shtyrov et al. 2003,
corded multiple repetitions of these stimuli and additionally one more segments [kI], [pI], and [fI], which had been separated from their own it from a similar word not used as such in the experiment. The sound [k] one of the actual stimuli and copied to the other 2), we selected to take acoustic cues (which would arise should the final plosion be drawn from this, one needs to use cross-splicing, that is, replacing the original sounds which is highly important in MMN experiments, we decided to use iden-
tical final phoneme [k] in each standard and deviant sound. To achieve
which is highly important in MMN experiments, we decided to use iden-
tical final phoneme [k] in each standard and deviant sound. To achieve
duration. To further minimize acoustic differences between the stimuli,
its fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
duration. To further minimize acoustic differences between the stimuli,
its fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall

**Materials and Methods**

**Subjects**

Eleven healthy right-handed (handedness assessed according to Oldfield
1971) native monolingual English-speaking volunteers (age 20–31 years,
5 females) with normal hearing and no record of neurological diseases
were presented with 4 sets of spoken English language stimuli in 4
separate experimental conditions (see Table 1 and Fig. 1).

**Stimuli**

The experimental stimuli included 2 short English words: [kIk] (kick)
and [pIk] (pick), which were, in 2 separate conditions, contrasted as
deviants against a frequent standard pseudoword [fIk]. We re-
corded multiple repetitions of these stimuli and additionally one more
word —[hIk]—uttered by a female native speaker of English and with
great care selected a combination of the 4 items whose vowels matched
in their fundamental frequency (F0) as well as sound energy and overall
duration. To further minimize acoustic differences between the stimuli,
which is highly important in MMN experiments, we decided to use identi-
cal final phoneme [k] in each standard and deviant sound. To achieve
this, one needs to use cross-splicing, that is, replacing the original sounds
in the recordings by different ones. To avoid differential effects of early
acoustic cues (which would arise should the final plosion be drawn from
one of the actual stimuli and copied to the other 2), we selected to take
it from a similar word not used as such in the experiment. The sound [k]
was therefore cross-spliced from the recording of [hIk] to the initial
segments [Ik], [pIk], and [fIk], which had been separated from their own
terminal [Ik]-plosives. The pause of about 80 ms preceding the final stop
consonants in this type of English monosyllabic stimuli (Fig. 1) makes
such stops an ideal target for cross-splicing, and we were able to
smoothly replace the phonemes producing naturally sounding stimuli
with precisely controlled acoustic features. The sounds were normal-
ized to have the same loudness by matching their root-mean-square
(RMS) power; to ensure even smaller acoustic differences between the
stimuli, RMS power was separately normalized for the initial consonant-
vowel segments and for the final stops of the stimuli. Such meticulous
procedures of stimulus preparation is essential for MMN experiments
because MMN is highly sensitive to acoustic differences between the
standard and deviant stimuli. All stimuli were 330 ms in duration. For
the analysis and production of the stimuli, we used the Cool Edit 2000
program (Syntrillium Software Corp., Phoenix, AZ).

**Acoustic Stimulation**

In condition 1a (see Table 1 for complete stimulus design), we used the word “kick” as the deviant stimulus and the pseudoword [fIk] as the
standard (see Table 1). In condition 2a, the word “pick” served as the deviant
stimulus against the same pseudoword. In conditions 1b and 2b, the
reversed design was used, that is, the deviant stimulus was the pseudo-
word, whereas the words were presented as standard stimuli. These
additional conditions were performed in order to obtain responses to
the same acoustic contrasts with the reversed lexical relationship
between the standard and deviant stimuli, which allowed us to disentangle purely acoustic effects (which should arise due to basic
phonetic differences between the stimuli) from the lexicality effects.
This design is based on our previous research, which suggested that
the deviant stimuli are important for activating word memory traces,
wheras the nature of standards seems of smaller significance (Shtriyov
and Pulvermüller 2002b). So, the standard-deviant acoustic-phonetic
contrast, the critical variable determining acoustical MMN (Na¨a¨ta¨nen
and Alho 1997), was identical in each pair of conditions, whereas the
deviant stimuli were either words (1a/2a) or a pseudoword (1b/2b).
The 4 experimental conditions were performed with every subject,
their order being counterbalanced across the subject group.

In each condition, the stimuli were presented in 90 trains consisting
of 7 sounds each with 800-ms interstimulus interval within trains
(onset-to-onset, see Fig. 2). The interval between the trains was 3.4 s. Fifty
percent of the train consisted of standard stimuli only; the remaining
50% had 6 standard stimuli and one deviant, which was placed in
positions 4–7 from the train onset, that is, commencing at 2.8, 2.0, 1.2,
and 0.4 s before the image acquisition (in pseudorandom fashion, with
equal probability for each position). This was done in order to position
the acoustic deviance within a few seconds from the image acquisition,
with some variability, in order to maximize the chances to register its
hemodynamic response (which was suggested to have a delay in the
range of 2–3 s for the auditory cortices, see e.g., Belin et al. 1999). The
echo planar images (EPIs) were obtained after each stimulus train in
order to ensure the stimuli are played in silence and not masked by the
fMRI scanner noise. This way, the probability of a deviant’s occurrence
in an allowed position was 12.5%, and the overall percentage of deviant
stimuli was one in 14 (i.e., ~7.1%), falling within the usual range for MMN
experiments (Sinkkonen and Tervaniemi 2000). The stimuli were
equally presented at 70 dB SPL via headphones connected to a PC
equipped with scanner-driven stimulation program (Medical Research
Council Institute for Hearing Research, Nottingham, UK), which was
triggered by the image acquisition pulse.

**Image Acquisition**

Subjects were positioned in a 3-T Bruker MR system and instructed to
watch a silent videofilm of their own choice (without subtitles to avoid
additional language-related activity and extraneous eye movements) and
to ignore any auditory signals while EPIs were obtained using a head
coil. The images were obtained in 3.4-s gaps between the stimulus trains
to avoid acoustic interference from the scanner noise with the stimuli
(so-called “sparse imaging,” Hall et al. 1999); in addition to 90 test trains,
6 scans were acquired following silent periods equal in length to the
trains (null events). EPI sequence parameters were time repetition 8.6 s,
etch time 115 ms, and flip angle 90 degrees. The functional images
consisted of 21 slices covering the whole brain (slice thickness 4 mm,
interslice distance I mm, and in-plane resolution 1.6 × 1.6 mm).

**Image Processing**

Imaging data were processed using SPM2000 software (Wellcome
Department of Cognitive Neurology, London, UK). The magnetic reso-
nance imaging (MRI) scanner used here performs “interleaved” EPIs to

**Table 1**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Condition 1a</th>
<th>Condition 1b</th>
<th>Condition 2a</th>
<th>Condition 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviant</td>
<td>[kIk] kick</td>
<td>[fIk] pseudoword</td>
<td>[pIk] pick</td>
<td>[fIk] pseudoword</td>
</tr>
<tr>
<td>Standard</td>
<td>[hIk]</td>
<td>[hIk]</td>
<td>[hIk]</td>
<td>[hIk]</td>
</tr>
</tbody>
</table>
| Note: All stimuli were maximally matched for their acoustic properties. The standard-deviant contrasts are identical in each pair of conditions, whereas the deviant stimuli in conditions 1a/2a are 2 words and in conditions 1b/2b, a meaningless pseudoword.

30 fMRI Correlate of Memory Traces for Spoken Words · Shtriyov et al.
reduce the effect adjacent slices have on each other: first the odd slices are collected, then the even ones. Images were off-line corrected for this interleaved slice order. Further still, the different time delays between each slice and the stimulation/scanning onset constitute the so-called time-slicing problem, which was solved here by realigning all scans to the first image using full sinc interpolation (Henson et al. 1999). The advantage of temporal interpolation is that inferences concerning differences in hemodynamic response function (HRF) height between slices are less likely to be confounded by different slice acquisition times. Phase maps were used to correct for inaccuracies resulting from inhomogeneities in the magnetic field (Jezzard and Balaban 1995; Cusack et al. 2003). The EPI images were coregistered to structural $T_1$ images using a mutual information coregistration procedure. This uses a basic concept from information theory, mutual information (relative entropy), as a matching criterion and applies it to measure the statistical dependence or information redundancy between the image intensities of corresponding voxels in the matched images, which is assumed to be maximal if the images are geometrically aligned. Such maximization is considered a very general and powerful criterion because no assumptions are made regarding the nature of this dependence and no limiting constraints are imposed on the image content of the modalities involved (Maes et al. 1997). The structural MRI was normalized to the 152-subject $T_1$ template of the Montreal Neurological Institute. The resulting transformation parameters were applied to the coregistered EPI images. During the spatial normalization process, images were resampled with a spatial resolution of $2 \times 2 \times 2$ mm. Finally, all normalized images were spatially smoothed with a 12-mm full-width half-maximum Gaussian kernel, and single-subject statistical contrasts were computed using general linear model (Friston et al. 1998). Responses to the deviant stimuli were contrasted against those to the standard ones from the same experimental condition (i.e., word deviants vs. pseudoword standards and vice versa). Group data were analyzed with a random-effects analysis in SPM2000; only effects surviving false discovery rate (FDR) correction are reported as statistically significant.

A brain locus was considered to be activated in a particular condition if its voxels passed the threshold of $P = 0.05$ (corrected for FDR). For region-of-interest (ROI) analysis of areas differentially activated by specific stimulus categories, we computed the average parameter estimates over voxels for each individual subject. This was done using the Marsbar software utility (http://marsbar.sourceforge.net), an SPM-integrated toolbox that provides an extensive set of routines for ROI analysis (Brett et al. 2002). Thereby extracted blood oxygenation level-dependent (BOLD) activation values from contrasts between deviant and standard blocks were subjected to an analysis of variance (ANOVA) including the factors stimulus type (word vs. pseudoword deviant) and hemisphere (left vs. right).

**Ethical Considerations**

All subjects gave their written consent to participate in the experiments and were paid for their participation. The experiments were performed in accordance with the Helsinki Declaration. Ethical permission for the experiments was issued by the Local Research Ethics Committee, Cambridge, UK.

**Results**

The first random-effect analysis pulled together all auditory stimuli contrasted against silence. This indicated strong auditory activation in the superior temporal (most likely primary and secondary auditory) cortices of both hemispheres ($P \leq 0.001$, FDR-corrected, see Fig. 3) indicating a robust auditory response even in a passive condition under strong attentional withdrawal and concurrent visual stimulation.
In the following analysis step, we contrasted deviant and standard blocks using the standard approach to MMN analysis in event-related potential (ERP) experiments. As it was found that none of the deviant trains with deviant sounds in position 7 (i.e., 400 ms before the EPI scan onset) produced any significant results (most likely due to insufficient time for the hemodynamic...
response to develop), these were excluded from the analysis, and the remaining deviant trains with deviants in positions 4–6 were used for contrasting against standards. This further analysis showed that the activation patterns were clearly distinct between the word and pseudoword blocks (Fig. 4). Whereas the word-elicited BOLD mismatch response in the temporal lobes (encompassing superior temporal gyrus and possibly extending into superior temporal sulcus and medial temporal

**Figure 4.** Random-effect analysis contrasting deviant versus standard stimuli for word and pseudoword blocks before and after correction for search volume. Word-elicited MMN in the temporal cortex was significant even after the correction for search volume in both temporal lobes; the pseudoword-elicited MMN did not survive the correction procedure.
To further analyze the latter, we decided to directly compare the activity in the left and right temporal areas for the different stimulus types. To this end, from deviant–standard contrasts, we extracted average parameter estimates in voxels within 15-mm sphere around the center of Heschl’s gyrus in each subject’s left and right hemispheres (based on Morosan et al. 2001) and submitted these to ANOVA for statistical verification. This volume included primary auditory areas and adjacent cortex attributable to auditory belt and parabelt areas (Rauschecker 1998; cf., also Gutschalk et al. 2002; Patterson et al. 2002). The analysis confirmed differential activation and produced significant hemisphere-by-stimulus type interaction \((F_{1,10} = 5.97, \ P < 0.035)\) indicating stronger BOLD mismatch responses to words than pseudowords in the left but not in the right hemisphere’s auditory cortex (Fig. 5).

To assess possible lexicality effects on the standard stimuli (see Introduction), we also directly contrasted the activation following the standard blocks of different types. This, however, did not produce any significant results.

**Discussion**

In the present study, we attempted to use fMRI to register hemodynamic counterpart of auditory MMN responses elicited by words presented among pseudowords or by pseudowords presented among words in passive oddball paradigm. In order to minimize acoustically related effects, phonetic stimulus properties and acoustic contrasts were carefully matched across conditions. Passive oddball paradigm was used in which the subjects were instructed to ignore the auditory stimuli and were additionally distracted from the stimulation by watching self-selected video. The stimulation was thus similar to that usually employed in MMN studies using EEG/MEG with an exception that the stimulation was periodically interrupted by the fMRI scanner noise. The sparse imaging was applied to make sure the stimuli were clearly audible and none of their features were masked by the scanner noise. In order to minimize possible effects of the resulting pause and reinstate the status of the standard stimulus, which serves as the basis of deviance detection by determining the context of sound sequence (Sussman et al. 2003), the first few stimuli after the scanner pulse were always standards.

In spite of the strong concurrent visual stimulation and the nonattend design, all stimuli showed a clear activation in the vicinity of the auditory cortex in both temporal lobes. This indicates that, similar to EEG and MEG experiments, passive auditory presentation simultaneously with visual distraction task can be used to study auditory processing in fMRI.

Furthermore, by contrasting the standard and deviant blocks, we were able to register a difference between BOLD activation for deviants and standards, that is, the putative hemodynamic analogue of the MMN. Such interpretation is supported by the earlier studies, which succeeded in recording MMN-like differences in fMRI using nonspeech stimuli (Opitz et al. 1999, 2002; Molholm et al. 2005; Gomot et al. 2006). (It needs to be understood that the application of the term “MMN” to fMRI results is only to highlight this indirect putative link between the neural processes and the BOLD activations; the response polarity implied by this term does not have any counterpart in fMRI domain.) Admittedly, an immediate correspondence between hemodynamic and EEG/MEG data cannot be unambiguously established at present, and it is conceivable that the usually registered electrophysiological MMNs and MMN-like hemodynamic phenomena are not necessarily directly related. The use of similar stimulation paradigm and the similarity in the result patterns suggest that the current fMRI data may be related to the same neural processes that underlie electric/magnetic MMNs to linguistic material; such analogies should, however, be treated with caution. To gain stronger evidence for this correspondence, multimodal studies using combined multichannel EEG/MEG and fMRI recordings and correlation analyses are necessary.

An important difference between this and the earlier hemodynamic MMN studies is the more subtle nature of the contrasts between the standard and deviant stimuli: previously, event-related designs similar to electrophysiological ERP studies were used estimating hemodynamic responses after each individual stimulus. Here, with a goal of minimizing acoustic disturbances

---

**Table 2**

Word-elicited hemodynamic response (deviant–standard contrasts): statistical values adjusted for search volume and coordinates for 3 local maxima in each hemisphere more than 8.0 mm apart (coordinates in Talairach space)

<table>
<thead>
<tr>
<th>P</th>
<th>FDR corrected</th>
<th>T</th>
<th>Z</th>
<th>P</th>
<th>x</th>
<th>y (mm)</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025</td>
<td>0.39</td>
<td>4.68</td>
<td>0.000</td>
<td>-48</td>
<td>-27</td>
<td>-5</td>
<td></td>
</tr>
<tr>
<td>0.025</td>
<td>0.31</td>
<td>4.45</td>
<td>0.000</td>
<td>-55</td>
<td>-23</td>
<td>-5</td>
<td></td>
</tr>
<tr>
<td>0.040</td>
<td>0.78</td>
<td>3.75</td>
<td>0.000</td>
<td>-57</td>
<td>-42</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>0.025</td>
<td>0.17</td>
<td>4.42</td>
<td>0.000</td>
<td>50</td>
<td>-29</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>0.025</td>
<td>0.45</td>
<td>4.24</td>
<td>0.000</td>
<td>54</td>
<td>-13</td>
<td>-8</td>
<td></td>
</tr>
<tr>
<td>0.027</td>
<td>0.61</td>
<td>4.01</td>
<td>0.000</td>
<td>50</td>
<td>-19</td>
<td>-3</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 5.** ROI analysis comparing word- and pseudoword-elicited MMNs in the left and right temporal lobes. ANOVA using ROI-extracted activations produced significant hemisphere-by-stimulus type interaction indicating stronger BOLD MMN responses to words than pseudowords in the left but not in the right hemisphere’s auditory cortex.
of scanner noise, we obtained EPIs after entire stimulus trains. The only difference between the standard and deviant trains, each consisting of 7 sounds, was a single deviant auditory event; the rest of the stimuli were identical (i.e., all standards) in both deviant and standard trains. The differences thus were minimal. Further, any difference-related BOLD responses was most likely smeared further by variable position of the individual deviant events, an inherent feature of MMN design requiring random un-expected changes for response elicitation. Still, in spite of such minute, brief, and variable acoustic differences, the deviant-standard contrasts produced hemodynamic mismatch responses. Again, this happened under distraction conditions during concurrent visual input in the confined and uncomfortable environment of fMRI scanner. This implies a certain degree of robustness of the BOLD mismatch response.

This BOLD correlate of the MMN activation was, however, distinct for the subblocks involving word and pseudoword deviant stimuli. Most notably, only the word deviants produced mismatch responses that could survive FDR corrections for search volume. This indicated that the word-elicited MMNs possess a more robust degree of hemodynamic activation than those evoked by nonword deviants. This is remarkably similar to the phenomenon of lexical MMN enhancement known from the previous EEG/MEG studies, which have demonstrated that MMN in response to individual words is always greater than for comparable meaningless pseudowords if the acoustic contrasts are kept the same (Korpinia et al. 2001; Pulvermüller et al. 2001, 2004; Shtyrov and Pulvermüller 2002b; Sittiprapaporn et al. 2003; Endrass et al. 2004; Pettigrew et al. 2004). The standard-deviant acoustic contrast, the critical variable determining the mismatch response (Nätänen and Alho 1997), was identical between the conditions; it is therefore unlikely that the difference in brain responses was due to acoustic factors. Instead, it appears likely that it is the lexicosemantic difference between the deviant stimuli (meaningful words vs. senseless pseudoword) that contributed to this dissociation. This is in line with the previous research, which demonstrated that oddball brain responses may reflect lexicosemantic features of the stimuli (Pulvermüller and Shtyrov 2006). Activation loci in superior and middle temporal areas had also been earlier reported to contribute to lexical and semantic processing (Price 2000; Salmelin et al. 2000; Scott and Johnsrude 2003; Scott and Johnsrude 2003; Poeppe and Hickok 2004; Pulvermüller and Shtyrov 2006; Uppenkamp et al. 2006), which all used different stimulation protocols. The activation of supratemporal and middle temporal areas has been linked to the processing of meaningful language by a range of studies exploiting different imaging modalities (Price 2000; Salmelin et al. 2000; Newman and Twieg 2001; Rissman et al. 2003; Scott and Johnsrude 2003; Poeppe et al. 2004), even though there is still a debate about the exact loci involved. Our data thus provide further support for lexicosemantic processing in superior temporal and middle temporal cortices. Even though STS activation had been seen in response to phonemes per se (e.g., Uppenkamp et al. 2006), STS is not known to become activated in oddball paradigms or to be sensitive to differences between phonemes, which also makes the lexicosemantic interpretation of its activation here more likely than that based on phonological or change-detection mechanisms.

Unlike some previous studies (including our own), here we did not find prefrontal/inferior frontal generators of the MMN (Alho 1995; Nätänen and Alho 1995; Opitz et al. 2002; Shtyrov and Pulvermüller 2002a; Pulvermüller and Shtyrov 2003; Pulvermüller et al. 2003; Rinne et al. 2005). As nearly all previous studies indicated that the frontal MMN sources may be more variable and exhibit smaller scale of activation, the subtle acoustic contrasts employed here may have been insufficient to register any putative frontal activity. Another potential explanation is that the HRF for auditory stimuli may have a substantially longer delay in the frontal areas compared with the particularly early HRF maximum in temporal areas (Bellin et al. 1999) and thus could not be registered with the stimulus timing used here. These tentative explanations cannot, however, be unequivocally supported or refuted by the current data and remain to be addressed in future research.
Notes
We wish to thank Olaf Hauk, Ingrid Johnsrude, Gary Chandler, Christine Schmalz, Adrian Owen, Debbie Davis, Ruth Bushbrown-Chippendale, Gloria Stocks-Geek, Vicky Lupson, and William Marslen-Wilson for their contribution at different stages of this work. We are also very grateful to 2 anonymous referees for their helpful comments and constructive critique. This work was supported by the Medical Research Council, UK. Conflict of Interest: None declared.

Address correspondence to Yury Shtyrov, Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Road CB2 7EF Cambridge, U.K. Email: yury.shtyrov@mrc-cbu.cam.ac.uk.

References
Alho K. 1995. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear Hear. 16:38–51.
Näätänien R. 2001. The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). Psychophysiology. 38:1–21.