

# On the Functional Neuroanatomy of Visual Word Processing: Effects of Case and Letter Deviance

Martin Kronbichler<sup>1,2</sup>, Johannes Klackl<sup>1</sup>, Fabio Richlan<sup>1</sup>,  
Matthias Schurz<sup>1</sup>, Wolfgang Staffen<sup>2</sup>, Gunther Ladurner<sup>2</sup>,  
and Heinz Wimmer<sup>1</sup>

## Abstract

■ This functional magnetic resonance imaging study contrasted case-deviant and letter-deviant forms with familiar forms of the same phonological words (e.g., *TaXi* and *Taksi* vs. *Taxi*) and found that both types of deviance led to increased activation in a left occipito-temporal region, corresponding to the visual word form area (VWFA). The sensitivity of the VWFA to both types of deviance may suggest that this region represents well-

known visual words not only as sequences of abstract letter identities but also includes information on the typical case-format pattern of visual words. Case-deviant items, in addition, led to increased activation in a right occipito-temporal region and in a left occipital and a left posterior occipito-temporal region, which may reflect increased demands on letter processing posed by the case-deviant forms. ■

## INTRODUCTION

In a recent study, we found that orthographically familiar forms of German nouns compared to orthographically unfamiliar forms of the very same phonological words (e.g., *Taxi* vs. *Taksi*) led to reduced activation in a left occipito-temporal region, in left inferior parietal regions, and in a large left inferior frontal language region (Kronbichler et al., 2007). The location of the left occipito-temporal region, which showed an orthographic familiarity effect, roughly corresponded to that of the visual word form area (VWFA) of Cohen and Dehaene (2004) and McCandliss, Cohen, and Dehaene (2003). In a preceding study, we identified a large left occipito-temporal region, which included the VWFA, to be modulated by the frequency with which the words are encountered in print (Kronbichler et al., 2004). The direction of the modulation corresponded to the orthographic familiarity effect, in that increasing frequency was accompanied by a systematic decrease of left occipito-temporal activation. These findings led us to propose that the left occipito-temporal cortex hosts a visual input lexicon which—in the case of high-frequency words and orthographically familiar forms—allows fast assimilation of the letter input by readily available orthographic representations of specific words, and these orthographic representations give direct access to word phonology and meaning (see Kronbichler

et al., 2004, 2007). This interpretation was inspired by studies which found that experimentally induced familiarity of pictured faces or objects (by repeated presentations) led to decreased activation in occipito-temporal regions (e.g., Rossion, Schiltz, & Crommelinck, 2003; van Turennout, Ellmore, & Martin, 2000).

An electroencephalogram study from our lab (Sauseng, Bergmann, & Wimmer, 2004) provided information on the time course of visual word processing by finding an event-related potential (ERP) divergence between familiar and letter-deviant forms from about 200 msec onwards, with higher negativity for the letter-deviant forms. However, unexpectedly, the ERPs to unfamiliar case-deviant forms (e.g., *TaXi*) differed from familiar forms in the same way as letter-deviant forms (e.g., *Taksi*). We had expected the letter-deviant forms to elicit more mismatch negativity than case-deviant forms, as the former violate the identity of one or two letters of stored orthographic representations, whereas the case-deviant forms violate only superficial letter-case information. We reasoned that, despite the unexpected similarity of the ERPs elicited by letter-case format and orthographic format violations, different brain regions may respond to the different types of deviance from the familiar pattern. To examine this expectation, we relied on event-related functional magnetic resonance imaging (fMRI). Similar to Sauseng et al. (2004), we contrasted case-deviant and letter-deviant forms with familiar forms of German nouns during a silent reading task. The case-deviant forms resulted from changing to uppercase one of the lowercase letters after the first capitalized one (e.g., *TaXi*, *ChAos*).

<sup>1</sup>University of Salzburg, Austria, <sup>2</sup>Paracelsus Private Medical University, Salzburg, Austria

This change is a moderate violation of the familiar word form compared to the usual cAsE-mIxInG. The letter-deviant forms resulted from replacing one or two letters of the familiar forms by homophonic ones (e.g., *Taxi-Taksi*, *Chaos-Kaos*).

For the letter-deviant forms, we expected replication of the Kronbichler et al. (2007) finding of enhanced activation in a region roughly corresponding to the VWFA in the left occipito-temporal cortex. The reduced VWFA activation, in response to familiar compared to unfamiliar forms of the same phonological words, was interpreted by Kronbichler et al. as a reflection of visual-orthographic whole-word recognition. This interpretation assumes that the VWFA hosts word-specific orthographic recognition units in addition to representations of recurrent letter clusters within words and to representations of letter forms. A familiar form such as *Taxi* instantiates a single whole-word orthographic recognition unit, whereas a letter-deviant form such as *Taksi* may partially instantiate more than one whole-word representation (e.g., TAKE and SISTER) or it may instantiate several sublexical orthographic units. In addition, successful instantiation of a fully corresponding word-specific recognition unit may quickly shut down activations of sublexical or partially instantiated word-level recognition units. No such quick shut down of activations is expected for letter-deviant items.

For the case-deviant forms (e.g., *TaXi*), no enhanced activation of the VWFA compared to familiar items is expected when the VWFA only operates on abstract representations (see Dehaene, Cohen, Sigman, & Vinckier, 2005) and word-specific orthographic recognition units represent visual words as sequences of abstract letter identities. This assumption is supported by several studies which found no difference between cross-case and same-case priming in the VWFA (Dehaene et al., 2001, 2004). However, there are behavioral findings suggesting that orthographic word representations not only specify the sequence of abstract letter identities but also letter-case information. Peressotti, Cubelli, and Job (2003) found enhanced perceptibility when Italian proper names were presented with first case letter capitalized (their usual appearance in Italian) than without capitalization, although the most frequent appearance of Italian words is all letters in lowercase format. A comparable phenomenon was demonstrated for German nouns which—different from all other grammatical categories—are always seen with first letter capitalized (Jacobs, Nuerk, Graf, Braun, & Nazir, in press). If, indeed, memory representations of specific visual words contain letter format information and if such representations are stored in the VWFA, then one would expect that the present case-deviant items similar to the letter-deviant items may lead to increased activation in the VWFA compared to familiar forms.

One may also reason that the present case-deviant items pose higher demands on low-level letter process-

ing than both familiar and letter-deviant items. This expectation follows from behavioral studies on the effect of case-mixing on reading time and on the perception of briefly presented mixed-case words (e.g., Jordan, Redwood, & Patching, 2003; Lavidor & Ellis, 2001; Fiset & Arguin, 1999). These effects are attributed to low-level letter processing. Specifically, case-mixing is assumed to increase the number of possible letter-shapes per position and may lead to lateral interference with the misplaced uppercase letter affecting perception of the neighboring lowercase letters or it may lead to problems in proper letter grouping (see Mayall, Humphreys, & Olson, 1997). These increased demands on low-level letter processing could be expected to lead to increased activity in posterior regions of the ventral visual pathway presumably involved in letter processing (Dehaene et al., 2005). However, existing imaging research provides only limited support for this expectation. Specifically, a positron emission tomography study by Mayall, Humphreys, Mechelli, Olson, and Price (2001) found no effect of case-mixing on activation in any occipital or occipito-temporal region, but found such an effect in a right parietal region previously associated with visual attention. In addition, transcranial magnetic stimulation of this region led to a pronounced negative effect on reading aloud mixed-case words (Braet & Humphreys, 2005, 2006). However, another positron emission tomography study by Xu et al. (2001) did not find increased right parietal activation, but—corresponding to the expectation from low-level letter processing—found enhanced activation in a left posterior occipito-temporal and an occipital cluster. The present fMRI study will provide additional evidence on the issue which brain regions are specifically engaged by letter-shape processing. We contrasted case-deviant forms not only with familiar forms (e.g., *TaXi* vs. *Taxi*) but also with letter-deviant forms (e.g., *TaXi* vs. *Taksi*). Increased activation of case-deviant forms in relation to letter-deviant forms would be specifically informative because letter-deviant forms can be considered to be more attention-demanding than case-deviant forms.

## METHODS

### Participants

Participants were 20 university students (13 men, 7 women) in the age range from 19 to 45 years ( $M = 29$  years). All of them were right-handed, native German speakers and had normal or corrected-to-normal vision. Written informed consent was given by all participants.

### Material

For each of 75 German nouns, two deviant forms were created. For the case-deviant items, one of the lowercase letters after the capitalized initial one was changed to

uppercase. For the letter-deviant items, one or two letters were replaced by homophonic ones. Examples are *Physik (physics)–PhySik–Fysik* and *Boot (boat)–BooT–Boht*. The mean frequency of the words according to the CELEX database (Baayen, Piepenbrock, & van Rijn, 1993) was 15.35 per million ( $SD = 5.5$ ). Table 1 shows that the letter-deviant items were similar to the familiar ones in terms of length, bigram frequency, and number of orthographic neighbors. For assessing the effects of case- and letter-deviance on reading performance, additional 20 adult readers read aloud lists of all 75 items of each type. For this behavioral experiment, the items of each type were divided in three lists. Each participant read nine lists (three for each word type). The order of the separate lists was randomly determined for each participant (with the constraint that two list with the same item types could not be read in immediate succession). Table 1 shows a small increase in reading time from the familiar to the case-deviant items and a large further increase from the case-deviant to the letter deviant items [ $F(1, 19) = 17.38, p < .001$ ], and pairwise comparisons found even the small increase from familiar words to case-deviant items reliable ( $p < .01$ ). Errors were infrequent with mean accuracies of 99.2%, 98.8%, and 99% for familiar, letter-deviant, and case-deviant items, respectively. An analysis of variance (ANOVA) found no reliable effect of item type on accuracy [ $F(1, 19) = 1.64, p = .21$ ].

## Procedure

The 225 stimuli were presented in three runs, each consisting of 75 items and 25 null events. Each run included 25 items of each type and within a run the same word was not repeated. Within these constraints, two pseudorandomized sequences of trials were created and optimized with a genetic algorithm (Wager & Nichols, 2003). Items had to be read silently, but participants were warned that a question mark after an item may

**Table 1.** Item Characteristics [Mean ( $SD$ )]

Characteristics	Familiar/	
	Case-deviant Items	Letter-deviant Items
Letter length	5.56 (1.17)	5.57 (1.19)
Syllable length	1.89 (0.56)	1.91 (0.55)
Type bigram frequency (per million)	3408.65 (1981.03)	3466.16 (1927.47)
Number of orthographic neighbors	1.48 (2.06)	1.72 (1.91)
Reading aloud (msec/word)	431 (82)/458 (81)	549 (152)

prompt articulation, which was the case for four items per type. Errors during these reading-aloud trial were extremely infrequent, 16 of the 20 participants made no errors at all, and the mean number of errors was 0.05 for familiar, 0.20 for letter-deviant, and 0.15 for case-deviant items.

Stimuli were displayed for 800 msec. During the interstimulus interval of 3400 msec, a fixation cross was presented. The horizontal visual angle of the display was about  $4^\circ$ . Participants were familiarized with the stimuli and the procedure outside the scanner. Stimulus delivery and timing were controlled with Presentation (Neurobehavioral Systems, Albany, CA, USA).

Functional and structural imaging was performed with a Philips Gyroscan NT 1.5-Tesla Scanner (Philips Medical System, Best, The Netherlands). Functional images sensitive to BOLD contrast were acquired with a T2\*-weighted gradient-echo, echo-planar imaging sequence (TR = 2200 msec; TE = 40 msec; matrix =  $64 \times 64$ ; FOV = 220 mm; FA =  $86^\circ$ ). Twenty-one axial slices with a slice thickness of 6 mm were imaged parallel to the bicommissural line. During each run, 194 whole head images were acquired with 6 dummy scans at the beginning. After functional scanning, a high-resolution structural scan (T1-weighted MP-RAGE sequence; matrix =  $256 \times 256$ ; FOV = 220 mm; 130 slices; 1.30 mm slice thickness) was acquired to facilitate normalization and localization of functional activations.

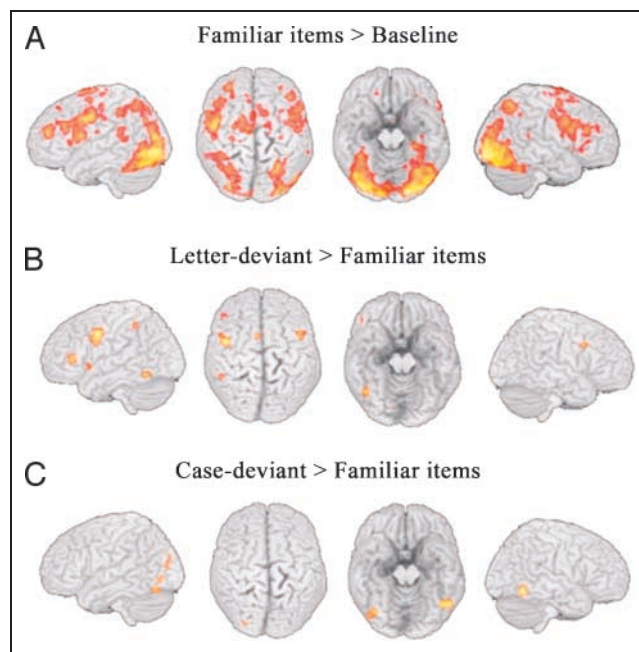
## fMRI Data Analysis

Data processing used SPM2 software (The Wellcome Department of Cognitive Neurology, London, UK; [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) running in a MATLAB 6.5 environment (Mathworks, Sherbon, MA, USA). All functional images were realigned to the first functional image and unwarped, slice time corrected, and coregistered to the high-resolution structural images. The structural image was normalized to the Montreal Neurological Institute T1 template image, and the resulting parameters were used for normalization of the functional images, which were resampled to isotropic  $3 \times 3 \times 3$  mm voxels and smoothed with a 6-mm full-width half-maximum Gaussian kernel. In the subject-specific first-level model, each stimulus type was modeled by a canonical hemodynamic response function and its temporal derivative. The 12 stimuli followed by a prompt were modeled separately and treated as covariates of no interest. The functional data from these first-level models were high-pass filtered with a cutoff of 128 sec and corrected for autocorrelation by an AR(1) model (Friston et al., 2002). Statistical analysis was performed within a two-level framework (Holmes & Friston, 1998). First, images for the contrasts of interest were calculated separately for each subject. In the following random effects analyses, contrast images of each subject were used to allow generalization to the population.

## RESULTS

In a first step, each item type was separately contrasted with the fixation baseline which consisted of the inter-stimulus intervals and the null events. Because all three item types activated largely the same regions (compared to the fixation baseline), an activation map is only shown for the familiar items. Figure 1A shows activation of bilateral posterior regions (occipital, occipito-temporal, parietal, and temporo-parietal). There were also extended activations in bilateral frontal regions (inferior frontal, precentral regions, and supplementary motor area).

The following analyses contrasted each deviant item type separately with familiar items using a false discovery rate (FDR) threshold (Genovese, Lazar, & Nichols, 2002) of  $q < .05$ . For these analyses, a reading mask was used. It included all voxels with activation at  $p < .001$ , uncorrected, when reading (irrespective of item type) was contrasted with baseline. This mask reduces the multiple comparison problem by restricting comparisons to reading relevant regions but does not bias the contrasts between item types, which are orthogonal to the average effect (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). Figure 1B and Table 2 (first section) show that letter-deviant items led to increased brain activity in a region of the left occipito-temporal cortex, in a large left precentral cluster, in left and right inferior frontal regions, in the supplementary motor area (SMA), and in the left inferior parietal lobule. None of these frontal or parietal regions exhibited higher activity for case-deviant compared to familiar items.



**Figure 1.** (A) Increased brain activation for familiar items compared to fixation baseline. (B) Increased brain activation for letter-deviant compared to familiar items baseline. (C) Increased brain activation for case-deviant compared to familiar items baseline. Regions with increased activation ( $FDR < .05$ ) are rendered on the surface of a standard brain ( $L = L$ ).

This latter contrast identified a left and a right occipito-temporal region and, additionally, a left occipital region (see Figure 1C and Table 2). With the mentioned FDR-corrected threshold, no region was found with higher activity for familiar compared to deviant items. Furthermore, no region was identified in the contrasts between the two types of deviant items. With an uncorrected voxel height threshold of  $p < .001$  (extent threshold = 10 voxels), a region in the left inferior frontal and precentral cortex (maximum at  $x = -39, y = 0, z = 33$ , extent =  $433 \text{ mm}^3$ ) was identified with higher activation for letter-deviant than case-deviant items. This region corresponds closely to the cluster with higher activity for letter-deviant than familiar items listed in Table 2. With the uncorrected threshold, higher activation for case-deviant compared to letter-deviant items was found in a right occipito-temporal region and in left posterior occipito-temporal and occipital regions (minimum extent =  $351 \text{ mm}^3$ ).

As the main focus of the present study was on visual word processing in occipito-temporal brain regions, we used a small-volume correction for the left and right occipito-temporal cortex to increase statistical sensitivity. For this small-volume correction, we combined two cube-sized volumes (one for the left, the other for the right hemisphere), which ranged from  $x = \pm 48$  to  $\pm 32, y = -86$  to  $-44$ , and  $z = -18$  to  $-6$ , into one volume. This small volume was based on previous studies (Kronbichler et al., 2004, 2007; Dehaene et al., 2001, 2004; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Xu et al., 2001).

Within this small volume, case-deviant items led to higher activity than letter-deviant items in a right occipito-temporal and in a left posterior occipito-temporal region (see Figure 2A and the lower section of Table 2) at an FDR of  $q < .05$ . The opposite comparison (i.e., letter-deviant vs. case-deviant items) did not identify any occipito-temporal cluster, even at an uncorrected threshold of  $p < .01$ . In a further step, a conjunction analysis (Nichols, Brett, Andersson, Wager, & Poline, 2005) was performed to identify occipito-temporal voxels, where each of the two deviant forms led to increased activity compared to familiar items. This analysis, based on an FDR of  $q < .05$  in the occipito-temporal volume of interest, identified a left middle occipito-temporal region (see Figure 2A and Table 2). For comparison, Figure 2B and Figure 2C also show the clusters in the occipito-temporal volume of interest, which showed increased activity when the two deviant item types were separately contrasted with the familiar items. These analyses showed that both letter-deviant and case-deviant items led to increased activation in a left middle occipito-temporal region and that case-deviant items additionally led to enhanced activation in left posterior occipito-temporal and right occipito-temporal regions.

For the left middle occipito-temporal region with increased activation for both letter-deviant and case-deviant



**Table 2.** Brain Regions Showing Effects of Deviance ( $FDR < .05$ ) in the Reading Mask (Upper Section) and in the Occipito-temporal Volume of Interest (Lower Section)

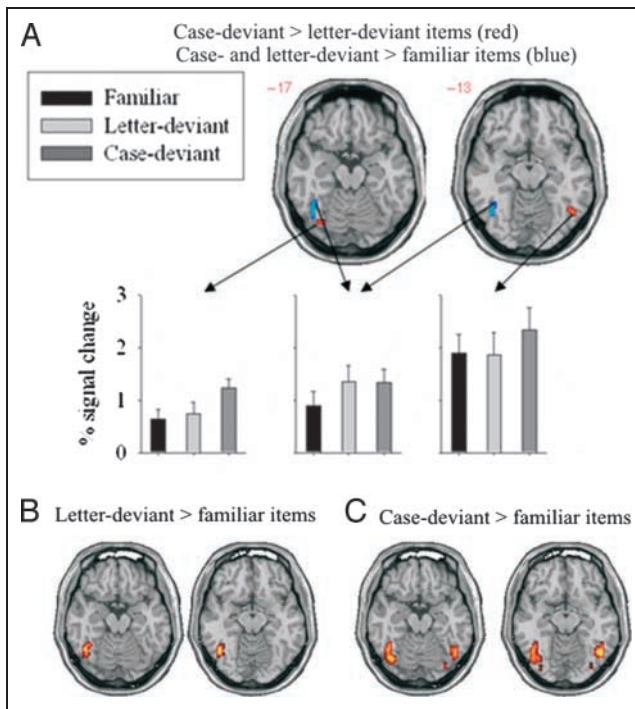
Region	MNI Coordinates			<i>t</i>	Extent ( $mm^3$ )
	<i>x</i>	<i>y</i>	<i>z</i>		
<i>Effects in Reading Mask (See Text)</i>					
Letter-deviant > Familiar items					
L Occipito-temporal	-48	-60	-15	4.22	351
L Precentral	-39	0	36	6.36	3024
L Inferior frontal	-45	33	6	4.75	756
L Supplementary motor area (SMA)	-9	9	57	4.49	324
L Inferior parietal	-54	-45	51	3.96	243
R Inferior frontal	45	12	36	4.58	621
Case-deviant > Familiar items					
L Occipito-temporal	-42	-69	-21	4.87	243
L Posterior occipito-temporal	-48	-75	-9	4.19	216
L Middle occipital	-27	-87	27	3.98	297
R Occipito-temporal	51	-60	-12	5.63	1134
<i>Effects in Occipito-temporal Volume of Interest (See Text)</i>					
Case-deviant > Letter-deviant					
L Posterior occipito-temporal	-39	-72	-18	4.16	270
R Occipito-temporal	42	-57	-9	3.29	81
Conjunction: letter-deviant > familiar items and case-deviant > familiar items					
L Middle occipito-temporal	-42	-57	-15	4.16	513

items, and for the two occipito-temporal regions with higher activity to case- than letter-deviant forms, Figure 2A shows mean percentages of signal change (compared to the fixation baseline) for each item type. The signal change values were extracted with the MARSBAR toolbox (Brett, Anton, Valabregue, & Poline, 2002). As evident from the means, in the right occipito-temporal and in the left posterior occipito-temporal region, case-deviant items evoked higher activation than letter-deviant and familiar items, whereas in the left middle occipito-temporal region, case-deviant and letter-deviant items elicited about the same increased activity compared to familiar items. To confirm the reliability of these apparently differential activation patterns, we calculated two ANOVAs with region and item type as factors and signal change as dependent variable (see Henson, 2006). In the first ANOVA, the left middle occipito-temporal region was contrasted with the left posterior occipito-temporal region; in the second ANOVA, the left middle occipito-temporal region was contrasted with the right occipito-temporal region. In both ANOVAs, the Item type by Region interaction was reliable [ $F_s(2, 38) > 5.9, ps < .007$ ].

As each phonological word was repeated three times—in one session as familiar, in one as letter-deviant, and in one as case-deviant item—one may be concerned that differential repetition effects may partly explain the item-type effects. To examine this possibility, we performed a repeated measures ANOVA in SPM2 including session as factor in addition to item type. For this analysis, we used contrast images for each item type versus fixation baseline for each session separately. If the item-type effects of the previous analyses, to some extent, were due to differential repetition effects, this analysis should reveal an Item type by Repetition interaction on brain activity. The critical finding is that none of the regions with differential item type effects listed in Table 1, and shown in Figures 1 and 2, showed an Item type by Session interaction, even at an uncorrected threshold of  $p < .05$ .

## DISCUSSION

The present fMRI study was designed as a follow-up to a previous electroencephalogram study from our lab (Sauseng et al., 2004) which, surprisingly, found no ERP



**Figure 2.** (A) Axial slices ( $L = L$ ) showing clusters with increased activation for case-deviant compared to letter-deviant items (red) and increased activation for both deviant item types compared to familiar items (blue) in the occipito-temporal volume of interest ( $FDR < .05$ ). Mean percentages of signal change for all item types (compared to fixation baseline) in these clusters are shown in the lower section. (B) Clusters with increased activation for letter-deviant compared to familiar items in the occipito-temporal volume of interest. (C) Clusters with increased activation for case-deviant compared to familiar items in the occipito-temporal volume of interest. Slices in (B) and (C) correspond to the slices in (A).

difference between letter-deviant and case-deviant items. Both types of deviance led to generally increased negativity from about 200 to 700 msec poststimulus. We expected that despite the similar ERP manifestation of orthographic and letter format violations, different brain regions are involved in orthographic word processing and letter format processing. We found support for this expectation. The only brain region with increased activation to both case-deviant and letter-deviant items was located in the left middle occipito-temporal cortex, and this region corresponds closely to the so-called VWFA (see below). The letter-deviant items, such as *Taksi*, compared to familiar items—in addition to the increased activation of the VWFA—led to increased activation in an extended left precentral region, in the left SMA, in bilateral inferior frontal regions, and in a left inferior parietal region. In contrast, the case-deviant items, such as *TaXi*, compared to familiar items—in addition to the increased activation of the VWFA—led to increased activation of an extended right occipito-temporal region and of a smaller left posterior occipito-temporal region. Importantly, the right occipito-temporal and the left posterior occipito-temporal activations elicited by case-deviant

items were also identified in the comparison with letter-deviant items when a small-volume correction was used.

Of methodological importance is that in no occipito-temporal region did letter-deviant items lead to higher activity than case-deviant items and that, in the right occipito-temporal and the left posterior occipito-temporal regions, case-deviant items did lead to higher activity than letter-deviant items. Specifically, the latter finding is just the opposite of the behavioral reading time results. As shown in Table 1, the average reading time per item was about 549 msec for the letter-deviant items and about 458 for the case-deviant items, and the reading time of the case-deviant items was only minimally increased compared to the reading time for the familiar items (about 27 msec). Actually, the finding that case-deviant items—despite much shorter reading time than letter-deviant items—led to the same activation in the left middle occipito-temporal and to increased activation in left posterior and right occipito-temporal regions indicates that brain activity elicited by the present letter strings in the occipito-temporal region does not just reflect task difficulty (e.g., prolonged visual inspection time, attentional demands, working memory demands). The only region in which the fMRI results resembled the reading latency pattern was the left precentral region. In our opinion, the lower activity in this region to familiar items and case-deviant items most plausibly reflects relatively easy access to whole-word phonology and the enhanced activity to letter-deviant items may reflect relatively effortful sublexical phonological processing and slow access to whole-word phonology (e.g., Jobard et al., 2003; Mechelli, Gorno-Tempini, & Price, 2003; Fiez, Balota, Raichle, & Petersen, 1999). However, we cannot exclude the possibility that the left precentral activation pattern is caused by task difficulty. Another concern is that the enhanced activity to both letter- and case-deviant items in the left occipito-temporal may reflect increased eye movements to the deviant items. However, this explanation seems unlikely as differences in eye movements should be accompanied by activation differences in the bilateral frontal eye fields and bilateral parietal eye movement regions (e.g., Kimmig et al., 2001), which was not observed in the present study.

A main finding of the present study is that case-deviant items similar to letter-deviant items led to increased activation (compared to familiar items) in a left middle occipito-temporal region at around  $y = -57$ . The common activation of a left middle occipito-temporal region by both letter-deviant and case-deviant items was further confirmed by a conjunction analysis. This region corresponds to the original VWFA location ( $-43, -54, -12$ ) of Cohen et al. (2002) and is close to mean coordinates ( $-44, -58, -15$ ) found in a meta-analysis of imaging studies on visual word processing (Jobard et al., 2003). One should note that the present study cannot shed light on the controversy about whether the VWFA is specialized just for visual word processing, as might

be suggested by the term VWFA (see Xue & Poldrack, 2007; Devlin, Jamison, Gonnerman, & Matthews, 2006; Cohen & Dehaene, 2004; Price & Devlin, 2003).

This finding of enhanced activation for letter- and case-deviant items is expected when the VWFA contains word-specific orthographic representations which, in addition to letter identities, also specify letter-case information. The existence of such concrete word-specific orthographic representation is suggested by behavioral findings showing a drop of perceptibility when Italian proper names or capitalized German nouns are presented without capitalization (Jacobs et al., in press; Peressotti et al., 2003). The finding that case-deviant items enhance activation in the VWFA to a similar extent as letter-deviant items obviously questions the assumption of orthographic representations consisting of abstract case-independent letter identities. For such abstract representations, there should be no difference between items in familiar case format such as *Taxi* and items in unfamiliar case format such as *TaXi*. The assumption of case-independent orthographic word representations in the VWFA is based on the results of subliminal priming studies, which found no difference between same-case and cross-case primes (Dehaene et al., 2001, 2004). Further research is needed to clarify the relation between the priming findings and the present finding of increased VWFA activation to case-deviant items. One may speculate that computing an abstract representation may be more difficult for case-deviant than familiar items, and this is reflected in increased activation. However, in the Dehaene et al. (2005) model, abstract letter and bigram representations should already have been computed in more posterior occipito-temporal areas (see below), and the VWFA should only contain completely abstract representations.

A second main finding was that case-deviant items compared to familiar items not only led to increased activity in the mentioned left middle occipito-temporal regions, corresponding to the VWFA, but also in posterior occipito-temporal regions of the left hemisphere and in a right middle occipito-temporal region. Furthermore, the increased activation elicited by case-deviant items in the left posterior occipito-temporal and in the right middle occipito-temporal region was confirmed by the contrast with letter-deviant items (in the occipito-temporal volume of interest). These activations were expected from increased demands on letter processing posed by the case-deviant items (see Introduction), and are generally consistent with the neural model of Dehaene et al. (2005), which assumes letter processing to engage regions of the left occipito-temporal posterior to the VWFA and also right occipito-temporal regions. An involvement of these regions in lower-level processing (as opposed to orthographic whole-word processing in more anterior occipito-temporal regions) is also suggested by recent fMRI studies of acquired letter-by-letter reading (e.g., Gaillard et al., 2006; Cohen et al., 2004). It

should be noted, however, that according to the model of Dehaene et al., it is not entirely clear if posterior letter processing regions should be affected by case-deviance, as these regions contain case-specific letter detectors and, more anteriorly, abstract (case-independent) letter and bigram detectors.

As noted in the Introduction, previous imaging studies using mixed-case presentations found only limited support for increased activity in occipito-temporal regions (Polk & Farah, 2002; Mayall et al., 2001; Xu et al., 2001). Specifically, Mayall et al. (2001) failed to find such an effect and found the case-mixing effect in only a right parietal region. This right parietal activation is expected from the increased demands on visual attention by case-mixing, but it is certainly surprising that this attentional effect was not accompanied by increased activity in occipito-temporal regions involved in visual letter processing. The present finding of increased activity in occipito-temporal regions to an only mild form of case-mixing (even compared to letter-deviant items) strongly points to the importance of these regions for visual aspects of letter-string processing.

## Acknowledgments

This research was supported by grants of the Austrian Science Foundation to Heinz Wimmer and Gunther Ladurner (Grant nos. P14494-SPR and P18832-B02). We thank the members of the Department of Radiology for assistance, and Bettina Lackner and Simon Schindlauer for their help in subject recruitment and data acquisition.

Reprint requests should be sent to Martin Kronbichler, Department of Psychology and Center for Neurocognitive Research, Hellbrunnerstr. 34, 5020 Salzburg, Austria, or via e-mail: martin.kronbichler@sbg.ac.at.

## REFERENCES

- Baayen, R. H., Piepenbrock, R., & van Rijn, H. (1993). *The CELEX lexical database (CD-ROM)*. Philadelphia, PA: Linguistic Data Consortium, University of Pennsylvania.
- Braet, W., & Humphreys, G. (2006). The "special effect" of case mixing on word identification: Neuropsychological and transcranial magnetic stimulation studies dissociating case mixing from contrast reduction. *Journal of Cognitive Neuroscience*, 18, 1666–1675.
- Braet, W., & Humphreys, G. W. (2005). Case mixing and the right parietal cortex: Evidence from rTMS. *Experimental Brain Research*, 168, 265–271.
- Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). *Region of interest analysis using an SPM toolbox*. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. *Abstract available on CD-ROM in Neuroimage*, Vol. 16, No. 2.
- Cohen, L., & Dehaene, S. (2004). Specialization within the ventral stream: The case for the visual word form area. *Neuroimage*, 22, 466–476.
- Cohen, L., Henry, C., Dehaene, S., Martinaud, O., Lehericy, S., Lemer, C., et al. (2004). The pathophysiology of letter-by-letter reading. *Neuropsychologia*, 42, 1768–1780.

- Cohen, L., Lehericy, S., Chochon, F., Lemer, C., Rivaud, S., & Dehaene, S. (2002). Language-specific tuning of visual cortex? Functional properties of the visual word form area. *Brain*, *125*, 1054–1069.
- Dehaene, S., Cohen, L., Sigman, M., & Vinckier, F. (2005). The neural code for written words: A proposal. *Trends in Cognitive Sciences*, *9*, 335–341.
- Dehaene, S., Jobert, A., Naccache, L., Ciuciu, P., Poline, J. B., Le Bihan, D., et al. (2004). Letter binding and invariant recognition of masked words—Behavioral and neuroimaging evidence. *Psychological Science*, *15*, 307–313.
- Dehaene, S., Naccache, L., Cohen, L., Le Bihan, D., Mangin, J. F., Poline, J. B., et al. (2001). Cerebral mechanisms of word masking and unconscious repetition priming. *Nature Neuroscience*, *4*, 752–758.
- Devlin, J. T., Jamison, H. L., Gonnerman, L. M., & Matthews, P. M. (2006). The role of the left posterior fusiform gyrus in reading. *Journal of Cognitive Neuroscience*, *18*, 911–922.
- Fiez, J. A., Balota, D. A., Raichle, M. E., & Petersen, S. E. (1999). Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron*, *24*, 205–218.
- Fiset, S., & Arguin, M. (1999). Case alternation and orthographic neighborhood size effects in the left and right cerebral hemispheres. *Brain and Cognition*, *40*, 116–118.
- Friston, K. J., Glaser, D. E., Henson, R. N. A., Kiebel, S., Phillips, C., & Ashburner, J. (2002). Classical and Bayesian inference in neuroimaging: Applications. *Neuroimage*, *16*, 484–512.
- Friston, K. J., Rotshtein, P., Geng, J. J., Sterzer, P., & Henson, R. N. (2006). A critique of functional localisers. *Neuroimage*, *30*, 1077–1087.
- Gaillard, R., Naccache, L., Pinel, P., Clemencau, S., Volle, E., Hasboun, D., et al. (2006). Direct intracranial, fMRI, and lesion evidence for the causal role of left inferotemporal cortex in reading. *Neuron*, *50*, 191–204.
- Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*, *15*, 870–878.
- Henson, R. (2006). Forward inference using functional neuroimaging: Dissociations versus associations. *Trends in Cognitive Sciences*, *10*, 64–69.
- Holmes, A. P., & Friston, K. J. (1998). Generalisability, random effects and population inference. *Neuroimage*, *7*, 754.
- Jacobs, A. M., Nuerk, H. C., Graf, R., Braun, M., & Nazir, T. (in press). The initial capitalization superiority effect in German: Evidence for a perceptual frequency variant of the orthographic cue hypothesis of visual word recognition. *Psychological Research*.
- Jobard, G., Crivello, F., & Tzourio-Mazoyer, N. (2003). Evaluation of the dual route theory of reading: A metanalysis of 35 neuroimaging studies. *Neuroimage*, *20*, 693–712.
- Jordan, T. R., Redwood, M., & Patching, G. R. (2003). Effects of form familiarity on perception of words, pseudowords, and nonwords in the two cerebral hemispheres. *Journal of Cognitive Neuroscience*, *15*, 537–548.
- Kimmig, H., Greenlee, M. W., Gondan, M., Schira, M., Kassubek, J., & Mergner, T. (2001). Relationship between saccadic eye movements and cortical activity as measured by fMRI: Quantitative and qualitative aspects. *Experimental Brain Research*, *141*, 184–194.
- Kronbichler, M., Bergmann, J., Hutzler, F., Staffen, W., Mair, A., Ladurner, G., et al. (2007). Taxi vs. Taksi: Orthographic word recognition in the left ventral occipitotemporal cortex. *Journal of Cognitive Neuroscience*, *19*, 1584–1594.
- Kronbichler, M., Hutzler, F., Wimmer, H., Mair, A., Staffen, W., & Ladurner, G. (2004). The visual word form area and the frequency with which words are encountered: Evidence from a parametric fMRI study. *Neuroimage*, *21*, 946–953.
- Lavidor, M., & Ellis, A. W. (2001). Mixed-case effects in lateralized word recognition. *Brain and Cognition*, *46*, 192–195.
- Mayall, K., Humphreys, G. W., Mechelli, A., Olson, A., & Price, C. J. (2001). The effects of case mixing on word recognition: Evidence from a PET study. *Journal of Cognitive Neuroscience*, *13*, 844–853.
- Mayall, K., Humphreys, G. W., & Olson, A. (1997). Disruption to word or letter processing? The origins of case-mixing effects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *23*, 1275–1286.
- McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: Expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences*, *7*, 293–299.
- Mechelli, A., Gorno-Tempini, M. L., & Price, C. J. (2003). Neuroimaging studies of word and pseudoword reading: Consistencies, inconsistencies, and limitations. *Journal of Cognitive Neuroscience*, *15*, 260–271.
- Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J.-B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage*, *25*, 653–660.
- Peressotti, F., Cubelli, R., & Job, R. (2003). On recognizing proper names: The orthographic cue hypothesis. *Cognitive Psychology*, *47*, 87–116.
- Polk, T. A., & Farah, M. J. (2002). Functional MRI evidence for an abstract, not perceptual, word-form area. *Journal of Experimental Psychology: General*, *131*, 65–72.
- Price, C. J., & Devlin, J. T. (2003). The myth of the visual word form area. *Neuroimage*, *19*, 473–481.
- Rossion, B., Schiltz, C., & Crommelinck, M. (2003). The functionally defined right occipital and fusiform “face areas” discriminate novel from visually familiar faces. *Neuroimage*, *19*, 877–883.
- Sauseng, P., Bergmann, J., & Wimmer, H. (2004). When does the brain register deviances from standard word spelling?—An ERP study. *Cognitive Brain Research*, *20*, 529–532.
- van Turennout, M., Ellmore, T., & Martin, A. (2000). Long-lasting cortical plasticity in the object naming system. *Nature Neuroscience*, *3*, 1329–1334.
- Wager, T. D., & Nichols, T. E. (2003). Optimization of experimental design in fMRI: A general framework using a genetic algorithm. *Neuroimage*, *18*, 293–309.
- Xu, B., Grafman, J., Gaillard, W. D., Ishii, K., Vega-Bermudez, F., Pietrini, P., et al. (2001). Conjoint and extended neural networks for the computation of speech codes: The neural basis of selective impairment in reading words and pseudowords. *Cerebral Cortex*, *11*, 267–277.
- Xue, G., & Poldrack, R. A. (2007). The neural substrates of visual perceptual learning of words: Implications for the visual word form area hypothesis. *Journal of Cognitive Neuroscience*, *19*, 1643–1655.