

Rapid Communication

The visual word form area and the frequency with which words are encountered: evidence from a parametric fMRI study

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Cohen and Dehaene et al. proposed that the Visual Word Form Area (VWFA) in the left midfusiform gyrus, contrary to its name, is limited to the extraction of an abstract letter string and not involved in proper visual word recognition. We examined this prelexical function of the VWFA by a parametric block design with five levels of written word frequency. The lowest level was represented by pseudowords and the highest level by words of very high frequency. Contrary to the assumed prelexical function of the VWFA, increasing frequency was associated with decreasing brain activation in a large posterior cluster of the left hemisphere including middle and posterior fusiform regions. The same negative relation between frequency and activation was found in several left frontal clusters. The relation of increasing frequency and decreasing activation in occipitotemporal regions corresponds to a similar relation in the same brain regions found by studies which experimentally manipulated object or face familiarity. This convergence suggests that fusiform regions are specialized for extracting and storing abstract patterns when processing visual objects and these patterns serve as recognition units in subsequent encounters with the same objects.

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Introduction

In several recent studies, Cohen et al. (2000, 2002), and Dehaene et al. (2001, 2002) provided a set of neuroimaging and electrophysiological findings to characterize the first steps of visual word processing. A recent comprehensive presentation of these and related findings by McCandliss et al. (2003) drew several conclusions: that visual words activate predominantly a patch of the left fusiform gyrus with a peak at approximately $x = -43$, $y = -54$, $z = -12$; that the activation of this Visual Word Form Area (VWFA) begins rapidly after about 150–200 ms of presentation; that it is specific to visual and not to auditory words; that it may occur even under subliminal presentation of visual words and that

it is relatively insensitive to retinal position and surface features of the presented words such as letter case, font, or size. A central part of this theorizing is the specialized role of the left midfusiform gyrus for visual word processing. This localization hypothesis was criticized by Price and Devlin (2003) by a compilation of findings showing that the left midfusiform gyrus is activated not only by visual words but also by non-visual stimuli as in Braille reading or by non-reading tasks, for example, when manual responses to pictured objects are required. As the present study was stimulated by the theoretical framework of Cohen, Dehaene et al. on visual word processing, we further use their term VWFA without necessarily subscribing to the position that the left midfusiform gyrus is specialized for visual word processing (but see Discussion).

The present study examined the hypothesis of Cohen, Dehaene et al. that the VWFA does not recognize a given letter string as instance of a familiar visual-orthographic pattern, but is limited to prelexical processing, that is, to the computation of an abstract letter string which then gives rise to phonological processing. In other words, this hypothesis denies that the VWFA is involved in proper visual word recognition and contends that it is limited to the perception and sequencing of letters. McCandliss et al. (2003) justify this hypothesis by findings showing similar VWFA activation by frequently encountered visual words and never-seen pseudowords (e.g., Dehaene et al., 2002) and by high-frequency words and low-frequency words (e.g., Fiebach et al., 2002).

This limitation of the left fusiform gyrus to low-level letter string processing in the case of visual words is astonishing with respect to recent findings showing that the same or nearby fusiform regions are sensitive to experimentally manipulated familiarity differences of pictured objects (e.g., van Turennout et al., 2003). Furthermore, one can argue that the existing neuroimaging evidence on the lexicality effect (words vs. pseudowords) and the frequency effect (high vs. low-frequency words) is not consistent enough for a definitive conclusion that the VWFA is limited to prelexical word processing. Mechelli et al. (2003) in a review of nine studies with comparison of words vs. pseudowords listed six studies, which found higher activation for pseudowords than words in areas corresponding to or near to the VWFA. Similarly, higher activation for low rather than high-frequency words in occipitotemporal brain regions was reported by Keller et al. (2001) and Kuo et al. (2003), but other studies failed to find such a word

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frequency effect (Chee et al., 2002, 2003; Fiebach et al., 2002; Fiez et al., 1999). Various methodological problems are discussed by Mechelli et al. (2003) which may be responsible for the limited convergence of neuroimaging reading results.

The concern about a limitation of the VWFA to letter string processing and the somewhat inconsistent neuroimaging findings on VWFA activation by words vs. pseudowords and high vs. low-frequency words prompted the present fMRI study. We used a sensitive parametric design of five frequency levels starting with pseudowords (i.e., novel, but readable letter strings) with definitive zero frequency of occurrence and ending with words of very high frequency (> 140 per million). Although “word frequency” is normally used for existing words only, we use it here to refer to this parametric variation of frequency, which includes pseudowords. The assumption is that the “objective” frequency of occurrence reflects the “subjective” frequency with which a reader may have actually processed a certain letter strings and this in turn should be reflected in the probability that this reader may have stored a “visual word form” for this specific string in the VWFA. In addition, the ease with which an existing visual-orthographic word representation is activated by an input should be affected by the frequency with which a specific visual word was encountered. The final assumption is that reduced brain activation in the VWFA is expected when for a given input, a well-established and often-used visual-orthographic representation exists. This expectation is contrary to the assumed prelexical function of the VWFA as formulated by the proponents of the VWFA theory.

The task of silent reading kept processing demands close to normal reading, but prevented acquisition of behavioral data during scanning. This disadvantage was considered unproblematic as reading is an obligatory response to visual words. Price et al. (1996) found comparable activation when explicit reading was contrasted with an implicit reading task, that is, when subjects in response to visual words had to search for a specific visual feature. Our silent reading task obviously involves not only visual processing, but also access to phonological-semantic representations (in the case of existing words) and the assembly of novel pronunciations (in the case of pseudowords). Therefore, frequency differences are not only expected in the VWFA of the left midfusiform region, but also in left ventral inferior frontal regions associated with semantic processing and in left dorsal inferior frontal and precentral regions associated with phonological/phonetic processing. (e.g., McDermott et al., 2003; Poldrack et al., 1999; Xu et al., 2002). A frequency effect in left frontal regions is not contentious and was found in several studies (Chee et al., 2002, 2003; Fiebach et al., 2002; Keller et al., 2001; Kuo et al., 2003).

As the goal of the present study was to detect a potentially subtle effect of word frequency on brain activation, we relied on a block design which according to Friston et al. (1999) has superior statistical power compared to an event-related design. A danger of the blocked presentation is that attention levels may be confounded with stimulus category, for example, a block of pseudowords may elicit a generally higher attention level than a block of words. However, recent direct comparisons of blocked vs. mixed presentation of stimuli in fMRI reading studies gave rather similar results (Chee et al., 2003; Cohen et al., 2002).

Method

Participants

Thirteen right-handed adult volunteers (three females) participated in the present study. Age ranged from 18 to 33. All were native speakers of German and reported no history of neurological or psychiatric disease. Informed consent was obtained from all participants before scanning. None of the participants mentioned reading difficulties and all had normal vision or vision was corrected to normal by lenses.

Material

Table 1 shows the results of our attempt to vary word frequency from pseudowords (level 0) to very high-frequency words (level 4) and keep constant several word characteristics which may affect brain activation. Furthermore, the lower part of Table 1 shows the effect of the frequency variation on two reading measures.

The selection of 80 items for each of the frequency levels representing existing words (levels 1 to 4 in Table 1) was based on the CELEX database of written words in the Mannheim corpus (Baayen et al., 1993). Selection was limited to nouns of maximally two syllables. The lowest level consisted of words with an occurrence of lower than 1 per million (low-frequency words). The frequency criteria for the next levels were > 20 and < 60 per million (medium frequency), > 80 and < 120 (high frequency) and > 140 (very high frequency). Examples for the very high-frequency words are *Buch* (book) and *Person* (person), examples for the low-frequency words are *Horror* (horror) and *Biber* (beaver). Eighty pseudowords (level 0 in Table 1) were created by exchanging the vowel letter(s) for 20 items of each the four word-frequency categories, for example, by changing *Provinz* into *Privanz*.

Table 1
Item characteristics for each frequency level

Characteristics	Word frequency				
	0 (lowest)	1	2	3	4 (highest)
Frequency (per one million words)	Pseudowords	0.29 (0.34)	36.43 (11.8)	98.0 (11.82)	257.85 (150.75)
Letter length	5.68 (1.01)	5.68 (1.22)	5.66 (0.99)	5.70 (1.23)	5.65 (1.31)
Syllable length	1.76 (0.43)	1.76 (0.43)	1.74 (0.44)	1.74 (0.44)	1.74 (0.44)
Bigram frequency (per one million words)	6949 (3640)	6933 (4231)	6920 (4000)	6919 (4385)	6845 (4053)
Concreteness rating	–	2.78 (1.34)	2.74 (1.38)	2.74 (1.32)	2.71 (1.27)
Words denoting living objects (%)	–	16.25	16.25	17.00	16.25
Voice onset time (ms)	616 (74)	547 (45)	524 (39)	518 (26)	517 (34)
Articulation duration (ms)	433 (113)	391 (94)	365 (80)	366 (65)	364 (84)

Note. Means (+SD) are given for all item characteristics, except for percentage of words denoting living objects. For details, see text.

As shown in Table 1, the selection of existing words and the construction of pseudowords were done in such a way that the items of the five frequency levels were close to identical with respect to length (both letter- and syllable-length) and bigram frequency. Bigram frequency was calculated by cumulating for each bigram, irrespective of position, the frequencies of the words in the CELEX database, which included the bigram. This value was scaled in such a way that it reflects the number of occurrences of a specific bigram in one million words. Table 1 shows the mean bigram frequency per word. Controlling bigram frequency rules out that word frequency effects could reflect low-level bigram frequency. Table 1 also shows that concreteness ratings and percentages of animate nouns were close to identical for the frequency categories of existing words. Concreteness was rated by six students on a five-point scale, ranging from 1 (very abstract) to 5 (very concrete).

To examine the effect of word frequency on reading performance, 14 adults—not identical with those participating in the fMRI study—were asked to read aloud 40 items from each level and both voice onset and offset time were registered by a voice key developed in our laboratory (Hutzler, 1999). Table 1 shows how frequency affected the onset of the reading response and the duration of articulation (offset-onset time). For onset time, an item-based ANOVA found increasing frequency resulting in decreasing onset time, $F(4,195) = 31.67$, $P < 0.001$. Post hoc comparisons showed the decrease to be reliable from pseudowords to low frequency, $P < 0.001$, and from low-frequency to medium-frequency words, $P < 0.05$, but not for the following small frequency-related decreases.

Unfortunately, the 40 items selected from each frequency category were not matched for initial phoneme so that the frequency-related decreases in onset time may reflect initial phoneme effects on voice key measurement. As shown by Kesler et al. (2002), initial consonants with one or more of the features obstruent, posterior, and voiceless resulted in delayed voice key response. However, such consonants in initial position were of about similar frequency among the 40 words of each frequency level. Furthermore, if the longer onset times for pseudowords and low-frequency words would have resulted simply from delayed registration of the actual onset, then one would expect shorter articulation times for these categories. However, Table 1 shows the opposite, as the two frequency levels with prolonged onset times (pseudowords and low-frequency words) also tended to exhibit prolonged articulation times.

Procedure

The presentation of stimuli was blocked with 10 items of a specific frequency category constituting a single reading epoch of 16 s. Each reading epoch was followed by a baseline epoch of equal length during which a fixation cross was presented. Ten reading and 10 baseline epochs were grouped into a run. The resulting four runs were separated by pauses of approximately 20 s. The order of the frequency levels within a run was pseudorandomized with the constraint that the two epochs from the same level were separated by two epochs from different levels. Each item was presented for 1000 ms with an interstimulus interval of 600 ms, during which a fixation cross was displayed. Stimulus presentation was synchronized with the scanner. Words were presented in yellow on dark-grey background.

Participants were familiarized with stimuli and procedure by a practice session outside the scanner. The instruction was to read

each item silently during the reading epochs and to fixate the cross during the baseline epochs. The stimuli were projected on a semi-transparent screen by a video projector outside the scanner room. Participants viewed the stimuli via a mirror, which was mounted in front of their eyes. Head movements were minimized by foam pads and a strap over the forehead. A scanning session lasted approximately 30 min.

Image Acquisition

Functional and structural imaging was performed with a Philips Gyroscan NT 1.5 Tesla scanner (Philips Medical System Inc., Maastricht, The Netherlands) equipped with a standard quadrature head coil. Functional images sensitive to blood oxygen level dependent (BOLD) contrast were acquired with a T2* weighted gradient echo EPI sequence (TR 2000 ms; TE 40 ms; matrix 64×64 ; FOV 220 mm; FA 90°). The chosen stimulus onset asynchrony (1600 ms) is no integer of the TR (2000 ms), thereby avoiding a biased sampling of the peristimulus time (Price et al., 1999). Twenty-four axial slices with a slice thickness of 4.5 mm were imaged parallel to the bicommissural line. The voxel size of the resulting whole head images was $3.44 \times 3.44 \times 4.50$ mm and included the whole cerebrum and the upper half of the cerebellum. During each of the four runs 160 whole head images were acquired, resulting in 640 whole head images. To compensate for T1 equilibration effects, six dummy scans were acquired at the beginning of each functional run before stimulus presentation started. After functional scanning, a high-resolution structural scan was acquired to facilitate normalization and localization of functional activations. For structural imaging a T1 weighted Turbo Field Echo sequence (matrix: 256×256 ; FOV 220 mm; 130 slices; 1 mm slice thickness) was used. These parameters yielded a voxel size of $0.86 \times 0.86 \times 1.00$ mm. The whole-head structural image was acquired in the same orientation as the functional images.

Data analysis

For data preprocessing and statistical analysis, SPM 99 software was used (The Wellcome Department of Cognitive Neurology, London, UK., <http://www.fil.ion.ucl.ac.uk/spm>) running in a MATLAB 6.5 environment (Mathworks Inc., Sherbon MA, USA). Motion was corrected by realigning all functional images to the first functional image. Subsequently, the functional images and the high-resolution structural scan were coregistered by mutual information coregistration. These coregistered images were normalized to the Montreal Neurological Institute stereotaxic template brain using nonlinear basis functions and then resliced to $2 \times 2 \times 2$ mm³ voxels. To compensate for residual variability after normalization and to facilitate intersubject comparisons, functional images were smoothed with an 8-mm FWHM isotropic Gaussian kernel. Each of the five stimulus categories was modeled separately by convolving a box-car function with a synthetic hemodynamic response function. A high-pass filter with a cut-off of 128 s was applied to remove low-frequency noise.

Statistical analysis was performed within a two-level framework (Holmes and Friston, 1998). First, contrast images were calculated for effects of interest separately for each subject (see following section). In the following random-effects analysis, contrast images of each subject were used for one-sample *t* tests to allow generalization to the population. To identify significantly activated regions,

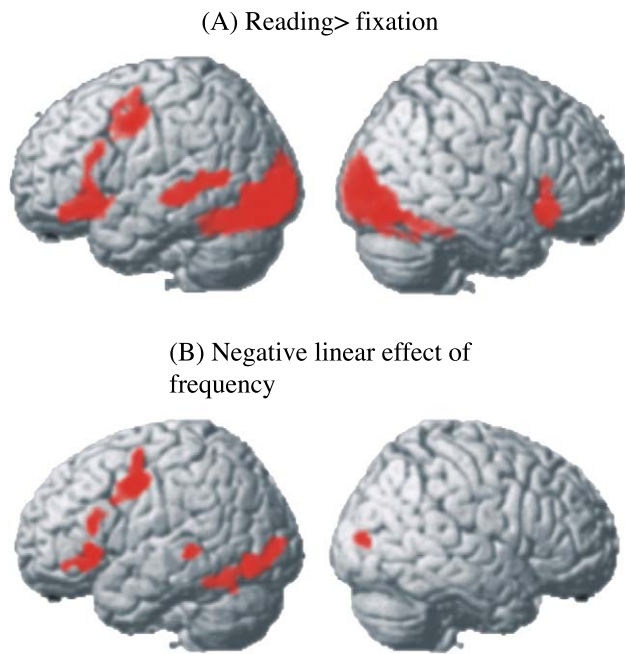


Fig. 1. Brain regions showing (A) increased activation for reading relative to fixation and (B) decreasing activation in response to increasing frequency (i.e., a negative linear effect). Activations were thresholded at $P < 0.05$ (cluster level corrected) and rendered on a standard brain conforming to stereotactic space.

a threshold of $P < 0.05$ (height threshold of $P < 0.001$), corrected at the cluster level for multiple comparisons, was used.

Results

Reading vs. fixation

A first analysis contrasted reading (all frequency levels combined) with viewing of the fixation cross. As shown in Fig. 1A,

reading resulted in higher activation of extended clusters in occipital and inferior temporal regions of both hemispheres. In the left hemisphere, there were additional clusters in the middle temporal region and in frontal regions including the inferior frontal and the precentral gyrus. In the right hemisphere, only a region in the inferior frontal gyrus was activated in addition to the mentioned occipital and inferior temporal activation. No reading activation was found in left temporoparietal regions including the angular gyrus.

Activations related to written word frequency

To identify clusters with systematically increasing or decreasing activation in response to increasing frequency, two analyses were done: one examining a positive linear effect of frequency; the other a negative linear effect. These analyses were limited to the clusters identified in the reading vs. fixation contrast. Of the two analyses, only the one testing a negative linear effect (i.e., increasing frequency resulting in decreasing activation) reliably identified several clusters, which are shown in Fig. 1B. Table 2 provides information on the extent of these clusters and on the coordinates of the peak voxels. Fig. 1B shows that, in contrast to the large bilateral clusters identified in the reading vs. fixation contrast (Fig. 1A), the clusters identified in the linear negative effect analysis were confined to the left hemisphere with the exception of a small cluster in the right occipital cortex.

The largest coherent cluster with a negative frequency effect was found in the posterior part of the left hemisphere. It included a region of the middle occipital gyrus and extended into the inferior occipitotemporal cortex with a peak voxel in the posterior fusiform and two additional ones in the midfusiform gyrus region. In the left frontal cortex, three clusters exhibited negative frequency effects: the largest was in the precentral gyrus, followed (in extent) by clusters in the ventral and dorsal inferior frontal gyrus. As evident from Table 2, together, the three left frontal clusters were more extended than the coherent left occipitotemporal cluster. Relatively small additional clusters were identified in the right middle occipital and in the left middle temporal gyrus.

Table 2
Regions exhibiting negative linear effects of frequency

Region	Extent (mm ³)	Coordinates in Tailarach Space			Z score	Size of frequency effect	
		x	y	z		All levels	Word levels
Right Occipital							
Middle occipital gyrus	344	34	-82	6	4.03	0.73***	0.47**
Left Occipital							
Middle Fusiform gyrus	3032	-42	-50	-18	4.30	0.78***	0.41*
Middle Fusiform gyrus		-42	-58	-16	4.25	0.79***	0.40*
Posterior Fusiform gyrus		-40	-70	-6	4.75	0.83***	0.68***
Left Temporal							
Middle temporal gyrus	440	-62	-36	0	3.91	0.71***	0.21
Left Frontal							
Precentral gyrus	2592	-54	-6	42	4.66	0.84***	0.41*
Dorsal inferior frontal gyrus	440	-48	22	22	4.03	0.74***	0.04
Ventral inferior frontal gyrus	1320	-52	30	-6	4.11	0.76***	0.78***

Note. Negative linear frequency effect analysis with pseudowords included was restricted to clusters with significantly higher activation for reading vs. fixation. Only clusters exceeding a threshold of $P < 0.05$ corrected for multiple comparisons are shown. Multiple local maxima are given for the large left occipitotemporal cluster only. Size of frequency effect for all levels (pseudowords included) and for words only (pseudowords excluded) is given as eta-squared for peak voxel based ROIs. Significance levels for the F values of the linear effects in each ROI: *** = < 0.001 ; ** = < 0.01 ; * = < 0.05 .

Hemisphere differences in fusiform gyrus regions

The SPM results showing reliable negative frequency effects only for left, but not right hemisphere fusiform regions provide no direct statistical evaluation of hemisphere differences in fusiform gyrus regions. Such an evaluation is important as the VWFA theory limits visual word processing to the fusiform regions of the left hemisphere. For an examination of hemisphere differences, a region of interest (ROI) analysis was performed. The ROIs—defined as spheres with 3 mm radius—were based on the four peak voxels in the right and left occipital clusters shown in Table 2. For each of these, a homologue ROI in the opposite hemisphere was defined by changing the sign of x coordinate. Fig. 2 shows the resulting four left–right pairs of ROIs in posterior-to-anterior direction and the mean signal change for each frequency level. An ANOVA with frequency (5 levels, linear contrast), posterior-to-anterior direction (4 levels) and hemisphere (left vs. right) found the main effect of hemisphere (i.e., larger left than right activation) to be highly reliable, $F(1,12) = 20.09$, $P = 0.001$. As evident from Fig. 2 and from the reliable hemisphere by direction interaction, $F(3, 36) = 15.87$, $P = 0.002$, this higher left than right activation was limited to the fusiform pairs and absent at the occipital pair. Furthermore, the three-way interaction was reliable, $F(1,12) = 9.86$, $P = 0.009$. The results of post hoc comparisons in Fig. 2 show that reliably higher left than right activations were largely limited to the pseudowords and low-frequency words of the three fusiform ROI pairs.

Frequency effects for existing words

A possible concern is that the frequency effect found for the VWFA may only be due to the inclusion of the pseudowords with zero frequency. Indeed, as evident from Fig. 2, pseudowords tended to exhibit the highest activations for each of the three left fusiform ROIs. To examine whether the frequency effect was also reliable when only the frequency levels of existing words were taken into account, separate ANOVAs for each ROI were run with word frequency (only four levels, linear effect) as factor. This was not only done for the three fusiform ROIs, but for all peak voxels listed in Table 2. The ROIs for the additional peak voxels were defined identically to the ones used in the examination of the hemisphere differences (i.e., spheres with 3-mm radius). The results of these ANOVAs are given in the final column of Table 2 as effect sizes (eta-squared), that is, as the proportion of activation variance explained by the linear increase of the frequency of existing words. Table 2 shows that the activation of two ROIs was massively affected by the frequency of existing words: the left posterior fusiform and the ventral inferior frontal ROI. The two middle fusiform, the right occipital, and the precentral ROI showed moderate, but still reliable effects, whereas the middle temporal and the dorsal inferior frontal ROI showed negligible effects.

For evaluation of the proportions of variance explained by the reduced frequency levels of the existing words (pseudowords excluded), the comparison with the proportions of variance explained by all the original five frequency levels is informative. The effect sizes resulting from the corresponding ANOVAs with five frequency levels are given in the next to the last column of Table 2. Interestingly, the exclusion of pseudowords resulted in no or little reduction in the proportion of explained variance for the posterior fusiform and the ventral inferior frontal ROI. It resulted in

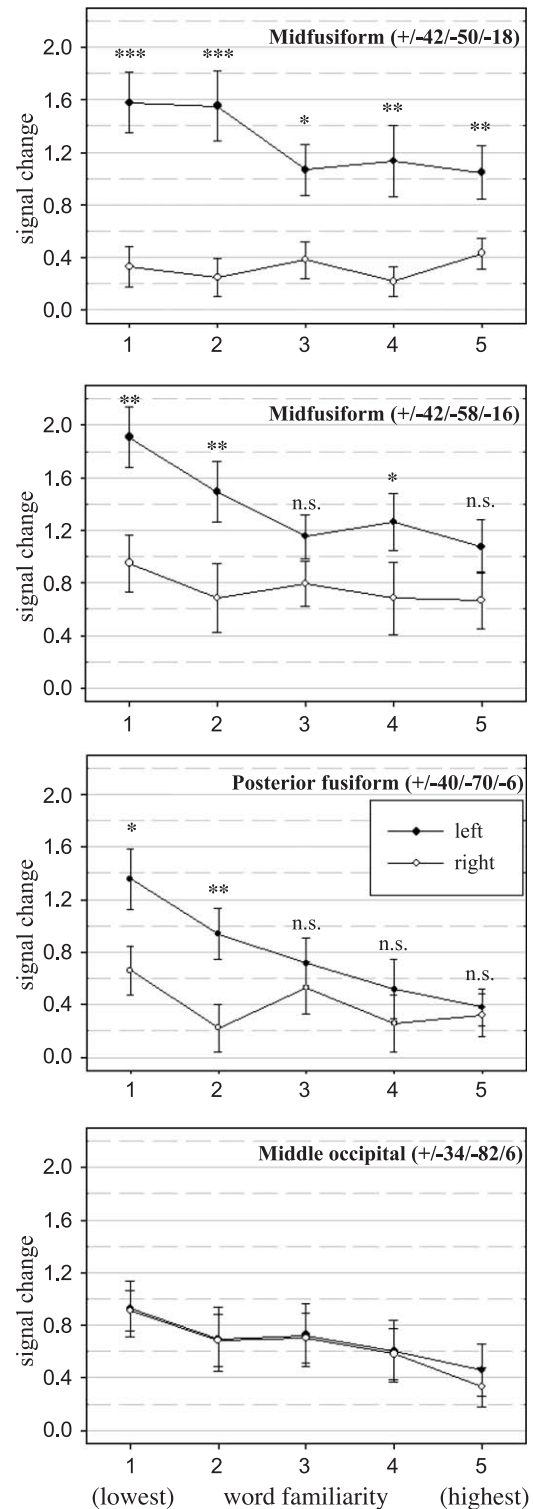


Fig. 2. Percentage signal change (means \pm SEM) in relation to frequency levels for posterior regions of interest. Closed circles represent left, open circles homologue right hemisphere regions. The regions are based on the peak voxels of the posterior clusters shown in Table 1. Significance levels for left vs. right hemisphere comparisons: *** = < 0.001 ; ** = < 0.01 ; * = < 0.05 ; n.s. = not significant.

a moderate reduction for the two middle fusiform ROIs, the right middle occipital, and the precentral ROI and in a massive reduction for the middle temporal and the dorsal inferior frontal ROI. Obviously, for these latter two regions, the decreasing activation resulting from increasing frequency was due to high activation in response to pseudowords.

Another observation evident from the eta-squared values in Table 2 is that the effect of all frequency levels was rather similar for the left occipital and the left frontal ROIs, whereas the effect of the word-specific frequency levels was more consistent for the three occipital than for the three frontal ROIs. As noted, the size of the word-specific frequency effect was very large for the ventral inferior frontal and absent for the dorsal inferior frontal ROI.

In a second attempt to identify brain regions which are sensitive to the frequency of existing words alone, an SPM analysis identified clusters exhibiting a negative linear relationship to the frequency of existing words. Similar to the original SPM analysis, which included pseudowords, it was limited to regions identified in the reading vs. fixation contrast. This additional analysis did not identify a new cluster, that is, a cluster located outside the ones identified by the original analysis. What it did identify were two clusters which were of comparatively small size and included in the original clusters: One in the posterior fusiform ($x = -40$, $y = -72$, $z = -8$; $Z = 3.87$; extent = 216 mm^3) and one in the ventral inferior frontal gyrus ($x = -52$, $y = 24$, $z = -4$; $Z = 4.49$; extent = 280 mm^3). As evident from Table 2, these peak voxels are near to the ones of the posterior fusiform and ventral inferior frontal regions of the original analysis of the overall frequency effect. However, as both clusters of the new analysis were smaller in extent than the ones of the original analysis, they did not survive the cluster level correction for multiple comparisons: $P = 0.087$ and 0.071 , for the posterior fusiform and the ventral inferior frontal cluster, respectively. Not surprisingly, the posterior fusiform and the ventral inferior frontal cluster identified in the analysis based on frequency of existing words are the ones which in the ROI-based analysis exhibited the largest effect sizes of the frequency effect for existing words (see Table 2).

Discussion

The main finding of the present study is that regions of the left fusiform gyrus which correspond to the VWFA were sensitive to the frequency with which letter strings are encountered by showing decreasing activation in response to increasing frequency. The inverse relation between frequency and activation was expected under the assumption that less activation of the VWFA is required when frequently encountered words are read. This inverse relation is in correspondence with the behavioral finding of an inverse relation between frequency and reading onset time. The similar effect of frequency on activation and reading time is important as our silent reading procedure during the imaging session prevented acquisition of a behavioral reading measure during scanning.

With respect to the VWFA theory, it is relevant that two peaks of the presently found left posterior cluster, which showed the negative frequency effect (pseudowords included) were near to the peak of the VWFA extracted by Cohen et al. (2000). The presently identified peaks were at $x = -42$, $y = -50$, and -58 , $z = -18$ and -16 , that of Cohen et al. at $x = -43$, $y = -52$, $z = -12$. Our frequency sensitive cluster in the occipitotemporal cortex also

included a more posterior region of the left fusiform gyrus with a peak at $x = -40$, $y = -70$, $z = -6$ and reached further back into the middle occipital region. The ROI-based analysis further substantiated the hemisphere difference in the fusiform region. It showed higher left than right activation for the fusiform, but not for the occipital ROIs, furthermore, the higher left than right activation of the fusiform ROIs resulted mainly from pseudowords and low-frequency words. The ROI-based analysis further showed that the frequency effect for the left fusiform ROIs was still reliable when pseudowords were excluded and analysis limited to the frequency levels of existing words. Actually, for the left posterior fusiform ROI, there was little reduction in the size of the frequency effect when pseudowords were excluded. The left posterior fusiform region was also identified in a further SPM analysis which included only the differing frequency levels of existing words, but, due to smaller extent of the cluster, this finding was only of borderline significance when corrected for multiple comparison.

Together these findings on the localization of the frequency effect are in correspondence with the VWFA theory as they stress the role of the left fusiform gyrus and even more posterior right and left hemisphere regions for visual word processing. As our study did not examine frequency effects for objects or faces, it cannot speak to the critique of Price and Devlin (2003) on the specialization of the left fusiform gyrus for visual word processing. Contrary to the VWFA theory stands, the present finding of a negative frequency effect in the left midfusiform region, which speaks against the functional characterization of the VWFA as being limited to the computation of abstract letter strings when presented with visual words. As outlined in Introduction, this limited processing was suggested by the proponents of the VWFA theory when characterizing the function of the VWFA as prelexical (Dehaene et al., 2002; McCandliss et al., 2003). A limitation to letter string computation should be reflected in similar activation relative to fixation independent from word frequency. This pattern was indeed found, but only for right fusiform regions. In left fusiform regions and in left and right middle occipital regions, frequency was systematically related to activation. Our suggestion is that these frequency-sensitive regions are involved in visual-orthographic processing. The output of this processing in response to a familiar visual word is not an abstract letter string, but an activated entry in an orthographic memory system which represents known visual words as specific letter sequences. Such an orthographic entry becomes activated when an input fits into its specific letter sequence. The often-used visual-orthographic representation of a frequent word may be more readily activated resulting in less brain activation than the seldomly used representation of an infrequent word. For a pseudoword, several visual-orthographic word representations may get partly activated or each letter or letter pattern may have to be processed separately resulting in higher activation. This may also explain why consonant strings result in less VWFA activation than words or pseudowords (Cohen et al., 2002): consonant strings may be too deviant from existing visual-orthographic word representations to cause larger activations.

Decreasing brain activation in response to increasing frequency levels was not only found in regions of the occipitotemporal cortex, but also in large areas of the left frontal cortex including the precentral gyrus and dorsal and ventral parts of the inferior frontal gyrus. Together, these frontal clusters were larger than the occipitotemporal ones. When pseudowords were excluded and only the frequency levels of existing words were taken into

account, then a small cluster in the ventral inferior frontal gyrus was identified which similar to the left posterior fusiform cluster did not survive the multiple comparison correction. This result corresponds to the findings of the ROI-based analyses. These showed no reduction in the size of the frequency effect for the ventral inferior frontal gyrus when pseudowords were excluded. Actually, this brain region showed the largest word-specific frequency effect. The exclusion of pseudowords led to a moderate reduction of effect size for the precentral and to a massive one for the dorsal inferior frontal gyrus suggesting that these regions are more involved in phonological processes required for pseudoword reading than the ventral inferior frontal region. This interpretation corresponds to the findings of other imaging studies which showed that phonological processing recruits the dorsal, whereas semantic processing involves the ventral part of the inferior frontal gyrus (see McDermott et al., 2003; Poldrack et al., 1999; Xu et al., 2002).

Interestingly, the angular gyrus region which according to Price (2000) is classically called reading centre, did not exhibit a frequency effect and was not even identified in the reading vs. fixation contrast. Negative findings on angular gyrus activation were also reported in other studies which similar to the present one only required reading of single words and no further processing (for review, see Price, 2000). Activation of the angular gyrus region was found in rhyme judgments tasks involving visual words and in orthographic judgments involving auditory words (Booth et al., 2002), but also during sentence reading (Bavelier et al., 1997).

The present study contributes to a convergence of neuroimaging findings on the lexicality effect. The review of Mechelli et al. (2003) of nine studies with a comparison of words and pseudowords listed six studies with higher activation for pseudowords than words in areas corresponding to or near to the VWFA. The original study by Mechelli et al. (2003) as well as the present results support this pattern. However, two recent studies used lexical decision instead of reading and found the opposite, that is, higher activation for words than pseudowords (Binder et al., 2003; Fiebach et al., 2002). These differing activation results may reflect task differences. A correct “no” response to a pseudoword in the lexical decision may be based on rather superficial visual-orthographic processing, whereas the correct “yes” response to a word may be preceded by an explicit identification of the word. In contrast, when participants have to read words and pseudowords—even when only silent reading is asked for as in the present study—then pseudowords may require more visual attention than words. The assumed superficial visual processing of pseudowords in the lexical decision task seems to be inconsistent with the prolonged reaction times to pseudowords in the lexical decision task (e.g., Fiebach et al., 2002). However, it could also be the case that the delayed “no” responses to pseudowords do not reflect reading processes, but a general delay to arrive at a negative decision. Interestingly, the discrepant results of neuroimaging studies using reading vs. lexical decision have an analogy in the study of face perception. Rossion et al. (2003) pointed out that neuroimaging studies of face perception, which—similar to lexical decision—required an explicit judgement of whether a face is familiar or not found higher activation for familiar than unfamiliar faces. In contrast, studies without explicit familiarity judgement (e.g., when a face had to be judged as male or female) found the present pattern of higher activation for unfamiliar than familiar faces.

As already noted, in contrast to the large clusters found to exhibit negative frequency effects when pseudowords were included, only two relatively small clusters of borderline significance (one

in the posterior fusiform gyrus and one in the ventral inferior frontal region) showed a negative frequency effect when the SPM analysis was limited to existing words. The present difficulty to reliably identify regions exhibiting word frequency effects even with a sensitive parametric design makes plausible why only few neuroimaging studies did find a frequency effect in the occipitotemporal cortex (Keller et al., 2001; Kuo et al., 2003) and the majority did not (Chee et al., 2002, 2003; Fiebach et al., 2002; Fiez et al., 1999). One may reason that competent adult readers may readily identify even words of very low frequency, particularly when, as in the present study, these low-frequency words are short and do not exhibit unusual “foreign” letter combinations. This interpretation is supported by the nearly identical reading onset and articulation times for words of medium, high and very high-frequency, and by the relatively small increase in reading time for low-frequency words.

Encouraging is the convergence between the presently found visual word frequency effect in left occipitotemporal regions and the findings of studies which experimentally manipulated familiarity by repeated presentations of pictures of objects (Chao et al., 2002; van Turennout et al., 2000, 2003). These studies found higher familiarity resulting in lower brain activation in left and right fusiform and left and right occipital regions. An inverse relationship between familiarity and brain activation was also found for experimentally manipulated face familiarity by Rossion et al. (2003), but interestingly, only for right and not for left fusiform regions. The frequency effects for visual words and the familiarity effects for objects and faces in the occipitotemporal cortex suggest that regions in this area are specialized for extracting and storing abstract patterns when processing visual input, and these patterns serve as recognition units in subsequent encounters with the same objects. From this it would follow that the VWFA—as its name implies—serves as repository for visual-orthographic patterns, which automatically attempts to assimilate visual word input. If this interpretation is correct, then the role of the VWFA for visual word processing would be more important than the prelexical function attributed to it by the proponents of the VWFA theory.

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References

- Baayen, R.H., Piepenbrock, R., van Rijn, H., 1993. The Celex Lexical Database (CD-ROM). Linguistic Data Consortium, University of Pennsylvania, Philadelphia, PA.
- Bavelier, D., Corina, D., Jezzard, P., Padmanabhan, S., Clark, V.P., Karni, A., Prinster, A., Braun, A., Lalwani, A., Rauschecker, J.P., Turner, R., Neville, H., 1997. Sentence reading: a functional MRI study at 4 Tesla. *J. Cogn. Neurosci.* 9, 664–686.

- Binder, J.R., McKiernan, K.A., Parsons, M.E., Westbury, C.F., Possing, E.T., Kaufman, J.N., Buchanan, L., 2003. Neural correlates of lexical access during visual word recognition. *J. Cogn. Neurosci.* 15, 372–393.
- Booth, J.R., Burman, D.D., Meyer, J.R., Gitelman, D.R., Parrish, T.B., Mesulam, M.M., 2002. Functional anatomy of intra and cross-modal tasks. *NeuroImage* 16, 7–22.
- Chao, L.L., Weisberg, J., Martin, A., 2002. Experience-dependent modulation of category-related cortical activity. *Cereb. Cortex* 12, 545–551.
- Chee, M.W.L., Hon, N.H.H., Caplan, D., Lee, H.L., Goh, J., 2002. Frequency of concrete words modulates prefrontal activation during semantic judgements. *NeuroImage* 16, 259–268.
- Chee, M.W.L., Venkatraman, V., Westphal, C., Siong, S.C., 2003. Comparison of block and event related fMRI designs in evaluating the word frequency effect. *Hum. Brain Mapp.* 18, 186–193.
- Cohen, L., Dehaene, L., Naccache, L., Lehericy, S., Dehaene-Lambertz, G., Henaff, A.M., Michel, F., 2000. The visual word form area. Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain* 123, 291–307.
- Cohen, L., Lehericy, S., Chochon, F., Lerner, C., Rivaud, S., Dehaene, S., 2002. Language-specific tuning of the visual cortex? Functional properties of the visual word form area. *Brain* 125, 1054–1069.
- Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., Riviere, D., 2001. Cerebral mechanisms of word masking and unconscious repetition priming. *Nat. Neurosci.* 4, 752–758.
- Dehaene, S., Le Clec'H, G., Poline, J.B., Le Bihan, D., Cohen, L., 2002. The visual word form area: a prelexical representation of visual words in the fusiform gyrus. *NeuroReport* 13 (4), 321–325.
- Fiebach, C.J., Friederici, A.D., Müller, K., von Cramon, D.Y., 2002. fMRI evidence for dual routes in the mental lexicon in visual word recognition. *J. Cogn. Neurosci.* 14, 11–23.
- 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.
- Friston, K.J., Zarahn, E., Josephs, O., Henson, R.N., Dale, A.M., 1999. Stochastic designs in event-related fMRI. *NeuroImage* 10, 607–619.
- Holmes, A.P., Friston, K.J., 1998. Generalisability, random effects and population inference. *NeuroImage* 7, S754.
- Hutzler, F., 1999. Voice-Key [On-line]. <http://www.sbg.ac.at/psy/hutzler/voicekey.htm>.
- Keller, T.A., Carpenter, P.A., Just, M.A., 2001. The neural basis of sentence comprehension: a fMRI examination of syntactic and lexical processing. *Cereb. Cortex* 11, 223–237.
- Kesler, B., Treiman, R., Mullenix, J., 2002. Phonetic bias in voice key response time measurements. *J. Mem. Lang.*, 145–171.
- Kuo, W.J., Yeh, T.C., Lee, C.Y., Wu, Y.T., Chou, C.C., Ho, L.T., Hung, D.L., Tzeng, O.J.L., Hsieh, J.C., 2003. Frequency effects of Chinese character processing in the brain: an event related fMRI study. *NeuroImage* 18, 720–730.
- McCandliss, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. *Trends Cogn. Sci.* 7, 293–299.
- McDermott, K.B., Petersen, S.E., Watson, J.M., Ojemann, J.G., 2003. A procedure for identifying regions preferentially activated by attention to semantic and phonological relations using functional magnetic resonance imaging. *Neuropsychologia* 41, 293–303.
- Mechelli, A., Gorno-Tempini, M.L., Price, C.J., 2003. Neuroimaging studies of word and pseudoword reading: consistencies, inconsistencies and limitations. *J. Cogn. Neurosci.* 15, 260–271.
- Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D.E., 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *NeuroImage* 10, 15–35.
- Price, C.J., 2000. The anatomy of language: contributions from functional neuroimaging. *J. Anat.* 197, 335–359.
- Price, C.J., Devlin, J.T., 2003. The myth of the visual word form area. *NeuroImage* 19, 473–481.
- Price, C.J., Wise, R.J., Frackowiak, R.S., 1996. Demonstrating the implicit processing of visually presented words and pseudowords. *Cereb. Cortex* 6, 62–70.
- Price, C.J., Veltman, D.J., Ashburner, J., Josephs, O., Friston, K.J., 1999. The critical relationship between timing of stimulus presentation and data acquisition in blocked designs with fMRI. *NeuroImage* 17, 1131–1143.
- Rossion, B., Schiltz, Ch., Crommelinck, M., 2003. The functionally defined right occipital and fusiform “face areas” discriminate novel from visually familiar faces. *NeuroImage* 19, 877–883.
- van Turennout, M., Ellmore, T., Martin, A., 2000. Long-lasting cortical plasticity in the object naming system. *Nat. Neurosci.* 3, 1329–1334.
- van Turennout, M., Bielaowicz, L., Martin, A., 2003. Modulation of neural activity during object naming: effects of time and practice. *Cereb. Cortex* 13, 381–391.
- Xu, B., Grafman, J., Gaillard, W.D., Spanaki, M., Ishii, K., Balsamo, L., Makale, M., Theodore, W.H., 2002. Neuroimaging reveals automatic speech coding during perception of written word meaning. *NeuroImage* 17, 859–870.