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# Modulation of brain activity by multiple lexical and word form variables in visual word recognition: A parametric fMRI study

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## ABSTRACT

Psycholinguistic research has documented a range of variables that influence visual word recognition performance. Many of these variables are highly intercorrelated. Most previous studies have used factorial designs, which do not exploit the full range of values available for continuous variables, and are prone to skewed stimulus selection as well as to effects of the baseline (e.g. when contrasting words with pseudowords). In our study, we used a parametric approach to study the effects of several psycholinguistic variables on brain activation. We focussed on the variable word frequency, which has been used in numerous previous behavioural, electrophysiological and neuroimaging studies, in order to investigate the neuronal network underlying visual word processing. Furthermore, we investigated the variable orthographic typicality as well as a combined variable for word length and orthographic neighbourhood size ( $N$ ), for which neuroimaging results are still either scarce or inconsistent. Data were analysed using multiple linear regression analysis of event-related fMRI data acquired from 21 subjects in a silent reading paradigm. The frequency variable correlated negatively with activation in left fusiform gyrus, bilateral inferior frontal gyri and bilateral insulae, indicating that word frequency can affect multiple aspects of word processing.  $N$  correlated positively with brain activity in left and right middle temporal gyri as well as right inferior frontal gyrus. Thus, our analysis revealed multiple distinct brain areas involved in visual word processing within one data set.

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## Introduction

Word recognition poses particular challenges to cognitive neuroscientists: Information about specific words can be retrieved from a vast memory store, and combined in extremely flexible ways, within fractions of a second. Until recently, the neuronal networks subserving word recognition were often described by a relatively small set of brain areas, motivated by classical neurological models of language processing (e.g. Damasio and Geschwind, 1984; Geschwind, 1970), such as left inferior frontal, left inferior temporal or angular gyrus (Binder et al., 2005; Bookheimer, 2002; Price, 2000). However, the specific role of individual brain areas in the word recognition process is still a matter of debate. A common procedure is to focus on one or a few aspects of word recognition, and control for potentially confounding variables as well as possible. This has the disadvantage that usually only few variables can be studied within the same set of subjects,

such that the “bigger picture” can only be created by comparing results across many different studies. It therefore introduces considerable variation with respect to recording and analysis techniques, tasks, stimulus and subject selection etc. It would obviously be desirable to be able to study as many psycholinguistic features as possible using the same group of subjects, study design and analysis technique. Furthermore, a recent study showed that activations reported for words compared to pseudowords might have resulted from deactivation for pseudowords, suggesting that results for factorial contrasts can be difficult to interpret (Mechelli et al., 2003).

A more promising way of disentangling the contributions of different parts of the networks would be to study their modulation by specific well-defined psycholinguistic properties. In this study, we therefore investigated the effect of several psycholinguistic parameters on metabolic brain activity, using multiple linear regression in the analysis of event-related fMRI data. Multiple linear regression analysis of neuroimaging data with respect to psycholinguistic variables has two main advantages over factorial approaches: 1) It uses information about the continuous distribution of values, e.g. of word frequencies for individual items. Thus, for continuous variables, regression designs may have greater statistical power than factorial designs (Cohen, 1983). 2) For factorial designs, “awkward”

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items on the extremes of the parameter distributions might have to be chosen (e.g. very high or low frequency items), which may not be representative for the stimulus population under study (Baayen et al., 1997; Ford et al., 2003). As Balota et al. (2004) put it: Regression analysis allows “the language, instead of the experimenter, to define the stimulus set”. Parametric analysis has already been applied in other research areas (e.g. picture naming, see Graves et al., 2007), but not in neuroimaging studies on visual word recognition. An initial set of 21 psycholinguistic features was analysed with respect to its intercorrelation pattern. From these we constructed five composite variables related to different aspects of the visual word recognition process, 3 of which will be the focus of this paper. These entered a multiple regression analysis of the event-related fMRI response, which allowed us to determine their individual contributions to the signal.

### Word frequency

One of the most extensively studied variables in visual word recognition is word frequency. Many studies have shown that high frequency words are responded to faster (Gernsbacher, 1984; Scarborough et al., 1977; Whaley, 1978) and generally produce lower amplitudes in electrophysiological (e.g. Assadollahi and Pulvermüller, 2003; Hauk and Pulvermüller, 2004a; Sereno et al., 1998) or metabolic (Carreiras et al., 2006; Chee et al., 2003; Fiebach et al., 2002; Fiez et al., 1999; Kronbichler et al., 2004) responses than their low frequency counterparts. It has been suggested that these effects reflect facilitation of early access to lexico-semantic information (Cleland et al., 2006; Hauk and Pulvermüller, 2004a). Word frequency therefore appears to be a crucial parameter for revealing core language areas involved in word recognition.

However, some authors have argued that effects of word frequency reflect post-access decision or verification processes. For example, McCann et al. (2000) reported that word frequency effects persisted in a dual-task paradigm, where a distractor task is assumed to interfere with early stages of word recognition processes. They interpreted this result as evidence for a late locus of word frequency effects. Similarly, Balota and Chumbley (1984) found word frequency effects to be larger in a lexical decision compared to a category verification and pronunciation task. They therefore suggested that these effects depend on the familiarity-based decision process, rather than word identification per se. The insensitivity of naming or lexical decision times to pseudohomophones (e.g. “brane”) with respect to base-word frequency (“brain”) has also been interpreted as evidence that this variable does not affect lexical access (McCann et al., 1988). However, a recent experiment using dual-task methodology similar to McCann et al. (2000) demonstrated that word frequency does produce effects at early stages of word recognition (Cleland et al., 2006). Other authors also reported effects of word frequency even for the case where the task was chosen in order to minimise them, e.g. using very short exposure durations (Allen et al., 2005). This is in agreement with a number of recent electrophysiological studies that reported early (i.e. <200 ms) effects of word frequency in the event-related potential or field (ERP/F) (Assadollahi and Pulvermüller, 2003; Dambacher et al., 2006; Hauk et al., 2006a; Hauk and Pulvermüller, 2004a; Sereno and Rayner, 2003). We conclude from these data that word frequency affects early stages of word processing, which does not exclude the possibility that it affects later stages as well, or that these effects can be modulated by

task demands. A more detailed analysis of the brain areas affected by word frequency might therefore reveal lexico-semantic areas without the requirement to contrast word stimuli to a non-word control condition. Importantly, neuroimaging allows us to measure the brain response without the need of overt responses, as in lexical or semantic decisions. We therefore employed a silent reading task, rendering it unlikely that the effects of psycholinguistic variables in this study can be explained on the basis of decision or verification processes.

The brain areas modulated by word frequency are still a matter of debate. Several previous studies using factorial designs reported left inferior frontal activation for word frequency, in silent reading (Joubert et al., 2004; Kronbichler et al., 2004), reading aloud (Fiez et al., 1999) and in visual lexical decision tasks (Fiebach et al., 2002; Nakic et al., Blair, 2006). Right hemispheric brain structures modulated by word frequency were reported by only few studies, namely right inferior frontal cortex (Joubert et al., 2004; Nakic et al., 2006), and bilateral insula (Fiebach et al., 2002). Similarly, areas in left inferior temporal or fusiform gyrus were found to be modulated by word frequency in two studies (Joubert et al., 2004; Kronbichler et al., 2004). Further cortical areas associated with word frequency were left middle (Kronbichler et al., 2004) and superior (Fiez et al., 1999) temporal gyrus, as well as left precentral gyrus and bilateral occipital gyri (Kronbichler et al., 2004). This brief overview suggests some consistency across studies with respect to word frequency effects in left inferior frontal cortex, but considerable inconsistency with regard to other language-related areas, e.g. in inferior temporal cortex or in the right hemisphere. The situation is further complicated by findings in studies on the task-dependency of word frequency effects: In the study of Carreiras et al. (2006), word frequency effects were found in left frontal cortex only for lexical decisions, but not for reading aloud. Similarly, Chee et al. (2002) found left inferior frontal activation for low frequency words for semantic judgments, but not for silent reading. These results would endorse the view already formulated in the behavioural literature that word frequency effects are more related to task-specific decision processes, rather than lexico-semantic processing. This, however, is in contrast to several aforementioned studies that have reported word frequency effects in overt and covert reading, i.e. in tasks that do not require a decision.

In general, the areas that have been reported as being sensitive to word frequency correspond to “classical” language-related areas, such as left inferior frontal, middle/superior temporal and inferior temporal/fusiform cortex (e.g. Price, 2000). Note also that these activations were consistently larger for low compared to high frequency words, which corresponds well to the above-mentioned behavioural and electrophysiological results. This supports the view that word frequency effects have the potential to reveal the cortical network of lexico-semantic processing. Thus, word frequency effects are of great importance for research on the cortical basis of word processing, but existing neuroimaging data are as yet inconsistent. We therefore investigated word frequency effects on metabolic brain activation using a silent reading task and a sensitive parametric analysis.

### Orthographic typicality, neighbourhood size (N) and word length

Word frequency is correlated with a number of other variables that may play a significant role in word recognition.

For example, it has long been known that longer words are generally of lower frequency than shorter ones (Whaley, 1978; Zipf, 1935). In order to allow us to identify brain areas involved in the retrieval of lexical information, it is necessary to rule out confounding variables that are potentially related to other processes, e.g. those underlying processing of the orthographic word form. We therefore included two variables into our study that reflect different aspects of letter string processing. This will also allow us to define the brain areas related to these variables in more detail.

The first surface form variable is orthographic typicality, defined by the frequencies of letter bi- and trigrams (e.g. “ert” occurs more frequently in written English than “cht”). This variable does not rely on semantic information, or even on knowledge whether a letter string is a word or not. Although this variable is often controlled for in neuroimaging experiments on word recognition, reports on actual effects for this variable are scarce. One fMRI study found larger activation for more “word-like” nonwords compared to nonwords with low frequency letter constellations in a letter detection task (Binder et al., 2006). Syllable frequency, which is related to typicality, has been shown to produce effects in a left anterior inferior temporal region in a lexical decision task, but in left anterior insula for reading aloud (Carreiras et al., 2006). A recent fMRI study found different areas in inferior temporal and fronto-insular cortex to be sensitive to different levels of orthographic typicality (Vinckier et al., 2007). Two recent ERP studies found the earliest effects of orthographic typicality around 100 ms after word onset, and localised them into left inferior temporal areas (Hauk et al., 2006a,b). Further data are necessary to corroborate these findings and specify the role of the corresponding brain areas in more detail.

Word length (usually quantified as number of letters) has been reported to be positively correlated with reaction times (Ellis, 2004; Weekes, 1997; Whaley, 1978). ERP/ERF studies found earliest effects of word length around 100 ms after word onset, with long words producing larger amplitudes than short ones (Assadollahi and Pulvermüller, 2003; Hauk and Pulvermüller, 2004a). In one recent PET study using a silent reading task, word length has been associated with early visual processing in fusiform and lingual gyrus (Mechelli et al., 2000).

The situation is further complicated by the fact the word length is generally negatively correlated with orthographic neighbourhood size (“N”), i.e. for a given word the number of words that can be created by exchanging only one letter (e.g. “cat” into “can”) (Coltheart et al., 1977). The pattern of results for *N* in behavioural tasks has been reported to differ between words and pseudowords: For words, higher *N* usually yields faster lexical decision times, while for pseudowords rejections take longer for higher *N*'s (Forster and Shen, 1996; Sears et al., 1995). This pattern has also been found in the behavioural data of (Holcomb et al., 2002), while their ERP data showed the same increase of N400 amplitudes with *N* for both words and pseudowords. It has been concluded that *N* facilitates the lexical retrieval process by means of competition between orthographically similar words (Andrews, 1989, 1997; Grainger and Jacobs, 1996). However, this interpretation has been challenged by other researchers, who found *N* effects to be absent in a semantic decision task (Forster and Shen, 1996), or to depend on the matching between word and non-word stimuli (Siakaluk et al., 2002). These doubts are further supported by the fMRI results of Binder et al. (2003), who did not find any brain areas for which activation significantly increased with neighbour-

hood size. Instead, they found that higher *N* decreased activation to words in left prefrontal, angular and ventrolateral temporal cortex. In contrast, Fiebach et al. (2007) found differential effects of *N* for words and pseudowords in medial prefrontal and mid-dorsolateral cortex. Because these areas are commonly related to executive control functions rather than lexico-semantic processing, the authors argue that effects of *N* might arise only at a late post-lexical level. Effects of *N* are therefore of great interest for psycholinguistic theories of lexical access, and more data are needed to establish its effect on brain activation. In our study, *N* was highly negatively correlated with word length (i.e. number of letters). In order to rule out both *N* and word length as confounds for effects of word frequency and orthographic typicality, we combined these two variables into one regressor variable (correlating positively with length and negatively with *N*). We did not attempt to fully disentangle the effects of *N* and word length in this study, because our stimulus set was not optimised for this purpose. However, the brain areas modulated by this variable can be compared to those found in previous studies reviewed above.

In the present study, we aimed at corroborating and extending previous neuroimaging results on variables related to lexico-semantic and orthographic processing, i.e. word frequency, orthographic typicality, and a combined variable for orthographic neighbourhood size and word length. We chose a silent reading task in order to minimise effects related to task-dependent decision or verification processes, as in several previous studies (Hauk et al., 2004; Joubert et al., 2004; Kronbichler et al., 2004; Mechelli et al., 2003). Data were analysed using a multiple linear regression design in order to extract results for several variables from the same data set, to gain statistical sensitivity, and to avoid problems associated with classical factorial designs.

## Methods

### Stimuli and experimental design

250 mono-syllabic and mono-morphemic English word stimuli were employed in the study, which mainly contained concrete action-related and visual-related words (see Hauk et al., 2004). 150 baseline trials consisting of strings of hash marks varying in length were interspersed among the word stimuli. The average length of words and hash marks was matched (2-tailed *t*-test  $p > 0.1$ ). In addition, 50 null events were included in which a fixation cross remained on the screen. The stimulus set also contained 50 pseudowords, which were modelled as separate events but not used in any of the following analyses.

Each stimulus was presented for 100 ms with a fixed SOA of 2.5 s within a visual angle of less than 4°. A fixation cross remained on the screen between experimental stimuli. Two pseudo-randomized stimulus sequences were alternated between subjects. Stimuli were presented to subjects in two blocks of approximately 11 minute duration each. Subjects were instructed to silently read the letter strings presented to them, similar to previous studies (Hauk et al., 2004; Joubert et al., 2004; Kronbichler et al., 2004; Mechelli et al., 2003). No responses were required from the subjects during these blocks. Previous research has shown that lexico-semantic representations are assessed in reading even if not explicitly required by the task (e.g. Heil et al., 2004; Neely and Kahan, 2001).

For each of the 250 word stimuli, we obtained 21 psycholinguistic parameters, either from the CELEX database

(Baayen et al., 1993) or from a separate rating study (Hauk and Pulvermüller, 2004b).

In the rating study, subjects had to give ratings between 1 and 7 with respect to specific properties of the words, summarised by the following questions, which were complemented by some additional information in the study:

Familiarity: "How familiar is this word to you, i.e. do you use or hear it frequently?"

Imageability: "How easily does this word evoke an image or any other sensory impression?"

Concreteness: "How concrete (or abstract) is this word?"

Arousal: "How arousing is this word or its meaning?"

Valence: "Do you evaluate this word or its meaning as pleasant or unpleasant?"

Potency: "Do you evaluate this word or its meaning as strong or weak?"

Action: "Does this word remind you of an action you could perform yourself?"

Face: "Does this word remind you of an action you could perform with your mouth, face, or head?"

Arm: "Does this word remind you of an action you could perform with your arms, hands or fingers?"

Leg: "Does this word remind you of an action you could perform with your legs, feet or toes?"

Body: "Does this word remind you of bodily sensations?"

Visual: "Does this word remind you of something you can visually perceive?"

Colour: "Does this word remind you of a particular colour?"

Form: "Does this word remind you of a particular form or visual pattern?"

For some of these rating categories, additional instructions (several sentences) were given in order to clarify the significance of these questions for our subjects who were naive with respect to the aim of the experiment.

The following variables were determined based on the CELEX database:

Word length (#lett): number of letters

Word form frequency: number of occurrences of a particular word form per million in the database

Lemma frequency: number of occurrences of a particular lemma per million in the database

Bigram frequency: number of letter bigrams per million in the database

Trigram frequency: number of letter trigrams per million in the database

Number of neighbours ( $N$ ): number of orthographic neighbours in the database (Coltheart et al., 1977)

Number of high frequency neighbours ( $N > \text{Freq}$ ): number of orthographic neighbours with higher frequency than the target word.

Because we presented words in isolation, i.e. without disambiguating word class or word category, we computed lemma frequency as the sum of lemma frequencies across all syntactic classes in the database. Bi- and trigram frequencies were computed as mean frequencies of all bi- and trigrams within each word independent of their position, except that space characters were padded to the beginning and end of each word prior to the procedure, in order to account for effects of frequency of first and last letters.

Mean values and standard deviations for those variables that are most important for the present study are: average number of letters: 4.22 (S.D. 0.81); word form frequency: 20 per million (S.D. 24); lemma frequency: 40 per million (S.D. 47); rated familiarity: 4.8 (out of 7, S.D. 0.9); bigram frequency: 34,919 per million (S.D. 16,860); trigram frequency: 3699 per million (S.D. 3695); number of orthographic neighbours: 7.2 (S.D. 5.4).

The intercorrelation matrix for all 21 parameters is shown in Fig. 1A. This table reflects some obvious inter-dependencies among these parameters, such as a high positive correlation between imageability and concreteness, lemma and word form frequency, bigram and trigram frequencies, the negative correlation between word length and number of orthographic neighbours, or the negative correlation between action- and colour-relatedness. In order to reduce this information to a tractable number of variables for the multiple regression analysis, we combined some of the parameters into groups of highly correlated variables that could be assumed to reflect similar properties of words (see below). For example, several variables in the list above describe the familiarity of a word in different ways: rated familiarity, word form frequency and lemma frequency. Although one might argue that these variables describe different aspects of the stimuli, these variables are certainly more similar to each other than they are, for example, to word length or bigram frequency. Previous neuroimaging studies usually used the term "word frequency" without disentangling contributions from different frequency measures. Similarly, bi- and trigram frequencies can be assumed to affect similar cognitive and neuronal processes. In the case of word length and  $N$ , we observed a high negative correlation between these variables in our stimulus set, as is natural for the English language (as discussed in the introduction). Estimates for both variables in the same multivariate design might therefore lead to unreliable results. Although these two variables clearly tap into different word recognition processes, we combined them into one variable. Comparing brain areas that show positive or negative correlation between this variable and brain activation with previous results might still allow conclusions about the brain processes modulated by  $N$  and word length.

For each of these groups of variables, the individual variables were  $z$ -normalized, and a Principal Component Analysis (PCA) was computed. The first principal components for each group entered the multiple regression analysis. In summary, we focussed on the following three variables in the present study:

Frequency; created from word form frequency, lemma frequency, and familiarity

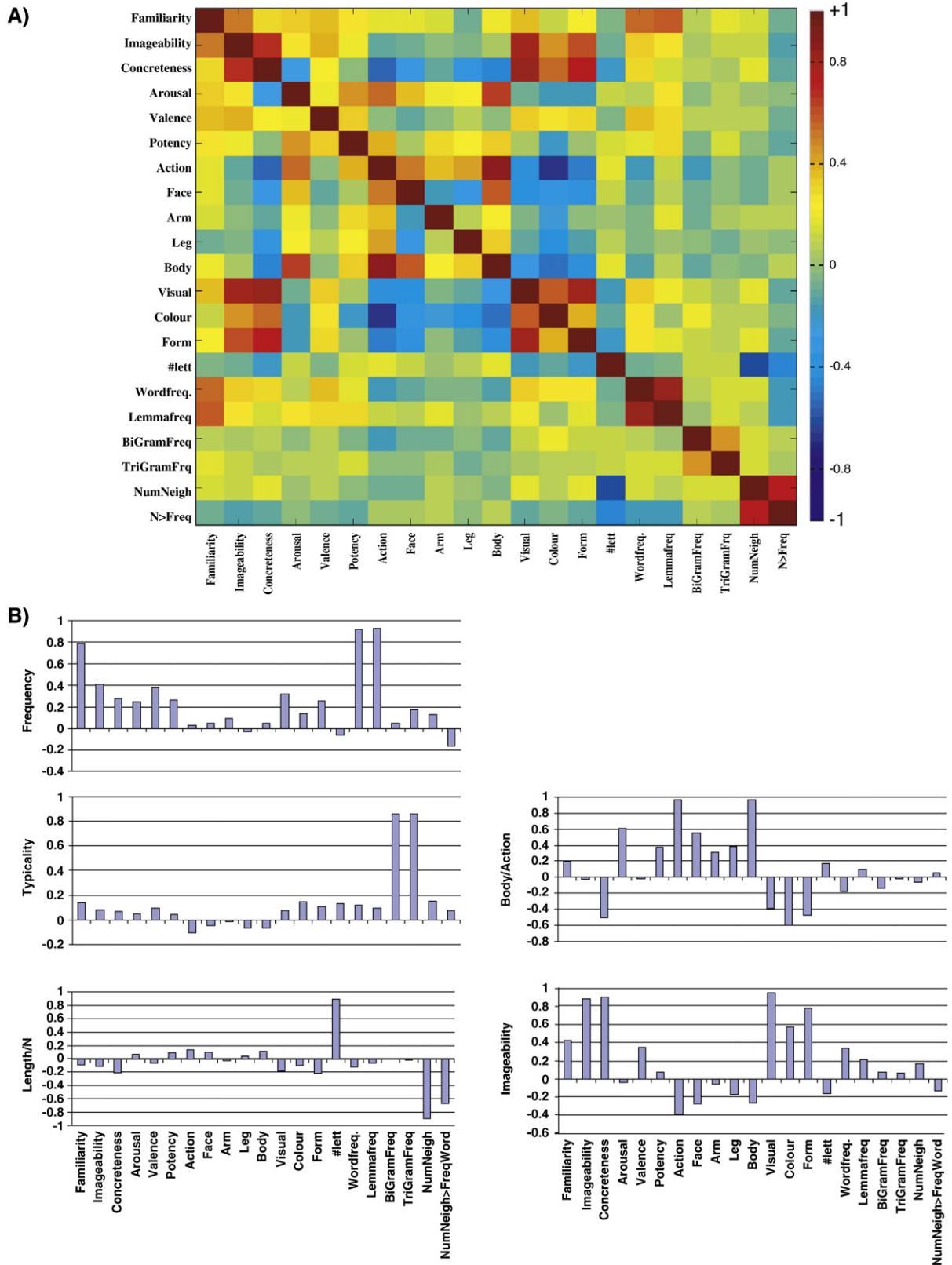
Typicality; created from bigram and trigram frequency

Length/ $N$ ; created from the parameters number of letters and neighbourhood size, which were highly negatively correlated. The following two variables were included as further covariates, but the corresponding results are reported elsewhere (Hauk et al., 2008):

Action-relatedness; created from body- and action-relatedness

Imageability; created from imageability, concreteness and visual-relatedness.

The correlations of the newly created predictor variables (i.e. the first principal components for each group of variables as described above) and the original parameters (which were used for Fig. 1A) are depicted in Fig. 1B. Note that in the



**Fig. 1.** A: Inter-correlation pattern of the original 21 psycholinguistic parameters. B: Correlations between the 5 final predictor variables as they entered the multiple regression design, and the original 21 variables (as used for panel A) from which they were constructed.

435 following, variable names with capital letters (e.g. Frequency)  
 436 refer to the variables that entered our fMRI analysis, while  
 437 lower case (e.g. word frequency) refers to the variable more  
 438 generally.

*Data acquisition and preprocessing*

439

21 monolingual, right-handed, healthy native English  
 440 speakers participated in the study. Their mean age was 24.5  
 441

years (S.D. 5.3), and their mean handedness score was 87 (S.D. 15, measured using a reduced version of Oldfield's Edinburgh Inventory (Oldfield, 1971)). 7 subjects had participated in a similar EEG experiment before the fMRI session (average delay 18 days, S.D. 11 days). Data sets for the remaining 14 subjects are the same as in Hauk et al. (2004). Scanning took place in a 3 T Bruker MR system using a head coil (echo planar imaging (EPI) parameters: TR=3.02 s, TE=27 ms, flip angle=90°, 21 slices covering the whole brain, slice thickness 4 mm, inter-slice distance 1 mm, in plane resolution 128\*128). Imaging data were processed using SPM99 software (Wellcome Department of Cognitive Neurology, London, UK). Images were corrected for slice timing, and then realigned to the first image using sinc interpolation. Phasemaps were used to correct for inaccuracies resulting from inhomogeneities in the magnetic field (Cusack et al., 2003; Jezzard and Balaban, 1995). Any non-brain parts were removed from the T1-weighted structural images using a surface model approach ("skull-stripping") (Smith, 2002). The EPI images were co-registered to these skull-stripped structural T1-images using a mutual information co-registration procedure (Maes et al., 1997). The structural MRI was normalized to the 152-subject T1 template of the Montreal Neurological Institute (MNI). The resulting transformation parameters were applied to the co-registered EPI images. During the spatial normalization process, images were resampled with a spatial resolution of 2\*2\*2 mm<sup>3</sup>. Finally, all normalized images were spatially smoothed with a 12 mm full-width half-maximum Gaussian kernel, globally normalized, and single-subject statistical contrasts were computed using a parametric general linear model (Buchel et al., 1998; Friston et al., 1998). Low-frequency noise was removed with a high-pass filter (time constant 60 s). It has been argued previously that multiple linear regression

**Table 2**

MNI coordinates and statistics for activations that showed significant correlations with Length/N, Typicality, and Frequency in our multiple linear regression analysis

Region	x	y	z	t
<i>Length/N -</i>				
R mid temporal	36	-58	12	5.97
L mid temporal	-62	-54	16	4.88
R IFG tri	42	32	16	4.38
R parahip	42	30	28	4.13
R supra-marginal	18	-2	-22	4.21
R inf parietal	52	-42	36	4.13
L precentral	36	-38	48	3.93
L inf temporal	-34	-18	46	3.80
R mid cingulate	-46	-46	-18	3.69
	12	22	34	3.65
<i>Length/N +</i>				
Vermis	2	-52	2	3.71
L thalamus	-6	-26	10	3.67
	-8	-28	8	3.63
<i>Typicality +</i>				
L precuneus	-4	-56	58	4.60
L precuneus	-8	-46	44	3.82
R precuneus	6	-50	22	3.61
<i>Frequency +</i>				
R mid cingulate	8	-16	46	4.28

Symbols and abbreviations are the same as those of Table 1. Peak voxels were significant at a threshold  $p < 0.001$  uncorrected.

designs in combination with random effects group statistics optimally account for between items as well as between subject variance (Lorch and Myers, 1990). In the context of multiple linear regression analysis, it is important to note that the general linear model determines the independent contribution of each regressor variable by solving a set of simultaneous linear equations, taking into account the correlation among variables (Friston et al., 1995).

*Statistical fMRI analysis*

Group data were analysed with a random effects analysis. Data are displayed at an uncorrected significance level of  $p < 0.001$ . Peak voxels that showed significant activation after FDR correction ( $p < 0.05$ ) or after small volume correction (SVC,  $p < 0.05$ , see below), are indicated in Tables 1 and 2. Stereotaxic coordinates for voxels with maximal z-values within activation clusters are reported in the MNI coordinate system. Anatomical labels of nearest cortical grey matter for peak coordinates were obtained from the MRICron software (<http://www.sph.sc.edu/comd/rorden/micro.html>), based on the anatomical parcellation of the MNI brain published by Tzourio-Mazoyer et al. (2002). To address specific questions about the specificity of activations across several activation clusters, we computed parameter estimates for peak voxels for each individual subject using standard procedures implemented in the MarsBar software (Brett et al., 2002). These values were subjected to an ANOVA including the factors Peak Location and Word Variable.

*Small volume correction (SVC)*

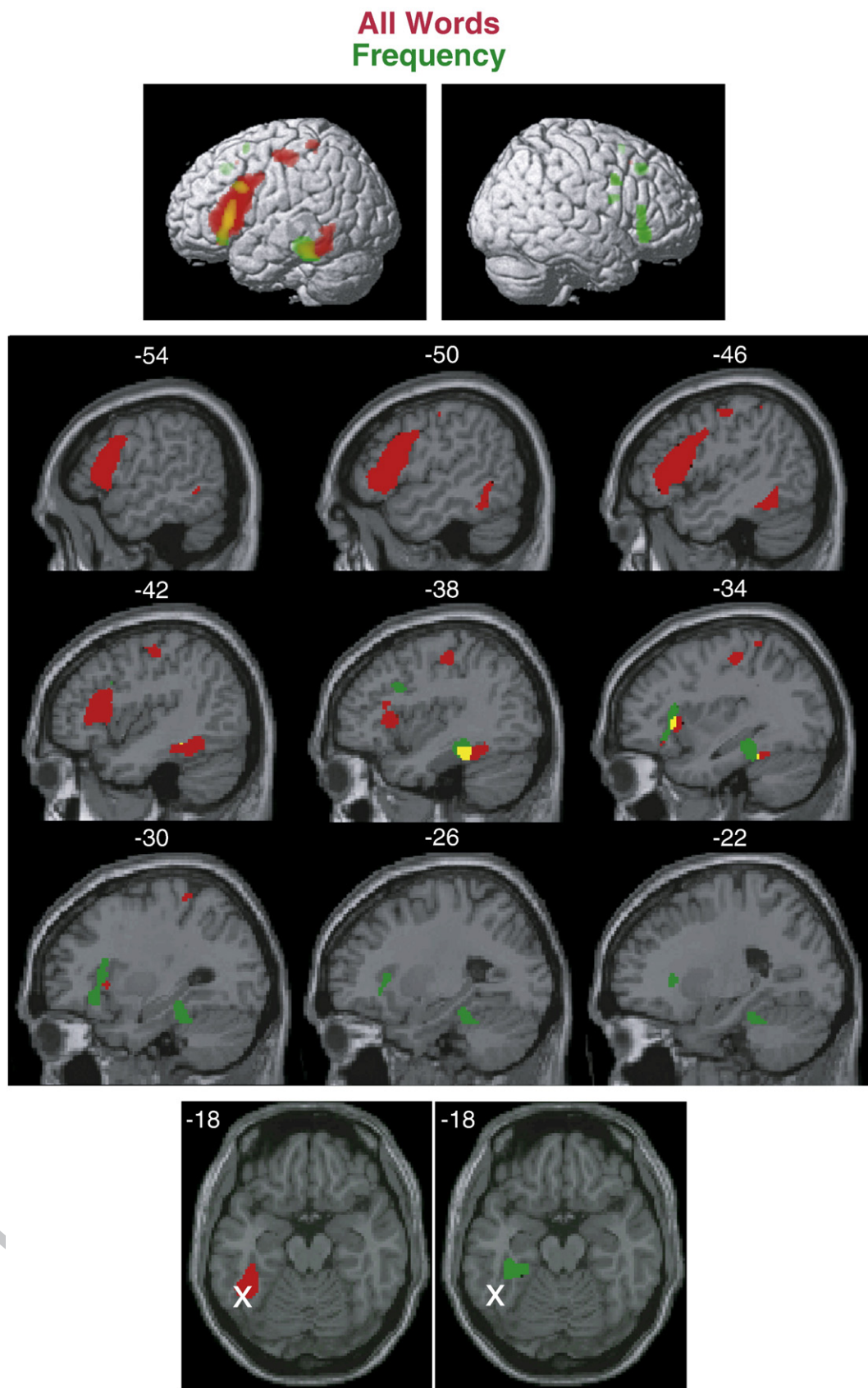
We formulated several hypotheses about activation patterns associated with our word variables. These were tested using SVC for 20\*20\*20 mm<sup>3</sup> cubic volumes centred at coordinates taken from the literature. Where necessary, mean coordinates were computed in the coordinate system reported

**Table 1**

MNI coordinates and statistics for the contrast All Words, as well as for voxels showing significant negative correlations with Frequency in our multiple linear regression analysis

Region	x	y	z	t
<i>Words &gt; hash marks</i>				
L fusiform	-42	-46	-22	7.77*
L precentral	-54	12	32	5.47*
L IFG tri	-44	24	16	5.39*
L IFG orb	-54	24	0	4.77*
L IFG orb	-32	30	-14	3.72*
L mid temporal	-56	-50	-4	3.77*
L postcentral	-36	-24	50	4.39*
	-46	-16	-54	4.19*
	-32	-40	62	4.15*
L SMA	-2	18	48	3.62
L inf parietal	-46	-42	56	3.6
<i>Frequency -</i>				
L fusiform	-36	-32	-18	7.91*†
	-28	-36	-22	6.12*†
L insula	-30	28	-12	5.32*†
	-32	24	8	4.44†
	-26	21	5	4.42†
R insula	30	26	10	4.11†
L IFG oper	-38	14	30	4.42†
R IFG orb	32	28	-6	4.59†
R precentral	50	6	36	4.34
R frontal sup med	10	26	44	4.04
L SMA	-8	12	60	3.85

+/-: positive/negative correlation; L: Left; R: Right; IFG: inferior frontal gyrus; sup: superior; mid: middle; med: medial; tri: triangularis; orb: orbitalis; oper: operculum; parahip: parahippocampal; SMA: supplementary motor area. Asterisks indicate peak voxels that survived FDR correction for multiple comparisons; † indicates voxels that were significant after SVC. The remaining listed voxels were significant at  $p < 0.001$  uncorrected.



**Fig. 2.** Activations for All Words and negative correlation with Frequency rendered on the surface of a standard brain (top), superimposed on sagittal slices of the left hemisphere (middle) and axial slices including inferior temporal regions (bottom). Red colour indicates activation for All Words, green for Frequency, and yellow their overlap. The white cross indicates the location of the "visual word form area" according to McCandliss et al. (2003). Images are shown with a statistical threshold  $p < 0.001$  uncorrected. Coordinates and statistics are provided in Table 1.

in the original study, and transformed to MNI coordinates afterwards which are reported below. With respect to word frequency, effects in left frontal areas have been reported by a number of studies, while involvement of right frontal areas is still a matter of debate. We took coordinates from the study of Fiebach et al. (2002), who found bilateral frontal activation for low frequency words. The mean coordinates were  $-47/16/14$  (mean of BA44 and BA45), and anterior insula,  $-29/28/-4$ , as well as symmetrical locations for the right hemisphere. An area in left fusiform gyrus ("VWFA"), which is of interest with respect to all word variables included in this analysis, was targeted on the basis of (McCandliss et al., 2003), i.e.  $-43/-54/-12$ . SVC was computed using the corresponding toolbox in SPM99.

## Results

### Effects of all words vs baseline

In the first analysis step, we contrasted activation for all words to the baseline condition (strings of hash marks) in a factorial design. Several activation spots correspond to classical language areas in the left hemisphere and will be compared to activation obtained for the other psycholinguistic variables reported below. These occurred in left fusiform, left precentral, left middle temporal and left inferior frontal gyrus (Fig. 2 and Table 1). Further activation spots appeared exclusively in the left hemisphere.

### Effects of Frequency

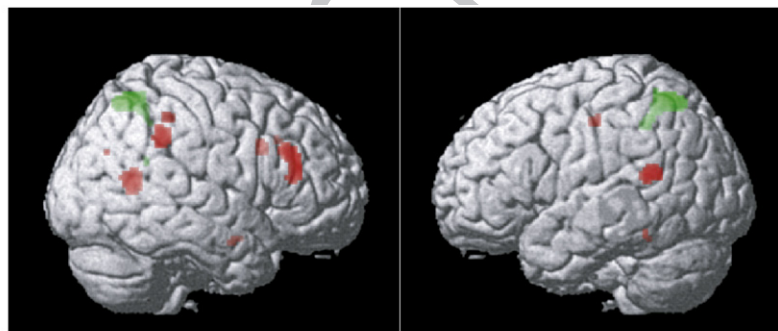
As described above, higher word frequencies are generally associated with less brain activation, both in metabolic imaging and electrophysiological studies. Our areas of interest were

defined on the basis of Fiebach et al. (2002) for the frontal regions, and on McCandliss et al. (2003) for a fusiform region. Significant negative correlations with frequency after SVC in the fusiform region were detected in left fusiform gyrus. In frontal areas, activations revealed by SVC occurred in left and right insulae as well as left and right inferior frontal gyri (Fig. 2 and Table 1). Further activation peaks at the more lenient uncorrected threshold  $p < 0.001$  were found in right precentral and frontal superior medial gyri as well in left SMA.

We had no predictions for positive correlations with Frequency. The only area that showed significant positive correlations with frequency at an uncorrected threshold  $p < 0.001$  was the right middle cingulate (Table 2 and Fig. 3).

### Differential effects of All Words and Frequency

We performed a separate analysis in order to determine whether the regression variable Frequency and the factorial contrast All Words activated distinct areas of left fusiform gyrus. *F*-tests revealed that parameter estimates for the All Words contrasts were significantly different from zero only for the All Words peak voxel ( $F(1,20) > 20.0$ ,  $p < 0.001$ ), but not for the Frequency peak voxel ( $F(1,20) = 0.005$ ,  $p > 0.9$ ). In turn, activation for Frequency was not significantly different from zero in the All Words peak voxel ( $F(1,20) = 3.49$ ,  $p > 0.05$ ), but it was in the Frequency peak voxel (both  $F(1,20) > 5.0$ ,  $p < 0.05$ ). There is still the possibility of an overlap in between peak activations for Frequency and All Words. As is common in metabolic neuroimaging, we used spatial smoothing in our analysis. Therefore, overlap of SPM activations between neighbouring clusters can reflect either a true overlap of neuronal activation, or an effect of spatial smoothing. At this point, we can conclude that the All Words contrast and



### Neighbourhood Size Orthographic Typicality

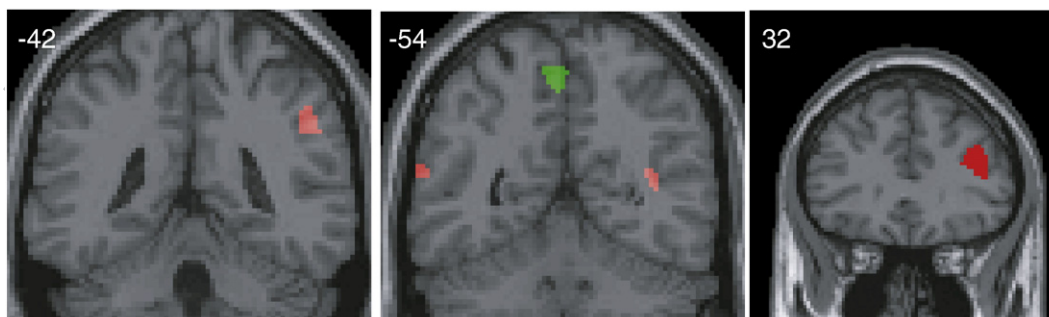


Fig. 3. Activation spots for the variables Typicality and *N* rendered on the surface of a standard brain. Images are shown with a statistical threshold  $p < 0.001$  uncorrected. Coordinates and statistics are provided in Table 2.

566 Frequency produce different, although possibly overlapping,  
567 patterns of activity in left fusiform gyrus.

#### 568 *Effects of Typicality and Length/N*

569 We had no specific predictions for the remaining variables,  
570 and will report activations obtained at the lenient uncorrected  
571 threshold  $p < 0.001$ , in order to compare results with the  
572 existing literature. Although we found a positive correlation  
573 between Typicality and brain activation in left and right  
574 precune, no significant negative correlations for this variable  
575 were detected at this lenient threshold. The combined  
576 variable Length/N showed negative correlations (i.e. positive  
577 correlation with  $N$ , negative correlation with Length) in  
578 several areas in both hemispheres (Table 2). In the left  
579 hemisphere, the strongest modulations occurred in middle  
580 temporal, precentral and inferior temporal gyri. In the right  
581 hemisphere, middle temporal, inferior frontal, supra-marginal  
582 and inferior parietal areas were most strongly modulated. We  
583 observed a positive correlation with Length/N only in the  
584 vermis and left thalamus.

#### 585 **Discussion**

##### 586 *Effects of Frequency and All Words*

587 Word frequency has been widely reported to be negatively  
588 correlated with reaction times (e.g. Cleland et al., 2006), ERP  
589 (e.g. Hauk and Pulvermüller, 2004a) or BOLD amplitudes (e.g.  
590 Fiebach et al., 2002). Based on behavioural and electrophysio-  
591 logical results, it has been argued that these effects reflect  
592 facilitated access to lexical information (Allen et al., 2005;  
593 Assadollahi and Pulvermüller, 2003; Cleland et al., 2006; Hauk  
594 and Pulvermüller, 2004a; Sereno and Rayner, 2003). Determin-  
595 ing brain areas that are sensitive to word frequency therefore  
596 appears to be a promising strategy for revealing the cortical  
597 network underlying lexical processing, as has been shown in  
598 several previous studies (e.g. Carreiras et al., 2006; Chee et al.,  
599 2003; Fiebach et al., 2002; Fiez et al., 1999; Kronbichler et al.,  
600 2004). However, inconsistencies still remain, for example with  
601 respect to the involvement of right-hemispheric brain areas or  
602 left inferior temporal cortex, or with regard to the task-  
603 dependency of effects. We therefore used a multiple linear  
604 regression approach in order to investigate effect of word  
605 frequency on the hemodynamic response in more detail. We  
606 used a silent reading task, ruling out effects that are specific to  
607 decision processes, as for example in standard lexical decision  
608 tasks. Although it is possible that, even in the absence of a  
609 response, words of different familiarity or typicality attract  
610 attention to different degrees, none of our activations were  
611 found in prefrontal areas commonly associated with attentional  
612 control or executive processes (Duncan and Owen, 2000). We  
613 also included variables describing orthographic typicality, word  
614 length and neighbourhood size into the analysis, which served  
615 as covariates and revealed further brain areas related to  
616 different aspects of word recognition.

617 With respect to Frequency, we found largest modulation of  
618 brain activation in left fusiform gyrus. This activation was  
619 close to, but not identical with, those areas consistently  
620 activated by All Words. The Frequency peak was more medial  
621 and anterior in left fusiform gyrus than the activation spot for  
622 All Words. In our post-hoc analyses, we found that activation  
623 for All Words was partly dissociated from effects of Frequency.

624 Interestingly, the peak voxel for the All Words contrast was  
625 close to the area previously termed “visual word form area”  
626 (VWFA). It has been suggested that this area in left fusiform  
627 cortex is specialized for the processing of abstract written  
628 word forms, independently of their position, font or size  
629 (Cohen et al., 2000; Dehaene et al., 2005; Dehaene et al., 2002;  
630 Vinckier et al., 2007). Some authors have argued that this area  
631 contains a “prelexical representation of visual words”  
632 (Dehaene et al., 2002). It should therefore be modulated by  
633 orthographic rather than lexical variables. In our study, we did  
634 not find effects of orthographic typicality, neighbourhood size  
635 or word length around the coordinate of the VWFA reported in  
636 McCandliss et al. (2003). The closest activation peak for word  
637 frequency was located approximately 2 cm anteriorly to this  
638 location, while an effect of All Words versus low-level baseline  
639 was found about 1 cm anteriorly. We could therefore corro-  
640 borate previous findings that areas in left fusiform gyrus are  
641 involved in visual word processing, and the modulation by  
642 word frequency argues in favour of a contribution to lexical  
643 processes. However, we did not find evidence that a part of  
644 fusiform gyrus responds specifically to abstract orthographic  
645 word properties, a view that has been criticized previously  
646 (Price and Devlin, 2003).

647 We found further negative correlation peaks for Frequency  
648 in bilateral inferior frontal gyri. Previous studies reported  
649 inferior frontal activation for word frequency only for the left  
650 hemisphere (Carreiras et al., 2006; Chee et al., 2002; Fiebach  
651 et al., 2002; Fiez et al., 1999; Kronbichler et al., 2004), with the  
652 exception of Nakiç et al. (2006).

653 Inferior frontal activation in language tasks has been  
654 associated with a range of different processes such as retrieval  
655 of semantic information (Bookheimer, 2002; Thompson-Schill,  
656 2003), phonology (Poldrack et al., 1999), and working memory  
657 (Owen, 1997; Swartz et al., 1995). Fiebach et al. (2002) found  
658 more activation for low compared to high frequency words as  
659 well as for pseudowords compared to words in left superior pars  
660 opercularis. They argued that this area should be involved in  
661 grapheme-to-phoneme conversion, because “lexical search is  
662 mediated more strongly by phonological information in these  
663 items”. Left pars triangularis showed an effect of frequency  
664 (low > high), but not of lexicality, which let the authors conclude  
665 that this area is involved in lexical-semantic selection. It has  
666 been demonstrated in another study that results from contrasts  
667 between words and pseudowords are difficult to interpret  
668 (Mechelli et al., 2003). We therefore did not contrast our words  
669 with pseudoword stimuli, and focussed on psycholinguistic  
670 variables that could be studied with our set of words in a linear  
671 regression design. We can confirm that activation in left inferior  
672 frontal gyrus shows a negative correlation with word frequency.  
673 Although the peak of this modulation appears to be located in  
674 pars opercularis, it does not exclude the possibility that it  
675 extends into pars triangularis as well. The fact that this activation  
676 hardly overlaps with that obtained by contrasting all words  
677 versus a low-level baseline indicates that left inferior frontal  
678 areas distinguish between different aspects of word processing.  
679 A more detailed analysis of these different processes must be left  
680 for future research. We suggest that inferior frontal gyri in both  
681 hemispheres are involved in word recognition, which possibly  
682 link and integrate lexical, phonological and semantic processing.

683 We also found activation in left and right insulae, comparable  
684 to Fiebach et al. (2002). Left anterior insula has been associated  
685 with the planning of speech (Dronkers, 1996). This would be  
686 consistent with behavioural findings suggesting that word

frequency effects in speech production arise on the level of access to the phonological word form (Jescheniak and Levelt, 1994). It is likely that silent reading, as used in our study, involves phonological processes to some degree, in particular for low frequency words as argued by Fiebach et al. (2002).

The wide range of cortical areas affected by the variable Frequency suggests that it does not affect only a single aspect of word processing. This is consistent with the proposal of distributed lexico-semantic representations, which involve inferior frontal, temporal and fusiform in both hemispheres. The frequency with which a word has been previously encountered might modulate the connections among these distributed areas according to Hebbian learning rules (Hebb, 1949; Pulvermüller, 1999). Activation within these networks might further depend on task demands (Carreiras et al., 2006; Chee et al., 2002).

Our design included a variable Length/*N* which was positively correlated with word length and negatively correlated with orthographic neighbourhood size (Colheart's *N*). Activation negatively correlated with Length/*N* in the left hemisphere was found in middle temporal, precentral and inferior temporal gyri. Several activations were found in the right hemisphere, such as in middle temporal, inferior frontal, parahippocampal, supra-marginal and inferior parietal cortex. If one interpreted a negative correlation with Length/*N* as a positive correlation with *N*, this would be in contrast to the study of Binder et al. (2003), who did not find any areas whose activation increased with *N*. Fiebach et al. (2007) reported differential effects of *N* for words and pseudowords in medial prefrontal and mid-dorsolateral cortex only. They concluded that these reflect executive control functions rather than lexico-semantic processing, i.e. arise at a late post-lexical level. In contrast, given that the negative correlation of brain activation with Length/*N* would be difficult to explain by a negative correlation with word length (i.e. more activation for short words), our results indicate that orthographic neighbourhood size may reveal brain areas involved in word processing. Future studies should address this issue in more detail.

We found no significant negative correlations with Typicality, and areas that showed positive correlation with Length occurred in areas that we would not have predicted on the basis of previous literature. These results should therefore be interpreted with caution. Only few studies have reported effects for these variables so far. Previous results on orthographic typicality are still inconsistent. Carreiras et al. (2006) reported effects of syllable frequency (related to typicality) in a left anterior inferior temporal region in a lexical decision task, but in left anterior insula for reading aloud. Binder et al. (2006) found larger activation in left fusiform gyrus for more typical letter strings. However, they used a letter detection task and included unpronounceable nonwords, which did not require subjects to match the orthographic input to lexico-semantic representations, and makes these results difficult to compare to previous studies. In contrast, two recent studies reported effects of orthographic typicality on ERPs already around 100 ms after word onset, with atypical items producing more activity than typical ones, and tentative source estimation suggested generators in left inferior temporal cortex (Hauk et al., 2006a,b). Vinckier et al. (2007) investigated different levels of typicality from the single letter to whole word level, and found differential fMRI activation for these different levels along a posterior–anterior gradient in inferior temporal and similarly in fronto-insular cortex. The localisation of typicality

effects to the precuneus in our study is not consistent with these earlier observations. With respect to word length, Mechelli et al. (2000) found larger activation for longer words in visual processing areas. The absence of such effects for length and typicality in our study can be explained by the fact that all our words were mono-syllabic, and therefore might not have provided enough variation to produce reliable length effects.

In conclusion, our study demonstrated that linear regression analysis of event-related fMRI data with respect to multiple psycholinguistic variables can reveal the cortical network underlying different aspects of word processing in the same set of subjects and stimulus items. The variable word frequency modulated a range of brain areas that have previously been linked to word processing, such as areas related to lexico-semantic processing in inferior frontal gyri, to phonological processing in the insulae, and to areas linking word form information to lexico-semantic representations in left fusiform gyrus. This result has implications for the interpretation of behavioural data, since our results indicate that word frequency can affect multiple stages of word processing. Effects observed in reaction times, for example, might thus reflect an accumulation of effects at different processing stages. This view is further supported by a number of electrophysiological studies cited above, which have shown that brain responses can be modulated by word frequency at different latencies. Our results with respect to orthographic typicality and word length did not reveal any brain areas exclusively involved in word form processing that were directly comparable to previous results. A positive correlation between brain activation and orthographic neighbourhood size *N* (in our study also negatively correlated with word length) was observed in several brain areas previously linked to word processing. However, so far the few studies that investigated this variable have produced inconsistent results. Our study demonstrated that multiple linear regression applied to event-related fMRI data is a promising tool for studying the complex cortical networks underlying word processing, and in the future might be able to resolve these inconsistencies.

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