Research Report

The role of the left Brodmann's areas 44 and 45 in reading words and pseudowords

Stefan Heim[a,b,c,*], Kai Alter[d], Anja K. Ischebeck[e], Katrin Amunts[a,f], Simon B. Eickhoff[a,g], Hartmut Mohlberg[a], Karl Zilles[a,b,g], D. Yves von Cramon[c], Angela D. Friederici[c]

[a]Research Centre Jülich, Institute of Medicine, AG Brain Mapping, 52425 Jülich, Germany
[b]Brain Imaging Center West (BICW), Jülich, Germany
[c]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[d]University of Newcastle, Medical School, School of Neurology, Neurobiology and Psychiatry, Newcastle, UK
[e]Innsbruck University Medical School, Clinic for Neurology, Innsbruck, Austria
[f]Department of Psychiatry and Psychotherapy, RWTH Aachen, Germany
[g]C. & O. Vogt Institut für Hirnforschung, Heinrich-Heine Universität, Düsseldorf, Germany

Abstract

In this functional magnetic resonance imaging (fMRI) study, we investigated the influence of two task (lexical decision, LDT; phonological decision, PDT) on activation in Broca's region (left Brodmann's areas [BA] 44 and 45) during the processing of visually presented words and pseudowords. Reaction times were longer for pseudowords than words in LDT but did not differ in PDT. By combining the fMRI data with cytoarchitectonic anatomical probability maps, we demonstrated that the left BA 44 and BA 45 were stronger activated for pseudowords than for words. Separate analyses for LDT and PDT revealed that the left BA 44 was activated in both tasks, whereas left BA 45 was only involved in LDT. The results are interpreted within a dual-route model of reading with the left BA 44 supporting grapheme-to-phoneme conversion and the left BA 45 being related to explicit lexical search.
© 2005 Elsevier B.V. All rights reserved.

1. Introduction

Broca's region comprises Brodmann's areas (BA) 44 and 45 in the left inferior frontal gyrus (IFG) [1,50]. Activation in this region has been frequently observed in neuroimaging studies of processing words, pseudowords, and non-words [5,8,12,13,17,19,24,27,32,35,39,41,46,47,55–59, 61,65,67,72,73]. In particular, many studies reported significant activation differences for pseudowords > words,

non-words > words, and low-frequency words > high-frequency words across various experimental tasks including silent or overt reading, lexical decisions, lexical-phonological decisions, or phonological decisions (Table 1; for reviews cf. [26,40,46]). Many authors have related this effect to the conversion of graphemes (i.e., letters) into phonemes. Grapheme-to-phoneme conversion (GPC) has been assumed to be stronger for processing pseudowords or non-words as compared to words since the former do not have a representation of their sound form in the mental lexicon. This implies that the sound form of pseudowords must be reconstructed in a letter-by-letter fashion during reading. Yet, given the substantial variability among the studies with respect to the target language, their actual GPC-

Table 1
Survey of neuroimaging studies on word, pseudoword, and non-word processing reporting activation in approximately the left BA 44 and BA 45

Study	Task	Language	Contrast	~BA	x	y	z
Ischebeck et al. [39]	Articulation	Japanese	Unfamiliar–familiar writing (words)	44	−50	10	23
Ischebeck et al. [39]	Articulation	Japanese	Pseudowords–familiar writing (words)	44	−56	10	27
Chee et al. [12]	Letter case decision	English	Words–fixation	44	−31	6	18
Binder et al. [5]	Lexical decision	English	Nonwords–words	44	−40	17	2
Edwards et al. [19]	Lexical decision	English	Pseudohomophones–words	44	−50	13	24
Fiebach et al. [24]	Lexical decision	German	Low–high-frequency words	44	−42	1	17
Fiebach et al. [24]	Lexical decision	German	Pseudowords–high-frequency words	44	−47	10	13
Rumsey et al. [61]	Lexical decision	English	Pseudowords–fixation	44	−42	6	20
Rumsey et al. [61]	Lexical decision	English	Words–fixation	44	−44	6	24
Xiao et al. [72]	Lexical decision	Chinese	Pseudowords–words	44	−51	15	14
Menard et al. [47]	Passive viewing	English	Words–pictures	44	−52	6	8
Menard et al. [47]	Passive viewing	English	Words–xxXxx	44	−43	7	0
Ischebeck et al. [39]	Phonological lexical decision	Japanese	Unfamiliar–familiar writing (words)	44	−53	15	4
Ischebeck et al. [39]	Phonological lexical decision	Japanese	Pseudowords–familiar writing (words)	44	−53	11	10
Fiez et al. [27]	Reading (aloud)	English	Irregular word–regular word	44	−49	11	11
Fiez et al. [27]	Reading (aloud)	English	Words–fixation	44	−49	11	10
Herbster et al. [35]	Reading (aloud)	English	Regular word–fixation	44	−48	6	0
Paulesu et al. [55]	Reading (aloud)	Italian	Words and pseudowords–rest	44	−44	4	20
Rumsey et al. [61]	Reading (aloud)	English	Pseudowords–fixation	44	−42	6	20
Rumsey et al. [61]	Reading (aloud)	English	Words–fixation	44	−44	6	24
Tan et al. [67]	Reading (aloud)	Chinese	Chinese characters–fixation	44	−51	15	7
Tan et al. [67]	Reading (aloud)	Chinese	Chinese characters–fixation	44	−61	11	1
Joubert et al. [41]	Reading (silently)	French	High-frequency words–consonant strings	44	−47	12	18
Joubert et al. [41]	Reading (silently)	French	Nonwords–consonant strings	44	−47	6	14
Mechelli et al. [46]	Reading (silently)	English	Pseudowords–words	44	−48	8	22
Mechelli et al. [46]	Reading (silently)	English	Pseudowords–fixation	44	−42	16	32
Mechelli et al. [46]	Reading (silently)	English	Words–fixation	44	−42	16	32
Xu et al. [73]	Rhyming	English	Pseudowords–words	44	−52	10	12
Chee et al. [12]	Semantic decision	English	Words–fixation	44	−46	12	18
Chee et al. [12]	Semantic decision	English	Words–fixation	44	−46	9	31
Chee et al. [12]	Semantic decision	English	Words–fixation	44	−43	3	28
Booth et al. [8]	Spelling, rhyming (words)	English	Spelling–rhyming	44	−42	9	27
Dehaene et al. [17]	Viewing	French	Words–blank	44	−48	8	4
Mean coordinates				44	−47	10	15
Fiebach et al. [24]	Lexical decision	German	Low–high-frequency words	45	−51	31	10
Perani et al. [56]	Lexical decision	Italian	Words–consonants	45	−50	20	16
Perani et al. [56]	Lexical decision	Italian	Words–consonants	45	−48	18	12
Price et al. [58]	Lexical decision	English	Words and pseudowords–false font	45	−51	22	23
Xiao et al. [72]	Lexical decision	Chinese	Pseudowords and words–rest	45	−50	18	10
Xiao et al. [72]	Lexical decision	Chinese	Pseudowords and words–rest	45	−32	32	9
Paulesu et al. [55]	Reading (aloud)	Italian	Pseudoword–word	45	−42	24	14
Tan et al. [67]	Reading (aloud)	Chinese	Chinese characters–fixation	45	−48	17	15
Tan et al. [67]	Reading (aloud)	Chinese	Chinese characters–fixation	45	−48	15	19
Hagoort et al. [32]	Reading (aloud and silently)	German	Pseudowords–words	45	−46	18	−9
Joubert et al. [41]	Reading (silently)	French	Low-frequency words–consonant strings	45	−45	32	7
Joubert et al. [41]	Reading (silently)	French	Nonwords–consonant strings	45	−45	22	17
Cappa et al. [11]	Semantic decision	Italian	Words–pseudowords	45	−44	22	20
Cappa et al. [11]	Semantic decision	Italian	Words (living objects)–pseudowords	45	−42	24	16
Cappa et al. [11]	Semantic decision	Italian	Words–pseudowords	45	−44	22	20
Chee et al. [12]	Semantic decision	English	Words–fixation	45	−46	27	25
Booth et al. [8]	Spelling–rhyming (auditory words)	English		45	−42	30	18
Mean coordinates				45	−45	24	16

The results are grouped as a function of region and of experimental design.

rules and even the tasks on the one hand the variability with respect to the peak and extent of the activations reported, it is yet an open issue whether all these activations are correlated with the same process (e.g., GPC) or rather several distinct processes [24,32]. One argument in favour of the latter possibility is the notion of distinguishable modules within the left IFG specialised for the processing of, e.g., semantic (anterior IFG), syntactic (inferior–posterior IFG), and phonological information (superior–posterior IFG) [7,29].

Although the reported imaging studies have increased our understanding of the neural circuitry of visual word and pseudoword processing, and despite a continuous increase in the spatial resolution of the neuroimaging signals, the neuroanatomical localisation of activation foci is thus far basically restricted to macroanatomical descriptions. Reference systems such as the MNI space or the Talairach atlas [66] only provide a coarse assignment of stereotaxic coordinates to microanatomically defined regions such as the Brodmann's areas (BA) [9]. This is because Brodmann's original map, a 2-dimensional sketch (Fig. 1A), contains no 3-dimensional information which would be required for such an assignment. Accordingly, the borders of the BAs are basically identified by means of the sulcal pattern of the brain. Some authors acknowledge this anatomical uncertainty by assigning tentative labels such as approximate Brodmann's area [54] or referring to macroanatomical terms, e.g., pars opercularis of the left IFG [24]. This precaution is justified since there is a substantial amount of intersubject variability with regard to the localisation of the cytoarchitectonic borders of BA 44 and BA 45, which, above all, do not necessarily coincide with macroanatomical landmarks such as gyri or sulci [1,2].

Thus, in order to provide more exact descriptions of IFG activations as well as to answer the question whether they reflect one or several distinct processes, a higher degree of anatomical precision is required. This can be achieved by superimposing the functional data on anatomical probability maps which are based on an observer-independent analysis of the cytoarchitecture in a sample of 10 post-mortem brains [1,2,20,21,62,76]. These probability maps provide information about the location and variability of cortical regions in a standard reference space (the MNI space) (Figs. 1B and C). These maps can be combined into a single summary map by using the maximum probability map approach [22]. In the resulting maximum probability map (MPM), each voxel in the brain is assigned to the cytoarchitectonic area which is most likely found at that position (Fig. 1D). The advantage of this method over others relying, e.g., on automatic labelling of anatomical structures [44] is that functions identified with imaging techniques can be related to brain structures with a much higher validity. The usefulness of this approach to neuroimaging studies of language processing has been recently demonstrated [2,37,38].

1.1. Objectives

The current functional magnetic resonance imaging (fMRI) study was designed to replicate previous findings demonstrating the activation of Broca's region during word and pseudoword processing. Furthermore, by superimposing the data on the cytoarchitectonic probabil-
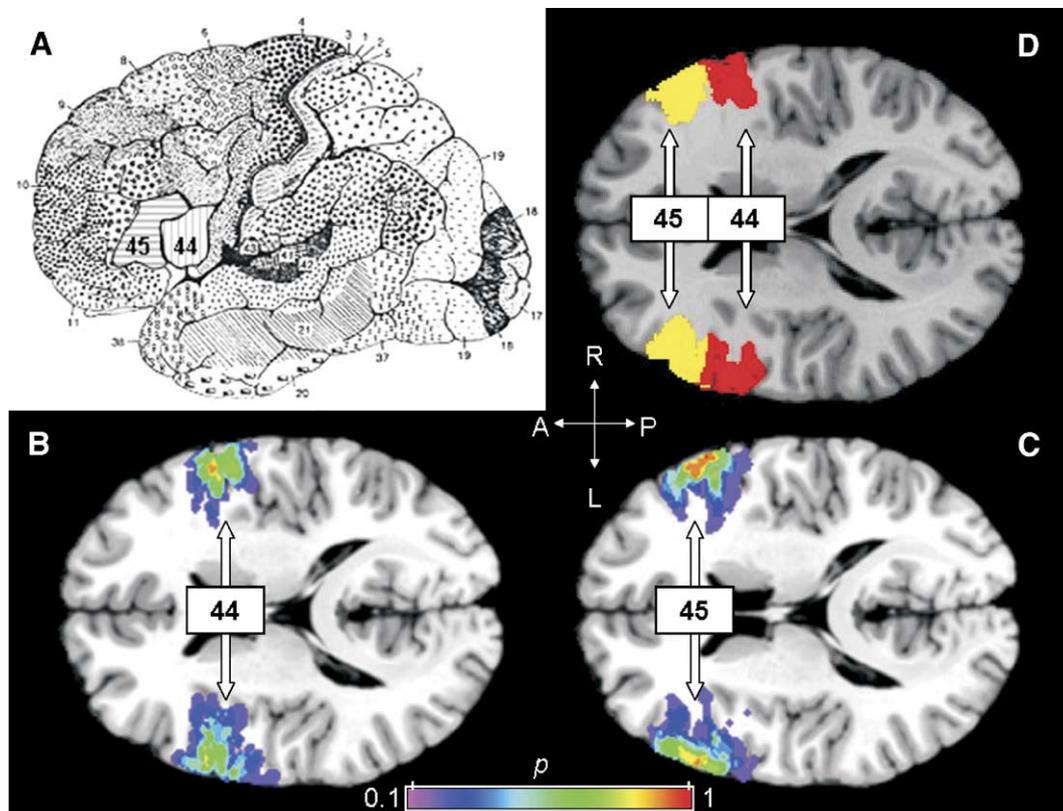

Fig. 1. (A) The 2-dimensional cytoarchitectonical map of Brodmann (modified from [9]). Brodmann's areas (BA) 44 and 45 in the left inferior frontal gyrus are highlighted. (B and C) Cytoarchitectonic probability map of BA 44 (B) and BA 45 (C), rendered on the high-resolution single-subject MNI template (axial view at $z = 15$). The probabilities of each voxel in the brain to belong to BA 44 or BA 45, respectively, are colour-coded. (D) Maximum probability maps of BA 44 and BA 45, rendered on the high-resolution single-subject MNI template (axial view at $z = 20$).

ity maps, we wanted to determine whether the left BA 44, the left BA 45, or both are involved. Finally, we tested whether the activation in Broca's region consists of one or more foci. The latter is suggested by the high variability of the activations reported in the literature (Table 1). If there were separable functional activation foci within Broca's region, the activation should vary with different task demands. For this purpose, we employed two of the commonly used tasks, a lexical decision (LDT) and a phonological decision (PDT). Both tasks include an explicit language-based decision while tapping different types of linguistic information, i.e., lexical status vs. phonetic properties. We did not include simple reading as a third task, which would have substantially differed from the two other tasks since no explicit decision making would have been required.

2. Experimental procedure

2.1. Participants

16 healthy right-handed subjects (8 females; mean age 25.6 years, SD 2.4 years) participated in the experiment. They all were native German speakers and had normal or corrected to normal vision. The subjects had no known history of neurological, major medical, or psychiatric disorders; none were taking medication at the time of measurement. Informed consent was obtained from all participants. The experimental standards were approved by the local ethics committee of the University of Leipzig. The data were handled confidentially. One subject aborted the experiment. These data were discarded from further analyses.

2.2. Stimulus materials

The stimulus materials consisted of 80 words (WO) (mean total frequency 164.8 per million, range 31–900, as determined on the basis of the CELEX database (http://www.kun.nl/celex/—last access 27 August 2005)) and 80 pronounceable orthographically legal pseudowords (PW) generated from the words by exchanging one or two vowels within the word. Thus, the pseudowords resembled closely the word stimuli. Nonetheless, pseudowords and words were easily to be distinguished, indicated by the low error rates in the lexical decision task (Table 2). 50% of the stimuli in both categories started with a fricative (F or S) and 50% with a stop consonant (P or T).

2.3. Procedure

In the LDT, subjects had to indicate whether a stimulus was a word or a pseudoword. In the PDT, subjects decided whether the stimulus started with a fricative or stop

Table 2
Mean reaction times (RT) in milliseconds and error rates (ER) in percent (standard deviations in parentheses) as a function of word-type (pseudo-words, PW; words, WO) and task (lexical decision, LDT; phonological decision, PDT)

Task	PW		WO	
	RT [ms]	ER [%]	RT [ms]	ER [%]
LDT	693 (36)	3 (0.3)	637 (37)	2 (0.2)
PDT	609 (31)	4 (0.3)	615 (34)	4 (0.4)

consonant. Participants responded by pressing one of two response buttons with the index or middle finger of the right hand, respectively. In each task, equal numbers of left and right responses were required. The assignment of the buttons to the response alternatives was balanced over subjects. Stimuli were presented in a pseudorandom order. In order to increase the experimental power, each stimulus was presented twice during the experiment. Each word and its corresponding pseudoword were separated by at least 10 other stimuli. There was a temporal jittering (blank screen for 0, 250, 500, or 750 ms) at the beginning of each trial. After 1900 ms, the stimulus was presented for 800 ms. The screen remained blank for a variable time interval, amounting to a total trial duration of 5000 ms. In addition, 16 null-events were included in order to allow a better estimation of the haemodynamic response in the experimental conditions.

2.4. Data acquisition and analysis

Reaction times were registered and analysed using repeated-measures ANOVAs with the factors TASK (LDT/PDT) and WORD-TYPE (PW/WO).

The experiment was carried out on a 3 T scanner (Medspec 30/100, Bruker, Ettlingen). A standard birdcage head coil was used. Visual stimuli were presented on a screen positioned at the head end of the magnet bore. Subjects viewed the screen through mirror glasses. Foam paddings were used to reduce head motion. T1-weighted EPI images were taken with a TE = 30 ms, flip angle 90°, acquisition bandwidth 100 kHz. The inversion time was 1200 ms, with a TR of 45 s and four averages. The functional data were recorded using a gradient-echo EPI sequence with TE = 30 ms, flip angle 90°, TR = 1 s, acquisition bandwidth 100 kHz. The matrix acquired was 64 × 64 with a FOV of 19.2 cm, resulting in an in-plane resolution of 3 mm × 3 mm. 14 axial slices covering the left IFG and surrounding areas were recorded (3 mm thickness, 1 mm gap).

The data processing was performed using MATLAB 6.5 (The Mathworks Inc., Natick, USA) and SPM2 (Wellcome Department of Cognitive Neurology, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm2—last access 27 August 2005). A total of 1655 scans were acquired for each subject. The first five scans were discarded to allow for magnetic saturation. The functional images of each participant were motion corrected. The individual slices

of a functional volume (14 in total) were corrected for slice time acquisition difference with respect to the middle (seventh) slice. An individual high-resolution ($1 \times 1 \times 1$ mm^3) anatomical 3D data set of each subject was coregistered to the individual EPI-T1 anatomy. Then, the individual anatomical 3D data set was normalised to the high-resolution data set of the MNI single subject template [14,23,36] using linear and non-linear transformations [3,4]. The normalisation parameters were then used for the normalisation of the functional images. Finally, the functional data were filtered in the spatial (isotropic Gaussian kernel, FWHM = 6 mm) and temporal domain (high-pass, cut-off 1/200 Hz).

Statistical analysis was performed using a mixed effects model. The delta-function of the stimulus onsets for each condition was convolved with the canonical haemodynamic response function (HRF) and its first temporal derivative, HRF′, to account for minor latency differences [30]. The predictors for the contribution of the HRF′, motion parameters, and a constant for global mean activation per subject were included in the model as covariates of no interest. Specific effects were tested by applying appropriate linear contrasts to the parameter estimates for each condition. The main analysis tested for the main effects of WORD-TYPE and TASK and their interaction. In addition, the contrasts PW > WO and WO > PW were calculated separately for the two tasks. For the group analysis, the individual contrast images were entered into one-sample *t* tests as a second level random effects analysis. This allows making inferences about the general population. The resulting *F* and *t* statistics constitute a statistical parametric map which was then

interpreted by referring to the probabilistic behaviour of Gaussian random fields [71].

According to the scope of this paper, we focused on activation in the left BA 44 and BA 45. We report only activation that passed a threshold of $P < 0.05$ FDR corrected at voxel level for the search volume containing either the left BA 44 or the left BA 45, respectively, depending on the location of the local maximum. This search volume was calculated on the basis of a mask image generated from the abovementioned MPMs using the SPM-Anatomy toolbox developed by Eickhoff et al. [20] (http://www.fz-juelich.de/ime/spm_anatomy_toolbox—last access 27 August 2005).

3. Results

3.1. Behavioural data

The average reaction times and error rates for the processing of PW and WO as a function of TASK are given in Table 2. For the reaction times, there were two significant main effects and a significant interaction (TASK: $F(1,7) = 76.174$, $P < 0.001$, LDT > PDT; WORD-TYPE: $F(1,7) = 15.226$, $P < 0.006$, PW > WO; TASK × WORD-TYPE: $F(1,7) = 37.153$, $P < 0.001$). This interaction was due to longer reaction times for pseudowords than words in LDT ($t(7) = 5.333$, $P < 0.001$) whereas no difference was observed in PDT ($t(7) = -1.233$, $P > 0.05$). For the error rates, there were no significant effects ($P > 0.05$).

Table 3
Results of the ANOVA TASK×WORD-TYPE for the fMRI data in the left BA 44 and BA 45

Task	Contrast	BA	Coordinates	$t_{(14)}$	$F_{(1,14)}$	P
Main effect WORD-TYPE						
	F test	44	−52, 10, 6	–	21.45	0.028
		45	−48, 32, 6	–	63.36	0.001
	PW > WO	44	−52, 10, 6	4.63	–	0.014
		45	−48, 32, 6	7.96	–	0.001
	WO > PW	n.s.				
Main Effect TASK						
	F test	n.s.				
Interaction WORD-TYPE×TASK						
	F test	45	−42, 26, −2	–	61.88	0.046
	(PDT_WO+LDT_PW) > (PDT_PW+LDT_WO)	45	−42, 26, −2	7.87	–	0.027
	(PDT_PW+LDT_WO) > (PDT_WO+LDT_PW)	n.s.				
Planned Contrasts						
LDT	PW > WO	44	−54, 12, 6	4.58	–	0.024
		45	−44, 36, 4	7.19	–	0.002
	WO > PW	n.s.				
PDT	PW > WO	44	−48, 6, 10	4.73	–	0.049
	WO > PW	n.s.				

Coordinates refer to the standard MNI space. Abbreviations: Brodmann's area as indicated by the cytoarchitectonic maximum probability map (MPM); *F*, *t*, *F* value or *t* value of effect at the given coordinates (degrees of freedom in parentheses); LDT, lexical decision task; PDT, phonological decision task; n.s., not significant.

3.2. Imaging data

As noted above, imaging results are reported for the left BA 44 and BA 45 as identified using the cytoarchitectonic probability maps of Amunts et al. [1]. There was a main effect of WORD-TYPE in BA 44 and BA 45 (Table 3). The planned contrasts revealed that there was activation PW > WO in the left BA 44 and BA 45 (Table 3 and Fig. 2). These two local maxima were present in 10 subjects ($P < 0.001$, uncorrected; Fig. 3 and Table 4). At a more lenient threshold ($P < 0.05$, uncorrected), the same pattern was observed in
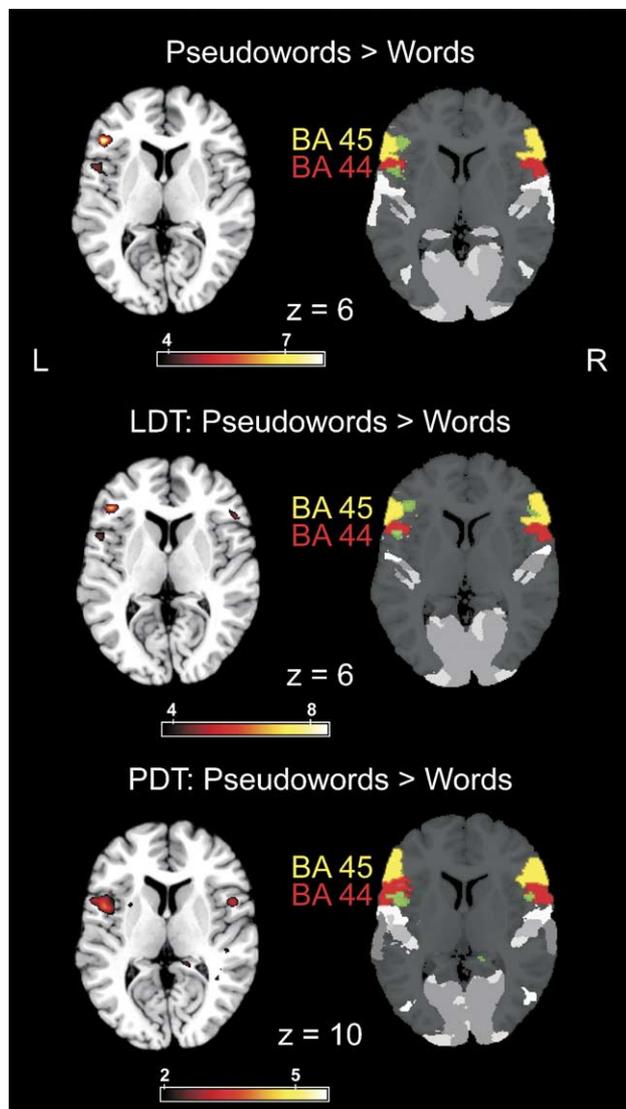
Fig. 2. Activation in the contrast Pseudowords (PW) > Words (WO) as a function of task. Top: Main effect. Middle: Effect for the lexical decision task (LDT). Bottom: Effect for the phonological decision task (PDT). The left picture in each column is a classical display featuring the SPM{t} map rendered on the high-resolution MNI template. The colour bar indicates the t value. The right picture in each column shows the same effect (in green colour) at the same coordinates as the left picture, superimposed on the cytoarchitectonic maximum probability maps (MPMs) of BA 44 (red) and BA 45 (yellow), rendered on a grey-level reduced version of high-resolution MNI template.

all but one subject. For the main effect of TASK, there was no significant main effect in BA 44 or BA 45 (Table 3). The interaction was significant in BA 45 (Table 3). In the planned contrasts, there was an effect PW > WO in BA 44 and BA 45 in LDT (Table 3 and Fig. 2). In PDT, there was activation PW > WO in BA 44 but not in BA 45 (Table 3 and Fig. 2). The reverse contrast WO > PW yielded no significant effects in any of the reported analyses.

In the contrasts that yielded significant effects within Broca's region, there were other significant effects (PW > WO, $P < 0.001$, uncorrected) in the remainder of the scanned part of the brain. Although these are not within the scope of the present study, they are reported here as they may provide additional cues for the interpretation of the relevant effects. For the main effect of WORD-TYPE, there was additional activation in the left inferior temporal gyrus (ITG) ($-50, -36, -22; t = 5.38$), the right area V4 ($36, -84, -14; t = 5.42$), and the orbital parts of the left and right IFG (left: $-40, 28, -2, t = 4.29$; right: $28, 24, -18, t = 4.01$). In the LDT, further effects were observed in the left ITG ($-52, -42, -20; t = 5.55$), the right area V4 ($36, -84, -14; t = 7.92$), the right BA 45 ($52, 28, 6; t = 4.83$), and the orbital parts of the left and right IFG (left: $-30, 36, -16, t = 4.43$; right: $38, 26, -8, t = 4.11$). At last, in the PDT, additional effects were in the left ITG/fusiform gyrus ($-46, -38, -20; t = 4.94; -42, -38, -20, t = 4.89$), the right area V4 ($40, -82, -6; t = 3.94$), the right area V5 ($38, -68, 2; t = 3.82$), the right BA 44 ($52, 10, 8; t = 3.83$), and the orbital part of the right IFG ($48, 38, -8, t = 5.70$).

Since strong gender differences with respect to verbal tasks are suggested for the frontal lobe [64], we also compared the data of male and female subjects in the main effect pseudowords > words. The F test did, however, not yield any significant effects, neither at a corrected level ($P < 0.05$) nor at an uncorrected threshold of $P < 0.001$ (extent > 5 voxels).

4. Discussion

In the present study, we investigated the processing of words (WO) and pseudowords (PW) as a function of task (lexical decision, LDT; phonological decision, PDT). We intended to replicate previous findings from imaging studies demonstrating the involvement of the left BA 44 and BA 45. Moreover, instead of relying on macroanatomical descriptions of the brain activations, we used cytoarchitectonic probability maps [1] for the identification of the cortical areas in which the observed effects were located.

4.1. Behavioural data

The reaction times in our study are comparable to those reported in the literature for similar tasks as they range between shorter values [39] and longer ones [5,24,42,48]. They reveal that explicit lexical processing took longer than phonological processing. Moreover, in LDT, but not in PDT,
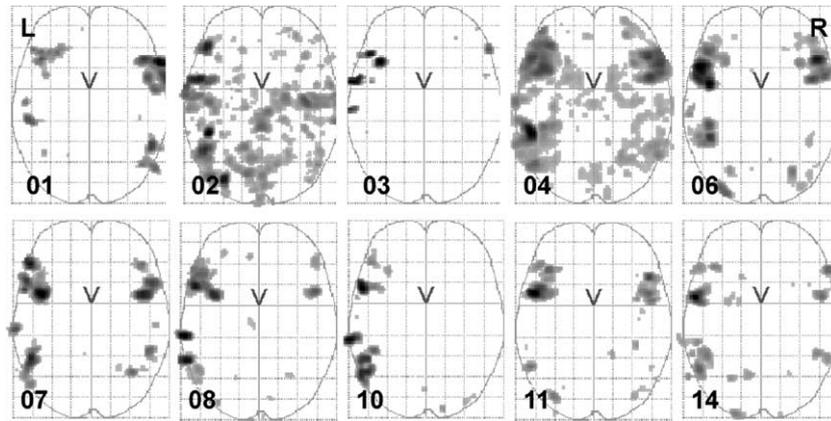
Fig. 3. Axial views of the effect Pseudowords > Words for the 10 subjects showing significant activation (*P* < 0.001 uncorrected) in the left BA 44, left BA 45, and left ITG, rendered on the SPM2 glass brain. Abbreviations: L, left; R, right.

pseudowords were processed more slowly than words, which led to the significant interaction between both factors. Considering that the phonological processing only required processing the first phoneme, it is reasonable that this task is faster than LDT which requires lexical access of the decision whether the stimulus is a word or not. With respect to the interaction of the task and the lexical status of the stimulus, the same argumentation holds. For a decision on the first phoneme, the lexical status of the stimulus does not matter. Therefore, no differences between pseudowords and words were observed here. In contrast, the lexical decision is faster for words than pseudowords, since for the latter, no lexical entry can be retrieved [28].

4.2. Imaging data

Observing a significant effect of WORD-TYPE (PW > WO) in Broca's region (both left BA 44 and BA 45), we

Table 4
MNI coordinates of the effect "Pseudowords>Words" nearest to the local maximum of the group random effects (RFX) analysis (lowest row)

Subject	BA 44			BA 45			ITG		
	x	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
01	−38	13	16	−42	32	2	−38	−56	−12
02	−54	8	12	−48	36	18	−50	−54	−10
03	−46	6	18	−48	30	0	−50	−38	−22
04	−48	14	12	−54	26	−6	−52	−48	−20
06	−44	4	16	−46	32	−8	−44	−42	−22
07	−42	8	22	−52	34	−2	−52	−48	−24
08	−54	16	12	−44	38	24	−52	−56	−16
10	−54	12	18	−48	36	20	−52	−48	−18
11	−50	10	8	−46	36	6	−54	−54	−18
14	−56	6	2	−52	32	6	−54	−48	−20
Mean	−48.6	9.7	13.6	−48	33.2	6	−49.8	−49.2	−18.2
RFX Mean	−44	12	10	−48	30	6	−52	−48	−20

Displayed are only data for subjects showing significant activation (*P* < 0.001, uncorrected) in the left BA 44, left BA 45, and left inferior temporal gyrus (ITG), and the mean coordinates of these 10 subjects in all three regions. Italic prints for subject #01 indicate an activation that was identifiable but no local maximum.

replicated results from previous neuroimaging studies [5,13,19,24,27,32,39,41,46,58,59,61,65,72]. Moreover, we demonstrated that the experimental task influenced the activation pattern. This holds in particular for BA 45 where there was an interaction of TASK and WORD-TYPE. The functional significance of these effects will now be discussed in more detail.

4.2.1. Activation in the left BA 44—grapheme-to-phoneme conversion

We observed stronger activation for pseudowords than words in the left BA 44 and BA 45. When activation was analysed separately for each task, it appeared that, in BA 44, this effect was present for both the PDT and the LDT. In other words, it was independent of the actual experimental task, and could thus be related to some process shared in both tasks. Our interpretation of this effect follows the suggestion put forth in prior studies [5,24,27,32,39,41,46,61] that the significantly stronger activation for pseudowords than for words is associated with grapheme-to-phoneme conversion (GPC).

GPC is assumed in the dual-route model of visual word recognition of Coltheart et al. [15] (Fig. 4). As many earlier dual-route models of visual word recognition, it proposes the existence of two qualitatively different types of access to the mental lexicon, i.e., the representation of language in the human mind. Words may be read by directly retrieving the word's sound form from the mental lexicon (addressed phonology, direct/lexical route) and by spelling out the word letter by letter (GPC, assembled phonology, indirect/non-lexical route). In the Coltheart et al. [15] model, processing on the two routes is not mutually exclusive. Rather, both routes are involved in parallel in visual word recognition. Whereas for high-frequency words, the correct entry will be retrieved via the lexical route before each grapheme is converted into a phoneme, the latter process may be faster when reading unfamiliar low-frequency words or complex words. In particular, this holds for pseudowords, i.e., pronounceable letter strings (e.g., RAME) and non-words, i.e., unpro-
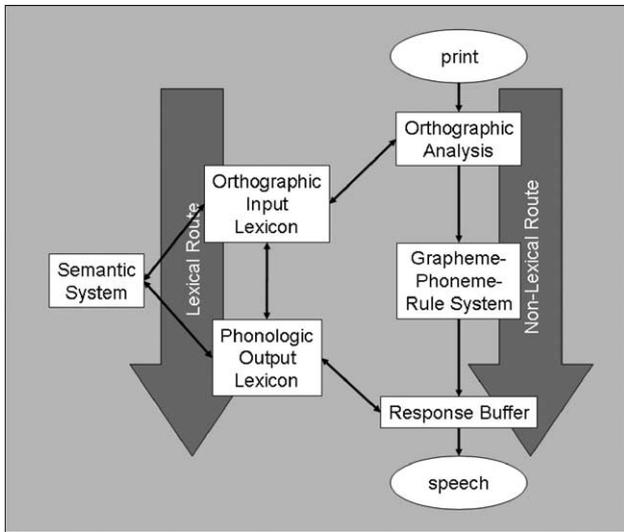
Fig. 4. Schematic display of the dual-route model of Coltheart et al. [15]. Visual word recognition is achieved by parallel processing in two paths, the non-lexical route (letter-by-letter grapheme-to-phoneme conversion) and the lexical route (lexical search for the whole phonological word form).

nounceable letter strings (e.g., GRTO) for which there is no lexical entry.

With respect to our data, the following task analysis is proposed. (1) In reading, both the direct, lexical and the indirect, phonological route work in parallel. (2) GPC for each grapheme is started via the indirect route. (3) When there is enough input (e.g., a word stem or an initial cohort), entries in the mental lexicon are searched via the direct route. (4) For high-frequency words, the word form may be retrieved via the lexical route even before the last grapheme was converted to a phoneme on the non-lexical route. (5) For low-frequency words, pseudowords, or non-words, the lexical search succeeds later or never. Thus, more or even all letters are translated to sounds via the indirect route. (6) Accordingly, not GPC per se (i.e., only the processing on the non-lexical route), but rather a higher demand on GPC is reflected in the activation of the left BA 44 (Fig. 5).

As mentioned above, the activation in BA 44 is independent of particular task demands. In our view, this BA 44 activation is related to task-independent GPC taking place during the reading process of the pseudowords and words before the explicit lexical or phonological decision. In other words, it is a prerequisite for subsequent explicit processing. A number of arguments support this notion. First, there was no main effect of TASK and no interaction in BA 44. Second, Newman and Twieg [49] reported no IFG activation (PW > WO) in a PDT when the stimuli were presented auditorily, i.e., when GPC was not necessary. Finally, Omura et al. [53] reported activation in similar areas for the reverse process, i.e., phoneme-to-grapheme conversion. In sum, our data agree with the view that GPC is correlated with activation in the left BA 44.

One might question whether the subjects really read the entire stimulus in the PDT. For the successful completion of

the task, it would suffice to focus the attention on the first letter of the word and make a letter decision instead of a phoneme decision. In this case, GPC would not be required. This implies that, if only the first letter of each stimulus had been processed, the lexical status (word or pseudoword) should not matter. However, we did observe a significant activation effect for pseudowords over words in PDT, indicating that the entire stimulus had been processed.

As mentioned earlier, the notion of grapheme-to-phoneme conversion was brought up in several recent neuroimaging studies. Many but not all agree that its neural correlate is located in the left inferior frontal gyrus. For example, Xu et al. [73] found that pseudowords elicited more activation than words in the left supramarginal gyrus (SMG) in the temporo-parietal cortex, which they interpreted as the brain region supporting GPC. These data are related to findings by Temple et al. [68] who scanned dyslexic children and normal controls performing a rhyme task on visual presented letters. Whereas left inferior frontal activation was present in both groups, only the normal readers showed additional temporo-parietal activation. These data stress the possible importance of the temporo-parietal region for the processing of phonological properties of written stimuli. In the present study, the temporo-parietal cortex was within the field of view. However, there was no
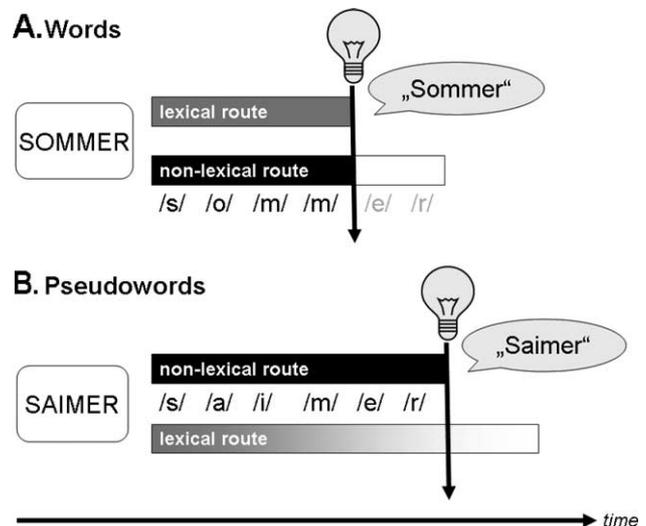

Fig. 5. Schematic display of the processes during word and pseudoword recognition according to the dual-route model of Coltheart et al. [15]. (A) When a (high-frequency) word is processed, its sound form will be retrieved from the mental lexicon via the lexical route, and the word can be pronounced. This is accomplished before all graphemes were converted to phonemes via the non-lexical route. (B) When a pseudoword is processed, no entry will be found in the mental lexicon via the lexical route, indicated by the fading grey bar. Meanwhile, all graphemes are converted into phonemes via the non-lexical route, and the pseudoword can be pronounced. Note: Comparing the processing of words and pseudowords, you see that more graphemes are converted for pseudowords then for words. This effect may be reflected in the activation PW > WO in BA 44. Similarly, the automatic lexical search is continued longer for pseudowords than for words. This is supposed to correlate with the activation PW > WO in the left inferior temporal gyrus.

effect in any of the two regions. Thus, our data do not provide further evidence for the discussion of the involvement of temporo-parietal regions in GPC.

4.2.2. Activation in the left BA 45—lexical search

Our study was also designed to test whether the activation in BA 45 reported in some imaging studies (Table 1) could be anatomically and functionally segregated from that in BA 44. We found the effect of WORD-TYPE (PW > WO) in BA 45 to be task-dependent as demonstrated by the significant interaction. Planned contrasts yielded a stronger activation for PW than for WO in BA 45 only in the LDT but not in the PDT.

The absence of a main effect of TASK indicates that the observed activation in BA 45 in LDT in the interaction contrast was not caused by increased task difficulty, as might be inferred from the longer reaction times in LDT. In contrast, the interaction effect suggests that there is a selective increase in activity only for the processing of PW in LDT. No such interaction was observed in BA 44, demonstrating equal levels of activation and processing here.

Thus, the present data indicate a direct relation of BA 45 and the way words and pseudowords are processed in a lexical decision task. We suggest the following interpretation for the stronger activation for PW than WO in BA 45 during LDT. In a lexical decision task, the written stimulus (no matter by which route the sound form had been retrieved before) must be explicitly checked whether it is a lexical entry or not. This controlled lexical search takes longer (as reflected by the reaction time data) and is more effortful for pseudowords and low-frequency words than high-frequency words [28] and therefore leads to an increased activation in BA 45.

This interpretation of the role of BA 45 in lexical search is concordant with a recent fMRI study on controlled lexico-semantic processing [2]. In this study, subjects had to generate either highly overlearnt words (e.g., days of the week; low lexical-semantic demands) or exemplars of particular categories (e.g., furniture; high-lexical semantic demands). When subtracting the signal in the low demanding task from the high demanding task, the authors found an effect in BA 45 as indicated by superimposing the imaging data on the cytoarchitectonic probability maps.

4.3. The roles of BA 44 and BA 45 in a cortical network

The above given interpretation of the inferior frontal activations implies that BA 44 supports stimulus-driven bottom-up processing during GPC, which runs in a letter-by-letter fashion. In contrast, the explicit lexical search reflected by the activation in BA 45 is task-driven top-down processing. Results supporting this notion were reported, e.g., by Noesselt et al. [52] who had subjects perform semantic judgements on words (top-down processing) presented auditorily at three different rates (bottom-up

processing). Passive listening to the same stimuli served as a baseline condition. The authors observed a main effect of task, i.e., top-down processing, in BA 45. In BA 44, there was an interaction of task and presentation rate, indicating its involvement in both bottom-up and top-down processing. The authors supposed that the latter effect was related to "the analysis of phonological features of those words entering semantic analysis later". This interpretation was based on earlier studies by Gabrieli et al. [31] and Fiez [25] who related activation of the left dorsal IFG to phonological processing. In fact, data supporting this notion had been reported even earlier, e.g., by Démonet et al. [18] and Zatorre et al. [74,75] for auditory language comprehension. Later, these findings were extended to phonological processing in language production [33,34] and phonological working memory [77]. All these processes have in common the processing of phonological information. In the context of the present study, these results provide further support for the interpretation that the effect in BA 44 is related to a phonological process, i.e., grapheme-to-phoneme conversion.

It is yet an open issue how BA 44 accomplishes these different phonological functions (and a number of other, non-linguistic functions such as processing syntactic information of music [43], the perception of rhythm of motion [63], imagery of motion [6], etc.). There are several possible explanations for this: (1) BA 44 is one multi-modal region subserving different specific functions. (2) BA 44 is functionally parcellated in different sub-regions. This is concordant with literature reviews provided, e.g., by Bookheimer [7] or the model of auditory sentence comprehension of Friederici [29]. (3) All the sketched functions have some common denominator. It is not the cognitive function per se but rather the format of the information that is processed by BA 44. Friederici [29] argued that all the types of information processed in Broca's area involve some aspect of sequencing, which might be the unknown shared feature. Such sequencing could also apply to the processing of a continuous stream of auditorily perceived phonemes or visually perceived letters requiring GPC which is supposed to be a linear process in the Coltheart et al. [15] model. It might also be involved in phonological working memory when operationalised by an n-back task in which the items that need to be memorised enter the phonological loop in a serial order. (4) BA 44 receives its functionality by its integration in different anatomical circuits, as proposed, e.g., by Marshall and Fink [45]. This alternative is supported by the fact that the network for phonological decisions in language production and comprehension comprises at least BA 44 and the posterior superior temporal gyrus (pSTG) [10,33,34,69], whereas in the present study, the left ITG but not the pSTG was part of the network. (5) One of the first to third alternatives could apply in combination with the fourth. This issue cannot be solved based on the present results. Data about anatomical and functional connectivity would provide valuable additional insights. For the purpose

of the present study, however, it is important to note that the literature about the involvement of BA 44 in phonological processing is in accordance with its role in phonology-based GPC proposed here.

As the present study was designed to elucidate the role of the left BA 44 and BA 45 in the processing of words and pseudowords, we focused the analyses on the left BA 44 and BA 45 as defined by the cytoarchitectonic probability maps. Recording only 14 slices instead of whole-brain scans, we achieved a higher sampling rate (TR = 1), resulting in an increased signal-to-noise ratio. Yet, the imaging data covered not only the inferior frontal parts of the brain but also the temporal and occipital lobes. Among these, we observed an effect (PW > WO) in the left ITG in both the LDT and the PDT as well as in the main effect of WORD-TYPE. Similar data have been reported in a number of studies (cf. [46] for a review and data on silent reading). Earlier imaging and patient work has revealed the involvement of the left inferior temporal lobe in lexical access, lexical retrieval, or semantic processing [16,51,55,60,70]. Taken together, the present data fit into a series of earlier results assigning lexico-semantic processing during reading to the left inferior temporal lobe. In terms of a dual-route account, the stronger activation for pseudowords than words could reflect the increased effort at lexical access in the mental lexicon during reading which takes longer until it times out in the case of pseudowords (Fig. 5). Recently developed approaches for identifying functional connectivity between brain regions may be helpful tools to further elucidate how this function of the left ITG interacts with the top-down and bottom-up processes in the left inferior frontal BA 44 and BA 45.

5. Conclusion

Using cytoarchitectonic probability maps, we demonstrated the differential involvement of the microstructurally defined BA 44 and BA 45 in visual word recognition. In this point, our data support the claim by Fiebach et al. [24] and Hagoort et al. [32] that distinct regions within Broca's area (i.e., BA 44 and BA 45) may subserve different functions in reading.

Our data could be interpreted as follows. The greater activation for pseudowords than words in the left BA 44 is correlated with increased GPC (non-lexical/indirect route in dual-route model terminology) during reading. The effect PW > WO in the left inferior temporal lobe reflects the extended lexical search in the mental lexicon during reading (lexical/direct route in dual-route model terminology). The stronger effect for pseudowords than for words in the left BA 45 only in the LDT is caused by the prolonged explicit lexical search after reading which is required for correct responses in the LDT.

From a methodological point of view, this study demonstrates how the integration of information from different fields, i.e., (micro)neuroanatomy, functional imaging, behavioural research, and cognitive modelling, may lead to a refined view of the processing in the human brain.

References

[1] K. Amunts, A. Schleicher, U. Bürgel, H. Mohlberg, H.B.M. Uylings, K. Zilles, Broca's regions revisited: cytoarchitecture and intersubject variability, J. Comp. Neurol. 412 (1999) 319–341.

[2] K. Amunts, P.H. Weiss, H. Mohlberg, P. Pieperhoff, S. Eickhoff, J.M. Gurd, J.C. Marshall, N.J. Shah, G.R. Fink, K. Zilles, Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space—The roles of Brodmann areas 44 and 45, NeuroImage 22 (2004) 42–56.

[3] J. Ashburner, K.J. Friston, Rigid body registration, in: R.S.J. Frackowiak, K.J. Friston, C.D. Frith, R.J. Dolan, C.J. Price, J. Ashburner, W.D. Penny, S. Zeki (Eds.), Human Brain Function, Academic Press, San Diego, 2003.

[4] J. Ashburner, K.J. Friston, Spatial normalization using basis functions, in: R.S.J. Frackowiak, K.J. Friston, C.D. Frith, R.J. Dolan, C.J. Price, J. Ashburner, W.D. Penny, S. Zeki (Eds.), Human Brain Function, Academic Press, San Diego, 2003.

[5] J.R. Binder, K.A. Mckiernan, M.E. Parsons, C.F. Westbury, E.T. Possing, J.N. Kaufman, L. Buchanan, Neural correlates of lexical access during visual word recognition, J. Cogn. Neurosci. 15 (2003) 372–393.

[6] F. Binkofski, K. Amunts, K.M. Stephan, S. Posse, T. Schorrmann, H.J. Freund, K. Zilles, R.J. Seitz, Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study, Hum. Brain Mapp. 11 (2000) 273–285.

[7] S. Bookheimer, Functional MRI of language: new approaches to understanding the cortical organization of semantic processing, Annu. Rev. Neurosci. 25 (2002) 151–188.

[8] J.R. Booth, D.D. Burman, J.R. Meyer, D.R. Gitelman, T.B. Parrish, M.M. Mesulam, Functional anatomy of intra- and cross-modal lexical tasks, NeuroImage 16 (2002) 7–22.

[9] K. Brodmann, Beiträge zur histologischen Lokalisation der Grosshirnrinde: VI. Die Cortexgliederung des Menschen, J. Psychol. Neurol. 10 (1909) 231–246.

[10] M.W. Burton, S.L. Small, S.E. Blumstein, The role of segmentation in phonological processing: an fMRI investigation, J. Cogn. Neurosci. 12 (2000) 679–690.

[11] S.F. Cappa, D. Perani, T. Schnur, M. Tettamanti, F. Fazio, The effects of semantic category and knowledge type on lexical-semantic access: a PET study, NeuroImage 8 (1998) 350–359.

[12] M.W. Chee, K.M. O'Craven, R. Bergida, B.R. Rosen, R.L. Savoy, Auditory and visual word processing studied with fMRI, Hum. Brain Mapp. 7 (1999) 15–28.

[13] J.M. Chein, J.A. Fiez, Dissociation of verbal working memory system components using a delayed serial recall task, Cereb. Cortex 11 (2001) 1003–1014.

[14] D.L. Collins, P. Neelin, T.M. Peters, A.C. Evans, Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space, J. Comput. Assist. Tomogr. 18 (1994) 192–205.

[15] M. Coltheart, K. Rastle, C. Perry, R. Langdon, J. Ziegler, DRC: a dual route cascaded model of visual word recognition and reading aloud, Psychol. Rev. 108 (2001) 204–256.

[16] H. Damasio, T.J. Grabowski, D. Tranel, R.D. Hichwa, A.R. Damasio, A neural basis for lexical retrieval, Nature 380 (1996) 499–505.

[17] S. Dehaene, L. Naccache, L. Cohen, D. Lebihan, J.F. Mangin, J.B. Poline, D. Rivière, Cerebral mechanisms of word masking and unconscious repetition priming, Nature 4 (2001) 752–758.

[18] J.-F. Démonet, F. Chollet, S. Ramsay, D. Cardebat, J.-L. Nespoulous, R. Wise, A. Rascol, R. Frackowiak, The anatomy of phonological and semantic processing in normal subjects, Brain 115 (1992) 1753–1768.

[19] J.D. Edwards, P.M. Pexman, B.G. Goodyear, C.G. Chambers, An fMRI investigation of strategies for word recognition, Cogn. Brain Res. 24 (2005) 648–662.

[20] S.B. Eickhoff, A. Schleicher, K. Zilles, K. Amunts, The human parietal operculum: I. Cytoarchitectonic mapping of subdivisions, Cereb. Cortex (2005) (Electronic publication ahead of print).

[21] S.B. Eickhoff, A. Schleicher, K. Zilles, K. Amunts, The human parietal operculum: II. Stereotaxic maps and correlation with functional imaging results, Cereb. Cortex (2005) (Electronic publication ahead of print).

[22] S.B. Eickhoff, K.E. Stephan, H. Mohlberg, C. Grefkes, G.R. Fink, K. Amunts, K. Zilles, A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data, NeuroImage 25 (2005) 1325–1335.

[23] A.C. Evans, S. Marrett, P. Neelin, L. Collins, K. Worsley, W. Dai, S. Milot, E. Meyer, D. Bub, Anatomical mapping of functional activation in stereotactic coordinate space, NeuroImage 1 (1992) 43–53.

[24] C.J. Fiebach, A.D. Friederici, K. Müller, D.Y. Von Cramon, FMRI evidence for dual routes to the mental lexicon in visual word recognition, J. Cogn. Neurosci. 14 (2002) 11–23.

[25] J.A. Fiez, Phonology, semantics, and the role of the left inferior prefrontal cortex, Hum. Brain Mapp. 5 (1997) 79–83.

[26] J.A. Fiez, S.E. Petersen, Neuroimaging studies of word reading, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 914–921.

[27] J.A. Fiez, D.A. Balota, M.E. Raichle, S.E. Petersen, Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading, Neuron 24 (1999) 205–218.

[28] K.I. Forster, E.S. Bednall, Terminating and exhaustive search in lexical access, Mem. Cogn. 4 (1976) 53–61.

[29] A.D. Friederici, Towards a neural basis of auditory sentence processing, Trends Cogn. Sci. 6 (2002) 78–84.

[30] K.J. Friston, P. Fletcher, O. Josephs, A. Holmes, M.D. Rugg, R. Turner, Event-related fMRI: characterizing differential responses, NeuroImage 7 (1998) 30–40.

[31] J.D. Gabrieli, R.A. Poldrack, J.E. Desmond, The role of left prefrontal cortex in language and memory, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 906–913.

[32] P. Hagoort, P. Indefrey, C. Brown, H. Herzog, H. Steinmetz, R.J. Seitz, The neural circuitry involved in the reading of German words and pseudowords: a PET study, J. Cogn. Neurosci. 11 (1999) 383–398.

[33] S. Heim, A.D. Friederci, Phonological processing in language production: time course of brain activity, NeuroReport 14 (2003) 2031–2033.

[34] S. Heim, B. Opitz, K. Müller, A.D. Friederici, Phonological processing during language production: fMRI evidence for a shared production—comprehension network, Cogn. Brain Res. 16 (2003) 285–296.

[35] A.N. Herbster, M.A. Mintun, R.D. Nebes, J.T. Becker, Regional cerebral blood flow during word and nonword reading, Hum. Brain Mapp. 5 (1997) 84–92.

[36] C.J. Holmes, R. Hoge, L. Collins, R. Woods, A.W. Toga, A.C. Evans, Enhancement of MR images using registration for signal averaging, J. Comput. Assist. Tomogr. 22 (1998) 324–333.

[37] P. Indefrey, C.M. Brown, F. Hellwig, K. Amunts, H. Herzog, R.J. Seitz, P. Hagoort, A neural correlate of syntactic encoding during speech production, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 5933–5936.

[38] P. Indefrey, F. Hellwig, H. Herzog, R. Seitz, P. Hagoort, Neural responses to the production and comprehension of syntax in identical utterances, Brain Lang. 89 (2004) 312–319.

[39] A. Ischebeck, P. Indefrey, N. Usui, I. Nose, F. Hellwig, M. Taira, Reading in a regular orthography: an fMRI study investigating the role of visual familiarity, J. Cogn. Neurosci. 16 (2004) 727–741.

[40] G. Jobard, F. Crivello, N. Tzourio-Mazoyer, Evaluation of the dual route theory of reading: a metaanalysis of 35 neuroimaging studies, NeuroImage 20 (2003) 693–712.

[41] S. Joubert, M. Beauregard, N. Walter, P. Bourgouin, G. Beaudoin, J.M. Leroux, S. Karama, A.R. Lecours, Neural correlates of lexical and sublexical processes in reading, Brain Lang. 89 (2003) 9–20.

[42] S.A. Kotz, S.F. Cappa, D.Y. Von Cramon, A.D. Friederici, Modulation of the lexical-semantic network by auditory semantic priming: an event-related functional MRI study, NeuroImage 17 (2002) 1761–1772.

[43] B. Maess, S. Kölsch, T.C. Gunter, A.D. Friederici, Musical syntax is processes in Broca's area: an MEG study, Nat. Neurosci. 4 (2001) 540–545.

[44] J.A. Maldjian, P.J. Laurienti, R.A. Kraft, J.H. Burdette, An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets, NeuroImage 19 (2003) 1233–1239.

[45] J.C. Marshall, G.R. Fink, Cerebral localization, then and now, NeuroImage 20 (2003) S2–S7.

[46] A. Mechelli, M.L. Gorno-Tempini, C.J. Price, Neuroimaging studies of words and pseudoword reading: consistencies, inconsistencies, and limitations, J. Cogn. Neurosci. 15 (2003) 260–271.

[47] M.T. Menard, S.M. Kosslyn, W.L. Thompson, N.M. Alpert, S.L. Rauch, Encoding words and pictures: a positron emission tomography study, Neuropsychologia 34 (1996) 185–194.

[48] C.J. Mummery, T. Shallice, C.J. Price, Dual-process model in semantic priming: a functional imaging perspective, NeuroImage 9 (1999) 516–525.

[49] S.D. Newman, D. Twieg, Differences in auditory processing of words and pseudowords: an fMRI study, Hum. Brain Mapp. 14 (2001) 39–47.

[50] N. Nishitani, M. Schurmann, K. Amunts, R. Hari, Broca's region: from action to language, Physiology 20 (2005) 60–69.

[51] A.C. Nobre, T. Allison, G. McCarthy, Word recognition in the human inferior temporal lobe, Nature 372 (1994) 260–263.

[52] T. Noesselt, N.J. Shah, L. Jäncke, Top-down and bottom-up modulation of language related areas—An fMRI study, BMC Neurosci. 4 (2003) (online. Available from: http://www.biomedcentral.com/1471-2202/4/13 Accessed 27 August 2005).

[53] K. Omura, T. Tsukamoto, Y. Kotani, Y. Ohgami, K. Yoshikawa, Neural correlates of phoneme-to-grapheme conversion, NeuroReport 15 (2004) 949–953.

[54] R. Padovani, G. Calandra-Buonaura, C. Cacciari, F. Benuzzi, P. Nichelli, Grammatical gender in the brain: evidence from an fMRI study on Italian, Brain Res. Bull. 65 (2005) 301–308.

[55] E. Paulesu, E. McCrory, F. Fazio, L. Menoncello, N. Brunswick, S.F. Cappa, M. Cotelli, G. Cossu, F. Corte, M. Lorusso, S. Pesenti, A. Gallagher, D. Perani, C. Price, C.D. Frith, U. Frith, A cultural effect on brain function, Nat. Neurosci. 3 (2000) 91–96.

[56] D. Perani, S. Cappa, T. Schnur, M. Tettamanti, S. Colina, M.M. Rosa, F. Fazio, The neural correlates of verb and noun processing. A PET study, Brain 122 (1999) 2337–2344.

[57] R.A. Poldrack, A.D. Wagner, M.W. Prull, J.E. Desmond, G.H. Glover, J.D.E. Gabrieli, Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex, NeuroImage 10 (1999) 15–35.

[58] C.J. Price, R.S. Wise, J.G. Watson, K. Patterson, D. Howard, R.J. Frackowiak, Brain activity during reading: the effect of exposure duration and task, Brain 117 (1994) 1255–1269.

[59] C.J. Price, R.J. Wise, R.J.S. Frackowiak, Demonstrating the implicit processing of visually presented words and pseudowords, Cereb. Cortex 6 (1996) 62–70.

[60] C.J. Price, C.J. Moore, G.W. Humphreys, R.J.S. Wise, Segregating semantic from phonological processes during reading, J. Cogn. Neurosci. 9 (1997) 727–733.

[61] J.M. Rumsey, B. Horwitz, B.C. Donohue, K. Nace, J.M. Maisog, P. Andreason, Phonological and orthographic components of word recognition, Brain 120 (1997) 739–759.

[62] A. Schleicher, K. Amunts, S. Geyer, P. Morosan, K. Zilles, Observer-independent method for microstructural parcellation of cerebral cortex: a quantitative approach to cytoarchitectonics, NeuroImage 9 (1999) 165–177.

[63] R.I. Schubotz, D.Y. Von Cramon, Interval and ordinal properties of sequences are associated with distinct premotor areas, Cereb. Cortex 11 (2001) 210–222.

[64] B.A. Shaywitz, S.E. Shaywitz, K.R. Pugh, R.T. Constable, P. Skudlarski, R.K. Fulbright, R.A. Bronen, J.M. Fletcher, D.P. Shankweiler, L. Katz, J.C. Gore, Sex differences in the functional organization of the brain for language, Nature 373 (1995) 607–609.

[65] K. Specht, C. Holtel, R. Zahn, H. Herzog, B.J. Krause, F.M. Mottaghy, I. Radermacher, D. Schmidt, L. Tellmann, S. Weis, K. Willmes, W. Huber, Lexical decisions of nonwords and pseudowords in humans: a positron emission tomography study, Neurosci. Lett. 345 (2003) 177–181.

[66] J. Talairach, P. Tournoux, Co-Planar Stereotaxic Atlas of The Human Brain, Thieme, Stuttgart, 1988.

[67] L.H. Tan, C.M. Feng, P.T. Fox, J.H. Gao, An fMRI study with written Chinese, NeuroReport 12 (2001) 83–88.

[68] E. Temple, R.A. Poldrack, J. Salidis, G.K. Deutsch, P. Tallal, M.M. Merzenich, J.D.E. Gabrieli, Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study, NeuroReport 12 (2001) 299–307.

[69] G. Thierry, K. Boulanouar, F. Kherif, J.P. Ranjeva, J.F. Démonet, Temporal sorting of neural components underlying phonological processing, NeuroReport 10 (1999) 2599–2603.

[70] R. Vandenberghe, C. Price, R. Wise, O. Josephs, R.S.J. Frackowiak, Functional anatomy of a common semantic system for words and pictures, Nature 383 (1996) 254–256.

[71] K.J. Worsley, S. Marrett, P. Neelin, A.C. Vandal, K.J. Friston, A.C. Evans, A unified statistical approach for determining significant signals in images of cerebral activation, Hum. Brain Mapp. 4 (1996) 58–74.

[72] Z. Xiao, J.X. Zhang, X. Wang, R. Wu, X. Hu, X. Weng, L.H. Tan, Differential activity in left inferior frontal gyrus for pseudowords and real words: an event-related fMRI study on auditory lexical decision, Hum. Brain Mapp. 25 (2005) 212–221.

[73] B. Xu, J. Grafman, W.D. Gaillard, K. Ishii, F. Vega-Bermudez, P. Pietrini, P. Reeves-Tyer, P. Dicamillo, W. Theodore, Conjoint and extended neural networks for the computation of speech codes: the neural basis of selective impairment in reading words and pseudowords, Cereb. Cortex 11 (2001) 267–277.

[74] R.J. Zatorre, A.C. Evans, E. Meyer, A. Gjedde, Lateralization of phonetic and pitch discrimination in speech processing, Science 256 (1992) 846–849.

[75] R.J. Zatorre, E. Meyer, A. Gjedde, A.C. Evans, PET studies of phonetic processing in speech: review, replication, and reanalysis, Cereb. Cortex 6 (1996) 21–30.

[76] K. Zilles, A. Schleicher, N. Palomero-Gallagher, K. Amunts, Quantitative analysis of cyto- and receptor architecture of the human brain, in: J. Mazziotta, A. Toga (Eds.), Brain Mapping, The Methods, 2nd ed., Academic Press, San Diego, 2002, pp. 573–602.

[77] B. Zurowski, J. Gostomzyk, G. Gron, R. Weller, H. Schirrmeister, B. Neumeier, M. Spitzer, S.N. Reske, H. Walter, Dissociating a common working memory network from different neural substrates of phonological and spatial stimulus processing, NeuroImage 15 (2002) 45–57.