Effective Connectivity of the Left BA 44, BA 45, and Inferior Temporal Gyrus During Lexical and Phonological Decisions Identified With DCM

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Abstract: Distinct regions in the left inferior frontal gyrus (IFG) preferentially support the processing of different word-types (e.g., real words, pseudowords) and tasks (e.g., lexical decisions, phonological decisions) in visual word recognition. However, the functional connectivity underlying the task-related specialisation of regions in the left IFG is not yet well understood. In this study we investigated the neural mechanisms driving the interaction of WORD-TYPE (real word vs. pseudoword) and TASK (lexical vs. phonological decision) in Brodmann's area (BA) 45 in the left IFG using dynamic causal modelling (DCM). Four different models were compared, all of which included left BA44, left BA45, and left inferior temporal gyrus (ITG). In each model, the visual presentation of words and pseudowords is assumed to directly evoke activity in the ITG and is then thought to be subsequently propagated to BA45 and to BA44 via direct intrinsic connections. The models differed with regard to which connections were modulated by the different tasks. Both tasks were assumed to either modulate the ITG_BA45 connection (Model #1), or the BA44_BA45 connection (Model #2), or both connections in parallel (Model #3). In Model #4 lexical decisions modulated the ITG_BA45 connection, whereas phonological decisions modulated the BA44_BA45 connection. Bayesian model selection revealed a superiority of Model #1. In this model, the strength of the ITG_BA45 connection was enhanced during lexical decisions. This model is in line with the hypothesis that left BA 45 supports explicit lexical decisions during visual word recognition based on lexical access in the ITG. *Hum Brain Mapp* 30:392–402, 2009. © 2007 Wiley-Liss, Inc.

Key words: dynamic causal modelling; fMRI; words; pseudowords; phonological decision; lexical decision; Broca's region

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INTRODUCTION

Neuroimaging studies of visual word processing have repeatedly demonstrated the involvement of left inferior frontal and left inferior temporal brain regions [for a survey see Table I; for reviews cf. Jobard et al., 2003; Mechelli et al., 2003a]. In many of these studies, words were compared with pseudowords. Pseudowords are pronounceable

TABLE I. Studies reporting stronger activation for pseudowords, nonwords, or irregular words than words in the left inferior frontal gyrus (IFG) and the left posterior inferior temporal lobe

Study	Contrast	<i>x</i>	<i>y</i>	<i>z</i>
Inferior frontal gyrus/~BA 44				
Fiebach et al., 2002	Lexical decision pseudowords > high frequency words	-47	10	13
Fiez et al., 1999	Reading irregular words > regular words	-49	11	11
Ischebeck et al., 2004	Articulation unfamiliar > familiar writing (words)	-50	10	23
Ischebeck et al., 2004	Articulation pseudowords > familiar writing (words)	-56	10	27
Ischebeck et al., 2004	Phonological lexical decision unfamiliar > familiar writing (words)	-53	15	4
Ischebeck et al., 2004	Phonological lexical decision pseudowords > familiar writing (words)	-53	11	10
Mechelli et al., 2003a,b	Reading pseudowords > words	-48	8	22
Mechelli et al., 2005	Reading > false fonts	-56	10	4
Mechelli et al., 2005	Reading pseudowords > words	-54	8	18
Mechelli et al., 2005	Reading pseudowords > words	-52	2	18
Xiao et al., 2005	Lexical decision pseudowords > words	-51	15	14
Xu et al., 2001	Rhyming pseudowords > words	-52	10	12
Inferior frontal gyrus/~BA 45/47				
Mechelli et al., 2005	Reading > false fonts	-52	34	4
Binder et al., 2003	Lexical decision nonwords > words	-40	17	2
Mechelli et al., 2005	Reading exception words > pseudowords	-52	34	4
Paulesu et al., 2000	Reading pseudowords > words	-42	24	14
Hagoort et al., 1999	Reading pseudowords > words	-46	18	-9
Inferior temporal lobe/~BA 37				
Fiez et al., 1999	Pseudowords > words	-43	-46	-12
Hagoort et al., 1999	Pseudowords > words	-34	-56	-16
Paulesu et al., 2000	Pseudowords > words (English and Italian subjects)	-48	-58	-6
Xu et al., 2001	Pseudoword rhyming > word rhyming	-46	-66	-10

word-like stimuli (e.g., SINT) that have no semantic meaning and no entry in the mental lexicon. Nonetheless, they can be read on the basis of sublexical orthographical information via the correspondence of graphemes and phonemes. As Table I shows, pseudowords tend to elicit stronger activation than words in the left inferior frontal gyrus (IFG) and/or in the left posterior inferior temporal lobe. This effect is assumed to be due to increased demands on the processing of pseudowords [e.g., Fiez et al., 1999; Forster and Bednall 1976; Mechelli et al., 2003a; Price et al., 1996].

Evidence from multiple studies suggests that different portions of the left IFG support the processing of different types of linguistic information [e.g., Bookheimer, 2002; Démonet et al., 1992; Friederici, 2002]. The posterior-dorsal aspect of the left IFG (roughly corresponding to the pars opercularis or to Brodmann's area (BA) 44 and, perhaps, parts of BA 6) is preferentially engaged in sublexical, phonology-related processes [e.g., Burton et al., 2000; Démonet et al., 1992; Heim et al., 2003; Zatorre et al., 1992; 1996; Zurowski et al., 2002], whereas its anterior-ventral portion (approximately covering BA 45 and BA 47 or the pars triangularis and pars orbitalis) contributes to lexico-semantic control and retrieval processes [e.g., Badre et al., 2005; Miceli et al., 2002].

In two recent functional magnetic resonance imaging (fMRI) studies, we demonstrated the differential involvement of left BA 44 and BA 45 during the processing of words and pseudowords as a function of task [Heim et al., 2005] and of stimulus modality [Heim et al., 2007]. Whereas BA 44 was activated independent of task and modality, BA 45 activation was dependent on task and on stimulus type. In particular, there was an interaction of

WORD-TYPE (pseudowords vs. words) and TASK (lexical decision task, LDT, vs. phonological decision task, PDT) in the left BA 45, with stronger activation for visual pseudowords than for visual words only during lexical decisions [Heim et al., 2005; see Fig. 1]. In contrast, no such interaction was observed in BA 44 or in the inferior temporal gyrus (ITG) which was also found to be part of the neural network supporting word processing. Both BA 44 and ITG revealed stronger activation for pseudowords than for words independently of whether the task was phonological or lexical (cf. Fiez et al. [1999] and Paulesu et al. [2000] for similar effects in BA 44 and the left inferior temporal cortex; cf. Bokde et al. [2001] for a positive correlation of activation in BA 44 and ITG during visual word processing).

The standard SPM analysis [Heim et al., 2005] could only reveal that there was an interaction in BA 45. It could not, however, explain how this interaction originated as a function of the modulatory influences of the tasks within the network of ITG, BA 44, and BA 45. Such information can be obtained with dynamic causal modelling [DCM; Friston et al., 2003], a method to identify the effective connectivity and its modulation in a given brain network. Consequently, in this study, we used DCM to clarify whether the interaction in BA 45 resulted from a task-dependent modulation or "gating" of afferent inputs from the left BA 44 and/or the left ITG, both of which showed a main effect of WORD-TYPE alone (cf. Fig. 1). Among the regions that showed a main effect of WORD-TYPE, the left ITG is the most likely one to receive bottom-up visual input about words and pseudowords [see e.g., Cohen

Figure 1.

fMRI results obtained of the conventional SPM2 analysis. The effect Pseudowords > Words was significant in the left inferior temporal gyrus, the left BA 44, and the left BA 45 during lexical decisions (left). In contrast, only the left ITG and the left BA 44 showed an effect Pseudowords > Words in the phonological decision task (right).

et al., 2004]. Since there is only a main effect of WORD-TYPE (i.e., the difference of pseudowords and words) in the ITG, but a TASK $\times$ WORD-TYPE interaction (i.e., a task-dependent change of the difference between words and pseudowords) in BA 45, the input from the words and pseudowords into the ITG must be modulated on its

way from the left ITG to the left BA 45. In other words, the task-dependent change of the difference between pseudowords and words must be elicited on a direct or indirect intrinsic connection from the ITG to BA 45.

To this end four different models were tested (Fig. 2) as alternative ways for modelling the cause of a TASK $\times$ WORD-TYPE interaction in BA 45. In Model #1 we propose that ITG output to BA 45 (which reflects the main effect of WORD-TYPE in ITG) is modulated differently by the two tasks. This implies a differential modulation of the strength of the direct connection from ITG into BA 45 by the lexical and the phonological decision tasks. Alternatively, in Model #2 the existence of an indirect route via BA 44 is assumed, with the two tasks modulating the connection from BA 44 to BA 45. In Model #3 a combination of both mechanisms is implemented, i.e., modulations by the two tasks may occur on the direct and the indirect connection. Finally, Model #4 features independent modulations of the activation by the lexical and the phonological decision task. This is because the interaction in BA 45 may be produced by a positive modulation of the connection from the ITG to BA 45 by lexical decisions and by a negative, zero, or weaker positive modulation of the connection from BA 44 to BA 45 by the phonological decision. In fact, this last scenario is not implausible, given the involvement of the left ITG in semantic processing [e.g., Vandenberghe et al., 1996] and of the (approximate) left BA 44 in phonological processing [e.g., Burton et al., 2000; Démonet et al., 1992; Heim et al., 2003; Zatorre et al., 1992; 1996; Zurowski

Figure 2.

Outline of the four DCM models tested in this study. Black filled circles indicate the brain regions involved in the network. Arrows between the regions symbolise the bi-directional intrinsic connections. White circles superimposed on the arrows stand for the modulation of the connections by the lexical decision task (LDT) and the phonological decision task (PDT). Grey rectangles indicate the inputs of pseudowords (PW) and words (WO) into the left inferior temporal gyrus (ITG).

et al., 2002]. Finally, in theory, a fifth model is possible in which the connection from the ITG to BA 44 would be differentially modulated by the two tasks. However, for the purpose of this study to explain the interaction in BA 45, this alternative model is not meaningful, since there was no interaction in BA 44 in our previous study [Heim et al., 2005], i.e., no differential effect of TASK on the difference of pseudowords and words. Without such interaction in BA 44, however, the observed interaction in BA 45 cannot be modelled in this alternative model. Therefore, it was not further considered.

METHODS

Experimental design and fMRI data acquisition

For the DCM analysis the data from the study by Heim et al. [2005] were used. Fifteen healthy right-handed native German speakers (8 females; mean age 25.6 years, SD 2.4 years) participated in the experiment. Informed consent was obtained from all participants. The experimental standards were approved by the local ethics committee of the University of Leipzig.

The stimulus materials consisted of 80 words (mean frequency 164.8 per million; CELEX database [<http://www.kun.nl/celex>]) and 80 pronounceable orthographically legal pseudowords generated from the words by exchanging one or two vowels within the word. Fifty percent of the stimuli in both categories started with the fricatives /f/ or /s/ and 50% with a stop consonants /p/ or /t/. (These consonants were chosen in the original study because in phonology they form a 2×2 schema with respect to the place and the manner of articulation, which allows for pair-wise contrasts).

LDT and PDT were performed in the same run. In the LDT, subjects had to indicate whether a stimulus was a word or a pseudoword. In the PDT, where subjects decided whether the stimulus started with a fricative or stop consonant. Participants responded by pressing one of two response buttons with the index or middle finger of the right hand, respectively. In each task, correct answers were assigned equally to the left and the right response button. The assignment of the buttons to the response alternatives (word – pseudoword; fricative – plosive) was balanced over subjects. Stimuli were presented in a pseudo-random 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 1,900 ms the stimulus was presented for 800 ms. The screen remained blank for a variable time interval, amounting to a total trial duration of 5,000 ms. Null events were included to allow a better estimation of the haemodynamic response in the experimental conditions.

The functional data were recorded on a 3T scanner (Medspec 30/100, Bruker, Ettlingen) 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 $3 \text{ mm} \times 3 \text{ mm}$. Fourteen axial slices (3 mm thickness, 1 mm gap) covering the left IFG and left temporal lobe were recorded.

The preprocessing with SPM2 included motion correction, slice timing, normalisation to MNI space, and spatial smoothing. The statistical model included onsets for the phonological task, the lexical task, pseudowords, and words (for more details cf. Heim et al. [2005]). The anatomical localisation of the activation data was performed using the cytoarchitectonic probability maps of BA 44 and BA 45 [Amunts et al., 1999; 2004] included in the SPM Anatomy toolbox [Eickhoff et al., 2005]. Since corresponding maps of the ITG were not available, the localisation in this region was based on macroanatomical landmarks. For more details about the study design and the standard SPM analysis cf. Heim et al. [2005].

Dynamic Causal Modelling

The central idea behind a dynamic causal model is to regard the brain as a dynamic input-state output system that is subject to experimentally controlled perturbations. Such perturbations affect the system in terms of inputs that either drive specific areas directly (e.g., sensory stimuli like visually presented words and pseudowords) or modulate the strengths of the functional connections between them (e.g., task requirements like lexical vs. phonological decisions). The neuronal states themselves are “hidden”, i.e., unobserved variables, and represent a simple index of neuronal population activity in each region [Friston et al., 2003]. The outputs of this system are the regional haemodynamic responses, which are connected to the neuronal state variables using a biophysically validated forward model of haemodynamic responses [Buxton et al., 1998; Friston et al., 2000]. In this framework fMRI data are conceptualised as arising from experimental manipulations of functionally integrated brain regions. The parameters of a DCM are estimated by means of Bayesian inversion, using biophysical priors on the haemodynamic parameters and shrinkage priors on the neural parameters. Iterative application of an expectation-maximisation (EM) algorithm yields three sets of model parameters: (1) Direct influences of driving inputs on the neuronal states. (2) Strengths of intrinsic connections that reflect the context-independent coupling between neuronal states in different regions (note that the intrinsic connections do not necessarily have to rely on anatomical connections). (3) Modulatory or bilinear inputs that reflect context-dependent changes in the coupling between regions. Often, there are several competing hypotheses about a system of interest, each of which can be represented by a specific DCM. Importantly, because of the general trade-off between model fit and model general-

TABLE II. MNI coordinates at which fMRI time courses for the DCM analysis were extracted in the left hemisphere

Subject	BA 45			BA 44			ITG		
	<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>y</i>	<i>z</i>
01	-50	36	-4	-40	12	16	-44	-28	-26
02	-34	26	0	-54	8	12	-50	-48	-24
03	-38	30	-4	-64	6	0	-50	-38	-22
04	-36	36	4	-44	18	16	-42	-32	-26
05	-44	40	4	-58	8	4	-	-	-
06	-48	32	-8	-44	4	16	-44	-42	-22
07	-40	40	2	-44	8	18	-48	-34	-30
08	-32	28	-4	-54	16	12	-54	-30	-10
09	-52	24	0	-58	12	8	-44	-34	-10
10	-36	22	-6	-52	12	4	-44	-42	-26
11	-48	28	-2	-50	10	8	-60	-40	-20
12	-44	30	4	-54	10	2	-52	-50	-22
13	-42	32	-2	-38	10	12	-50	-38	-22
14	-56	32	-4	-56	6	2	-46	-46	-18
16	-42	36	10	-42	8	18	-50	-38	-16
Mean	-42.8	26.1	-0.7	-50.1	9.9	9.9	-48.4	-38.6	-21.0
RFX Mean	-42.0	26.0	-2.0	-52.0	10.0	6.0	-50.0	-36.0	-22.0

The coordinates refer to the individual local maximum of the effect “Pseudowords > Words” which was nearest to the local maximum of the group random effects (RFX) analysis (bottom row) in a sphere with radius 16 mm around the group maximum. For subject #05, there was no local maximum in the ITG.

isability, the optimal model cannot be determined on the basis of its fit alone. Instead, the relative complexity (e.g., the number of free parameters) of different models needs to be considered as well. Bayesian model selection [BMS; Penny et al., 2004b] can be used to identify the DCM that optimally explains the word type by task interaction in BA 45. Both DCM and BMS were implemented using the latest version of SPM5 which uses a far more robust optimisation scheme than SPM2.

Extraction of fMRI signals for the DCM analysis

The three brain regions previously identified in the contrasts “pseudowords > words” (left BA 44, left ITG) and “word-type by task interaction” (left BA 45) were regarded as volumes of interest (VOI). For each subject and each VOI, the individual local maximum ($P < 0.05$ uncorrected; cf. Mechelli et al., [2005]) was identified that was closest to the group maximum within a spherical search volume of 16-mm radius and within the same cytoarchitectonically defined anatomical region (i.e., BA 44 or BA 45; see Table II). This method ensured the comparability of extracted time series across subjects by combining anatomical and functional constraints, despite the variability between individual activation patterns. Fourteen of the 15 subjects had activations meeting this criterion in all three VOIs and were considered for further analysis. For each VOI, time series was extracted as the first principal component of all voxel time series within a sphere (radius 3 mm) centred on the individual local maximum. Note that the all centres of the VOIs in BA 45 (MNI *y* coordinates: 22–40) were located anterior to those in BA 44

(MNI *y* coordinates: 4–18) and no volumes overlapped in any subject.

Definition of the DCMs

In accordance with the 2×2 factorial design four stimulus classes were entered as inputs into the four tested DCMs (cf. Fig. 2):

- pseudowords: all trials containing pseudowords, irrespective of experimental task;
- words: all trials containing words, irrespective of experimental task;
- lexical decision task: all trials in which a lexical decision was made, irrespective of word-type;
- phonological decision task: all trials in which a phonological decision was made, irrespective of word-type.

In all models words and pseudowords served as direct inputs into the ITG. Moreover, bi-directional intrinsic connections were defined between all three VOIs in all models to test for positive and negative influences of each region over each other region.

Four alternative ways for modelling the cause of a TASK $\times$ WORD-TYPE interaction in BA 45 were assessed.

- In Model #1 we propose that the influence of ITG activity on BA 45 is modulated differently by the two tasks.
- Alternatively, in Model #2 the two tasks modulate the intrinsic connection from BA 44 to BA 45, i.e., the interaction in BA 45 is driven by the differential influence of the lexical and the phonological task on the

strength of the intrinsic connection from BA 44 (in which activity showed a main effect of word type, like in ITG).

- In Model #3 a combination of both mechanisms is implemented, i.e., modulations by the two tasks may occur on the direct and the indirect connection.
- A further alternative (Model #4), which was suggested by one of the reviewers, considers the possibility that lexical and phonological decisions may affect different afferent connections to BA45. Specifically, in this model the ITG→BA 45 connection was modulated by lexical decisions alone, whereas the BA44→BA45 connection was exclusively modulated by phonological decisions.

Note that while the first three models allow for independent modulations of connections by the lexical and the phonological decision task, Model #3 has the extra flexibility that these modulations can also differ across connections. For example, the interaction in BA 45 may be produced by a positive modulation of the connection from the ITG to BA 45 by lexical decisions and by a negative, zero, or weaker positive modulation of the connection from BA 44 to BA 45 by the phonological decision. In fact, this last scenario is not implausible, given the involvement of the left ITG in semantic processing [e.g., Vandenberghe et al., 1996] and of the (approximate) left BA 44 in phonological processing [e.g., Burton et al., 2000; Démonet et al., 1992; Heim et al., 2003; Zatorre et al., 1992; 1996; Zurowski et al., 2002].

Finally, in theory, a fifth model is possible in which the connection from the ITG to BA 44 would be differentially modulated by the two tasks. However, this model would only make sense in the presence of a significant WORD-TYPE $\times$ TASK interaction in BA 44, which, however, was not observed in the SPM analysis.

DCM model selection and parameter test

Any inferences about the model parameters are contingent upon assumptions about the model structure, i.e., the connectivity pattern between the regions included in the model as well as the nature and entry points of direct and modulatory inputs. To compare the four different DCM setups we used a BMS procedure for DCM [Penny et al., 2004b]. BMS rests on the so-called “model evidence”, i.e. the probability $P(y|m)$ of the data y given a particular model m . Given two Models i and j and their evidences, the Bayes factor (BF) B_{ij} is defined as the ratio $P(y|m = i)/P(y|m = j)$ and thus expresses how much better Model i is relative to Model j . This implies that a BF = 1 indicates equivalence of models; a BF > 1 means evidence in favour of the first model, while a BF < 1 signifies evidence for the second model of a pair-wise comparison. However, the model evidence can usually not be derived analytically. The procedure proposed by Penny et al. [2004b] therefore uses two measures (Bayesian Information Criterion, BIC, and Akaike’s Information Criterion, AIC) to approximate

TABLE III. Individual Bayes Factors, Group Bayes Factors (GBF), and Positive Evidence Ratios (PER) for the comparison of Models #1–3.

Subject	Model 1 vs. 2	Model 1 vs. 3	Model 2 vs. 3	Model 1 vs. 4
1	1.03E+000	7.04E+000	7.25E+000	1.00E+000
2	3.20E-008	1.31E-004	1.83E+001	8.30E-001
3	4.10E-001	7.28E+000	3.01E+000	1.01E+000
4	4.41E+000	5.12E+000	—	1.02E+000
6	1.71E+001	5.01E+004	8.56E+005	5.50E+002
7	9.50E-001	6.68E+000	6.35E+000	1.07E+000
8	4.70E-001	—	—	2.06E+000
9	8.50E-001	7.38E+000	6.31E+000	9.70E-001
10	3.50E+000	7.17E+000	—	6.80E-001
11	1.05E+000	6.20E+000	6.50E+000	1.24E+000
12	7.24E+000	7.33E+000	—	5.35E+000
13	9.70E-001	7.39E+000	7.15E+000	9.80E-001
14	1.03E-010	3.85E-011	—	4.29E+001
16	8.80E-001	7.39E+000	6.52E+000	9.60E-001
PER	4:2	11:2	9:0	3:0
GBF	9.00E-016	5.79E-002	4.15E+012	1.83E+005
GBF w/o subj. 2,14	2.74E+002	1.15E+013	2.27E+011	5.13E+003

Bayes Factors smaller than 1 indicate that there is positive evidence for the second model in the comparison. Bold print indicates significant evidence for the first model in a comparison, italics indicate significant evidence for the second model (but see the comments in the text). Regular print is used for comparisons that yielded consistent but nonsignificant evidence for one of the two models. If no value is provided (—), the model comparison did not yield consistent evidence for either model. Consequently, no Bayes Factor could be calculated.

the log model evidence, both of which take into account the fit as well as the complexity of the different models. As noted by Penny et al. [2004b], the BIC is biased towards simpler models, whereas the AIC favours more complex models. The reason for this behaviour is that BIC imposes a heavier complexity penalty than AIC. The usual convention, to which we also adhere in this study, is to make a decision only if the two BFs based on the AIC and BIC approximations concur. The decision which model is better is then based on the more conservative BF of the two. The results of the model comparisons are shown in Table III. If AIC and BIC did not yield consistent evidence for either model, no BF could be calculated. All comparisons where this ambiguity arose are marked with a dash (—) in Table III.

The model selection was performed as follows. First, the BFs for the pair-wise comparisons of the four models for each subject were calculated with SPM5. As the individual subjects represent independent observations, the group Bayes factor (GBF) for each pair-wise comparison is calculated by multiplying all subject-specific BFs (see Smith et al. [2006] or Stephan and Penny [2007]).

It should be noted that, as any other fixed-effects group statistics, the GBF can be very sensitive to the influence of

TABLE IV. Parameters of the model with the best fit, including inputs, intrinsic connections, and modulations of the intrinsic connections

	Mean	SD	t_{13}	P
Intrinsic connections				
Left BA 44 → left BA 45	0.22	0.15	5.18	<0.001
Left BA 45 → left BA 44	0.21	0.15	4.88	<0.001
Left BA 44 → left ITG	0.30	0.22	4.69	0.001
Left ITG → left BA 44	0.21	0.14	5.11	<0.001
Left BA 45 → left ITG	0.49	0.23	7.22	<0.001
Left ITG → left BA 45	0.34	0.13	9.01	<0.001
Driving inputs				
Left ITG: pseudowords	0.04	0.04	3.02	0.012
Left ITG: words	-0.044	0.03	-5.44	<0.001
Modulations				
Left ITG → left BA 45 by phonological decisions	-0.10	0.16	-2.08	0.062
Left ITG → left BA 45 by lexical decisions	0.14	0.09	5.40	<0.001

Significant parameters ($P < 0.05$, Bonferroni-corrected for multiple comparisons) are printed in bold face.

outliers or subgroups [Stephan and Penny, 2007]. Therefore, the positive evidence ratio [PER; Stephan and Penny, 2007] was calculated as a complementary measure. The PER gives the number of subjects for which there is positive ($BF > 3$), or stronger, evidence for one model, divided by the number of subjects who show positive, or stronger, evidence for the other model.

After determining the optimal model, its parameter estimates (driving inputs, intrinsic connections, and modulations) from all subjects were entered into one-sample t -tests to test which of them was significantly different from zero. Within each parameter class, a Bonferroni correction for multiple comparisons was applied. This approach corresponds to a second level analysis which treats individual parameter estimates as random effects across subjects.

RESULTS

Table II shows the means of the coordinates of the maximally activated voxel for each individual and region as well as the coordinate of the maximum from the group GLM random effects analysis. The means of the individual maximum coordinates are close to the maximum coordinate given in the group analysis.

For each model comparison, the individual BFs, the GBF, and the PER are given in Table III. In this table, bold print represent comparisons which yielded positive evidence in favour of Model #1, italics represent comparisons which gave positive evidence in favour of the alternative model, and normal font indicates comparisons in which the AIC and BIC approximations to log the model evidence gave conflicting results (cf. Methods). Comparing Model #1 to Models #2 and #3 on the basis of the GBF

alone, Model #1 would be considered inferior to both alternatives. Closer inspection, however, revealed that this result is driven by two subjects that diverged from the rest of the group (subjects 2 and 14). Computing the GBF without these two subjects gave results clearly in favour of Model #1 ($GBF = 274$ for comparing Model #1 to Model #2, and $GBF > 10^{13}$ for comparing Model #1 to Model #3). As discussed previously [Stephan et al., 2007a; Stephan and Penny, 2007], inferences based on GBF, like any other fixed-effects group statistics, are problematic when the group studied shows considerable heterogeneity with strong outlier cases. In such cases, a simpler, but more robust, measure like the PER is preferable [Stephan and Penny, 2007]. Computing the PER for all subjects demonstrated that Model #1 was superior to the other models ($PER = 4:2$ for comparing Model #1 to Model #2, and $PER = 11:2$ for comparing Model #1 to Model #3). Finally, we compared Model #1 with another alternative model (Model #4) in which the modulatory influences of lexical and phonological decisions affected different connections (cf. Fig. 2). In this comparison, both the GBF (1.83×10^5) and the PER (3:0) indicated that Model #1 was superior.

In a next step, we tested statistically whether the mechanisms represented by Model #1 were consistently expressed across subjects. The results of the t -tests on the subject-specific parameter estimates for Model #1 at $P < 0.05$ (Bonferroni-corrected for multiple comparisons) are displayed in Table IV and in Figure 3. All intrinsic connections were significant. All significant parameters for the intrinsic connections were positive.

Most importantly, the parameter for the modulation of the ITG→45 connection by lexical decisions was signifi-

Figure 3.

Significant parameters in the selected Model #1. Numbers along-side connections or modulations indicate their average parameter estimates. The symbols are identical to Figure 2.

cant: there was a positive modulation (0.14 s^{-1} ; $P < 0.001$) of this connection during lexical decisions. Compared to the fixed (intrinsic) ITG→45 connection strength (0.34 s^{-1}), these modulatory influences corresponded to an increase in connection strength by 41% during lexical decisions.

DISCUSSION

In this study, we investigated the dynamics within a brain network for word and pseudoword processing consisting of the left BA 44, BA 45, and the left ITG. The aim was to reveal the neuronal mechanisms driving the statistical interaction of TASK (lexical vs. phonological decision) and WORD-TYPE (word vs. pseudoword) in the left BA 45 [cf. Heim et al., 2005]. The Bayesian model selection procedure used to compare the four alternative models for this interaction revealed that it was best explained by Model #1 which featured a selective modulation of the ITG→BA 45 connection by the two tasks.

Before discussing any of the results from this study in detail, we would like to point out a general caveat: although our model selection procedure identified an optimal model across the subjects studied, it also indicated that there is some degree of population heterogeneity. Specifically, in two out of our 14 volunteers, Models #2 and #3 were found to be much better explanations of the measured data than Model #1 (cf. Table III). In fact, in these two subjects the superiority of Models #2 and #3 was so striking that one would have concluded at the group level that Model #1 was not the optimal model if one had based model comparison on the GBF measure alone. This conclusion, however, would have been in contrast to the finding that far more subjects showed positive evidence for Model #1 when compared with the two other models than vice versa. Such a constellation, i.e., heterogeneous groups with a small number of subjects significantly biasing the results of the GBF, is not uncommon and has been observed in previous studies [Garrido et al., 2007; Stephan et al., 2007b]. A standard procedure in this case is to base model comparison on the PER, a simpler, but more robust, index of model goodness at the group level [Stephan and Penny, 2007]. As is evident from Table III, this criterion clearly favoured Model #1 over the other models. In the remainder of this article, we will therefore discuss the mechanisms represented by Model #1 and its implications for our understanding of visual word processing during lexical and phonological decisions. It should be kept in mind, however, that, as with other cognitive processes, the architecture of the neural system mediating visual word processing may exhibit some variability across the population.

Identifying Model #1 as the optimal model for explaining the measured data at the group level has two implications for the assessment of the functions of BA 44 and the ITG. First, the results indicate different modulatory effects of ITG and BA 44 on BA 45. The two tasks modulate the effects of left ITG activity on BA 45 activity, but not the

effects of left BA 44 activity on BA 45 activity. This indicates that the ITG and BA 44 support different cognitive functions during visual word (and pseudoword) processing. This information could not be derived from the standard SPM analysis [Heim et al., 2005] in which both the left BA 44 and the left ITG showed a main effect of WORD-TYPE.

Second, the architecture of the selected model provides additional insights into the possible nature of the cognitive processes supported by the ITG and BA 44. In particular, the locations of the modulatory effects in the selected model and the sign of intrinsic functional connections (positive or negative) are relevant for the discussion of the results.

The Bayesian model selection procedure indicated that the WORD-TYPE by TASK interaction in BA 45 may be understood as task-dependent gating of left ITG inputs which have different strengths for words and pseudowords. The intrinsic functional connection from the ITG to BA 45 was not significant by itself but it was significantly modulated by both tasks. In other words, the BA 45 receives input from the ITG which is determined by the task requirements. The ITG→BA 45 connection was significantly strengthened (and thus established) during lexical decisions. This implies that this intrinsic connection is relevant for visual lexical decisions. Since visual lexical decisions are based on previous lexical retrieval [e.g., Ratcliff et al., 2004], and since the left BA 45 seems to play a role in visual lexical decision making [Heim et al., 2007; Thuy et al., 2004], this functional pattern fits with the idea that the ITG is involved in lexical access. This argumentation is also in line with recent findings by Gold et al. [2006] that a network consisting of the anterior portion of the left IFG and the middle fusiform gyrus in the left inferior temporal lobe was involved in lexical-semantic retrieval during visual word recognition. A slightly different account of the function of the left inferior temporal cortex (in particular the inferior temporal sulcus) has recently been put forth by Hickok and Poeppel [2007], who interpret it as a lexical interface which links phonological and semantic information. This interpretation would also be in accordance with the pattern of effective connectivity observed in this analysis, i.e., the more difficult it is to map the phonological form of the stimulus to some lexical meaning the stronger the activation gets in the ITG and, under explicit lexical decisions, in BA 45. Taking one step further, one might assume that the left inferior temporal cortex consists of a number of functionally distinct modules (see for e.g., Mechelli et al. [2005] or Cohen et al. [2004]) subserving lexical or lexico-semantic retrieval, phonology-to-semantics mapping, visual word form identification, etc. However, in the context of this study the notion of such functional modularity must remain theoretical. This is because, in contrast to our account on the distinction between BA 44 and BA 45 in the left IFG, no cytoarchitectonic data are yet available that would permit a comparable structure-function mapping in the inferior temporal cortex.

In contrast to the modulation of the connection from ITG to BA 45, no such modulation was present for the connection from BA 44 into BA 45 in Model #1. Thus, whatever function BA 44 supports during visual word recognition, this function is independent of the task and has positive influence on the activation in BA 45. Previous studies have suggested that the left BA 44 is involved in grapheme-to-phoneme conversion [e.g., Fiez et al., 1999; Mechelli et al., 2005], i.e., a nonlexical process during reading [e.g., Coltheart et al., 2001]. Alternative explanations for the role of BA 44 might refer to other processes that are even nonspecific for reading, such as visual exploration [Manjaly et al., 2005] or working memory [e.g., Zuroski et al., 2002]. However, these processes should possibly apply equally to words and pseudowords. Keeping in mind that the effect in BA 44 in the standard SPM analysis was a main effect of WORD-TYPE, i.e., stronger activation for pseudowords than for words, interpretations alluding to such general and language-unspecific processes do not account for the entire pattern of effects. To conclude, the data reveal that BA 44 exerts influence on BA 45 that differs from the influence of the ITG onto BA 45, and which might reflect grapheme-to-phoneme conversion.

The fact that a task-driven modulation was present only on a connection to BA 45 but not on any intrinsic connection involving BA 44 is in line with earlier findings [Noeselt et al., 2003] that BA 44 receives only bottom-up input (here: grapheme information needing transformation to phonemes) but not top-down input (here: task-related influence).

Grapheme-to-phoneme conversion and lexical retrieval are the two routes on which visual word identification is presumably accomplished [Coltheart et al., 2001]. Therefore, one might be tempted to regard BA 44 as part of the neural network consisting the sublexical route and the ITG as part of the lexical route of this model [cf. Jobard et al., 2003]. This conclusion, however, is too far-fetched since it presumes a one-to-one mapping of neurophysiological and cognitive processes, which is not necessarily the case. For this reason, we only speak of “involvement in” or “support of” rather than localising a cognitive function such as grapheme-to-phoneme conversion exclusively in one brain region. As a consequence of these considerations, precaution should be taken when drawing conclusions about the architecture of the mental lexicon from the pattern of intrinsic connections in the selected model. Rather, the presence of positive intrinsic connections between the left BA 44, BA 45, and ITG in this study reveals some organisation principles in (a part of the) brain network for visual language processing, i.e., provides information on the neurofunctional rather than the cognitive level. This point will be discussed in the remainder of the article.

Only little is known about the functional connectivity of brain regions involved in visual word processing. In a previous DCM analysis of a reading task Mechelli et al. [2005]

observed stronger activation for exception words than pseudowords in the pars triangularis (approximate BA 45) of the left IFG, for both pseudowords and exception words when compared with regular words in the pars opercularis (approximate BA 44), and for pseudowords compared to exception words in the dorsal premotor cortex. Most interestingly, these three regions also showed different effective connectivity to the anterior, middle, or posterior portion of the left fusiform gyrus in the inferior temporal lobe. The strongest functional coupling was found between the anterior fusiform gyrus and the pars triangularis, and the middle fusiform gyrus and the pars opercularis, for exception words. The posterior portion of the left fusiform gyrus showed a connection towards the dorsal premotor cortex, which was strongest for pseudowords. However, this study did not investigate the effective connectivity among the three inferior frontal regions.

This study adds to these findings that the left BA 44 and BA 45, which were identified based on cytoarchitectonic probability maps [Amunts et al., 2004] instead of macroanatomical landmarks, have bidirectional positive intrinsic connections. This result also goes beyond the previous observation of a positive correlation of fMRI time courses in different parts of the left inferior frontal gyrus for words, pseudowords, and letter strings [Bokde et al., 2001]. This is because a correlation analysis only reveals coincidence whereas DCM identifies causal influences that the activation in one brain region exerts over that in another region under particular circumstances. Finally, whereas the DCM analysis by Mechelli et al. [2005] established the functional links of distinct inferior temporal regions to distinct inferior frontal regions, it did not provide information about a possible functional differentiation between the inferior temporal and the inferior frontal regions to which they were connected. This study goes beyond this finding by demonstrating that activation in the ITG and in BA 44 is likely to support different cognitive processes, as the influence of this activation on the effects in BA 45 is modulated by lexical decisions.

CONCLUSION

DCM and Bayesian model selection were used to test alternative hypotheses about the functions of distinct brain regions during lexical and phonological processing of words and pseudowords. It was shown that the left BA 44 and the left ITG differentially contribute to the occurrence of a WORD-TYPE (pseudowords vs. words) by TASK (lexical vs. phonological decision) interaction in the left BA 45, which is driven by the task-dependent gating of the input from the ITG into BA 45. Specifically, DCM revealed that the connection from the ITG into BA 45, but not from BA 44 into BA 45, was modulated by task demands. Notably, these insights could not be obtained from the conventional SPM analysis [Heim et al., 2005], but required an analysis of effective connectivity.

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