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Neural underpinnings for model-oriented therapy of aphasic word production

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ABSTRACT

Model-oriented therapies of aphasic word production have been shown to be effective, with item-specific therapy effects being larger than generalisation effects for untrained items. However, it remains unclear whether semantic versus phonological therapy lead to differential effects, depending on type of lexical impairment. Functional imaging studies revealed that mainly left-hemisphere, perisylvian brain areas were involved in successful therapy-induced recovery of aphasic word production. However, the neural underpinnings for model-oriented therapy effects have not received much attention yet.

We aimed at identifying brain areas indicating (1) general therapy effects using a naming task measured by functional magnetic resonance imaging (fMRI) in 14 patients before and after a 4-week naming therapy, which comprised increasing semantic and phonological cueing-hierarchies. We also intended to reveal differential effects (2) of training versus generalisation, (3) of therapy methods, and (4) of type of impairment as assessed by the connectionist Dell model.

Training effects were stronger than generalisation effects, even though both were significant. Furthermore, significant impairment-specific therapy effects were observed for patients with phonological disorders (P-patients). (1) Left inferior frontal gyrus, pars opercularis (IFGoper), was a positive predictor of therapy gains while the right caudate was a negative predictor. Moreover, less activation decrease due to therapy in left-hemisphere temporo-parietal language areas was positively correlated with therapy gains. (2) Naming of trained compared to untrained words yielded less activation decrease in left superior temporal gyrus (STG) and precuneus, bilateral thalamus, and right caudate due to therapy. (3) Differential therapy effects could be detected in the right superior parietal lobule for the semantic method, and in regions involving bilateral anterior and mid cingulate, right precuneus, and left middle/superior frontal gyrus for the phonological method. (4) Impairment-specific changes of activation were found for P-patients in left IFGoper. Patients with semantic disorders (S-patients) relied on right frontal areas involving IFG, pars triangularis. After therapy, they revealed less activation decrease in areas involving left STG, caudate, paracentral lobule, and right rolandic operculum.

Regarding naming performance, the present study corroborates previous findings on training and generalisation effects and reveals differential therapy effects for P-patients. Moreover, brain imaging results confirm a predominance of (1) general effects in the left brain hemisphere. (2) Brain regions related to visual strategy, monitoring/feedback, and articulatory patterns were characteristic for the familiar trained items. (3) Distinct regions associated with strategies, monitoring capacities, and linguistic information indicate the specific therapeutic influence on word retrieval. (4) While P-patients relied more on preserved phonological functions in the left hemisphere, S-patients revealed right-sided compensation of semantic processing as well as increased strategic efforts in both hemispheres.

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1. Introduction

The model-oriented approach, which targets language treatment at impaired processing components or stages, has high priority in aphasia therapy (Cicerone et al., 2000). Clinically, word-finding difficulties are the most common symptom in aphasia (Laine & Martin, 2006). The lexical impairment is usually attributed to the semantic and/or phonological stages of processing, as explained in cognitive-functional models of word production (e.g., Howard & Gatehouse, 2006; Schwartz, Dell, Martin, Gahl, & Sobel, 2006). Meta-analyses revealed (1) that treatments of aphasic word-finding difficulties are efficacious (Wisenburn & Mahoney, 2009)—with (2) higher gains for trained compared to untrained words. Moreover, (3) impairment-specific therapy effects could be found for the group of patients with phonological deficits only (Wisenburn, 2010), (4) with the respective literature being inconclusive regarding which type of therapy is best designed for which type of patient. Both semantic and phonological treatments considered in the two meta-analyses involved a variety of techniques and inter-individual comparisons. An intra-individual comparison of parallelized methods at the group level should be well suited to reveal differential therapy effects. In the present study, we aimed to illuminate the neural underpinnings of model-oriented therapy of word production in aphasia, focussing on all four aspects mentioned.

Neural correlates of spontaneous and therapy-induced aphasia recovery have been investigated using functional brain imaging (for overviews, see Meinzer, Harnish, Conway, & Crosson, 2011; Zahn, Schwarz, & Huber, 2006; Crosson et al., 2007; Crinion & Leff, 2007). Both hemispheres were reported to subserve word production in healthy participants (Abel et al., 2011; Vigneau et al., 2011) as well as recovery of word production deficits in aphasia (Crosson et al., 2007). The right hemisphere (RH) appears be less efficient than the usually language-dominant left hemisphere (LH). The RH nevertheless tends to take over language functions, if LH capacities have become insufficient (Heiss & Thiel, 2006; Crosson et al., 2007).

Changes of brain activations related to therapy effects were rarely reported for RH activations (Crosson et al., 2005; Raboyeau et al., 2008) and more frequently for bilateral (Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006; Fridriksson et al., 2007; Meinzer, Obleser, Flaisch, Eulitz, & Rockstroh, 2007; Menke et al., 2009) and LH (peri-lesional) activations (Leger et al., 2002; Cornelissen et al., 2003; Meinzer et al., 2008; Vitali et al., 2007; Fridriksson, Richardson, Fillmore, & Cai, 2012). Brain imaging studies on training effects have been dominated by (multiple) single-case studies, and only recently a few group studies have been conducted (Meinzer et al., 2011; Fridriksson et al., 2012).

To date, specific therapy effects and impairment type have not received much attention in brain imaging studies (Meinzer et al., 2008; Rochon et al., 2010). In a study including 11 patients with aphasia, Meinzer et al. (2008) investigated changes of fMRI activity in regions of interest showing abnormally slow wave activity as identified by magnetoencephalography (MEG). Cortical plasticity for picture naming was mainly observed in peri-lesional areas with dysfunctional processing. Despite behavioural generalisation effects, these brain areas correlated with therapy success for trained, but not for untrained items. Moreover, only in a few patients the brain activations for naming trained versus untrained items were partially overlapping. A direct comparison of both item sets might have helped to reveal the underlying differences assumed by the authors. Rochon et al. (2010) examined neural correlates of a semantic versus phonological fMRI task before and after phonological therapy. Both of the two patients improved in naming and revealed left frontal and temporal activation changes for the semantic task in the post-therapy scan.

In order to further enlighten neural underpinnings of model-oriented therapy, larger patient groups and a detailed characterisation of brain damage and language performance are considered to be crucial (Crinion & Leff, 2007). Among fMRI treatment studies, the present patient sample of 14 patients stands among the larger group studies executed to date. We aim to report each patient's brain damage to characterise the lesion, and to inform about pre-test naming abilities and type of lexical impairment to characterise his/her language performance. The computer-assisted assessment of impairment type in a model-oriented framework, as featured by the interactive and connectionist lexical model of Dell (Foygel & Dell, 2000), provides an easy to use, automated, and objective classification of the disorder as semantic (S) or phonological (P) (Abel, Huber, & Dell, 2009b). An application of parallelised cueing-hierarchies, a well-known and effective stimulation technique, is optimal for a comparison of therapy methods guided by impairment type (e.g., Abel, Willmes, & Huber, 2007; Abel, Schultz, Radermacher, Willmes, & Huber, 2003). In this approach, cues with increasing semantic or phonological information about the target word are delivered and assist the patient's attempts to name depicted objects short-term and improve word finding long-term.

Fridriksson et al. (2007) investigated neural correlates of semantic and phonological cueing-therapy in three single cases. The two non-fluent patients showed significant improvements after both methods, while performance of the fluent patient remained relatively stable. The semantic method yielded differential activation in right superior frontal gyrus (Brodmann area (BA) 10) in one non-fluent patient. All in all, changes of activation were found in brain regions that are unrelated to language processing per se, e.g., in precuneus or thalamus. Even though patient error patterns were left unclassified by the authors, the predominance of semantic paraphasias over non-words is indicative for an S-disorder according to the Dell model. Our analysis at the group level might help to reveal language-related brain areas in response to semantic versus phonological cueing-therapies. Moreover, our group study intended to include lexical disorders both of the semantic and phonological type.

The two basic error types according to the Dell model have been localised by the research group of Schwartz et al. (2009), Schwartz, Faseyitan, Kim, and Coslett (2012). They found distinct structural left-hemisphere lesions to be associated with either semantic or phonological errors, namely anterior to mid portions of temporal and frontal gyri for the former and postcentral, supramarginal (SMG) and posterior portions of the inferior frontal gyrus (IFG) for the latter error type according to the Dell model. Moreover, Fridriksson, Baker, and Moser (2009) found compensatory activations for the production of semantic errors in left posterior peri-lesional occipital and temporal regions, while for the production of phonological errors nearly homologuous areas in the right hemisphere were detected. However, activations of patients classified as predominantly semantic or phonological have not been investigated yet. Thus, we were set to examine the relation between impairment type and brain activations.

To summarise, we applied lexical therapy, which was evaluated both with behavioural performance measures and with fMRI activation contrasts, to a group of 14 patients with aphasic word retrieval deficits after left-hemisphere stroke. We looked for possible correlations between changes of brain activations due to the therapy regimen and subsequent therapy gains (1). Moreover, we intended to investigate activation changes associated with specific therapy effects for trained versus untrained items (2) and semantically versus phonologically trained items (3). Finally, we aimed to detect activations related to the type of lexical impairment (semantic (S) versus phonological (P)) (4).

We expected to find especially left-hemisphere brain areas related to therapy gains (1), as well as distinct brain areas related

to the other three distinctions: Stronger involvement of language areas for trained compared to untrained items (2), differential modification of semantic and phonological brain areas related to the method chosen (3), and differential compensation for both patient groups, with S-patients probably revealing stronger right-hemisphere compensation (4).

2. Material and methods

2.1. Subjects

We included in-patients of the Aachen aphasia ward with an at least moderate naming deficit (Aachen Aphasia Test (AAT) subtest naming: Percentile rank [PR] <60 (Huber, Poeck, Weniger & Willmes, 1983)), unless there was urgent demand for treatment of their milder naming deficit. They were supposed to be in the post-acute/chronic recovery phase (>4 months) after a first-ever left-hemisphere stroke. We excluded patients with severe apraxia of speech or dysarthria, and contraindications for fMRI-examinations.

Patients who met the inclusion criteria were considered for pre-testing of naming, but were excluded if naming performance was at a mastery level (≥ 112/132 items correct, i.e. at least 90% correct with a confidence level of 95% according to the binomial model; cf. e.g., Willmes, 2010) in at least one pre-test. Patients finally selected for therapy were pseuro-randomly attributed to one of the two possible orders of therapy methods (see Therapy Regimen below and Fig. 2). The study was approved by the ethics committee at the Medical Faculty of the RWTH Aachen University (EK 124/05).

2.2. Overall study design

The study design is presented in Fig. 1. In week 1, patients were pre-tested for confrontation naming on a laptop (T1) and at least one day later in the MRI-scanner (T2). In week 2, items were allocated to individual item sets, and the four-week lexical therapy started in week 3. The model-oriented therapy was administered in a block design: Each semantic and phonological therapy block was tied to its item set to prevent confounding of methods and to be able to perform within-patient comparisons. Post-test performance (T3) was assessed in the week after termination of therapy.

2.3. Material

132 pictures from Snodgrass and Vanderwart (1980) as well as the assigned cueing-hierarchies were used. 90 picture names with the lowest baseline performance were attributed to experimental sets of 30 items each for semantic therapy (SEM), phonological therapy (PHO), and untrained control (CON) (see Fig. 1). The individually chosen item sets were controlled for comparable performance during baseline as well as linguistic parameters of spoken lemma frequency (CELEX German Database, 2001), visual complexity and familiarity of pictures (Genzel, Kerkhoff, & Scheffter, 1995), as well as word length measured by the number of syllables (all $F<1.0$, $p>.1$ for each parameter and patient). Moreover, we also attempted to balance various semantic fields. The remaining 42 untrained items should be relatively well mastered (MAS).

Semantic cueing-hierarchies for SEM consisted of a superordinate, a definition, a closure sentence, and auditory target comprehension. Phonological cueing-hierarchies for PHO comprised the number of syllables, the onset, the first syllable, and overt repetition of the target (see also Abel et al., 2007, for a similar therapy approach).

2.4. Language testing

2.4.1. Naming test

The first baseline naming test was performed on a laptop (T1). Patients were to overtly name each of the 132 pictures within a time frame of 10 s. Pictures were consecutively presented by an audio-visual presentation software (Audio-visuelles Messprogramm (AVMP), 1997). The software also enabled sound-recordings of the patients' responses.

2.4.2. Language assessment: Semantic test

Impairments of visual object perception, object recognition, and conceptual–semantic processing were assessed using parts of the Birmingham Object Recognition Battery (subtests 8, 11, 12 with cut-off values; Riddoch & Humphreys, 2005).

2.5. Therapy regimen

The semantic and phonological therapy methods were given in weekly blocks which altered within and among patients (see Fig. 1). Half of the patients were attributed to phonology first (ABBA), the other half to semantics first (BAAB). Each training set (PHO and SEM) was carefully split in half to practice 15 items each week. In each session, six picture names were treated in six trials, and again presented in a later session, resulting in 12 repetitions per item. Patients were asked to name each picture consecutively presented in a paper/pencil version. If the patient failed to produce the correct response, he/she was given increasing assistance according to the semantic or phonological cueing-hierarchy (see Abel et al., 2007, for a similar procedure).

2.6. Behavioural data analysis

A 4-point "naming score" was used to evaluate verbal responses in the naming tests (T1–T3). We assigned a score of 3 if the response was the target word or a

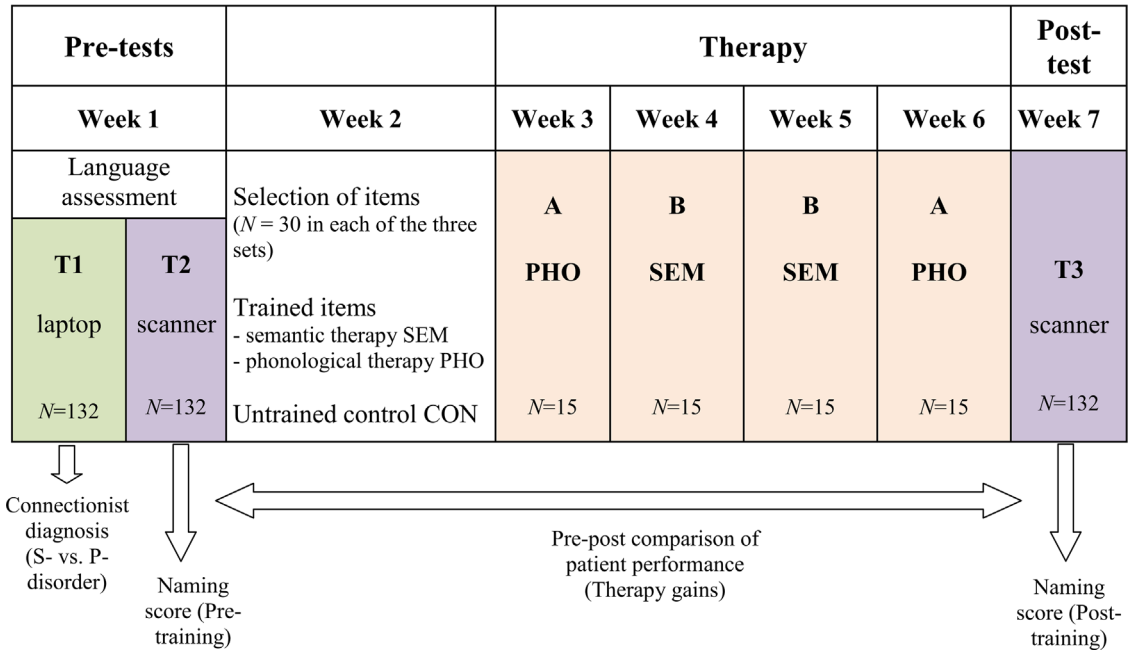

Fig. 1. Design of therapy study and analyses. The order of therapy methods changed within and among patients. Half of the patients were attributed to the ABBA group starting with phonology, for the other half the order was BAAB with semantics first.

synonym; a score of 2 for a correct response after indications of uncertainty, a successful self-correction, or minor phoneme deviations (less than 1/3 of target phonemes changed); a score of 1 for all remaining sound or word substitutions (paraphasias) and for semantically appropriate circumlocutions; and a score of 0 for inappropriate circumlocutions, automated speech, or no response.

In order to calculate therapy gains, each patient's total naming score considering all items before training (T2) was subtracted from the respective naming score after training (T3) (see Fig. 1). Furthermore, all verbal responses in the first pre-test (T1) were classified according to the error analysis of Dell and colleagues and simulated by their model (Foygel & Dell, 2000), resulting in a classification of patients (connectionist diagnosis) to show either semantic or phonological disorders (S- vs. P-patients) (Abel et al., 2009b). The error analysis of Dell and colleagues (Foygel & Dell, 2000) had been adapted to the German language (Abel et al., 2009b). The first complete naming response was classified as correct, if it was the target word or a synonym. A word error was classified depending on its relation to the target word as semantic, phonological, mixed semantic–phonological, or unrelated. A phoneme string without an entry in the mental lexicon was taken to be a nonword. The category omissions comprised circumlocutions, visual errors, or incomplete responses.

Based on each patient's error pattern at T1, we determined the type of lexical impairment in the Dell model by means of computer simulation (Foygel & Dell, 2000). The internet-based computer program attributed the individual error patterns to reduced connection weights between semantic and lexical levels of processing, and/or between lexical and phonological levels (default settings; http://langprod.cogsci.illinois.edu/cgi-bin/webfit.cgi). The access stage with lowest connection weights, either lexical–semantic or lexical–phonological, was considered to be the main source of lexical impairment (Abel et al., 2009b).

2.7. fMRI event-related experiment

2.7.1. Stimuli and experimental design

Stimuli and task of the fMRI paradigm and purely behavioural pre-test T1 were identical. The first scan (T2) completed pre-testing and the second one (T3) represented post-testing. The fMRI-experiment was performed in an event-related design. 16 null events with a mean length of 8 s were included in the fMRI experiment. Picture stimuli were presented with Presentation software (http://nbs.neurobs.com). Subjects saw the pictures via MR-compatible video goggles, and their responses were registered using MR-compatible microphones (VisuaStimDigital, Resonance Technology Company). Spoken responses were recorded using Adobe Audition. Patients had about 8 s time for each naming attempt: Each picture to be named was followed by a fixation cross after 1.2 s and a blank screen after another 4.8 s plus some random jitter (mean duration 2 s, range 1–3 s) (see also Abel et al., 2009a). Verbal responses were registered and sound-recorded.

2.7.2. Data acquisition and analysis

Structural and functional brain data were acquired on a 3T MRI-scanner and analysed with SPM8 using standard procedures for first-level analyses, and sound recordings of verbal responses were analysed.

We used a 3T Philips Achieva with an 8-element SENSE head coil to acquire structural data (high-resolution T1-weighted anatomical scan, 180 slices, voxel size = 1 mm^3, FOV = 180 × 256 × 256) as well as functional data (gradient echo planar (EPI) T2* sequence: TR = 2190 ms, TE = 30 ms, flip angle = 90°, matrix = 64 × 64 pixel; 140 volumes per session, 32 transversal slices in an interleaved order covering the whole brain (voxel size 4 × 4 × 4 mm)). We applied a noise cancellation tool (Cusack, Cumming, Bor, Norris, & Lyzenga, 2005) to sound-recordings of vocal responses. Moreover, naming responses were transcribed and classified (see behavioural data analysis).

The anatomical MR-image was segmented into gray matter, white matter, and cerebrospinal fluid (CSF) compartments using the unified segmentation procedure (Ashburner & Friston, 2005; Crinion et al., 2007; Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). Normalisation parameters were estimated to be applied to the functional images later on, and finally the images were spatially smoothed (Gaussian kernel of 8 mm full width at half maximum). Functional images were corrected for slice timing. For statistical analyses, brain images of all four sessions were merged on the single-subject level. Sessions and estimated realignment parameters were used as regressors of no interest. Picture onsets were convolved with a canonical hemodynamic response function (HRF).

We performed the following second-level analyses at the group level: (1) Associations between brain activations for naming the complete corpus and according therapy gains combining *t*-tests with covariate analyses, taking T2 results as predictors and pre-post (T2–T3) results as general therapy effects. (2) Activations for item sets TRA versus CON pre-post (paired *t*-test, T2–T3), for training and generalisation effects. (3) Activations for item sets SEM versus PHO pre-post revealing differential therapy effects. (4) Activations for patient subgroups (S- versus P-patients) in order to illuminate impairment-specific effects before therapy (T2) and pre-post (T2–T3) applying two-sample *t*-tests.

The *t*-tests and covariate analyses were performed at an intensity threshold of $p < 0.01$ uncorrected with an extend threshold of $k = 11$ voxels. In a Monte Carlo simulation with 10,000 repetitions, this cluster extent cut-off provided an experiment-wise threshold of $p < .05$ corrected for multiple comparisons (Slotnick, Moo, Segal, & Hart, 2003). In the results tables for the functional imaging data, the right column informs about the presumed function of the respective activation peak in healthy subjects as found in the literature (e.g., Price, 2000; Cabeza & Nyberg, 2000; Vigneau et al., 2006; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004).

The brain figures were created using xjview (http://www.alivelearn.net/xjview) and MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

3. Results

3.1. Subjects

Fig. 2 presents the patient flow (according to Doesborgh et al., 2004). We considered 23 patients for inclusion in the fMRI-therapy study. Nine patients were excluded after pre-testing due to naming performance near ceiling ($n = 4$), scanner artefacts ($n = 2$), or technical problems ($n = 3$). 14 right-handed patients completed the therapy study. None of them had visual/conceptual–semantic or severe motor speech deficits.

Full characteristics of all 14 patients are given in Table 1. The left-hemisphere brain lesions involved frontal ($n = 11$), temporal ($n = 14$), and/or parietal regions ($n = 10$), as well as basal ganglia ($n = 12$) and insula ($n = 1$). Only for one patient was the lesion restricted to one lobe (i.e. the temporal lobe in P5). Moreover, the strongest overlap of lesion site for the group of patients was located in insula and inferior frontal gyrus (see Supplementary Fig. S1).

3.2. Behavioural analysis

3.2.1. Language profile and connectionist diagnosis

The mean pre-training performancer for confrontation naming at the first pre-test (T1) was 47% of the maximally attainable naming score (188/396; range 26–82%) or a proportion of 0.61 (range 0.26–0.84) spontaneously correct naming responses (see Table 2 for individual values). Naming error patterns at T1 and the model parameters resulting from computer simulations, i.e. the connectionist diagnosis, revealed that deficits in confrontation naming could be attributed to a predominantly lexical–phonological impairment (P-disorder) in 6 patients and to a predominantly lexical–semantic impairment (S-disorder) in 8 patients (see Table 2).

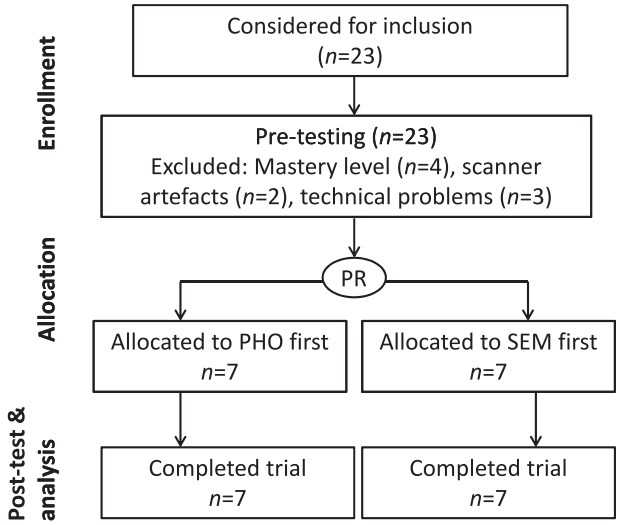

Fig. 2. Patient flow. Created according to Doesborgh et al. (2004) (*PR* = pseudo-randomised).

Table 1
Subject characteristics.

Sub.	Sex	Handedness[a]	Age (yrs)	Degree (yrs) of education	Profession	Time post-onset (mths)[b]	Syn-drome[c]	Concomitant symptoms[d]	Etiology	Localization of brain lesion[e]	Assigned order of methods[f]
P1	f	R.10	48	High school (9)	Shoe seller	57	TS	BA, Hem, Dyspr, E	V–I	Left MCA: FTP & BG	BAAB
P2	m	R.10	74	High school (10)	Engineer	49	W	Hem, Dys	V–I	Left MCA: FTP & BG	ABBA
P3	m	R.10	46	High school (10)	Metalworker	11	W	FM	V–I	Left MCA: TP & insula	ABBA
P4	m	R.10	58	High school (9)	Locksmith	49	G	SA, BA, Dys	V–I	Left MCA: FTP & BG	BAAB
P5	m	R.6	68	High school (13) and university	Public management	13	F	BA, Stu, FP	V–I	Left MCA: T	ABBA
P6	f	R.10	37	High school (13) and university	Business administration	40	B	FM	V–I	Left MCA: FT & BG	BAAB
P7	m	R.10	46	High school (10)	Electronic technician	28	B	Hem, E	V–H	Left MCA: TP & BG	BAAB
P9	m	R.10	47	High school (13) and university (dropped out)	Car mechanic	38	B	SA, BA, Hem	V–I	Left MCA: FTP & BG	ABBA
P10	m	R.10	53	High school (13) and university	Business administration	55	B	SA, BA, Hem	V–I	Left MCA: FTP & BG	BAAB
P11	f	R.10	35	High school (10)	Design draftswoman	72	B	SA, Hem	V–I	Left MCA, ACA: FTP & BG	ABBA
P13	m	R.10	65	High school (9)	Locksmith	41	W	FM	V–I	Left MCA: FT & BG	BAAB
P14	m	R10	41	High school (9)	Car mechanic	25	B	SA, Hem, E	V–I	Left MCA: FT & BG	ABBA
P15	f	R.10	44	High school (10)	Midwife	45	B	SA, BA, E, IA	V–I	Left MCA, ACA: FTP & BG	BAAB
P16	m	R.10	H	High school (13) and university	Physicists and software developer	24	B	SA, BA, Hem, E	V–I–H	Left MCA: FTP & BG	ABBA
Md (range)			Age: 48 (35–74)			PO^2: 41 (11–72)					

Sub.=subject; P=patient; Md=median; Sex: f=female, m=male.

[a] Handedness: R=right-handed. Deciles for handedness according to Edinburgh Handedness Inventory (Oldfield, 1971).

[b] PO=months post-onset at the time of admission to the Aachen aphasia ward.

[c] B=Broca, F=fluent non-classifiable, G=global, TS=transcortical-sensory, W=Wernicke.

[d] BA=buccofacial apraxia, Dys=dysarthria, Dyspr=Dysprosody, E=Epilepsy, FM=impaired fine motor skills to the right, FP=facial nerve paresis; Hem=right hemiparesis, IA=ideomotor apraxia, SA=speech apraxia, Stu=premorbid stuttering symptoms.

[e] Etiology and distribution of brain lesions: V=vascular, I=ischemic, H=hemorrhagic; MCA=middle cerebral artery; F=frontal, T=temporal, P=parietal; BG=basal ganglia. For all patients, cortical lesion extended to white matter.

[f] A=block of phonological therapy; B=block of semantic therapy; ABBA=phonology first, BAAB=semantics first.

Table 2
Patient performance and connectionist diagnosis before training.

Patient	Naming score T1	Connectionist diagnosis at T1	RMSD	Parameter *s*	Parameter *p*	Correct	Semantic	Formal	Mixed	Unrelated	Nonword	Omissions
P1	151	S	0.063	0.0175	0.3100	0.781	0.047	0.000	0.125	0.016	0.031	68
P2	262	S	0.049	0.016	0.038	0.730	0.096	0.026	0.122	0.017	0.009	17
P3	180	P	0.029	0.0184	0.0149	0.442	0.063	0.116	0.074	0.021	0.284	37
P4	138	P	0.016	0.0994	0.0020	0.441	0.034	0.051	0.051	0.000	0.424	73
P5	238	P	0.010	0.0265	0.0251	0.839	0.051	0.042	0.025	0.000	0.042	14
P6	325	S	0.029	0.0209	0.0279	0.787	0.090	0.000	0.066	0.008	0.049	10
P7	259	P	0.017	0.0248	0.0166	0.636	0.033	0.066	0.050	0.008	0.207	11
P9	150	P	0.021	0.0230	0.0170	0.632	0.066	0.026	0.053	0.026	0.197	56
P10	174	P	0.026	0.0235	0.0153	0.632	0.039	0.026	0.026	0.026	0.250	56
P11	223	S	0.050	0.0170	0.0360	0.752	0.099	0.011	0.109	0.021	0.011	31
P13	188	S	0.039	0.0140	0.0250	0.566	0.070	0.093	0.101	0.078	0.093	3
P14	105	S	0.077	0.0090	0.0170	0.261	0.116	0.072	0.145	0.058	0.348	63
P15	104	S	0.054	0.0096	0.0160	0.284	0.049	0.235	0.037	0.062	0.333	51
P16	136	S	0.052	0.0175	0.0220	0.690	0.069	0.000	0.000	0.103	0.138	71

Patient performance according to the naming score and computer simulation of error patterns in the semantic–phonological Dell model considering all 132 items. S=semantic impairment ($s < p$), P=phonological impairment ($s > p$); RMSD=root mean squared deviation; s=semantic weight parameter; p=phonological weight parameter. Normal parameter values would be s=.07 and p=.08 (Abel et al., 2009b).

3.2.2. Group analysis

There was no difference in average improvement for patients allocated to phonology versus those allocated to semantics first (ABBA vs. BAAB, see Fig. 2; Mann Whitney *U*-test, two-tailed, $p > .10$). As intended, the whole group of 14 subjects presented with low baseline performance for the pre-selected trained (TRA) and control (CON) items, and high performance for the pre-selected mastered (MAS) items in the fMRI scanner before therapy (T2) (see Fig. 3). Comparing pre- to post-test (T3–T2), there were highly significant improvements for TRA and CON, revealing training effects of a medium effect size (mean therapy gain 22.0%, standard deviation (SD) 11.4%; Cohen's d=.54, effect size

$r=0.26$) and generalisation effects of a small effect size (mean gain 13.3%, SD 10.8%; Cohen's $d=.33$, effect size $r=0.16$). To the contrary, there was a highly significant decrease for MAS items, most likely due to a regression to the mean for those items which were only accidently particularly well performed at pre-testing. TRA improved highly significantly more than CON (Mann Whitney *U*-test, one-tailed, $p<.001$; for the S-group $p=.006$, for the *P*-group $p=.002$). Altogether, there was no instance of a (marginal) significant deterioration of naming performance in our patient group.

Significant improvements occurred across all experimental sets and groups (all $p<.001$). For the group of 14 patients, both item sets SEM and PHO nevertheless showed significantly more improvement than CON (difference in naming score T2–T3, Mann Whitney *U*-test, one-tailed; $p=.012$ and $p<.001$, respectively). Testing impairment-specific therapy effects, a training advantage compared to CON was present in the S-group for both SEM and PHO ($p=.045$ and $p=.009$, respectively), for the P-group only for PHO, not SEM ($p=.022$ and $p=.069$, respectively). There were no direct differential effects for SEM versus PHO. Taken together, the P-group showed significantly stronger gains for trained items than the S-group (Mann Whitney *U*-test, two-tailed, $p=.008$); for the control items, the group difference did not reach significance ($p=.054$).

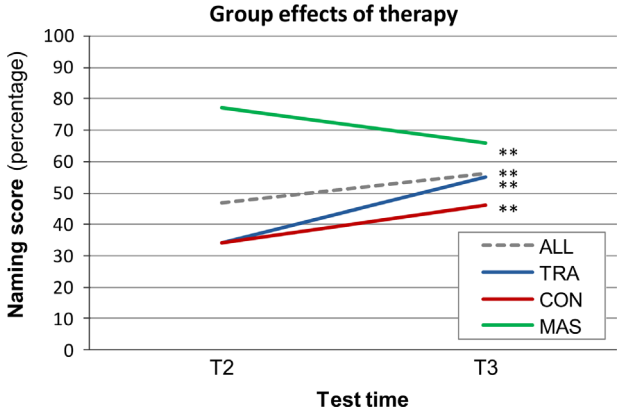

Fig. 3. Group effects ($n=14$) of therapy. Performance expressed as raw total score percentage of theoretical maximum. Development for all items (ALL) and for pools of trained (TRA), untrained control (CON) and untrained mastered (MAS) items. The diagram indicates the effects of training (TRA), generalisation (CON), and regression to the mean (MAS). $^{**}p<.001$, one- (TRA, CON) or two-tailed (MAS), difference according to the Wilcoxon signed ranks test (pre-test T2 vs. post-test T3).

3.3. Correlations with therapy gains (expectation 1)

We examined correlations between behavioural therapy gains, i.e. improvements for all items in the naming score from pre- to post-test, and brain activations before training (T2) or pre-post (T2–T3) (Table 3). At T2, an (1A) activation peak in left (L) inferior frontal gyrus, pars opercularis (IFGoper) (BA 44) predicted higher therapy gains, while (1B) activation in right (R) caudate predicted lower gains (Fig. 4). Moreover, (1C) a decrease of activation in LH language areas including left superior temporal sulcus (STS), supramarginal gyrus (SMG), paracentral lobule, and middle temporal gyrus (MTG) was associated with decreasing therapy gains. Fig. 5 presents the respective brain areas and the negative correlation between activation decreases and increasing therapy gains for the maximum of activation in the left STS.

3.4. Item-specific effects (expectations 2 and 3)

We examined differential effects of therapy on item sets applying *t*-tests (Table 4). Activation for all item sets (TRA, CON; SEM, PHO, CON) was generally decreasing from pre- to post-test, i.e. there was no pre-post increase of activation. This was the case for the complete corpus of naming items as well (joint independent component analysis in Abel, Huber, Weiller, & Specht, 2013; Abel, Weiller, Huber, Willmes, & Specht, 2014). Therefore, we want to stress the relevance of a particularly small pre versus post decrease for the respective item set 1 (e.g., trained items TRA) compared to another comparison item set 2 (e.g., control items CON). Equivalently, we could have pointed out the stronger pre-post decrease for the

Table 3
Relation between brain activations and therapy gains for all patients.

Extent	Cluster *p* unc.	*t*-Value	Voxel *p*	Coordinates *x*, *y*, *z* {mm}			Brain structure (Brodmann area)	Presumed function in healthy subjects
1A. Pre-training activations as positive predictors								
15	0.285	3.25	0.003	−46	12	10	L IFG pars opercularis-v (44)	Articulatory recoding[1]
1B. Pre-training activations as negative predictors								
15	0.285	3.33	0.003	26	0	22	R caudate (head)	Suppression of irrelevant words[1]
		3.13	0.004	18	4	18	R caudate (head)	Suppression of irrelevant words[1]
		2.93	0.006	18	16	22	R caudate/corpus callosum	Suppression of irrelevant words[1]
1C. Activation decrease related to decreasing gains								
20	0.192	4.38	0.000	−46	−32	2	L superior temporal sulcus-p	Integrating familiar sounds, articulation and meaning[1]
17	0.227	4.08	0.001	−50	−32	42	L inferior parietal lobule (2/40)	Articulation[1]/working memory[4]
		3.58	0.002	−50	−36	50	L inferior parietal (40)/postcentral gyrus	Working memory[4]/articulation[1]
20	0.192	3.79	0.001	−46	−32	22	L inferior parietal gyrus/STG (temporo-parietal junction)	Words[1]
		3.49	0.002	−50	−40	26	L inferior parietal/SMG-v	Articulatory loop, auditory expectations[1]
		3.00	0.006	−62	−36	26	L inferior parietal/SMG-v (40)	Articulatory loop, auditory expectations[1]
17	0.227	3.65	0.002	−10	−32	70	L postcentral gyrus/paracentral lobule	Articulation[1]
		3.05	0.005	−2	−28	66	L paracentral lobule (6)	Articulation[1]
12	0.309	3.36	0.003	−42	−68	10	L MTG	Accessing semantics[1]
		3.20	0.004	−30	−76	10	L middle occipital gyrus	Visual[1]

Areas of significant brain activations when calculating correlations between therapy gains (naming scores for all items, T3 > T2) with pre-training activations (T2) in all patients, revealing (1A) positive predictors (i.e. increasing naming scores) and (1B) negative predictors (i.e. decreasing naming scores), as well as (1C) correlations of therapy gains with training pre-post (significant results for correlation of activation decrease T2 > T3 with decreasing gains only). Activations were thresholded at Monte Carlo-corrected $p<.05$ with at least 11 voxels. Co-ordinates refer to MNI space. Abbreviations: R=right hemisphere, L=left hemisphere; IFG=inferior frontal gyrus, SMG=supramarginal gyrus, MTG=middle temporal gyrus, STG=superior temporal gyrus. Numbers given in the right column refer to publications listed in the reference section.

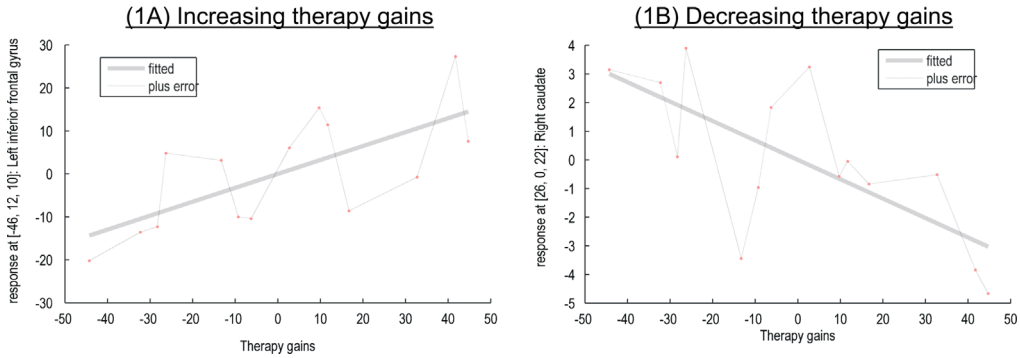

Fig. 4. Plots of predicted responses at pre-test T2 in activation maxima for increasing therapy gains (1A) or decreasing therapy gains (1B) (cf. Table 3). (Please note that real values of gains lie between −2 and 20% of the maximally attainable naming score).

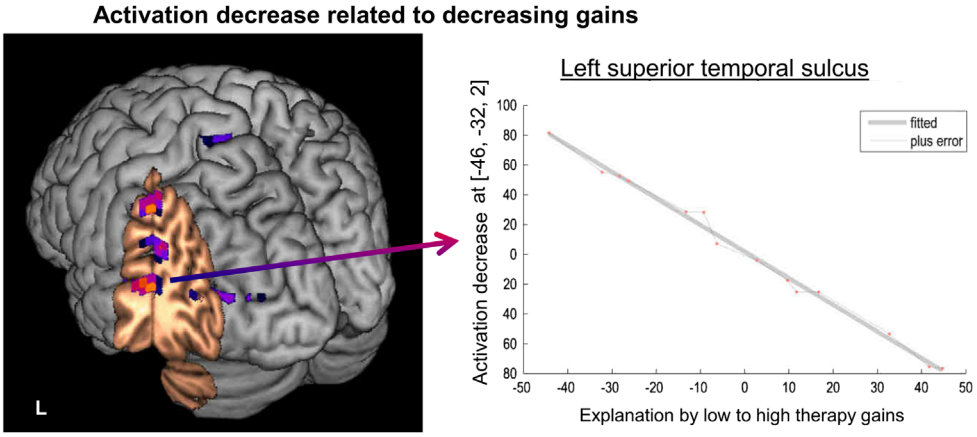

Fig. 5. Therapy gains for the 14 patients as covariate in the pre-post comparison (T2–T3), and plot of fitted responses (predicted) against the explanatory variable of therapy gains at the maximum of activation in left superior temporal sulcus (cf. Table 3, contrast 1C). (Please note that real values of gains lie between −2 and 20% of the maximally attainable naming score).

comparison condition 2, but we preferred to accentuate the relatively stronger recruitment of a respective brain area after compared to before therapy. Thus, the decrease was less pronounced (2) for trained (TRA) compared to control items (CON) in right postcentral gyrus and caudate, left superior temporal gyrus (STG) and precuneus, left posterior and right mid cingulate cortex, as well as bilateral thalamus (pulvinar).

Moreover, there was less decrease (3A) for SEM compared to PHO in right superior parietal lobule (SPL). For (3B) PHO compared to SEM, the decrease was less pronounced in bilateral anterior and mid cingulate gyrus, left precentral gyrus, calcarine, middle/superior frontal gyrus as well as right lingual gyrus, hippocampus, cuneus, and precuneus. A medial view of the differential deactivations for both item sets is shown in Fig. 6.

3.5. Impairment-specific effects (expectation 4)

Moreover, we found (4) some differences for the two patient groups (Table 5). Before training, (4A) S-patients showed more activation in right inferior frontal gyrus, pars triangularis (IFGtri) (BA 45) and right superior/middle frontal gyrus compared to P-patients, while (4B) P-patients did not show more activation than S-patients. Due to training (4C), there was less decrease of activation for P-patients in left IFGoper (BA 44) and for S-patients in areas involving right rolandic operculum and left paracentral lobule, caudate, calcarine cortex, and STG. (There was even a minor increase for S-patients in left caudate and pallidum, as shown in Tab. S1). Fig. 7 demonstrates the disorder-specific signal changes from pre to post training in IFG and paracentral lobule.

4. Discussion

4.1. Behavioural therapy effects

The model-based lexical therapy was very effective (Fig. 3), yielding highly significant general therapy effects; more specifically, we found item-specific training effects and generalisation to untrained items for both types of impairment in the Dell model (Foygel & Dell, 2000). Nevertheless, there was a significant advantage for trained items. Even though there was no direct differential impairment-specific therapy effect, patients with a phonological disorder showed therapy gains that were stronger than pure generalisation effects only for the phonologically-trained items; for patients with semantic disorder, the therapy method applied did not matter. Thus, our intra-individual comparisons are in accordance with previous findings from meta-analyses comprising inter-individual group comparisons of therapy methods (Wisenburn & Mahoney, 2009; Wisenburn, 2010) and reveal that the phonological cueing-therapy is favourable for patients with P-disorder.

Moreover, our behavioural data offers a good basis to examine neural effects of therapy and impairment type as discussed below.

4.2. Correlations with therapy gains

Pre-activation of left IFGoper (BA 44) was a good predictor of later improvements due to lexical therapy. To the contrary, the recruitment of right caudate appeared to be less beneficial for later gains (Fig. 4). Moreover, a pre-post decrease of LH areas related to semantic access in MTG, phonology-phonetics in SMG/inferior

Table 4
Differential neural effects of therapy on item sets.

Extent	Cluster *p* unc.	*t*-Value	Voxel *p*	Coordinates *x*, *y*, *z* {mm}			Brain structure (Brodmann area)	Presumed function in healthy subjects
2. Less activation decrease pre-post training for TRA compared to CON								
19	0.200	6.09	0.000	66	−4	22	R postcentral (4)	Articulation[1]
74	0.019	5.35	0.000	14	−32	6	R thalamus (pulvinar)	Articulation[1]
		4.00	0.001	38	−28	6	R Heschl	Acoustic processing[1]
45	0.057	4.46	0.000	−6	−24	2	L thalamus	Articulation[1]
		4.31	0.000	−18	−44	6	L precuneus	Semantics, visual imagery[1]
		4.12	0.001	−18	−32	6	L thalamus (pulvinar)	Articulation[1]
90	0.011	3.97	0.001	−6	−36	30	L posterior cingulate gyrus	Semantics[1]
		3.72	0.001	2	−28	30	R mid cingulate gyrus	Semantics[1]
		3.69	0.001	−10	−52	34	L precuneus	Semantics, visual imagery[1]
16	0.238	3.58	0.002	−58	−12	6	L STG-a (22)	Early auditory processing of complex sounds[1]; feedback[6]
		2.88	0.006	−50	−20	6	L STG (22)	Auditory processing[1]; feedback[6]
15	0.253	3.50	0.002	−42	−28	10	L STG (41)	Auditory processing[1]; feedback[6]
19	0.200	3.41	0.002	26	0	26	R caudate (head)	Suppression of irrelevant words[1]
		3.24	0.003	38	−4	26	R frontal lobe, subgyral, medial to precentral gyrus	Articulation[1]
		2.90	0.006	18	0	22	R caudate (head)	Suppression of irrelevant words[1]
3A. Less activation decrease pre-post-training for SEM compared to PHO								
12	0.302	4.28	0.000	22	−60	62	R superior parietal lobule (7)	Visual, attention, working memory[4]
		3.95	0.001	30	−56	62	R superior parietal lobule (7)	Visual, attention, working memory[4]
3B. Less activation decrease pre-post-training for PHO compared to SEM								
96	0.008	5.18	0.000	2	−28	30	R mid cingulate gyrus	Semantics[1]
		4.28	0.000	−14	−40	34	L mid cingulate gyrus	Semantics[1]
		4.07	0.001	14	−32	34	R mid cingulate gyrus	Semantics[1]
17	0.221	4.55	0.000	−26	−16	62	L precentral gyrus (6)	Articulation[1]
119	0.004	4.25	0.000	−18	−64	10	L calcarine	Visual[1]
		3.84	0.001	2	−68	−2	R lingual gyrus	Visual[3]
		3.72	0.001	−30	−56	10	L calcarine	Visual[1]
16	0.234	3.76	0.001	18	−36	2	R hippocampus	Word acquisition, semantic retrieval[1]
		3.70	0.001	10	−44	2	R lingual gyrus (30)	Visual[3]
37	0.079	3.66	0.001	−22	48	6	L middle/superior frontal gyrus (10)	Semantics[1], cognitive control[6]
		3.33	0.003	−6	44	10	L ACC-a	Suppressing production of unintended words[1]
		3.23	0.003	6	44	10	R ACC-a	Suppressing production of unintended words[1]
15	0.249	3.23	0.003	22	−56	30	R precuneus	Semantics, visual imagery[1]
		3.00	0.005	18	−68	30	R cuneus	Visual[5]

Areas of significant brain activations when pre-post training in patients was considered (2) for the control set (CON) compared to the training set (TRA) ((CON > TRA) at T2 > (CON > TRA) at T3) and (3A) for the semantically trained SEM set compared to the phonologically trained PHO set ((SEM > PHO) at T3 > (SEM > PHO) at T2), and (3B) the reverse contrast ((PHO > SEM) at T3 > (PHO > SEM) at T2). Contrasts were calculated applying paired *t*-tests, and activations were thresholded at Monte Carlo-corrected $p < .05$ with at least 11 voxels. Co-ordinates refer to MNI space. Abbreviations: R=right hemisphere, L=left hemisphere; STG=superior temporal gyrus; ACC=anterior cingulate cortex; a=anterior. Numbers given in the right column refer to publications listed in the reference section.

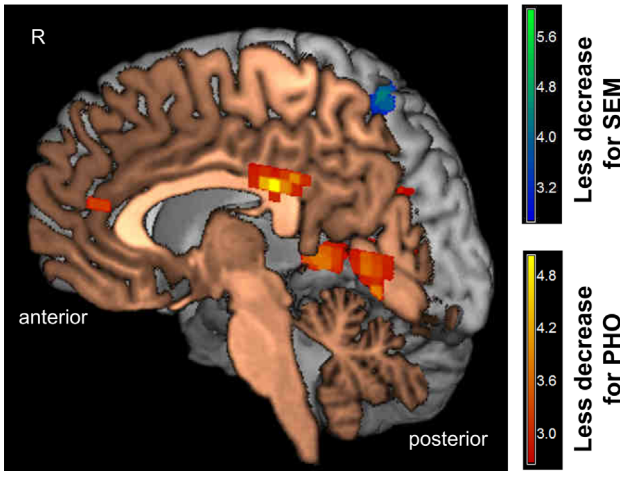

Fig. 6. Brain activations for semantically (SEM) versus phonologically (PHO) trained items pre-post training. Specific activations for SEM (contrast 3A) and PHO (3B) rendered onto the medial cut of the right (R) hemisphere (see Table 4) (paired *t*-tests, MC-corrected, $p < .05$, 11 voxels).

parietal lobule and paracentral lobule, and their integration in STS was related to lower gains. Effects were relatively small in extent with *t*-values around 3–4.

As expected, preserved pre-training language functions of the LH played a major role in successful aphasia recovery. The importance of core LH language regions for compensation of language functions in aphasia as found in our patients was underlined by previous studies already, with a focus on inferior frontal (Weiller et al., 1995; Saur et al., 2006; Hillis et al., 2006), superior temporal (Musso et al., 1999; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Hillis et al., 2006), or middle temporal areas (Fridriksson, 2010). We did not find increased activations correlated with therapy gains in the LH as found in previous studies (Fridriksson et al., 2006, 2007; Meinzer et al., 2007; Leger et al., 2002; Cornelissen et al., 2003; Meinzer et al., 2008; Vitali et al., 2007)—we found decreased activations instead. Thus, for improved naming the continued reliance on several left temporo-parietal language areas was crucial, revealed by a lower degree of deactivation. Richter, Miltner, and Straube (2008) found decreases of activations to be correlated with therapy success in their 24 aphasic patients as well. Since their fMRI tasks consisted of reading and comprehension, it is not surprising that they found other therapy-related regions, comprising right IFG/insula. In a study by Fridriksson (2010), left inferior and superior parietal lobules, precentral gyrus, and IFGoper were implicated in improvements. Marcotte et al. (2012) underlined the importance of left inferior parietal lobe for improvements due to therapy based on semantic feature analysis.

Since the right caudate was specially required for trained items (see below), its involvement might indicate RH compensation to

Table 5
Differential effects of type of lexical impairment.

Extent	Cluster *p* unc.	*t*-Value	Voxel *p*	Coordinates *x*, *y*, *z* {mm}			Brain structure (Brodmann area)	Presumed function in healthy subjects
4A. Specific pre-training activations for patients with S-disorder								
35	0.109	4.25	0.001	42	24	22	R IFG pars triangularis (45)	Sentence/text, semantics[2]; L: word retrieval, semantic decisions[1]
16	0.268	3.24	0.004	18	32	34	R superior frontal gyrus	Semantics[1]
		2.77	0.008	30	36	34	R middle frontal gyrus (9)	Semantics[1]
4B. Disorder-specific effects pre-post: less decrease for P-patients								
21	0.184	3.52	0.002	−50	16	14	L IFG pars opercularis (44)	STM, integrating inputs, Expectations, meanings[1]
4C. Disorder-specific effects pre-post: less decrease for S-patients								
16	0.244	5.48	0.000	−2	−28	54	L paracentral lobule	Articulation[1]
16	0.244	4.91	0.000	54	−4	6	R rolandic operculum (6)	Articulation[1]
21	0.184	3.85	0.001	−22	0	10	L putamen	Timing of motor output[1]
		3.38	0.003	−14	−4	18	L caudate (head)	Suppression of irrelevant words[1]
12	0.312	3.68	0.002	−6	−60	10	L calcarine	Visual[1]
12	0.312	3.27	0.003	−14	−20	10	L thalamus (lateral posterior ncl.)	Articulation[1]
20	0.194	3.26	0.003	−50	−8	6	L Heschl (6)	Acoustic[1]
		2.97	0.006	−54	4	2	L STG-a (22)	Early auditory processing of complex words[1]; feedback[6]

Areas of significant brain activations when patients with semantic (S-disorder) and phonological (P-disorder) types of lexical impairment were compared, considering (4A) activations for naming before training (T2) (significant effects for S-group > P-group only) and activations pre-post training (T3–T2) revealing (4B) effects for P-patients (P-group > S-group) and (4C) S-patients (S-group > P-group). Contrasts were calculated applying two-sample *t*-tests, and activations were thresholded at Monte Carlo-corrected $p < .05$ with at least 11 voxels. Co-ordinates refer to MNI space. Abbreviations: R=right hemisphere, L=left hemisphere; IFG=inferior frontal gyrus; STM=short-term memory; a=anterior. Numbers given in the right column refer to publications listed in the reference section.

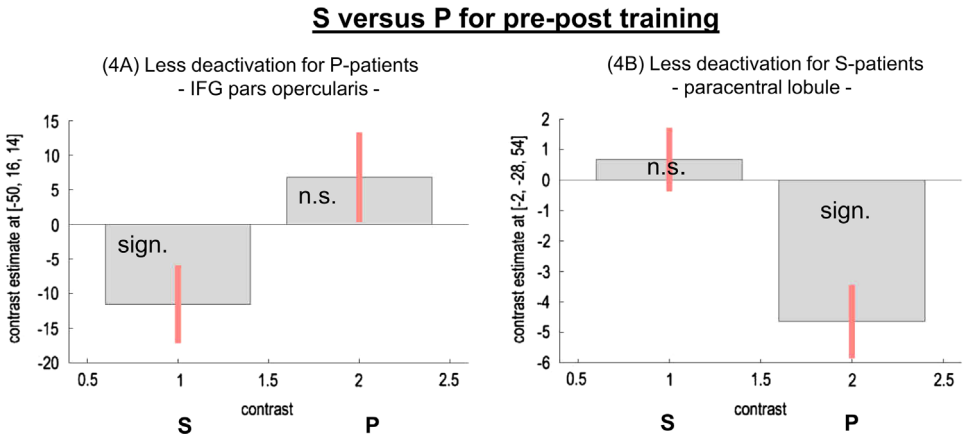

Fig. 7. Plot of activation maximum of the specific pre-post deactivations by type of impairments. (4A) P-patients ((T3 > T2) for P > (T3 > T2) for S) in left inferior frontal gyrus (IFG) or for (4B) S-patients ((T3 > T2) for S > (T3 > T2) for P) in the left paracentral lobule (see Table 5). Label for significance (sign.)/no significance (n.s.) refers to the contrast T2 versus T3 for P and S, respectively (paired *t*-tests, MC-corrected, $p < .05$, 11 voxels).

monitor word production. Since it usually is the LH counterpart that is involved in language processing (Price, 2012), i.e. in the suppression of irrelevant words, the recruitment of the right homologue might not be optimal. It may nevertheless reveal the need to suppress errors before therapy and during amelioration of performance.

4.3. Item-specific effects

In accordance with the findings of Meinzer et al. (2008) trained items resulted in more activation than untrained control items (Table 4), even though the latter improved as well (generalisation). Thus, we found lower activation decreases in the expected language-related areas, namely in left STG related to auditory and feedback processing. However, the majority of activation was detected outside the core language areas: In bilateral thalamus and right postcentral gyrus associated with articulation, in left posterior and right mid-cingulate cortex and left precuneus related to semantics, and in right caudate related to the suppression of irrelevant words. Fridriksson et al. (2009) also reported activations in precuneus and thalamus for naming words that were trained with semantic/phonological therapy compared to a visual baseline condition. The precuneus has also been associated with semantics and visual imagery (Price, 2012). Calvert et al. (2000) attributed more left precuneus activation compared to controls in a semantic task to a cognitive strategy, which relies more strongly on visual word features to solve the task. Our results might therefore represent the strategic use of visual imagery to assist word retrieval, the reliance on monitoring and feedback processing to verify correct word production, as well as access to articulatory patterns for items that had been repeatedly and successfully produced in training sessions.

Moreover, items trained with semantic cues (SEM) elicited more activation in right SPL, which is also associated with working memory. Items trained with phonological target information (PHO) yielded more activation for visual processing in left calcarine, right cuneus, and right lingual gyrus, for semantic processing in bilateral mid cingulate cortex, right hippocampus, right precuneus, left middle/superior frontal gyrus also implicated in cognitive control, and monitoring in bilateral ACC (Fig. 6). Minor activation was observed in left precentral gyrus for articulation. Thus, the untrained aspects of word retrieval appear to be especially required for production of the previously trained items; or the other way around, each method seems to lead to more

efficient processing of aspects of the trained words. Thus, the semantic therapy might not only feature visual–semantic aspects of words, but also monitoring and control processing including visual strategies. Fridriksson et al. found differential activation for the semantic method in right superior frontal gyrus (BA 10) after therapy; however, this activation was only found in one of the three single cases.

4.4. Impairment-specific effects

Before therapy, patients with semantic (P-) disorder specifically recruited RH areas related to semantic processing involving IFGtri and middle/superior frontal gyrus, which might be taken as compensation of their impaired semantic processing. Due to therapy, they revealed less decrease in areas related to acoustic processing and monitoring (Heschl, STG, caudate) as well as articulatory processing (left paracentral lobule, putamen and thalamus, right rolandic operculum). In contrast phonological (P-) patients preferred left IFGoper involvement. Since we identified left IFGoper as a positive predictor of therapy gains, this may be linked to the finding that P-patients showed significantly more improvements. The effects again were relatively small ($t \geq 2.7$). In accordance with this finding, left anterior to mid IFG has been associated with semantic errors, while left posterior IFG has been associated with phonological errors (Schwartz et al., 2009, 2012), or, when looking at fluency, pars opercularis seems to be needed for phonological tasks, and pars triangularis for semantic tasks (Katzev, Tuscher, Hennig, Weiller, & Kaller, 2013). Our patients with P-disorder are well able to modify activation in the former brain area. Thus, P-patients appear to rely on their relatively preserved processing stages in the course of therapy. S-patients appear to compensate for their deficit using right frontal brain areas for semantic processing, recruit left brain areas for monitoring of responses, and rely on bilateral brain areas related to articulation to assist word production.

This is in accordance with Gold and Kertesz (2000) who assume that RH contributions to aphasia recovery are task-dependent, i.e. RH activation can compensate for lexical–semantic processing but not for more left-lateralised phonological processing (see also Fridriksson et al., 2009). Indeed, S-patients specifically activated right frontal areas before therapy, which have been found for sentence/text and semantic processing in healthy participants (Vigneau et al., 2011). However, previous results indicate that right IFGtri activation, as found for S-patients, may be associated with low performance, while compensation in right IFGoper might be favourable (Crosson et al., 2007; Naeser et al., 2005; Winhuisen et al., 2005). Thus- pre-activation for S-patients might be attributed to their erroneous naming responses, i.e. their semantically-related errors.

5. Conclusion

The present study intended to investigate the neural underpinnings of model-oriented therapy of word production. Six patients with phonological and 8 patients with semantic disorder according to the Dell model received a 4-week cueing-therapy that was evaluated employing behavioural and neural responses assessed in an fMRI naming task.

Behaviourally, the group of patients showed significant training and generalisation effects, corroborating previous findings. Our intra-individual comparison of impairment-specific therapy outcomes revealed that phonological disorders in aphasia after stroke profit from more specific, impairment-based therapies of word production, while semantic disorders benefit from treatment of the lexical system as a whole by means of semantic and phonological therapy.

Functional brain imaging revealed (1) that the left inferior frontal gyrus, pars opercularis, was a positive predictor of therapy gains, while the right caudate was a negative predictor. Moreover, less decrease in left-hemisphere temporo-parietal language areas was positively related with therapy gains. Results again undermine the importance of LH core language regions for successful aphasia recovery, even though in the aphasic population there appears to be high variability regarding the presumably optimal language region for reorganisation.

(2) As expected, there were higher demands for trained compared to untrained items in a language-related region (left STG); however, the general familiarity of trained items appears to have influenced the activation pattern: For trained items, the application of strategies (left precuneus), reliance on monitoring (right caudate) and feedback (left STG), as well as access to articulatory patterns (bilateral thalamus) seem to be characteristic. The involvement of right caudate before training and in the course of recovery might reveal the important role of word suppression and monitoring in aphasia recovery.

(3) We observed, as predicted, differential modification of semantic and phonological brain areas related to therapy methods: Semantic cueing hierarchies resulted in continuous involvement of superior parietal lobule which might be attributed to working memory processes. Phonological hierarchies led to continuous recruitment of areas presumably related to visual–semantics (e.g., bilateral mid cingulate, left calcarine, right precuneus, right hippocampus), control processing (left middle/superior frontal gyrus), and monitoring (bilateral anterior cingulate gyrus). Therefore, during naming of previously cued items, the semantic or phonological word features and processing strategies seem to be retrieved at ease, while untrained aspects still remain demanding.

(4) Finally, we were able to detect differential compensation for both patient groups. P-patients appear to focus on preserved phonology-related processes in left inferior frontal gyrus, pars opercularis, due to training. As predicted, S-patients relied strongly on right-hemisphere compensation, namely in presumably semantically-related right frontal areas involving inferior frontal gyrus, pars triangularis. Due to therapy, they appear to expand their strategic competence in response monitoring (left STG and caudate) and articulation (e.g., left paracentral lobule, right rolandic operculum).

Our results for the first time revealed specific effects over and above the usually reported general therapy effects in the left hemisphere, performing direct comparisons between item sets and patient subgroups in an fMRI group analysis. We found distinct activation patterns for training effects as compared to generalisation, for differential therapy effects, as well as for type of impairment. Results may have consequences for planning model-oriented therapy: It reveals that linguistic information delivered to assist word production as well as monitoring competence and strategies addressed during therapy might remain associated with the word, and this may cause its improved access long-term. On the contrary, those aspects not addressed during therapy later on might need to be gathered with effort. Moreover, it seems that P-patients need to rely on preserved left-hemisphere competence in phonology, while S-patients might exploit right-hemisphere semantics and refer to monitoring and articulatory processes.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2014.03.010.

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