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Research Report

Interhemispheric interactions during sentence comprehension in patients with aphasia

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ABSTRACT

Right-hemisphere involvement in language processing following left-hemisphere damage may reflect either compensatory processes, or a release from homotopic transcallosal inhibition, resulting in excessive right-to-left suppression that is maladaptive for language performance. Using fMRI, we assessed inter-hemispheric effective connectivity in fifteen patients with post-stroke aphasia, along with age-matched and younger controls during a sentence comprehension task. Dynamic Causal Modeling was used with four bilateral regions including inferior frontal gyri (IFG) and primary auditory cortices (A1). Despite the presence of lesions, satisfactory model fit was obtained in 9/15 patients. In young controls, the only significant homotopic connection (RA1-LA1), was excitatory, while inhibitory connections emanated from LIFG to both left and right A1's. Interestingly, these connections were also correlated with language comprehension scores in patients. The results for homotopic connections show that excitatory connectivity from RA1-to-LA1 and inhibitory connectivity from LA1-to-RA1 are associated with general auditory verbal comprehension. Moreover, negative correlations were found between sentence comprehension and top-down coupling for both heterotopic (LIFG-to-RA1) and intra-hemispheric (LIFG-to-LA1) connections. These results do not show an emergence of a new compensatory right to left excitation in patients nor do they support the existence of left to right transcallosal suppression in controls. Nevertheless, the correlations with performance in patients are consistent with some aspects of both the compensation model, and the transcallosal suppression account for the role of the RH. Altogether our results suggest that changes to both excitatory and inhibitory homotopic and heterotopic connections due to LH damage may be maladaptive, as they disrupt the normal inter-hemispheric coordination and communication.

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1. Introduction

This study examines the role of interhemispheric connections in recovery from aphasia. One of the most prevalent questions in brain plasticity research considers the involvement of the right hemisphere (RH) in recovery from aphasia and specifically whether it plays a compensatory or maladaptive role in language processing after stroke. This question has clinical implications as well as theoretical significance for the understanding of brain lateralization in healthy individuals, and of mechanisms underlying brain plasticity after unilateral damage.

The adaptive account suggests that increased RH activation in post-stroke patients reflects compensatory recruitment of intact regions homologous to the lesioned areas, facilitating language processing and thus enhancing recovery (Abo et al., 2004; Blasi et al., 2002; Cappa et al., 1997; Winhuisen et al., 2005). In contrast, other studies argue that the RH involvement in language processing in post-stroke patients is maladaptive (Postman-Caucheteux et al., 2010) and is the result of a release from transcallosal lateral inhibition (Heiss et al., 2003; Naeser et al., 2004; Price & Crinion, 2005). According to this view, excitatory activity in the left hemisphere (LH) of the intact brain suppresses homotopic areas in the contralateral hemisphere via transcallosal pathways, resulting in the typical left lateralized pattern of activation in language tasks (Kinsbourne, 1974, pp. 239–259). When the LH is lesioned, transcallosal inhibition on the RH is released, resulting in increased RH activation (Selnes, 2000; Thiel et al., 2006). In turn, this increase in RH activation suppresses homotopic areas in the LH via transcortical inhibition, further interfering with language performance and impeding recovery (Naeser et al., 2004; Price & Crinion, 2005). However, it should be noted that maladaptive involvement of the RH in post-stroke aphasia is not necessarily mediated by direct transcallosal inhibition on LH homotopic regions. A negative effect of RH activity on language performance can also be a result of inefficient processing occurring in the RH and interfering with LH processing through excitatory coupling of both homotopic and heterotopic connections (Chiarello & Maxfield, 1996; Clarke et al., 1993). Therefore, directly measuring interhemispheric connectivity is important for understanding the role of the RH in aphasia recovery. Recently, several studies have measured task-related interhemispheric connectivity in patients with aphasia (Kiran et al., 2015; Meier et al., 2016; Schofield et al., 2012; Teki et al., 2013), and focused on naming tasks or on single word judgment tasks. In contrast to these tasks, which are typically left lateralized, sentence comprehension relies on bilateral activation in healthy individuals (Friederici, 2011; Price, 2010; Vigneau et al., 2011). Differences in lateralization between tasks are very likely to affect the value, strength, and direction of interhemispheric interactions in both healthy and brain damaged individuals (Price & Crinion, 2005). The current study examines interhemispheric connectivity in a sentence comprehension task performed by patients with chronic aphasia, seeking to clarify the role of the RH in language recovery.

Numerous neuroimaging studies show enhanced RH activation during language tasks in patients with aphasia following LH lesions (Abo et al., 2004; Basso et al., 1989; Blank et al., 2003; Buckner et al., 1996; Calvert et al., 2000; Gold & Kertesz, 2000; Ohyama et al., 1996; Rosen et al., 2000; Thulborn et al., 1999). The finding that such RH activation is correlated with better language performance in patients (Abo et al., 2004; Blasi et al., 2002; Cappa et al., 1997; Winhuisen et al., 2005) supports the view that the RH plays a compensatory role in language recovery. Furthermore, it was shown that compensatory changes in RH activation following language therapy in these patients are more likely in RH regions homologous to the LH lesion (Abel et al., 2015).

In contrast to these findings, other neuroimaging studies suggest that recovery-related language reorganization in patients with aphasia occurs only in perilesional areas in the LH, while RH activation during language tasks is an epiphenomenon which does not contribute to performance (Heiss et al., 1997; Rosen et al., 2000; Thiel et al., 2001; Warburton et al., 1999). Moreover findings showing that RH activation is associated with incorrect naming responses in patients with LH lesions suggest that RH activation is not only unnecessary but is actually interfering with language recovery (Fridriksson et al., 2009; Postman-Caucheteux et al., 2010). Other studies suggest that RH activation may play a compensatory role, but may occur in different non-homologous regions, reflecting the use of an alternative cognitive strategy rather than homologous disinhibition. For example, a magnetoencephalography (MEG) study that used a sentence comprehension task showed that although aphasic patients activated RH areas homologous to the temporal lobe region in which lesions predicted comprehension deficits, functional activation was correlated with performance not in that homologous region but rather in bilateral dorsal fronto-parietal regions (Meltzer, Wagage, Ryder, Solomon, & Braun, 2013).

The apparent contradiction between findings supporting the compensatory or the maladaptive accounts may be settled by other explanatory factors such as the time since injury (Fernandez et al., 2004; Saur et al., 2006), the specific RH regions involved (Crosson et al., 2007), or the nature of the tasks used for measuring language recovery (Heiss et al., 2003; Price & Crinion, 2005). Price and Crinion (2005) suggest that RH activation is compensatory in speech comprehension tasks (Sharp et al., 2004), but plays a maladaptive role in speech production tasks (Fernandez et al., 2004; Heiss et al., 1997; Postman-Caucheteux et al., 2010; Rosen et al., 2000; Saur et al., 2006).

Neuroimaging studies using PET and FMRI can only provide correlational findings, so even a negative correlation between RH activation and language recovery across participants does not provide causal evidence for a maladaptive role of the RH. Increased RH involvement may be the consequence of a more severe or extensive LH damage which results in a poor outcome for recovery not directly caused by the RH (Heiss et al., 1997; Karbe et al., 1998). In contrast, numerous transcranial brain stimulation studies in the last decade overcome this weakness by showing a causal effect of RH inhibitory or excitatory stimulation on language function within subjects (Baker et al., 2010; Floel et al., 2008; Monti et al., 2008; Naeser et al., 2005; Sandars et al., 2016; Winhuisen et al., 2005). For example, a meta-analysis of 9 randomized control trials, including 215 patients with post-stroke aphasia, tested the effect of inhibitory stimulation with low frequency repetitive Transcranial Magnetic Stimulation (rTMS) or cathodal Transcranial Direct Current Stimulation (tDCS) over the right hemisphere as an adjunct to speech language therapy (Otal et al., 2015). The results show a significant improvement in naming accuracy across studies, suggesting that these RH areas play a maladaptive role in naming in patients with aphasia, so that inhibiting them can improve performance. However, even within naming studies the results are not always consistent. For example, results of a study showing that anodal tDCS (an excitatory stimulation technique), rather than cathodal tDCS over the right temporo-parietal cortex improves naming in patients with aphasia (Floel et al., 2011), are more consistent with a compensatory role for some regions in the RH.

Speech comprehension studies show even more variable results. A meta-analysis across 160 patients shows that low frequency rTMS over the right IFG improves performance in various language tasks including speech comprehension (Ren et al., 2014). However, other studies using rTMS over the right IFG do not find clear evidence for improvement in speech comprehension tasks (Li et al., 2015; Thiel et al., 2013). Interestingly, a tDCS study using cathodal (inhibitory) stimulation to the right superior temporal gyrus as adjuvant to therapy, found improved auditory verbal comprehension in subacute stroke patients (You et al., 2011), highlighting possible differential effects for different anatomical areas within the RH.

It is important to remember that even causal evidence from transcranial stimulation studies showing that inhibiting the RH leads to improvement in language performance does not explain how the RH plays this maladaptive role in recovery. A case study of a patient with a LH lesion reported evidence of both compensatory and maladaptive effects of the RH within the same patient (Turkeltaub et al., 2012). Although the patient's performance improved after suppression of the right IFG pars Triangularis using rTMS, a subsequent lesion to the RH resulted in worsening of the aphasia, suggesting that while some RH regions may support recovery, others interfere with it. Importantly, the study showed that the improvement in performance following rTMS to the right Triangularis was associated with reduced activation in the right Triangularis, but with no increase in activation in the LH. These results are not consistent with the hypothesis that transcallosal suppression induced by RH regions on perilesional regions in the LH underlie the maladaptive role of the RH in recovery (Naeser et al., 2004; Price & Crinion, 2005). An alternative hypothesis is that the output from ineffective processing in the RH is integrated with the information processed in the LH through excitatory coupling, thus reducing performance (Chiarello & Maxfield, 1996). In order to find more direct evidence for transcallosal suppression or other mechanisms underlying the recruitment of the RH in patients with aphasia it is therefore necessary to examine inter-hemispheric connectivity in this population.

Resting state connectivity studies in healthy individuals are based on the assumption that positive connectivity reflects coordination and integration between hemispheres whereas negative connectivity reflects segregated or competing systems (Fair et al., 2007; Fox et al., 2005; Gee et al., 2011)). Although several studies examined intra- and inter-hemispheric functional connectivity in post stroke patients with aphasia (Griffis et al., 2016; Kiran et al., 2015; Marcotte et al., 2013; Meier et al., 2016; Schofield et al., 2012; Teki et al., 2013), there is still no clear evidence that RH activation in these patients results from a release from transcallosal inhibition induced by the LH, or that RH regions suppress perilesional areas in the LH. An association between decreased activation in the LH and increased activation in the RH in patients with LH lesions was demonstrated in a SPECT study (Uruma et al., 2010). This association was also demonstrated in an fMRI study measuring activation during a verb generation task in chronic stroke patients with aphasia (Griffis et al., 2016). The results showed that theta-burst stimulation enhancing activation in left IFG was associated with decreased activation in right IFG and decreased connectivity from right to left IFG. Activation in right IFG was negatively correlated with improvements in a fluency task following stimulation suggesting that activation in right IFG and its input to left IFG are maladaptive for word generation.

In the area of speech perception, inter-hemispheric connectivity following LH lesion was measured by two studies that focused on low level auditory and temporal cortices. An fMRI study showed enhanced reliance on the RH when patients with auditory comprehension deficits following LH lesions listened to word pairs (Schofield et al., 2012). Patients showed weaker bidirectional connectivity between right and left primary auditory cortices (A1) compared to controls, and asymmetric right to left excitatory connectivity at the level of the planum temporale, suggesting increased reliance on the RH. A MEG study with LH lesioned patients performing a phonemic task (Teki et al., 2013) also showed evidence for greater reliance of patients on the RH, but this was reflected in stronger connectivity in the other direction (from the lesioned to the contralesional A1 LA1 − RA1) in patients compared to controls. Importantly, patients also showed a negative correlation between performance on a phonemic discrimination task and left to right connectivity (LSTG − RSTG) (Teki et al., 2013). Although these results suggest that the involvement of the RH is not beneficial for phonemic processing, they do not constitute evidence for transcallosal inhibition.

The present study examined the role of inter-hemispheric connectivity in language performance in patients suffering from aphasia following LH lesion, in order to shed light on the mechanisms underlying compensation and recovery of language function. Previous studies that found negative correlations of performance with RH activation (Postman-Caucheteux et al., 2010), and improved performance after inhibiting RH regions (Otal et al., 2015; Ren et al., 2014) suggested that these effects can be explained by transcortical suppression between homotopic regions, but there has not been direct evidence for interhemispheric suppression from functional connectivity studies. In the present study, we measured interhemispheric connectivity using fMRI during a sentence comprehension task, which typically relies on both hemispheres (Friederici, 2011; Price, 2010; Vigneau et al., 2011), and is therefore expected to show strong inter-hemispheric connectivity in both patients and controls. Inter- and intra-hemispheric connectivity was examined in a network comprising four regions of interest involved in sentence comprehension in typical adults, namely bilateral A1, and bilateral IFG. In order to identify the direction of the effects (right-left *vs* left-right) we used Dynamic Causal Modeling (DCM) analysis, which quantifies task-dependent effective connectivity (Friston et al., 2003).

Previous studies have shown increased involvement of the RH in language processing in patients compared to controls and suggested that this is a result of release from transcallosal inhibition exerted from the LH on homotopic regions in the RH, especially in IFG (Heiss et al., 2003; Naeser et al., 2004; Price & Crinion, 2005). If the transcallosal inhibition account of RH activation is true, we would expect two main findings: First, 1a) stronger negative connectivity from the LH to RH in controls compared to patients. 1b) Release from this inhibition in patients would be negatively correlated with behavior, so we expect a negative correlation between LH-to-RH connectivity and behavior. Second, 2a) we expect stronger inhibition emanating from the RH to the LH in patients compared to controls. 2b) This RH to LH inhibition is expected to be maladaptive so RH-to-LH connectivity should be positively correlated with behavior in patients. Our third hypothesis, which is not based on the transcallosal suppression account, is specific to the primary auditory cortices. Previous studies that examined speech perception tasks in patients showed a compensatory role for lower level auditory processing regions in the RH (Schofield et al., 2012; Teki et al., 2013). We therefore expect: 3a) excitatory RA1-to-LA1 connectivity, which will be stronger in patients compared to controls, and 3b) this RA1-LA1 connectivity would be positively correlated with behavior.

2. Materials & methods

2.1. *Participants*

Patient and control participants in this study also participated in a previously published MEG study using a similar task (Meltzer et al., 2013). FMRI data was collected for twenty patients with aphasia. Each had suffered a single left-hemisphere ischemic stroke at least six months previously, resulting in mild to moderate aphasia confirmed by a research Speech-Language Pathologist. Five participants were excluded due to insignificant activation in at least one of the regions of interest. Of the remaining fifteen participants, nine (ages 34–71, mean = 55, five females) showed adequate model fit (>10%) and were included in the final DCM analysis. DCM analyses from the full group of fifteen patients are also reported to confirm that the results from the included and full groups do not differ. Table 1 presents participants' lesion extents relative to the volume of the left hemisphere, their performance on standardized language assessments, and performance on the experimental task for the nine patients included in the final DCM analysis and the six excluded due to low model fit. Fig. 1 presents the lesion overlap of these groups of patients. No differences were found between the two groups of patients in lesion size, demographics or any behavior measures.

Twenty-four young adults participated in the study as a control group. fMRI activation data from the young adults were previously published in Meltzer, McArdle, Schafer, & Braun (2010). Five participants were excluded due to insignificant activation in at least one of the regions of interest and one participant was excluded due to poor model fit; the data from 18 young adults (ages 22–36, mean = 27, nine females) were entered into the final analysis. Seven age-matched controls also participated in the study. Two participants were excluded due to insignificant activation in at least one of the regions of interest; the data from five age-matched controls (ages 42–49, mean = 46, four females) were entered into the DCM analysis. All five of these age-matched control participants had adequate model fit in the DCM analysis.

2.2. *Behavioral assessment*

Prior to the fMRI experiment, all aphasic and age-matched control participants were administered an extensive test battery to assess behavioral deficits, including the Western Aphasia Battery (WAB) (Kertesz, 1982), selected tests from Psycholinguistic Assessments of Language Processing in Aphasia, (PALPA) (Kay et al., 1992) and the Object & Action Naming Battery (Druks & Masterson, 2000). Three composite scores were computed from the different subtests and are reported in Table 1. Table 1 also reports participants' scores on the Auditory Verbal Comprehension (AVC) subtest of the WAB, used as a general measure of comprehension ability. Finally, for an offline measure of grammatical sentence comprehension, we administered a sentence picture matching task consisting of 40 sentences of various structures (Psycholinguistic Assessment of Language- PAL; Rochon et al., 1994). This task resembles the task performed in the scanner but samples a wider range of syntactic structures. Further details on the behavioral tests can be found in Meltzer et al. (2013). The kind of aphasia for each participant was classified by a professional speech-language pathologist (author JR from Meltzer et al., 2013), on the basis of the WAB guidelines and clinical impression. Clinical diagnosis was not influenced by lesion location. Performance on all language measures was at ceiling for age-matched controls. Young controls did not undergo cognitive testing, but performed at or near ceiling on the experimental task conducted in the scanner.

2.3. *FMRI task*

Patients performed a sentence picture-matching task during fMRI scanning, providing a measure of BOLD activity related to comprehension of sentences. Complete details of the sentence and picture materials can be found in our previous report from young healthy controls, which used the same paradigm (Meltzer et al., 2010). The experiment manipulated two factors, syntactic complexity and semantic reversibility, but the current analysis focused only on general sentence comprehension, and collapsed across all trial types. Reversible sentences involved humans as both subjects and objects and were constructed so that both were plausibly interchangeable (e.g., “The boy is pushing the girl” or “The girl is pushing the boy”). Irreversible sentences on the other hand involved a human and an inanimate object, and thus the subject and object were not plausibly interchangeable (e.g., “The boy is eating a sandwich”). The Syntactic complexity factor included three types of sentences that increased in difficulty by using embedded clauses and manipulation of agent-patient word order: simple active sentences ("The boy is

Table 1 – Characteristics of individual patients. Patients included in the DCM analysis and those excluded due to low model fit are presented separately.

Group	Patient ID	Age	Gender	Years post-stroke	Education	Repetition composite/100	Lexical receptive composite/100	Lexical expressive composite/100	PAL sentence-picture matching/40	WAB: AVC/200	% Left cortex damage	% LIFG ROI damage	% LA1 ROI damage	SLP	Chance-corrected task performance
Included patients	PI	71	F	7.3	17	68	98	87	35	183	19%	37%	87%	mild-moderate anomic aphasia	91%
	P2	71	F	24	18	65	95	96	37	182	15%	31%	97%	mild conduction aphasia	3%
	P3	47	F	1.2	17	79	93	96	27	175	23%	0%	95%	mild anomic aphasia	49%
	P4	50	M	2.3	17	80	88	98	32	182	8%	0%	90%	mild anomic aphasia	59%
	P5	56	M	2.6	20	88	97	95	38	166	7%	0%	67%	mild-moderate anomic aphasia	63%
	P6	62	F	2.1	14	86	87	84	27	161	6%	0%	60%	moderate anomic aphasia	42%
	P7	71	M	5.3	19	84	95	97	36	200	4%	0%	32%	mild anomic aphasia	61%
	P8	34	M	1.3	18	96	97	99	35	191	1%	0%	16%	very mild anomic aphasia	76%
	P9	34	F	5.2	18	68	98	99	38	199	10%	0%	96%	mild anomic aphasia	58%
Excluded patients		51	F	6.3	13	65	94	96	36	187	16%	1%	91%	mild nonfluent aphasia	52%
		53	M	2.8	13	92	93	95	28	180	1%	0%	10%	mild to moderate fluent aphasia	45%
		59	M	10.4	16	97	98	97	37	200	1%	0%	35%	mild anomic aphasia	63%
		39	M	10.4	17	60	97	98	28	193	23%	0%	92%	mild anomic aphasia	48%
		49	F	1.8	15	98	94	94	32	193	0%	0%	34%	mild anomic aphasia	73%
		48	M	2.8	12	95	94	93	31	190	11%	2%	95%	mild anomic aphasia	37%

Repetition composite score: Average of scores from the Nonwords Repetition subtest (#8) of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) and Sentence Repetition subtest of the Western Aphasia Battery (WAB).
Lexical receptive composite score: Average of scores from the Auditory Word Recognition subtest of the WAB and three subtests of the PALPA (#5, Auditory Lexical Decision, #47, Spoken Picture Matching, and #49, Auditory Synonym Judgment).
Lexical expressive composite score: Average scores on Object Naming subtest from the WAB, and the Druks and Masterson Action and Object naming batteries.
PAL sentence-picture matching: A measure of sentence comprehension taken from the *Psycholinguistic Assessment of Language*.
WAB:AVC: Score of the Auditory Verbal Comprehension subtest from the WAB.
% of left cortex damage: Computed based on the overlap between Left Hemisphere Cortex mask and individual lesion masks warped into MNI space.
% of LIFG ROI damage: Computed based on the overlap between the 10 mm LIFG ROI centered on the group activation peak and the individual lesion warped into MNI space.
% of LA1 ROI damage: Computed based on the overlap between the10 mm LA1 ROI centered on the group activation peak and the individual lesion warped into MNI space.
Aphasia diagnosis: Given by a speech pathologist (author JR from Meltzer et al., 2013).
Chance-corrected task performance: These scores are chance corrected with the formula [1 − 2 (proportion incorrect)], yielding performance ranges from 0 (chance) to 100%; scores below chance are negative. The condition of reversible object-embedded clause-containing sentences is excluded from the behavioural measure, as aphasic patients performed consistently at chance in this condition (Meltzer et al., 2013).

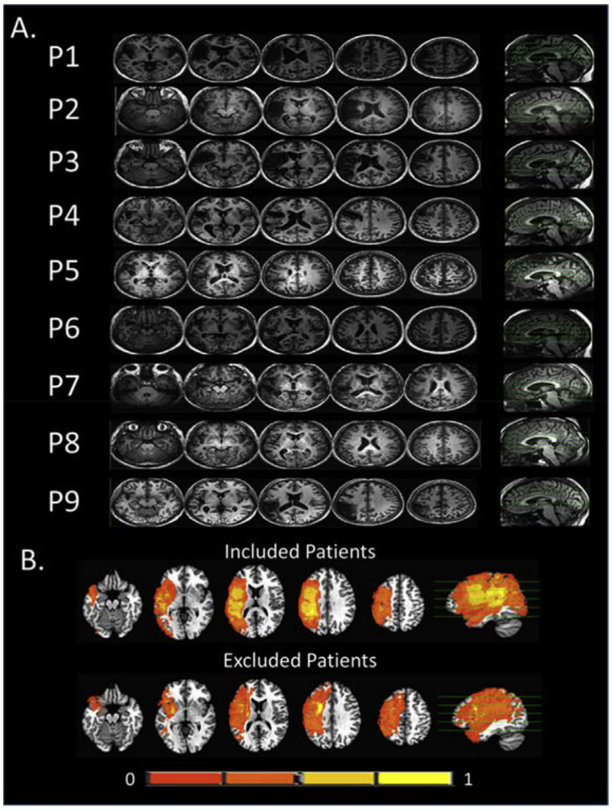

Fig. 1 – Lesion extent and locations. A. Lesions of the nine patients included in the DCM analysis. B. Lesion overlap across patients included in the DCM analysis and across those excluded due to low model fit. Values are standardized according to the sample size within each group; 1 = location is lesioned in all patients within the group.

pushing the girl out of the way"), subject-embedded relative clauses ("The boy who is pushing the girl wants to win the race"), and object-embedded relative clauses ("The girl who the boy is pushing wants to win the race"). Altogether, there were six sentence types (2-reversibility x 3-complexity), but all contrasts reported in the current study collapsed across them.

In the sentence picture-matching task, participants first heard a spoken sentence and then viewed 2 pictures, selecting the matching picture via a button press. Registration of the subject's choice was confirmed by highlighting the selected picture in a green box, but no accuracy feedback was given. For reversible sentences, the 2 pictures featured 1 correct depiction and 1 syntactic foil in which the roles of the 2 people are reversed. For irreversible trials, the foil picture randomly substituted either the agent (the person performing the action) or the patient (the inanimate object acted upon). The experimental design is illustrated in Meltzer et al. (2013) Fig. 1. Patients' overall task performance are presented in Table 1. Performance for the young control group (M = 92.34%, SD = 6.21%) and the age-matched control group (M = 85.75%, SD = 7.88%) were both at ceiling.

In order to separately model the hemodynamic responses related to listening to sentences, and those related to picture selection, despite the fact that these events followed each other in a fixed order, two techniques were used (Miezin et al., 2000). 1) Temporal jitter of 6, 8, or 10 sec was inserted not only between trials but also between sentence and picture presentation within the same trial. 2) Partial trials (Ollinger et al., 2001): only 50% of the sentences were followed by a picture-matching trial. Subjects were informed that a random subset of the sentences would be followed by a picture-matching trial, and instructed to attend to each sentence in preparation for a possible response. Subjects were informed that they could forget about the preceding sentence as soon as a new one began. The "partial trial" method, allows all sentences in a given condition to be treated identically in the statistical analysis, regardless of whether or not they were followed by a picture, as the picture events were modeled separately. Since we were mostly interested in the response to the sentences, the large proportion of partial trials (50%) allowed us to increase the separability between the sentence and picture events, while also increasing the number of presented sentences and the statistical power.

2.4. FMRI acquisition

Whole-brain gradient-echo echo-planar imaging (EPI) data were acquired on a 3-T GE Signa scanner with an 8-channel head coil (repetition time [TR] = 2000 msec, echo time = 30 msec, flip angle = 90,64 × 64matrix, field of view 224 mm, 38 slices, 3.5 mm thick, obliquely aligned to the plane between the anterior and posterior commissures). A 1-mm isotropic magnetization prepared rapid acquisition gradient echo (MPRAGE) image was also acquired. Two hundred and twenty-six volumes were acquired in each run (preceded by dummy scans to achieve steady-state magnetization), with 7 runs total. Auditory stimuli were presented through pneumatic headphones (Avotec, Inc., Stuart, FL) at an individually adjusted volume level.

2.5. Image analysis

Univariate analysis of task activation was performed using the General Linear Model implemented in SPM12b (http://www.fil.ion.ucl.ac.uk/spm). Functional images were spatially realigned to the first volume to correct for head movements. No individual runs had greater than 4 mm of displacement, with an average of 1.2 mm per individual run. 2nd Degree B-Spline interpolation was used to minimize timing errors between slices. The functional images were co-registered with the anatomical image and normalized to the standard T1 template volume (Montreal Neurological Institute). Normalization was accomplished using the updated unified segmentation procedure in SPM12b, which segments, bias corrects and normalizes all in the same model (Ashburner & Friston, 2005). The normalized images were then smoothed with a 6 mm FWHM Gaussian kernel and resliced to an isotropic voxel size of 2 mm.

Statistical analyses at the first level were calculated using an event-related design, in which sentence onsets were modeled as 'miniblocks' rather than point events, with a duration of 3.45 sec, representing the mean auditory sentence length. In order to ensure that miniblocks of this duration would capture even the longer sentences in the experiment we inspected the distribution of sentence duration and found that 90% of the sentences fall between 3.15 and 4.07 sec. Furthermore, a previous analysis of the dataset from young controls using Finite Infinite Response models of the hemodynamic response showed that variability in response size was primarily attributed to the experimental manipulations of sentence type, and not sentence length (Meltzer et al., 2010). We modeled the six linguistic conditions separately: three levels of syntactic complexity x two levels of reversibility (reversible *vs* irreversible sentences).

Following the design of previous DCM studies in post stroke patients (Abutalebi, Rosa, Tettamanti, Green, & Cappa, 2009; Grefkes & Fink, 2011; Radman et al., 2016) our GLM analysis used the canonical HRF without temporal or dispersion derivatives. Hence, although an abnormal HRF in post stroke patient may affect GLM analyses (Bonakdarpour, Parrish, & Thompson, 2007; Fridriksson, Rorden, Morgan, Morrow, & Baylis, 2006), these studies suggest that DCM is more robust to these variations (Grefkes & Fink, 2011; Rehme, Eickhoff, Wang, Fink, & Grefkes, 2011), because its nonlinear convolution model, which is applied separately to each individual region (Friston et al., 2003; Stephan et al., 2007), accommodates responses that are different from the standard canonical HRF (Friston, 2002; Friston, Harrison, & Penny, 2003; Kahan & Foltynie, 2013).

A high-pass filter with a cutoff period of 128 sec was applied. Six motion realignment regressors and six picture onset regressors (for the six linguistic conditions) were included in the model as covariates of no interest. Statistical analyses at the first level were calculated using an event-related design, with the six linguistic conditions as contrasts of interest. Group results were obtained using random effects analyses by combining subject-specific summary statistics across the group as implemented in SPM12b. An all-sentence contrast, which included activation for all sentence types, was entered into the second level analysis to identify peaks for the group. These group analyses were used to determine the location of volumes of interest (VOIs) for the effective connectivity analysis.

2.6. VOI selection

Table 2 presents the MNI coordinates for the four VOIs chosen for the effective connectivity analysis. The bilateral Inferior Frontal Gyri (IFG) were chosen as regions of interest because these regions (on the left hemisphere) are typically involved in sentence comprehension (e.g., Fiebach et al., 2002; Friederici et al., 2003; Meltzer & Braun, 2011), and were strongly activated by healthy participants in this task in a previous study (Meltzer et al., 2010). Moreover, these areas are typical targets for stimulation studies (e.g., Naeser et al., 2004; Price & Crinion, 2005) and are therefore potential sources of transcallosal suppression. Bilateral primary auditory cortices (A1) VOIs were selected as the locations of the auditory driving input. Although the temporo-parietal cortices were also implicated in sentence comprehension, a previous analysis of the data from the young-control group showed that these regions were specifically responsive to the semantically reversible sentences, but not to irreversible sentences (Meltzer et al., 2010). In the current study, because we were interested in measuring intrinsic connectivity associated with basic sentence comprehension across all sentence types we did not include the temporo-parietal cortices.

Table 2 – Spatial coordinates and Brodmann areas for the four VOIs across the three different groups. L = Left, R = Right, IFG = Inferior Frontal Gyrus, A1 = Primary Auditory Cortex, BA = Brodmann Area.

	X	Y	Z	BA
Young controls				
LIFG	−42	14	20	44
RIFG	38	14	22	44
LA1	−54	−20	4	41
RA1	56	−14	2	41
Age-matched controls				
LIFG	−44	6	20	44
RIFG	46	10	16	44
LA1	−56	−22	6	41
RA1	58	−12	4	41
Patients				
LIFG	−48	12	28	44
RIFG	40	14	22	44
LA1	−56	−16	4	41
RA1	58	−12	2	41

To select the IFG and A1 VOIs at the individual level, we first computed the group-level contrast of all sentences *vs* baseline, and thresholded it at a familywise error rate of $p < .05$, according to Gaussian random field theory. All four VOIs showed above threshold group activation for all groups in this contrast. The peak coordinates of activation in the appropriate regions were identified separately for each group. Individual VOIs were 6 mm spheres centered on the individual peak activations in the same contrast from the first level analysis, thresholded at $p < .1$ with a minimum of four active voxels (Richardson et al., 2011), within a 10 mm search radius of the group peak. Anatomical masks defined by the WFU PickAtlas in SPM12b were used to ensure that the IFG VOIs were spatially constrained to the three IFG subdivisions. A 10 mm search radius was chosen to account for the large anatomical variability in patients. Principal eigenvariates of hemodynamic time-series within each 6 mm sphere were used for VOI extraction. Because the utility of DCM analysis depends on the region showing above threshold activation in the relevant contrast, only participants in which all four VOIs showed enough activation were included in the final analysis. Five patients, five young controls and two age-matched controls were excluded due to insignificant activation in at least one of the VOIs.

2.7. Bayesian model selection

Effective connectivity between VOIs was examined using the Dynamic Causal Modeling (DCM) tool in SPM12b. Two sets of parameters were estimated: 1) the direct influence of all sentences on regional activity, and 2) the intrinsic connections between regions across all experimental conditions; (Mechelli et al., 2003). We did not include modulatory effects in the models (as was previously done in other studies (Ethofer et al., 2006).

Sixteen one-state deterministic models were included in model space in order to compare intrinsic interhemispheric homotopic connections between left and right IFG and between left and right A1 (Fig. 2). The models differed in the presence of the four homotopic connections between right and left IFG and between right and left A1; their combinations resulted in 16 models. All other possible connections, including self-connections, intra-hemispheric connections, and heterotopic-interhemispheric connections were fixed across the models. Bi-directional connections between A1 and IFG within each hemisphere are based on solid neuroanatomical evidence for white matter pathways connecting IFG and the posterior dorsal aspect of the superior temporal gyrus (Frey et al., 2014; Petrides & Pandya, 2009). Even though we were more interested in *homo*topic inter-hemispheric connections, we decided not to exclude *hetero*topic connections because there is some evidence for their existence from humans (Brus-Ramer, Carmel, & Martin, 2009; De Benedictis et al., 2016) and other species (Lanz et al., 2017; Swanson, Hahn, & Sporns, 2017). The bilateral A1's were set as the sources of the driving input, because they are primary sensory areas. Participants whose best fitting model did not explain at least 10% of the variance in the data were excluded from the analysis. Six patients and one participant from the young-control group were excluded due to low model fit. The demographic information of these patients and lesion extent are presented separately on Table 1 and Fig. 1.

Model comparison involved random-effects Bayesian model selection (Stephan, Penny, Daunizeau, Moran, & Friston, 2009) which compared the exceedance probabilities of each of the 16 models, separately for each group. The BMS procedure revealed the same winning model for all three groups, the model that includes all four homotopic connections (Fig. 3). Parameter estimates from this model were used in all subsequent analyses.

The individual parameter estimates from the winning model were subjected to one sample *t*-tests separately for each group, which tested the null hypothesis that a given parameter estimate was zero across individuals in the group,

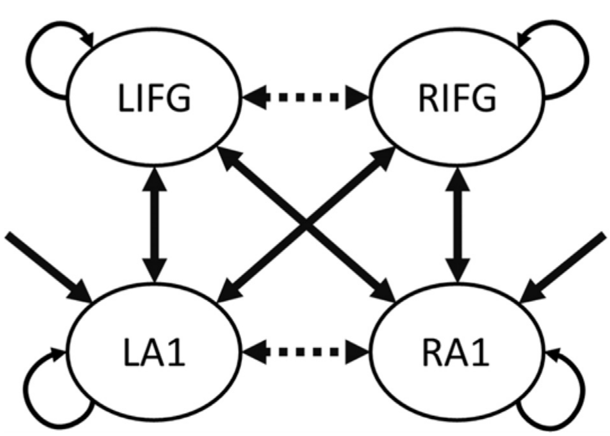

Fig. 2 – Model Space. Arrows indicate the direction of driving input and intrinsic connections. Dashed lines represent the four parameters manipulated across the 16 models; solid lines represent connections that were held constant across all 16 models.

and independent sample *t*-tests to compare between patients and each one of the control groups (Stephan et al., 2010). We then assessed the correlations between these parameter estimates and three independent estimates of language comprehension ability. First, each parameter estimate was correlated with an overall measure of task performance. However, because of the acoustic noise in the scanner, this performance may underestimate participants' ability, as was evident by better performance of these patients in the same task in an MEG experiment (Meltzer et al., 2013). Therefore, correlation was also tested between parameter estimates and two offline measures. The auditory-verbal comprehension score on the Western Aphasia Battery (WAB:AVC) was used as a general offline measure of language comprehension, which was shown to be correlated with performance in the experimental task (Meltzer et al., 2013). In addition, performance on the sentence-picture matching task from the Psycholinguistic Assessment of Language (PAL; Rochon et al., 1994) was used as an offline measure of sentence-picture matching ability. Bonferonni correction was applied to all three sets of tests by multiplying each *p*-value by eight, to account for all eight interhemispheric connections that were correlated with these measures.

3. Results

3.1. *GLM analysis*

The group activation maps from the second level analysis for the contrast of all sentences *vs* baseline in the final analysis are presented in Fig. 4. As expected, given that participants' selection criterion for inclusion in the DCM analysis was above threshold activation in all VOIs, all groups exhibited bilateral perisylvian activation, including in our selected VOIs: bilateral IFG and A1. Fig. 4 also shows a comparison between patients with adequate model fit to be included in the DCM analysis and those with low model fit (<10% variance explained) which were therefore excluded from the analysis. This comparison shows similar activation between the two patient groups.

3.2. *DCM analysis*

3.2.1. *Model selection*

Bayesian model selection of all 16 models showed one consistent winning model for all groups, the model that includes all homotopic connections. The same winning model was evident for the patients even when including the six patients with low model fit. This was also the winning model for age-matched controls, but a second model, one that does not include the LIFG-to-RIFG connection had a comparable exceedance probability. A within-group analysis of parameter estimates for both of these models within age-matched controls yielded the same results, as such, the analyses will focus on the universal winning model across the three groups.

3.2.2. *Parameter estimates*

Parameter estimates from the winning model within each group were subjected to one-sample *t*-tests. Fig. 5a presents

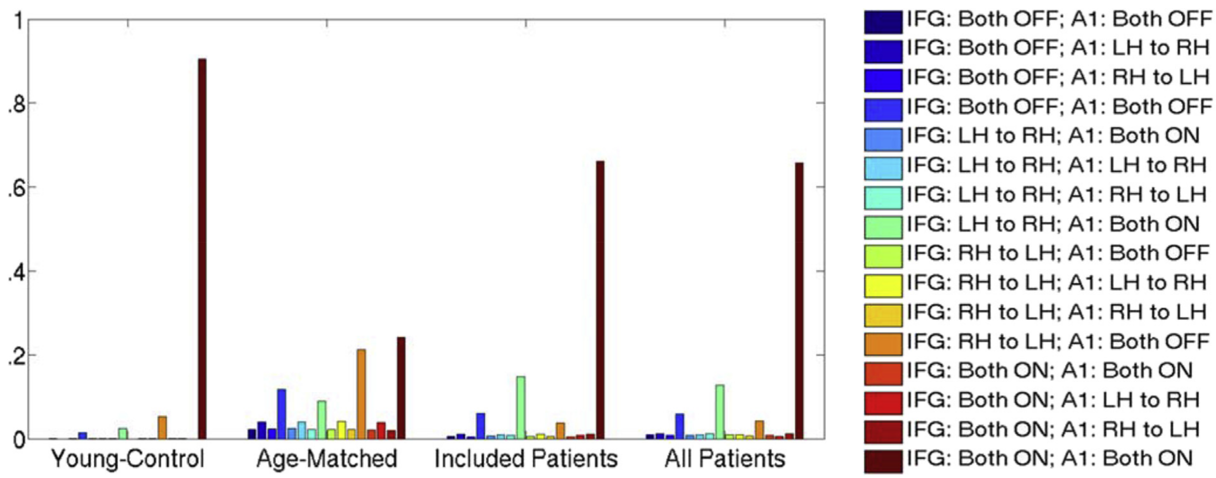

Fig. 3 – Exceedance probabilities of individual models across the three participant groups. Also shown are the results for the group with all fifteen patients including those with low model fit.

significant intrinsic parameter estimates for the young controls; p-values were corrected for sixteen connections (including intra- and inter-hemispheric connections as well as self-connections). None of the between-group comparisons of parameter estimates were significant.

3.2.3. *Driving inputs*

There was significant driving input into the RA1 for both young ($p < .05$, corrected) and age-matched controls ($p < .05$, uncorrected). This driving input was not significant in patients.

3.2.4. *Excitatory connections*

Young controls showed significant excitatory coupling from the RA1 to LA1 ($p < .05$, corrected) and from the LA1 to LIFG ($p < .05$, uncorrected). Neither of these connections were significant in patients and age-matched controls, but their parameter estimates were positive in magnitude.

3.2.5. *Inhibitory connections*

Young controls showed significant inhibitory coupling from the LIFG to LA1 ($p < .05$, uncorrected) and LIFG to RA1 ($p < .05$, corrected). Age-matched controls also showed significant LIFG to RA1 inhibitory coupling ($p < .05$, uncorrected), and non-significant LIFG-LA1 inhibitory coupling. In patients, both LIFG to LA1 and LIFG to RA1 connections were negative but non-significant.

Figure 5 also presents, within the age-matched control and included patient groups, the parameter estimates of non-significant connections that were significant in young controls. The magnitude and sign of these parameter estimates demonstrate that the connectivity pattern in age-matched controls and patients is similar to that of young controls. The lack of statistical significance of these parameters is likely due to the small sample size in the age-matched control group and the inherent variability in the patient group.

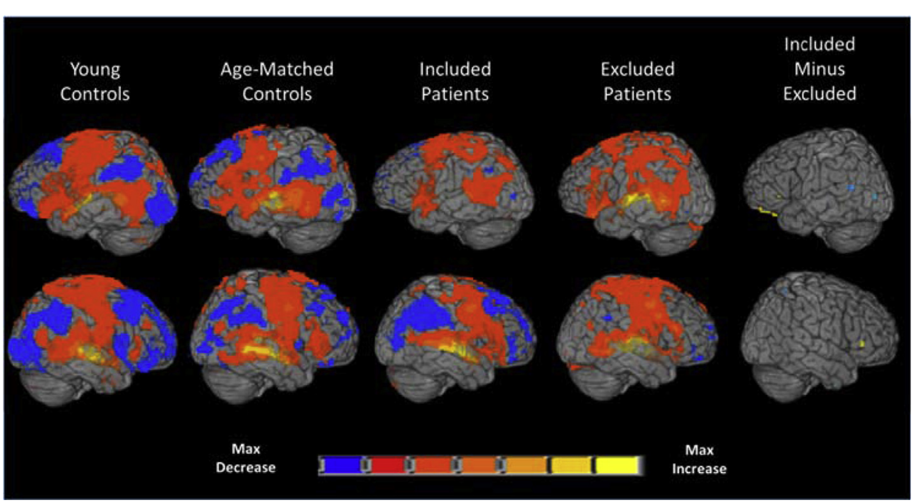

Fig. 4 – fMRI activation maps for all sentence conditions minus baseline within each group and one map contrasting activation between patients included in the DCM analysis and patients excluded due to poor model fit. One-sample t-test within each group is thresholded at p uncorrected <.0001, group comparison: p uncorrected <.005.

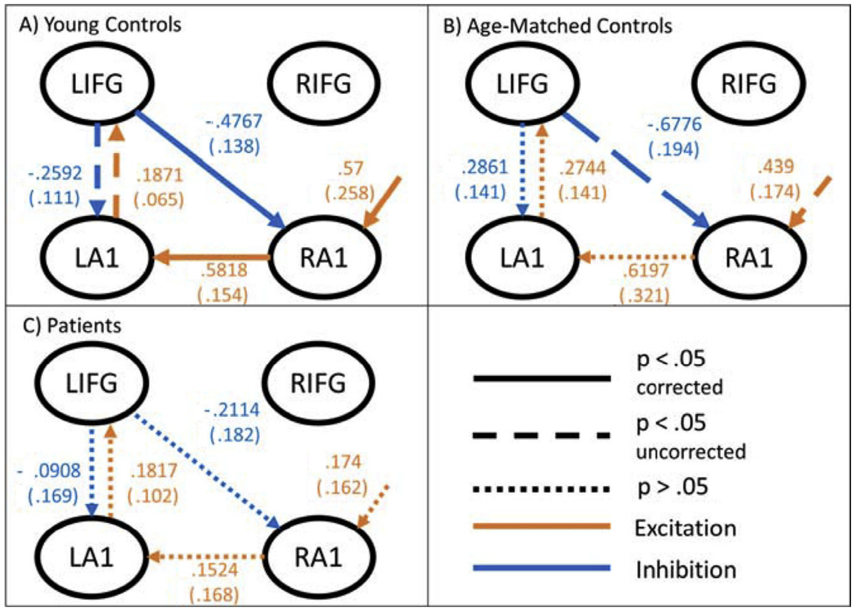

Fig. 5 – Mean parameter estimates (SEM in parentheses) of intrinsic connections from the winning model presented separately for A) young controls, B) age-matched controls and C) included patients. Line type indicates the level of significance. Non-significant parameter estimates are presented for the age-matched control and patient groups for connections which were significant in the young control group. Arrow color represents excitatory (orange) and inhibitory (blue) connections.

3.3. *Correlations of parameter estimates and behavior*

In order to examine the contribution of inter-hemispheric connections to language performance and to recovery from aphasia we tested the correlation between parameter estimates of the eight interhemispheric intrinsic connections in patients with performance in the experimental task and with offline measures of general language comprehension (the WAB:AVC score), and performance on sentence comprehension in a sentence-picture matching task (the PAL score).

Figure 6 presents all significant correlations from the included patient group. Offline sentence picture matching ability (PAL) is negatively correlated with coupling from LIFG to RA1 [r (7) = −.843, $p < .05$, corrected]. To test whether this is unique to the inter-hemispheric connection we also tested the correlation for the equivalent intra-hemispheric connection LIFG to LA1, and found a similar negative correlation [r (7) = −.742, $p < .05$, uncorrected]. General language comprehension, as measured by the WAB:AVC score, is positively correlated with coupling from RA1 to LA1, [r (7) = .672, $p < .05$,

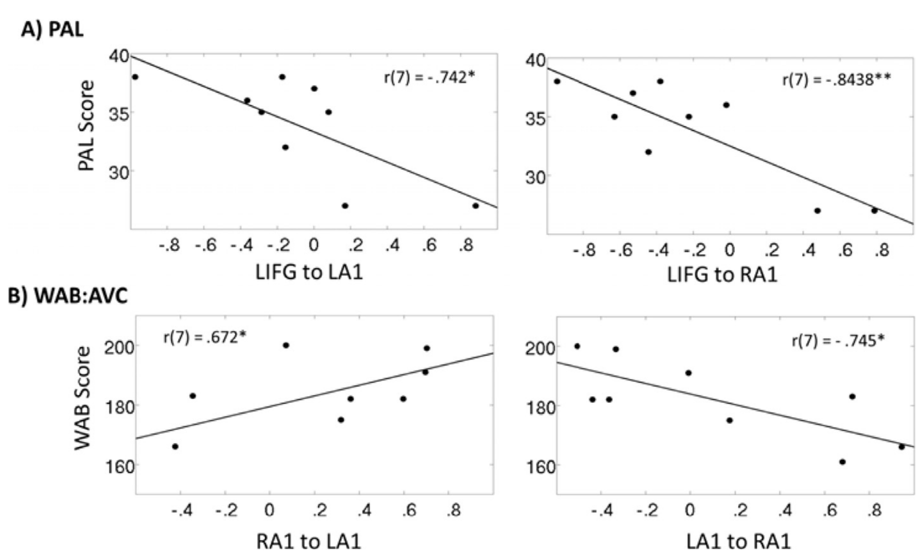

Fig. 6 – Correlations between parameter estimates of intrinsic connections and A) PAL score; B) WAB:AVC score from the included patient group. Correlations are significant at **$p < .05$ (corrected) and * $p < .05$ (uncorrected).

uncorrected] and negatively correlated with coupling from LA1 to RA1, [r (7) = −.745, $p < .05$, uncorrected]. There were no significant correlations between parameter estimates and overall task performance in the scanner.

3.4. *Post-hoc analysis with full patient group*

In order to ensure that our findings were not biased by the exclusion of the six patients with low model fit, we also tested these correlations in the full group of 15 patients. Fig. 7 shows that as with the smaller sample, offline sentence picture matching ability (PAL) is negatively correlated with coupling from LIFG to RA1 [r (13) = −.707, $p < .05$, corrected] and from LIFG to LA1 [r (13) = −.615, $p < .05$, uncorrected]. The connection from RA1 to LA1 is only marginally positively correlated with WAB:AVC [r (13) = .5039, $p < .1$, uncorrected]. However, the negative correlation between LA1 to RA1 coupling and WAB:AVC is stronger in this group, and survived correction for multiple comparison [r (13) = −.680, $p < .05$, corrected].

There were no significant correlations between parameter estimates and overall task performance in the scanner. In summary, the pattern of correlations was very similar between the set of nine patients with adequate model fit, and the full set of 15 patients. As expected, parameter estimates in the six patients with poor model fit were near-zero, which is evident by the group of data points clustered around zero in the *x*-axis in all panels of Fig. 7. The fact that the same correlations were maintained in the larger group increases our confidence in the generalizability of the results obtained from the nine patients with satisfactory model fits.

4. Discussion

The current study examined inter-hemispheric connectivity in patients suffering from chronic aphasia following a LH lesion, during the performance of a sentence comprehension task. The patients were compared to two groups of healthy controls: a young control group and an age-matched control group. Effective connectivity was measured using Dynamic Causal Modeling (DCM) that estimated intrinsic connectivity, which is the connectivity during sentence comprehension in all sentence conditions, driven by input to bilateral A1. All estimated models included two symmetrical pairs of regions in the two hemispheres: A1 and IFG. Sixteen models were compared that manipulated the intrinsic homotopic connectivity between left and right IFG and between left and right A1. Although the winning model, selected for all three groups by the Bayesian model selection procedure included all of the homotopic connections, not all of these connections were significantly different from zero in one sample *t*-tests.

An interesting pattern of intrinsic connectivity emerged in which some connections which were significant in the control groups, also showed correlations with performance in patients. Specifically, the young control group showed a significant driving input into the right A1, from which excitatory information flows into left A1. From left A1 the excitatory bottom-up connection projects into left IFG. Inhibitory top-down connections emanating from left IFG close a feedback loop by projecting into both left and right A1 (see Fig. 5a). The inhibitory interhemispheric connection (LIFG-to-RA1) is also found in the smaller age-matched control group (Fig. 5b). In patients, these connections are not significantly different from zero across the group, but the strength of the same interhemispheric connections is correlated with their individual level of language performance. Specifically, a strong negative correlation was found between the connection from left IFG into right A1 and performance on the PAL sentence-picture matching task, so that high performing patients showed an inhibitory connection, similar to controls, while patients with poor performance show zero or excitatory connectivity. A similar correlation was found in a post-hoc analysis for the intra-hemispheric connection LIFG-to-LA1 (see Fig. 6), indicating that this effect was not unique to the interhemispheric connection. We also found a positive correlation between the homotopic connection from right to left A1 and

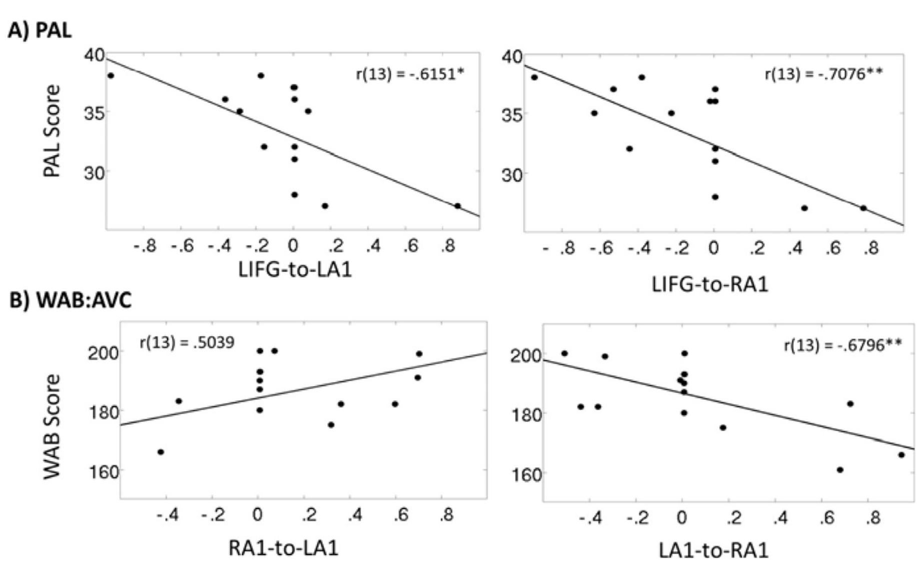

Fig. 7 – Correlations between parameter estimates of intrinsic connections and A) PAL score; B) WAB:AVC score from the full patient group (of 15 patients). Correlations are significant at **$p < .05$ (corrected) and * $p < .05$ (uncorrected).

performance on an independent test of auditory verbal comprehension (WAB: AVC). Here too, patients with good performance showed an excitatory connection, similar to controls, while poor performing patients showed inhibitory coupling. Note that in all of these correlations, the pattern of connectivity in high performing patients was similar to healthy individuals, whereas altered connectivity was associated with poor performance. Finally, patients also showed a negative correlation between language performance (WAB: AVC) and LA1-to-RA1 coupling; high performing patients showed left to right homotopic suppression whereas poor performing patients showed positive coupling from the left to right hemisphere.

The analyses revealed no significant correlations between parameter estimates and overall task performance in the fMRI scanner. It should be noted that the same patients who participated in this study performed much better in a similar MEG experiment using the same task (Meltzer et al., 2013). We posit that noise from the MRI scanner contributed additional difficulty for patients, given previous findings that patients with cortical lesions frequently have exaggerated difficulty understanding speech in noise (Hausler & Levine, 2000). As such, we believe that the offline tests WAB:AVC and PAL are more appropriate measures of language ability. The following sections focus on the connections that showed significant correlations with these offline measures in patients.

4.1. Interhemispheric connectivity between homotopic regions

Our results show no evidence of transcallosal inhibition between *homotopic* regions in controls. On the contrary, young controls show excitatory homotopic connections from RA1 to LA1. This finding is consistent with previous studies showing transfer of sensory information from right to left in language perception tasks (Bitan et al., 2010; Krumbholz et al., 2007; Nowicka et al., 1996). This asymmetric flow of information may reflect transfer of information from the non-language-dominant hemisphere to the language dominant LH for more specialized processing (Gazzaniga, 2000; Hugdahl et al., 1997). The need for such transfer of information from RH to LH may be related to the finding that only the driving input into RA1 was significant, whereas the input into LA1 was not. While the reason for this asymmetry in the driving input is unclear, this finding is robust and consistent with the age matched controls, and with findings from a DCM study showing that the direction of connectivity between primary auditory cortices in speech perception is modulated by different factors including phonetic ones (Specht, Baumgartner, Stadler, Hugdahl, & Pollmann, 2014).

For patients, the connection from RA1-to-LA1 was not significant across the group, but was positively correlated with performance on the WAB:AVC (Fig. 6b). Importantly, patients with good comprehension showed excitatory right to left connectivity, similar to controls, while two patients with poor comprehension showed inhibitory connectivity from right to left A1. This finding is partly consistent with our 3rd hypothesis, which was based on the compensatory account for the RH and predicted that (3a) RA1-to- LA1 connectivity would be stronger in patients compared to controls, and (3b) RA1-to-LA1 would be positively correlated with performance in patients. The excitatory RA1-to- LA1 connection in young controls, and the absence of group differences (no support for 3a) suggest that this excitatory flow of information from RH to LH is part of the healthy process of auditory comprehension, and does not emerge specifically in patients to compensate for the LH impairment. Nevertheless, the positive correlation of this connection with auditory comprehension suggests that this excitatory connection is important for auditory comprehension. This positive correlation is consistent with previous findings (Andoh & Zatorre, 2013) and suggest that cooperation between hemispheres at the level of the auditory cortex is beneficial for auditory verbal comprehension. They are also consistent with a recent speech perception study that reported more positive right to left coupling between auditory VOIs in healthy controls, when compared to aphasic patients (Schofield et al., 2012). It should also be noted that two patients who showed inhibitory RA1-to-LA1 connectivity, also showed poor auditory comprehension. This is consistent with hypothesis #2b, predicting that transcallosal inhibition from RH to LH would be associated with poor performance, although the small number of participants showing this effect mandates caution in interpreting these results.

The current results also showed a negative correlation between LA1-to-RA1 coupling and performance on the WAB:AVC (see Fig. 6b), reflecting poor language comprehension in patients with excitatory LA1-to-RA1 coupling. It should be noted that this connection was not significant in controls. These findings are consistent with a previous study (Teki et al., 2013) showing increased LA1-to-RA1 coupling in patients with aphasia compared to controls, and negative correlations between LSTG-to-RSTG coupling and three tests of phonemic discrimination. These results are partially consistent with the predictions of the transcallosal suppression account (hypothesis #1b) predicting that LH to RH inhibition would be associated with good performance, although there was no difference between groups (namely, there was no support for hypothesis #1a).

Altogether, these results suggest that good verbal comprehension is associated with excitatory coupling from RA1 to LA1, and inhibitory coupling from LA1 to RA1. The opposite is true for impaired verbal comprehension, which is associated with inhibitory RA1-to-LA1 and excitatory LA1-to-RA1 coupling. While these results suggest that excitatory connections from RH to LH can play a facilitatory role in some individuals, they are also partially consistent with the transcallosal suppression account (hypotheses #1b and #2b), indicating that the opposite is true when these are reversed. However, in contrast to previous theoretical accounts of transcallosal suppression (Heiss et al., 2003; Naeser et al., 2004; Price & Crinion, 2005) these results were found at the primary auditory cortices.

4.2. Top-down connectivity

The results of the young control group show inhibitory interhemispheric connections between non-homotopic regions; namely, from left IFG to right A1 and its intrahemispheric counterpart LIFG to LA1 (Fig. 5a). The top-down connection LIFG-to-RA1 is also found in the age-matched control group (Fig. 5b). Moreover, in patients, there was a very strong negative correlation between LIFG-to-RA1 connectivity and performance on the PAL, an offline measure of sentence-picture matching (see Fig. 6a). Namely, patients with good sentence comprehension showed inhibitory connectivity, like controls, while poor performance was associated with zero or excitatory connectivity. A post-hoc analysis showed that this correlation was not unique to the inter-hemispheric connections, but was also found for the intra-hemispheric top-down connection LIFG-LA1.

Several neurobiological language models suggest that top-down connections from left IFG to posterior superior temporal areas play an important role in both speech recognition (Davis & Johnsrude, 2007; Hickok & Poeppel, 2007; Obleser & Kotz, 2010) as well as syntactic processing during sentence comprehension (Friederici, 2012). These top-down connections are typically associated with the Dorsal pathway for language processing (Friederici, 2012; Hickok & Poeppel, 2007). Our findings are in line with these models. These inhibitory top-down connections may be part of a feedback loop through which higher level language areas modulate the sensory input based on prior knowledge and expectation and increase speech clarity (Sohoglu et al., 2012; Wild et al., 2012). The functional connection between IFG and posterior superior cortex could be mediated by cortico-cortical mono-synaptic connections in the Arcuate Fasciculus (AF), or by poly-synaptic connections which involve the second branch of the Superior Longitudinal Fasciculus (SLF-II), the Middle Longitudinal Fasciculus (MLF) and the AF (Frey et al., 2014; Petrides & Pandya, 2009). Our findings add to these models by showing that these top-down connections from left IFG to auditory cortices can be inhibitory, and that this inhibitory top-down connection is a critical component in the network involved in sentence comprehension in both healthy individuals and patients. When this inhibition is released due to LH damage, it is associated with impaired performance.

Our findings also add the surprisingly strong effects for the heterotopic connection LIFG-to-RA1 in both healthy and patient groups. Although some neurobiological language models suggest an important role for the integration of information from both the right and the left hemispheres (Friederici, 2012; Hickok & Poeppel, 2007), it is not clear which pathways are involved in this integration process. While the homotopic and intra-hemispheric connections characterized in this study are associated with well-known fiber tracts, the anatomical basis for heterotopic connections between LIFG and RA1is less certain. One possibility is that these heterotopic connections are comprised of a poly-synaptic pathway, going through a different population of neurons within LA1. A second possibility is a direct heterotopic projection. These are well known to exist in numerous areas of the human brain (de Lacoste, Kirkpatrick, & Ross, 1985) although they have not yet been extensively characterized. Extensive heterotopic connections were found in rodent (Swanson et al., 2017) and monkey connectivity studies (Lanz et al., 2017). Several studies have shown that interhemispheric interactions can be mediated by projections from cortex to contralateral subcortical regions (Brus-Ramer et al., 2009; De Benedictis et al., 2016) raising the possibility that heterotopic connections are mediated by a poly-synaptic pathway that includes heterotopic fiber projections.

It is worth noting that while the homotopic connections between the primary auditory cortices were correlated with a general measure of auditory comprehension (WAB:AVC), the top-down connections from LIFG to the primary auditory cortices were correlated with a more specific measure of sentence comprehension (PAL). One potential interpretation of this difference is that the primary auditory cortices are involved in all types of auditory comprehension tasks, whereas the involvement of the LIFG in syntactic processing may explain the specific relevance of the connections from LIFG to sentence comprehension.

4.3. *Limitations*

The main limitation of the current study is the small number of patients (9) included in the final analysis. Although a much larger sample of 20 patients were scanned, the data from many of them could not be included in the DCM analysis because they showed no activation in at least one of the VOIs (5 patients) or because the best fit model explained less than 10% of the variance in the data (6 patients). These limitations are inherent to the DCM analysis method, and were used to increase the validity of the DCM parameters. In order to ensure that our exclusionary criteria have not biased our results, we compared patients included in the DCM analysis with those excluded from the DCM analysis due to low model fit. No differences were found in lesion size, demographics or behavioral performance on standardized measures or the experimental task. We have also compared the two groups of patients in their activation patterns and found no differences. Furthermore, a separate set of DCM analyses were conducted on all 15 patients with adequate VOI activation, regardless of their model fit. These analyses showed the same results for model selection and parameter estimates as the original analyses with 9 patients. The correlations with behavioral measures were also very similar, with the main difference being that the positive correlation between WAB:AVC and the coupling RA1-LA1 is significant in the original analysis and only marginally significant in the larger group of patients. These results suggest that the exclusion of the six patients with low model fit did not bias our results. Thus while the reason for the failure of model fit in some patients is unknown, these results suggest that our results can be generalized to other patients with similar types of chronic post-stroke aphasia.

Regarding aphasia type, it should also be noted that while many of our patients were diagnosed with anomic aphasia, their performance on the sentence comprehension task in the scanner was varied, as was the extent and location of their lesions. The diagnosis of anomic aphasia may reflect the post-recovery state of other types of aphasia, which may have been evident in more acute stages (Goodglass & Wingfield, 1997). Hence, it is not clear to what extent our results can be generalized to patients with other types of aphasia or in earlier stages of recovery.

4.4. *Conclusions*

While some studies have suggested that the RH has a compensatory role in language recovery (Abo et al., 2004; Blasi et al., 2002; Cappa et al., 1997; Winhuisen et al., 2005), other recent studies suggested that the increased involvement of the RH in language processing in patients with aphasia following LH damage was a consequence of release from left-to-right transcallosal suppression between homotopic regions (Selnes, 2000; Thiel et al., 2006). This model has been supported by animal studies (Buchkremer-Ratzmann & Witte, 1997; Reinecke et al., 1999) and studies of human patients with motor disorders following unilateral brain damage (Rehme et al., 2011; Shimizu et al., 2002), although the role of the unaffected hemisphere in cortical reorganization after stroke is still highly controversial even within the motor domain (Butefisch et al., 2005; Fridman et al., 2004; Gerloff et al., 2006). Within the language domain there is considerable indirect evidence in support of this model, but this comes mainly from studies of naming and word generation tasks (Monti, Cogiamanian et al., 2008; Naeser et al., 2005; Otal et al., 2015) with less consistent support from speech perception studies (Li et al., 2015; Thiel et al., 2013).

Our result are partially consistent with some aspects of both of the above models. The results for homotopic connections show that excitatory connectivity from RA1-to-LA1 and inhibitory connectivity from LA1-to-RA1 are associated with general auditory verbal comprehension. In other words, inhibitory RA1-to-LA1 coupling and excitatory LA1-to-RA1 coupling are associated with poor auditory verbal comprehension, which is consistent with the predictions of the transcallosal suppression account. Nevertheless, no transcallosal suppression from left to right homotopic regions was found for the healthy controls. The results are also partially consistent with the compensation model, in showing that excitatory right to left connectivity is associated with good performance, although this connectivity did not emerge only to compensate for LH damage, as it is also evident in healthy controls. The importance of the right to left excitatory coupling at the level of the primary auditory cortex may be related to the bilateral nature of auditory sentence comprehension tasks.

Finally, our results also show the importance of healthy top-down inhibition through both heterotopic (LIFG-to-RA1) and intra-hemispheric (LIFG-to-LA1) connections for sentence comprehension in post-stroke patients with aphasia. Here too, connectivity in high performing patients is similar to controls, whereas the release of this inhibition due to LH damage is associated with poor sentence comprehension. Although this release of left to right inhibition is consistent with the transcallosal suppression model, here it is evident in the context of heterotopic and intra-hemispheric connections, rather than connection between homotopic regions.

Although these results are correlational, they demonstrate how changes in both excitatory and inhibitory connections between hemispheres can be maladaptive. The collaboration between hemispheres in a typically bilateral sentence comprehension task depends on a specific division of labor and coordination in an intricate network of excitatory and inhibitory interactions between pairs of homotopic and heterotopic regions in both directions. When this balance is disrupted due to damage to the left hemisphere, this results in poor performance.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Appendix

Connection	PAL	WAB:AVC
LIFG to RIFG	.602	.353
LIFG to RA1	−.843**	−.536
LA1 to RIFG	−.274	−.202
LA1 to RA1	−.223	−.745*
RIFG to LIFG	.619	.180
RIFG to LA1	.147	.133
RA1 to LIFG	.560	.112
RA1 to LA1	.213	.672*

Correlations between all 8 possible interhemispheric parameter estimates and two offline measures of performance, PAL and WAV:AVC. Correlations are significant at $^{**}p < .05$ corrected for 8 comparisons and $^{*}p < .05$ uncorrected.

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