Bilingual aphasia and language control: a follow-up fMRI and intrinsic connectivity study

Jubin Abutalebi *, Pasquale Anthony Della Rosa *, Marco Tettamanti *, David W. Green °, & Stefano F. Cappa *

* *Vita-Salute San Raffaele University and Division of Neuroscience, San Raffaele Scientific Institute, Milan; National Neuroscience Institute, Italy*

° *Division of Psychology and Language Sciences, University College London, United Kingdom*

Correspondence to:

Dr. Jubin Abutalebi, Faculty of Psychology, Vita-Salute San Raffaele University, Via Olgettina 58, 20132 Milano, Italy, Tel.: +390226434888, Fax.: +390226434892, e-mail: abutalebi.jubin@hsr.it

ABSTRACT

In a world that is becoming more multilingual, bilingual aphasia is a clinical problem with a major clinical impact. However, at present we lack causal explanations of the many features of recovery patterns and there is no consensus about the language in which the patient should receive speech therapy. Further advance requires an understanding of the dynamics of recovery. In a novel longitudinal, single-case study, we combine fMRI and dynamic causal modeling to examine the effects of specific language treatment for picture naming on the representation and control of language areas during the course of recovery. Improved performance in the treated language was associated with increased activation in language areas. Consistent with theoretical expectations, causal modeling indicated increased connectedness of the control and language networks for the treated language. This functional approach holds great promise for investigating recovery patterns and the effects of specific language treatment in bilingual aphasic patients.

INTRODUCTION

The social impact of bilingual aphasia is becoming a clinical issue of primary importance because modern society is becoming more and more bilingual and multilingual. As a result, the incidence of bilingual aphasia is growing. For the United States, Michel Paradis (2001) estimated, on the basis of census data, that there will be well over 45,000 new cases per annum. A similar or higher figure is to be expected in Western Europe because of immigration flows. Hence, there is a pressing need to understand the causal basis of recovery patterns in bilingual aphasia in order to have a principled basis for treatment. However, we lack such understanding (Paradis, 1995; and see Marrero, Golden, & Espe-Pfeiffer, 2002).

Pitres (1895) was the first to draw attention to the incidence of different patterns of language recovery in bilingual aphasics. In some cases L1 is recovered better than a L2. In other cases, the converse obtains. As pointed out by Ansaldo, Marcotte, Scherer, & Raboyeau (2008) the diversity of recovery patterns is almost endless. However, some form of classification of the most frequently encountered recovery patterns is clinically and theoretically helpful. The commonly used classification of Paradis (1998) includes: 1) differential recovery (as above); 2) selective recovery of a given language (i.e., one language remains impaired while the other recovers); 3) parallel recovery of both languages (i.e., when both impaired languages improve to a similar extent and concurrently; 4) successive recovery (i.e., when complete recovery of one language precedes the recovery of the other); 5) alternating recovery (i.e., the language that was first recovered will be lost again due to the recovery of the language that was not first recovered); 6) alternating antagonistic recovery (i.e., on one day the patient is able to speak in one language while the next day only in the other); and 7) pathological mixing of two languages (i.e., the elements of the two languages are involuntarily mixed during language production), also called blended-recovery.

The population incidence of these distinct patterns is unknown (Green, 2005) but

there are retrospective analyses of case reports. Fabbro (1999) compared the prevalence of two patterns of recovery: parallel and non-parallel; in the latter case, either L1 recovers faster than L2 or vice versa. Overall, 40% of bilingual aphasics experienced parallel recovery, 32% were reported to have a better recovery of L1 than L2, whereas 28% showed better recovery in L2 than in L1. Likewise, Paradis (2001) reported that parallel recovery was the most frequently observed pattern (61%), while differential recovery (18%), blended recovery (9%), selective recovery (7%), and successive selective recovery (5%) were less frequent.

The clinical management of bilingual patients with aphasia raises several unanswered questions. For instance, the scientific community is still discussing if a bilingual aphasic should be rehabilitated only in one language or in both languages. Moreover, it is also not known whether rehabilitation should take place in L1 or rather in L2 (see Paradis, 2004). These questions have immense practical impact. For instance, if there is a total transfer from one language to the other, this would mean that aphasia therapy in communities where only monolingual speech-pathologists are available would nonetheless help both languages. However, given the diversity of the bilingual population, and the variety of patterns of recovery, it is difficult to generalize preliminary results to the whole of this population. As is the case with the non-brain damaged bilingual population (see for review, Perani & Abutalebi, 2005; Abutalebi, 2008), age of L2 acquisition, the relative level of L2 proficiency and exposure may exert an important role in bilingual aphasia (Green & Abutalebi, 2008). Brain damage, as a consequence of the lesion, adds to the complexity as it leads to increased variability. It is vital to develop theoretical approaches that offer the prospect of accounting for patterns of recovery in terms of neuronal mechanisms.

Theoretical accounts of recovery patterns in bilingual aphasia

Theoretical conjectures arising from the study of bilingual aphasia developed along

two distinct lines, a more traditional approach and a more dynamic approach. The more traditional 'localizationist' view argued that the specific loss of one language would occur because the bilingual's languages are represented in different brain areas or even in different hemispheres, and hence, a focal brain lesion within a language-specific area may alter only that specific language leaving the other language intact (Albert & Obler, 1978). The roots of the localizationist approach may be dated back to the early days of the anatomo-clinical approach. Indeed, following the well-known discoveries of Paul Broca (1861), Scoresby-Jackson (1867) postulated that the foot of the third frontal convolution (Broca's area) should be a sort of language organ only for native languages, whereas the remaining part of the convolution might be responsible for L2s. He gave this explanation to account for an aphasic patient who selectively lost the use of his L2 after brain damage. Pitres (1895) argued against this localizationist view on grounds of plausibility. Pitres founded his criticism on Charcot's theory, which assumed the existence of four independent speech centers (articulatory, auditory, graphic, and reading centers). Pitres indicated that, if one is to recognize separate independent centers for each language, then four centers must be admitted for each language. The impairment of one language would then presuppose the existence of four lesion foci, which is unlikely. However, the claim of differential localization for the L2 has dominated neurolinguistics for over a century and its effects are still present when interpreting functional neuroimaging data in bilinguals. In fact, functional neuroimaging studies in healthy bilinguals have so far contradicted the 'localizationist' view (see for review, Perani & Abutalebi, 2005; Indefrey, 2006; Abutalebi & Green, 2007, Abutalebi, 2008; see Paradis, 2004 for a critical overview). The patterns of brain activation associated with tasks that engage specific aspects of linguistic processing are remarkably consistent among different languages. L1 and L2 are apparently processed by the same neural structures. Neural differences from L1 may be observed in the case of a weaker L2 (an L2 that is mastered with a low degree of proficiency) but these are mostly found within the left prefrontal cortex and other areas related to cognitive control such as

the basal ganglia and the ACC. According to a dynamic view, less proficient bilinguals are in need of greater cognitive resources when processing a weaker L2. A less proficient L2 speaker has to inhibit L1 during L2 production, and as argued by Abutalebi & Green (2007), the activity found in areas related to cognitive control during L2 processing may be related to this inhibition.

In contrast, a 'dynamic view' of selective language recovery in those with bilingual aphasia supposes a compromise to the system of language representation and control (Paradis, 1998; Green, 1998; Abutalebi & Green, 2007; Green & Abutalebi, 2008) and is consistent with functional imaging data of normal bilinguals. A selective loss of a language arises because of increased inhibition, that is, of a raised activation threshold for the affected or lost language or even because of an imbalance in the means to activate the language because of the lesion (i.e., the so-called activation threshold hypothesis (Paradis, 1998). Indeed, Pitres (1895) proposed that language recovery could occur only if the lesion had not entirely destroyed language areas, but only temporarily inhibited them through a sort of pathological inertia. The advantage of the 'dynamic' view is that it offers a way to account not only for selective recovery of a language but many reported recovery patterns in bilingual aphasia. As outlined by Paradis (1998), a parallel recovery would occur when both languages are inhibited to the same degree. When inhibition affects only one language for a period of time, and then shifts to the other language (with disinhibition of the prior inhibited language) a pattern of antagonistic recovery occurs (Green, 1986; 1998). Selective recovery would occur if the lesion permanently raised the activation threshold for one language, and pathological mixing among languages would occur when languages cannot be selectively inhibited anymore.

We lack direct neural evidence regarding this dynamic view. However the functional approach of the present study that measures the strength of neural connections during language recovery, offers a way to explore it and shed light on treatment effects.

Language therapy in bilinguals: the neural basis of treatment effects

Several clinical studies have shown that therapeutic interventions targeted on one language transfer to another language, at least to a certain degree (Watamori & Sasanuma, 1978; Filiputti, Tavano, Vorano, de Luca, & Fabbro, 2002; Gil & Goral; 2004; Edmonds & Kiran, 2006). Transfer may be restricted to items similar in both languages (cognates; Kohnert, 2004) or when tasks are used that rely on the same computational strategy for both languages (Laganaro & Overton-Venet, 2001). In contrast, other studies report no transfer (Galvez & Hinckley, 2003; Meinzer, Obleser, Flaisch, Eulitz, & Rockstroh, 2007). It has even been postulated that the non-treated language may be inhibited (Paradis, 1998).

The neural correlates of rehabilitation-induced improvements of aphasia after brain damage remain incompletely understood. An important role of the right hemisphere was suggested by the study of Musso et al. (1999) that used positron emission tomography to examine the neural correlates of intensive verbal comprehension training in a group of aphasics. Post-training comprehension performance was positively correlated with activity in the right homologues of Wernicke's area and of Broca's area. Similar results were reported by Blasi et al., (2002) and Crosson et al., (2005) (see for review, Price & Crinion, 2005). Other investigations in monolingual aphasics, suggest that the engagement of spared left hemispheric regions is also crucial (Belin et al., 1996).

A more direct approach is based on follow-up studies that compare brain activity at different times after stroke or before and after speech therapy (see Small, Kendall Flores, & Noll, 1998, for one of those pioneer studies). The Saur et al. study (2006) indicated that in the initial stages of recovery right homologue area may be more important, while in later stages, the role of left perilesional areas becomes prevailing and is correlated with superior recovery. Vitali et al. (2007) showed that successful anomia training in monolingual aphasics was correlated with left perilesional hemispheric activation, but only if the lesion spared remnant parts of language areas. In the case of extensive destruction

of left hemispheric language areas, the right homologue areas may take over successful recovery (Vitali et al., 2007). A further study (Raboyeau et al. 2008) suggests that during lexical learning the same selected inferior frontal-insular right hemispheric regions are engaged in patients and in normal subjects. Lastly, Meizner et al (2008) reported that the training-induced improvement in picture naming observed in chronic aphasia was mediated by the reactivation of perilesional areas.

In this study we aim to shed more light on this intriguing issue. We address the neural basis of treatment effects on picture naming using fMRI. To date we know of only one published neuroimaging study that examined the effects of short-term intensive language training in one language (Meinzer et al., 2007). The authors reported bilateral activation increases restricted to the trained language. However this study did not employ an event-related fMRI (er-fMRI) method and so the contrast between the trained and the untrained language is potentially compromised by differences in error rate. In the present study we separated out correct and incorrect responses and were also in a position to examine a cross-over in performance between L1 and L2 that provides robust evidence of treatment selective effects.

Our basic supposition was that any improved naming performance in the rehabilitated language will be associated with increased response in areas relevant to picture naming and its control. We therefore combined follow-up er-fMRI with dynamic causal modeling (DCM). The use of the DCM approach may be particularly fruitful since it allows us to investigate whether recovery induced by speech therapy entails changes in connectivity of brain areas involved in language representation and in its control. Our hypothesis was that in the case of selective recovery of the rehabilitated language the strength of connections between areas involved in language and its control should be different for the two languages. One possibility is that the coupling between control regions and regions associated with lexical retrieval and production may be stronger for the rehabilitated language. On the other hand, if both languages recover then the strength of

connections will be similar.

Our fMRI study examined changes in regional response in picture naming as a function of treatment in the second language. It is restricted therefore to the paradigmatic dimension of language use and is silent on sentence level changes, i.e., regional changes associated with recovery at the syntagmatic level (de Saussure, 1916/1983). However, our neuropsychological tests also assessed sentence level processes and we report these data as well.

CASE REPORT

Clinical history

JRC, a 56-year-old right-handed man, was born in Argentina and had formal schooling in Spanish (L1, his first language) until the age of 16, when he and his family emigrated to Italy. At the age of 16 he learnt Italian (L2, his second language) and finished high school in Italy. JRC communicated with his parents and nearest relatives in L1 while L2 was primarily used at work and with friends. As testified by his relatives and his wife, his premorbid oral and written language proficiency was good for both L1 and L2 though the patient was more exposed to his L2.

JRC was admitted to our hospital in mid-June 2005 because of right-sided hemiparesis and severe aphasia due to a cerebral hemorrhage. As shown by MR scanning performed in the acute phase (Figure 1A), the hemorrhage affected the left lenticular nucleus and surrounding areas. Medical history was normal except for untreated hypertension. Clinically, global aphasia developed within a few days into a fluent aphasia, and his main language deficit was a severe anomia that affected both languages to the same degree. During spontaneous speech and during naming tasks, interferences from the non-target language (i.e., from the language not required during examination) were often observed. Finally, in the lesion phase (3 months post-onset), MR scanning was repeated and the full reabsorption of the cerebral hemorrhage was observed (Figure 1B).

In agreement with a three epoch time-frame model of aphasia (Mazzocchi & Vignolo, 1979), language functions were investigated on a temporal basis. In the “acute phase” of the stroke, closely-spaced behavioral follow-up and bedside screenings were performed. During the first two to three weeks post-onset remote functional effects of the hemorrhagic lesion are responsible for the instability of the aphasic picture. More extensive language investigations were performed in the “lesion phase”, at four weeks after the stroke (see experimental study below).

EXPERIMENTAL STUDY

From the beginning of the lesion-phase (>4 weeks post onset) the patient participated in the follow-up experimental study. This study was designed to investigate both the behavioral (by means of neurolinguistic testing) and neural effects (by means of fMRI and DCM analysis) of speech therapy restricted only to one language, and to investigate the possible effects of generalization to the non-treated language. Prior to the study the patient and his wife were asked in which language they would prefer to have speech therapy. Both JRC and his wife agreed that speech therapy should be provided in Italian, the patient’s L2.

1. Behavioral study

On a general intelligence test (Raven’s Coloured Progressive Matrices) the patient had a normal score (33/36). The neurolinguistic test battery consisted of Part B of Bilingual Aphasia Tests (BAT) (Bilingual Aphasia Test, Paradis, 1987) for Italian and Spanish and the Snodgrass Naming battery (Snodgrass, 1980). 90 pictures were used to assess picture naming in L1 and 144 pictures of the Snodgrass battery were used to assess picture naming in L2. We also included in the behavioral study his picture naming performance within each fMRI scanning session. In the fMRI session, we used 80 pictures for L1 and

120 pictures for L2 from the Snodgrass battery (Snodgrass, 1980). Cognates were discarded from the Snodgrass battery both for the behavioral assessment and for the fMRI naming sessions. All tests were administered in both languages to the patient at three different time epochs: T0 (prior to speech therapy), T1 (after the deficit-specific speech therapy that lasted six weeks), and T2 (after the global speech therapy that lasted four months). In order to avoid inducing cross-linguistic phenomena such as switching among languages, each language at each epoch was evaluated in sessions using a single language with an interlocutor fluent in only one of the languages.

The deficit-specific speech therapy carried out between T0 and T1 consisted in training the patient in L2 on a set of 60 pictures that the patient could not name as assessed at T0. Training consisted of repeatedly cueing the patient with the initial syllable of the target word, and subsequently adding missing syllables, until the correct answer was produced. Phonological training was administered daily in 1-hour sessions. After six weeks the patient's naming performance on this set of images was close to 100% correct. In the time period between T1 and T2, a global speech therapy in L2 was carried out. Global speech therapy consisted of the following tasks: word repetition of abstract and concrete nouns, writing of abstract and concrete nouns, synonym generation, antonym generation, fluency tasks, word generation on semantic cues, picture and picture sequence description and naming. This period lasted approximately 4 months with four speech therapy sessions per week each lasting one hour.

2. fMRI study

Experimental procedures & paradigm

We used event-related fMRI (er-fMRI) to study the neural correlates of picture naming performance in L1 and, separately, in L2 prior to speech therapy (T0), after the deficit-specific speech therapy (T1) and after the global speech therapy (T2). Each of the three

sessions consisted of 5 runs comprising 2 runs in Spanish (L1) and 3 runs in Italian (L2). Each run consisted of 40 images to be-named for a total of 80 images for L1 and a 120 images for L2. These images were selected from the Snodgrass battery administered during the first behavioral assessment session and consisted of a number of pictures that the patient could name (35 for L1 and 57 for L2) and pictures that the patient could not name (45 for L1 and 63 for L2). The total dataset consisted of 200 pictures, respectively 80 pictures randomly assigned to each of the two runs for L1 and 120 pictures randomly distributed across the three runs for L2. Items were matched for word length, number of syllables and frequency in Italian and Spanish. Cognates were excluded from the experimental dataset. During er-fMRI acquisitions, all the pictures from the two experimental sets (Italian and Spanish) were visually presented for 4,500 ms and the patient was asked to name them aloud. The ISI (inter-stimulus interval) was jittered (from 2850 ms to 8750ms; mean 4615 msec) according to Dale (1999). Recordings of the oral responses made by the patient enabled us to monitor his performance during scanning.

Image acquisition

The er-fMRI technique used a 3T Intera Philips body scanner (Philips Medical Systems, Best, NL) with an 8 channels-sense head coil, where the sense reduction factor = 2, TE = 30 ms, TR = 3000 ms, FOV = 240 x 240, matrix size = 128 x 128. There were 30 contiguous axial slices per volume (slice thickness = 4 mm) and 136 volumes per each run. Each run was preceded by 10 dummy scans that were discarded prior to data analysis to optimize the signal of the EPI images.

A high resolution structural MRI was acquired for each of the three follow-up scanning sessions (MPRAGE, 150 slice T1- weighted image, TR = 8.32 ms, TE = 4.1 ms; flip angle = 8°, TA = 4.8 min, resolution = 1mm x 1mm x 1mm) in the axial plane. SPM2 (Wellcome Department of Cognitive Neurology, London, UK), running on Matlab 6.5 (Mathworks, Natick, MA) was used for all preprocessing steps and statistical analysis.

Image processing

Slice timing procedures were applied to all EPI images in order to correct for differences in acquisition time between slices. For each scanning session, all volumes were realigned to the first volume of the first run in order to neutralize effects of intra- and intersession movements. The extent and location of the brain lesion for each of the three scanning sessions was defined and visualized on the high resolution structural MRI using the MRIcro software package (Rorden and Brett, 2000). For each structural volume, the area of damage was determined by visual inspection of the digital brain image for every single slice, and separately corroborated. The boundary of the lesion was delineated directly on the digital image as a 2D ROI at the level of individual voxels, traced by hand on each 1 mm axial image slice, using the graphics tablet implemented in the MRIcro software package. Merging of these slices produced a 3D lesion ROI for each structural volume.

The structural volume for each session was realigned to the first EPI volume of that specific session. Normalization to the smoothed T1 MNI template was performed by applying the normalized 3D lesion ROI as a mask. This procedure allows to minimize the contribution of abnormal brain tissue to the normalization process (Brett, Leff, Rorden,& Ashburner, 2001). Normalization parameters were then applied to the realigned functional and anatomical volumes, obtaining normalized volumes with a voxel size of 2 x 2 x 4. All images were then smoothed with a Gaussian kernel of 8 x 8 x 8 in order to increase the signal to noise ratio

Statistical analysis

A first statistical analysis was performed based on a general linear model for each single scanning session (T0, T1, T2). Events for each session were time-locked to the onset of stimulus presentation. Effects of interest (overall naming performance in L1, overall naming performance in L2) were modeled as a stick-function convolved with the

hemodynamic response function. User-specified regressors were defined to account for the unequal number of runs for each of the two languages, namely 3 for Italian and 2 for Spanish. Additional regressors were added to partial out the possible variance due to between-run changes in the number of stimuli for the two languages. In a second statistical analysis, effects of interest were represented by 'only correct responses in L1' and 'only correct responses in L2' in T0 and T2 and were independently modeled in the statistical design along with effects of no interest (anomias, paraphasias and non-target language interferences). Again, additional user-specified regressors were defined to account for the unequal number of runs for each of the two languages.

Thus, for all er-fMRI sessions (T0, T1, and T2), simple main effects for overall naming performance in L1 and for overall naming performance in L2 were calculated. In addition, for T0 and T2 simple main effects for only correct responses in L1 and correct responses in L2 were calculated. A threshold of $p< 0.005$, FWE corrected was set for all simple main effects. An extent threshold of 20 contiguous voxel was applied to all simple main effects.

3. Dynamic causal modeling and intrinsic connectivity

Changes in the coupling between different brain regions (i.e., as investigated by means of fMRI activations) as a function of naming in each language were investigated using dynamic causal modeling (DCM). In DCM, the brain is treated as a dynamic input–state–output system. A given experiment is considered as a designed perturbation of neuronal dynamics that is propagated throughout a network of interconnected anatomical nodes. In DCM, three sets of parameters are estimated: the direct influence of stimuli on regional activity, the intrinsic or latent connections between regions (i.e., the interregional influences in the absence of modulating experimental effects), and the changes in the intrinsic connectivity between regions induced by adding or removing a modulatory influence (contextual modulation) (Mechelli, Penny, Price, Gitelman, & Friston, 2002)

In the present study, we focused on the intrinsic connections and on the strength of connections between regions across an entire time series in which JRC performed the naming task either in Spanish (L1 session) or Italian (L2 session) across T0, T1 and T2. We then compared the strength of each intrinsic connection for L1 and L2 at T0, T1 and T2.

Analysis of intrinsic connections and definition of the model

In each single session, activations related to picture naming in L1 and in L2 were acquired in distinct time series, and hence they were treated as such in our DCM analysis. The strength of the intrinsic connections reflects coupling strength in the absence of contextual modulation computed across the entire time series. Since the present study is a sequential follow-up study with three independent sessions in which naming occurred separately in either of the two languages, we treated each session in L1 and L2 as an independent time series. In this way we were able to model how a main effect of a specific language vs. baseline induced in an input area is conveyed, via the specified connections, to other areas. This model assumes, however, that all regions show the main effect of both languages in the same direction (L1 > baseline or L2 > baseline). Given these assumptions, we focused on the intrinsic connections and we assessed how these may change as a function of the task of naming in Spanish relative to naming in Italian at T0, T1 and T2.

Therefore, a specific model was constructed that included five of the regions found to be activated in our functional maps over sessions and for both languages. The five regions were defined as 6-mm-radius spheres centered on the maxima of session-specific statistical parametric maps for each time period, testing for the overall effect of naming in Spanish (L1) and for the overall effect of naming in Italian (L2). Regional activations were extracted in terms of the principal eigenvariate from each region, in a session-specific fashion. The following coordinates were chosen for the five regions of interest that

constitute our model: BA 37/19, x = -44, y = -72, z = -12: BA 45, x = -56, y = 22, z = 16; BA 47, x = -56, y = 20, z = 0; LC (head of caudate), x = -6, y = 10, z = 4; and ACC (anterior cingulate cortex), x = -4, y = 36, z = 0. We include only left hemispheric regions because our main focus was the effect of control areas on the intra-hemispheric re-organization of language areas.

Our model is based on the theory that language production in bilinguals is mediated by neural devices related to cognitive control (Abutalebi & Green, 2007) and that the same structures are a determinant for language recovery in bilingual aphasics (Green & Abutalebi, 2008). In detail, the model (see figure 2) for the current study "connected" the five chosen regions of the left hemisphere in multiple ways (i.e. BA 45, BA 47, BA 19/37, the head of the caudate (LC) and the anterior cingulate cortex (ACC), in accordance with anatomical tracer literature in primates (Pandya & Seltzer, 1982; Mesulam, 1990; Seltzer & Pandya, 1989; Webster, Bachevalier, & Ungerleider, 1994; Pandya & Yeterian, 1996; Petrides & Pandya, 1999), with diffusion tensor imaging studies in humans (Catani, Howard, Pajevic, & Jones, 2002, Catani, Jones, & ffytche, 2005), and with the functional and effective connectivity studies of language and picture naming (Mechelli et al., 2002; Démonet, Thierry, & Cardebat, 2005; Bitan et al., 2005; Sonty et al, 2007). Key areas in picture naming comprise the posterior part of the left inferior temporal gyrus (also referred to as the 'temporal basal language area'; BA 37/19) which has a prominent role in semantic decoding during picture naming (Démonet et al., 2005), BA 45 because of its role in word production and BA 47 because of its role during lexical retrieval and competition (Démonet et al., 2005) and also in language control (Abutalebi & Green, 2007). Finally, the head of the left caudate (LC) and the ACC were included since they may exert modulatory influence on the bilingual naming network and help select the correct language for naming (Abutalebi & Green, 2007; Green & Abutalebi, 2008; Abutalebi, 2008). In detail, our DCM model included forward ''intrinsic connections'' between Ba 37/19 and the two inferior frontal areas, forward and backward connections between the left caudate nucleus and the

anterior cingulate cortex; between the left caudate nucleus and the two inferior frontal areas and the anterior cingulate cortex; and between the anterior cingulate cortex and the two inferior frontal areas and the left caudate nucleus as represented graphically in Figure 2.

Intrinsic connectivity analysis was performed using the DCM tool in SPM2 (Friston et al., 2003; Penny et al., 2004). We computed mean coupling parameters across all three sessions for each connection specified in our model and used one sample t-tests (JMP, SAS Institute) to assess if each connection specified in our model was significantly different from 0 across T0, T1 and T2. Since the main aim of this study was to investigate the effects of speech therapy over time on the network established by a picture naming task observed at T0 and at two different later times (T1 and T2), we computed mean parameters for the regional connectivity established by the naming task in L1 and L2 'within' each of the three experimental sessions (T0, T1 and T2). We considered for each intrinsic connection, a pair of values for each language in the same session. We used paired t-tests (JMP, SAS Institute) to assess the significance of the mean difference of connection strengths between L1 and L2 at each specific session (T0, T1 and T2) and of the differences between L1 strength values and L2 strength values for each single connection in each specific session (T0, T1 and T2).

RESULTS

1. Behavioral study

We used part B of the Italian and Spanish BAT to assess JRC at the three time points (T0, T1 and T2). The overall pattern (see table 1 for the results) is one in which JRC was more impaired in Italian (his L2) than Spanish (his L1) at T0 but following speech-therapy in Italian showed greater impairment in Spanish at T2 with full recovery of Italian.

At T0, for L1 (Spanish), the patient had a pathological performance on the following subtests: naming (9 correct out of 20), verbal-auditory discrimination (8/18), and

generation of semantic opposites (7/20). His performance of these subtests in L1 were stable at T1, but he became more impaired on other subtests such as generation of antonyms (3/5), reading comprehension (8/10) and lexical decision (27/30). Finally, at T2, his performance worsened even more: apart from his impaired performance on the above mentioned tests at T0 and T1, the patient performed poorly also in syntactic comprehension (80/86). Globally, his language performance worsened during the follow-up study not only on those tests that were already poorly performed at T0, but also because some subtests that he performed correctly at T0 (i.e., the generation of antonyms, reading comprehension for words) became pathological either by T1 or by T2 (i.e., syntactic comprehension).

A different outcome was observed for his L2, the language in which speech therapy was carried out. At T0, JRC had pathological performance on many more tests compared to L1. Indeed, he scored poorly on the following subtests: simple commands (2/5), semi-complex-commands (3/5), verbal-auditory discrimination (9/18), syntactic comprehension (76/86), series (this task was performed in L1 instead of the requested L2), naming (8/20), generation of semantic opposites (8/10), and lexical decision (24/30). After the deficit-specific speech therapy in L2, the patient performed significantly better in the L2 subtests. Only naming (16/20) and verbal-auditory discrimination (14/18) remained pathological. Finally, at T2 the patient's assessment in L2 was flawless, indicating a complete recovery.

The specific assessment of the patient's naming performance gave the following results. At T0, out of a total corpus of 90 items for L1, he named correctly 35 and produced 30 anomias, 18 semantic/phonological errors and 6 correct responses by using the non-target language (L2). His naming performance for L1 was quite stable at T1, except for the decrease of semantic/phonological errors. Indeed, he named correctly 40 items out of 90, produced 30 anomias, 5 semantic/phonological errors and 5 correct answers by using the non-target language. The number of correct items (34/90) and anomies (33/90) was stable also at T2 for L1, but with an increase of intrusions from the non-target language (12/90)

and semantic/phonological errors (12/90).

On the other hand, in L2 at T0 he named correctly 57 out of the total corpus of 144 items, produced 60 anomias, 10 semantic/phonological errors, and 17 correct responses by using the non-target language. A significant improvement of naming performance was observed at T1. Correctly named items were 112/144, anomias were 20/144, semantic/phonological errors were 7/144, and language intrusions were 5/144. Further improvement was observed at T2, Correct named items amounted at 122/144, anomias were 11/144, semantic/phonological errors 11/114, and there were no intrusions from L1.

In conclusion, a global improvement for naming was observed only in the language in which speech therapy was carried out. Naming performance was recorded also during the fMRI sessions, and the patient's performance is illustrated in Figure 3. His naming performance during fMRI, hence in an experimental setting, showed good correspondence with the behavioral assessment carried out in the clinical setting.

2. fMRI results

In table 2A (see Figure 4 top) we report the pattern of brain activity related to the patient's overall naming performance (i.e., taking together all types of response, such as correct naming and anomias). As a check on the validity of these data we also analysed the pattern of response on correct naming trials only at T0 (before treatment) and at T2 (after treatment). We report these data in table 2B (see Figure 3 bottom). There is good agreement with the overall data and we focus on the latter.

The basic picture is one in which activation patterns for L1 and L2 are similar at T0 but diverge progressively. Furthermore areas undergoing change involve not only the classical language areas (e.g., Broca's area and the fusiform gyrus) but also regions associated with language control (e.g., anterior cingulate cortex, left caudate).

At T0, during L1 naming, the following brain areas were activated (see Table 2 for stereotactic coordinates and Brodmann's nomenclature): in the left hemisphere, the

inferior and middle frontal gyrus, the left precentral gyrus, the anterior cingulate cortex, the superior parietal lobule, the fusiform gyrus, the inferior and middle occipital gyrus, and the caudate nucleus. In the right hemisphere, the inferior and middle frontal gyrus, the orbitofrontal cortex, the precentral gyrus, the angular gyrus, the inferior occipital gyrus and the cerebellar hemisphere.

At T1, the following areas were activated for L1 naming: in the left hemisphere, the inferior frontal gyrus, the anterior part of the superior temporal gyrus, the fusiform gyrus, the lingual gyrus, the middle occipital gyrus, the thalamus and the caudate nucleus; and in the right hemisphere in the inferior frontal and precentral gyrus, the angular gyrus, the fusiform gyrus, the inferior occipital gyrus and the cerebellar hemisphere.

Finally, at T2, the patient activated during L1 naming, the left inferior and middle frontal gyrus, the left precentral gyrus, the left superior parietal lobule and the precuneus, the left inferior and middle occipital gyrus, the left thalamus and cerebellar hemisphere. In the right hemisphere, the inferior and middle frontal gyrus, the SMA and precentral gyrus, the angular gyrus, the fusiform gyrus and the cerebellar hemisphere.

Brain activity related to naming in L2 at T0 involved a very similar pattern to that of L1 naming at T0. In the left hemisphere: the inferior, middle and dorsal frontal gyrus, the precentral gyrus, the anterior cingulate cortex, the superior parietal lobe, the fusiform and lingual gyrus, the inferior occipital gyrus and the thalamus. In the right hemisphere, the inferior, middle frontal gyrus and the frontal operculum, the orbitofrontal cortex, the precentral gyrus, the angular gyrus, the superior parietal lobule, the inferior occipital gyrus and the cerebellar hemisphere.

In contrast, at T1, a much more extended activation pattern was observed for L2 than for L1. Indeed, as reported also in Figure 4, naming activated in the left hemisphere, the inferior frontal gyrus, the orbitofrontal cortex, the superior frontal gyrus, the anterior cingulate cortex, the precentral cortex, the anterior part of the superior temporal gyrus, the fusiform gyrus, the inferior and superior occipital gyrus, the thalamus and caudate. In the

right hemisphere, activity was found in the inferior and middle frontal gyrus, the precentral gyrus, the angular gyrus and the inferior occipital gyrus.

At the end of the experimental study, at T2 the pattern of activity for L2 remained expanded in comparison to L1 (see Figure 4). The patient activated for L2 the following areas: in the left hemisphere, the inferior frontal gyrus, the anterior cingulate cortex, the precentral gyrus, the superior parietal lobule, the fusiform and lingual gyrus, the cuneus and the inferior occipital gyrus, and the caudate. In the right hemisphere, he activated the inferior frontal gyrus, the precentral and paracentral gyrus, the angular gyrus, the superior parietal lobule, the anterior part of the superior temporal gyrus, the middle temporal gyrus, the fusiform gyrus, the inferior occipital gyrus and the cerebellar hemisphere.

In order to ascertain that the differences between these two main effects (i.e., main effects of L1 overall naming performance and L2 overall naming performance) were not due to differences in the number of correct responses, we analyzed the activity pattern for correctly named pictures in L1 and in L2 at T0 and T2 (table 2B and Figure 4, bottom).

For naming correctly in L1, at T0 the patient activated the left inferior and middle frontal gyrus, the left precentral gyrus, the left anterior cingulate cortex, the left lingual gyrus and the left inferior occipital gyrus, the right inferior and middle frontal gyrus, the right orbitofrontal cortex, the right precentral gyrus, the right angular gyrus, the right inferior occipital gyrus, and the right cerebellar hemisphere. At T2, in the the left hemisphere, the patient activated for L1 naming, the inferior frontal gyrus and the precentral gyrus, the inferior parietal lobule, and the right hemisphere, the inferior frontal gyrus, the fusiform gyrus, the inferior occipital gyrus and the cerebellar hemisphere.

For naming correctly in L2 at T0, the brain areas activated in the left hemisphere were the inferior frontal gyrus and the orbitofrontal cortex, the anterior cingulate cortex, the fusiform gyrus, the inferior and middle frontal gyrus, and in the right hemisphere, the areas were the inferior frontal gyrus, the frontal operculum, the orbitofrontal cortex, the precentral

gyrus, the angular gyrus, the inferior occipital gyrus and the cerebellar hemisphere. At T2, correct naming in L2 revealed the following activation foci in the left hemisphere: the inferior frontal gyrus, the anterior cingulate cortex, the precentral and paracentral gyrus, the fusiform and lingual gyrus, the cuneus, the inferior occipital gyrus and the caudate nucleus. In the right hemisphere, the foci were: the inferior frontal gyrus, the precentral and paracentral gyrus, the angular gyrus, the superior parietal lobule, the anterior part of the superior temporal gyrus, the middle temporal gyrus, the fusiform gyrus, the inferior occipital gyrus, and the cerebellar hemisphere.

In brief, in line with the overall data, as may be seen in Figure 4 (bottom), the extension of the pattern of brain activity was much larger for L2 than for L1 at T2.

3. DCM results

As noted above (methods), our model comprised five left hemisphere regions of interest (basal temporal language area, two prefrontal regions, the anterior cingulate cortex, ACC, and the left caudate, LC) because our focus was the effect of control areas on the intra-hemispheric re-organization of language areas. Our DCM analyses used the full set of fMRI data in order to chart the changes in connectivity patterns.

Intrinsic Connections: Regional connectivity

We analysed the mean difference of connection strengths between L1 and L2 at each specific session (T0, T1 and T2) and the differences between L1 strength values and L2 strength values for each single connection in each specific session (T0, T1 and T2). All intrinsic connections (in the sense of mean coupling values) of our model were significantly different from 0 as specified in table 3.

All connections exhibited positive mean values indicating that an increase of activity in area X was associated with an increase in area Y. Specifically, the forward connections

between BA 37/19 and BA 45 and BA 47 were significantly greater than 0 ($p < 0.0001$) indicating that the 'temporal basal language area' was positively coupled with the two prefrontal areas in the naming network. The basal temporal language area was also significantly connected to the LC (mean coupling value > 0, $p = 0.004$). Furthermore the forward and backward connections between the frontal areas of the naming network were significantly greater than 0 (BA 47 to BA 45 at $p = 0.004$; BA 45 to BA 47 at $p = 0.005$). These two frontal areas were also significantly coupled to the two areas of our 'language control' network with values that were greater than 0 ($p < .001$) indicating that these areas were positively coupled and the language control areas exerted an influence on the naming network (BA47 to LC at $p < 0.001$; BA47 to AAC at $p = 0.003$; BA 45 to LC at $p < 0.001$; BA 45 to AAC at $p < 0.001$; LC to BA 47 at $p = 0.061$; LC to BA 45 at $p < 0.001$; AAC to BA 47 at $p = 0.009$; AAC to BA 45 at $p < 0.001$). Finally, both areas involved in language control were connected at values > 0 (LC to ACC at $p = 0.003$; ACC to LC at $p < 0.001$).

Effects of languages on regional connectivity

To investigate whether the strength of the intrinsic connections between the areas of our model would change for the two languages as an effect of speech therapy only in L2, we took into account the differences of ‘mean coupling values’. In detail, the 'strength of connections' between L2 and L1 ‘within’ the same session were calculated and tested, first, globally in terms of effects upon the whole network, and second, upon all single connections (see table 4 for further specifying details). Note that when it comes to the single connections (i.e., between two specific areas), we will report below the results of those connections that are related to the main scope of the current work, i.e., the influence of language control areas on the recovery process in bilingual aphasics. However, the “mean coupling values” of all single connections are reported in Table 4 and Figure 5.

a) Global changes

Globally observed, i.e., considering the whole network established by the experimental context (the naming task), we compared the mean difference between all the connections for the two languages at each time period (T0, T1 and T2). We used 0 as the hypothesized mean (for no difference) to highlight shifts between the two languages in the global strength of the connections driving the network at the three different time points. These comparisons showed for L2 an overall progressive increase in regional connectivity for all the connections specified in our model from T0 through T1 to T2 (see Table 4). On the other hand, for L1 we observed an overall slight increase in connectivity in the network at time T1 but a decrease of the strength of the connections at T2 (see Figure 5). In detail, if at T0 the whole network had the tendency to be significantly more strongly connected for L1 (mean difference = -0.041 at $p = 0.0214$), at T1 there was no longer a significant difference between the two languages (mean difference = -0.001 at $p = 0.9573$). Indeed, it is noteworthy that at T2 the mean difference shifted heavily in favor of L2 (mean difference = 0.28584 at $p < 0.001$).

b) Single connections

As may be observed in Figure 5, at T0, all single connections showed higher mean coupling values during L1 naming with respect to L2 naming, except the forward connections between the LC and BA 47 (mean coupling value = 0.068) and between the LC and the AAC (mean coupling value = 0.020) which were significantly more engaged during L2 naming. The behavior of these two areas is of especial interest: at T1, the forward connection between LC and BA 47 became instead stronger for L1 naming (mean coupling value = -0.084) and at T2, this increased further (mean coupling value = -0.111). Likewise, at T1, the forward connection between LC and ACC (mean coupling value = 0.046) shifted away from being engaged more strongly for L2 and became, at T2, significantly more strongly engaged for L1 (mean coupling value = -0.070). Hence, as an

overall result, these two connections which were significantly more engaged by L2 at T0, shifted significantly to being more engaged by L1 at T2. A similar behavior was observed for the forward connection between BA 37/19 and the LC. The strength of connection at T0 (mean coupling value = -0.006) and T1 (mean coupling value = 0.030) did not differ significantly between languages, but at T2 it was significantly more strongly connected for L1 (mean coupling value = -0.292). Finally, at T2 all single connections showed higher mean coupling values during L2 naming with respect to L2 naming, except the three aforementioned connections (see Figure 5). The shift of connection strengths will be the focus of our discussion of these results.

DISCUSSION

We examined the clinical and experimental effects of selective language treatment in Italian in a bilingual individual with chronic aphasia in Spanish (his L1) and Italian (his L2). We also explored the neural correlates of these effects. Our data accord with a dynamic view of language recovery and the necessity of understanding the nature of the control processes involved. Our longitudinal study with an assessment and a functional study at three time points (T0, T1 and T2) showed a benefit on clinical and experimental language tasks only for the treated language. Further, in line with expectation, the improvement in picture naming performance was mediated by increased activation in regions associated with naming. Model analyses also indicated increased coupling within these regions as well as selective changes with regions associated with language control. We discuss each of these aspects in turn and conclude with implications for the treatment of bilingual aphasia.

Language recovery: behavioral aspects

Despite the trend towards a better recovery of L1, JRC at his own wish and that of his family was rehabilitated in his L2. At the behavioral level, this language specific

approach was successful in restoring the treated language (L2) to normal levels. However, we observed no generalization to the non-treated language. On the contrary, there were negative effects. Performance on the Spanish (L1) version of the Bilingual Aphasia Test (BAT) worsened at T2. Recovery of the treated language apparently "inhibited" the recovery of the non-treated language and induced a pattern of antagonistic recovery of L1 (see Paradis, 1998). From our perspective, these behavioral outcomes suggest that treatment benefits arose in the context of continued impairments of control.

If this is the case, then there should be direct behavioral evidence. JRC's recovery provides such evidence. At T0, when L1 was better recovered than L2, JRC, when required to name in L2, named pictures unintentionally in L1 (see Figure 3). Such between-language errors of interference were uncommon when he named in L1. Crucially, following speech therapy, this pattern reversed at T2 and the patient named pictures in L2 when asked to name in L1. This pattern is consistent with an impairment in control. If recovery of L2 was also associated with the recovery of the means to control languages then this reversal should not have occurred. Control is presumed to be more effortful when a person has to use a less active or less proficient language (Green, 1998 and Abutalebi, Annoni, Zimine, et al., 2008 for imaging evidence). It follows that when the means or resources to regulate or to inhibit another language are constrained, language control (here, the ability to name in a designated language) is at risk (Green, 1986, 2002; Green & Abutalebi, 2008; Paradis, 1987, 1998). As a result, successful production of the more active language will be associated with interference from this language in the production of the less active language. Such an account leads us to expect certain patterns of activation in the functional data.

Language recovery: Neural plasticity

Aphasia in our patient was due to a subcortical lesion and it is worth underlining, that language areas such as Broca's area and the fusiform gyrus were always activated at

T0 and T1 (see Table 2). Subcortical lesions causing aphasia are known to functionally deactivate cortical areas responsible for language processing, and recovery of subcortical aphasia has been correlated with the regression of diaschisis (Vallar et al, 1988) and hypoperfusion (Hillis et al., 2002). In the present case, we observed reactivation of cortical areas that mediate naming only for L2 and not for L1. This fact refutes the view that the reactivation of cortical areas in patients with subcortical lesions is due only to the regression of the functional disconnection, because in that case we should have observed the same pattern of brain activity also for L1. Instead the functional data point to the importance of language control (e.g., the ability to maintain the language for naming) in the recovery pattern. We first review and draw out the implications of the functional data and then assess the results of the DCM analyses for our interpretation.

As to the pattern of brain activity in our study, we underline that changes cannot be attributed to differences in the number of correct responses made in the two languages because we observed the same pattern in both our overall analysis (table 2a) and in the analysis restricted to correct responses only (table 2b). Observing the figures reporting the functional brain activation patterns (figure 3a), it is evident at first glance that significant brain reorganization took place only for L2, both in left hemispheric language areas and in right homologues. In detail, while at T0 the pattern of activity was quite similar for L1 and L2, both in extension and in the location of activated brain areas (see table 2a), a neural reorganization was present only for L2, the language treated in speech therapy. Indeed, at T2, when the patient fully recovered in L2, the pattern of brain activity closely resembled the pattern of activity usually observed in normal healthy subjects (see for review of brain activity patterns during various language tasks, Démonet et al., 2005) with extensive activation of the left inferior frontal gyrus and the left fusiform gyrus as key areas for picture naming. The same cannot be said for L1, in which little brain reorganization took place in terms of extension of brain activity.

The anatomical differences were not solely in extent but also in their localization. In

the case of L2, the distribution of activity had changed already at T1. Extensive and significant foci of brain activity were observed bilaterally in the prefrontal cortex, anterior to the classical language areas, in BA 11, BA 10 and BA47. This pattern was not observed for L1, in which no behavioral improvement took place. These prefrontal areas have been proposed to play a key role in language control in bilingual language processing (Abutalebi & Green, 2007; 2008), such as correctly selecting a given language and preventing the language in use from unwanted intrusions from the language not in use. It should be underlined too that T1 was only six weeks after T0. At this time point these cognitive control areas may have reconfigured to correctly activate and control access to L2 lexical concepts and word forms.

Recent functional neuroimaging studies have shown that not only the left prefrontal cortex but also the left caudate and the ACC are involved in language control in bilinguals (Crinion et al., 2006; Abutalebi et al., 2007; Wang et al., 2007; Abutalebi et al., 2008). These two structures are crucial for monitoring and controlling the language in use (i.e., the caudate) and signaling potential errors (i.e., the ACC) to the prefrontal cortex (see for review Abutalebi & Green, 2007; 2008). In the current study, the time course of the involvement of these structures is highly informative (see table 2a). In essence, these structures are differentially involved as a function of training in L2. At T0, both the left caudate and the ACC were significantly activated for L1, i.e., the language that showed the tendency to recover spontaneously. For L2, only the ACC was significantly activated. At T1, for L1 the left caudate was still activated but the ACC was not, while now for L2, both the left caudate and the ACC were activated. At T2, for L1 neither the left caudate nor the ACC were activated while both were engaged for L2. Thus, we observed a gradual functional shift in the engagement of these control areas from L1 to L2.

Treatment-based effects in JRC are mediated by increased activation in naming areas and increased activation in regions associated with control. The precise factors mediating the benefits of the deficit-specific training in L2 naming remain to be determined.

It is possible, as Paradis has argued (e.g., Paradis, 2004, pp. 53-57), that declarative representations mediate recovery by supporting the exercise of procedures involved in naming. In the present case, such representations were not supported by any therapeutic intervention in L1 and so naming responses in L1 may have regressed through lack of exercise. However, only a subset of naming responses were trained in L2 and so improved naming of other L2 items requires explanation. Our suggestion is that item-specific training in L2 naming strengthened connections across the naming network for these items but also entrained the control network and so reduced interference from competing items in L1. Such entrainment enhanced the prospects of recovery of untrained items. In contrast, naming in L1, was not practised. In consequence, given a constraint on control and the ability to control interference from L2, naming in L1 became impaired.

The functional interpretation of our findings may be refined by means of the results of the DCM analysis.

Coupling of regions involved in naming and in its control

DCM is an independent approach to the investigation of functional integration. DCM estimates the interregional influences of brain areas and the modulatory influence of experimental manipulations upon the strength of the coupling between areas in the model.

Two key observations should be highlighted: first, the changes of the coupling of the global network from T0 to T2, and second, the redistribution of the coupling of some connections that are involved in language control and illuminate the mechanisms of such control.

As to the first observation, in line with the overall functional data, figure 5 illustrates changes in the coupling of the whole network. At T0, all but three single connections (forward connection between LC and BA 47; forward connection between LC and ACC, forward connection between ACC and BA 47) were more strongly coupled for the language that was better recovered, i.e. L1. At T1, an initial redistribution took place: half

of the connections were more coupled for L1, while the other half for L2 (i.e., the language that was then recovering due to speech therapy). Crucially, at T2 we observed the reverse pattern in comparison to T0. Indeed, the whole network became more strongly connected for L2 as compared to L1, except three single connections of which two showed the reverse pattern in comparison to T0 (i.e., the forward connections between LC and BA 47 and between LC and ACC). Hence, in the case of the naming network, the DCM analysis elegantly shows that the selective recovery of one language (L2) is paralleled by increasing connections strength of the network mediating naming and language production. Concomitantly, there was weaker engagement of the naming network for L1 that showed impaired recovery.

As to the second observation, this qualifies the overall pattern of increased connectedness of the naming and control networks for the better recovered language. Two single connections showed a marked difference from the rest of the model. The forward connections between LC and BA 47 and between LC and ACC behaved in a reverse manner when compared to the rest of our model. Their coupling was stronger for L2 at T0, but became stronger for L1 at T2. In other words their coupling was stronger for production in the more impaired language.

We propose that these connections form part of a circuit that is more engaged in resolving competition from a more active, i.e., better recovered language. This interpretation is consistent with theoretical proposals about language control in normal bilinguals (Abutalebi & Green, 2007) in which the LC and ACC are strongly connected to the prefrontal cortex (McCormick, Ziebell, Nopoulos, Cassell, Andreasen, & Brumm, 2006), and work together with this structure to inhibit interferences from the non-target language. The ACC signals to the prefrontal cortex potential response conflicts or errors (i.e., in the case that an erroneous language was chosen) and the prefrontal cortex then seeks to avoid incorrect selection. Finally, the basal ganglia may subserve language planning (i.e., the activation of a given language) through a left basal ganglia-left prefrontal cortex

circuitry, and may act to inhibit a prepotent response (see Sumner, Nachev, Morris, Peters, Jackson, Kennard & Husain, 2007). In the present case, because of damage to subcortical structures, there are constraints on the ability of the system to reconfigure itself in order to speak the less well recovered language. On this proposal, the full circuit (including left prefrontal structures) is engaged for the treated language but not for the untreated language.

Finally, it should be mentioned that the DCM approach may provide neurobiological evidence for the activation threshold theory postulated by Paradis (1987). Aphasia-producing lesions in bilinguals, if the language areas are not totally destroyed, cause an imbalance in activating and inhibiting languages (Green, 1986; Paradis, 1998). Providing the correct balance for language use is a function likely to be carried out by areas mediating language control. The present study shows that the engagement of these areas plays a crucial role in language recovery in bilinguals. The connections are stronger for the language that recovers better, receiving, as originally proposed by Paradis (1987), more resources for its activation.

It is important to extend the current DCM approach to sentence level processes. We know from neuropsychological assessment that performance in L2 improved on sentence level tasks too and it would be useful in future work to examine the functional basis of such recovery.

A further challenge is to understand the engagement of control processes in more spontaneous settings. Our fMRI study concerns the nature of control when individuals are responding to a request to perform an action (e.g., name this picture) as opposed to that when they elect to name a picture as part of some other ongoing task. To the extent that an individual intends to name in one language rather than another, this information is part of the speaker's message and must be represented explicitly. It plausible then the circuits identified here are relevant to all instances where a speaker chooses to name in one language rather than another because, for instance, the addressee only knows that

language. This was true of the therapeutic interventions and our fMRI study and is typically the case for non-native speakers of a language working in their L2 environment. How control is exercised in the case of recovered patients fluently and appropriately code-switching (i.e., where speaker and addressee speak the same two languages and routinely switch between them) remains to be addressed (see Paradis, 2009, pp. 163-169 for an informative discussion of explicit versus implicit control).

Implications for treatment research in bilingual aphasia

What are the implications of this study for treatment research in bilingual aphasia? From a practical point of view, clinicians wish to know how best to encourage language recovery. One source of guidance is case study evidence. Some studies favor rehabilitation of both languages (Kohnert, 2004) especially when the bilingual was formerly proficient in both (Ansaldo et al., 2008; see also, Ansaldo & Marcotte, 2007). Selecting one language for rehabilitation (Chlenov, 1948; Fabbro, 2001) is supported by the claim that treating more than one language may inhibit global speech recovery (Chlenov, 1948) and may also delay the recovery of all languages (Wald, 1958, 1961). The pattern shown here may be restricted to instances where the language of intervention coincides with exclusive use of that language in the person's home environment. Indeed a case could be made that there was no therapeutic effect as such. If this were so then selective recovery of L2 post-stroke in immigrant bilingual speakers would be the norm in the absence of any therapeutic effect. We know of no decisive data on this point though selective recovery is not the norm in published cases (Fabbro, 1999; Paradis, 2004). But it seems implausible that there was no therapeutic effect because intervention in monolingual aphasic patients does achieve substantial benefits that exceed those achieved spontaneously (Crinion and Leff, 2007) and the interventions used here fully meet the criteria for an effective intervention. It is possible that the treatment effects in the present case benefitted from support for L2 within the home environment. Such support might serve to enhance

recovery through practice in the retrieval of word names (the paradigmatic dimension) in the context of sentence production (the syntagmatic dimension). Selective use of the L2 in the home environment may also have led to the continued inhibition of L1 beyond the therapeutic context. Recent behavioural data suggest that at least for L2 immersion learners L1 is relatively inhibited (Linck, Kroll and Sunderman, in revision). Identification of the boundary conditions for the effects observed here require selective language treatment in a context where both languages are used. For example, the treated language could be the one used in the work environment and the untreated one, the language used at home. According to our position, recovery will also depend on the integrity of the circuits normally involved in language control and that will reflect the effects of stroke.

The way forward in our view is to develop testable theoretical accounts. Our position is that the precise impact of treatment depends upon the integrity of the naming pathways and the control pathways. As illustrated here a combination of behavioral, neuroimaging data and modeling provides a way forward. For JRC, the selective treatment effects on picture naming in L2 increased the strength of naming pathways in that language and selectively engaged regions involved in its control. Improvements in L2 coincided with decreased control of L1. Meinzer et. (2007) also reported selective behavioral and functional changes in the treated language of their early bilingual patient. However, their use of covert picture naming during fMRI scanning makes interpretation problematic because it is unknown whether the pattern of overall naming differs in their patient from that for correct naming. We cannot therefore test our proposals against their data.

On the behavioural front, JRC produced language interference errors that provide direct evidence of a problem of control. However, issues of control also arise when there is parallel recovery of language with no overt errors of language interference (Green et al., in press). In such cases, and in our view more generally, it is essential to examine how patients perform on a range of interference tasks (e.g., Stroop, the flanker task) in order to

assess the nature of any problems in resolving interference. Problems in resolving interference (because of damage to one or more components of the frontal-basal ganglia circuits may suggest selective language treatment is desirable.

Of course implementation relies on the ability of the individual to maintain a specific language goal. It seems to us therefore that it is desirable to test patients on a wide range of executive tasks that bear on the circuits implicated in language control. In this way, treatment effects can be examined in the light of the patient's wider ability to exercise control over their actions. Further, it becomes possible to chart the relationship between recovery and the various control processes and so set up and test patient specific models of the recovery process.

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Table 1. The patient's follow-up aphasia profile on neurolinguistic testing as assessed with the part B of the BAT (Bilingual Aphasia Test) for L1 and L2 through the 3 distinct sessions

1) BAT – part B –SPANISH (L1)

TASK	11/07/2005	09/2005	23/12/2005
Pointing	9/10	9/10	8/10
Simple commands	5/5	5/5	5/5
Semi-complex commands	5/5	5/5	5/5
Verbal-auditory discrimination	8/18 **	10/18 **	10/18 **
Syntactic comprehension	85/86	84/86	80/86 **
Synonyms	4/5	4/5	4/5
Antonyms	4/5	3/5 **	3/5 **
Word repetition	30/30	30/30	30/30
Sentence repetition	7/7	7/7	7/7
Series	3/3	3/3	3/3
Naming	9/20 **	8/20 **	8/20 **
Semantic opposites	7/10 **	8/10 **	7/10 **
Lexical decision	28/30	27/30 **	26/30 **
Listening comprehension	5/5	5/5	5/5
Reading of words	10/10	10/10	10/10
Reading of sentences	10/10	10/10	10/10
Reading of paragraph	5/6	5/6	5/6
Copying	5/5	5/5	5/5
Dictation (words)	5/5	5/5	5/5
Dictation (sentences)	5/5	5/5	5/5
Reading comprehension (words)	9/10	8/10 **	8/10 **
Reading comprehension (sentences)	10/10	10/10	9/10

2) BAT - part B - ITALIAN (L2)

TASK	T0	T1	T2
Pointing	9/10	10/10	10/10
Simple commands	2/5 **	5/5	5/5
Semi-complex commands	3/5 **	5/5	5/5
Verbal-auditory discrimination	9/18 **	14/18 **	18/18
Syntactic comprehension	76/86 **	83/86	85/86
Synonyms	5/5	5/5	5/5
Antonyms	9/10	10/10	10/10
Word repetition	30/30	30/30	30/30
Sentence repetition	7/7	7/7	7/7
Series	3/3 (in L1) **	3/3	3/3
Naming	8/20 **	16/20 **	19/20
Semantic opposites	8/10 **	9/10	10/10
Lexical decision	24/30 **	30/30	30/30
Listening comprehension	4/5	5/5	5/5
Reading of words	10/10	10/10	10/10
Reading of sentences	10/10	10/10	10/10
Reading of paragraph	5/6	6/6	6/6

Copying	5/5	5/5	5/5
Dictation (words)	5/5	5/5	5/5
Dictation (sentences)	5/5	5/5	5/5
Reading comprehension (words)	9/10	10/10	5/5
Reading comprehension (sentences)	8/10	9/10	10/10

Table 2A
The stereotactical coordinates for the pattern of brain activity during the overall naming performance of the patient through T0, T1 and T2, respectively, for L1 (left columns) and L2 (right columns).

L1 – Spanish				L2 – Italian			
Anatomical location	Coordinates *x, y, z*	Z-value	BA	Anatomical location	Coordinates *x, y, z*	Z-value	BA
(a) First fMRI session (=T0)							
L inf frontal gyrus	−56, 22, 16	5.31	45	L inf frontal gyrus	−54, 30, 16	7.48	45
L middle frontal gyrus	−36, 54, 0	6.17	10/46		−56, 16, −4	5.12	47
L precentral gyrus	−62, −4; 8	8.57	6	L middle frontal gyrus	−28, 52, 4	5.44	10/46
	−46, −12, 36	6.45	4/6	L dorsal frontal gyrus	−22, 48, −8	5.24	10
L ant cingulated cortex	−2, 28, −8	5.94	32	L precentral gyrus	−46, −12, 36	9.99	4/6
L sup parietal lobule	−18, −30, 64	6.42	5/7		−62, −2, 8	6.85	6
L fusiform gyrus	−50, −70, −12	6.32	19/37	L ant cingulated cortex	−2, 36, −8	6.77	32
L middle occipital gyrus	−42, −90, 8	5.77	18/19	L sup parietal lobule	−16, −30, 64	8.46	5/7
L inf occipital gyrus	−18, −102, −8	7.71	17	L fusiform gyrus	−48, −72, −8	9.49	19/37
L caudate	−4, 22, 0	5.14		L lingual gyrus	−12, −66, 4	5.85	18
	−6, 4, 4	4.31		L inf occipital gyrus	−18, −102, −8	11.25	17
				L thalamus	−4, −4, 4	5.97	
R inf frontal gyrus	56, 40, 4	5.86	45				
R middle frontal gyrus	34, 52, 20	5.93	10	R inf frontal gyrus	60, 28, 20	9.55	45
R orbitofrontal cortex	18, 40, −20	5.71	11	R frontal operculum	32, 26, −8	7.21	
R precentral gyrus	60, −8, 20	8.38	4/6	R middle frontal gyrus	46, 54, 4	6.89	10
R angular gyrus	28, −70, 32	7.50	39		34, 52, 12	5.29	10
R inf occipital gyrus	12, −102, 0	9.74	17	R orbitofrontal cortex	22, 40, −16	8.16	11
R cerebellar hemisphere	28, −66, −16	8.27		R precentral gyrus	60, −8, 20	9.02	4/6
				R angular gyrus	28, −68, 32	10.00	39
				R sup parietal lobule	26, −66, 56	7.44	7
					32, −52, 52	6.44	7
				R inf occipital gyrus	12, −102, 0	14.29	17
				R cerebellar hemisphere	28, −72, −16	10.46	
(b) Second fMRI session (=T1)							
L inf frontal gyrus	−62, 14, 8	6.35	44	L inf frontal gyrus	−60, 20, 28	6.92	44
	−58, 20, 4	6.27	45		−54, 26, 16	6.61	45
L ant sup temporal gyrus	−40, 10, −16	7.09	38		−50, 44, −8	5.29	47
	−44, −6, −4	6.95	22	L orbitofrontal cortex	−2, 46, −12	6.86	11
L fusiform gyrus	−40, −64, −16	8.51	19/37	L ant cingulated cortex	−6, 30, −8	4.95	32
	−50, −72, −16	6.38	19/37	L sup frontal gyrus	−14, 58, 20	6.34	10
L lingual gyrus	−10, −62, 0	5.68	19	L precentral gyrus	−46, −8, 32	8.15	6
L middle occipital gyrus	−42, −86, 12	5.76	19	L ant sup temporal gyrus	−40, 14, −12	5.98	38
L thalamus	−2, −12, 4	5.44		L fusiform gyrus	−48, −78, −12	8.51	19/37
L caudate	−2, 6, 4	6.19		L sup occipital gyrus	−8, −78, 32	6.31	19
				L inf occipital gyrus	−14, −102, −12	9.35	17
R inf frontal gyrus	60, 26, 20	5.87	45	L thalamus	−8, −6, 8	9.60	
R precentral gyrus	56, −6, 32	6.62	6	L caudate	−4, 12, 0	5.84	
R angular gyrus	30, −68, 32	7.94	39				
R fusiform gyrus	52, −68, −12	6.88	19/37	R inf frontal gyrus	56, 38, 4	5.96	45
R inf occipital gyrus	36, −92, −8	9.22	18	R middle frontal gyrus	38, 52, 20	6.17	10
R cerebellar hemisphere	44, −82, −20	7.14		R precentral gyrus	58, −8, 24	6.53	6
				R angular gyrus	34, −78, 32	8.11	39
				R inf occipital gyrus	10, −98, −4	11.06	18
(c) Third fMRI session (=T2)							
L inf frontal gyrus	−56, 22, 12	6.44	45	L inf frontal gyrus	−60, 18, 16	10.70	44/45
L middle frontal gyrus	−26, 62, 4	7.55	10		−50, 8, 12	9.16	44
L precentral gyrus	−40, −10, 40	8.86	6		−56, 24, 0	8.11	47
L sup parietal lobule	−16, −30, 64	7.40	5/7	L ant cingulated cortex	−6, 36, −12	8.29	32
L precuneus	−22, −78, 48	7.38	7	L precentral gyrus	−44, −10, 36	10.04	4/6
L fusiform gyrus	−44, −72, −12	8.65	19/37	L sup parietal lobule	−16, −30, 64	11.85	5/7
L middle occipital gyrus	−32, −92, 16	7.68	19	L fusiform gyrus	−44, −72, −12	9.65	19/37
L inf occipital gyrus	−14,−100,−16	10.61	17	L lingual gyrus	−14, −72, 4	6.42	18
L thalamus	−4, −10, 4	7.50		L cuneus	−2, −88, 32	7.99	19
L cerebellar hemisphere	−40, −58, −24	8.82		L inf occipital gyrus	−16,−100,−16	12.06	17
				L caudate	−10, 4, 8	10.98	
R inf frontal gyrus	60, 28, 16	6.29	45				
R inf middle gyrus	52, 50, 0	8.32	10	R inf frontal gyrus	62, 24, 24	10.16	44
R SMA	12, 14, 68	6.08	6		58, 36, 4	9.90	45
R precentral gyrus	56, −6, 32	8.24	6		38, 16, −16	8.35	47
R angular gyrus	28, −68, 32	9.47	39	R precentral gyrus	54, −8, 24	10.36	4/6
R fusiform gyrus	28, −68, −16	10.28	19/37	R paracentral gyrus	20, −26, 60	7.61	5/7
R cerebellar hemisphere	28, −82, −20	10.38		R angular gyrus	32, −76, 32	13.56	39
	34, −48, −24	10.37		R sup parietal lobule	32, −52, 52	8.38	7
				R ant sup temporal gyrus	46, −6, −4	8.36	22
				R middle temporal gyrus	62, −34, 0	7.45	21
				R fusiform gyrus	52, −60, −12	7.00	19/37
				R inf occipital gyrus	14, −98, 0	11.79	17/18
				R cerebellar hemisphere	34, −48, −24	11.85	11.85

Table 2 B. The stereotactical coordinates for the pattern of brain activity related to "only correct" responses during the naming tasks in T0 and T2, respectively for L1 (left columns) and L2 (right columns).

L1 - Spanish				*L2 - Italian*			
a) first fMRI session (= T0)							
Anatomical location	***Coordinates x, y, z***	***Z-value***	***BA***	***Anatomical location***	***Coordinates x, y, z***	***Z-value***	***BA***
L inf frontal gyrus	-58, 26, 16	4.97	45	**L** inf frontal gyrus	-54, 32, 16	6.00	45
L middle frontal gyrus	-48, 48, 4	4.81	10/46	**L** orbitofrontal cortex	-22, 38, -16	5.89	11
L precentral gyrus	-62, -4; 8	7.27	6	**L** precentral gyrus	-46, -12, 36	7.03	4/6
L ant cingulated cortex	-2, 42, 0	4.89	32		-62, -2, 8	6.85	6
	-4, 30, -8	5.00	32	**L** ant cingulated cortex	-2, 40, -8	6.11	32
L lingual gyrus	-2, -62, 4	5.48	18	**L** fusiform gyrus	-48, -80, -8	7.28	19/37
L inf occipital gyrus	-12, -100, -8	6.18	17	**L** middle occipital gyrus	-38, -96, 4	7.06	18
L caudate	-4, 22, 0	5.24		**L** inf occipital gyrus	-16, -102, -8	8.39	17
R inf frontal gyrus	56, 40, 4	5.46	45				
R middle frontal gyrus	32, 48, 20	4.98	10	**R** inf frontal gyrus	58, 28, 20	7.68	45
R orbitofrontal cortex	18, 42, -20	4.76	11	**R** frontal operculum	32, 12, -4	6.46	
R precentral gyrus	60, -8, 20	6.49	4/6	**R** orbitofrontal cortex	22, 40, -16	6.79	11
R angular gyrus	30, -76, 36	5.19	39	**R** precentral gyrus	62, -6, 20	6.52	4/6
R inf occipital gyrus	32, -94, 0	6.93	18	**R** angular gyrus	28, -68, 32	6.58	39
R cerebellar hemisphere	28, -64, -8	6.04		**R** inf occipital gyrus	12, -102, 0	10.71	17
				R cerebellar hemisphere	28, -72, -16	8.45	
c) third fMRI session (= T2)							
L inf frontal gyrus	-54, 30, 12	5.76	45	**L** inf frontal gyrus	-60, 18, 16	10.64	44/45
L precentral gyrus	-64, -8, 8	6.09	6		-50, 8, 12	9.19	44
L inf parietal lobule	-56, -54, 32	5.17	40		-56, 24, 0	8.12	47
				L ant cingulated cortex	-6, 36, -12	8.25	32
R inf frontal gyrus	58, 38, 0	6.05	45	**L** precentral gyrus	-44, -10, 36	9.76	4/6
					-62, -2, 8	9.25	6
	60, 28, 20	5.78	45	**L** paracentral gyrus	-16, -30, 64	11.49	5/7
	54, 46, 0	5.45	10	**L** fusiform gyrus	-44, -72, -12	9.55	19/37
R fusiform gyrus	42, -78, -8	6.66	19/37	**L** lingual gyrus	-14, -72, 4	6.42	18
R inf occipital gyrus	12, -96, 0	5.22	17	**L** cuneus	-2, -88, 32	7.92	19
R cerebellar hemisphere	38, -46, -24	6.08		**L** inf occipital gyrus	-16,-100,-16	11.68	17
				L caudate	-10, 4, 8	10.90	
				R inf frontal gyrus	62, 24, 24	10.12	44
					58, 36, 4	9.84	45
					38, 16, -16	8.29	47
				R precentral gyrus	54, -8, 24	10.25	4/6
				R paracentral gyrus	20, -26, 60	7.60	5/7
				R angular gyrus	32, -76, 32	13.26	39
				R sup parietal lobule	26, -64, 56	8.57	7
				R ant sup temporal gyrus	46, -6, -4	8.36	22
				R middle temporal gyrus	62, -34, 0	7.53	21
				R fusiform gyrus	52, -60, -12	7.04	19/37
				R inf occipital gyrus	14, -98, 0	11.48	17/18
				R cerebellar hemisphere	36, -48, -28	11.59	

Table 3. Intrinsic connections within the chosen network

Mean coupling parameters over subjects (mean), standard deviation (SD),and two-tailed statistical significance (p) are reported.

Intrinsic Connections	*Mean*	*Std. Dev.*	*p-values*
Area 37/19 to Area 47	0.268	0.176	< 0,0001
Area 37/19 to Area 45	0.318	0.196	< 0,0001
Area 37/19 to LC	0.207	0.230	0.004
Area 47 to Area 45	0.135	0.153	0.004
Area 47 to LC	0.110	0.107	< 0,001
Area 47 to ACC	0.132	0.140	0.003
Area 45 to Area 47	0.076	0.089	0.005
Area 45 to LC	0.191	0.174	< 0,001
Area 45 to ACC	0.187	0.165	< 0,001
LC to Area 47	0.038	0.073	0.061
LC to Area 45	0.161	0.147	< 0,001
LC to ACC	0.137	0.147	0.003
ACC to Area 47	0.090	0.116	0.009
ACC to Area 45	0.211	0.196	< 0,001
ACC to LC	0.185	0.160	< 0,001

Table 4. Single connections related to L1 and L2 through T0, T1 and T2.

The differences highlighted in red indicate that the estimated parameter relative to a specific intrinsic connection is significantly higher for L2 than L1 (L2>L1) and the difference between the parameters relative to that specific connection is significantly different with respect to the overall mean difference between the pairs of values related to the connections for the two languages in a specific session (i.e., T0, T1, T2). Likewise, the blue-highlighted differences indicate that the estimated parameter relative to a specific intrinsic connection is significantly higher for L1 than for L2 (L2<L1) and the difference between the parameters relative to that specific connection is significantly different with respect to the overall mean difference between the pairs of values related to the connections for the two languages in the specific session. The differences in black indicate that the difference between the pair of values for the specific connection does not differ significantly from the overall mean difference between the pairs of values for the connections for the two languages in that specific session.
On the other hand, as to the lower part of the table (i.e., mean difference), the values highlighted in red indicate that the mean difference between the pairs of values related to the connections for the two languages in a specific session is significantly different from zero and is significantly higher for L2 than L1 (L2>L1). The values highlighted in blue indicate that the mean difference between the pairs of values related to the connections for the two languages in a specific session is significantly different from zero and is significantly higher for L1 with respect to L2 (L2<L1). The values in black indicate that the mean difference between the pairs of values related to the connections for the two languages is not significantly different from zero and that there isn't an overall shift in connectivity in the direction of L1 or L2.

Intrinsic Connections	**T0**	**T1**	**T2**
	IT-SP	**IT-SP**	**IT-SP**
Area 37/19 to Area 47	**-0.137**	**-0.091**	**0.508**
Area 37/19 to Area 45	-0.034	**0.246**	0.344
Area 37/19 to LC	-0.006	0.030	**-0.292**
Area 47 to Area 45	**-0.124**	**-0.075**	**0.479**
Area 47 to LC	-0.027	**-0.068**	0.303
Area 47 to ACC	-0.059	**-0.067**	**0.438**
Area 45 to Area 47	-0.009	0.002	0.305
Area 45 to LC	-0.043	**0.076**	**0.519**
Area 45 to ACC	-0.018	**0.111**	0.378
LC to Area 47	**0.068**	**-0.084**	**-0.111**
LC to Area 45	**-0.125**	-0.055	0.149
LC to ACC	**0.020**	0.046	**-0.070**
ACC to Area 47	0.007	**-0.116**	**0.426**
ACC to Area 45	**-0.125**	-0.024	**0.549**
ACC to LC	-0.004	0.049	0.363
Mean Difference	**-0.041**	-0.001	**0.28584**
Std Error	0.01582	0.02495	0.06575
Prob > |t|	**0.0214**	0.9573	**0.001**

FIGURE LEGENDS

Figure 1.
The figure reports the MR scanning performed in the acute phase (A) and as may be observed the hemorrhage affected the left lenticular nucleus and surrounding areas. MR scanning performed at T2, showed the complete reabsorption of the bleeding (B).

Figure 2.
The figure depicts the connections between brain areas that we have chosen for our model in the current paper. The ACC (anterior cingulate cortex) and the LC are involved in language control and are depicted in red, BA 45 and Ba19/37 are involved in picture naming, and BA 47 is involved either in naming or in cognitive control.

Figure 3.
The graph reports the patient's picture naming performance under the fMRI scanner (see results section for number of correct responses) for L1 (right) and L2 (left) at T0 (top), T1 (middle) and T2 (bottom).

Figure 4.
Functional activation data as revealed with event-related fMRI scanning during the picture naming task. In A we report the pattern of brain activity related to the overall performance for L1 (left) and L2 (right) at T0 (top), T1 (middle) and T2 (bottom). In B, we report brain activity related only to the correct responses for L1 (left) and L2 (right) at T0 (top) and T2 (bottom).

Figure 5.
Differences between L1 strength values and L2 strength values for each single connection in each specific session, i.e., T0 (top), T1 (middle) and T2 (bottom). In each single graph, i.e., for T0, T1 and T2 respectively, the 0 value is marked by a black line in the graph. Strength values of the single connections above the 0 line are higher for L2 while those below the 0 are higher for L1. Each number in the graphs (from 1 to 15) characterize a specific connection. The intrinsic connections that were investigated and their enumeration are reported at the bottom right of the figure.

Figure 1

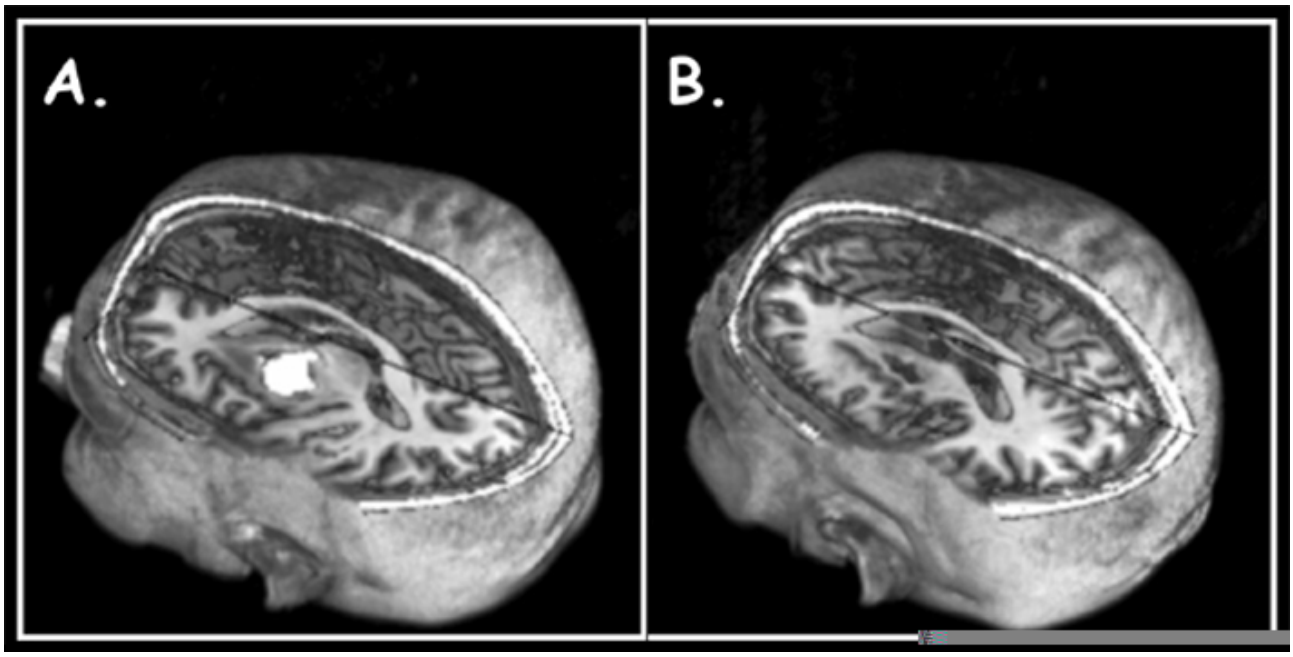


Figure 2

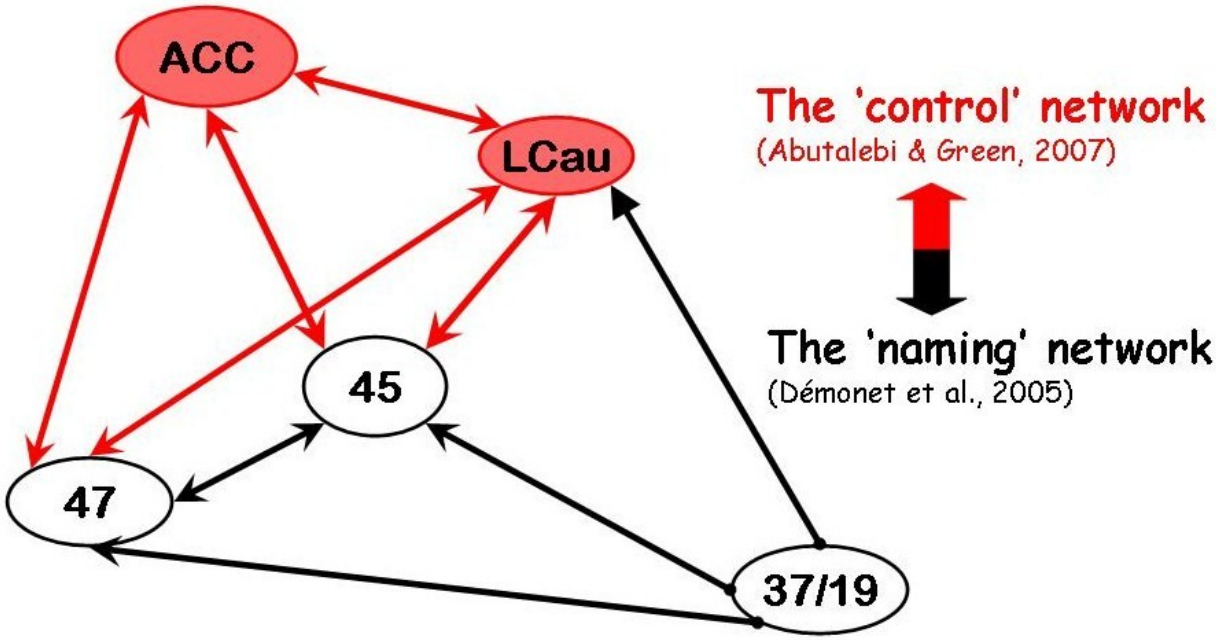

ACC
LCau
45
47
37/19
The 'control' network
(Abutalebi & Green, 2007)
The 'naming' network
(Démonet et al., 2005)

Figure 3

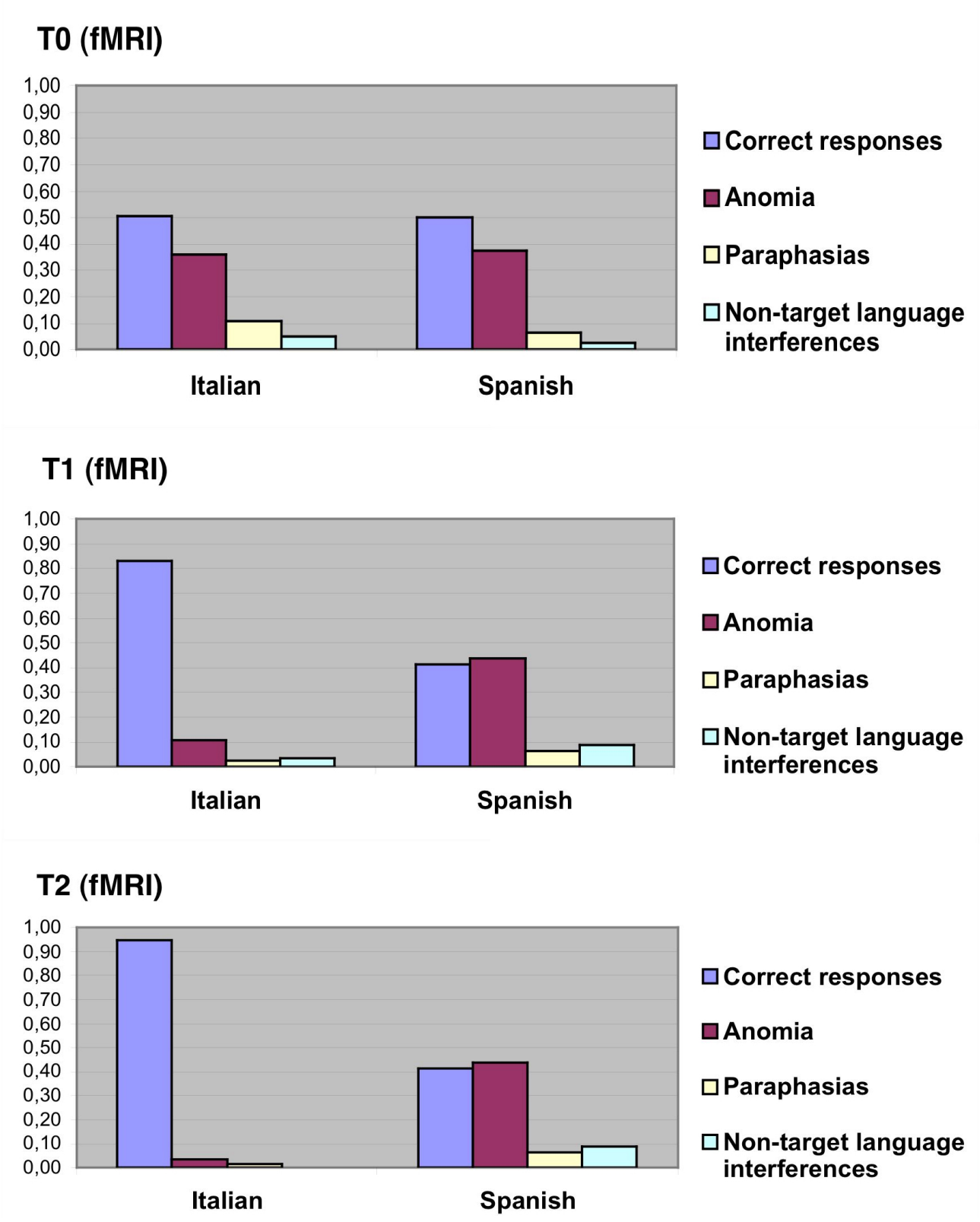

T0 (fMRI)
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
Italian
Spanish
Correct responses
Anomia
Paraphasias
Non-target language interferences
T1 (fMRI)
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
Italian
Spanish
Correct responses
Anomia
Paraphasias
Non-target language interferences
T2 (fMRI)
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
Italian
Spanish
Correct responses
Anomia
Paraphasias
Non-target language interferences

Figure 4

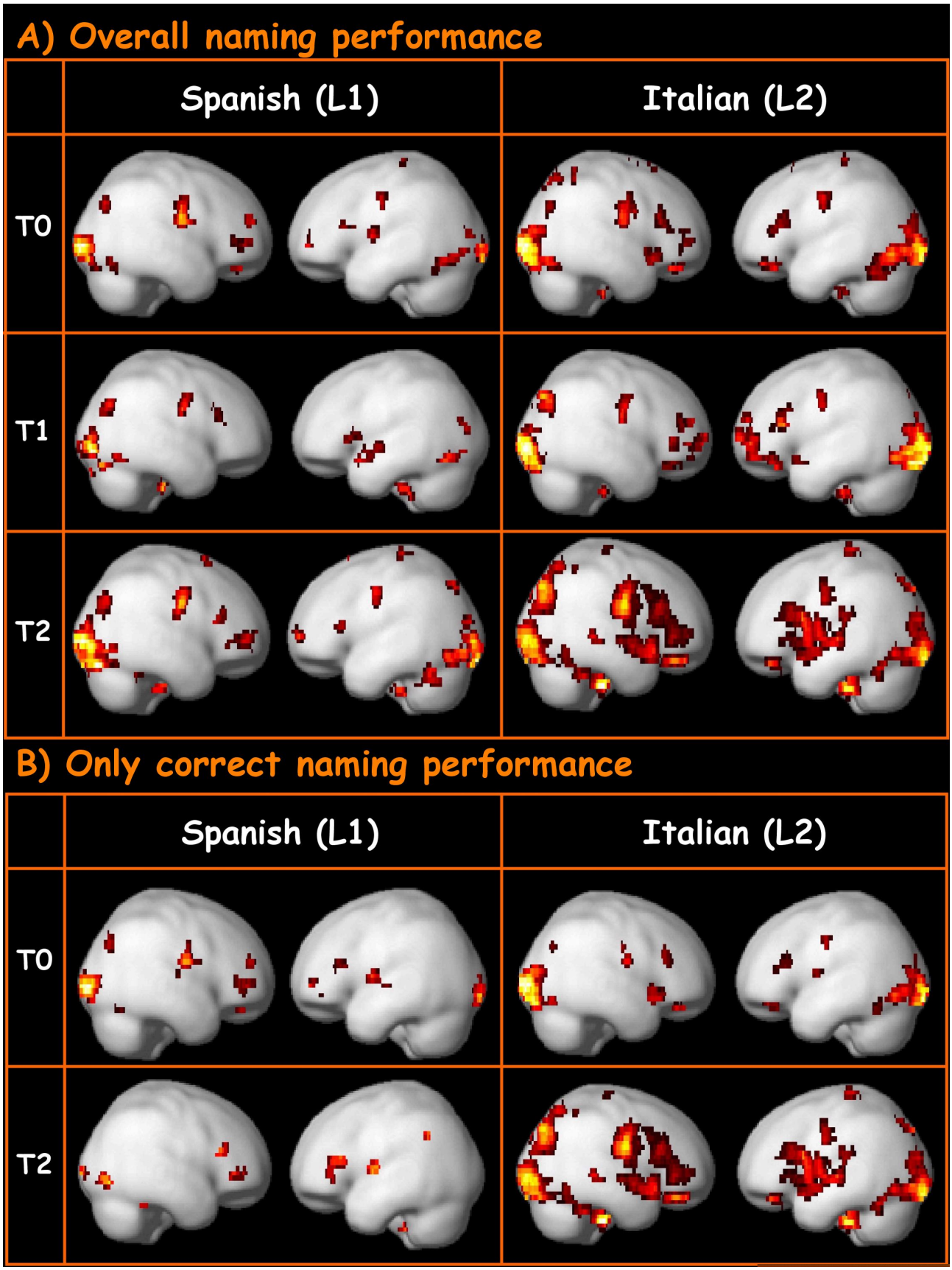
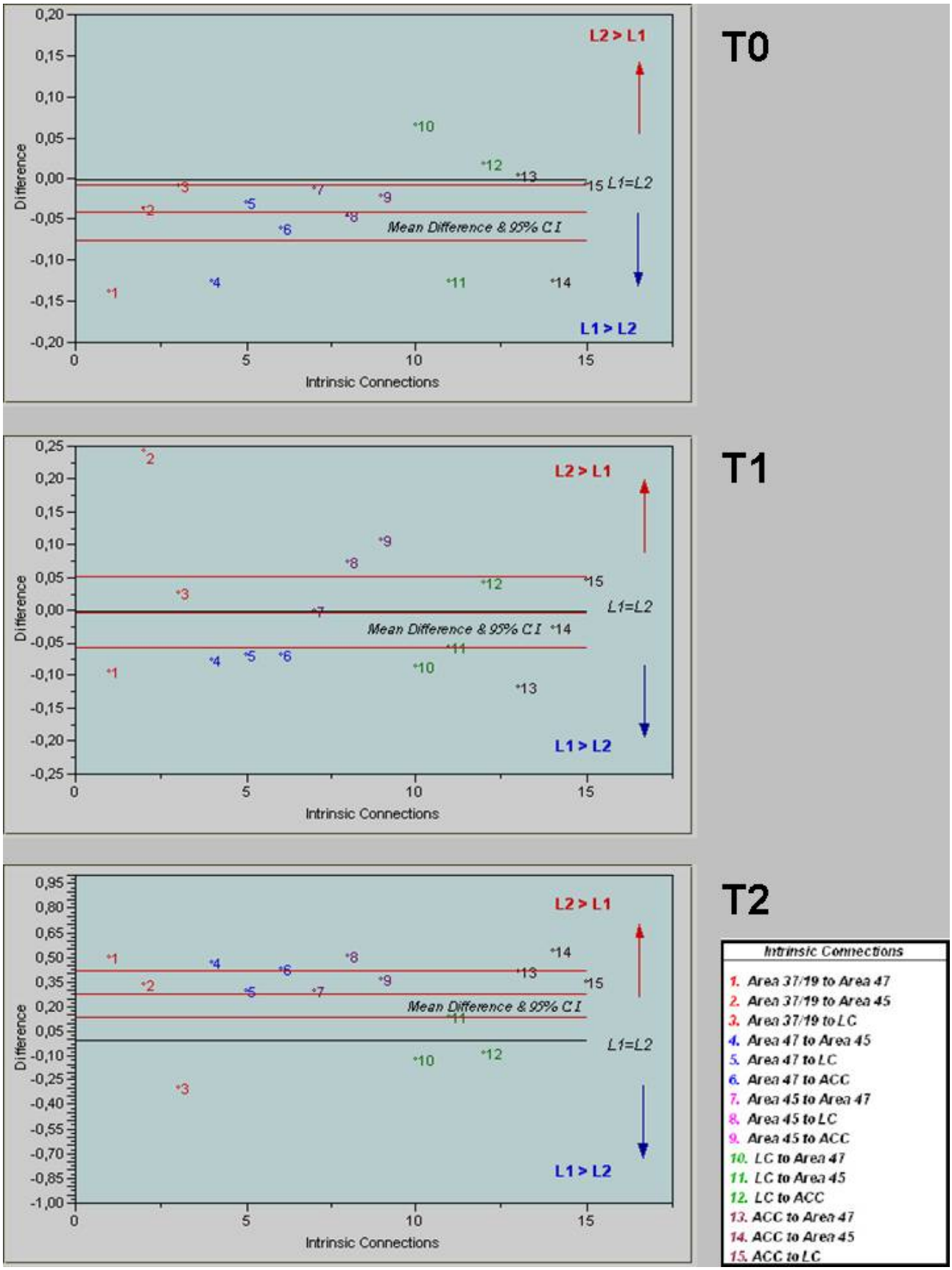

A) Overall naming performance
Spanish (L1)
Italian (L2)
T0
T1
T2
B) Only correct naming performance
Spanish (L1)
Italian (L2)
T0
T2

Figure 5


T0
L2 > L1
L1=L2
L1 > L2
Mean Difference & 95% C I
Difference
Intrinsic Connections
T1
L2 > L1
L1=L2
L1 > L2
Mean Difference & 95% C I
Difference
Intrinsic Connections
T2
L2 > L1
L1=L2
L1 > L2
Mean Difference & 95% C I
Difference
Intrinsic Connections
Intrinsic Connections
1. Area 37/19 to Area 47
2. Area 37/19 to Area 45
3. Area 37/19 to LC
4. Area 47 to Area 45
5. Area 47 to LC
6. Area 47 to ACC
7. Area 45 to Area 47
8. Area 45 to LC
9. Area 45 to ACC
10. LC to Area 47
11. LC to Area 45
12. LC to ACC
13. ACC to Area 47
14. ACC to Area 45
15. ACC to LC