The Role of the Dominant versus the Non-Dominant Hemisphere: An fMRI

Study of Aphasia Recovery Following Stroke

by

Jessica C. Hodgson[1], Abdelmalek Benattayallah[2] and Timothy L. Hodgson[1]

[1] School of Psychology

College of Social Science

University of Lincoln

Lincoln

UK

[2] Peninsula MR Research Centre,

Peninsula Medical School,

University of Exeter,

Exeter

UK

Corresponding author:
Jessica C Hodgson
School of Psychology
College of Social Science
Brayford Pool
Lincoln LN6 7TS
UK
Email: jhodgson@lincoln.ac.uk Tel: 01522 837366

Abstract

Background: Speech production is one of the most frequently affected cognitive functions following stroke, however the neural mechanisms underlying the recovery of speech function are still incompletely understood.

Aims: The current study aims to address the differential contributions of the dominant and non dominant hemispheres in recovery from aphasia following stroke by comparing data from 4 stroke patients and 12 control participants to assess patterns of activation during speech production tasks during fMRI scanning.

Methods and Procedures: Four chronic stroke patients (3 left hemisphere lesion and 1 right hemisphere lesion) diagnosed with Broca's aphasia at the acute phase, but now recovered to near normal speech ability, were tested on speech production tasks (phonemic fluency, categorical fluency and picture naming) whilst undergoing functional magnetic resonance imaging (fMRI). These patients were compared with 12 healthy controls undergoing the same procedure.

Results: Individual subjects analysis showed activation peaks in perilesional areas in three out of four patients. This included one patient with right hemisphere lesion, who also showed predominant perilesional activation. Group analysis of control participants showed predominately left hemisphere activation, but not exclusively so. Laterality indexes were calculated and showed predominant left hemisphere lateralisation in the control group (LI = 0.4). Three out of the four patients showed speech lateralised to the same hemisphere as their lesion and the 4th patient showed speech lateralised to the opposite hemisphere to their lesion. Different speech production tasks resulted in varying lateralisation indices within participants.

Conclusions: The data suggest that peri-lesional areas support recovery of speech in the chronic phase post-stroke regardless of the site of the lesion. The study has implications for the understanding of functional recovery as well as for the paradigms used in fMRI to localise speech production areas. Specifically, a variety of speech tasks are required to elicit activation that is representative of the range of cortical involvement in speech in healthy adults, and that also allows for accurate reporting of the extent of recovery experienced in patients.

Introduction

Aphasia is one of the most common consequences of middle cerebral artery (MCA) stroke, due to the extended network of cortical and sub cortical structures perfused by it. Research suggests that whilst most patients suffering from aphasia resulting from an MCA stroke will experience some degree of recovery in the acute phase, there is often a residual speech deficit that remains into the chronic phase (e.g. Pedersen, Jorgensen, Nakayama, Raaschou & Olsen, 1995). One of the fundamental debates within the literature on neurological recovery of speech function post stroke is the role of the contra-lesional hemisphere versus the role of peri-lesional cortex in facilitating this recovery. Recent accounts have also questioned whether traditional language regions, such as Broca's area, are truly language specific or also subserve domain general functions, such as cognitive control and working memory (e.g Fedorenko, Duncan & Kanwisher, 2012). However, there is still conflicting evidence regarding the exact role of each hemisphere in supporting speech production following stroke, and as research techniques have become more precise, the contribution of differing brain regions to recovery has become less clear (Turkeltaub et al., 2012).

Historically two dominant theories have been used to explain the brain regions most important for effective speech recovery post stroke. The first of these theories posits that regions in the non dominant hemisphere (usually the right) homologous to those damaged in the dominant hemisphere (usually the left) may be activated in order to sustain some degree of speech function. This perspective has received the majority of its more recent support from functional imaging studies that show increased activation occurring in the right hemisphere of brain injured patients during language tasks, compared to healthy control subjects (eg. Gold & Kertesz, 2000;

Rosen et al., 2000; see Crosson, et al., 2007, for review). Thulborn, Carpenter & Just (1999) report a patient who showed rapid recovery following a left hemisphere stroke affecting Broca's area. Three days into the recovery pattern fMRI scans revealed a shift of activation from the left to the right hemisphere, a functional adjustment that continued rightward over the following six months post stoke. The authors concluded that recovery from aphasia not only occurs rapidly, but that homologous right hemisphere regions are responsible for the accurate recovery of language abilities. Cappa et al. (1997) used PET to carry out a follow-up study of patients who had demonstrated recovery from aphasia at two weeks post stroke. The follow-up session took place six months post stroke and the results showed significant correlations between improved language performance and activation of regions within the right hemisphere.

Further evidence that supports the right hemisphere lateralisation approach comes from work by Musso et al. (1999). They conducted a longitudinal study using PET imaging whereby patients were scanned on twelve separate occasions. In the periods between each scanning session the patients underwent intensive language training, specifically in comprehension tasks. Results showed that following the training performance on these tasks significantly improved and that this improvement significantly correlated with increased activation within right hemisphere regions, whilst no further activation of left hemisphere language regions was detected. The right hemisphere perspective also has support from work carried out by Nelles, Sullivan, Kaplan, Klein & Calvanio (1998). This study found that patients who had originally suffered aphasia following a left hemisphere stroke and who had subsequently showed significant recovery of language function become aphasic again following a right hemisphere stroke. The authors argue that this demonstrates that language capabilities had been taken over by the right hemisphere after the original

lesion, due to the fact that the recovered ability was lost following a stroke to the right hemisphere.

A second theory proposes that peri-lesional cortical areas immediately surrounding the damaged region take over responsibility for speech processes (Fernandez et al., 2004). Warburton, Price, Swinburn & Wise (1999) conducted a study that compared healthy participants to patients showing some recovery from aphasia following left hemisphere strokes. They found that the patients showed significant differences in the location of activation within the left hemisphere despite task performances being comparable with healthy participants, indicating that peri-lesional tissue was being recruited for language generation tasks. Furthermore, the activation patterns seen within the right hemisphere in the patient group were not significantly greater than the right hemisphere activation patterns seen in the healthy control group. This suggests that recovery of speech is not dependent on the recruitment of homologous networks which aren't ordinarily associated with language tasks. Similarly, work by Leger et al. (2002) showed that in a patient with left IFG lesions caused by stroke intensive speech therapy not only improved speech task performance but also revealed left sided activation patterns surrounding the lesion, as opposed to right hemisphere activation patterns.

Further evidence in support of the hypothesis that left hemisphere peri-lesional regions recover to sustain speech function comes from studies which show that activation observed in the right hemisphere does not correlate with degree of recovery. Heiss, Kessler, Thiel, Ghaemi, & Karbe (1999) compared the contribution of both the sub-dominant and dominant hemispheres to a variety of language related tasks. They found that whilst there was activation observed in both hemispheres, task performance levels differed in relation to the patterns of activation shown, with left hemisphere activation dominating effective task performance. The authors concluded

that although right hemisphere areas may contribute, effective recovery could only be demonstrated if left hemisphere regions were either preserved or integrated into existing networks. This perspective has been supported by other neuroimaging studies that have concluded that the right hemisphere is less efficient and less effective at supporting language and speech processing, especially when compared to more typical left hemisphere areas (Postman-Caucheteux et al., 2010; Winhuisen et al., 2005; Karbe, Thiel & Weber-Luxenburger, 1998).

One of the other crucial variables in terms of the activation patterns observed in neuroimaging studies is the duration of the recovery period, or time post stroke, upon testing. Saur et al. (2006) conducted a longitudinal fMRI study in order to address the issue of differential results depending on the point at which testing occurred during recovery. They demonstrated that recovery seemed to be occurring in a multi-stage process, involving both the left and right hemispheres. Their results showed that at the acute stage of recovery, task performance was low and activation patterns were relatively dispersed. At the sub-acute stage however performance had improved and there was greater activation in right hemisphere regions. Finally, when the patients were tested again at the chronic stage, task performance was normal and activation had returned to a left hemisphere dominant pattern (see also Fernandez et al., 2004).

Explanations for the neural basis behind the apparent shift in function from the dominant left hemisphere to the sub-dominant right hemisphere and back again during the course of recovery have not yet been satisfactorily tested. However one of the most widely accepted theories is that the activation observed in the right hemisphere represents residual activation resulting from the damaged network, and not, as some reports suggested, the creation of a novel neural pathway for language. Heiss & Thiel

(2006) postulate that this residual activation observed in the right hemisphere is a consequence of reduced bilateral cortical inhibition. They state that "for the specialisation of different brain areas for definitive functions and for the lateralisation of higher functions, the neurons involved in the special tasks must inhibit neurons in neighbouring areas and in those parts of the bilateral network which are not involved in this performance" (Heiss & Thiel, 2006, p118). Therefore when the dominant network is damaged, as in the case of stroke, there is no means of mediating the residual activation of the non-dominant hemisphere, which could be why during the early stages of recovery these regions are significantly more activated. However, as the system recovers and function is regained, cortical plasticity results in the dominant hemisphere working more efficiently which subsequently normalises activation patterns. This would explain why there are differential patterns of activation depending on time of recovery, and also would indicate that effective recovery of speech function can only occur with the restoration of the typically left hemisphere language systems. What is obvious from this debate is that recovery patterns post stroke are not clear cut. As argued by other researchers (Crosson et. al, 2007) it is indeed too simplistic to view speech production as either a left or right hemisphere process, and yet the exact interaction of the two hemispheres remains unclear.

More recent accounts argue that recovery related activation could be related to domain general processing rather than activation that is specific to language networks (e.g. Brownsett et al., 2014; Federenko et al., 2012). This challenges the common view that behavioural speech production tasks activate language specific networks and that any activation observed in patients not seen in the same regions in controls is indicative of a reorganised language pathway (Brownsett et al. 2014). Instead it suggests that the differences in activation patterns seen in aphasic patients is in part a result of increased activity in domain general networks, i.e. those responsible for

cognitive control and executive function, because the demands of speech production tasks are greater for these individuals. Fedorenko et al. (2012) addressed this issue in an fMRI study by comparing significantly activated voxels within Brodmann Areas 44 and 45 in either language tasks or in domain general tasks. They report that both sets of tasks activated adjacent voxels within these regions and conclude that Broca's area contains both language specific and domain general pathways.

The primary focus of this study was to use functional imaging to examine the extent of neurological recovery within the dominant hemisphere following post stroke aphasia, and to move away from focussing on left vs. right hemisphere distinctions. The patients in this study were in the chronic phase of their recovery and so had regained a relatively high degree of speech capability. Therefore, based on the literature reviewed above, the study worked with the hypothesis that activation during specific speech production tasks will be predominantly evident in the peri-lesional regions of the dominant hemisphere when compared to controls, thus reflecting the increased activation in language specific networks in these regions. It was hypothesised that non-dominant hemisphere activation will not be significantly greater than in control subjects and that this reflects an adaptive response to the recovery process. The second aim was to assess the effectiveness of the speech tasks used to elicit measurable fMRI activation in participants and to report any differences in activation patterns elicited by different speech tasks.

Methods

Participants

Patients

Four participants in chronic stage of recovery post-stroke completed the experiment, three with left frontal lesions and one with a right frontal lesion (see Figure 1.). Participants were recruited via the ExAda Speakability group, Exeter. All were in the chronic stage of recovery from aphasia and therefore not considered medically unwell, however all had received a diagnosis of Broca's aphasia at the time of their stroke. The presence of aphasia at diagnosis was defined as impairment in language following damage to the brain and not due to developmental or cognitive impairments. Inclusion criteria for participation consisted of (i) first and only stroke; (ii) an interval of at least one year since the stroke; (iii) a Broca's aphasia diagnosis resulting from this stroke. Exclusion criteria consisted of (i) the inability to perform the language tasks in the study; (ii) the inability to tolerate a 30-minute fMRI session; (iii) lesions that extended too far throughout the hemisphere (lesion volume > 150 CCs) and (iv) failure to pass the Peninsula MRI Centre safety screening protocol; this is designed to prevent individuals undergoing MRI scanning where they may suffer adverse reactions to the procedure. Examples of these exclusions are individuals with specific medical conditions, individuals with medical device implants such as pacemakers or those who are pregnant.

Three participants were male and one was female, all with normal hearing and normal or corrected-to-normal vision. All were right-handed, determined by self report of preferred hand for writing and general usage.

Participant 1 was a 74 year old female, with Broca's aphasia following a right hemisphere MCA stroke; structural images taken at the time of participation revealed areas of ischaemic tissue damage in the right insula cortex, approximating to Brodmann areas 44 and 47 with the lesion also extending into the postero-lateral

frontal cortex (see figure 1). Lesion volume was estimated at 70.6 cc's via MRIcro image analysis software. P1 had an education level of 17 years (completed University), English as a first language, and was 3 years post-onset of aphasia at the time of the study. P1 had no evidence for contralesional paralysis or hemi-spatial neglect and no other reported neurological disease/disorder, or evidence for dementia or general cognitive impairment. P1 also completed two oculomotor tests in an earlier testing date as part of a separate study (see Hodgson et al., 2007). In the pro-saccade response task a peripheral target onset is presented to either the left or the right and must be fixated with an eye movement. In this task, P1 responded on all 60 trials with a normal response amplitude but significantly longer than normal mean saccade response times of 383ms (left) 392ms (right) as judged relative to 95% confidence intervals of control performance. She also completed the anti-saccade task, a test of volitional inhibitory control in which a saccade must be away from a target onset towards the mirror image opposite location. In this test, P1 made a higher than normal rate of anti-saccade errors in which the target was fixated by a saccade to both left and right side target locations (69% left and 70% rightward directed errors) suggestive of a deficit in inhibitory behavioural control in this task.

Participant 2 was an 81 year old male with Broca's aphasia following a left hemisphere MCA stroke. Structural images taken at the time of participation revealed damage to a large part of the ventro-lateral frontal lobe corresponding to the inferior frontal gyrus and anterior insula (see figure 1). Lesion volume was estimated at 63.8 cc. P2 was had an educational level of 14 years, English as a first language and was 13 years post onset of aphasia at the time of testing. P2 had no evidence for contralesional paralysis or hemi-spatial neglect and no other reported neurological disease/disorder, or evidence for dementia or general cognitive impairment.

Participant 3 was a 69 years old male with Broca's aphasia following a left hemisphere MCA stroke. Structural images taken at the time of participation revealed a somewhat more extensive area of ischaemic tissue loss than was the case for patients 1 and 2, revealing a lesion which included a large part of the left dorsal and ventro-lateral frontal lobe, extending posteriorly into the inferior parietal lobule (see figure 1). Lesion volume for this patient was estimated at 103.4 cc's. P3 had an educational level of 17 years, English as a first language and was 14 years post onset of aphasia at the time of testing. P3 had no reported paralysis or neglect and no other reported neurological disease/disorder. P3 did not have a diagnosis of cognitive impairment or any reported changes in cognitive functioning.

Participant 4 was a 69 year old male with Broca's aphasia following a left hemisphere MCA stroke. Structural images taken at the time of participation revealed that damage in this patient was centred on a more dorsal regions of the frontal lobe than was the case in patients 1-3, but included parts of the left inferior frontal gyrus approximating to Broca's area as was the case with patients 2 and 3 (see figure 1). Lesion volume for this patient was estimated at 89.4 cc's. P4 had an educational level of 14 years, English as a first language and was 6 years post onset of aphasia at the time of testing. P4 had no reported paralysis or neglect and no other reported neurological disease/disorder. P4 had no evidence for contralesional paralysis or hemi-spatial neglect and no other reported neurological disease/disorder, or evidence for dementia or general cognitive impairment. P4 also completed the saccade task described above. He had normal pro-saccade reaction times: 223ms (left) 180ms (right) but abnormal anti-saccade error rates relative to 95% confidence intervals of

control performance, particularly for errors directed towards right sided target onsets with 43% and 63% errors to the left and right respectively.

[INSERT FIGURE 1 HERE]

Behavioural Evaluation

Each of the patients was given a short behavioural evaluation to measure the extent of their aphasia at the time of testing. This was done via the Western Aphasia Battery (WAB) (Shewan & Kertesz, 1980) to establish a standardised Aphasia Quotient score. Patients also completed the phonemic verbal fluency F, A, S test. The FAS test requires individuals to generate as many words beginning with a given letter as possible in 60 seconds, normative scores for healthy adults in this age group and education level are around 30 – 40 items generated (see Tombaugh, Kozak & Rees, 1999). These tests were chosen as they best represented the specific language functions being examined in this study, namely speech production, and were related to the tasks the participants would be undertaking (Rosen et al, 2000). Using sub tests was appropriate in order to reduce the length of time taken to administer the evaluations, and also due to the stage of recovery the participants had reached. Table 1 outlines the WAB component scores for Spontaneous Speech, Comprehension, Repetition and Naming standardised scores for each patient along with the calculated Aphasia Quotient score and classification of aphasia based on these scores according to Lezak (1995). Each participant had recovered to low normal speech function or remained at mild aphasic levels.

[INSERT TABLE 1 HERE]

Control Participants

A mixed age control group consisting of twelve participants (6 males and 6 females) were recruited via the University of Exeter's School of Psychology participant database. The controls were aged between 18 and 69 years of age (M = 37, SD = 19.75) and were all right hand dominant and had normal or corrected to normal vision. None of the control participants had any history of neurological disorders, head trauma, substance abuse, psychiatric disorders, or developmental speech/language disorders. Prior to the commencement of the experiment, informed consent was obtained in writing from all participants. Ethical approval for this project was obtained from the School of Psychology Research Ethics Committee at the University of Exeter.

Procedure and Design

Participants attended the MRI centre at Peninsula Medical School, University of Exeter where they completed the MRI Centre safety checklists and informed consent procedure.

Prior to commencing the study, participants were given a practice trial on each of the three paradigms outside of the MRI scanner to ensure they correctly understood the task instructions and the sub-vocal (whispering) technique. This was to ensure that their technique was correct to reduce the possibility of individual variability (for example, in terms of minimising head movements) during the scanning session. In addition, the four patients who participated also underwent the behavioural evaluation described above, prior to the fMRI test phase.

The fMRI testing phase used three speech production tasks previously shown to elicit effective activation levels in fMRI (e.g. Rosen et al., 2000) and required participants to make sub-vocal (whispered) responses to the stimuli. This technique was used to minimise jaw and muscle movements, which would lead to movement-

by-field-inhomogeneity artefacts in the MRI signal, potentially leading to anomalous activations, whilst ensuring speech responses were performed. It was necessary to ensure patients did produce overt articulations, firstly to ensure task compliance, but also because previous research has shown that aphasic patients report having fluent 'inner speech' (e.g. Marshall et al., 1994), thus rendering silent speech paradigms problematic.

The tasks were: Phonemic verbal fluency, where participants were presented with a letter (e.g. A, B, C) and were asked to generate as many words starting with that letter as they can within a given time frame; Categorical verbal fluency, where participants were presented with the title of a category (e.g. animals) and were required to generate as many members of that category as they can within a given time frame; Picture naming, where participants were shown line drawings (Snodgrass figures) of objects and were asked to name them.

The two fluency tasks (phonemic and categorical) were presented in the form of a block design, where stimuli were on the screen for 30 seconds and were then followed by a period of 30 seconds rest, to allow for the blood oxygen level dependent (BOLD) signal to realign. The picture naming task consisted of an event related design where stimuli were presented for 5 seconds interspersed with varying stimulus onset times (6.7, 9.1, 17.9 seconds). Therefore each task lasted approximately six minutes and participants were given a chance to rest between each session. The total scanning time took approximately 20 minutes per participant.

Data Acquisition

Scanning was performed on the 1.5-T Philips Gyroscan magnet at the Peninsula MRI research centre, University of Exeter, UK. A T2*-weighted echo-

planar sequence was adopted (TR = 3000 msec, TE = 50 msec, flip angle 908, 32

transverse slices, 3.6 _ 3.6 _ 4 mm3, ascending acquisition) using a quadrature head

coil. A total of 125 volumes were acquired in each of the three tasks per participant.

The stimuli were projected onto a screen situated at the foot end of the MRI scanner

and viewed through a mirror mounted on the head coil. The stimuli were presented

centrally on the screen as black line drawings on a white background, for the picture

naming task, and as black lowercase Times New Roman 22-point font on a white

background for the fluency tasks. Vocal responses were not recorded during this

procedure.

Image Analysis

Blood oxygen level dependent (BOLD) responses were analysed using SPM 8

software (www.fil.ion.ucl.ac.uk/spm). There were two approaches used to assess

changes in activity, first was a whole brain approach where significant changes in

activation across the cortex were recorded. This approach was adopted for both the

control group and the individual patient analysis. Secondly two region of interest

(ROI) analyses were used, where changes in activation magnitude were assessed

within predefined language areas, namely Brodmann Areas (BAs) 44 and 45 in both

hemispheres as well as a separate analysis examining other regions implicated in the

hypothesised domain general cognitive network underlying language production

comprising the anterior cingulate cortex and superior frontal gyrus (Brownsett et al.

2014). ROIs were generated using the WFUPickAtlas Toolbox (Maldjian, Laurienti,

Kraft & Burdette, 2003). The ROI masks were dilated by 1 voxel. Images were

realigned to remove unwanted changes in signal intensity caused by head movements,

normalised to a standard EPI template and smoothed with a Gaussian kernel of 6 mm.

For the two fluency tasks a box car function (comprising 30 sec task / rest periods)

was convolved with hemodynamic to create model regressors. The picture naming task used an event related design (0 sec event duration), where inter-event periods were selected to ensure stimulus onsets did not correlate with brain volume acquisition time. Picture onset times were used to create unique regressors by convolving onset times with a canonical hemodynamic response function.

Patient Scan Normalisation

During spatial normalisation processes each brain image is transformed into a standard space defined by a template image. This technique utilises algorithms that work by minimising the difference between the image to be normalised and the template image. In the presence of focal lesions, these algorithms attempt to reduce the discrepancy between the image and its template, which subsequently leads to distortion at the site of the lesion (Price, Crinion & Friston, 2006). Therefore, to overcome this problem cost-function masking was employed to exclude the lesion area from calculation of the image difference. Lesion masks were created for the each of the patients to ensure that data from these areas was excluded upon normalisation. This was done using MRIcro software (www.sph.sc.edu/comd/rorden/mricro.html) to draw around the lesion area on each slice of the T1* structural images obtained for each patient. From this lesion overlays were created and then transformed into lesion masks. Lesion masks were then exported as analyse images for use in the standard normalisation stage.

Statistical Analysis

In the first level analysis, a general linear model approach was used to calculate parameter values for each regressor and a series of one-sample t tests were carried out to determine whether the fitted parameter values at each voxel for each

participant were significantly greater than zero for each modelled event. This generated a series of t contrast images for each effect and participant, which were then entered into a second level (random effects) analysis to test which voxels showed consistent activation across participants. This analysis used one-sample t tests with an uncorrected statistical threshold ($p<0.001$) and a voxel cluster size threshold of 12. Finally, two-sample unrelated t tests uncorrected for multiple comparisons were used to assess the differences in significantly activated voxels between the control subjects and the three left IFG lesion patients in a between-subjects groups analysis. The x, y, z coordinates of all activation clusters were transformed from normalised MNI space to Talairach space (www.mrc-cbu.cam.ac.uk/imaging/mnispace.html) in order to ascertain the site of activation relative to the atlas of Talairach & Tournoux (1988).

Laterality Index

To determine the differential contributions of the two hemispheres to these speech production tasks a laterality profile was calculated producing a Lateralisation Index (LI) score for each participant. This was done using the fMRI LI Toolbox 1.02 provided by Wilke & Lidzba (2007). LI scores were based on a region of interest consisting of Brodmann Areas 44 and 45 in the left and right hemisphere. For each region on which the LI scores were based, 20 equally sized steps from 0 to the maximum t-value were taken as thresholds. At each level, 100 bootstrap resamples with a resample ratio of $k = 0.25$ were taken in the left and right investigated area. Then, all 10 000 possible LI combinations were calculated but only the central 50% of data were kept in order to exclude statistical outliers. In the last step, a weighted mean LI for each individual was calculated with higher thresholds receiving a higher weight. A more detailed description of this procedure can be found in Wilke & Schmithorst (2006).

LI values range from -1 (when there are only voxels active in the right

hemisphere) to +1 (when there is only signal in the left hemisphere) as they reflect the

normalized difference of activated voxels in the left and the right hemispheres. This

study used the following criteria to classify participants: Participants with LI < -.20

were classified as RH dominant, those with LI >+ .20 as LH dominant, and those with

LI between –.20 and +.20 as bilateral (e.g. Springer, et al., 1999).

Results

Control group:

One-sample t tests were used (random effects, uncorrected, p<0.001, t > 3.27)

to assess the significantly activated voxels using a whole brain approach across each

task. Figure 2 indicates that the control group showed left lateralised language

activation consistent across all tasks. When the tasks were combined the strongest

activation was evident within the anterior cingulate gyrus (BA 32) indicative of

response control processes. Activations were also evident within the left pre-central

gyrus (BA 44) and left IFG (BA 47), with weak but significant activation occurring in

the right IFG (BA 6). This activation pattern was also similar when each of the tasks

were contrasted separately, however greater activation in regions such as the occipital

lobe (BA 17) and the fusiform gyrus (BA 20) were also evident. For the letter fluency

and picture naming tasks increased activation was present in right hemisphere IFG

regions suggesting a contributing effect of right hemisphere to speech production

within these specific tasks (activation peaks in and around right pre-central gyrus, BA

6).

ROI analysis at group level was undertaken using Brodmann Areas 44 and 45,

left and right IFG; a one sample t-test (random effects, uncorrected, p<0.001) was

used to calculate significantly activated voxels. This showed predominant activation

in the left hemisphere, as seen in Figure 2. Laterality indices (LIs) show an overall left

hemisphere pattern of lateralisation (LI = 0.42), and can be seen for each participant

in Table 3. Histograms of LIs calculated from the bootstrap resampling method

applied during analysis are shown for each participant in Figure 4a.

[INSERT FIGURE 2 HERE]

Patient group:

The four patients were analysed on an individual basis using a whole brain

approach followed by a ROI analysis similar to that used in the control participants.

Whole brain activation was assessed using one-sample t tests (random effects,

uncorrected, $p<0.001$) and a varying pattern of activation was found. Across all tasks

combined Patient 1 (RH lesion) showed peak activation in the left hemisphere within

the middle occipital gyrus (BA 18) and the cingulate gyrus (BA 32). This was

accompanied by weaker, but significant, activation along the right post central gyrus

(BA 43). Patient 2 showed generalised global activation, with peaks in the pre-central

gyrus (BA 4) and middle frontal gyrus (BA 11) bilaterally. Patient 3 demonstrated

predominantly right lateralised activation around the IFG, which due to the left

hemisphere lesion indicates that contralesional regions have acquired language

function. This patient also had the biggest lesion of the group, which may suggest

why left hemisphere perilesional regions were not highly activated (see discussion).

Patient 4 showed predominantly right lateralised activation, however this activation

occurred more medially (e.g. cingulate gyrus, BA 32) and not along the IFG.

ROI analysis was undertaken for each patient across tasks focussing on

Brodmann Areas 44 and 45, left and right IFG, and using a one sample t-test (random

effects, uncorrected) analysis. The results of this can be seen in Table 2. This analysis

shows that three of the four patients exhibited peri-lesional activation and the fourth

contra-lesional; see Figure 3.

[INSERT TABLE 2 HERE]

[INSERT FIGURE 3 HERE]

Laterality indices outlined in Table 3 and plotted in Figure 4b show that the

patients were all significantly lateralised to one hemisphere or the other across tasks,

and none showed bi-lateral activation overall. This analysis also shows that different

tasks elicited different lateralisation indices, sometimes switching hemisphere within

the same patient. There was not a consistent pattern between the patients as to which

tasks resulted in most bi-lateral activation, as each showed an individual pattern. In

control participants category fluency seemed to elicit a less strongly lateralised pattern

of activation than the other two tasks, however when assessing each participant

individually it is possible to see that, like the patients, there were large individual

differences between the tasks eliciting highly lateralised scores and those creating low

lateralised, or bi-lateral, patterns.

[INSERT TABLE 3 HERE]

[INSERT FIGUREs 4a and 4b HERE]

Recent work by Brownsett et al. (2014) has implicated the dorsal anterior cingulate

cortex (dACC) and adjacent superior frontal gyrus (SFG) in fMRI studies of aphasic

recovery as a region separate from the infarct but likely to be involved in domain

general networks underlying language production and recover. An additional ROI

analysis was therefore carried out confined to the ACC and SFG region. A Two sample, between groups t-test comparison of activity within this region between the four patients and the control group revealed areas of increased activity within the bilateral superior frontal gyrus (BA 8, peak activation coordinates -20, 28, 52 and 30, 28, 48) and rostral anterior cingulate gyrus (BA 32, coordinates 10, 38, -6 and -6, 36, 0), suggestive of compensatory increases in activity within these regions in patients relative to controls (data thresholded at $p<0.005$ uncorrected with cluster threshold >12 voxels).

Laterality index analysis of activity in this dorso-medial frontal ROI show that the mean LI of the control participants and the individual patient LIs both display a bilateral pattern of activation, with LIs of between -0.2 and 0.2. Closer scrutiny of the indexes shows that within the range of bilateral activation there is a slight right sided bias, but this is not significant enough to be classified as right sided activation (e.g. Springer, et al., 1999); mean LI for control group is -0.05; Patient 1 LI is -0.02; Patient 2 LI is -0.4; Patient 3 LI is -0.01; Patient 4 LI is -0.09.

Discussion

This study examined the activation patterns in four stroke patients who had been diagnosed with Broca's aphasia at the time of their stroke, but who had recovered speech ability to moderately normal levels in the years following. The aim of the study was to assess the patterns of activation seen as a result of this recovery, and to compare it to a group of healthy control participants on a range of speech production tasks.

The results showed that the control participants exhibited activation peaks within the left inferior frontal gyrus (IFG), namely in and around Broca's area (Brodmann Areas 44 and 45), which was expected based upon previous research into

speech production (e.g. Fernandez et al., 2004; Hillis, 2006). In addition to this there were significant peaks of activation within the contralateral IFG regions of the right hemisphere, which again is similar to results found in previous studies of this kind (Winhuisen et al., 2005; Cardebat et al., 2003).

The region of interest (ROI) analysis on BAs 44 and 45 revealed that control participants showed an overall left lateralisation (LI = 0.4) across all tasks. This lateralisation index is slightly lower than those found by previous studies (LIs of 0.5-0.8 found in other cohorts e.g. Abbott, Waites, Lillywhite & Jackson, 2010; Van der Haegen, Cai, Seurinck & Brysbaert, 2011), but still demonstrates a consistent left hemisphere dominance for speech in line with much of the literature on speech production and neurological language networks. There are several possibilities that could explain the slightly lower LI found in these control participants. Firstly it could be due to the presence of two RH language dominant individuals and one bi-lateral individual within the controls, which, at 25% of the sample, is higher than the expected 5-10 % of right lateralised right handers in the population (eg. Knecht et al. 2000a). As we relied on self report of handedness and did not use a standardised handedness inventory to determine hand dominance, it might be argued some of the controls (and patients) were in fact not strongly right handed. However, there is considerable debate about the effectiveness of inventories at determining hand dominance (e.g. Groen, Whitehouse, Badcock & Bishop, 2013), their relatedness to results from lateralisation studies of hemispheric language dominance (e.g. Bishop, Watt & Papadatou-Pastou, 2009) and to the view that such inventories are fairly uninformative for the purpose of making predictions about laterality of language function (McManus, 2002), due to the subjective nature of items included on an inventory and the variability in the scoring and classification of the responses. As a result many neuroimaging studies do not use handedness inventories to select

participants (e.g. Brownsett et al, 2014; Rosen et al, 2000). Previous research has demonstrated that self reported general hand usage is a good indicator of actual hand dominance classifications following handedness inventories (e.g Bishop, Ross, Daniels & Bright, 1996).

Another possibility for the relatively low left lateralisation pattern seen in the controls is that the study used a variety of speech production tasks, whereas similar studies have tended to rely on one task alone. It has been demonstrated extensively that task design determines the types of activation patterns revealed via fMRI (eg Ramsey, Sommer, Rutten & Kahn, 2001; Hund-Georgiadis, Lex & von Cramon, 2001; for review see Crosson et al., 2007), which formed the rationale for using a variety of tasks in this study so as to obtain a truer indication of speech activation patterns. These results show that within individual participants lateralisation indices vary across tasks, sometimes extensively so. This could be indicative of participants trying harder on some tasks than others, but due to the concise nature of the study (total time was 20 minutes) it is unlikely that boredom or fatigue were significantly contributing factors. This could be tested in future by employing an overt speech paradigm and by then recording the responses for subsequent errors analysis. However, the authors favour another explanation, which is that due to the complex nature of speech production processes, it is likely that hemispheric differences do exist when generating the responses required to such tasks. Given that this study was designed in part to scrutinise the paradigms used for activation efficiency, the LI results shown in these control participants suggests that this distribution of laterality is more representative of speech production patterns in the healthy brain. This interpretation is consistent with other literature on lateralisation in healthy individuals, in that it is too simplistic to view people as *either* left or right hemisphere dominant for language production and that a more comprehensive perspective is one where

individuals are viewed as being on a continuum of laterality across the hemispheres

(e.g. Crosson, et al., 2007; Hamilton et al. 2011).

The second focus for this study was to assess speech activation patterns in four

patients who were recovering from Broca's aphasia. The results from the analyses of

this data revealed interesting evidence for specific patterns of activation shown during

recovery. In line with recent accounts from fMRI studies of aphasic stroke (e.g.

Brownsett et al., 2014; Federenko et al., 2012) that hemispheric activation could

either be classified as domain general activation or activation that is specific to

language networks, an ROI analysis of domain general regions (namely the dorsal

anterior cingulate cortex and superior frontal gyrus) showed increased activity within

the patients relative to control participants. This data therefore supports the view that

tasks intended to activate language specific networks in order to compare patients

with controls may actually result in increased activation in patients in regions more

related to domain general processing. This could be due to the increased demands of

the task for these patients, requiring such regions to be activated to a greater extent in

order to keep on task.

The lateralisation indexes (LIs) from the ROI of Bas 44 and 45 showed that

three of the four patients were lateralised to the same hemisphere as their lesion. This

indicates that in the chronic phase of recovery from aphasia it is networks located in

the same region as the lesion that support the function of speech production. This may

be due to extension of language specific networks into surrounding tissue, or due to

up regulation of domain general networks to support language function (Federenko et

al., 2012). In addition, and crucial to the literature on aphasia recovery, this finding

serves irrespective of which hemisphere was damaged. This is shown due to the fact

that one of the cohort of patients tested had a right hemisphere lesion. This patient had

an LI of -0.9 across all tasks demonstrating that they had strong right sided activation

during speech production. This suggests that this individual was right hemisphere

dominant for language prior to their stroke and that recovery is occurring through

utilisation of their remaining language networks surrounding the lesion site. This is

contrary to the view that RH activation supports reduced language functioning (e.g.

Rosen et al., 2000; Saur, et al. 2006), as Patient 1 performed better on the test

batteries than the other patients. This data shows that it is not the case that sub-

optimal recovery is demonstrated by right hemisphere activation,

Recent literature on aphasia recovery has framed a key question to be

addressed as when does the left hemisphere support recovery and when is it the right

hemisphere that supports recovery? (Crosson et al. 2007). The present data suggests

the hemisphere dominant for language that supports recovery in the chronic phase of

recovery post stroke. However, consistent with other studies, there must be some

caveats to the suggestion that the neural pattern of recovery in the chronic phase

following stroke is consistent across individuals. Patient 3 in this study demonstrated

a consistent contra-lesional pattern of activation, meaning they showed activation in

the right hemisphere despite having a left hemisphere lesion. This patient therefore

does not follow the pattern of evidence produced by the other three patients. There are

several possible reasons for this such as the fact that Patient 3 had the biggest lesion

of the four patients who participated, and it was a lesion that extended more

posteriorly than the other patients. Consistent with arguments put forward by (Price &

Crinion, 2005), the greater the lesion volume the lower the likelihood of peri-lesional

activation occurring, simply because a greater proportion of the language network is

damaged in that hemisphere. Patient 3 also had the lowest set of scores on the aphasia

sub tests, as well as the longest time since their stroke. Previous research indicates

that reduced speech ability is related to time post stroke and that the greatest amount of recovery would be seen in the acute and sub acute phases of recovery (e.g. Thulborn, Carpenter & Just). The data is therefore consistent with other literature suggesting that bigger lesions and less good recovery is associated with more RH activation. Furthermore, since this study as well as previous literature (e.g. Cardebat et al., 2003), has noted a consistent weak, but significant, locus of activity within the right hemisphere during speech production, it may be the case that lesion size is a determining factor in the successful suppression of residual, or additional, homologous activation.

Similar to the control participants, there were also differences in the lateralisation patterns shown in the patients' LI data as a result of the different speech production tasks used in the study. Lateralisation indices ranged from showing strong lateralisation to more bi-lateral activation depending on the tasks used. This however was not consistently the case for any one task in particular and so it can be assumed that individual differences are crucial to how effective the speech paradigm used is at eliciting reliable activation. This has implications for future research paradigms designed to probe recovery of speech production in aphasic patients, as the results from this set of patients indicates that a range of tasks are required to ensure reliable activation is captured.

Conclusions

This study contributes to existing data on the complex interaction of the right and left hemispheres in recovery of speech production post stoke. It has shown that right hemisphere lesions can result in aphasia and that recovery in this individual was supported through that same damaged hemisphere. The data suggests that the type of task used to elicit speech in fMRI paradigms matters to the extent that activation

patterns, and hemispheric lateralisation indices, vary accordingly. There was not one overall task which performed better at eliciting activation, and so a range of tasks should be employed in future research of this nature. What was also clear from this fMRI study was that all four patients had some evidence for activation in both hemispheres across the speech production tasks implicating both hemispheres as having a role in the recovery and the continued support of this function. In addition, an ROI comparison between patient and control groups was found to be consistent with the existence of up-regulation of activity in patients within domain general cognitive control regions within the anterior cingulate and superior frontal gyrus.

Acknowledgements

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Table 1. *Behavioural evaluation of Aphasia scores for each patient using the Aphasia Quotient component of the Western Aphasia Battery (WAB) and the FAS verbal fluency test (Lezak, 1995).*

Patient Number	Age	Sex	Years Post Stroke	Western Aphasia Battery Component Results					Mean FAS score	Classification across both tests
				Spontaneous Speech	Comprehension	Repetition	Naming	WAB Aphasia Quotient (standardised score)		
1	74	F	3	18	8	6	10	84	37	Low Normal/ Mild Aphasia
2	81	M	13	14	10	6	8	78	25	Mild Aphasia
3	69	M	14	16	7	8	8	76	35	Mild Aphasia
4	69	M	6	16	8	8	8	80	26	Mild Aphasia

Table 2. *Shows the main activation peaks in each patient across tasks for the ROI (BAs 44 and 45 dilated) analysis. Statistical threshold of 0.001 (uncorrected) unless otherwise stated. * indicates statistical threshold of 0.01 (uncorrected). # Indicates statistical threshold of 0.05 (uncorrected). Dashed line equates to no suprathreshold clusters indentified in the ROI. MNI indicates coordinates that refer to the Montreal Neurological Institute reference brain.*

Patient Number	Task	Region	Side of Peak	MNI			
				x	y	z	t
1	All Tasks	IFG, BA 9	R	48	0	24	2.48*
	Letter Fluency	-	-	-	-	-	-
	Category Fluency	IFG, BA 46	R	56	42	4	2.88*
	Picture Naming	Pre-central Gyrus, BA 6	R	58	0	24	5.37
2	All Tasks	IFG	L	-54	22	0	4.45
	Letter Fluency	IFG, BA 47	L	-54	20	2	2.77*
	Category Fluency	IFG, BA 45	L	-52	24	4	2.87*
	Picture Naming	Pre-central Gyrus, BA 6	R	64	4	8	3.23
3	All Tasks	IFG, BA 46	R	48	12	18	4.52
	Letter Fluency	Insula, BA 13	R	42	14	14	3.36
	Category Fluency	IFG, BA 44	L	-60	18	16	2.04#
	Picture Naming	IFG, BA 46	R	48	26	12	4.62
4	All Tasks	IFG, BA 45	L	-52	34	6	2.97*
	Letter Fluency	-	-	-	-	-	-
	Category Fluency	IFG, BA 45	L	-58	22	12	3.57
	Picture Naming	IFG, BA 47	L	-46	24	0	2.10#

**Table 3.** *Laterality Indices for the patients and the control participants across tasks.*
Participants with LI < -0.2 were classified as RH dominant, those with LI >+ 0.2 as
LH dominant, and those with LI between –0.2 and +0.2 as bilateral.

Participant	Overall LI	Letter Fluency	Category Fluency	Picture Naming
Control 1	0.82	0.83	0.85	0.26
Control 2	0.54	-0.09	-0.65	0.15
Control 3	0.06	0.18	-0.05	-0.08
Control 4	0.9	0.63	0.97	0.67
Control 5	0.34	0.38	-0.21	0.47
Control 6	0.77	0.61	0.63	0.61
Control 7	-0.53	0.05	-0.34	-0.42
Control 8	0.78	0.48	-0.73	0.74
Control 9	0.61	0.17	0.55	-0.25
Control 10	0.78	0.78	0.76	0.59
Control 11	0.68	0.84	0.17	-0.01
Control 12	-0.74	-0.68	-0.71	-0.07
Group Means for Controls	**0.42**	**0.35**	**0.10**	**0.22**
Patient 1	-0.91	0.65	-0.98	-0.35
Patient 2	0.2	-0.14	0.05	-0.56
Patient 3	-0.81	-0.41	0.95	-0.9
Patient 4	0.67	0.28	0.79	-0.4

Patient 1   Patient 2   Patient 3   Patient 4
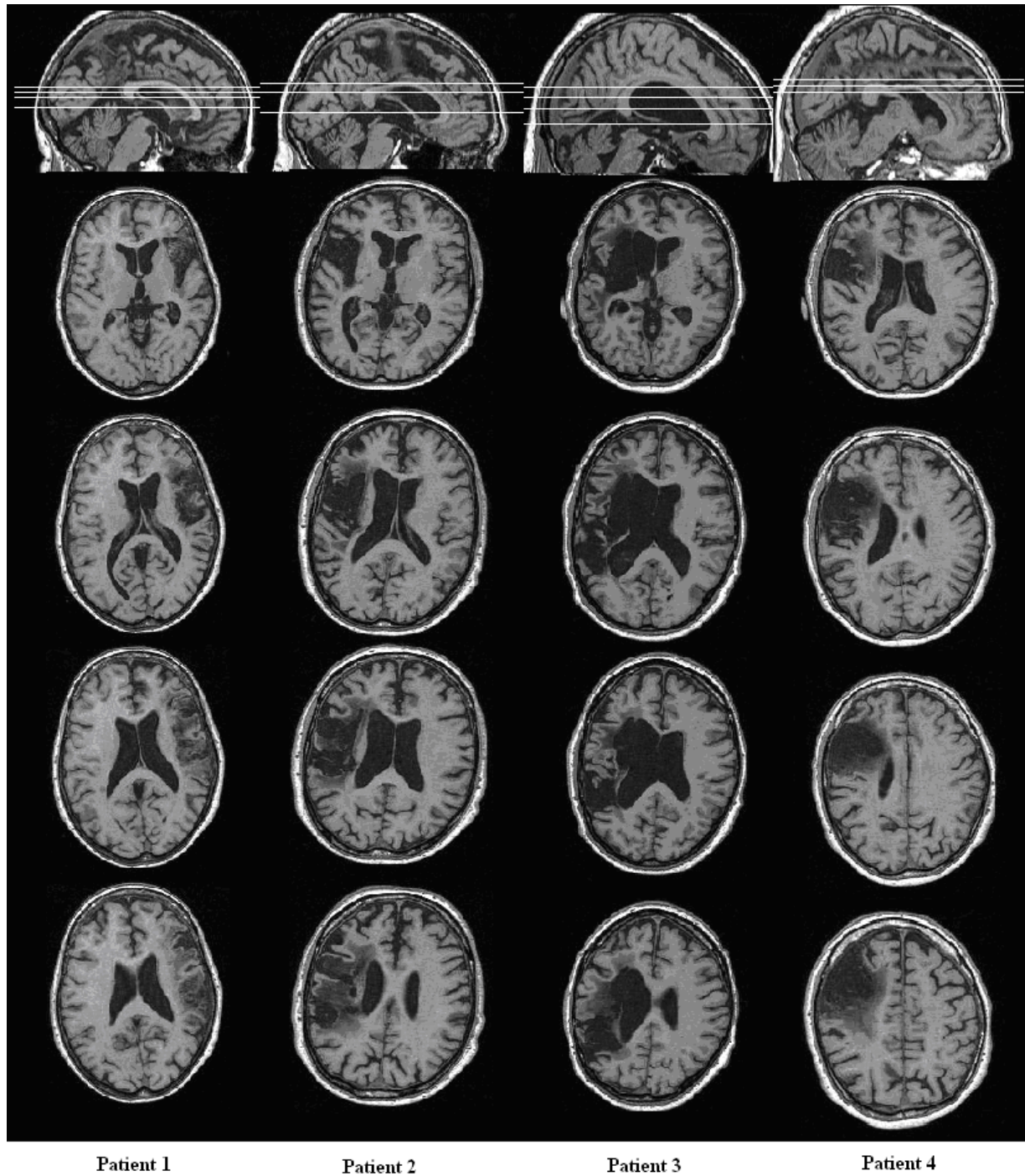
Figure 1. *T1 –weighted MR structural images showing the lesion anatomy of the 4*

patients. The left side of the image refers to the left side of the brain. Axial slice view is

selected to illustrate maximum extent of lesion and are indicated on a sagittal view for

each patient scan.
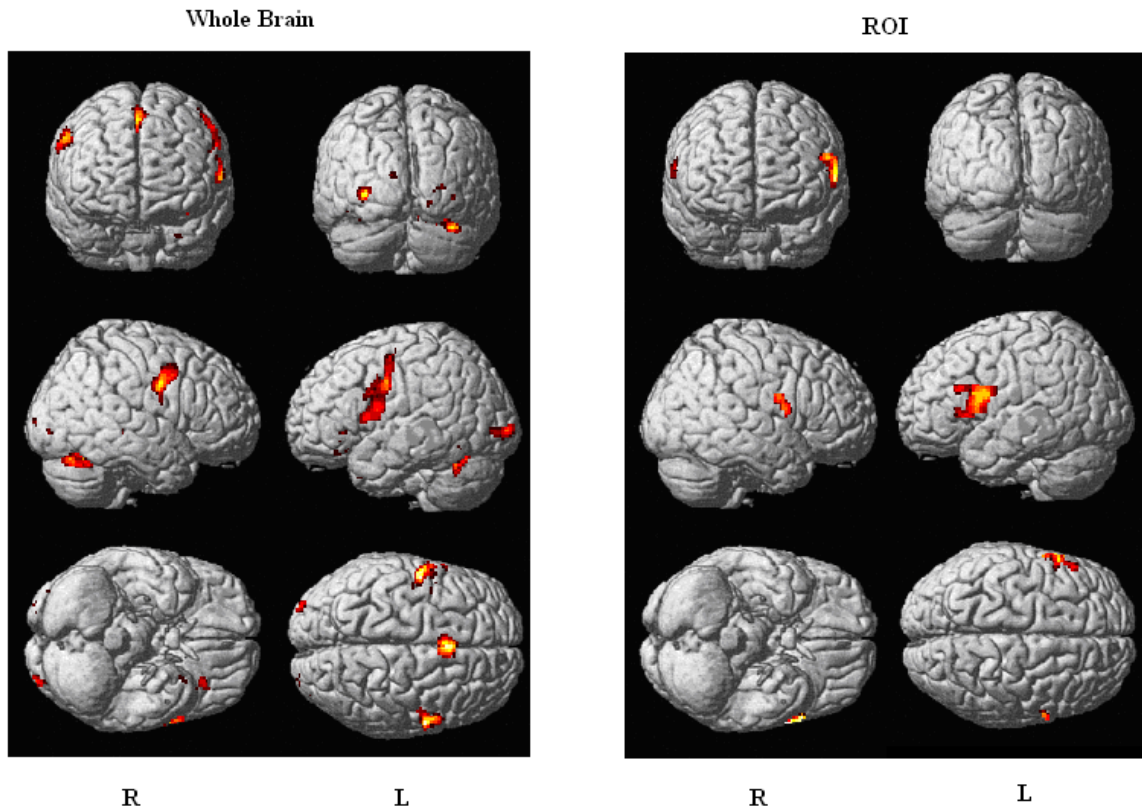
Figure 2. *Rendered normalised images of activation in control participants across all tasks combined using random effects analysis on whole brain activation and ROI (Brodmann Areas 44 and 45) activation.*
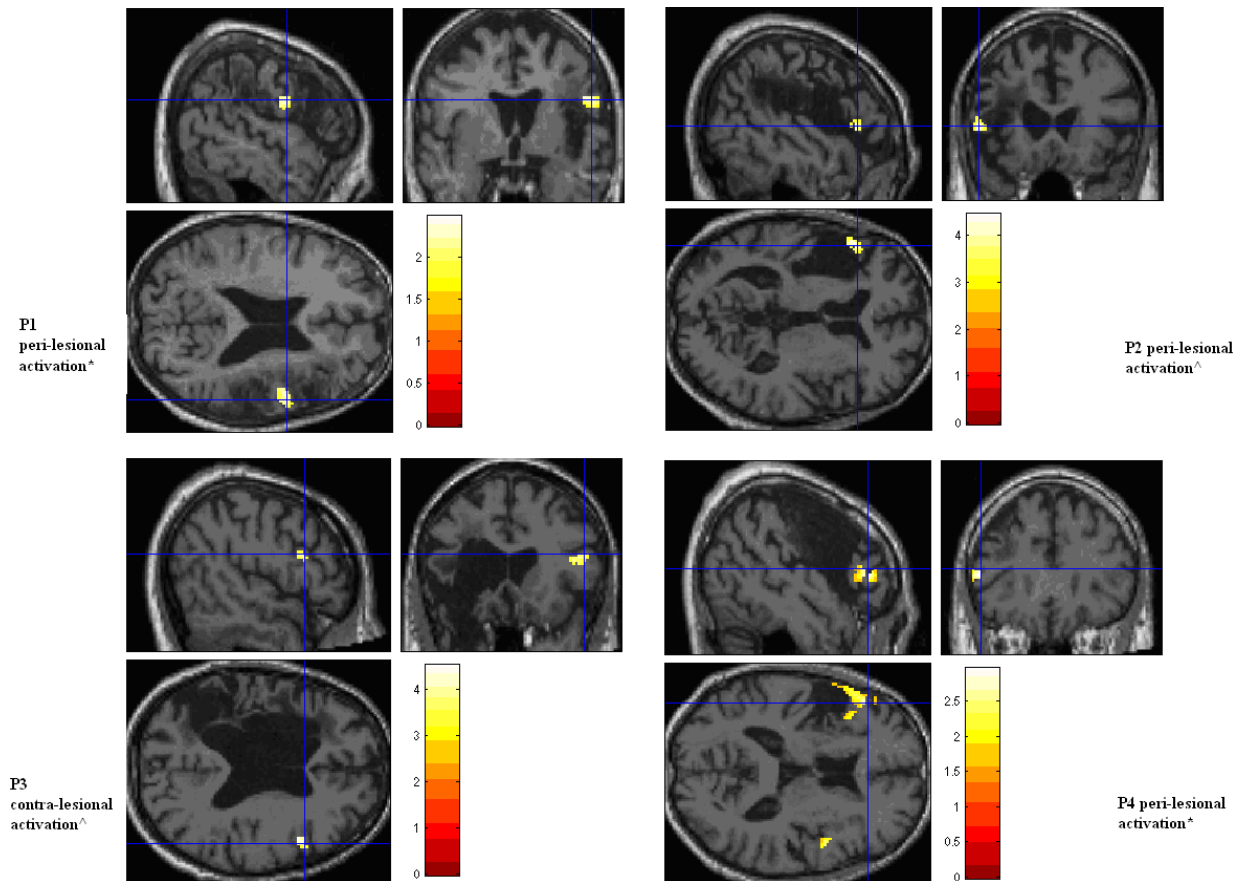
Figure 3. *Images showing either peri-lesional or contra-lesional activation resulting from ROI analysis across all tasks in each of the four patients. * indicates statistical threshold of 0.001 (uncorrected). ^ indicates statistical threshold of 0.05 (uncorrected).*
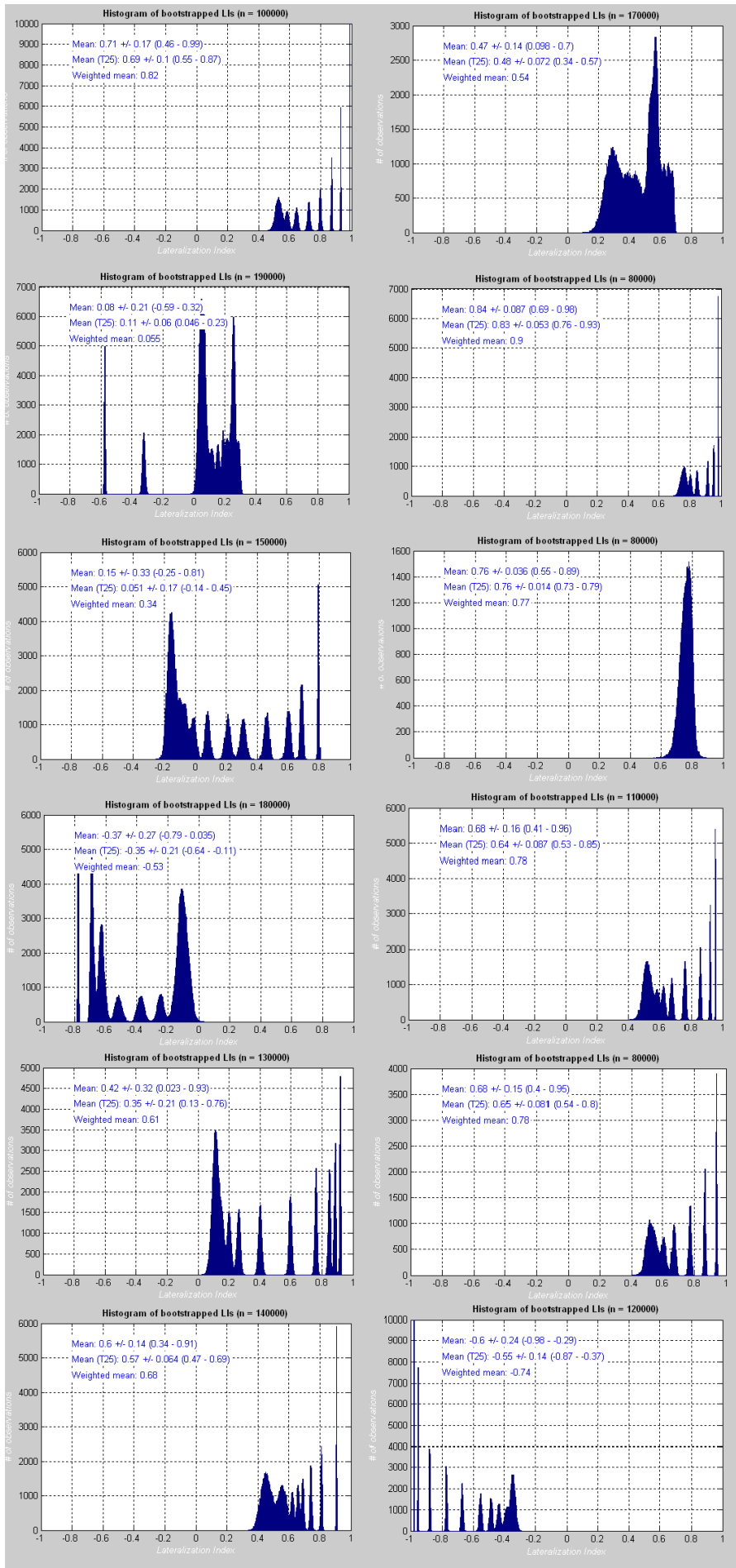
Figure 4a. *Lateralisation plots for the 12 control participants. X axis denotes lateralisation index on a scale from -1 to 1, where a positive number reflects left hemisphere lateralisation and a negative number right hemisphere lateralisation. Y axis denotes the number of observations made in the bootstrapping resampling method as performed by the LI Toolbox (Wilke and Lidzba, 2007).*
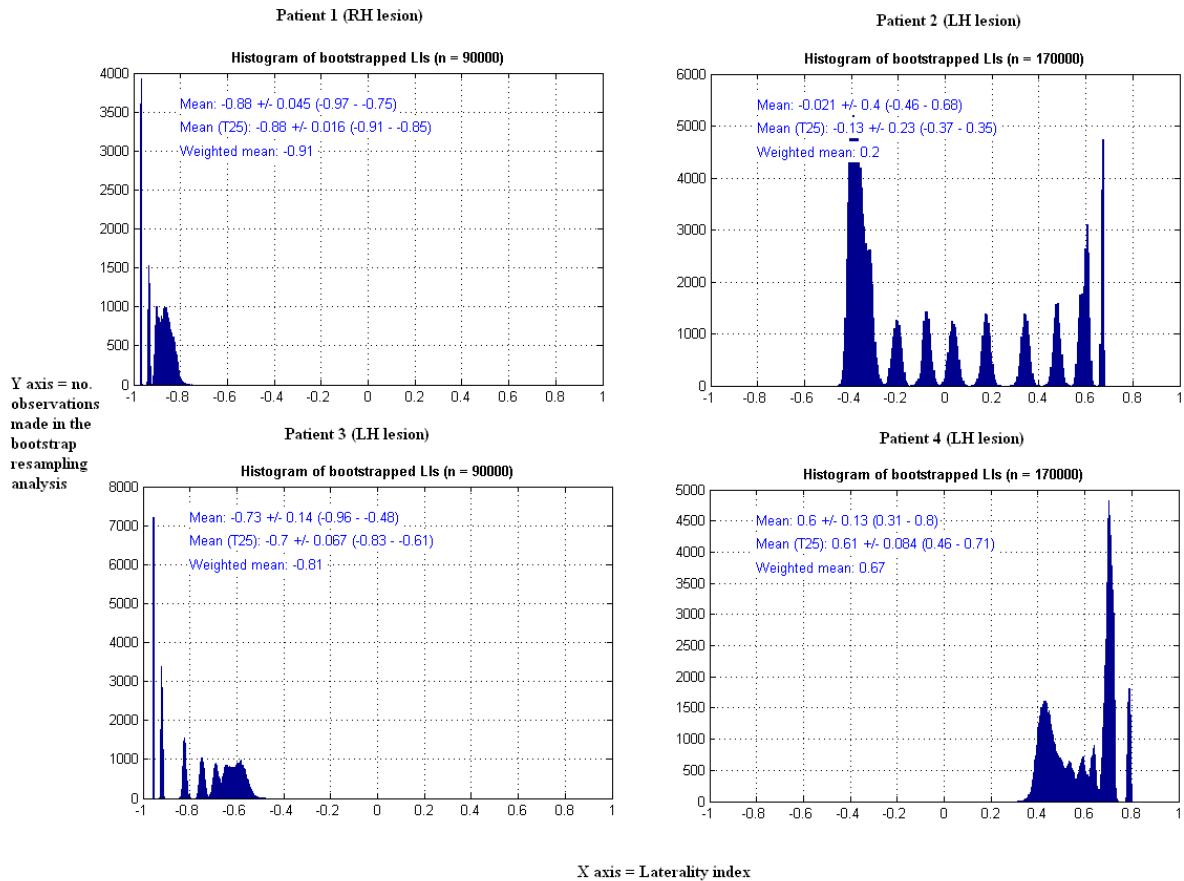
Figure 4b. *Lateralisation plots for the 4 patients. X axis denotes lateralisation index on a scale from -1 to 1, where a positive number reflects left hemisphere lateralisation and a negative number right hemisphere lateralisation. Y axis denotes the number of observations made in the bootstrapping resampling method as performed by the LI Toolbox (Wilke and Lidzba, 2007).*