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Anatomical predictors of aphasia recovery: a tractography study of bilateral perisylvian language networks

Running title: Predictors of aphasia recovery

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Abstract

Stroke-induced aphasia is associated with adverse effects on quality of life and the ability to return to work. For patients and clinicians the possibility of relying on valid predictors of recovery is an important asset in the clinical management of stroke-related impairment. Age, level of education, type and severity of initial symptoms are established predictors of recovery. However, anatomical predictors are still poorly understood.

In this prospective longitudinal study, we intended to assess anatomical predictors of recovery derived from diffusion tractography of the perisylvian language networks. Our study focused on the arcuate fasciculus, a language pathway composed of three segments connecting Wernicke's to Broca's region (i.e. long segment), Wernicke's to Geschwind's region (i.e. posterior segment) and Broca's to Geschwind's region (i.e. anterior segment). In our study we were particularly interested in understanding how lateralisation of the arcuate fasciculus impacts on severity of symptoms and their recovery.

Sixteen patients (10 males; mean age 60±17 years, range 28-87 years) underwent post stroke language (mean 5±5 days) and neuroimaging (mean 10±6 days) assessments and neuropsychological follow-up at six months. Aphasia was assessed with the Western Aphasia Battery (Aphasia Quotient, AQ). Backward elimination analysis identified a subset of predictor variables (age, gender, lesion size) to be introduced to further regression analyses. A hierarchical regression was conducted with the longitudinal aphasia severity as the dependent variable. The first model included the subset of variables as previously defined. The second model additionally introduced the left and right arcuate fasciculus (separate analysis for each segment).

Lesion size was identified as independent predictor of longitudinal aphasia severity in the left hemisphere [beta=–.630, *t*(–3.129), *p*=.011]. For the right hemisphere, age [beta=–.678, *t*(–3.087), *p*=.010] and arcuate volume [beta=.730, *t*(2.732), *p*=.020] were predictors of longitudinal aphasia severity. Adding the right arcuate volume to the first-level model increased the overall predictive power of the model from 28% to 57% ($F_{(1,11)}$=7.46, *p*=.02).

These findings suggest that different predictors of recovery are at play in the left and right hemisphere. The right hemisphere language network seems to be important in aphasia recovery after left hemispheric stroke.

Keywords: (1) Diffusion Tensor Imaging tractography, (2) language, (3) aphasia, (4) stroke, (5) arcuate network

Introduction

Every year 15 million people worldwide are suffering a stroke, amongst which nearly six million patients die and five million survivors are left permanently disabled (WHO). About one third of all stroke patients are affected by language problems, collectively referred to as aphasia (Pedersen et al., 2004). Aphasia has an adverse effect on functional outcome, mood, quality of life and the ability to return to work (Ferro and Madureira, 1997).

Clinically, established predictors of language recovery include age, lesion characteristics, education, and possibly gender {Pedersen:2004gj, Eslinger:1981ug, Laska:2001il, Ferro:1997jy, McDermott:1996um}. However, taken together these factors only explain about 40% of the variance (Pedersen et al., 2004); hence other factors may contribute to recovery.

The use of structural and functional neuroimaging applied to stroke patients has helped to better understand anatomical and metabolic factors associated with aphasia recovery. These can be distinguished into ipsilateral and contralateral factors (Hillis, 2005; 2006). Established ipsilateral factors include lesion location at the cortical level (Ferro et al., 1999), the extension of the damage to subcortical structures (Ferro et al., 1999; Naeser et al., 1982; Vallar et al., 1988), the extent of the area of ischemic penumbra and the degree of reperfusion (Croquelois et al., 2003; Hillis et al., 2001; 2006). Hillis et al. (2001), for example, reported that in aphasia patients improved perfusion of Wernicke's area within three days post onset is associated with better language outcomes. The study highlighted the importance of mapping those areas that show significant diffusion–perfusion mismatch (i.e. perfusion delay but normal diffusion-weighted imaging signal) as these areas may exhibit functional improvement if blood flow can be restored. Likewise, the magnitude of perfusion delay provides a proxy of the degree of functional

impairment. Moreover, the authors suggest that dysfunction of other language related areas could be due to a diaschisis mechanism affecting areas not directly damaged by the stroke.

Recovery may also depend on contralateral factors. Previous functional imaging and case report studies suggested that language recovery may also be explained by the recruitment of right hemispheric homologues of language areas (Weiller et al., 1995; Musso et al., 1999); Rosen et al., 2000; Leff et al., 2002; Sharp et al., 2004; Crinion and Price, 2005). Early studies indicated a compensatory role of the right hemisphere in patients who recovered their language after a left-hemispheric stroke and later became aphasic again, following a right-hemispheric stroke (Nielsen, 1946) or as a consequence of temporary right-hemispheric anaesthesia (i.e. WADA test) (Cappa et al., 1997; Ohyama et al., 1996; Thulborn et al., 1999) (Kinsbourne 1971). A more recent fMRI study investigated the evolution of language recovery after stroke and proposed a three-stage-model whereby (i) the acute stage is characterised by reduced activation in intact perilesional left hemispheric language areas, (ii) during the subacute stage a bilateral upregulation occurs and the peak activation in right homologues areas significantly correlated with language improvements, and (iii) a re-shift of peak activation to the left hemisphere in the chronic stage (Saur et al., 2006). The authors suggested that a shift to the right facilitates recovery only if transient and followed by a return of the peak activation to the left hemisphere. Indeed, sustained right hemisphere activation at one year has been associated with poor language performances, which could reflect a maladaptive compensatory mechanism in chronic stroke patients (Szaflarski et al. 2013).

Overall, these and other studies suggest that that recovery of language after stroke is a dynamic process in which the right hemisphere is important for longitudinal outcomes

(Lazar et al., 2000, Lazar et al., 1997, Schlosser et al., 2002, Thiel et al., 2001; Thiel et al., 2006) (Cappa et al., 1997; Leff et al., 2002; Ohyama et al., 1996; Saur et al., 2006; Thulborn et al., 1999).

The individual variability observed in functional imaging studies may also be related to underlying anatomical patterns of lateralisation of language networks (Knecht et al., 2002). This structural variability has been studied both at cortical and subcortical level. The planum temporale, part of Wernicke's region, is an area of the superior temporal gyrus located behind the primary auditory cortex and includes the associative auditory cortex involved in auditory comprehension. The planum temporale is consistently reported to be larger in the left compared to the right hemisphere (for a review see Chance and Crow, 2007). (Geschwind and Levitsky, 1968; Shapleske et al., 1999; Steinmetz, 1996). Geschwind and Levitsky hypothesised that this asymmetry of the planum temporale is associated with functional lateralisation (Geschwind and Levitsky, 1968). Initial studies that were supportive of an association between functional lateralisation and asymmetry of the planum temporale have not been replicated in a recent study where Dorsaint-Pierre et al. (2006) used MRI scans and sodium amytal procedure. Similarly, studies using fMRI for single word comprehension and dichotic listening tasks found no correspondence between left lateralisation of language and leftward asymmetry of the planum temporale (Eckert et al., 2006; Dos Santos Sequeira et al., 2006). The lack of structure-function correlation may explain the absence of evidence for the influence of planum temporale asymmetries in aphasia recovery after stroke.

Other structural asymmetries underlying functional dominance have been proposed.

Leftwards asymmetry has been reported for Broca's region using cytoarchitectonic analysis (Brodmann area 44 in the pars opercularis) (Amunts et al., 1999). Significant leftward asymmetry in the volume of the pars opercularis has also been reported based on in vivo MRI-based measurements (Keller et al., 2007). Grey matter concentration differences in the posterior part of the inferior frontal gyrus (pars opercularis) have been found to correlate with language dominance assessed by the sodium amytal procedure (Dorsaint-Pierre et al., 2006), however there is no evidence that this asymmetry is related to recovery of language after stroke.

Recent methodological advances in diffusion imaging tractography permitted to study the *in vivo* asymmetries of language networks, including the arcuate fasciculus connecting temporal, parietal, and frontal language regions (Catani et al., 2005; Glasser and Rilling, 2008; Powell et al., 2006). This tract is composed of a direct long segment between classical Broca's and Wernicke's regions and an indirect pathway relaying on in the inferior parietal lobule (i.e. Geschwind's region) that includes the anterior fronto-parietal and the posterior temporal-parietal segments (Catani et al., 2005). The pattern of lateralisation for the individual segments show a significant interindividual variability among the healthy population (Catani et al., 2007). This is particularly evident for the direct long segment, which is bilateral in about 40% of the healthy population and extremely left lateralised in the remaining 60%, where the segment is either absent, or very small in the right hemisphere (Catani et al., 2007). There is some preliminary evidence that this individual variability in the pattern of lateralisation of the arcuate fasciculus could be related to differences in functional dominance and behavioural performances. A study combining WADA test and DTI tractography reported a good concordance between language dominance and anatomical

lateralisation of perisylvian networks (Matsumoto et al., 2008). In particular 95% of individuals with an anatomical left lateralisation of the long segment of the arcuate fasciculus were also functionally left dominant on the WADA test. Conversely, two thirds of the subjects with functional right dominance on the WADA test presented with a right lateralisation of the long segment of the arcuate fasciculus. Furthermore, a more bilateral pattern of lateralisation of the long segment has been found to correlate with better performances on auditory verbal learning tasks in healthy subjects (Catani et al., 2007). Overall, these studies suggest a possible role of the right hemisphere in language recovery.

In this study, we investigated prospectively whether tractography-based measurements of different segments of the arcuate fasciculus with tractography could help to predict language recovery at six month in left hemispheric stroke patients.

Patients and Methods

Patients

Patients with left hemisphere stroke and language impairment were consecutively recruited from the hyperacute stroke unit at King's College Hospital, London between 2009 and 2012. Patients were screened within three days of admission using the Western Aphasia Battery Bedside Screening (WAB-R) (Kertesz, 2007). Inclusion criteria were: (1) right-handedness (based on Edinburgh Handedness Inventory; (Oldfield, 1971)), (2) first ever left middle cerebral artery infarct, (3) presence of aphasia, (4) no previous neurological or psychiatric diagnoses, (5) medically stable to tolerate ambulance transport, (6) no MRI contraindications, and (7) native English speaker. A total of nineteen eligible patients underwent comprehensive WAB-R assessment within 10 days of symptom onset (mean 5±5 days) and research MRI within

two weeks, except for two patients who were scanned at day 20 and 24 after admission (overall mean 10±6 days). WAB-R provides a global measure of aphasia severity, the Aphasia Quotient (AQ), which ranges from 0-100. A score above 93.8 is indicative of normal language function (Pedersen et al., 2004).

Six months after admission patients were re-invited for a repeated WAB-R assessment (mean 200±55 days). Sixteen patients completed the follow-up assessment (10 males; mean age 60±17 years; age range 28-87 years). Out of these sixteen patients, eleven had received thrombolysis as a clinical intervention on admission to hospital. Unfortunately, information regarding the nature or intensity of community-based speech and language therapy amongst the patients who received such intervention, nor a comparison group of those who did not receive therapy was available at the completion of the study. This limited the possibility of analysing the impact of therapy on recovery in our cohort.

For this study, all patients or their next of kin gave written informed consent. The study was approved by the Wandsworth Ethical Research Committee (09/H0803/95) and the local review board (KCH1700).

Neuroradiological acquisition and processing

MRI data were acquired using a 3T HDx GE scanner (General Electric, Milwaukee, US) equipped with an 8-channel radio frequency (RF) receiver head coil. For each subject a high-resolution structural T1-weighted brain volume (1x1x1mm) was acquired. Diffusion tensor imaging (DTI) data were acquired using a spin echo, single shot EPI pulse sequence optimised for subjects with high risk of movement during the scan. This consisted of two different scans of 30 diffusion-weighted directions (b-value 1500 mm^2/s) combined together for a total of 60 directions and seven non-diffusion

weighted volumes. Matrix size was 128x128x60 and voxel size was 2.4x2.4x2.4mm. Peripheral gating was applied to avoid brain pulsation artefacts (Dell'Acqua et al., 2012).

Lesions were manually delineated on T1-weighted images and the volume of interest (number of voxels) was extracted using FMRIB Software Library package (FSL, http://www.fmrib.ox.ac.uk/fsl/) and subsequently normalised to MNI space. Lesion overlay percentage maps were obtained by binarising (i.e. assigning a value of 0 or 1 to each voxel) the normalised lesion volumes and calculating percentage overlays.

Diffusion tensor imaging (DTI) data was pre-processed using ExploreDTI (www.exploredti.org) and corrected for eddy current and motion artefacts through iterative correction to the non-weighted B_0 scans. For each subject data quality was visually inspected. In compliance with the study protocol, participants who generated corrupted images on more than two diffusion-weighted imaging volumes would have been excluded. No participant had to be excluded after inspection. RESTORE was also run to exclude outliers (Chang et al., 2005). The diffusion tensor was estimated using a non-linear least squares approach (Jones and Basser, 2004).

Whole brain tractography was performed by selecting as seed voxels all brain voxels with fractional anisotropy (FA)>0.2. Streamlines were propagated with a step-size of 1mm, using Euler integration and b-spline interpolation of the diffusion tensor field (Basser et al., 2000). Where FA<0.2 or when the angle between two consecutive tractography steps was larger than 45°, streamline propagation was stopped.

Tractography dissections were obtained using a three regions of interest (ROIs) approach as described in previous reports (Catani et al., 2005).

ROIs for both hemispheres were defined on FA images in the patients' native space (Fig. 1A). The frontal ROI was defined anterior to the central sulcus to encompass the white matter of the posterior region of the inferior and middle frontal gyri and the inferior part of the precentral gyrus. The temporal ROI was defined in the white matter of the posterior part of the superior and middle temporal gyri. The parietal ROI included the white matter of the supramarginal and angular gyri. Direct connections between Broca's and Wernicke's regions (and right-side homologues) were visualised as streamlines passing through both frontal and temporal ROIs and were considered as long segment of the arcuate fasciculus. All streamlines between temporal and parietal ROIs were classified as posterior segment of the arcuate fasciculus. Finally, streamlines between parietal and frontal ROIs were labelled as anterior segment of the arcuate fasciculus (Fig. 1B).

Fig. 1 (ROIs) about here

Two anatomists used TrackVis (www.trackvis.org) for virtual dissections and volume measurements of the three segments of the arcuate fasciculus in all participants and showed a high inter-rater reliability ($r = 0.635$; $p<0.001$). The second rater was blinded and was only informed of the presence of the lesion without any information of symptoms. The volume was calculated as the number of voxels intersected by the streamlines of each segment. This measure indicates the space occupied by the

reconstructed streamlines but its relationship with the underlying anatomy of the fibres (e.g. axonal diameter, myelination and density) is not entirely clear (Beaulieu, 2002). To control for the possibility that hemisphere size might be driving the volume of the arcuate segments (i.e. larger hemisphere means larger arcuate fasciculus) the absolute segment volume was normalised by the hemisphere volume (segment volume/hemisphere volume). The hemispheric volume was obtained using FMRIB Software Library package (FSL, http://www.fmrib.ox.ac.uk/fsl/). The normalised segment volume was then used for further analysis (referred to as segment index size hereafter).

Statistical analysis

In this study, our primary goal was to identify anatomical predictors of aphasia recovery. Hence, we limited our model to factors that could directly influence the anatomy of the three segments of the arcuate fasciculus. Previous studies have shown that amongst these factors are age (i.e. smaller arcuate in older patients; Bava et al., 2011; Lebel et al., 2011), gender (i.e. larger right arcuate in females; Catani et al., 2007; Kanaan et al., 2012; Inamo et al., 2011; Hsu et al., 2008), lesion size (i.e. smaller arcuate in larger lesions; Johansen-Berg & Behrens, 2006; Goldberg & Ransom, 2003; Ciccarelli et al., 2008), and level of education (i.e. higher education level might be neuroprotective; Stern et al., 1994; Ott et al., 1995; Letenneur et al, 1999; Brayne et al., 2010). Other studies have also shown baseline aphasia severity is predictive of longitudinal out come (Ferro et al., 1999; Pedersen et al., 2004; Laska et al., 2001; Lazar et al., 2007; Kertesz 1988b), which we were not able to include in our analysis. Previous studies show that baseline measurement fluctuations occur within a fortnight of symptom onset due to clinical-physiological processes and the influence of

psychodynamic mechanisms (Hillis et al., 2001; Hackett et al., 2005; Gottesman et al., 2010; Lazar et al., 2008). For this reason, baseline language measures in relation to longitudinal therapeutic goals are usually obtained after two weeks from onset to allow sufficient time for acute processes to settle. In the current study, baseline measures were obtained on admission (mean 5±5 days) and therefore are not reliable indices of language impairment. Indeed, in our sample severity of aphasia at baseline is not correlated with the language score obtained six months after ($r(16)=.49$, $p>.05$).

To determine which one of these variables (age, gender, lesion size, level of education) are most relevant to our data and to identify the best subset of variables explaining the dependent variable (i.e. longitudinal aphasia severity) they were introduced to a backward elimination analysis. This method places all possible variables, as identified from the literature or driven by a hypothesis, in the model and calculates the contribution of each of them. Their contribution is then compared against a removal criterion (here we used a probability value for the test statistic of $p>0.001$). The variable with the least contribution to the model is then removed and the reduced model re-estimated for the remaining variables. The contribution of the remaining variables is re-assessed in an iterative way until the model reaches statistical significance.

The resulting subset of variables was introduced into subsequent regression analyses. The primary analysis employed a hierarchical multiple linear regression. In this analysis, two subsequent models were defined with the longitudinal aphasia severity, defined as the absolute aphasia Quotient (AQ) value obtained after six months, as the dependent variable. The first-level model included the variable subset identified by the

backward elimination, namely age, gender, and lesion size. In the second-level of the model the three segment index sizes were separately added to model.

Where both models were significant, the fit of each model was estimated by calculating the corrected Akaike information criterion for small sample sizes (AICc) (Akaike, 1974; Hurvich and Tsai, 1989). The AICc is a goodness of fit measure corrected for model complexity (i.e. penalising increasing number of predictors). We used this analysis to compare both levels of the regression models and to verify that the increase in predictive power of the second-level model is not merely driven by a higher number of predictors.

The secondary analysis addressed group differences between gender, fluent vs. non-fluent aphasia types (defined according to a cut-off of 4 on the WAB-R fluency scale), and thrombolysis groups (thrombolysed vs. non thrombolysed).

Statistical analyses were performed using *R* 2.15.1 software (www.R-project.org). Power analysis was conducted using the software package G*Power (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/).

Results

Patient details and demographics are available in Table 1. A total of 18 patients were included at baseline, whereof 16 were followed-up six months post stroke. Eleven of these 16 patients had received thrombolysis treatment as part of their standard clinical intervention.

Table 1 (patient demographics) about here

Identification of previously established predictors of symptoms severity

Based on previous studies we considered age, gender, lesion size, and education as potential predictors of aphasia severity at 6 months {Eslinger:1981ug, Laska:2001il, Ferro:1997jy, McDermott:1996um}. In addition these factors can also influence the anatomy of the white matter tracts (Catani et al., 2007; Lebel et al., 2008; Thiebaut de Schotten et al., 2012). In order to confirm whether these factors significantly influence language outcomes in our dataset a backward regression analysis was conducted. This method introduces all potential variables into the model at once before subsequently eliminating each independent variable, starting with the variable with the smallest partial correlation coefficient. A conventional significance level of 0.1 was assumed for this analysis. The analysis shows that when all variables are included, the model is not significant for predicting longitudinal language outcomes (R2=.605, $F_{(4,9)}$=3.448, *p*=.06). The subsequent analysis removed education from the variables and the model become significant including only age, gender, and lesion size (R2=.596, $F_{(3,10)}$=4.921, p=.024). This result is in line with the literature where education has no strong evidence of being an independent predictor of long-term recovery (Ferro et al., 1999). Based on these findings age, gender and lesion size are good predictors of recovery in our dataset. This subset of variables was therefore taken into account for subsequent regression analyses.

Percentage Lesion Overlay maps

As first investigation we computed percentage lesion overlay maps. The group comparison lesion analysis identified the inferior frontal gyrus, the internal and external/extreme capsules, the claustrum, the putamen, the medial thalamic nuclei, and

the peri-insular white matter as areas that were most commonly damaged in our sample of stroke patients (Figure 2).

Figure 2 (Lesion_Map) about here

Diffusion Tensor Imaging (DTI) tractography

The volume, defined as the number of voxels intersected by the streamlines of each segment, was extracted for the left and right hemispheres for each patient (Table 2).

Table 2 (volume measures) about here

Left hemisphere. The hierarchical regression analysis showed that a model including age, gender and lesion size was predictive of longitudinal aphasia severity (R^2=.502, $F_{(3,11)}$=3.689, *p*=.047). The predictive value of the model improved but not significantly when the volume of the left long segment was included in addition to age, gender and lesion size (R^2=.623, $F_{(4,10)}$=4.138, *p*=.031; R^2 change: $F_{(1,10)}$=3.235, *p*=.102). Among the four variables entered only lesion size was an independent predictor [beta=–.630, *t*(–3.129), *p*=.011] of longitudinal aphasia severity.

The same analysis was repeated for the left anterior and posterior segments of the arcuate fasciculus and both models were not predictive (anterior segment index size:

R^2=.541, $F_{(4,10)}$=2.943, *p*=.076; posterior segment index size: R^2=.577, $F_{(4,10)}$=3.411, *p*=.053). The result indicates that by taking into account all three predictors the left hemispheric model can explain approximately 50% of the variability in language recovery. By adding the volume of the left long segment the model can explain 62% of the variability, which represents only a 12% increase in predicting value. Overall, this analysis indicates that in the left hemisphere the only independent predictor of longitudinal aphasia is the lesion size. It should be taken into consideration here, however, that the volume measurements of the left and right arcuate segments reflect two different anatomical properties of these fibres. In the right hemisphere the volume of the tracts reflects the anatomy of a pre-existing tract, which is unaffected by the stroke. By contrast, in the left hemisphere tract volume measurements are indicative of the residual fibres whose quantity depends on the amount of damage occurred in the middle cerebral artery territory. Hence, while the right tract measurements reflects the anatomical volume of the pre-existing arcuate the left tract volume is an indirect measure of lesion load specifically to the arcuate fasciculus. We therefore investigated if the lesion size and the volume of the left arcuate segments correlate, which was not the case for the left long segment nor the sum of the three segments in the left hemisphere (left long segment: r(18)=.224, p=.372; sum of left three segments: r(18)=.078, p=.760). Also when adding the sum of the three segment as a predictor to the regression model, the model did not explain the observed data (level 1(age, gender, lesion size): R^2=.275, $F_{(3,12)}$=1.52, *p*=.260; level 2 (addition of the left three segments: R^2=.305, $F_{(4,11)}$=1.206, *p*=.362; R^2 change: R^2=.030, $F_{(1,11)}$=.467, *p*=.508).

Right hemisphere. The hierarchical regression analysis showed that a model including age, gender and lesion size was not predictive of longitudinal aphasia severity (R^2=.275,

$F_{(3,12)}$=1.52, *p*=.260). The predictive value of the model improved significantly when the volume of the right long segment was included in addition to age, gender and lesion size (R^2=.568, $F_{(4,11)}$=3.62, *p*=.041; R^2 change: $F_{(1,11)}$=7.462, *p*=.020). Of the four predictors only age [beta=–.678, *t*(–3.087), *p*=.010] and the right long segment [beta=.730, *t*(2.732), *p*=.020] were independent predictors. Gender [beta=.505, *t*(1.920), *p*=.081] and lesion size [beta=-.441, *t*(–2.04), *p*=.066] were marginally significant. For the right hemisphere the model that includes only age, gender and lesion size explains about 30% of the variance of language performances at 6 months (R^2=.275, $F_{(3,12)}$=1.520, *p*=.260). By adding the volume of the right long segment the model increases to 57%, which represents a statistically significant increase in predictive value.

Cross-validation of the model

The corrected Akaike Information Criterion (AICc) was used to estimate the fit of each model. The AICc is used for small sample size data to calculate the goodness of fit measure corrected for model complexity (i.e. increased number of predictors). Given that the predictive power of the model did not improve for left-hemispheric analysis the AICc model comparison only applies to the right-hemispheric models. The AICc showed that the three-predictor model has an AICc of 121.13 and the four-predictor model has an AICc of 114.84. The model with the lower AICc, hence the four-predictor model, is the preferred model. This indicates that the increased predictive power of the four-predictor model is not simply due to the benefits of an added variable *per se* but it is specific to the right long segment.

Fig. 3 (Results_I) about here

Power calculation analysis

A sensitivity analysis was conducted using the software package G*power. The result of this analysis demonstrated that our study was able to detect an effect size (f^2) of 1.14 with a power of 1- β =.80 given the sample size (n=16) and a specified α of 0.05. This indicates that a minimum effect size of 1.14 is necessary to reach sufficient sensitivity. The two-level hierarchical regression model (i.e. hierarchical analysis of the three- and four-predictor model) has an effect size of f^2=1.88. This effect size is larger than the critical value (f^2=1.44) determined in the previous sensitivity analysis and we could therefore assume that this analysis is sufficiently powered to detect a genuine effect with at least an 80% chance (see supplementary material for more details).

Changes in symptoms severity

Amongst the 16 patients who returned after six months, 81.25% were still aphasic according to the WAB-R and three patients (18.75%) recovered fully. As a group, there was significant overall improvement in language functioning six months after stroke onset ($AQ_{(baseline)}$=43.48±28, $AQ_{(6\ months)}$= 85.68±8.44; t(15)= – 6.759, p<.001; Figure 4A).

Irrespective of the severity of aphasia, improvements were seen in all aphasic patients, however, with different recovery slopes (Figure 4B). None of our patients deteriorated between the two assessments.

Fig. 4 (Results_II) about here

At baseline, the non-fluent group presented with more severe aphasia (as estimated by the AQ score) compared to the fluent group ($AQ_{(fluent)}$=64.4±25.2, $AQ_{(non\ fluent)}$=32.1±21.9; t(14)= –2.85, p<.01). This difference was lost at six months ($AQ_{(fluent)}$=88.9±9.1, $AQ_{(non\ fluent)}$=84.2±8.1; t(14)= –1.03, p>.05). No gender differences were observed for aphasia severity at the baseline and after six months (see Table 2 for mean and deviations, $t_{(Baseline)}(16)$= –.087, p>.05; $t_{(6\ months)}(14)$= –.510, p>.05). Thrombolysed patients (11/16) did not differ in their baseline severity or language recovery compared to non-thrombolysed patients ($t_{(Baseline)}(16)$=.808, p>.05; $t_{(6\ months)}(14)$= –.153, p>.05; see supplementary material for details). Lesion size correlated negatively with baseline severity (r(18)= –0.637, p<.004). This significant negative correlation implies that bigger lesions are associated with a lower score on the WAB-R (i.e. more severe language impairments). The same test statistic applied to the follow-up severity was not significant (r(16)= –.276, p=.30).

Table 3 about here

Tract-specific measurements of fractional anisotropy. Previous studies have shown that the asymmetry of the long segment is evident only for the volume measurements and not for fractional anisotropy (FA) (Thiebaut de Schotten et al., 2010). Nonetheless,

we additionally investigated if FA measures within each arcuate segment in both hemispheres are associated with the aphasia severity (AQ) at baseline or after six months. No correlations were found between FA measures in the three segments in either hemisphere and aphasia severity at either time point (see table 4).

Table 4 about here

Discussion

This longitudinal tractography study in acute stroke is the first to prospectively examine anatomical predictors of language recovery with diffusion tensor imaging tractography. We observed that the volume of the long segment of the arcuate fasciculus in the right hemisphere (contralateral to the lesion) is an important predictive factor for recovery of language after stroke. The volume of the other segments in the right and left hemisphere was not correlated with recovery. In addition we have confirmed the importance of other predictive factors, including age, gender and lesion size.

In particular, in our sample, lesion size in the left hemisphere is the strongest predictor of post stroke aphasia recovery after six months. Lesion size has previously been shown to play an important role in recovery through a variety of different mechanisms, including tissue neuronal repair, reperfusion of stroke tissue, and recruitment of peri-lesional spared areas (Croquelois et al., 2003; Heiss et al., 1999; Warburton et al., 1999). In larger lesions, compensation could also occur after recruitment of ipsilateral

circuits not previously concerned with language (Code, 2001; Crosson et al., 2007; Hillis and Heidler, 2002).

An original finding of our study is the predictive value of tractography-derived measurements of tract volume in the right hemisphere. Specifically, the volume of the long segment connecting posterior temporal and inferior frontal regions is a good predictor of longitudinal recovery of aphasia after stroke.

This result indicates that different mechanisms might be at play across the two hemispheres. As inferred from the model, lesion size is predictive of long-term outcome regardless of added DTI measures. However, in the right hemisphere model the classical predictors do not sufficiently predict recovery, but when DTI measures are added, the model significantly improves and can explain up to nearly 60% of the variance in language performances at follow-up.

Recent tractography imaging studies show that this tract is involved in auditory memory (Catani et al., 2007; López-Barroso et al., 2013) and may have a role in recovery after stroke (Tuomiranta et al., 2013). Lopez-Barroso et al. (2013) reported a correlation between higher performances in an auditory memory tasks for pseudo-words and strength of connectivity of the left long segment measured with both tractography (i.e. radial diffusivity) and functional connectivity (i.e. temporal correlation of BOLD response between the three peri-sylvian regions connected by the arcuate) in healthy people. The right long segments has also a role in auditory memory tasks based on semantic clustering strategies, where a larger volume of this segment is related to better performances (Catani et al., 2007). Furthermore, a recent single case study reported a woman with stroke affecting the left arcuate fasciculus and resulting in aphasia. After rehabilitation the patient was able to recover the ability to learn novel active vocabulary

and the authors speculate that this was due to the presence of compensatory pathways in the right hemisphere (Tuomiranta et al., 2013).

This hypothesis is in line with previous PET and fMRI studies that indicated an important role of the right hemisphere for aphasia recovery after stroke (Cappa, 2000; Karbe et al., 1998; Saur et al., 2006). Two possible mechanisms have been suggested: unmasking of previously ready language capacities or reorganisation of right hemisphere language areas (Cappa, 2000). In both cases the presence of larger right long segment volume could facilitate direct cross-talk between right hemisphere homologues of Broca's and Wernicke's regions. Additionally, these studies revealed a dynamic activational shift to the contralesional hemisphere during recovery (Saur et al., 2006). This shift seems to be only advantageous for recovery if of temporary nature (Hillis, 2006; Saur et al., 2006; Szaflarski et al., 2013). Nonetheless, in such cases the right hemisphere appears to be able of temporarily adopting linguistic competence beyond the non-verbal aspects already been assigned to the non-dominant hemisphere (e.g. prosody, intonation, and affective content) (Ross et al., 1988; Turkeltaub et al., 2012). Our study suggests that these right-hemispheric language functions could be mediated by specific portion of the arcuate fasciculus.

Currently, it remains difficult to determine how a pre-existing right arcuate could facilitate functional recovery. In our study, we used the number of voxels visited by the streamlines as a surrogate of tract volume. The determinants of right hemisphere tract size is currently unknown but most likely depends on several factors, including the degree of fibre myelination, axonal number and diameter, and organisation of fibres (Beaulieu, 2002). All these biological characteristics of white matter are correlated with

the speed of signal propagation and therefore could influence efficiency of signal processing between distant areas (López-Barroso et al., 2013; Thiebaut de Schotten et al., 2011). Hence, we hypothesise that in people with smaller long segment in the right hemisphere communication between Broca's and Wernicke's right homologues would mainly rely on an indirect multi-synaptic pathway mediated by the anterior and posterior indirect segments. The absence of a direct long segment could, therefore, affect the efficiency of communication between distant areas and hinder right hemisphere mechanisms of language recovery.

An alternative hypothesis of the specific contribution of the right long segment to recovery could be related to the functional specialisation of the right anterior and posterior segments. These segments connect to the right inferior parietal lobule, a region involved in visuo-spatial attention tasks and often damaged in patients with visuo-spatial neglect. This suggests that while both direct and indirect pathways on the left hemisphere are involved in language functions (Fridriksson et al., 2013), in the right hemisphere the two pathways may have a different role (Corbetta et al., 2000; Kaplan et al., 2008; Thiebaut de Schotten et al., 2011). Future studies combining anatomical and functional imaging will be able to elucidate the relationship between white matter anatomy, cortical plasticity and functional activation.

The study benefitted from cutting edge diffusion methodology applied to a clinical setting and our results encourage the use of tractography as part of the clinical routine. However, several limitations should also be acknowledged. Current DTI algorithms are prone to implicit limitations, including generating the presence of false positives (i.e. non-existing tracts) and false negatives (i.e. absence of truly existing tracts) (Basser et

al., 2000; Ciccarelli et al., 2008; Dell'Acqua and Catani, 2012). These obstacles have to be considered with caution, especially when trying to extract quantitative measures within the lesioned hemisphere. In addition, the current study focused on the perisylvian pathways of the right hemisphere but it cannot be excluded that other tracts might play an important role for recovering or redistribution of language capacities. Also, our observations reflect results derived from a selected group of patients that were able to tolerate a 45-minutes MRI scanning session in the acute stage of stroke. This patient group can be considered otherwise healthy prior to the stroke. Arguably, a high potential for plasticity can be assumed in these patients, which may not be as efficient in wider cohorts with known comorbidities and/or multiple strokes. Finally, the inclusion criteria for this study can be considered restrictive but did allow us to exclude various potential nuisance variables, which would have otherwise reduced the power.

In conclusion, early recovery of aphasia is likely to be secondary to reperfusion and lesion dynamics, whilst later stages may be linked to structural and functional reorganization. In addition, tractography-based measurements of the arcuate fasciculus may provide a good estimate of the presence of pre-existing right hemisphere networks that may serve as vehicle for functional compensation after stroke. Our findings, if confirmed in a larger cohort, could represent a step forward in our understanding of brain mechanisms underlying language recovery following stroke and may provide clinically useful predictive biomarkers.

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Supplementary material: Provided.

Figures

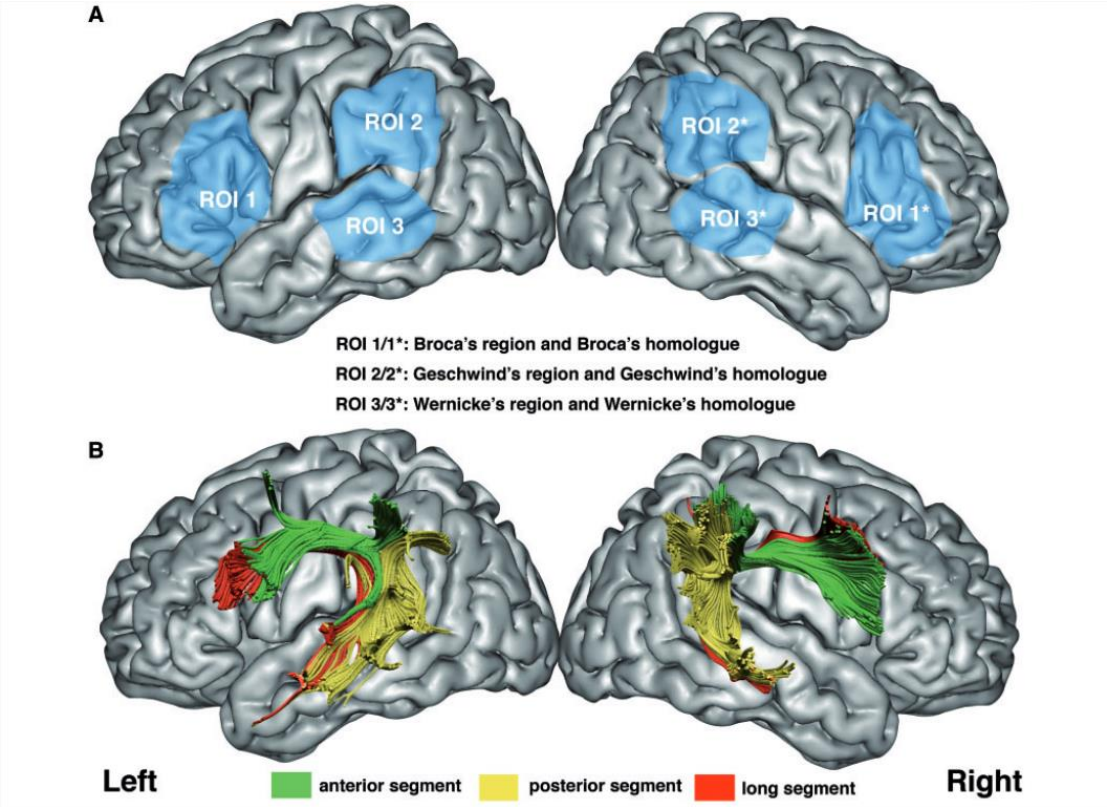

Figure 1: Bilateral regions of interest (ROI) used to perform virtual tractography reconstruction of the three segments of the arcuate fasciculus. (A) ROI 1: Broca's region; ROI 2: Geschwind's region; ROI 3: Wernicke's region. The three segments are obtained when combining ROI 1 + 2 (anterior segment), ROI 1 + 3 (long segment), and ROI 2 + 3 (posterior segment). (B) Visualization of the three segments bilaterally.

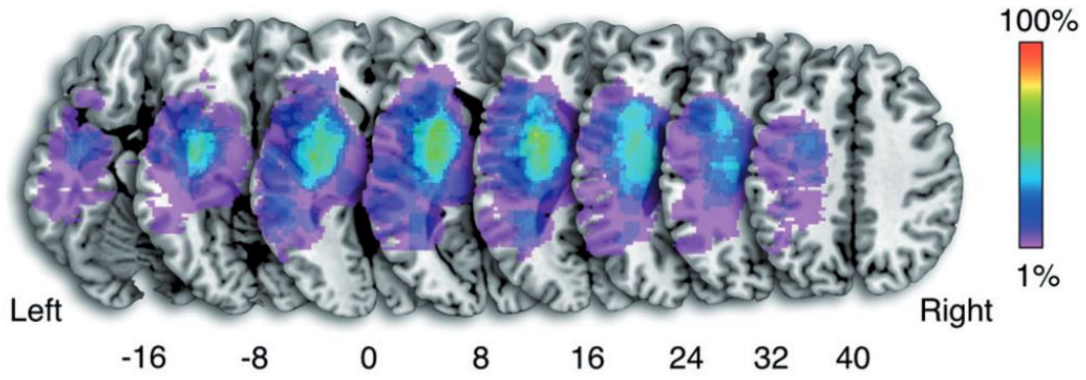

Figure 2: Percentage lesion overlay map (0-100%) for all acute patients. The highest overlay is seen in the perisylvian white matter of the external/extreme capsule and internal capsule, the claustrum, striatum and lateral thalamus. At the cortical level the lesion overaly was highest in the insula and perisylvian cortex.

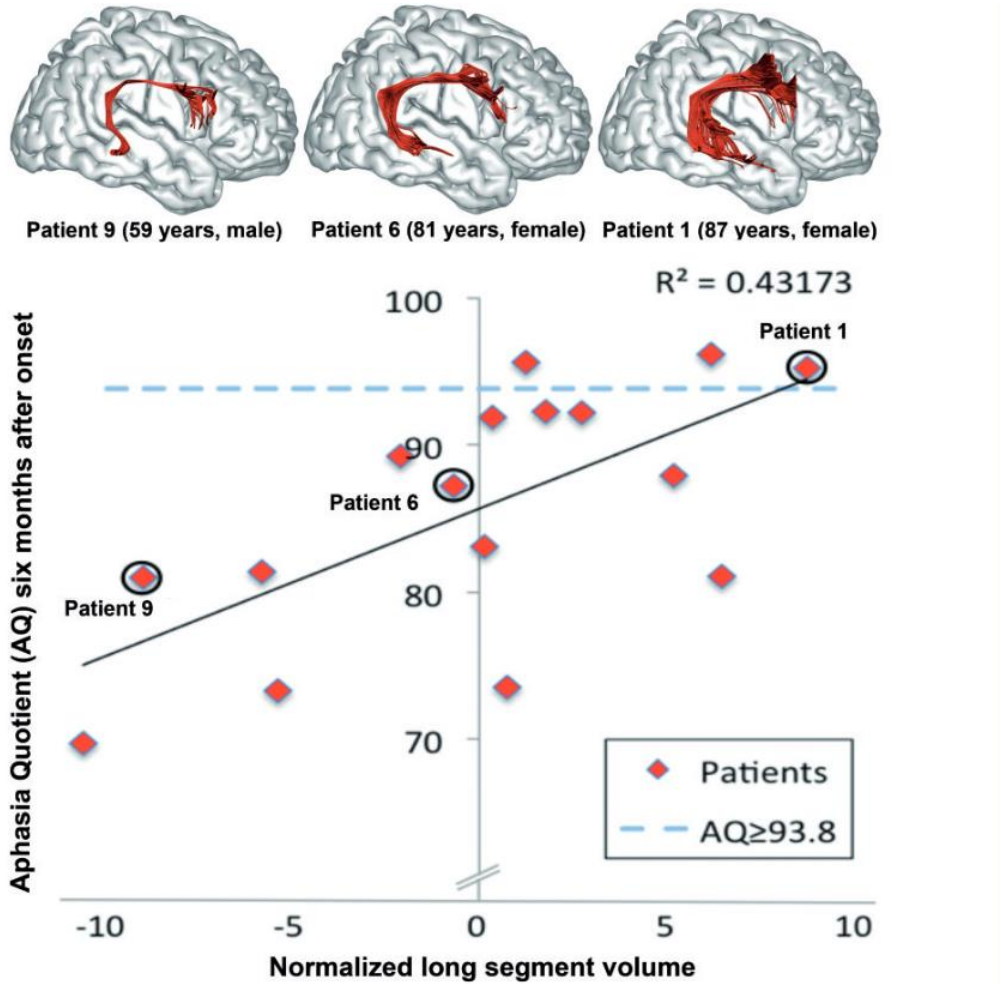

Figure 3: Anatomical variability in perisylvian white matter anatomy and its relation to post stroke language recovery. The right long segment of the arcuate fasciculus is shown for three patients presenting with a different degree of language recovery at six months. These patients are indicated in the regression plot of the standardised residual values of the right long segment index size plotted against the longitudinal aphasia quotient (AQ) (corrected for age, sex, and lesion size).

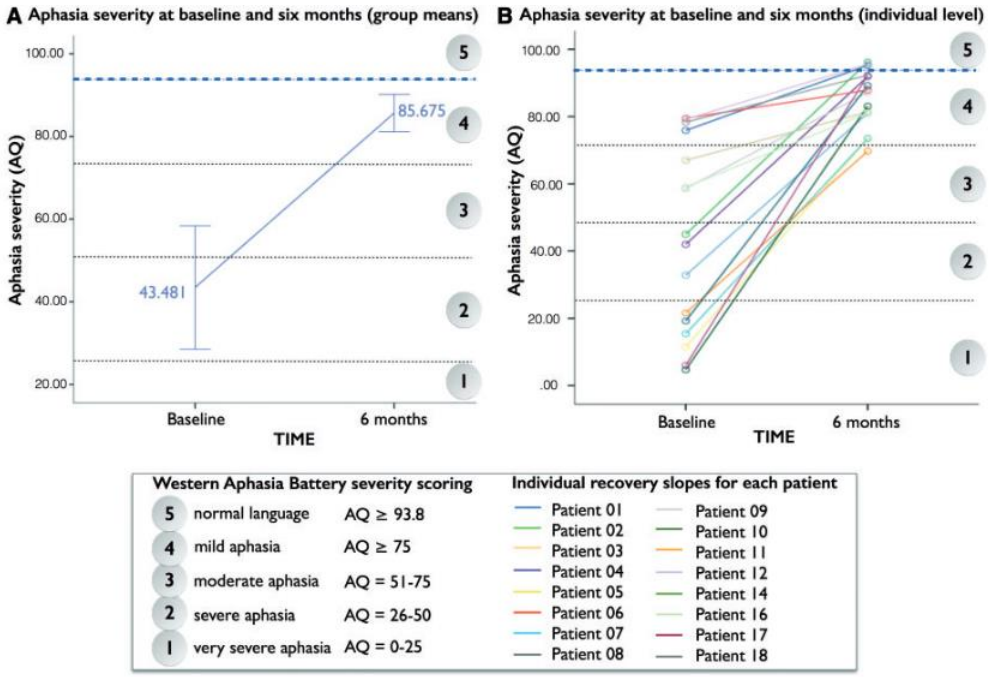

Figure 4. Mean (A) and individual (B) language function curves (total possible=100) at baseline and longitudinally (n=16). Values 1-5 correspond to the severity classifications according to the Western Aphasia Battery Revised manual. The blue dotted line signals the cut-off for normal language functions (AQ>93.8, category 5 according to the severity score). Only three patients reached the cut-off for normal language function at follow-up..

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