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Dynamics of language reorganization after left temporo-parietal and frontal stroke

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The loss and recovery of language functions are still incompletely understood. This longitudinal functional MRI study investigated the neural mechanisms underlying language recovery in patients with post-stroke aphasia putting particular emphasis on the impact of lesion site. To identify patterns of language-related activation, an auditory functional MRI sentence comprehension paradigm was administered to patients with circumscribed lesions of either left frontal ($n = 17$) or temporo-parietal ($n = 17$) cortex. Patients were examined repeatedly during the acute ($\leqslant 1$ week, t1), subacute (1–2 weeks, t2) and chronic phase (>6 months, t3) post-stroke; healthy age-matched control subjects ($n = 17$) were tested once. The separation into two patient groups with circumscribed lesions allowed for a direct comparison of the contributions of distinct lesion-dependent network components to language reorganization between both groups. We hypothesized that activation of left hemisphere spared and perilesional cortex as well as lesion-homologue cortex in the right hemisphere varies between patient groups and across time. In addition, we expected that domain-general networks serving cognitive control independently contribute to language recovery. First, we found a global network disturbance in the acute phase that is characterized by reduced functional MRI language activation including areas distant to the lesion (i.e. diaschisis) and subsequent subacute network reactivation (i.e. resolution of diaschisis). These phenomena were driven by temporo-parietal lesions. Second, we identified a lesion-independent sequential activation pattern with increased activity of perilesional cortex and bilateral domain-general networks in the subacute phase followed by reorganization of left temporal language areas in the chronic phase. Third, we observed involvement of lesion-homologue cortex only in patients with frontal but not temporo-parietal lesions. Fourth, irrespective of lesion location, language reorganization predominantly occurred in pre-existing networks showing comparable activation in healthy controls. Finally, we detected different relationships of performance and activation in language and domain-general networks demonstrating the functional relevance for language recovery. Our findings highlight that the dynamics of language reorganization clearly depend on lesion location and hence open new perspectives for neurobiologically motivated strategies of language rehabilitation, such as individually-tailored targeted application of neurostimulation.

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Abbreviation: ATL = anterior temporal lobe; dACC = dorsal anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; IFG(tri/orb/op) = inferior frontal gyrus (pars triangularis/orbitalis/opercularis); $LRS_{COMP/PROD}$ = language recovery score comprehension/production; PTL = posterior temporal lobe; REV = unintelligible reversed speech; SMA = supplementary motor area; SP = intelligible speech

Introduction

Aphasia is one of the most devastating conditions after stroke that significantly affects the patients' private and professional life (Flowers *et al.*, 2016). A profound understanding of the neural mechanisms underlying aphasia recovery is essential for developing novel, efficient treatment strategies.

The view of language organization in anatomically distributed yet functionally integrated large-scale networks is integral to the understanding of loss and recovery of function. Modern views emphasize that language is not attributable to single brain areas, but critically depends on coordinated interactions of multiple sets of brain regions including the inferior frontal gyrus (IFG), anterior, posterior and inferior temporal lobes (ATL/PTL/ITL) that constitute a left-lateralized fronto-temporal network (Friederici and Alter, 2004; Hickok and Poeppel, 2004). During successful language processing, this network for language interacts with bilateral domain-general networks that are involved in various types of higher-order processing (Geranmayeh *et al.*, 2014*b*; Davis and Cabeza, 2015). These networks can be subdivided into a fronto-parietal network comprising dorsolateral prefrontal (DLPFC), middle cingulate cortex, precuneus, inferior parietal lobe and intraparietal sulcus (IPL/IPS) and a cingulo-opercular network including anterior prefrontal cortex, anterior insula, frontal operculum, dorsal anterior cingulate cortices (dACC) and supplementary motor area (SMA) (Dosenbach *et al.*, 2008). Both networks have been implicated in efficient cognitive processing by providing flexible resources for the initiation and maintenance of cognitive control, respectively (Dosenbach *et al.*, 2007). Applying this extended network perspective to stroke patients, post-stroke aphasia can be considered a network disorder (Carrera and Tononi, 2014; Corbetta *et al.*, 2015; Fornito *et al.*, 2015; Siegel *et al.*, 2016) that harnesses dynamic reorganization processes within language and domain-general networks throughout the course of recovery (Crinion and Leff, 2007; Thompson and den Ouden, 2008; Brownsett *et al.*, 2014; Geranmayeh *et al.*, 2014*a*; Stockert *et al.*, 2016; Hartwigsen and Saur, 2019).

Previous cross-sectional functional imaging studies in chronic stroke patients with aphasia support the hypothesis of a hierarchical reorganization of language (Heiss and Thiel, 2006). It implies that undamaged left hemisphere language networks primarily contribute to language recovery (Karbe *et al.*, 1998; Warburton *et al.*, 1999; Winhuisen *et al.*, 2007; Fridriksson *et al.*, 2010, 2012; Tyler *et al.*, 2011; Szaflarski *et al.*, 2013; Thiel *et al.*, 2013; Thompson *et al.*, 2013; Griffis *et al.*, 2017*b*). However, in cases of large lesions or incomplete recovery, recruitment of right hemisphere lesion-homologue and bilateral domain-general areas may support residual language functions (Perani *et al.*, 2003; Winhuisen *et al.*, 2005; Breier *et al.*, 2009; Sharp *et al.*, 2010; Turkeltaub *et al.*, 2012; Meltzer *et al.*, 2013; Szaflarski *et al.*, 2013; Geranmayeh *et al.*, 2016; Sims *et al.*, 2016; Griffis *et al.*, 2017*b*). The understanding of dynamic network changes that underlie aphasia recovery, however, obligatorily requires longitudinal observations. Previous longitudinal functional imaging studies focusing on the subacute (2 weeks to several months) to the chronic phase mapped either changes in the state of functional network integrity (Siegel *et al.*, 2018) or neural activity of different brain regions (Heiss *et al.*, 1999; Cardebat *et al.*, 2003; de Boissezon *et al.*, 2005; Saur *et al.*, 2006; van Oers *et al.*, 2010; Nenert *et al.*, 2018). In this regard, the functional MRI study of Saur *et al.* (2006) is of particular importance, as this study also included the early acute phase, for which the greatest dynamic in functional improvement was observed (Pedersen *et al.*, 1995). Results of that study were summarized in a three-phase model of language reorganization that comprised decreased language-related activation during the acute phase (<1 week), increased activation in bilateral IFG, SMA and left PTL during the subacute phase (~2 weeks) and subsequent normalization of frontal activation in the chronic phase (~1 year).

Nonetheless, the timing and necessity of temporary or persistent activation changes in left hemisphere language and bilateral domain-general regions (Geranmayeh *et al.*, 2014*a*, 2017) as well as right hemisphere regions (Cardebat *et al.*, 2003; de Boissezon *et al.*, 2005; van Oers *et al.*, 2010) for recovery remain incompletely understood. Moreover, owing to the heterogeneity of lesion locations that were pooled in previous cross-sectional and longitudinal studies, the distinction of undamaged left hemisphere and lesion-homologue right hemisphere regions remains insufficient. Assuming at least some degree of functional segregation within networks subserving language functions, distinct lesion locations are likely to entail differential effects on network integrity and the dynamics of aphasia recovery (Siegel *et al.*, 2018; for a computational approach see Ueno *et al.*, 2011). In this regard, few cross-sectional investigations considered the effect of frontal (Rosen *et al.*, 2000) or temporal lesions (Weiller *et al.*, 1995; Robson *et al.*, 2014) or the sparing of left hemisphere structures (Crinion and Price, 2005; Crinion *et al.*, 2006; Griffis *et al.*, 2017*a*, *b*) on language activity. In line with the primary role of left hemisphere language networks (Heiss and Thiel, 2006), spared left IFG, ATL and PTL favourably contribute to language performance in patients

with left frontal (Rosen *et al.*, 2000; Crinion and Price, 2005) and temporal stroke (Robson *et al.*, 2014), respectively. Yet, discrepancies remain regarding a variable contribution of increased right lesion-homologue IFG (Rosen *et al.*, 2000), PTL (Weiller *et al.*, 1995) or ATL (Robson *et al.*, 2014) activation in these patient groups. To date, only one study separately investigated patients with left frontal and temporal lesions repeatedly with the same protocol (Heiss *et al.*, 1999). In this study, patients with frontal stroke showed early subacute recruitment of right IFG and PTL transitioning into left PTL activation in the later subacute phase. In contrast, in patients with temporal stroke and poorer performance, language activation transitioned from early subacute recruitment of left IFG and SMA to later bilateral prefrontal and right PTL activation. While this study provides empirical evidence for activity patterns in patients with different lesion locations at different time points, the lack of direct statistical comparisons between lesion groups over time does not allow for the identification of lesion-specific mechanisms that underlie recovery. Therefore, the question of lesion location as a potential moderating factor remains unanswered.

Here, we aimed to refine the neurobiological processes supporting aphasia recovery by putting a particular emphasis on how changes in language-related activation across time depend on the site of left hemisphere lesions. The present functional MRI study builds upon our previous study (Saur *et al.*, 2006) and addresses the question of lesion-specific in comparison to general lesion-independent reorganization patterns. We investigated patients with aphasia repeatedly during the acute, subacute and chronic phases after stroke by implementing a simple sentence-level language comprehension functional MRI task that was feasible for patients with acute aphasia. Selection of circumscribed lesions that were confined to either frontal or temporo-parietal cortices allowed us to compile two distinct lesion groups. This group assignment was motivated by the commonly used distinction of clinical and anatomical phenotypes that are representative of other patients with aphasic stroke. It allowed for an unequivocal attribution of functional MRI activation patterns to undamaged (but lesion-remote) or perilesional tissue in the left hemisphere, and lesion-homologue areas in the right hemisphere. We followed two different lines of analyses: (i) by examining patterns of language-related activation in these patient groups at each time point, we were able to map regions involved in language processing during the different phases; and (ii) the identification of a global activation pattern derived from all patients across all time points allowed for the definition of volumes of interest that could be assigned either to language-related or domain-general cortices. These served for activation-informed volume of interest-based statistical analyses to test for time-specific (but lesion-independent), lesion-specific (but time-independent) and lesion-specific spatial dynamics of language activation. Joint consideration of these analyses provides novel and unique insights into the complex mechanisms of post-stroke language reorganization. It allows for the identification of phenotypical, generic functional MRI activation patterns that are representative of patients with frontal or temporo-parietal stroke and may ultimately provide targets for supportive therapies with non-invasive brain stimulation.

Materials and methods

Participants

Thirty-four patients with first ischaemic stroke, primarily affecting the left frontal ($n = 17$) or temporo-parietal ($n = 17$) cortex (Fig. 1, Supplementary Table 1 and Supplementary Fig. 1) and 17 age-matched healthy control subjects were included in the analyses. Group assignment was performed by visual inspection of the structural MRI scans and then quantitatively validated using hierarchical cluster analysis with Ward linkage (Ward, 1963) based on Dice distances (Dice, 1945) reflecting the spatial similarity of the patients' lesion patterns (see the Supplementary material for details on participants and group assignment).

Study design

Patients were prospectively enrolled and longitudinally examined within the first week (acute phase, t1 = 1–7 days post-stroke onset), the second to third week (subacute phase, t2 = 8–21 days post-stroke onset) and the chronic phase post-stroke (t3, >6 months) (Fig. 1). Testing included behavioural evaluation and acquisition of functional MRI data at each time point in patients. Control subjects underwent functional MRI scanning once.

Behavioural evaluation

Behavioural assessment was carried out by trained speech-language pathologists using the Aachen Aphasia Test (AAT) (Huber *et al.*, 1984). Based on AAT subtests, composite scores (language recovery scores, LRS) for language comprehension (auditory and written comprehension and Token Test Scores, LRS_{COMP}) and production (naming and repetition, LRS_{PROD}) were computed separately for each time point and patient (see the Supplementary material for details). The resulting range between 0 and 1 reflected the level of overall performance, with a score of 1 representing full recovery (Fig. 1). The LRS_{COMP} was taken as behavioural index at each measurement because it was assumed to be a reasonable variable for establishing a relationship between impaired language comprehension and the magnitude of activation during auditory language processing. Statistical significance ($P < 0.05$, two-tailed) for within- and between-group comparisons of behavioural performance was determined using multifactorial mixed-design ANOVAs in SPSS version 24 (SPSS Inc., Chicago, IL, USA). Significant main effects and interactions were followed up by *post hoc t*-test that compared performance over time and between groups at different time points using the Bonferroni-Holm procedure (Holm, 1979) to account for multiple comparisons. All reported results were corrected by the Greenhouse-Geisser procedure where appropriate (violation of sphericity assumption).

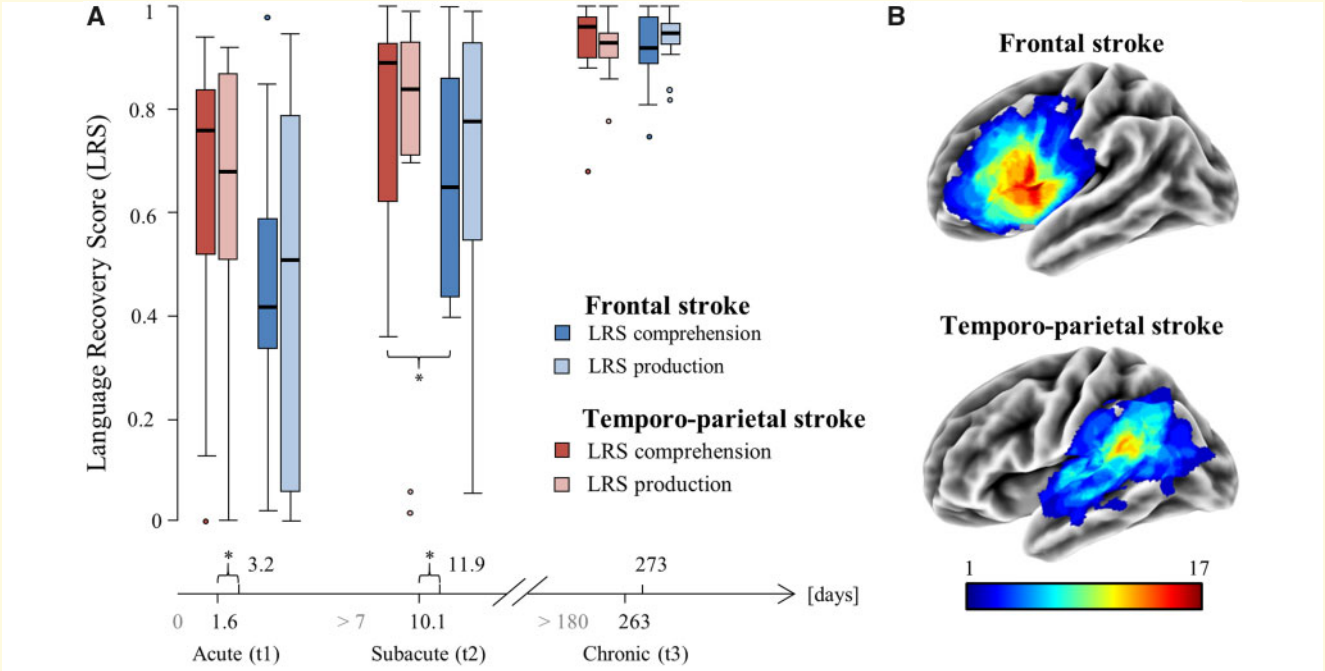

Figure 1 Behavioural improvement and lesion distribution. (**A**) Behavioural improvement and (**B**) lesion distribution. (**A**) LRSs were calculated in patients with left temporo-parietal (n = 17, red) and frontal lesions (n = 17, blue) based on the AAT and indicate the overall level of language comprehension (darker colours) and production (lighter colours) performance and ranged from 0 to 1 (1 = full recovery) at each examination (t1–t3). Box and whisker plots indicate median and interquartile range (IQR) with first (25 percentile) and third (75 percentile) quartiles; circles indicate outliers extending 1.5 times the box height. On average, patients with temporo-parietal stroke were examined earlier during the acute and subacute phase. Nonetheless, patients with temporo-parietal stroke showed a better recovery of language comprehension in the subacute phase. Significant differences of behavioural performance or time of examination between groups are labelled with asterisks (*$P < 0.05$, corrected for multiple comparisons in *post hoc* t-tests using the Bonferroni-Holm procedure). (**B**) Visualization of left hemisphere lesion distribution in both patient groups with colour bar representing the extent of lesion overlap (i.e. number of subjects with lesions at each voxel, warmer colours denote higher overlap).

Imaging

MRI acquisition and preprocessing

Functional, diffusion-weighted and high-resolution T_1-weighted MRI sequences were acquired for each participant. Imaging acquisition, lesion mapping and preprocessing are described in the Supplementary material.

Functional MRI paradigms and data analysis

Changes in participants' brain activity during language processing were measured using two similar event-related functional MRI paradigms (*cf.* Saur *et al.*, 2006, 2008). These involved attentive listening to short German sentences (intelligible speech, SP) and temporally reversed versions of the same stimuli (unintelligible reversed speech, REV). As the focus of our research was on plasticity in the language network, we contrasted the responses to SP and REV (SP > REV) to obtain patterns of language-related activation. This allowed us to identify brain regions contributing to post-stroke language reorganization across time and compare those patterns with language processing in healthy subjects.

To visualize time-specific patterns of language activation in relation to the lesion site, t-contrasts for language activation were calculated for each time point and group (Fig. 2).

To quantify changes across time and differences between groups, we followed a two-stage procedure. First, a global pattern of language-related activation was identified on the whole brain level across all patients and time points, defining peaks for volumes of interest that represent areas relevant for language processing (i.e. the language-processing related network, Supplementary Table 2). To account for variation of lesion location, we defined additional volumes of interest for perilesional (i.e. 3–15 mm beyond the lesion surface) and lesion-homologue tissue (i.e. mirrored lesion) on an individual basis. Second, activation-informed volume of interest-based statistical analyses were carried out in all regions to test for group (frontal versus temporo-parietal lesions), time (acute, subacute, chronic) and interaction effects (Group × Time) on language activation (SP > REV) by means of 2 × 3 factorial mixed effects repeated-measures ANOVAs in SPSS version 24 (SPSS Inc., Chicago, IL, USA). Based on these analyses, we sought to identify brain regions

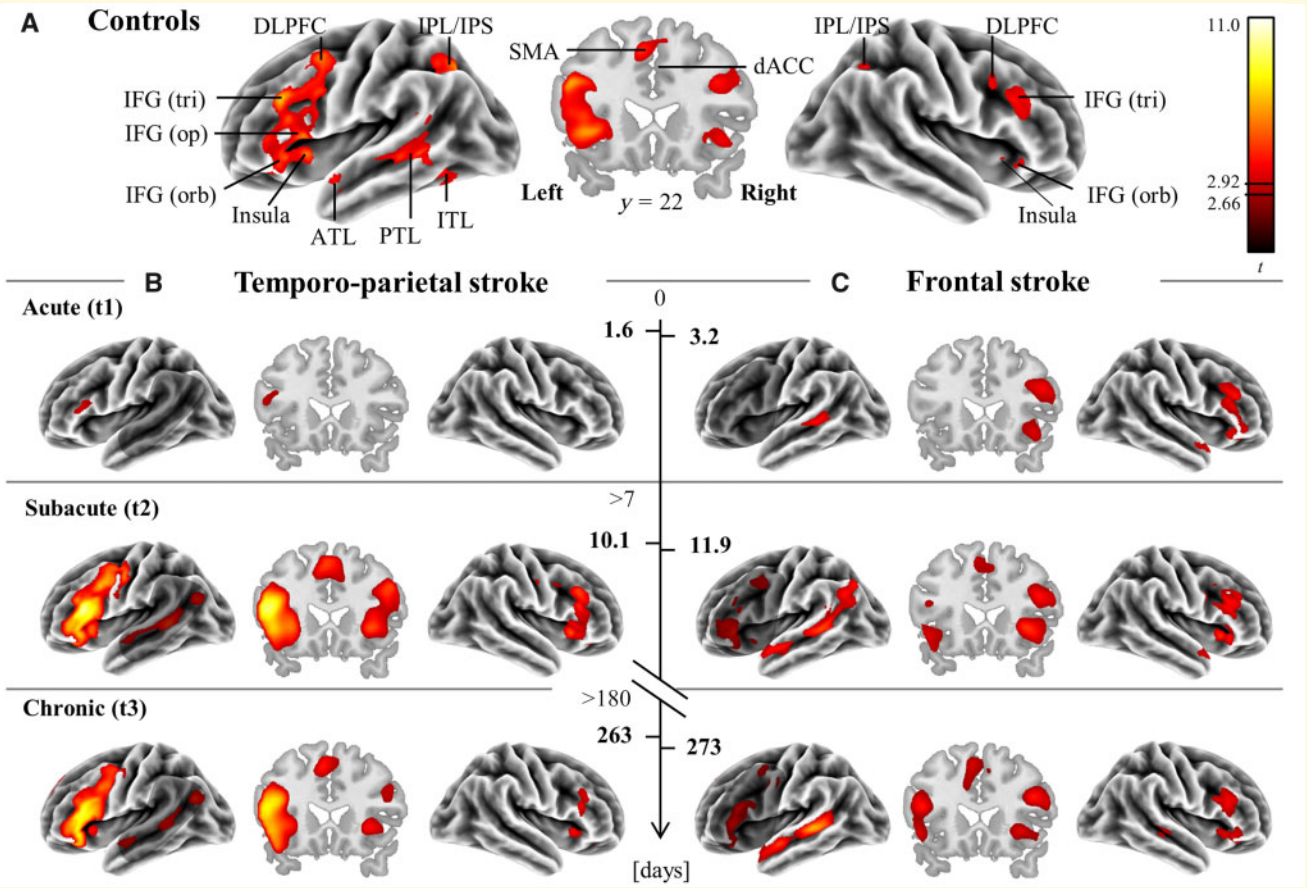

Figure 2 Patterns of language activation in controls and stroke patients. Surface renderings of statistical *t*-maps showing language-related activation (SP > REV) for (**A**) controls (n = 17, *top*) and for patients with (**B**) left temporo-parietal (n = 17, *left*) and (**C**) left frontal lesions (n = 17, *right*), separately at each time point (t1, acute; t2, subacute; t3, chronic phase); left side of the brain facing left, right side facing right. Group lesions are drawn schematically in semi-transparent black. Colour bar indicates *t*-statistics, displayed activation passed threshold of $P < 0.005$ and a minimum cluster extent of k = 27 for controls and k = 32 for patients ($P < 0.05$ FWE-corrected for multiple comparisons at the cluster level; controls, $t > 2.92$; patients, $t > 2.66$).

that support language reorganization either dependent or independent of lesion site (Figs 3–5). Our approach further enabled us to identify patterns that exhibit lesion-specific changes over the course of aphasia recovery (Fig. 4).

To evaluate the observed language activation in relation to control participants, we compared language activation in each volume of interest for each time point of both patient groups with controls using separate one-way ANOVAs with the between-subject factor Group (patients with frontal, temporo-parietal lesions and controls; Supplementary Fig. 6 and Supplementary Table 7). In addition, activation in perilesional and lesion-homologue cortex was compared to controls using the same volumes of interest in individually matched control participants using separate two-sample *t*-tests (Supplementary Fig. 7).

Changes in functional MRI activation patterns over time and differences between groups were first analysed independent of behavioural performance. As all patients showed improved language performance (see 'Results' section), these patterns reflect activated brain regions paralleling aphasia recovery. To determine linear relationships between language performance and brain activity, we additionally investigated the effect of behaviour (LRS_{COMP}) or behavioural improvement (ΔLRS_{COMP}) using regression analyses on language activation or activation change in the same volumes of interest in SPSS (Figs 5, 6 and Supplementary Tables 8 and 9). To test whether this relationship was different between lesion-groups we included a LRS_{COMP} × Group interaction effect. Regression analyses were carried out with and without adjusting for lesion volume.

Anatomical labelling was based on Automated Anatomical Labelling (Tzourio-Mazoyer *et al.*, 2002) and the Anatomy toolbox version 2.2b (Eickhoff *et al.*, 2005). The experimental design and paradigms, as well as the first- and second-level functional MRI data and statistical analyses are described in detail in the Supplementary material.

Statistical inference

Significant patterns of language activation for the control group and patient groups at each time point were obtained

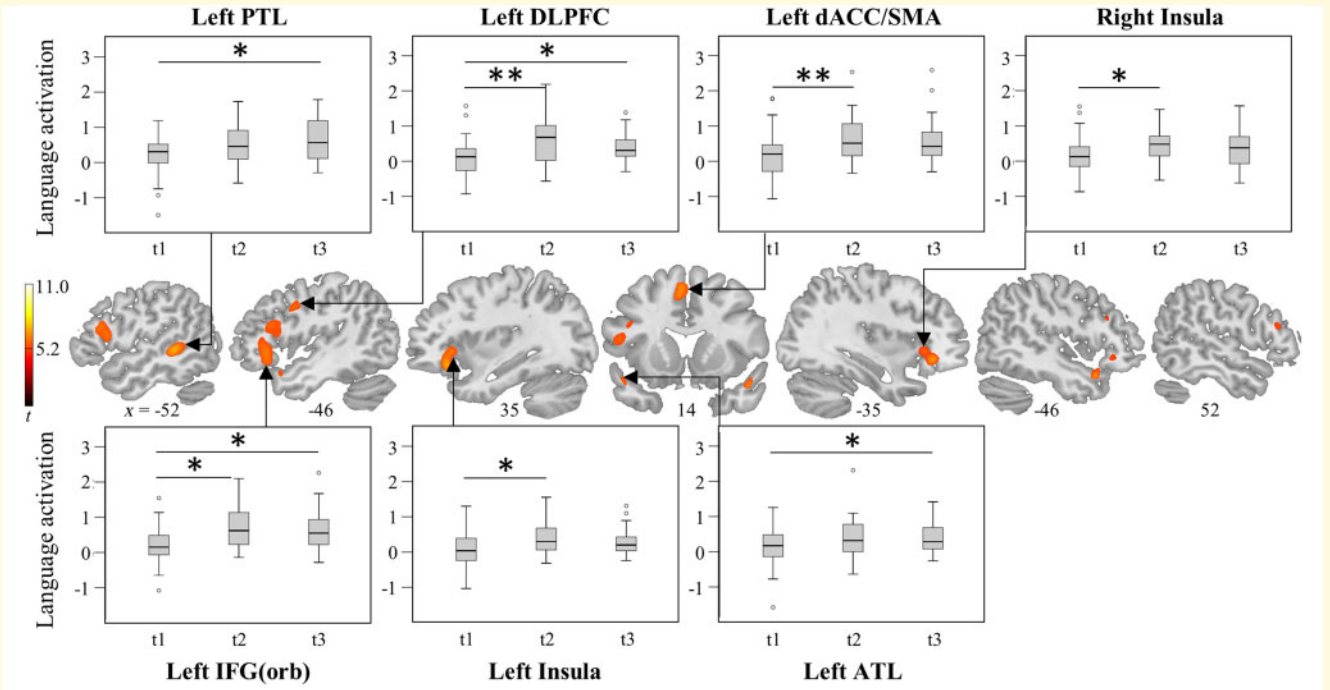

Figure 3 Time-specific language activation in stroke patients. Slices display the volume of interest-defining contrast of language-related activation (SP > REV) across all patients and time points ($P < 0.05$, FWE-corrected for multiple comparisons, $t > 5.23$, Supplementary Table 2). Extracted language activation (i.e. mean parameter estimates of SP > REV) of the volumes of interest was entered into a 3 × 2 factorial mixed-design repeated-measures ANOVA with factors Time (t1 – t3) and Group (temporo-parietal, frontal) on language activation. Box plots depict language activation over time for those volumes of interest that show a significant main effect of time. Significant *post hoc* differences between acute (t1), subacute (t2) and chronic (t3) language activation are labelled with asterisks (*$P < 0.05$, **$P < 0.01$, corrected for multiple comparisons in *post hoc* tests using the Bonferroni-Holm procedure). Volumes of interest with a significant interaction of time and group are displayed in Fig. 4 [left IFG (tri), left IFG (op), right IFG (tri), right DLPFC]. Box and whisker plots indicate median and IQR with first (25 percentile) and third (75 percentile) quartiles; circles indicate outliers extending 1.5 times the box height.

by a Monte-Carlo simulation-based cluster-extent thresholding (Forman *et al.*, 1995), corresponding to $P < 0.05$ family-wise error (FWE)-corrected at cluster level using a height threshold of $P < 0.005$.

To obtain the global pattern of language-related activation for defining volumes of interest, we applied a threshold of $P < 0.05$ FWE-corrected at the voxel level based on Gaussian random fields theory (Worsley *et al.*, 1996). Mean language activation was extracted for all significant activation peaks, using spherical volumes of interest (r = 9 mm). This resulted in a set of 13 volumes of interest. Statistical significance ($P < 0.05$, two-tailed) for within- and between-group comparisons of language activation in each volume of interest was determined using multifactorial mixed-design ANOVAs. Significant main effects and interactions were followed-up by *post hoc t*-test that compared activation differences over time and between groups at different time points using the Bonferroni-Holm procedure (Holm, 1979) to account for multiple comparisons.

Activation-behaviour relationships were analysed in the same volumes of interest using multiple regression analyses. The directions of significant main and interaction effects ($P < 0.05$) were followed-up by calculating Pearson's correlation coefficients and plotting LRS_{COMP} against activation.

Data availability

Relevant data including pseudomized behavioural and normalized functional MRI data are publicly available through the figshare repository (doi: 10.6084/m9.figshare.7093481).

Results

Clinical and demographic characteristics

Patients' characteristics are reported in Supplementary Table 1. We included 17 patients with left frontal, 17 patients with temporo-parietal lesions (Fig. 1 and Supplementary Fig. 1) and 17 healthy controls. Group assignment validated by hierarchical cluster analysis confirmed that heterogeneity was larger between- than within-group (Supplementary Figs 2–5). Comparisons between patient groups (Supplementary Table 3) showed that there was no significant difference in age [$t(2) = 0.097$, $P = 0.908$] or lesion volume between groups [$t(32) = 1.122$, $P = 0.27$]. Because of more

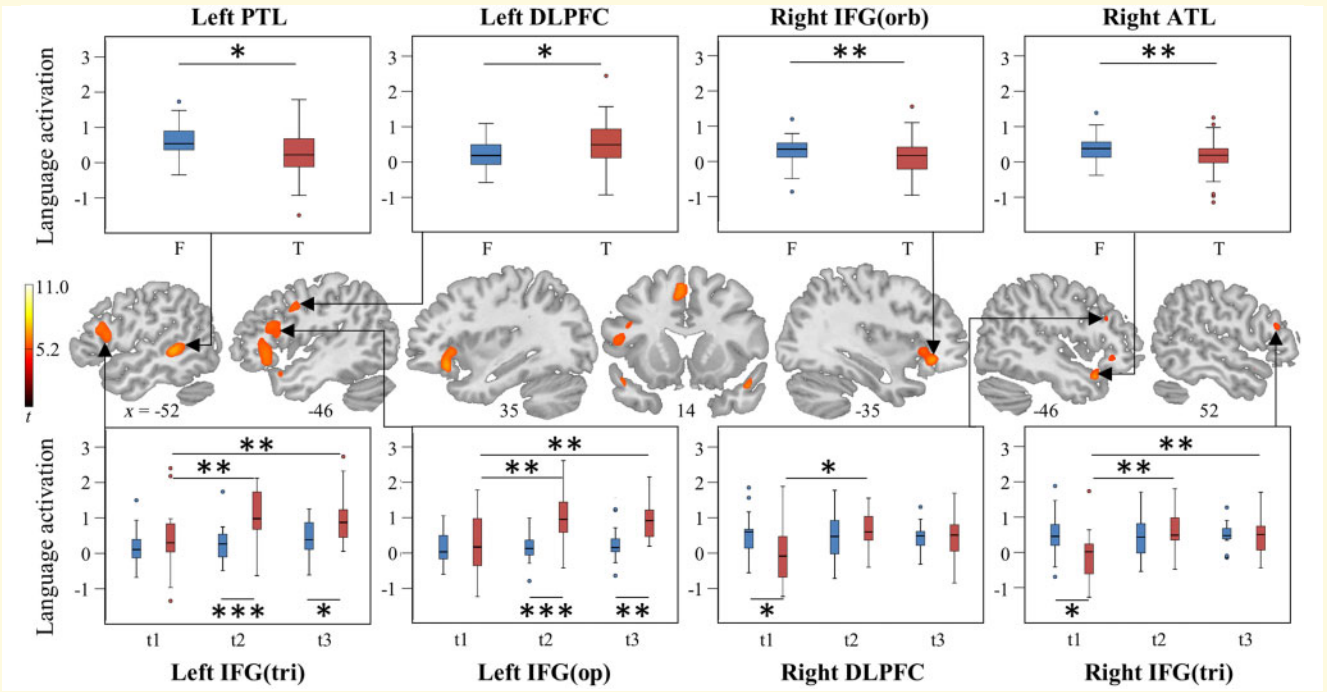

Figure 4 Lesion-specific language activation in patients with temporo-parietal and frontal stroke. Slices display the volume of interest-defining contrast of language-related activation (SP > REV) across all patients and time points ($P < 0.05$, FWE-corrected for multiple comparisons, $t > 5.23$, Supplementary Table 2). Extracted language activation (i.e. mean parameter estimates of SP > REV) of the volumes of interest was entered into a 3 × 2 factorial mixed-design repeated-measures ANOVA with factors Time (t1–t3) and Group (temporo-parietal, frontal) on language activation. *Top row*: boxplots depict the language activation for those volumes of interest that show a significant main effect of group independent of time. *Bottom row*: boxplots depict the language activation for those volumes of interest that show a significant interaction effect of Time × Group. Significant *post hoc* differences between acute (t1), subacute (t2) and chronic (t3) language activation and between patients with left frontal (F) and temporo-parietal (T) stroke are labelled with asterisks (*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$, corrected for multiple comparisons in *post hoc* tests using the Bonferroni-Holm procedure). Box and whisker plots indicate median and IQR with first (25 percentile) and third (75 percentile) quartiles; circles indicate outliers extending 1.5 times the box height.

pronounced motor deficits, the initial deficit measured with the NIHSS (National Institutes of Health Stroke Scale) was more severe in patients with frontal lesions [$t(32) = 2.494$, $P = 0.018$]. Patients with frontal lesions were examined significantly later during the acute [$t(20.7) = 2.89$, $P = 0.01$] and subacute phase [$t(32) = 2.65$, $P = 0.01$]. Time since stroke was comparable during the chronic phase [$t(32) = 0.36$, $P = 0.72$].

Behavioural improvement and functional MRI task performance

In all patients, language comprehension [LRS_{COMP}: $F(1.28,64) = 66.68$, $P < 0.001$] and production [LRS_{PROD}: $F(1.65,64) = 41.94$, $P < 0.001$] improved over time. A significant Time × Group interaction on language comprehension [$F(1.28,64) = 4.02$, $P = 0.042$] indicated better performance (mean ± standard error of the mean, SEM) in patients with temporo-parietal [$LRS_{COMP}(t2) = 0.79 \pm 0.2$] as compared to patients with frontal lesions [$LRS_{COMP}(t2) = 0.64 \pm 0.21$, Bonferroni-corrected $P = 0.043$] during the subacute phase (Fig. 1 and Supplementary Table 3). Lesion volume significantly affected behavioural performance and improvement, i.e. larger lesions were associated with poorer language comprehension (LRS_{COMP}) at all time points (t1: r = –0.604; t2: r = –0.623; t3: r = –0.629, all $P < 0.001$) and with greater improvement (ΔLRS_{COMP} t2–t1: r = 0.335, $P = 0.052$; t3–t2: r = 0.469, $P = 0.005$; t3–t1: r = 0.430, $P = 0.11$).

In both functional MRI tasks, subjects listened attentively to the stimuli as confirmed by the recorded button-presses. Mean task performance (±SEM) across both paradigms was comparable between groups in the acute [patients with frontal lesions = 81.1 ± 5.3%, temporo-parietal = 70.7 ± 8.5% of expected button presses, $t(32) = 1.05$, $P = 0.31$], subacute [frontal = 80.2 ± 5.5%, temporo-parietal = 78.4 ± 4.5%, $t(32) = 0.26$, $P = 0.80$] and chronic [frontal = 85.4 ± 4.5%, temporo-parietal = 85.7 ± 4.3%, $t(32) = 0.05$, $P = 0.96$] phase. Across paradigms and lesion-groups in-scanner task performance was not different between the acute and subacute phase [$t(31) = –0.89$, $P = 0.381$] or the acute and chronic phase [$t(31) = –1.96$, $P = 0.059$].

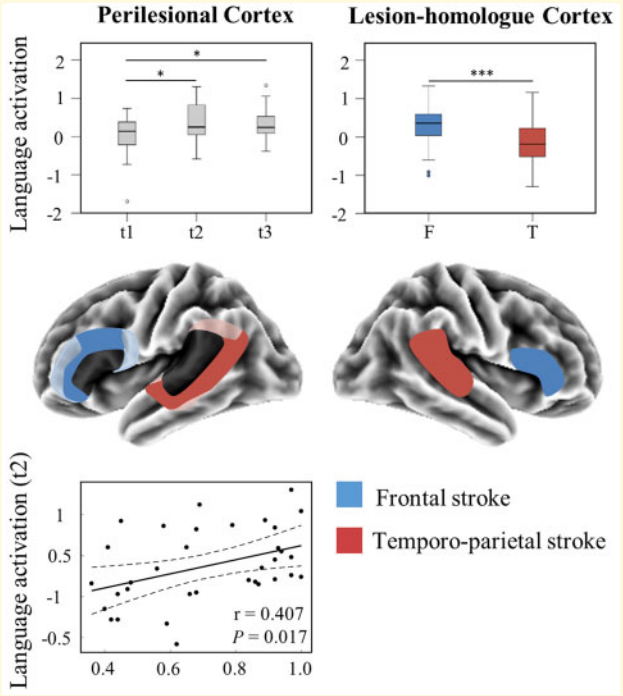

Figure 5 Perilesional and lesion-homologue language activation. Language activation in individually defined perilesional and lesion-homologue volumes of interest. Schematic view of the definition of individual perilesional cortex (*left*) as the area that extends 3–15 mm beyond the lesion, masked with either frontal or temporal lobe (light blue or red) and a language activation mask derived from the control group (darker blue or red). Lesion-homologue cortex was defined as mirrored right hemisphere grey matter (*right*). Extracted language activation (i.e. mean parameter estimates of SP > REV) of the volumes of interest was entered into a 3 × 2 factorial mixed-design repeated-measures ANOVA with factors Time (t1–t3) and Group (temporo-parietal, frontal) on perilesional or lesion-homologue language activation and to regression analyses with language recovery scores (LRS_{COMP}) as regressor. Box plots depict language activation over time in perilesional cortex that show a significant main effect of Time (*left*) and between groups in lesion-homologue cortex that show a significant main effect of Group (*right*). Regression analysis shows the association between perilesional activation and language comprehension abilities (LSR_{COMP}) in the subacute phase. *Post hoc* differences between acute (t1), subacute (t2) and chronic (t3) language activation and between patients with left frontal (F) and temporo-parietal (T) stroke are labelled with asterisks (*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$, corrected for multiple comparisons in *post hoc* tests using the Bonferroni-Holm procedure). Box and whisker plots indicate median and IQR with first (25 percentile) and third (75 percentile) quartiles; circles indicate outliers extending 1.5 times the box height. Scatter plot: solid lines represent best linear fit with its 95% confidence interval (dashed lines).

Patterns of language activation in controls and patients

In healthy controls, language processing (SP > REV) evoked significant activation in a set of left-lateralized temporo-frontal regions including the IFG, ATL, PTL and ITL (Fig. 2A and Supplementary Table 4). Besides these areas typically associated with language processing, activation also included bilateral fronto-parietal and cingulo-opercular networks consisting of areas typically attributable to task-associated, domain-general cognitive control (i.e. DLPFC, IPL/IPS, SMA extending into dACC, insula and opercular IFG) (Dosenbach *et al.*, 2008; Geranmayeh *et al.*, 2014*b*). In summary, the results are in line with our earlier study (Saur *et al.*, 2006) and confirm that our functional MRI paradigm provides a reliable measure of language processing in healthy elderly participants.

Patterns of language-related activation (SP > REV) in patients during the acute, subacute and chronic phase are displayed in Fig. 2B and C. Patients with temporo-parietal lesions (Fig. 2B and Supplementary Table 5) showed a marked network dysfunction during the acute phase with the only significant language activation detected in the left IFG. In the subacute and chronic phase, a left-lateralized activation of the language network comprising bilateral IFG and left temporal lobe (ATL, PTL) was observed next to bilateral activation of domain-general fronto-parietal (DLPFC, IPL) and cingulo-opercular networks [insula, IFG(op), SMA/dACC]. No significant lesion-homologue activation in the right PTL and ATL was present at any time. In patients with frontal lesions (Fig. 2C and Supplementary Table 6), preserved parts of the language network were activated in the acute phase, including left PTL, right ATL and lesion-homologue right IFG. In the subacute and chronic phase, patients with frontal stroke showed significant bilateral activation in language (IFG, ATL, PTL) and domain-general networks [DLPFC, IPL, insula, IFG(op), SMA/dACC].

Effects of time and lesion on language activation

Subsequent volume of interest-based statistical analyses further elaborated the effects of time post-stroke and lesion location as well as the interaction of lesion and time on language activation. To this end, we performed a 3 × 2 factorial mixed-design repeated-measures ANOVA with the factors Time (t1 – t3) and Group (temporo-parietal, frontal) on language activation (SP > REV) extracted from the 13 volumes of interest that reflect a language-processing related network across all patients and time points (Supplementary Table 2). This allowed us to determine: (i) time-specific language activation (main effect of time); (ii) lesion-specific language activation (main effect of group); and (iii) lesion-specific dynamics of language activation (Time × Group interaction) (Table 1).

Time-specific language activation

Changes in language-related activation across time, irrespective of lesion location (main effect of time; Fig. 3 and Table 1) were identified in left hemispheric language regions (IFG, ATL, PTL), but also involved domain-general bilateral cingulo-opercular network (insula, SMA/dACC) and prefrontal

cortices (DLPFC). *Post hoc t*-tests confirmed a significant early activation increase in left IFG, bilateral prefrontal and insular regions from the acute to subacute phase. This was contrasted by a later activation increase in left hemisphere ATL and PTL that occurred from the acute to chronic phase. These findings indicate that, independent of lesion location, activation in inferior frontal and domain-general regions precedes activation in left temporal language regions during reorganization.

Lesion-specific language activation

In addition to these time-specific effects, activation in some regions depended on lesion location (main effect of group) independent of time post-stroke (Fig. 4 and Table 1). The impact of the lesion is reflected in significantly stronger language-related activation in left frontal regions (IFG, DLPFC) in patients with temporo-parietal lesions and, vice versa, left temporal regions (PTL) in patients with frontal lesions. Significantly stronger activation was found in the lesion-homologue right IFG and in right ATL in patients with frontal lesions. In contrast, no lesion-homologue language activation was detectable in the right PTL in patients with temporo-parietal lesions.

Together, these results show that language reorganization involves preserved language areas in the left hemisphere in both groups but recruitment of lesion-homologue areas only in patients with frontal lesions.

Lesion-specific dynamics of language activation

Lesion-specific dynamics of language activation, identified by a significant Time × Group interaction, were found in bilateral IFG and right DLPFC (Fig. 4 and Table 1). These regions revealed a more pronounced early network disturbance followed by a stronger activation increase in patients with temporo-parietal lesions. In the subacute and chronic phase, activation increase in left IFG in patients with temporo-parietal lesions significantly exceeded that in patients with frontal lesions. In contrast, in patients with frontal lesions, no significant change in language activation across time was observed in these areas. In particular, right IFG and DLPFC showed significantly stronger activation early on, which was stable across time.

Together, these results reveal fundamental differences between the impact of temporo-parietal and frontal lesions on the dynamics of language reorganization.

Perilesional and lesion-homologue activation

In addition to activation-informed volume of interest analyses, we defined perilesional and lesion-homologue regions on an individual basis. Independent of group assignment, we found an early perilesional activation increase that persisted into the chronic phase (Fig. 5 and Table 1). In the subacute phase, language comprehension abilities correlated with the amount of perilesional activation (Fig. 5). Considering direct lesion-homologue cortex (i.e. mirrored lesions), in accordance with the lesion-specific volume of interest-based analysis, we found that patients with frontal lesions showed significantly stronger right frontal activation than patients with temporo-parietal lesions show right temporal activation (Fig. 5).

Comparison with controls

To contrast the observed language activation of both patient groups with healthy controls, we again used a volume of interest-based approach and performed three separate one-way ANOVAs for each volume of interest (Supplementary Fig. 6 and Supplementary Table 7). As expected, we found significantly reduced language activation in patients in left hemisphere regions directly affected by the lesion. This reduced activation normalized to the level of controls during the subacute phase in patients with temporo-parietal lesions (PTL, ATL) but persists until the chronic phase in patients with frontal lesions [IFG(tri), insula, DLPFC]. In addition, in patients with temporo-parietal lesions, dysfunction in regions remote from the lesion (i.e. the diaschisis effect) is reflected in reduced frontal activation in the left [IFG(tri), insula, DLPFC, dACC/SMA] as well as right hemisphere [IFG(tri)]. The left opercular IFG, a region assigned to the domain-general network, was the only region with a trend towards increased activation in the subacute phase in patients with temporal lesions relative to controls.

Comparison of perilesional and lesion-homologue activation with controls was achieved by extracting language activation from the same volumes of interest in matched controls and analysing activation by use of two-sample *t*-tests (Supplementary Fig. 7). Again, the direct lesion effect was reflected in reduced perilesional activation in the acute phase that normalized to the degree of controls only in patients with temporo-parietal lesions. Regarding lesion-homologue activation, it should be emphasized that the lack of right temporo-parietal activation in patients with temporo-parietal strokes was also reflected in significantly lower activation relative to controls (Supplementary Fig. 7), while the amount of lesion-homologue frontal activation did not exceed the amount of controls.

In summary, we essentially observed reactivation in a pre-existing network activated by controls to a similar degree rather than recruitment of novel areas.

Relationships between language performance and language activation

To examine the relationship between language performance and language activation at different post-stroke intervals, we performed regression analyses with comprehension recovery scores (LRS_{COMP}) as regressor on language activation for all volumes of interest.

Independent of lesion location, we found a statistically significant positive relationship between the magnitude of IFG(tri) activation and language performance in the acute,

Table 1 Time- and lesion-specific language activation in stroke patients

Anatomical regions (volumes of interest)	Side	MNI coordinates			Statistics	
Effect: Time		***x***	***y***	***z***	***F*(2,64)**	P_{unc}
IFG(tri)	Left	−51	23	23	7.92	0.001
IFG(orb)	Left	−39	29	−13	5.13	0.009
IFG(op)	Left	−54	17	14	6.85	0.002
Insula	Left	−33	25	−1	4.57	0.014
DLPFC	Left	−42	2	35	7.85	0.001
SMA/dACC	Left	−6	17	50	5.28	0.008
PTL	Left	−54	−37	2	4.65	0.010
ATL	Left	−48	14	−19	3.86	0.026
Perilesional cortex	Left	3–15 mm beyond lesion surface			6.38	0.003
Insula	Right	33	26	−1	4.15	0.020
IFG(tri)	Right	51	29	20	4.47	0.015
DLPFC	Right	47	25	28	3.27	0.044
Effect: Lesion group		***x***	***y***	***z***	***F*(1,32)**	P_{unc}
IFG(tri)	Left	−51	23	23	8.42	0.007
IFG(op)	Left	−54	17	14	12.68	0.001
DLPFC	Left	−42	2	35	5.22	0.029
PTL	Left	−54	−37	2	4.68	0.038
ATL	Right	54	11	−16	7.53	0.010
IFG(orb)	Right	42	35	−10	7.87	0.008
Lesion-homologue	Right	Mirrored lesion			16.72	<0.001
Effect: Time × Lesion group		***x***	***y***	***z***	***F*(2,64)**	P_{unc}
IFG(tri)	Left	−51	23	23	3.30	0.043
IFG(op)	Left	−54	17	14	4.59	0.014
IFG(tri)	Right	51	29	20	4.54	0.014
DLPFC	Right	47	25	28	3.66	0.031

Effects of time and lesion on language-related activation (SP > REV). Volumes of interest were defined by spherical seeds (radius 9 mm) of the eight left and five right hemisphere voxel-wise significant ($P < 0.05$, FWE corrected) activation peaks (MNI, Montreal Neurological Institute coordinates in mm) across all patients and time points as reported in Supplementary Table 2. Perilesional and lesion-homologue cortex was defined on the basis of individual and mirrored lesions. Extracted mean parameter estimates (SP > REV) were entered into a 3 x 2 factorial mixed-design repeated-measures ANOVA with factors Time (t1–t3) and lesion Group (temporo-parietal and frontal) ($n = 34$). *Top*: Main effect of Time shows regions with changing activation across time independent of lesion location; *middle*: main effect of Group shows regions that exhibit activation difference between temporo-parietal and frontal lesion location independent of time; *bottom*: Time × Group interaction shows lesion-specific dynamics of language activation. *F*-values (df1, df2) and uncorrected *P*-values (P_{unc}) are reported for each volume of interest.

subacute and chronic phase (Fig. 6 and Supplementary Table 8), i.e. higher IFG activation at these time points was associated with better language comprehension. In addition, a stronger early (t2 – t1) increase in right DLPFC language activation was related to a greater improvement of language comprehension (Fig. 6 and Supplementary Table 9). As mentioned above, irrespective of group assignment, perilesional activation positively correlated with performance in the subacute phase. That is, higher perilesional activation was associated with better performance during this phase (Fig. 5 and Supplementary Table 8).

Lesion-specific activation-performance relationships were only found in patients with temporo-parietal stroke. In the acute phase, activation in right ATL and in the subacute phase in left PTL and domain-general IFG(op) were associated with better performance (Fig. 6 and Supplementary Table 8). This relationship was significantly different from patients with frontal stroke [right ATL(t1): $z = 2.54$, $P = 0.011$; left PTL(t1): $z = 2.49$, $P = 0.013$, left IFG(op)(t1): $z = 2.61$, $P = 0.009$]. Further, acute to subacute activation increase in left insula was associated with better recovery of language comprehension (Fig. 6 and Supplementary Table 9). Again, this relationship was significantly different between patients with frontal and temporo-parietal stroke ($z = 2.22$, $P = 0.026$). Results of regression analyses that were adjusted for lesion volume are presented in the Supplementary material.

To summarize, irrespective of lesion location, the behavioural relevance of functional MRI-activation during language recovery was supported by (i) a significant relationship between aphasia severity and reduced left hemisphere inferior frontal and perilesional activation; and (ii) a significant association between aphasia recovery and increased right prefrontal cortex activation. Additional areas of the frontal control networks [i.e. left insula and IFG(op)] contributed to improved language functions exclusively in patients with temporo-parietal stroke.

Discussion

This study represents the first longitudinal investigation that directly compared functional MRI activation between two patient groups with circumscribed lesions from the acute to the chronic phase after stroke. This allowed us to refine the

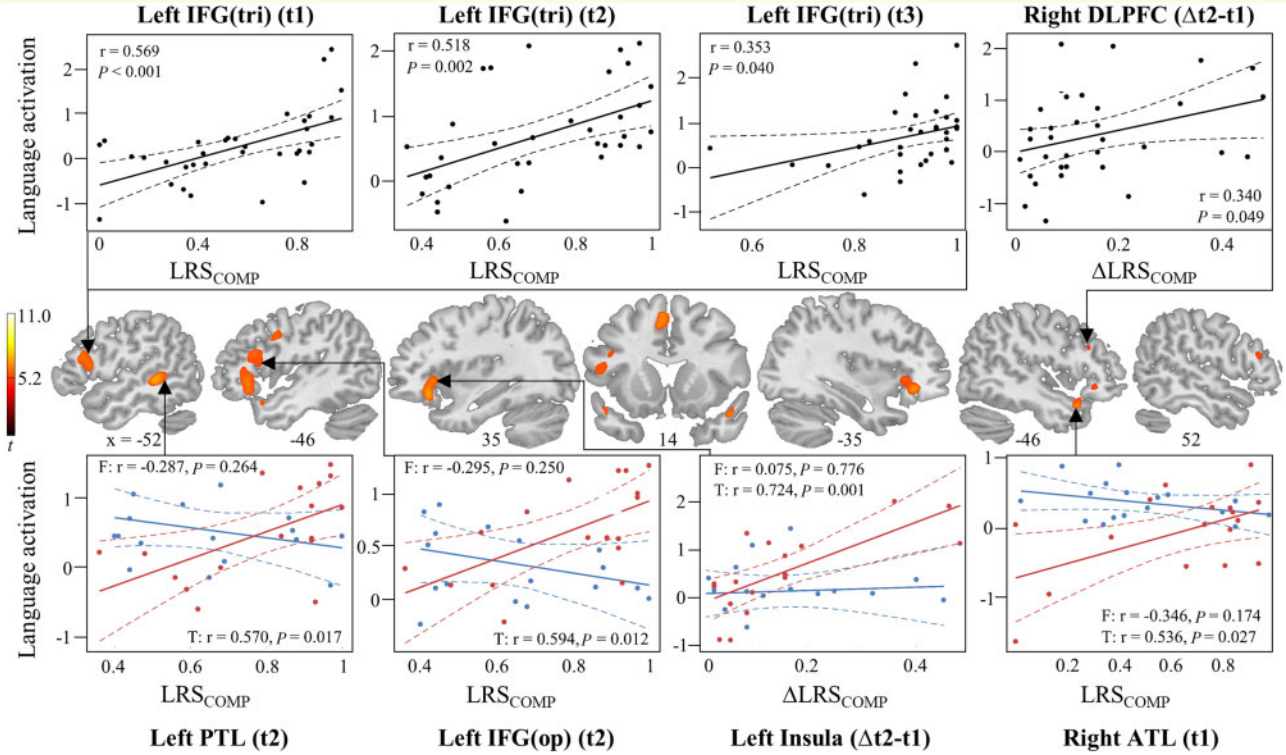

Figure 6 Relationship of language performance and activation during language recovery. Slices display the volume of interest-defining contrast of speech versus reversed speech across all patients and time points ($P < 0.05$, FWE-corrected for multiple comparisons, $t > 5.23$, Supplementary Table 2). Mean extracted parameter estimates for language activation (t1, t2, t3) or activation change (t2 – t1, t3 – t1, t3 – t2) were entered into regression analyses that tested for effects of (change in) language recovery scores for comprehension (LRS_{COMP}, ΔLRS_{COMP}) and for group differences (LRS_{COMP} × Group interaction). Significant main effects and interactions are presented (*F*, statistics, df 3,30; Supplementary Table 8 and 9). Pearson's correlation coefficients (r) and scatter plots ($n = 34$) indicate the direction of significant main and interaction effects. Solid lines represent best linear fit with its 95% confidence interval (dashed lines).

previously proposed three-phase model of language reorganization arguing for acute network disturbance, subacute upregulation and chronic normalization of activation (Saur *et al.*, 2006). Considering the frameworks of a hierarchical reorganization of language (Heiss and Thiel, 2006) and functional segregation within language networks (Ueno *et al.*, 2011), our goal was to assess whether lesion location differently moderated a preferred restoration of activation in spared and perilesional left hemisphere language regions as compared to a secondary involvement of lesion-homologue cortex, domain-general networks and regions outside pre-existing language networks.

Figure 7 gives a schematic overview of our main findings that were as follows. First, global network disturbance in the acute phase, that is characterized by reduced functional MRI language activation including areas distant to the lesion (i.e. diaschisis) and subsequent subacute network reactivation (i.e. resolution of diaschisis) are phenomena driven by temporo-parietal lesions. Second, independent of lesion location, early compensation in subacute stroke is paralleled by increased activation of bilateral domain-general networks and perilesional cortex reactivation, while later chronic reorganization is mainly conveyed by left hemisphere language areas in the ATL and PTL. Third, involvement of lesion-homologue cortex is only observed in patients with frontal but not temporo-parietal lesions. Fourth, irrespective of lesion location, language reorganization predominantly occurs in pre-existing networks showing comparable activation in healthy controls. Finally, different relationships of performance and activation in language and domain-general networks could be detected that either apply to both lesion types or were specific for temporo-parietal lesions.

Together, these findings extend our knowledge about lesion-specific and general lesion-independent dynamics of language reorganization and might open new opportunities for neurobiologically motivated language rehabilitation strategies, such as the application of non-invasive brain stimulation. In the following sections, we discuss these findings and their clinical consequences in more detail.

Lesion-dependent diaschisis

With respect to the phenomenon of acute diaschisis, analyses of longitudinal activation patterns revealed a predominant effect of left temporo-parietal stroke. Temporo-parietal lesions induced a strong widespread network

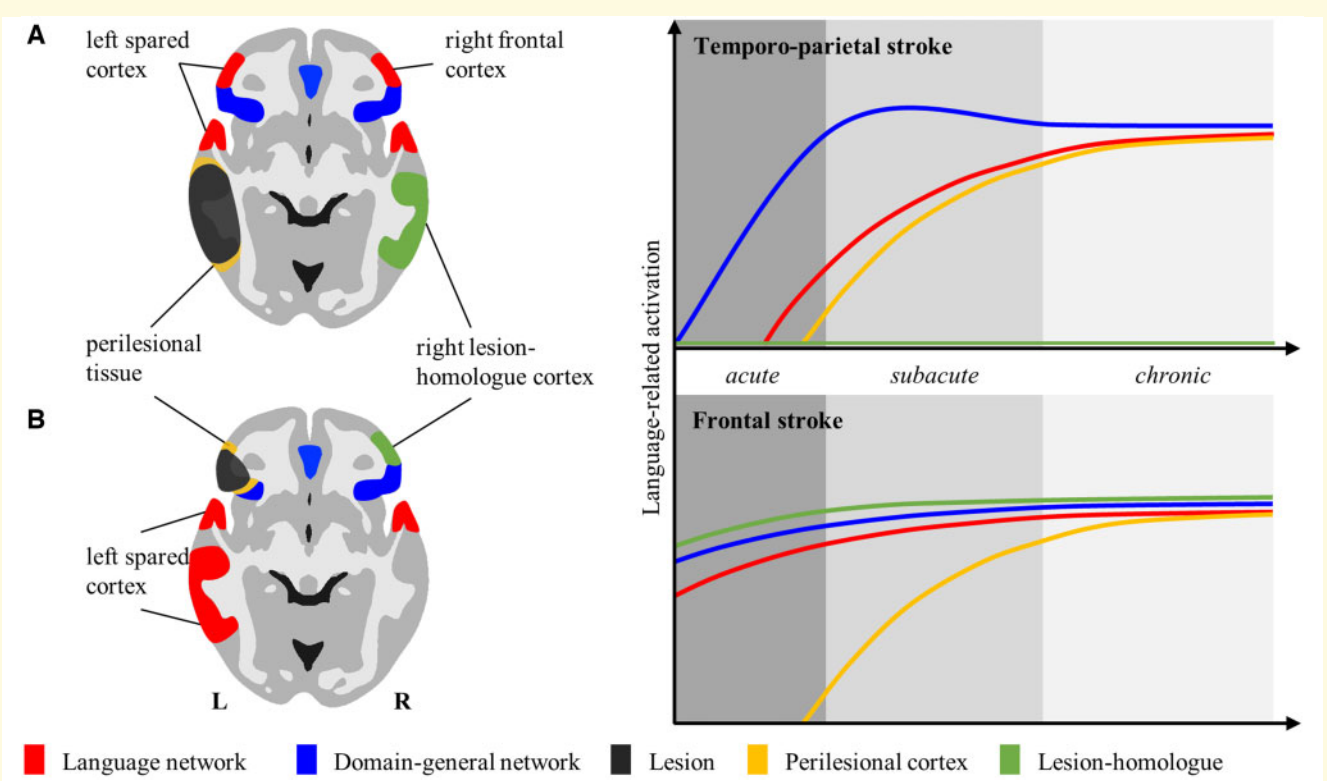

Figure 7 Lesion-dependent model of post-stroke language reorganization. Schematic view of lesion-dependent changes in language-related activation (SP > REV) from the acute to the chronic phase after (**A**) left temporo-parietal or (**B**) frontal stroke. In patients with left temporo-parietal lesions, acute global network disturbance is followed by subsequent network reactivation in spared left language (in red) and bilateral domain-general (in blue) networks (i.e. resolution of diaschisis). Both lesion types share a pattern of subacute activation of domain-general networks (blue) and subsequent activation of language networks (in red) including gradual perilesional cortex reactivation (in orange). Lesion-homologue activation in the right hemisphere (in green) is exclusive to patients with left frontal lesions that in general exhibited greater early language-related activation and a less pronounced effect of diaschisis than patients with temporo-parietal lesions. L/R = left/right hemisphere.

down regulation including local dysfunction of damaged temporo-parietal cortex but also disturbance in remote, functionally connected frontal areas that were undamaged. Conversely, in patients with left frontal lesions, we observed local dysfunction but almost preserved activation in bilateral temporal and lesion-homologue right frontal cortices already in the acute phase. This indicates that the ability to activate spared parts of the language network early after stroke varies depending on lesion location and emphasizes the different functional embedding of temporal and frontal areas into the language network. In this regard, during auditory language comprehension, the temporal cortex is assumed to access lexical and semantic representations serving as input to higher-order semantic processes that involve, among other regions, the left IFG, which contributes to controlled retrieval and selection of these representations (Lau *et al.*, 2008). This, in turn, implies a functional dependency of frontal on temporal cortex in language comprehension and might in part account for the frontal dysfunction observed after temporo-parietal stroke (i.e. functional diaschisis) (Carrera and Tononi, 2014). The stronger impact of left temporo-parietal relative to frontal lesions on acute network disturbance is in agreement with general principles of the network architecture, according to which, the superior temporal cortex is a densely connected hub (van den Heuvel and Sporns, 2011) and would therefore be prone to widespread detrimental response to damage (Fornito *et al.*, 2015). In contrast, other studies have attributed acute diaschisis primarily to lesions of subcortical structures (Vallar *et al.*, 1988; Hillis *et al.*, 2000). However, it is unlikely that differences in the engagement of subcortical regions explain the observed effects in our study, because subcortical involvement was mainly present in patients with frontal stroke (Supplementary Fig. 1).

In view of severe initial diaschisis, we observed an early subacute reactivation of bilateral frontal cortices dominated by patients with temporo-parietal lesions that is suggestive of a resolution of diaschisis, i.e. recovery of function in undamaged remote bilateral frontal parts of the network. As diaschisis is most pronounced immediately after stroke and gradually resolves during the subacute phase (Witte *et al.*, 2000), other longitudinal studies have been unable to fully capture this lesion-specific mechanism due to the lack of acute measurements (Heiss *et al.*, 1999; Cardebat *et al.*, 2003; de Boissezon *et al.*, 2005; van Oers *et al.*, 2010;

Geranmayeh *et al.*, 2017; Nenert *et al.*, 2018) and the missing consideration of lesion location (Saur *et al.*, 2006). Concerning recent research, the underlying mechanism of diaschisis in patients with temporo-parietal stroke may be reflected by a loss of integration between frontal and temporo-parietal regions and a subacute restoration of functional connectivity with distant frontal regions (Siegel *et al.*, 2018).

Sequential reactivation of domain-general and language networks

Our second main finding was that, irrespective of lesion location, acute to subacute recovery is paralleled by recruitment of bilateral frontal regions of domain-general networks and re-emergence of perilesional activation while reorganization of language areas in the left ATL and PTL can be observed until the chronic phase.

Although we are unable to distinguish specific cognitive processes with our task, the bilateral involvement of domain-general networks can be interpreted as a response to increased cognitive effort and compensatory reallocation of cognitive resources. That is, domain-general networks are assumed to support impaired language networks, which are not (yet) sufficient enough to maintain language functioning in the subacute phase (Brownsett *et al.*, 2014; Geranmayeh *et al.*, 2014*a*, 2017). In our experiments, we tried to keep task demands as low as possible by using tasks that were achievable for patients with acute aphasia. By implementing a high-level baseline condition (i.e. reversed speech which always required a button press) we aimed to keep task-associated executive activation to a minimum. We assigned subacute increase of activation of bilateral anterior insula and dACC (extending dorsally into the SMA) to the cingulo-opercular network. This network has been shown to contribute to goal-directed behaviour through the maintenance of cognitive control for task sets and detection of salient events (Dosenbach *et al.*, 2008; Geranmayeh *et al.*, 2014*a*), processes that also may have played a role in our task (i.e. maintaining attention to detect speech in the context of reversed speech). In addition, activation of bilateral DLPFC likely reflects recruitment of the domain-general fronto-parietal network. This network has been linked to the initiation of cognitive control or general decision-making processes (Heekeren *et al.*, 2006; Dosenbach *et al.*, 2007) and executive control over sematic processing in particular (Thompson-Schill *et al.*, 1997; Noonan *et al.*, 2013). These processes also may have been relevant for our task, when patients had to decide whether speech or reversed speech was presented.

In parallel to subacute recruitment of domain-general networks we also observed re-emergence of activation in perilesional cortex in both patient groups. Perilesional activation has been documented during the chronic phase after stroke in previous studies (Warburton *et al.*, 1999; Rosen *et al.*, 2000; Meinzer *et al.*, 2008; Fridriksson *et al.*, 2012). However, animal studies provide evidence that perilesional reorganization may already manifest early (i.e. in the acute to subacute phase), after local changes in tissue properties (e.g. oedema) have resolved (Cramer and Riley, 2008). As a potential basis for the acute initiation of perilesional plasticity, increased excitability due to reduced GABAergic inhibition was described around one week after stroke (Schiene *et al.*, 1996). In accordance with these physiological findings, we were able to demonstrate an early acute to subacute perilesional activation increase in both patient groups. Although we assume that perilesional reactivation also reflects restitution of left-lateralized language networks, we cannot rule out the possibility that the individual perilesional volume of interest may additionally have captured domain-general prefrontal and parietal activation in the vicinity of the lesion. Further, despite a significant activation-behaviour relationship during the subacute phase, the interpretation of results in relation to its role for language recovery should be taken with caution because reduced functional MRI-activation during the acute phase might simply indicate altered blood oxygen level-dependent signal due to an abnormal perilesional neurovascular coupling that resolves over time (de Haan *et al.*, 2013).

As another important aspect, we described that reactivation of domain-general networks precedes activation of language networks. Geranmayeh *et al.* (2014*a*) argued that subacute activation of domain-general networks is explained by different task engagement that depends on time post-stroke, i.e. patients in the acute phase are presumed to muster less cognitive effort than in the subacute phase when greater engagement in the attempt to solve the task leads to increased domain-general activation. However, as engagement expressed by in-scanner task performance was comparable between the acute and subacute phase in our study, another possible explanation could be that support by domain-general networks requires a certain amount of specific processing and thus at least partial recovery of language networks as, for example, is reflected in concomitant subacute reactivation of the perilesional cortex. This general mechanism is further supported by the observed significant behaviour-activation relationship for both, subacute perilesional activation and right DLPFC acute to subacute activation increase independent of lesion location. These observations essentially extend the framework of a hierarchical reorganization of language in chronic aphasia postulated by Heiss and Thiel (2006). In this extended framework, early subacute recovery of perilesional cortex is supported by bilateral domain-general resources and is followed by a long-term chronic restitution of left temporal language networks. In the long term, this right (and left) hemisphere domain-general compensation may further become increasingly relevant, if the left hemisphere network lacks the capacity to recover, for instance, because of large lesions stretching across fronto-parieto-temporal cortex (Heiss and Thiel, 2006; Hamilton *et al.*, 2011; Griffis *et al.*, 2017*b*). Supporting this hypothesis, it has been demonstrated that

relative to patients with smaller lesions, those with larger lesions benefit from stronger activation in the SMA and opercular IFG (Griffis *et al.*, 2017*b*), whereas left-lateralized activation of language networks was related to the intactness of core posterior temporo-parietal language regions (Griffis *et al.*, 2017*a*).

Contribution of spared left and lesion-homologue areas

We observed lesion-specific activation differences when pooling across all examinations. First, we found the expected local lesion effect with significantly higher activation in left hemisphere spared regions, respectively. Independent of time post-stroke, an overall higher left PTL activation was present in patients with frontal lesions and, vice versa, higher IFG activation was found in patients with temporo-parietal lesions. This demonstrates involvement of lesion-remote spared areas and preserved functioning of these areas within the residual left-hemisphere network.

Second, we detected lesion-homologue activation only in patients with frontal lesions. This means that, in contrast to other studies (Weiller *et al.*, 1995; Cardebat *et al.*, 2003; de Boissezon *et al.*, 2005), no lesion-homologue right PTL activation or change in activation was found in patients with temporo-parietal lesions. Differences in patient populations (subcortical lesions in de Boissezon *et al.*, 2005) and paradigms (speech production in Cardebat *et al.*, 2003; visual stimulus presenstation in van Oers *et al.*, 2010) or imaging modality (PET in Weiller *et al.*, 1995; Cardebat *et al.*, 2003; de Boissezon *et al.*, 2005) may explain why neither controls nor patients showed significant right PTL activation in our study. Our results, however, are consistent with another study that demonstrated that right temporal activation critically depended on the integrity of its left hemispheric counterpart (Skipper-Kallal *et al.*, 2017). In this context, a study by Davis and Cabeza (2015) is of interest. In healthy subjects, increasing cross-hemispheric connectivity between domain-general fronto-polar regions was associated with increasing processing demands, likely reflecting an intensified bilateral higher-order collaboration. In contrast, regions related to language processing in the temporal cortex responded with decreasing cross-hemispheric connectivity, indicating that these regions segregate from the contralateral hemisphere in response to increasing processing demands. To some extent, increased processing demands in healthy subjects may be comparable with processing in stroke patients as in both cases, network resources need to be recruited to accomplish the task. The difference in interhemispheric interactions of language-related and domain-general cortices may also be reflected in the results of a meta-analysis on language recovery in chronic aphasia that showed across a range of functional MRI paradigms substantially more right hemispheric activation in frontal compared to temporal regions (Turkeltaub *et al.*, 2011). A missing contribution of temporo-parietal lesion-homologue activation to recovery, however, does not rule out its involvement in other patient populations that were not part of the current study cohort. For example, in patients with larger lesions in which left perilesional resources do not suffice for left hemisphere recovery, right hemisphere resources could be utilized for improvement of language (Schlaug *et al.*, 2010).

Reorganization exploits pre-existing networks

The comparison with age-matched healthy subjects showed that patients revealed comparable activation relative to healthy controls during the course of recovery. This is in line with the majority of previous work that reported either reduced or close to normal activation, while only weak evidence exists for recruitment of left and right hemisphere areas that are not (or less) activated in healthy controls (Turkeltaub *et al.*, 2011). Overall, our analyses suggest that language recovery takes place in a pre-existing network and does not strongly rely on the recruitment of additional brain regions. This implies that for highly specialized functions such as language, restoration within left-lateralized language and compensation in domain-general networks dominates over *de novo* recruitment of functionally unrelated networks.

Activity in language and domain-general networks relates to language recovery

We focused our study on the description of different neural mechanisms contributing to language reorganization depending on lesion site and post-stroke interval. However, the functional relevance of these mechanisms for aphasia recovery remains less clear. As behavioural data showed significant language improvement for both patient groups from the acute to chronic phase, it is reasonable to infer that the described mechanisms that parallel recovery are to some degree responsible for this improvement. To investigate this relationship, we used regression analyses to test whether performance was related to brain activation at different time points. Independent of lesion location, activation of left IFG is associated with better performance in all phases, which is in line with previous studies in patients with temporal (Heiss *et al.*, 1999) and frontal stroke (Rosen *et al.*, 2000; Crinion and Price, 2005). This emphasizes the importance of the responsiveness of the residual language network for performance. In consideration of an overall reduced activation, a lesion-specific relationship was found between performance and right ATL activation in patients with temporo-parietal stroke during the acute phase. While overall reduced right activation might be an effect of diaschisis following left temporo-parietal damage, it further suggests that even in the acute phase the functional integrity of residual connected language networks beneficially contributes to a lesser degree of the aphasic disorder. In addition, we found an association

between subacute activation of left PTL and domain-general left opercular IFG, which again is in line with previous work in patients with chronic temporal stroke lesions (Crinion and Price, 2005). In light of a stronger acute global network disturbance in patients with temporo-parietal stroke, it highlights the importance of subacute domain-general support of beginning restitution of language networks.

Finally, we asked whether behavioural improvement was associated with changes in language activation. In line with the proposed extension of a hierarchical dynamic of reorganization (see above), we found an association between stronger activation increase in right DLPFC and greater improvement that was especially true for patients with larger lesions (Supplementary Fig. 8). This is in line with previous work (Griffis *et al.*, 2017*b*), which reports that in patients with larger lesions, better performance relates to higher right inferior frontal activation. Based on our results, the opposite relationship between higher activation increase and poorer performance in patients with smaller lesion was statistically not significant (Supplementary Fig. 8 and Supplementary material). This contradicts the notion that right hemisphere activation is maladaptive even in patients with smaller lesions (Naeser *et al.*, 2005), but mainly supports recovery in the event of extensive left hemisphere damage. Note, however, that we were not able to fully capture this phenomenon as patients with extensive left hemisphere damage were not studied. Finally, the relationship between higher left insula activation increase and behavioural improvement in patients with temporo-parietal stroke highlights another region of domain-general networks that contributes to recovery.

The absence of a correlation between late improvement and subacute to chronic activation increase or activation in the chronic phase and comprehension abilities might be best explained by the small variance in both performance and activation patterns at these time points. Moreover, there were no significant lesion-specific associations between behaviour and activation in patients with left frontal lesions. This might be due to methodological constraints of our paradigm (see 'Limitations' section). Alternatively, one may speculate that the lack of correspondence between behaviour and activation in other areas is due to the fact that aphasia must be considered a network disorder. Therefore, loss and recovery of function may be insufficiently described by mere (changes in) activation and instead be explained by changes in the functional interaction between areas (Siegel *et al.*, 2018). In support of this notion, a recent study in aphasic stroke patients found that neither mean activation in domain-general nor language networks but their activation in relation to each other predicted residual speech production (Geranmayeh *et al.*, 2016).

Limitations

The lesion-specific dynamics reported in this study were dominated by patients with temporo-parietal lesions. Although we argue that the lesion-specific behaviour of these patients is likely explained by a different functional embedding of temporal as compared to frontal language areas, it might in part also be explained by the auditory comprehension paradigms used to map language activation. These may have been more sensitive to mapping dysfunction of temporal cortex as mere listening was sufficient and no demanding selection processes or speech production were required.

A more general limitation to the data analysis and the resulting group activation patterns is that the clinically and anatomically motivated, rather coarse split into two groups based on lesion location does not account for within-group lesion variability. This leaves the possibility that within-group variance might be better explained by an even more detailed lesion-based allocation or less constrained approaches (Specht *et al.*, 2009; Abel *et al.*, 2015; Griffis *et al.*, 2017*a*). However, the cluster analysis validating our group assignment showed that lesion variability was higher between groups than within-group. Further subgrouping, especially in the temporo-parietal lesion group, might have led to spatially more homogeneous groups and therefore could have given a more precise activation pattern linked to specific anatomical lesion locations. Therefore, further investigations are needed to identify other anatomical factors such as the involvement or sparing of specific subregions (i.e. the anterior temporal cortex) or other domain-general networks (i.e. the default mode network), but also to evaluate the effect of extensive left hemisphere damage.

Conclusion

In summary, the following conclusions can be drawn from our study. We showed that different mechanisms contribute to initial language impairment (global network dysfunction, i.e. diaschisis), subacute improvement (i.e. resolution of diaschisis, compensatory upregulation of bilateral domain-general networks, beginning restoration of perilesional cortex) and chronic recovery (e.g. reintegration of left temporal language regions) of language functions. For the first time, we demonstrate how these phase-specific mechanisms depend on lesion location. We believe that the identified lesion-dependent and lesion-independent phenotypic activation patterns might provide targets for supportive therapies, e.g. application of non-invasive brain stimulation to modulate excitability in functionally relevant networks. Based on our results, we propose that, independent of lesion location, individual perilesional cortex provides a promising target for excitatory non-invasive brain stimulation as shown in a previous study by Fridriksson *et al.* (2011). In patients with left temporo-parietal lesions and spared frontal cortex, bilateral domain-general networks in the frontal lobe might provide promising targets for excitatory non-invasive brain stimulation. Because activation emerged in the subacute and continued into the chronic phase, stimulation might be supplied in either phase. In contrast, specific mechanisms supporting functional improvement in patients with frontal lesions remain incompletely understood. Although we

detected different mechanisms specific to left frontal stroke, including lesion-homologue activation and overall high ability to activate spared parts of the network from early on, none of these mechanisms proved to be only relevant in these patients. Regarding domain-general networks that have a close spatial relationship or are part of the frontal lesion, it must be assumed that, despite activated, these systems may work dysfunctionally and thus functional compensation provided by these networks could be less efficient compared to temporo-parietal stroke. On the one hand, one could argue that exactly this could be the reason for stimulation of these networks to enhance reorganization, and in particular, dACC might be an appropriate target because it is typically spared in middle cerebral artery stroke. On the other hand, well-activated spared left temporal language regions could be alternative stimulation targets.

Taken together, our study opens up new perspectives for non-invasive brain stimulation, which is supposed to be most efficient when applied to the right site and at the right time depending on individual lesion location.

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Competing interests

The authors report not competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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