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Coherent neural oscillations predict future motor and language improvement after stroke

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Running title: Network plasticity after stroke

Abstract

Recent findings have demonstrated that stroke lesions affect neural communication in the entire brain. However, it is less clear whether network interactions are also relevant for plasticity and repair. This study investigated whether the coherence of neural oscillations at language or motor nodes is associated with future clinical improvement.

Twenty-four stroke patients underwent high-density EEG recordings and standardised motor and language tests at 2-3 weeks (T0) and 3 months (T1) after stroke onset. In addition, EEG and motor assessments were obtained from a second population of eighteen stroke patients. The graph theoretical measure of weighted node degree (WND) at language and motor areas was computed as the sum of absolute imaginary coherence with all other brain regions and compared to the amount of clinical improvement from T0 to T1.

At T0, beta-band WND at the ipsilesional motor cortex was linearly correlated with better subsequent motor improvement, while beta-band WND at Broca's area was correlated with better language improvement. Clinical recovery was further associated with contralesional theta-band WND. These correlations were each specific to the corresponding brain area and independent of initial clinical severity, age, and lesion size. Findings were reproduced in the second stroke group. Conversely, later coherence increases occurring between T0 and T1 were associated with less clinical improvement.

Improvement of language and motor functions after stroke is therefore associated with interregional synchronization of neural oscillations in the first weeks after stroke. A better understanding of network mechanisms of plasticity may lead to new prognostic biomarkers and therapeutic targets.

Introduction

Stroke lesions have impact on neural interactions in the entire brain (Grefkes and Fink, 2011; Corbetta, 2012; Carrera and Tononi, 2014; Dijkhuizen *et al.*, 2014). Evidence that this is the case comes from modelling (Alstott *et al.*, 2009), animal experiments (van Meer *et al.*, 2010), as well as from imaging studies investigating neural interactions (i.e., functional connectivity, FC, or effective connectivity) between brain regions of human stroke patients.

Functional magnetic resonance imaging (fMRI) has revealed disruptions in inter-hemispheric FC between homologous motor, language, and spatial attention areas, which were linearly associated with corresponding neurological deficits of the patients (He *et al.*, 2007; Warren *et al.*, 2009; Carter *et al.*, 2010). Other studies have observed generally reduced interactions among nodes of the motor network (Sharma *et al.*, 2009), and in particular between premotor and primary motor areas (Grefkes *et al.*, 2008). These network changes evolve over time and seem to be maximal about 1 month after stroke onset (Park *et al.*, 2011). In addition, stroke patients with severe motor deficit also build up enhanced inhibitory influence from the unaffected to the affected motor cortex in subacute to chronic stages (Grefkes *et al.*, 2008; Rehme *et al.*, 2011). Improvements of motor performance are associated with a reduction of pathological influences from contralesional motor cortex and a restitution of ipsilesional effective connectivity between premotor and primary motor areas (Grefkes *et al.*, 2010).

Changes in network interactions occur also at the time scales of actual neural oscillations. EEG and magnetoencephalography (MEG) recordings in a task-free resting-state have revealed reduced phase synchronization between the affected hemisphere and other brain areas in the alpha frequency band (Dubovik *et al.*, 2012; Westlake *et al.*, 2012). The magnitude of alpha-band phase synchronization between a given brain area and the rest of the brain was found to be linearly associated with behavioural performance in tasks depending on this brain area. For instance, the more spontaneous alpha oscillations in Broca's area were phase synchronised with the rest of the brain, the better patients were able to produce words (Dubovik *et al.*, 2012; Guggisberg *et al.*, 2015). Improvement of neurological deficits during rehabilitation goes in parallel with increases in alpha-band phase synchronization (Westlake *et al.*, 2012), and, vice versa, enhancing alpha-band coherence with neurofeedback seems to reduce motor deficits after stroke (Mottaz *et al.*, in press). During movement tasks, network dynamics of beta oscillations seem to be affected and associated with movement performance (Gerloff *et al.*, 2006; De Vico Fallani *et al.*, 2013).

In contrast to the solid evidence that neurological deficits after stroke are associated with disturbed neural interactions among brain regions, it is less clear whether network interactions are also relevant for brain plasticity and repair after stroke. The identification of such network mechanisms of plasticity would be important as this might yield new therapeutic targets and help predict future improvement of stroke patients.

Experiments in rats have suggested that axonal sprouting is associated with widespread synchronous neural activity at low oscillation frequencies on the first days after thermal-ischemic lesions (Carmichael and Chesselet, 2002). In human stroke patients, correlations between different kinds of network interactions before therapy and clinical improvement during therapy periods have been observed at various time points after stroke (Wang *et al.*, 2010; Buch *et al.*, 2012; Westlake *et al.*, 2012; Várkuti *et al.*, 2013). In particular, nodes associated with deficient neurological functions were found to enhance their overall importance in the brain network during recovery by increasing their functional connectivity with other areas (Wang *et al.*, 2010; Buch *et al.*, 2012; Westlake *et al.*, 2012). However, it remains unknown whether these observations are robust across different populations and whether they are predictive for improvement of different neurological functions. Furthermore, the time course of adaptive network changes after stroke is unclear.

The present study aimed to identify EEG network changes occurring within the first 2-3 weeks after stroke indicative of subsequent clinical language and motor improvement. Based on current concepts of plasticity after stroke, we hypothesised that FC changes relevant for repair would involve primarily ipsilesional areas adjacent to the region normally responsible for the deficient function as well as homologous contralateral areas. Furthermore, we supposed that preserved or even enhanced FC between these areas and the rest of the brain should help reshape network interactions towards functional brain tissue and lead to more clinical improvement. Conversely, a functional disconnection of these critical areas from the rest of the brain would impede plasticity and lead to less clinical improvements. To test this, we calculated a global index of FC between critical brain areas and the rest of the brain: the graph theoretical measure of node degree in weighted networks (weighted node degree, WND) (Newman, 2004). We then investigated the association of WND with future clinical improvement in motor and language functions in 2 independent patient populations with acute to subacute stroke.

Materials and methods

Patients and subjects

The study comprised two independent groups of human stroke patients as well as group of age-matched healthy controls. All participants gave written informed consent to participate in this study. Procedures were approved by the Geneva Ethics Committee and conducted according to the Declaration of Helsinki.

Stroke population 1 was used for main analyses and for an exploration of network correlates of clinical improvement. It was composed of twenty-four stroke patients (mean age 60.7 years, range 37-81, 9 women, 15 had left hemispheric stroke). Mean National Institute Stroke Scale (NIHSS) was 13, range 3-27. Inclusion criteria were: (i) clinical diagnosis of first ever, territorial ischemic stroke, (ii) unilateral ischemic lesion in the territory of the middle cerebral artery (MCA) as demonstrated by structural MRI, (iii) at least mild motor or language impairment at the beginning of rehabilitation. Excluded were patients with neurological or psychiatric comorbidities, history of seizures, presence of metallic objects in the brain, or skull breach. Patients' demographic and clinical characteristics are listed in Supplementary Table 1. The lesion distribution is shown in Supplementary Fig. 1. All patients received standard therapy at the stroke unit during the acute phase and an individually tailored multidisciplinary rehabilitation program in the sub-acute and chronic phases. Two patients took short-acting benzodiazepines exclusively at bed-time (>12h before EEG recordings), three patients received serotonin-reuptake inhibitors (Table 1). These drugs were treated as confounding covariates in statistical analyses. High-density EEG and standardised clinical assessments were obtained at two time-points: 2-3 weeks (T0) and three months (T1) after stroke onset.

The second group of stroke patients was used for cross-validation of the findings in an independent group. It was composed of eighteen patients satisfying the same inclusion criteria and exclusion criteria as population 1, with the following exceptions: not only ischemic but also hemorrhagic strokes were accepted, and only motor recovery was examined. For this reason, patients with severe language comprehension deficits were excluded, and patients needed to have at least mild motor impairment at the beginning of rehabilitation. Mean age was 67 years (range 32-85), mean NIHSS 13.8 (range 3-22), 8 were women, and 7 had left hemispheric lesions. Patient's demographic and clinical characteristics are listed in Supplementary Table 2. Three patients received benzodiazepines at bedtime, one of whom

also during the day, four patients took serotonin-reuptake inhibitors and one a low-dose neuroleptic at bedtime. Standardized clinical assessments of motor function were obtained at 3 weeks (T0) and 3 months (T1) after stroke and high-density EEG at 3 weeks after stroke.

As a control group, twenty-six age-matched volunteers without neurological or psychiatric disease were included. Their mean age was 62.4 years, range 32-88, 12 women. Age ($F_{2,62}$=1.0, p=0.38) and gender (p>0.58, Fisher's exact test) were not significantly different between patient and control populations.

Clinical assessments

Motor function was assessed with the following standardised measures: the Jamar dynamometer (Mathiowetz *et al.*, 1985), the Fugl-Meyer motor assessment of the upper extremity (Fugl-Meyer *et al.*, 1975), the Nine Hole Peg test (Oxford Grice *et al.*, 2003), and the stroke rehabilitation assessment of movement (STREAM) instrument (Wang *et al.*, 2002). The Nine Hole Peg test was expressed in pegs/sec. All scores were normalised to values of the unaffected arm of each patient. Since the four motor scores were highly correlated (r>0.7), we used the average of all items in our analyses as compound motor score.

Language function was quantified with the Geneva Bedside Aphasia Score (GeBAS) (Boukrid and Laganaro, 2013). It was developed for quantification of overall performance in language comprehension and production in acute and subacute phases of neurological disease. Its subtests assess spontaneous language production, orientation, production of automatic series, denomination, repetition, verbal fluency, comprehension, writing, reading and calculating. The score for maximum performance is 100, minimum score is 0.

Clinical improvement of patients was quantified by subtracting their corresponding scores at T1 from T0. Henceforth, we use the term *recovery* in reference to this measure.

EEG acquisition

EEG data was collected with a 128-channel Biosemi ActiveTwo EEG-system (Biosemi B.V., Amsterdam, Netherlands). Spontaneous activity in a task-free state was recorded with a sampling rate of 512 Hz. Participants were instructed to keep their eyes closed and to remain relaxed but awake. Data segments with artefacts or signs of reduced vigilance were excluded by visual inspection of the data. Five-minutes of artefact-free data were recalculated against the average reference.

Connectivity analysis

Source functional connectivity (FC) was calculated in *Matlab* (The MathWorks Inc., Natick, USA) with the open-source toolbox *NUTMEG* (http://nutmeg.berkeley.edu) (Dalal *et al.*, 2011) and its *functional connectivity mapping (FCM) toolbox* (Guggisberg *et al.*, 2011). The lead-potential with 10 mm grid spacing was computed using a spherical head model with anatomical constraints (SMAC) (Spinelli *et al.*, 2000) in stroke population 1 and in healthy controls, and a boundary element model (BEM) in stroke population 2. The BEM model was created with the Helsinki BEM library (http://peili.hut.fi/BEM/) (Stenroos *et al.*, 2007). Artefact-free EEG segments were bandpass filtered between 1 and 20 Hz and projected to grey matter voxels with an adaptive spatial filter (scalar minimum variance beamformer) (Sekihara *et al.*, 2004). The absolute imaginary component of coherence **I** (Nolte *et al.*, 2004; Sekihara *et al.*, 2011) between estimated source time series at each voxel *x* and all other voxels *y* was subsequently calculated as index of FC. From this, we computed the weighted node degree (WND) *k* at each voxel *x* as the sum of its coherence with all other cortical voxels (Newman, 2004):

$$k_x = \sum_y \mathbf{I}_{xy} \quad (1)$$

WND can be seen as an index of the overall importance of an area in the brain network (Stam and van Straaten, 2012; De Vico Fallani *et al.*, 2014).

Separate values were obtained at each of seven frequency bands: delta (1-3 Hz), low theta (4-5 Hz), high theta (6-7 Hz), low alpha (8-10 Hz), high alpha (11-12 Hz), low beta (13-16 Hz), and high beta (17-20 Hz). Between-subject variation in synchronization magnitude (and hence WND) can be due to variations in signal-to-noise ratios of the recordings. To avoid this potential confound in our analyses of the association between variations in WND and clinical improvement, we normalised WND maps. This was achieved by subtracting, for each subject, the mean WND across all voxels of the subject and by dividing by the standard deviation, hence yielding z-scores. Z-score maps were spatially normalised to canonical Montreal Neurological Institute (MNI) space using functions of the toolbox *SPM8* (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Ischemic lesions were masked during spatial normalization to avoid distortions (Brett *et al.*, 2001).

Regions of interest (ROIs)

Ipsilesional and contralesional ROIs were defined *a priori* for each clinical function with anatomical templates. They comprised the areas supposed to be responsible for the respective function and their homologous contralateral areas. For motor function, we used the ipsilesional and contralesional primary motor cortex (M1). Language ROI was the left posterior inferior frontal gyrus (Broca's area) and its right homologue. Motor ROIs were defined with the human motor area template (Mayka *et al.*, 2006), language ROIs using the automated anatomical labelling template (Tzourio-Mazoyer *et al.*, 2002). WND at each ROI was calculated as the average of its voxels.

Statistical analyses

Our hypothesis postulated that greater WND should help reshape network interactions towards more clinical improvement while functional disconnection of critical areas would lead to less clinical improvements. Accordingly, we tested WND at T0 for positive correlations with changes in motor and language performance from T0 to T1 using a Pearson correlation analysis. All variables were normally distributed and parametric tests were therefore used. Only patients showing at least mild motor impairment at T0 (<90% of maximum compound motor score) were included for the correlation analysis of motor improvement (N=21). Left and right hemispheric lesions were relabelled as *ipsilesional* and *contralesional* and combined for analysis, but we verified that results hold true for both lesion sides. For correlation analysis of language improvement, only patients with left hemispheric stroke and with at least mild language impairment at T0 were included (N=14). In population 1, correlations were performed at each of the seven frequency bands and at both ROIs of each function, using a Bonferroni correction to correct for multiple testing. In population 2, correlations were performed only at frequency bands found to be significant in population 1, and Bonferroni corrected for testing two ROIs.

Next, we characterized the evolution over time of network predictors by analyzing their association with clinical variables at different time points. In twenty-one out of the twenty-four patients of population 1, EEG recordings could also be obtained at T1. These patients were separated into two groups according to their clinical improvement, using a median split of their change in behavioural score from T0 to T1. WND values at frequency bands with significant correlations were tested for differences between good and bad recovery groups, both at T0 and T1, with unpaired t-tests. To further investigate the impact of changes in

network predictors over time with clinical improvement, we also correlated change in WND from T0 to T1 with clinical changes from T0 to T1.

To assess the spatial specificity of ROI correlations, we performed voxel-wise correlations between WND and clinical recovery and reproduced voxel maps without correction for multiple testing to visualise the full spatial extent of network predictors. Furthermore, we verified whether correlations with recovery were different between language and motor ROIs using permutation tests. At each of 2000 permutation loops, we shuffled the order of the clinical scores across patients and recalculated the Pearson correlations between WND at each ROI and the clinical variable. The correlation coefficient difference between the two ROIs was then compared to the distribution of correlation coefficient differences obtained with permutation. Permutation tests were also performed on pairs of correlations at different frequency bands of the same ROI, in order to verify the frequency specificity of the associations.

We verified that bivariate correlations were independent of initial motor/language score, initial NIHSS, age, lesion size, and CNS-active medication with a multivariate linear regression model using forward stepwise selection as well as with partial correlation analyses. In addition, WND at T0 was correlated with clinical scores at T0 and WND values at T1 with clinical scores at T1.

In addition, we also compared WND of good and bad recovery groups to values of the age-matched healthy control population.

Results

In accordance with our hypothesis, we observed areas with high WND in patients with good clinical improvement. This concerned ipsilesional as well as homologous contralateral areas. Fig. 1 shows two typical examples.

The correlation analysis across all patients of population 1 showed that higher WND values in ipsilesional and contralesional ROIs were indeed linearly associated with better clinical improvement. In ipsilesional ROIs, correlations could be observed exclusively in the beta frequency band. The more beta oscillations in the ipsilesional motor areas were coherent with the rest of the cortex, the more patients improved in motor function ($r=0.57$, $p=0.047$, Bonferroni corrected, Fig. 2A, C). Similarly, the more left inferior frontal regions were

coherent with the rest of the cortex, the better patients improved in language function ($r=0.69$, $p=0.042$, Bonferroni corrected, Fig. 2B, D).

Associations between WND and clinical scores were then followed over time in order to characterize their temporal evolution. When patients were segregated into 2 groups according to their clinical recovery, we found a trend for greater WND at T0 in the group with good compared to the group with bad corresponding improvement ($t>1.9$, $p<0.084$, Fig. 2E-F). This difference was not observed at T1. On the contrary, a delayed increase in WND from T0 to T1 was significantly negatively correlated with the corresponding clinical recovery during the same period ($r<-0.56$, $p<0.040$, Fig. 2G-H). Hence, whereas high WND at 2-3 weeks after stroke was positively associated with recovery, the opposite was the case for later increases.

A similar pattern was found in contralesional ROIs, but for theta oscillations. Language recovery was associated with larger WND in the right Broca homologue at 2 weeks ($r=0.70$, $p=0.039$, Bonferroni corrected, Fig. 3B, D, F). In the case of motor improvement, no correlation was at first observed in any frequency band. However, when we used a more fine graded template of motor areas and defined motor ROIs covering more exclusively upper extremity representations [Area 4p of the Jülich Anatomy Toolbox (Eickhoff *et al.*, 2005)], we also found an association of theta-band WND with motor recovery, although it did not survive corrections for multiple testing ($r=0.52$, $p=0.008$, uncorrected, Fig. 3 A, C). Again, the association tended to be inversed for later increases occurring between 2-3 weeks and 3 months post stroke onset ($r<-0.4$, $p<0.110$, Fig. 3G-H).

Correlations were spatially specific: WND at motor areas did not correlate with language improvement ($r<0.38$, $p>0.18$), and language WND not with motor improvement ($r<0.36$, $p>0.10$). Correlation between motor ROI WND and motor improvement was significantly greater than the correlation between WND at Broca's area and motor improvement (ipsilesiponal $p<0.0001$, contralesional $p<0.06$), and correlation between WND at language ROIs and language recovery tended to be greater than the correlation between motor WND and language improvement (ipsi- and contalesional $p<0.06$). Furthermore, a voxel-wise analysis showed that the correlations were regionally specific in that only voxels around motor areas correlated with motor improvement and only voxels around language areas correlated with language improvement (Fig. 4). Correlations were also frequency specific. In ipsilesional ROIs, correlation with recovery was significantly greater at the beta than at the theta frequency band ($p<0.02$), while the opposite was the case for contralesional ROIs ($p<0.06$).

In contrast to coherence, local oscillation power at the same ROIs and frequency bands was not correlated with recovery ($r<0.28$, $p>0.17$), thus confirming that our findings reflect interregional coherence, not local oscillation amplitude.

In a multiple stepwise regression, only ipsi- and contralesional WND, but not initial motor/language scores, initial NIHSS, age, lesion size, and medication were retained as independent predictors of motor and language improvement (final model for motor improvement: $F_{2,18}=11$, $R^2=0.55$, $p=0.0007$; language improvement $F_{2,11}=9$, $R^2=0.61$, $p=0.005$). Similarly, a partial correlation analysis including these factors as confounding covariates remained significant ($r>0.56$, $p<0.03$). No significant correlations were found between WND values at T0 and clinical scores at T0 ($r<0.36$, $p>0.19$) or between WND at T1 and clinical scores at T1 ($r<0.21$, $p>0.49$), confirming that the association with recovery was not merely due to severity at baseline or follow-up.

We verified the robustness of these findings in a second stroke population (in whom only motor assessments were obtained). When using the same motor ROIs and frequency bands as in population 1, we reproduced similar positive correlations between WND at T0 and subsequent motor improvement ($r>0.47$, $p<0.05$, Fig. 5).

Next, we compared ipsilesional beta-band WND and contralesional theta-band WND of stroke population 1 to an age-matched healthy control population. The bad recovery group had lower WND in contralesional M1 ($t=-2.1$, $p=0.045$), as well as in the ipsilesional Broca area ($t=-2.6$, $p=0.015$) and its contralesional homologue ($t=-1.9$, $p=0.071$) than healthy controls. The good language recovery group had significantly greater WND in Broca's area than healthy controls ($t=3.2$, $p=0.003$). The difference in the remaining ROIs was not significant ($p>0.16$).

Discussion

Brain repair after stroke depends on a cascade of a growth-promoting molecular and cellular events (reviewed, e.g., in Carmichael (2006), Nudo (2007), Murphy and Corbett (2009)), on a transient recruitment of perilesional as well as contralesional brain areas (e.g., Nudo *et al.*, 1996; Feydy *et al.*, 2002; Ward *et al.*, 2003; Gerloff *et al.*, 2006; Saur *et al.*, 2006), as well as on early, intensive, and task-specific exercise (e.g., Kwakkel *et al.*, 1999; Kleim and Jones, 2008; Dancause and Nudo, 2011; Langhorne *et al.*, 2011). Our study provides evidence that

plasticity is further associated with a synchronization of spontaneous neural oscillations between brain areas. The more neural oscillations in language and motor areas were coherent with the rest of the cortex at 2-3 weeks after stroke, the better patients improved in corresponding clinical functions during the subsequent weeks. This association was robust as it was reproduced in two different patient populations and two key neurological functions. Network interactions therefore seem to be relevant for brain plasticity. This might be a consequence of processes taking place on cellular and molecular levels. For instance, the creation of new synaptic connections might be associated with a transient increase in synchronous beta oscillations between the involved brain areas. In this case, EEG connectivity could be useful as non-invasive biomarker of cellular processes. In addition, oscillation synchrony might also contribute actively to plasticity. For instance, it might help preserve and strengthen newly-formed projections. A better understanding of these network processes could then eventually result in new or improved therapy procedures.

We will first characterise connectivity changes associated with future recovery and then consider possible confounds and limitations. Finally, we will compare network markers of stroke recovery with previously described predictors.

Characteristics of network plasticity

Network analyses begin to reveal characteristics of stroke plasticity which have been hidden to local analyses. They show that critical brain areas enhance their overall importance and interactions in the brain network, probably to promote their reintegration. This is suggested not only by our finding of larger WND in patients with good recovery, but also by similar observations made in previous studies which have used fMRI (Wang *et al.*, 2010), MEG (Buch *et al.*, 2012), or EEG during motor tasks (De Vico Fallani *et al.*, 2013) to reconstruct comparable graph theoretical measures of node degree or node centrality. This increase in overall interactions is therefore remarkably reproducible and observable during tasks and at rest, and in several recording techniques.

Our study further suggests that specific oscillation frequencies are preferred for recovery-related neural interactions in the first weeks after stroke. Thereby, ipsi- and contralesional hemispheres use different rhythms. This might reflect distinct molecular environments after unilateral stroke. Animal models of stroke have shown that two main synaptic signalling systems are implicated in stroke plasticity, but with opposing effects. Gamma-aminobutyric acid (GABA) mediated inhibition of the periinfarct tissue reduces recovery, while

glutamatergic excitation mediated by alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors promotes plasticity (Clarkson *et al.*, 2010; Carmichael, 2012; Kim *et al.*, 2014). These neurotransmitters also modulate the amplitude and phases of EEG rhythms at specific frequencies. GABA influences beta rhythms in the motor cortex (Jensen *et al.*, 2005; Yamawaki *et al.*, 2008; Farzan *et al.*, 2013; Ronnqvist *et al.*, 2013) and seems to influence spike timing of individual neurones during theta oscillations (Kohl and Paulsen, 2010). AMPA agonists have been reported to induce long-term theta oscillations (Li *et al.*, 2014). The association of ipsilesional beta coherence with clinical improvement might therefore reflect a GABAergic processes. The preference of the contralesional hemisphere for theta rhythms might also be related to neurotransmitter changes (Schiene *et al.*, 1996; Kim *et al.*, 2014). If such associations between neurotransmitters and coherence frequencies can be confirmed in future studies, they might enable us to link clinical observations with synaptic processes using non-invasive and convenient EEG recordings.

In addition to the frequencies observed here, synchronous neural activity at delta and infra-delta frequencies (0.1 – 2 Hz) have been reported during the first days after stroke in rats (Carmichael and Chesselet, 2002). It is unknown whether such slow frequency synchronization also occurs in humans. The fact the we did not observe it in our study may be due to later times of recordings, difficulties in obtaining artefact-free recordings of very slow rhythms at the skull, and our measure of functional connectivity which masks zero-lag synchrony.

In healthy humans, alpha rhythms are the main carrier for phase synchronization during the task-free state. The healthy human brain has a prominent peak of resting-state oscillation coherence in the alpha frequency range (~7-13 Hz) (Guggisberg *et al.*, 2008; Hillebrand *et al.*, 2012) corresponding to the prominence of the alpha rhythm in the human EEG. Moreover, the magnitude of resting-state alpha-band coherence is linearly associated with performance in subsequent tasks (Dubovik *et al.*, 2013; Rizk *et al.*, 2013; Guggisberg *et al.*, 2015). The present study provides evidence that recent stroke lesions induce an adaptive deviation from the usual alpha frequencies towards beta and theta frequencies. This deviation is transient and limited to the first weeks after stroke. A return to usual alpha interactions has to occur during the period between 4 to 12 weeks after stroke. The negative correlation between changes in coherence and clinical improvement indicates that theta and beta coherence become maladaptive at these later stages. Moreover, previous studies have shown that, 3 months after stroke, motor and cognitive performance of stroke patients is again correlated with alpha-band

connectivity of critical nodes, as in healthy subjects (Dubovik *et al.*, 2012). A study investigating mostly chronic stroke patients found also predictors of future recovery when focusing on alpha-band coherence (Westlake *et al.*, 2012). In sum, EEG and MEG network analyses suggest that the brain uses several communication frequencies in order to adapt to stroke lesions, and that the involved frequencies evolve dynamically over time. The time course of adaptive network changes observed here corresponds to the time window of opportunity known from repair-related genetic, molecular, and cellular events which also peak during the first weeks after stroke onset (Carmichael, 2006; Cramer, 2008; Murphy and Corbett, 2009). This provides further evidence that EEG network markers are linked to molecular repair processes.

Network changes associated with recovery also follow several principles of plasticity known from local processes. Increases in FC are functionally and regionally specific, such that nodes mediating a particular function are also specifically associated with recovery of the same function. Moreover, they involve ipsilesional and homologous contralesional brain areas, in accordance with findings from studies of local activity changes (Feydy *et al.*, 2002; Ward *et al.*, 2003; Gerloff *et al.*, 2006; Saur *et al.*, 2006).

It is noteworthy that network plasticity takes place not only after stroke but also in other conditions such as traumatic brain injury, multiple sclerosis, and early Alzheimer's disease. Some of the mechanisms observed in stroke seem to generalise to other pathologies. For instance, the hyperconnectivity of critical areas seems to be a general response to brain affections occurring also in traumatic brain injury and multiple sclerosis (Hillary *et al.*, 2015). An adaptive shift of neural interaction frequency occurs also after traumatic brain injury (Castellanos *et al.*, 2010; 2011) and in patients with early Alzheimer's disease (Dubovik *et al.*, 2013). Yet, the involved frequencies seem to differ among conditions. This opens the interesting possibility that network imaging with EEG or MEG might provide a fingerprint of frequency responses which are characteristic to particular conditions.

Potential confounds

We verified that the correlations observed here were not merely due to the presence of lesions, which might have led to a general suppression of oscillations and hence to trivially low coherence in patients with worse recovery. When ipsilesional ROIs were defined individually for each patient by masking voxels that were affected by anatomical lesions, this did not change our findings of correlations with clinical recovery ($r>0.50$, $p<0.035$). One may

argue that the limited spatial resolution of EEG source reconstruction leads to spread of reduced oscillations around lesions which would be difficult to control. However, this possibility is unlikely for several reasons. First, we used a measure of FC which is robust to artefacts resulting from the limited spatial resolution of source imaging (Sekihara *et al.*, 2011). Second, a general suppression of neural activity would likely concern all oscillation frequencies, whereas we observed selective correlations only at particular frequency bands. Third, the presence of lesions could not explain the fact that we found similar correlations in the contralesional hemisphere. Fourth, many patients with good recovery had increased FC (Fig. 1), which cannot be explained by a lesion-induced absence of neural oscillations.

Our study reports the largest sample of stroke patients so far investigated for network plasticity and is the first to crossvalidate the findings in an independent population. Yet, the sample size remains moderate with variable lesions, clinical cofactors, and analyses procedures, which might partially influence some of the findings.

Predictors of recovery

Multiple parameters have been proposed as predictors of functional outcome after stroke (i.e., of the severity of deficits in the chronic stage), including initial clinical severity (Kwakkel *et al.*, 2003; Nijland *et al.*, 2010), lesion location (Shelton and Reding, 2001; Hope *et al.*, 2013), diffusion tensor imaging of white matter tracts (Stinear *et al.*, 2007; Liu *et al.*, 2010; Marchina *et al.*, 2011; Riley *et al.*, 2011), magnetic resonance spectroscopy (Cirstea *et al.*, 2011), functional magnetic resonance imaging (Saur *et al.*, 2010), motor and somatosensory evoked potentials (Feys *et al.*, 2000; Hendricks *et al.*, 2002; Stinear *et al.*, 2007), and EEG/MEG spectral power (Tecchio *et al.*, 2007; Finnigan and van Putten, 2013). In the case of motor outcome, best prediction accuracy has been reported by a combination of clinical examinations and assessments of the cortico-spinal tract with diffusion tensor imaging and motor evoked potentials (Coupar *et al.*, 2012; Stinear *et al.*, 2012).

In contrast, the prediction of clinical improvement from the acute/subacute to the chronic stage has proven more difficult. It seems to rely less on the severity of initial clinical deficits and local neural damage, and more on reparation processes in distributed areas. Functional magnetic resonance imaging (fMRI) can help identify patients with good likelihood of improvement if multivariate analyses of activation changes at multiple brain regions are used (Cramer *et al.*, 2007; Marshall *et al.*, 2009; Saur *et al.*, 2010). Our and previous studies underscore the relevance of network interactions. Future studies will need to compare the

reliability of different markers and assess whether a combination can result in clinical applications.

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Figure Captions

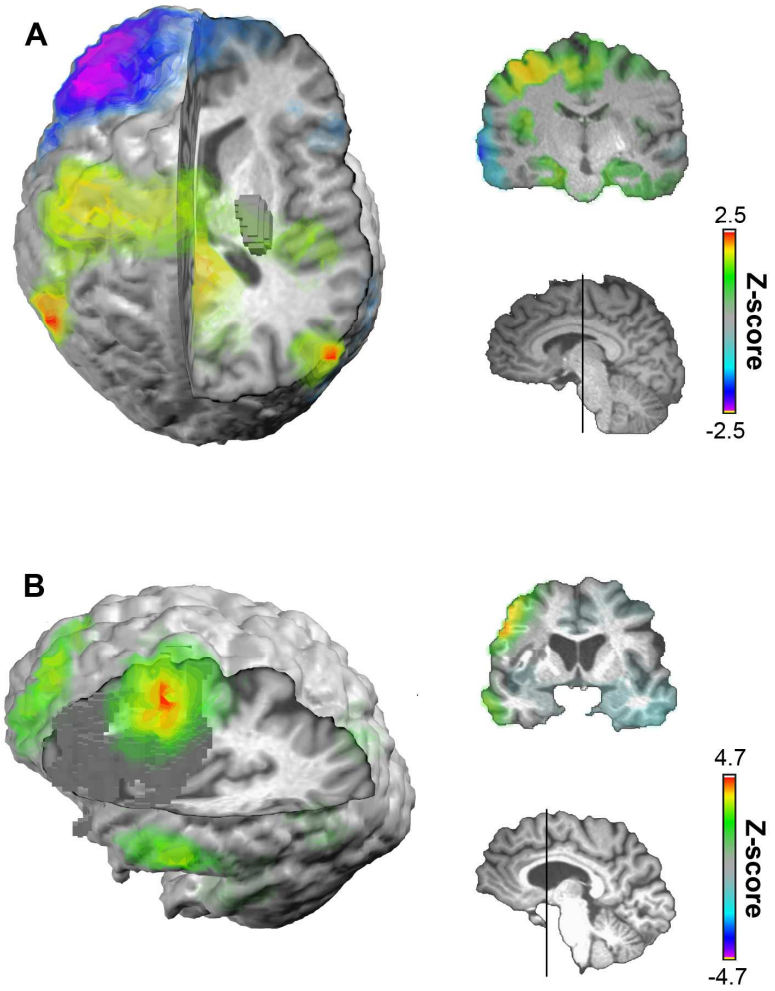

Figure 1. Examples of hyperconnectivity after stroke resulting in increased WND in contralesional (A) and ipsilesional (B) hemispheres. Stroke lesions are marked with dark gray cubes, regions with increased WND with yellow and red colours. (**A**) Patient with paresis of the left arm resulting from a lesion involving the right internal capsule. EEG network imaging revealed hyperconnectivity of the contralesional motor cortex at 2-3 weeks after stroke onset. The patient improved from 7 points at 2 weeks to 21 points at 3 months in the Upper Extremity Fugl Meyer score. (**B**) Patient with Broca aphasia due to stroke in the territory of the left anterior middle cerebral artery. Hyperconnectivity was present in the perilesional tissue at 2 weeks and associated with an improvement in language performance from 40 to 78 out of 100 points in the subsequent weeks. Coronal slices are in neurological orientation.

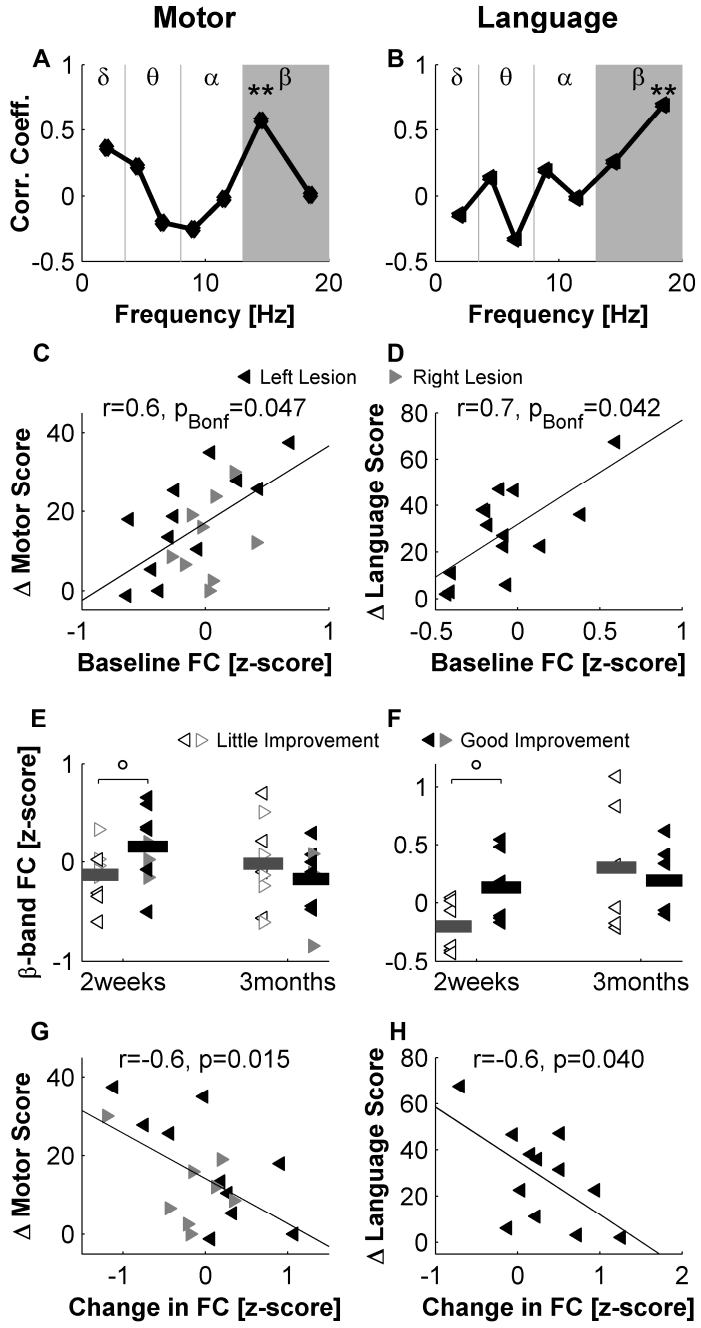

Figure 2. Ipsilesional network correlates of clinical recovery. Global FC of the affected primary motor cortex (**A**) or of Broca's area (**B**) with other areas (i.e., their WND) correlated with future clinical improvement at beta oscillation frequencies. Double asterisks indicate frequency bands with significant correlations ($p<0.05$, Bonferroni corrected). (**C, D**) Scatter plots illustrating the association between beta-band WND and clinical recovery. (**E, F**) Patients with good recovery tended to show greater WND at 2-3 weeks after stroke, but not at 3 months. White circles denote marginally significant differences ($p<0.09$). (**G, H**) In contrast to the situation at T0, an increase of WND between T0 and T1 was associated with worse clinical improvement in the corresponding function.

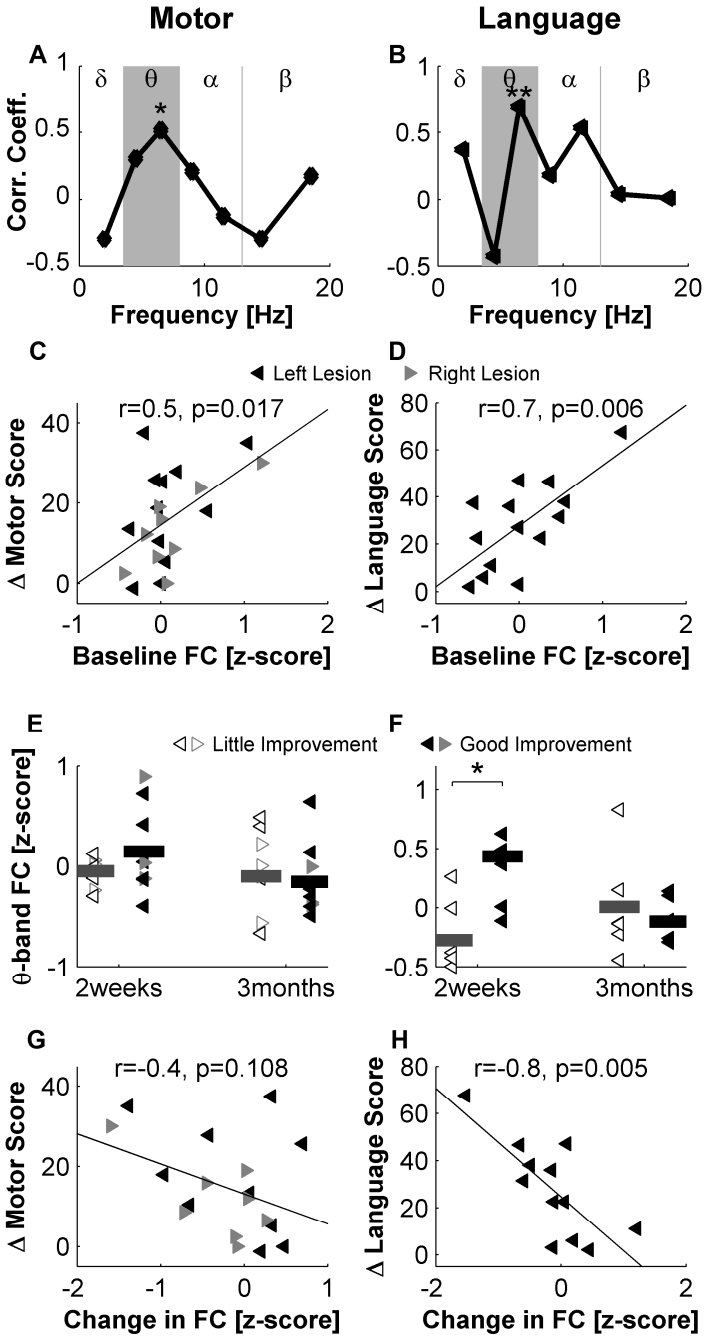

Figure 3. Contralesional network correlates of clinical recovery. WND of the contralesional primary motor cortex (**A**) and the right Broca homologue (**B**) was correlated with corresponding future clinical improvement at theta oscillation frequencies. Asterisks indicate frequency bands with significant correlations: ** $p<0.05$, Bonferroni corrected; * $p<0.05$, uncorrected. (**C, D**) Scatter plots illustrating the association between theta-band WND and clinical recovery. (**E, F**) Patients with good language recovery tended to show greater WND at 2-3 weeks after stroke, but not at 3 months. The asterisk indicates significant differences ($p<0.05$). (**G, H**) In contrast to the situation at T0, an increase of WND between T0 and T1 was associated with worse clinical improvement in language function.

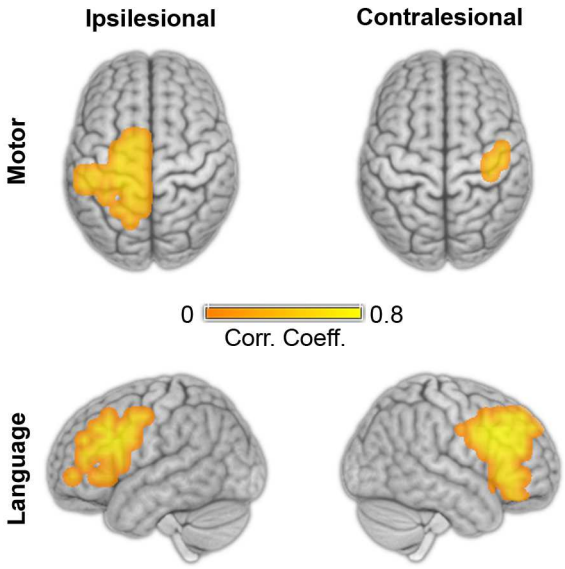

Figure 4. Associations between network interactions and clinical improvement were regionally specific. A voxel-wise correlation between WND and clinical recovery shows that only voxels around motor areas correlated with motor improvement and only voxels around language areas correlated with language improvement. Functional maps are thresholded at p<0.05, uncorrected, to visualize the full extent of network predictors.

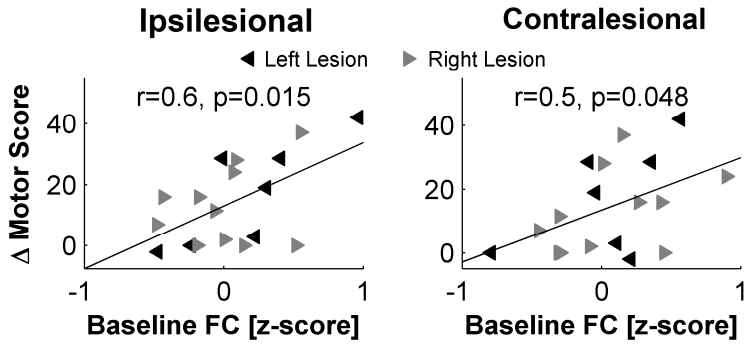

Figure 5. Correlations in an independent population. Significant associations between FC at T0 and subsequent recovery were reproduced in the second stroke population, using the same regions of interest and the same frequency bands.

Supplementary Material to

Coherent neural oscillations predict future motor and language recovery after stroke

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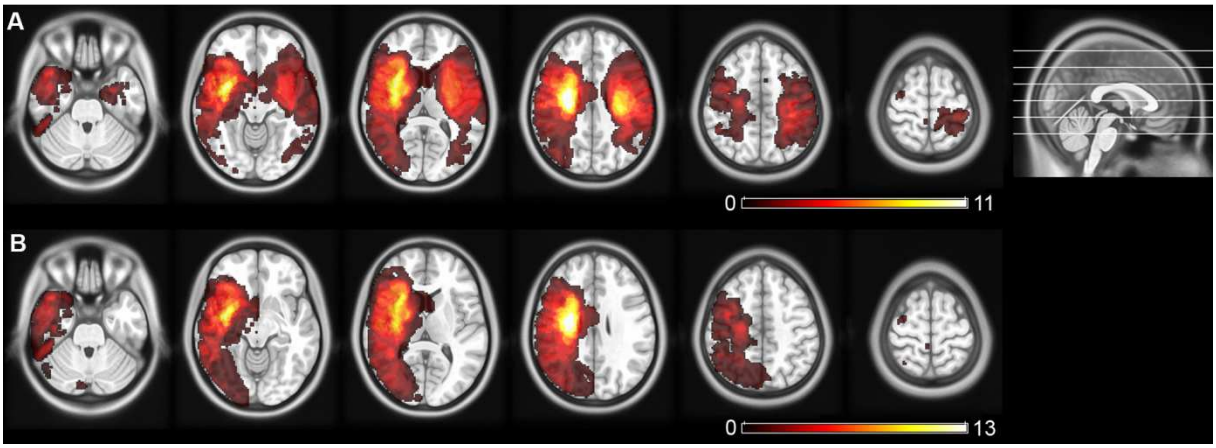
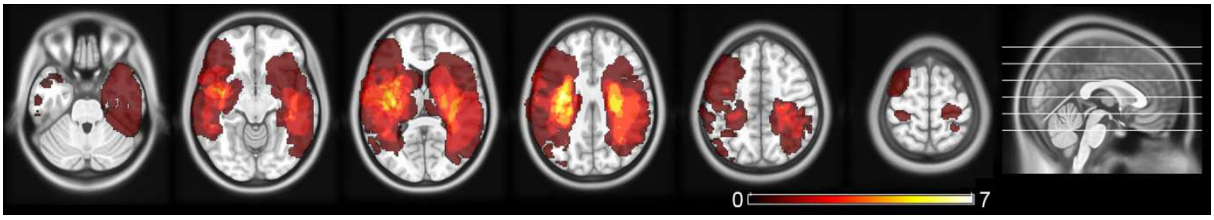
Supplementary Figures



Supplementary Figure 1: Lesion distribution of stroke population 1. A Patients with motor deficits. **B** Patients with language deficits. The color encodes the number of patients with ischemic lesion at a given voxel. The lesion was cortical in 2 out of 24 patients, subcortical in 6, and mixed in 16. Images are presented in neurological convention (left is left).



Supplementary Figure 2: Lesion distribution of stroke population 2. The lesion was cortical in 1 patient, subcortical in 8, and mixed in 6. Images are presented in neurological convention (left is left).

Supplementary Tables

Supplementary Table 1. Characteristics of patient population 1.

Age	Gender	Lesion Side	Admission NIHSS	Handedness	Suspected Stroke Etiology	CNS-active medication
67	M	R	13	R	Internal carotid artery stenosis	-
51	M	L	15	L	Internal carotid artery dissection	-
60	M	L	16	R	Cryptogenic	-
64	F	L	7	R	Cryptogenic	-
80	F	R	5	R	Atrial fibrillation	Oxazepam
68	M	R	15	R	Cryptogenic	-
74	F	L	14	R	Akinetic left ventricular segment	Citalopram
48	F	L	27	R	Cryptogenic	-
54	F	L	6	R	Patent foramen ovale	-
62	M	R	9	R	Internal carotid artery occlusion	-
68	M	R	16	R	Atrial fibrillation	-
37	M	L	8	R	Patent foramen ovale and DVT	-
63	M	L	12	R	Internal carotid artery occlusion	-
70	F	L	14	R	Atrial fibrillation	Fluoxetin
53	M	L	20	R	Internal carotid artery dissection	Escitalopram
79	M	R	18	R	Internal carotid artery occlusion	-
60	M	R	18	R	Internal carotid artery stenosis	-
46	M	L	7	R	Patent foramen ovale and DVT	-
73	F	L	3	R	Cryptogenic	-
78	F	R	9	R	Atrial fibrillation	-
56	M	L	19	R	Cryptogenic	Zolpidem

67	F	L	11	R	Atrial flutter and mitral valve	-
43	M	L	18	L	Patent foramen ovale and DVT	-
52	M	R	14	R	Middle cerebral artery stenosis	-

Supplementary Table 2. Characteristics of patient population 2.

Age	Gender	Lesion Side	Admission NIHSS	Handedness	Suspected Stroke Etiology	CNS-active medication
43	F	R	43	R	Common carotid artery dissection	-
65	M	L	19	R	Atrial fibrillation	-
64	F	R	21	R	Internal carotid artery occlusion	-
32	M	L	3	R	Middle cerebral artery stenosis	Escitalopram
67	F	L	8	R	Cryptogenic	-
77	F	L	22	R	Atrial fibrillation	-
56	M	R	15	R	Arterial hypertension (hemorrhage)	-
83	M	R	16	R	Atrial fibrillation	-
80	F	R	10	R	Cryptogenic	-
77	M	R	6	R	Internal carotid artery stenosis	Citalopram
77	F	R	17	R	Carotid artery atheromatosis	Zolpidem, Quetiapin
85	F	L	13	R	Carotid artery atheromatosis	-
51	F	L	7	R	Internal carotid artery thrombus	Clonazepam, Fluoxetin
83	M	L	14	L	Arterial hypertension (hemorrhage)	-
67	M	R	18	R	Arterial hypertension (hemorrhage)	-

62	M	R	17	R	Carotid artery atheromatosis	-
49	F	R	16	R	Cryptogenic	Escitalopram
73	M	R	9	R	Atrial fibrillation	Bromazepam