Network changes after stroke – results of longitudinal SFB data

Eckhard Schlemm

1 Results

A total of 30 patients were recruited to the study. Clinical assessment by NIHSS score, FM score and grip strength was complete with recordings from all four time points (3-5 days; 1, 3, and 12 months after stroke) in 23 patients. The pattern of missing clinical data is displayed in Tab S1. In 24 patients probabilsitic tracking and network reconstruction could be performed at all four time points. ??quality, ??missing imaging. In three subjects, network data were missing from the acute phase, networks from one subject each could not be obtained at three and twelve months after stroke, and from one subject at both those times.

1.1 Clinical data

1.1.1 Baseline demographics

Of the 30 stroke patients 12 were female, their age was 64.6667 +/- 12.4577 (mean +/- standard deviation). 16 (53.3333%, CI_{95} [34.6399, 71.2035]%) had a lesion in the left hemisphere; the infarct volume as measured by ZZ{>> Segmentation on FLAIR in first available scan? <<} ranged from 0.61 ml to 69.15 ml (median 3.38 ml, IQR [1.72, 16.48] ml). The lesions were predominantly subcortical, involving the centrum ovale, the corona radiata and the internal capsule (Fig0). There was no statistically significant association of lesion volume with side of the lesion (d=-0.423, t_{27}=1.1329, p=0.2672); nor with age (β=-0.0237, t_{27}=-1.1151, p=0.2746) or sex of the patient (d=0.1153, t_{27}=-0.3014, p=0.7654).

Overall severity of stroke symptoms at initial presentation ranged from 0 to 13 on the NIH Stroke Scale (median 3, IQR [2,7]). Quasi-Poisson regressions indicated that patients with larger infarct volumes were affected more severely at the acute ($p_{3\text{-}5d}$=0.0359), but not the subacute or chronic stages. There was no effect of side of the lesion, nor age or sex of the patient on stroke severity.

Impairment in strength and dexterity of the affected hand were quantified in the acute phase as relative grip strength ranging from 0 to 1.12 (median 0.68, IQR [0.26, 0.83]) and Fugl-Meyer score ranging from 4 to 66 (median 56, IQR [32, 63]). In these motor specific outcome measures there was no statistically significant association with volume or side of the lesion, nor with age or sex of the patient.

1.1.2 Time course of symptom severity and motor function

Over the course of the study most patients improved clinically. The median NIHSS score, the ratio of grip strength in affected to unaffected hand, and FM score improved to 0 (IQR [0, 2.25]), 0.91 (IQR [0.82, 1.02]) and 66 (IQR [57.5, 66]) at 12 months follow-up, respectively (Fig1a). Growth curve analyses indicated statistical superiority of exponential models (AIC_{exp}^{NIHSS} = 490.217, AIC_{exp}^{FM} = 877.1913, AIC_{exp}^{GS} = -17.1655) over linear fits (AIC_{lin}^{NIHSS} = 524.1948, AIC_{lin}^{FM} = 905.2152, AIC_{lin}^{GS} = 10.6629) for each of the three outcome variables (Tab1b).

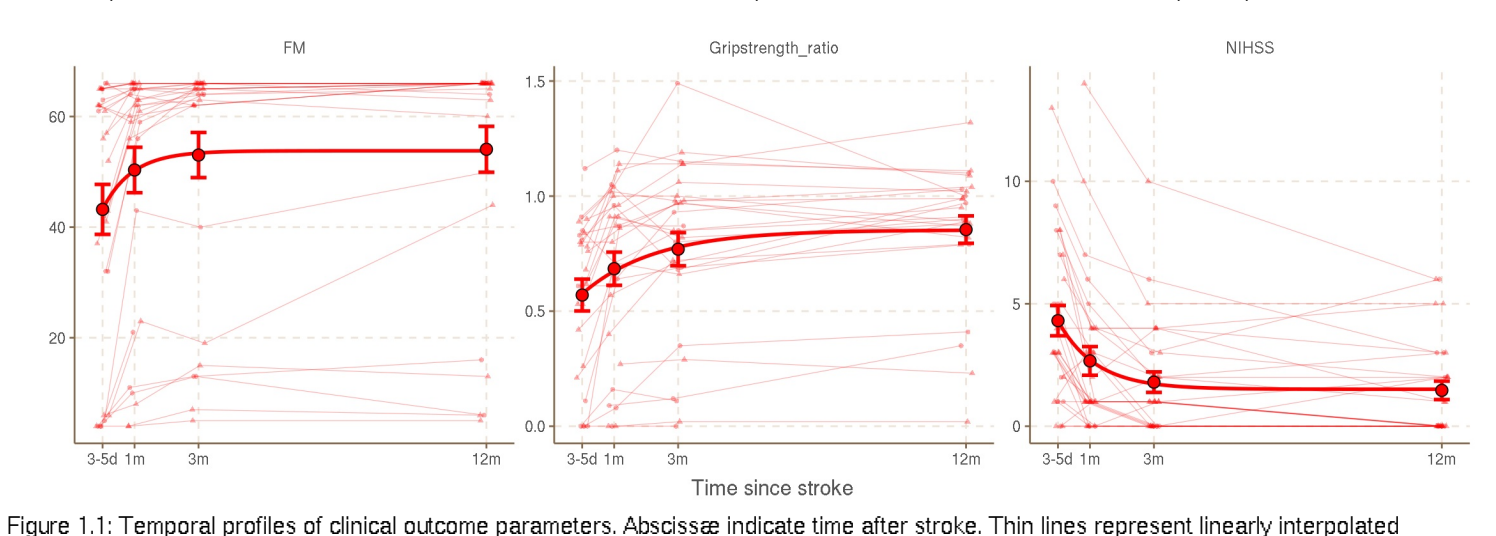

Figure 1.1: Temporal profiles of clinical outcome parameters. Abscissæ indicate time after stroke. Thin lines represent linearly interpolated profiles for individual patients. Circles and bars denote cross sectional means and asymptotic standard errors, respectively. Thick lines visualise the non-linear model $\mathrm{Outcome}_t \sim a + \Delta(1 - \exp(-b\,t))$.

term	FM	Gripstrength_ratio	NIHSS
a	41.69 +/- 4.22, p=1.0580e-15	0.48 +/- 0.07, p=3.2590e-09	4.55 +/- 0.52, p=1.7530e-13
b	5.09 +/- 21.09, p=8.0980e-01	1.04 +/- 0.33, p=2.5160e-03	1.20 +/- 0.34, p=6.9990e-04
del	10.86 +/- 1.43, p=3.9830e-11	0.29 +/- 0.04, p=8.7120e-12	-3.03 +/- 0.32, p=6.0310e-15

Model parameters (estimate +/- standard error) a, b, Δ obtained from fitting the exponential model (1) to temporal profiles of clinical outcome parameters. Standard errors and p-values result from non-linear mixed-effects regressions fit using the R package nlme.

1.2 Network properties

Mean network density, i.e. the proportion of non-zero connections, was (95.6 +/- 1.8) % with no significant differences between left and right hemispheres or between time points.

1.2.1 Effects of time and lesion status

1.2.1.1 Numerical global connectivity

Analysis of numerical measures of intrahemispheric connectivity revealed that, based on the Akaike information criterion (AIC), the time course of median edge weight was better described by an exponential than a linear model (AIC_{exp} = -1038.3179, AIC_{lin} = -992.1659). The temporal profiles of q_{50} did not differ significantly between ipsi- and contralesional hemispheres with a trend towards larger decline in stroke hemispheres (Δ_{relpos}=-0.006 +/- 0.0038, p=0.1122). Subgroup modelling showed a significant exponential decline of median edge weight in stroke hemispheres (Δ=-0.0076 +/- 0.0037, p=0.0426; AIC_{exp} = -544.1233, AIC_{lin} = -522.9882), but did not reveal a significant effect of time on connectivity in contralesional hemispheres (Δ=-0.0038 +/- 0.0045, p=0.3932; AIC_{exp} = -509.16, AIC_{lin} = -486.6726).

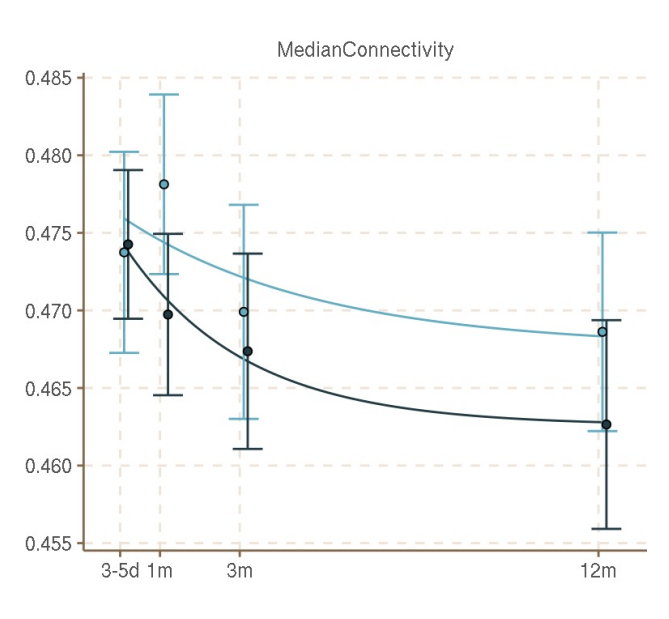

Figure 1.2: Temporal profile of numerical intrahemispheric connectivity in ipsilesional (orange) and contralesional (red) hemispheres. Abscissæ indicate time after stroke. Circles and bars represent crosssectional means and standard errors, respectively. Thick lines visualise modelled exponential decline.

```
temp
```

term	MedianConnectivity
a	0.47 +/- 0.01, p=0.0000
b	1.01 +/- 1.39, p=0.4674
del.(Intercept)	-0.00 +/- 0.00, p=0.4975
del.relposipsi	-0.01 +/- 0.00, p=0.1122
AIC_exp	-1038.31785386872
AIC_lin	-992.165933477689

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of intrahemispheric median connectivity. The model parameter of structural decline, Δ, was allowed to vary between stroke and intact hemispheres. Standard errors and p-values result from joint non-linear mixed-effects regressions fit using the R package nlme.

term	contra	ipsi
a	0.47 +/- 0.01, p=0.0000	0.47 +/- 0.01, p=0.0000
b	1.02 +/- 3.01, p=0.7361	1.01 +/- 1.24, p=0.4186
del	-0.00 +/- 0.00, p=0.3932	-0.01 +/- 0.00, p=0.0426
AIC_exp	-509.159997928263	-544.123275316186
AIC_lin	-486.672600664215	-522.988242991055

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of intrahemispheric median connectivity. Standard errors and p-values result from non-linear mixed-effects regressions fit separately for stroke and intact hemispheres using the R package nlme.

1.2.1.2 Global network architecture

Growth curve analysis of whole-brain global graph parameters using non-linear mixed-effects regression modelling revealed consistent effects of time (Tab2). Global efficiency declined exponentially over time in stroke but not intact hemispheres. Modularity increased significantly in both stroke and intact hemispheres, with a numerically larger effect ipsilesionally. These effects were not sensitive to the choice of network density and persisted over a wide range of thresholds (Supplement). Inclusion of age and sex as nuisance regressors did not qualitatively change the results (not shown).

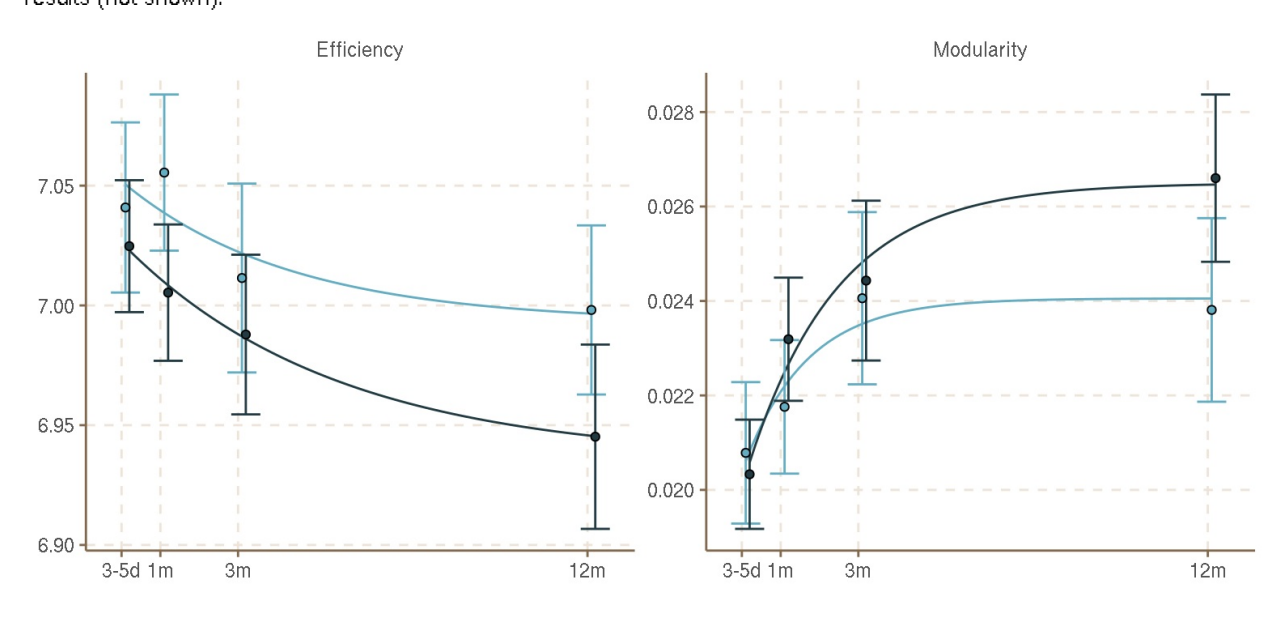

Figure 1.3: Temporal profile of intrahemispheric global graph parameters in ipsilesional (orange) and contralesional (red) hemispheres. Abscissæ indicate time after stroke. Circles and bars represent crosssectional means and standard errors, respectively. Thick lines visualise modelled exponential change.

term	Efficiency	Modularity
a	7.02 +/- 0.03, p=0.0000	0.02 +/- 0.00, p=0.0000
b	1.09 +/- 1.11, p=0.3272	1.00 +/- 0.59, p=0.0952
del.(Intercept)	-0.02 +/- 0.02, p=0.4101	0.00 +/- 0.00, p=0.0045
del.relposipsi	-0.05 +/- 0.02, p=0.0215	0.00 +/- 0.00, p=0.0663
AIC_exp	-274.46084482183	-1639.76192812281
AIC_lin	-243.666733881391	-1579.08011746238

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of intrahemispheric global graph parameters. The model parameter of topological change, Δ, was allowed to vary between stroke and intact hemispheres. Standard errors and p-values result from joint non-linear mixed-effects regressions fit using the R package nlme.

term	Efficiency_contra	Efficiency_ipsi	Modularity_contra	Modularity_ipsi
a	7.04 +/- 0.04, p=0.0000	7.01 +/- 0.03, p=0.0000	0.02 +/- 0.00, p=0.0000	0.02 +/- 0.00, p=0.0000
b	1.10 +/- 1.91, p=0.5683	1.09 +/- 1.07, p=0.3117	1.00 +/- 0.96, p=0.2994	1.00 +/- 0.54, p=0.0668
del	-0.03 +/- 0.02, p=0.1465	-0.05 +/- 0.02, p=0.0110	0.00 +/- 0.00, p=0.0098	0.00 +/- 0.00, p=0.0000
AIC_exp	-145.546032083443	-165.874415747312	-809.100746315999	-846.718213579506
AIC_lin	-130.021863523311	-152.877296189649	-779.745141510454	-819.099074049463

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of intrahemispheric global graph parameters. Standard errors and p-values result from non-linear mixed-effects regressions fit separately for stroke and intact hemispheres using the R package nlme.

Both global efficiency and modularity were correlated strongly with median connectivity strength. After correcting for median connectivity strength using a two-stage approach to regress global graph parameters against subject-specific median connectivity predictions from a non-linear mixed-effects regression of q_{50} against time (reported in Tab SXX), a significant positive effect of time on ipsilesional modularity persisted, which was most pronounced at small predicted connectivities. There was no additional effect of time on global efficiency or contralesional global graph parameters.

1.2.1.3 Local network changes

Non-linear mixed effects modelling with an exponential effect of time revealed significant changes in the time course of local graph parameters between ipsi- and contralesional hemispheres in a total of 8 brain regions, see Tab 1.4. The lentiform nucleus was excluded from the mass-univariate analysis because it was contained in or had significant overlap with the ischemic lesion. Local network architecture was disrupted in the acute stage, as indicated by a significant effect of lesion status on the model parameter a, in the pre- and postcentral, lateralorbitofrontal and inferior frontal (partes orbitalis and triangularis) gyri as well as the lentiform nucleus. The change of local network integrity over the study period (model parameter Δ) was localised to the ipsilesional rostral and caudal anterior cingulate cortices. Ipsilesionally, significant decline in local network measures over time was detected in more widespread brain areas, including regions of frontal, temporal and parietal lobes as well as the thalamus.

FigSX in the supplement displays the time course of local connectivity measures of the those regions in stroke and intact hemispheres. Consistent with the global analysis, changes occurred predominantly in the hyperacute phase until three months post stroke with little further decline beyond that time in any ROI.

node	term	clustering	efficiency	strength
lentiform	a.relposcontra	0.22 +/- 0.07, p=0.0020	0.24 +/- 0.06, p=0.0002	14.01 +/- 3.59, p=0.0001
	del.relposcontra	-0.16 +/- 0.09, p=0.0665	-0.21 +/- 0.08, p=0.0075	-13.85 +/- 4.26, p=0.0014
lateralorbitofrontal	a.relposcontra	0.08 +/- 0.04, p=0.0428	0.09 +/- 0.03, p=0.0035	4.44 +/- 1.38, p=0.0015
	del.relposcontra	0.03 +/- 0.05, p=0.5907	-0.01 +/- 0.04, p=0.8390	-1.27 +/- 8.77, p=0.8852
parsorbitalis	a.relposcontra	0.10 +/- 0.04, p=0.0108	0.10 +/- 0.04, p=0.0055	
	del.relposcontra	0.01 +/- 0.05, p=0.8265	-0.01 +/- 0.05, p=0.8555	
rostralanteriorcingulate	a.relposcontra	-0.06 +/- 0.04, p=0.2002	-0.05 +/- 0.04, p=0.2229	-4.08 +/- 2.35, p=0.0836
	del.relposcontra	0.12 +/- 0.06, p=0.0280	0.10 +/- 0.05, p=0.0473	7.66 +/- 2.82, p=0.0072
parstriangularis	a.relposcontra	0.08 +/- 0.04, p=0.0398	0.08 +/- 0.03, p=0.0196	
	del.relposcontra	0.01 +/- 0.05, p=0.8372	-0.00 +/- 0.04, p=0.9587	
postcentral	a.relposcontra		0.07 +/- 0.03, p=0.0197	4.01 +/- 1.81, p=0.0276
	del.relposcontra		0.03 +/- 0.04, p=0.4410	1.10 +/- 2.16, p=0.6124
precentral	a.relposcontra		0.07 +/- 0.03, p=0.0267	
	del.relposcontra		0.04 +/- 0.04, p=0.2746	
caudalanteriorcingulate	a.relposcontra			-0.59 +/- 1.76, p=0.7364
	del.relposcontra			4.33 +/- 2.09, p=0.0399

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of local graph measures in individual ROIs. The intercept a and total change Δ were allowed to vary between stroke and intact hemispheres. Standard errors and p-values result from non-linear mixed-effects regressions fit jointly for stroke and intact hemispheres using the R package nlme. ROIs with a comparable temporal profile of all three local graph measures ipsi- and contralesionally are not shown.

node	term	clustering	efficiency	strength
thalamus	del	-0.09 +/- 0.03, p=0.0012	-0.06 +/- 0.02, p=0.0009	-2.87 +/- 0.71, p=0.0001
superiorfrontal	del	-0.07 +/- 0.03, p=0.0193	-0.05 +/- 0.02, p=0.0070	-3.31 +/- 0.85, p=0.0002
lentiform	del	0.16 +/- 0.06, p=0.0124	0.20 +/- 0.06, p=0.0012	12.95 +/- 3.54, p=0.0005
rostralanteriorcingulate	del	-0.09 +/- 0.03, p=0.0069	-0.08 +/- 0.03, p=0.0115	-6.30 +/- 1.78, p=0.0007
caudalanteriorcingulate	del	-0.10 +/- 0.03, p=0.0031	-0.08 +/- 0.03, p=0.0035	-4.42 +/- 1.27, p=0.0008
parsopercularis	del			-5.33 +/- 1.75, p=0.0032
postcentral	del	-0.07 +/- 0.02, p=0.0054	-0.05 +/- 0.02, p=0.0343	
bankssts	del	-0.06 +/- 0.02, p=0.0061	-0.04 +/- 0.02, p=0.0343	
parsorbitalis	del			-4.96 +/- 1.80, p=0.0072
precentral	del	-0.07 +/- 0.03, p=0.0091	-0.05 +/- 0.02, p=0.0216	-2.76 +/- 1.18, p=0.0224
middletemporal	del	-0.08 +/- 0.03, p=0.0114	-0.05 +/- 0.02, p=0.0376	
temporalpole	del	-0.09 +/- 0.04, p=0.0260	-0.08 +/- 0.04, p=0.0406	-5.49 +/- 2.15, p=0.0123
parstriangularis	del	-0.08 +/- 0.03, p=0.0125	-0.06 +/- 0.03, p=0.0284	
pericalcarine	del			-7.14 +/- 2.83, p=0.0137
posteriorcingulate	del	-0.08 +/- 0.03, p=0.0163	-0.06 +/- 0.03, p=0.0325	
paracentral	del	-0.08 +/- 0.03, p=0.0181	-0.06 +/- 0.03, p=0.0443	
supramarginal	del	-0.06 +/- 0.03, p=0.0254		
insula	del	-0.06 +/- 0.03, p=0.0298		
superiorparietal	del	-0.06 +/- 0.03, p=0.0331		
cuneus	del	-0.07 +/- 0.03, p=0.0375		
superiortemporal	del	-0.06 +/- 0.03, p=0.0401		

Model parameter Δ (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of ipsilesional local graph measures in individual ROIs. Standard errors and p-values result from non-linear mixed-effects regressions fit using the R package nlme. ROIs without significant change over time in any of the three local graph parameters are now shown.

1.2.2 Association with lesion volume

1.2.2.1 Numerical connectivity and GGPs

Non-linear-mixed effects modelling revealed a significant positive association between lesion volume and global connectivity decline in ipsilesional but not contralesional hemispheres. This effect did not depend on age or sex of the patient, nor on the side of the lesion. Specifically, the largest decline in ipsilesional median connectivity over time was observed in patients with the largest stroke lesions, while there was no significant decline in patients with very small lesions. Orthogonally, median connectivity in stroke hemispheres did not depend on lesion volume in the acute phase, but a significant negative association was observed at all three later time points. Similar effects were observed for global graph parameters. Specifically, larger lesion volumes were associated with a larger decline in ipsilesional global efficiency, as well as a larger increase in ipsilesional modularity. Ipsilesional measures of network topology were associated with lesion volume in the subacute and chronic, but not the acute phase. There was no evidence of a relationship between size of the infarct and contralesional network metrics.

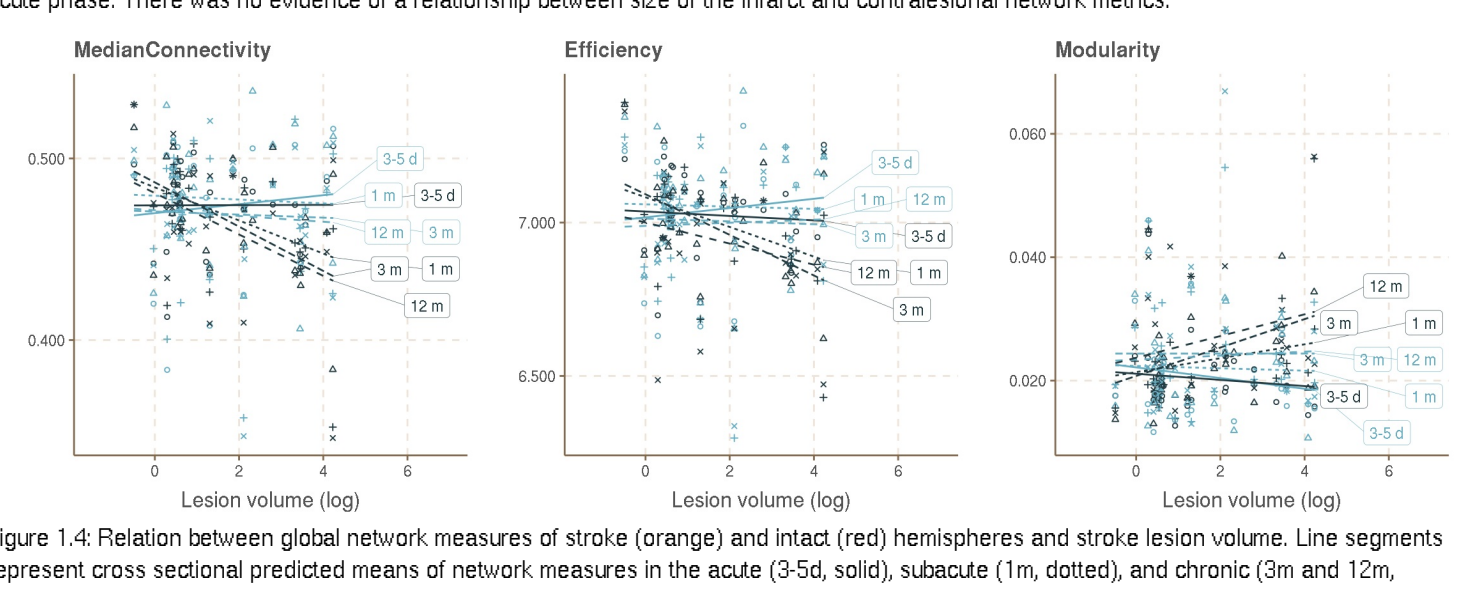

Figure 1.4: Relation between global network measures of stroke (orange) and intact (red) hemispheres and stroke lesion volume. Line segments represent cross sectional predicted means of network measures in the acute (3-5d, solid), subacute (1m, dotted), and chronic (3m and 12m, dashed) stage.

term	MedianConnectivity	Efficiency	Modularity
a	4.73e-01 +/- 5.29e-03, p=6.62e-155	7.03e+00 +/- 3.02e-02, p=2.16e-231	2.09e-02 +/- 1.39e-03, p=3.67e-34
b	1.05e+00 +/- 7.36e-01, p=1.54e-01	1.16e+00 +/- 8.85e-01, p=1.92e-01	6.04e-01 +/- 2.93e-01, p=4.03e-02
del.(Intercept)	-2.42e-03 +/- 5.44e-03, p=6.57e-01	-2.49e-02 +/- 2.97e-02, p=4.03e-01	2.80e-03 +/- 1.57e-03, p=7.60e-02
del.logvol	4.58e-04 +/- 2.50e-03, p=8.55e-01	8.63e-03 +/- 1.37e-02, p=5.29e-01	2.01e-04 +/- 7.14e-04, p=7.79e-01
del.logvol:relposipsi	-1.11e-02 +/- 2.67e-03, p=4.90e-05	-5.41e-02 +/- 1.42e-02, p=1.88e-04	2.09e-03 +/- 7.48e-04, p=5.80e-03
del.relposipsi	1.18e-02 +/- 5.32e-03, p=2.74e-02	4.29e-02 +/- 2.83e-02, p=1.30e-01	-1.69e-03 +/- 1.57e-03, p=2.85e-01

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of median connectivity and global graph masures. Total change Δ is modelled as a linear function of log lesion volume, both intercept and slope are allowed to vary between stroke und intact hemispheres. Standard errors and p-values result from non-linear mixed-effects regressions fit using the R package nlme.

term	Efficiency_contra	Efficiency_ipsi	MedianConnectivity_contra	MedianConnectivity_ipsi	Modularity_contra	Modularity_ipsi
a	7.04e+00 +/- 3.61e-02 p=1.36e-106	7.01e+00 +/- 3.10e-02 p=1.14e-111	4.73e-01 +/- 6.46e-03 p=1.20e-73	4.71e-01 +/- 5.36e-03 p=8.29e-80	2.08e-02 +/- 1.68e-03 p=3.93e-20	2.13e-02 +/- 1.48e-03 p=1.27e-23
b	1.09e+00 +/- 1.94e+00 p=5.75e-01	1.09e+00 +/- 7.87e-01 p=1.70e-01	1.02e+00 +/- 3.00e+00 p=7.36e-01	1.01e+00 +/- 5.99e-01 p=9.62e-02	9.99e-01 +/- 9.60e-01 p=3.01e-01	9.96e-01 +/- 4.55e-01 p=3.15e-02
del.(Intercept)	-2.69e-02 +/- 3.06e-02 p=3.83e-01	1.59e-03 +/- 2.78e-02 p=9.55e-01	-1.90e-03 +/- 6.38e-03 p=7.66e-01	6.97e-03 +/- 5.07e-03 p=1.73e-01	2.30e-03 +/- 1.69e-03 p=1.78e-01	1.67e-03 +/- 1.35e-03 p=2.21e-01
del.logvol	-2.53e-03 +/- 1.39e-02 p=8.57e-01	-3.30e-02 +/- 1.27e-02 p=1.15e-02	-1.07e-03 +/- 2.87e-03 p=7.09e-01	-9.21e-03 +/- 2.32e-03 p=1.61e-04	5.16e-04 +/- 7.54e-04 p=4.96e-01	1.84e-03 +/- 6.17e-04 p=3.83e-03

Model parameters (estimate +/- standard error) obtained from fitting the exponential model (1) to temporal profiles of ipsilesional median connectivity and global graph masures. Standard errors and p-values result from non-linear mixed-effects regressions fit using the R package nlme.

1.2.2.2 Local graph measures

The effect of lesion volume on local network change differed between stroke and intact hemispheres in 23 ROIs. Ipsilesional decline of local network measures strength, efficiency and clustering was associated with lesion volume in the same 23 brain regions concentrating in the territory of the middle cerebral artery. No such association was observed in any contralesional ROI. Details are provided in the supplement.

1.2.3 Association with clinical variables

1.2.3.1 Global network measures

Two-stage regressions revealed a significant association between decline of ipsilesional median connectivity until one, three and twelve months and the clinical outcome parameters NIHSS score (p=0.0042), FM score (p=8e-04), and relative grip strength (p=7e-04) at these time points. Similarly, loss of global efficiency and gain of global modularity in stroke hemispheres was associated with higher NIHSS scores (p_{Eff}=0.0056, p_{Mod}=0.0022) as well as lower FM score (p_{Eff}=0.0139, p_{Mod}=0.0045) and grip strength (p_{Eff}=0.0126, p_{Mod}=0.0265).

clin.meas.name	Efficiency	Modularity	MedianConnectivity	Efficiency_1	Efficiency_12	Efficiency_3	MedianConnectivity_1	MedianConnectivity_12	MedianConnectivity_3	Modularity_1	Modularity_12	Modularity_3
FM	-5.98 +/- 2.37 p=0.0139	191.07 +/- 65.26 p=0.0045	-41.46 +/- 11.81 p=0.0008	-3.57 +/- 2.59 p=0.1802	-3.28 +/- 2.83 p=0.2575	-4.20 +/- 3.14 p=0.1942	-23.00 +/- 15.05 p=0.1390	-29.00 +/- 15.16 p=0.0684	-26.77 +/- 16.45 p=0.1173	42.27 +/- 69.31 p=0.5475	101.71 +/- 56.15 p=0.0831	140.90 +/- 71.27 p=0.0602
Gripstrength_ratio	1.45 +/- 0.56 p=0.0126	-39.44 +/- 17.39 p=0.0265	8.63 +/- 2.42 p=0.0007	1.41 +/- 0.68 p=0.0503	0.54 +/- 0.56 p=0.3495	0.99 +/- 0.70 p=0.1737	5.25 +/- 3.30 p=0.1247	5.24 +/- 2.61 p=0.0589	5.83 +/- 3.60 p=0.1207	-13.49 +/- 19.56 p=0.4971	-22.21 +/- 13.75 p=0.1219	-28.30 +/- 20.31 p=0.1781
NIHSS	-5.16 +/- 1.81 p=0.0056	159.68 +/- 50.43 p=0.0022	-26.55 +/- 9.00 p=0.0042	-2.16 +/- 2.17 p=0.3304	-2.79 +/- 2.14 p=0.2051	-5.43 +/- 2.17 p=0.0198	-9.16 +/- 11.32 p=0.4259	-17.34 +/- 11.25 p=0.1368	-28.23 +/- 12.05 p=0.0282	41.80 +/- 56.76 p=0.4683	60.25 +/- 46.97 p=0.2124	174.60 +/- 44.64 p=0.0007

Regression coefficients (estimate +/- standard error) on the link scale between change in global network measures and clinical outcome. In the case of FM and NIHSS scores, quasi-Poisson regressions with a $\log$-link are used; in the case of relative grip strength a Gaussian regression with identity link is used. The first three columns represent pooled estimates from joint two-stage regressions across the subacute and chronic stages.

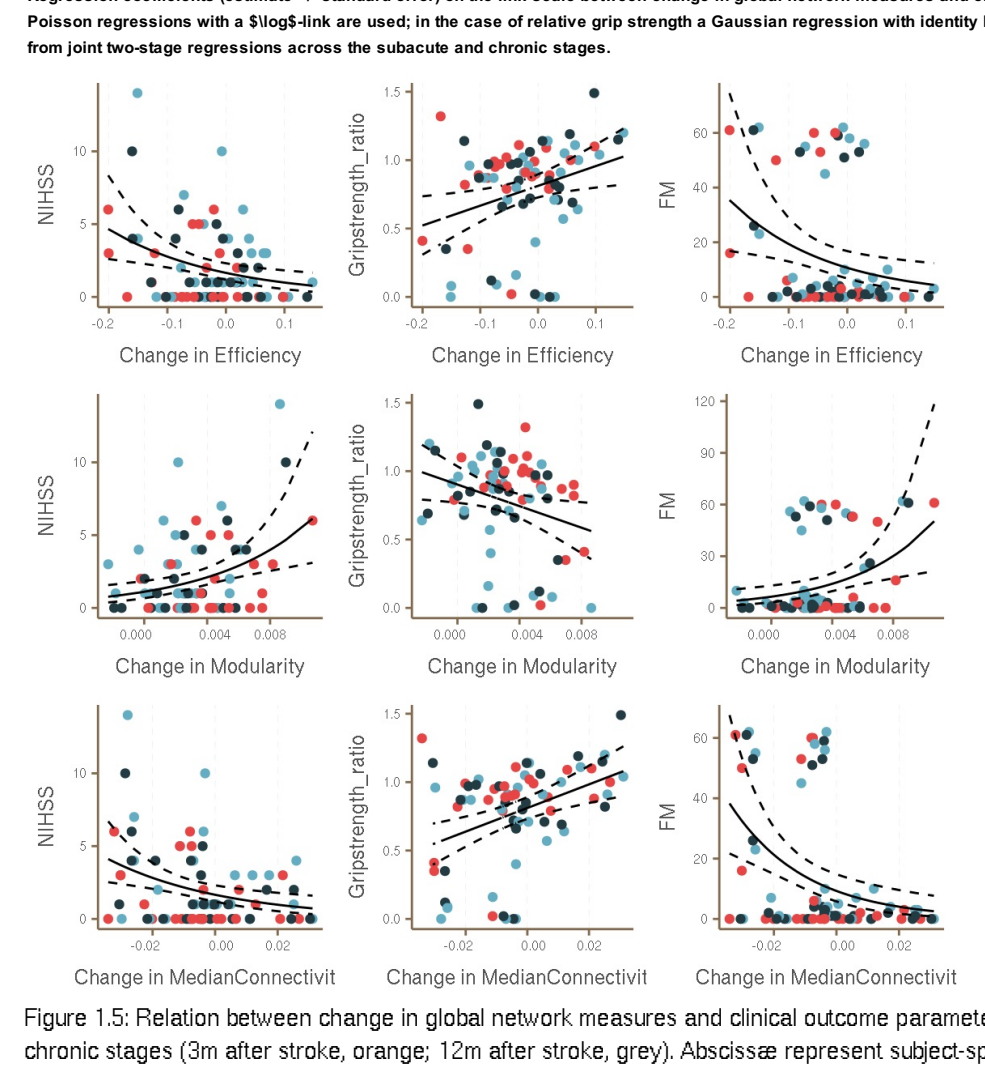

Figure 1.5: Relation between change in global network measures and clinical outcome parameters in the subacute (3-5d after stroke, red) and chronic stages (3m after stroke, orange; 12m after stroke, grey). Abscissæ represent subject-specific predictions of network change from a linear random-intercept model. Solid lines indicate predicted mean clinical outcome under a quasi-Poisson (NIHSS, FM) or Gaussian (grip strength) model. Dashed lines represent upper und lower 95% confidence band for the predicted mean.

After including lesion volume as a nuisance regressor, the associations of change in global network architecture and NIHSS and FM scores persisted at a lower statistical siginificance. The relationship between global topology and relative grip strength failed to maintain statistical significance.

clin.meas.name	Efficiency	Modularity	MedianConnectivity	Efficiency_1	Efficiency_12	Efficiency_3	MedianConnectivity_1	MedianConnectivity_12	MedianConnectivity_3	Modularity_1	Modularity_12	Modularity_3
FM	-5.19 +/- 2.61 p=0.0504	180.02 +/- 81.49 p=0.0303	-36.73 +/- 13.22 p=0.0069	-2.29 +/- 2.72 p=0.4083	-3.09 +/- 2.84 p=0.2886	-2.62 +/- 3.61 p=0.4751	-17.40 +/- 15.79 p=0.2814	-26.29 +/- 16.53 p=0.1259	-19.11 +/- 18.98 p=0.3251	-4.03 +/- 70.27 p=0.9548	91.11 +/- 60.57 p=0.1468	105.83 +/- 90.11 p=0.2528
Gripstrength_ratio	1.18 +/- 0.59 p=0.0485	-29.93 +/- 20.99 p=0.1585	6.24 +/- 2.65 p=0.0218	1.06 +/- 0.73 p=0.1567	0.44 +/- 0.52 p=0.4094	0.45 +/- 0.78 p=0.5691	3.53 +/- 3.43 p=0.3139	3.24 +/- 2.82 p=0.2654	3.17 +/- 4.09 p=0.4472	1.02 +/- 20.55 p=0.9610	-12.81 +/- 14.04 p=0.3729	-9.41 +/- 24.30 p=0.7028
NIHSS	-5.14 +/- 1.94 p=0.0100	178.00 +/- 60.61 p=0.0044	-21.68 +/- 10.11 p=0.0354	-1.25 +/- 2.36 p=0.5998	-2.60 +/- 2.17 p=0.2446	-4.16 +/- 2.49 p=0.1092	-4.81 +/- 12.14 p=0.6956	-13.20 +/- 12.75 p=0.3120	-20.70 +/- 13.94 p=0.1517	11.98 +/- 61.47 p=0.8471	44.01 +/- 52.64 p=0.4121	157.38 +/- 58.34 p=0.0132

Regression coefficients (estimate +/- standard error) on the link scale between change in global network measures and clinical outcome. Log lesion volume is included as a nuisance predictor. In the case of FM and NIHSS scores, quasi-Poisson regressions with a $\log$-link are used; in the case of relative grip strength a Gaussian regression with identity link is used. The first three columns represent pooled estimates from joint two-stage regressions across the subacute and chronic stages.

Post-hoc tests for associations between decline of connectivity and clinical outcome at fixed time points revealed consistent effects that were strongest after three months, but did not, indivdiually, reach statistical signifiance (see Supplement).

1.2.3.2 Local graph measures

Mass-univariate two-stage linear and quasi-Poisson regressions identified associations between clinical outcome and change in local connectivity (strength) in a total of 14 brain areas. Higher residual NIHSS scores were most strongly associated with connectivity decline in pre-/paracental, inferior frontal, middle-/superior temporal gyri, as well as the thalamus, posterior cingulum and visual areas (cuneus, pericalcarine gyrus). Statistical details including lesion volume corrected regression results are provided in the Supplement.