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Intrinsic functional brain connectivity is resilient to chronic hypoperfusion caused by unilateral carotid artery stenosis

Felix Fischer [a,*], Caroline Malherbe [a,b], Eckhard Schlemm [a], Julian Schröder [a], Marlene Heinze [a], Bastian Cheng [a], Maximilian Schulz [a], Jens Fiehler [c], Axel Larena-Avellaneda [d], Christian Gerloff [a], Götz Thomalla [a]

[a] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[b] Institute of Computational Neuroscience, University Medical Center Hamburg Eppendorf, Hamburg, Germany
[c] Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[d] Department of Vascular Medicine, Asklepios Klinik Altona, Hamburg, Germany

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ABSTRACT

Introduction: Chronic cerebral hypoperfusion caused by asymptomatic high-grade stenosis of the internal carotid artery (ICA) has been associated with impaired cognitive function. Only few studies exist on underlying changes of functional connectivity (FC).

Methods: 20 patients with unilateral high-grade ICA stenosis without MRI lesions and 25 aged-match controls underwent resting-state functional MRI (rsfMRI) and neuropsychological assessment. Patients were examined within ten days before and 6–10 weeks after surgical or interventional revascularization of carotid stenosis. We examined mean resting-state FC ipsi- and contralateral to stenosis and network topology using graph-theoretical measures.

Results: At baseline, intrahemispheric FC was similar for patients and healthy controls. After revascularization mean FC increased moderately without an effect on network topology. Patients performed worse in TMT B and Stroop test, while performance in global screening tests for dementia (Mini Mental Status Examination, DemTect) were comparable. Test results did not improve after revascularization.

Conclusion: In our study population, we find no effect of chronic hypoperfusion on FC and global cognitive function, although we observe minor impairments in processing speed and mental flexibility. The subtle increase of FC after revascularization could indicate excessive upregulation after restoration of perfusion. However, it might as well be a coincidental finding due to the limited sample size.

1. Introduction

Asymptomatic high-grade (>60%) stenosis of the internal carotid artery (ICA) is associated with an increased risk of stroke in the supplied vascular territory, which can be reduced by revascularization of the stenosis (Study EC for the ACA, 1995; Halliday et al., 2010). This can be achieved by surgical treatment with carotid endarterectomy (CEA) and interventional treatment with carotid artery stenting (CAS) (Brott et al. 2010; Rosenfield et al. 2016). Besides an increased risk of stroke, several studies have described an association of asymptomatic ICA stenosis with subtle cognitive impairment (Mathiesen et al. 2004; Romero et al. 2009; Lal et al. 2017). A reversibility of these changes after revascularization would support a direct causal link to the stenosis. However, data on effects of revascularization of ICA stenosis on cognitive function are contradictory. Some studies report an improvement of cognitive performance after revascularization, while others do not observe this effect or even describe a decline of neuropsychological test results (Norling et al. 2019).

The notion that ICA stenosis is associated with reduced cognitive performance raises the question whether this is the result of local or global hypoperfusion-induced changes in functional neural networks. Resting-state functional MRI (rsfMRI), which estimates functional connectivity (FC) between brain areas as the correlation of their blood-oxygen-level-dependent (BOLD) signals, provides the option to examine functional networks without focusing on changes related to a specific task. The classic approach to rsfMRI is the analysis of FC changes

* Corresponding author at: Department of Neurology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany.
E-mail address: f.fischer@uke.de (F. Fischer).

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within and between segregated rsfMRI-networks such as default-mode network or dorsal attention network (Fox and Raichle 2007). An alternative approach is the characterization of various aspects of functional networks architecture using graph-theoretical measures (Sporns et al. 2004; Rubinov and Sporns 2010). Until now, only few rsfMRI studies have been conducted in patients with unilateral high-grade ICA stenosis. These obtained heterogeneous findings, which may result from different approaches of analysis and of inclusion or exclusion of patients with structural brain lesions. Reduced connection strength in different resting-state networks has been reported (Cheng et al. 2012; Avirame et al., 2014; Lin et al. 2014), as well as interhemispheric differences in graph-theoretical network architecture (Chang et al., 2016). One study re-examined patients after revascularization and observed an increase of FC for some connections (Cheng et al. 2012).

Here, we analyze rsfMRI connectivity and cognitive performance in patients with unilateral high-grade ICA stenosis without MRI lesions before and after revascularization. A previous analysis of brain perfusion in the same study population showed hypoperfusion in the middle cerebral artery (MCA) boarder zone ipsilateral to carotid stenosis which normalized after revascularization (Schröder et al. 2019).

2. Methods

2.1. Subjects

Patients aged 50 years and older with high-grade unilateral stenosis of the internal carotid arteria (≥70% according to NASCET criteria (Moneta et al. 1993; Staikov et al. 2002)) without structural brain lesions other than minimal leukoaraiosis on cranial MRI were prospectively included before they underwent interventional or operative treatment of the stenosis at the University Medical Center Hamburg-Eppendorf, Germany. For each patient, the treatment decision was made in an interdisciplinary board meeting (Rimmele et al. 2017). Further inclusion criteria were lacking history of stroke, no history of dementia or depression, and lack of significant neurological symptoms and disability. Patients with severe systemic or neuropsychiatric disease and history of cognitive impairment were excluded. The control group consisted of age-matched healthy subjects without any history of neurological or psychiatric disease.

2.2. Neuropsychological assessment

Patients underwent cognitive testing within ten days before and 6 to 10 weeks after revascularization of the stenosis. Global cognitive performance was examined by Mini-Mental State Examination (MMSE) and DemTect. MMSE has a maximum score of 30, values of 24 or more indicate normal cognition (Folstein et al. 1975). The DemTect is a screening test to detect mild cognitive impairment in early stages of dementia including a word list with immediate and delayed recall, a number transcoding task, a word fluency task and the reverse repetition of a digit span. A maximum of 18 points can be achieved, values above 13 points indicate normal cognitive performance (Kalbe et al. 2004). Additionally, subjects performed the Trail Making Test (TMT), which provides a measure of psychomotor speed, visuospatial search and target-directed motor tracking (TMT A) and additionally of set-switching (TMT B) (Bowie and Harvey 2006), and the Stroop test (Stroop 1935) to assess selective attention and cognitive flexibility.

2.3. Magnetic resonance imaging

Structural MRI, resting-state fMRI and diffusion weighted images were acquired within ten days before and 6 to 10 weeks after revascularization of the stenosis on a 3 T Skyra MRI Scanner (Siemens, Erlangen, Germany). Sequence settings were as follows: T1 MPRage (flip angle = 9°, TR = 2500 ms, TE = 2.12 ms, slice thickness = 0.9 mm, inversion time 1100 ms, matrix = 232 × 288, FOV = 193 × 293 mm), T2 FLAIR (flip angle = 150°, TR = 9000 ms, TE = 90 ms, slice thickness = 5 mm, inversion time = 2500 ms, matrix = 320 × 270, FOV = 194 × 230 mm), resting-state (flip angle = 90°, TR = 2500 ms, TE = 25.0 ms, slice thickness = 3.0 mm, matrix = 94x94, FOV = 250x250 mm, 250 whole-brain volumes), diffusion weighted imaging with gradients (b = 1500 s/mm^2) applied along 64 non-collinear directions (TR = 10 000 ms, TE = 82 ms, slice thickness = 2 mm, FOV = 256 × 204 mm). After intervention, MRI scanning and cognitive testing were always performed on the same day.

2.4. MRI-preprocessing and functional network definition

Image analysis, network construction and graph-theoretical analysis was conducted using FSL (version 5.0.2.2), SPM12, the Brain Connectivity Toolbox (version 2017–15-01; Rubinov and Sporns 2010) and custom-build scripts using Matlab R2015a. We assessed whole-brain connectivity based on regions of interest (ROIs) of the Desikan-Killiany-Atlas as implemented in freesurfer (Desikan et al. 2006; Fischl 2012). For ROI definition, T1-images were scull-stripped, parceled into 80 cortical and subcortical regions of interest, white matter and cerebrospinal fluid (CSF) using freesurfer. The resulting ROIs where linearly registered on the mean fMRI image via a diffusion-weighted image. Because of overlapping susceptibility artifacts temporal pole, entorhinal cortex and frontal pole were excluded from the following analysis and subcortical ROIs were discarded. Thus, our whole-brain network consisted of 80 cortical ROIs.

rsfMRI data were analyzed as followed: The first four frames of resting state-fMRI data were discarded. Data were spatially realigned, slice-timing corrected and spatially smoothed with a 6 mm kernel. The mean signal of each ROI was extracted, corrected for motion parameters, deep white matter signal, CSF signal and mean global signal using multiple linear regression and band-pass filtered between 0.01 and 0.1 Hz. Thus, all image analysis was conducted in the individual subject space. To measure functional connectivity, Pearson linear correlation coefficient was calculated between the preprocessed mean fMRI signals of all pairs of ROIs. We used the absolute value of the correlation coefficient to determine FC. This resulted in an 80x80 connectivity matrix representing the functional connectome of the cortex of each subject.

2.5. Graph-theoretical analysis

Separately for the two hemispheres of each patient, we calculated mean FC and graph-theoretical measures of functional integration (global efficiency) and functional segregation (clustering coefficient, modularity).

In graph-theoretical analysis, the choice of the appropriate threshold for the connectivity matrix to separate weaker, potentially spurious correlations representing background noise from the stronger “true” connections of the network remains an unsolved problem. Furthermore, different approaches to the manner of thresholding itself exist. The most common methods are absolute thresholding, in which all connections below a defined threshold are discarded in all subjects, and proportional thresholding, in which a fixed proportion of weakest connections is discarded in every subject. We used proportional thresholding in our analysis, since this method equalizes between-subject differences in degree distribution and these differences are likely to have technical causes rather than represent true physiological differences between the subjects. Each graph-theoretical measure was analyzed across a range of proportional thresholds from 0 to 0.5. Specifically, a threshold of 0 means that all connections were considered, while a threshold of 0.5 removed the weaker fifty percent of the connections. For robustness, the analysis was repeated using absolute thresholding, which besides showing a higher variation of the parameters across subjects in both groups yielded similar results (data not shown). To access network characteristics independently from the influence of the degree distribution, each parameter was normalized by calculating the ratio to the

mean of 1000 randomized networks with identical degree-distribution.

2.6. Statistical analysis

Cognitive tests were compared between groups with a Wilcoxon rank sum test, within patients before and after revascularization with a signed rank tests and Bonferroni-Holm-corrected for multiple comparisons. Graph-theoretical parameters were assessed using a mixed-effects linear model. The fixed effects comprised *position relative to stenosis* (healthy/ipsilateral/contralateral), *side* (left/right), *age* and *sex*. In the comparison of subjects before and after treatment of the stenosis, an additional fixed effect *timepoint* was included. In all models, we included a random within-subject factor *ID* to account for the fact that the two hemispheres of a subject are not independent. Significant effects in the model were confirmed using a post-hoc Wilcoxon rank sum test. Statistical analysis was conducted in R (version 3.5.0).

3. Results

29 patients with high-grade unilateral stenosis of the internal carotid artery without lesions other than minimal leukoaraiosis on structural MRI, who presented to our hospital for treatment of the stenosis, were enrolled in the study. Of these, four did not complete the imaging due to withdrawal of consent, three were lost to follow-up and two were excluded from analysis due to poor image quality, leaving 20 patients in the analysis. Patients and 25 age-matched healthy subjects were examined with structural MRI, rsfMRI and neuropsychological testing. Patients were re-examined 6 to 10 weeks after successful treatment of the stenosis.

3.1. General sample characteristics and neuropsychological assessment

Mean age of patients was 65.6 ± 8.9 years, of healthy subjects 63.7 ± 8.4 years, with 7 women/13 men in the patient group and 9 women/16 men in the control group. Stenosis grade was 70–90% according to NASCET in 10 and ≥ 90% in 10 patients. The stenosis was located in the right ICA in 9 and in the left ICA in 11 patients. 15 patients were treated by endarterectomy, 5 by interventional stenting of the carotid artery.

All subjects underwent cognitive testing with MMSE, DemTect, TMT and Stroop-test. MMSE and DemTect showed values within the normal range in both groups, and no significant differences between groups were found. Patients performed worse in TMT B and Stroop-test than control subjects ($p < 0.05$ after Bonferoni-Holm-correction). There was no significant change in patients' performance in cognitive tests in the follow-up-examination after revascularization of the stenosis as compared to baseline (Table 1).

Table 1
General sample characteristics and neuropsychological assessment.

	Healthy subjects	Patients before treatment	p comparison to healthy subjects	Patients after treatment	p comparison to patients before treatment
Age (years)	63.68 ± 8.36	65.6 ± 8.9	0.583		
MMSE	28.48 ± 1.42	28.05 ± 1.61	0.366	28.17 ± 1.72	0.765
DemTect	17.4 ± 1.12	15.95 ± 2.58	0.018	16.11 ± 2.16	0.965
TMT A (s)	38.04 ± 11.68	42.21 ± 10.84	0.222	38.1 ± 8.36	0.354
TMT B (s)	88.92 ± 47.41	121.43 ± 66.71	**0.009***	109.02 ± 64.39	0.222
Stroop-Test (s)	37.53 ± 11.11	50.31 ± 11.44	**0.001***	49.93 ± 13.9	0.747

*p-values significant at $p = 0.05$ after Bonferoni-Holm-correction.

3.2. Functional connectivity

In order to assess possible effects of perfusion alterations on global FC, we analyzed FC in a whole-brain network based on the freesurfer ROIs using the Desikan-Killiany-Atlas. Calculation of Pearson linear correlation coefficient between each pair of ROIs after preprocessing resulted in the construction of an 80x80 connectivity matrix representing resting-state functional connectivity in the whole-brain network of each patient. Separately for the two hemispheres, we calculated mean FC and weighted graph-theoretical measures of functional integration (global efficiency) and functional segregation (clustering coefficient, modularity). Except mean FC, all parameters were normalized to the mean value of a set of randomized matrices with the same degree distribution. Parameters were assessed across a range of thresholds from 0 to 0.5.

We compared intrahemispheric connectivity of patients before treatment to that of healthy controls. There was no effect of position relative to stenosis (ipsilateral, contralateral or healthy) on mean FC or any of the network parameters (Fig. 1, Suppl. Fig. 1).

All patients underwent follow-up imaging 6–10 weeks after treatment of the stenosis. We calculated a mixed-effects linear model including, as the fixed effects, time-point before or after treatment of the stenosis, position relative to stenosis, side, age and sex as well as a random effect for the factor subject. Timepoint before/after revascularization had a significant effect on mean FC at all matrix thresholds ($p = 0.003$ for unthresholded matrix; Fig. 2A, Suppl. Fig. 2C). In the post-hoc Wilcoxon rank sum test, mean FC increased significantly after revascularization contralateral to stenosis (at threshold 0, $p = 0.035$, however this effect was not significant at higher matrix thresholds) and showed a trend towards increase ipsilateral to stenosis (at threshold 0, $p = 0.084$). An additional comparison of patients after intervention to healthy controls showed no effect of position relative to stenosis (ipsilateral, contralateral or healthy) on mean connectivity. There was no significant effect of timepoint before/after revascularization on any of the network parameters (Fig. 2B, Suppl. Fig. 2). Mean interhemispheric FC was similar between patients and controls at baseline and increased within the patient group after recanalization (at threshold 0, $p = 0.02$).

4. Discussion

We assessed effects of chronic hypoperfusion caused by unilateral carotid stenosis on resting-state FC and cognitive function in a population of carefully selected patients without brain lesions on structural MRI. A previous analysis of alterations of brain perfusion in a majority of the subjects showed hypoperfusion in the MCA boarder zone ipsilateral to carotid stenosis which normalized after revascularization (Schröder et al. 2019).

4.1. Neuropsychological results: Comparison to literature

While MMSE and DemTect showed no major cognitive deficit in patients, worse performance in TMT B and Stroop-Test indicated subtle deficits in processing speed and mental flexibility in patients. This is in line with previous data showing deficits in various cognitive domains in patients with ICA stenosis (e.g. Mathiesen et al. 2004; Romero et al. 2009; Lal et al. 2017, for an overview, Norling et al. 2019). Accordingly, the studies on resting state networks in ICA stenosis discussed below report in patients compared to controls worse performance for TMT (Avirame et al., 2014; Lin et al. 2014) and a variety of other cognitive tests (Avirame et al., 2014; Chang et al., 2016; Cheng et al., 2012; Lin et al., 2014).

Data on the reversibility of cognitive changes after revascularization of ICA stenosis are inconclusive. In line with our results, Cheng et al. 2012 report no improvement of cognitive function after recanalization. Results from some larger studies suggest that cognitive performance might improve after ICA revascularization (for an overview, see Norling

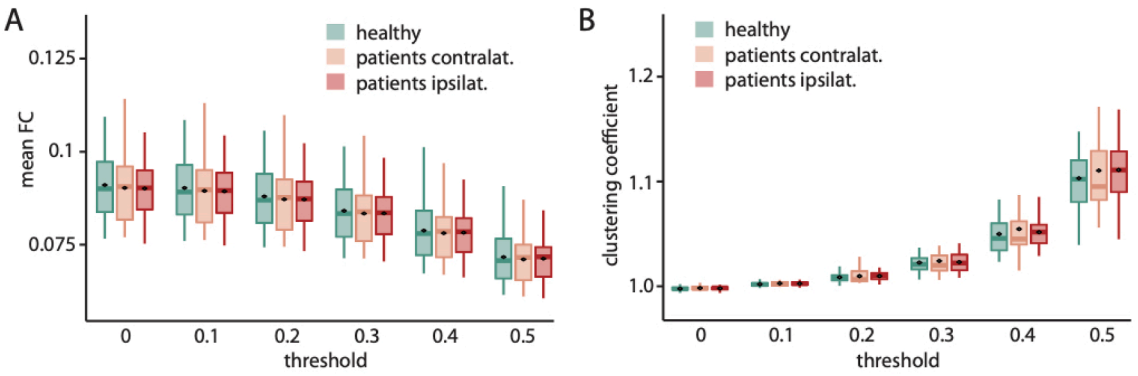

Fig. 1. Intrahemispheric mean FC (A) and clustering coefficient (B) of patients ipsi- and contralateral to stenosis at baseline in comparison to the mean value of healthy controls for network thresholds from 0 to 0.5. There was no significant difference between hemisphere ipsilateral to stenosis, hemisphere contralateral to stenosis and healthy controls (Supp. Fig. 1).

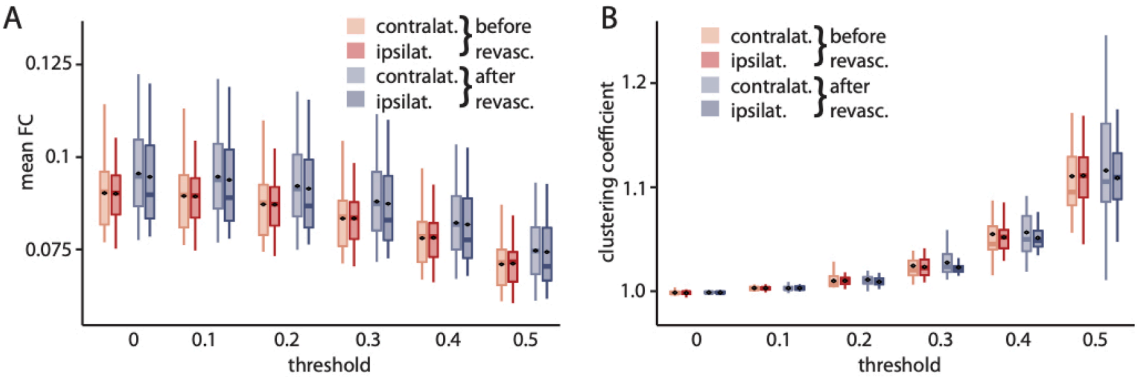

Fig. 2. Intrahemispheric mean FC (A) and clustering coefficient (B) of patients ipsi- and contralateral to stenosis at baseline and after revascularization for network thresholds from 0 to 0.5. Timepoint before and after revascularization showed a significant effect on mean FC. In the post-hoc-test, this effect was significant for network thresholds from 0 to 0.2 contralateral to stenosis and showed trend to significance ipsilateral to stenosis (Supp. Fig. 2).

et al. 2019). However, no randomized controlled trial has been completed to address this question. The currently ongoing CREST-2 (Howard et al. 2017) trial may improve our understanding of this matter. The follow-up period in our study may also have been too short to allow for recovery or improvement of cognitive function after revascularization of carotid stenosis.

If unilateral ICA stenosis directly causes cognitive impairment, this would presuppose a neurobiological mechanism by which hemodynamic changes lead to subtle impairment of neural function without causing other clinical signs or ischemic MRI lesions. In this case, the results of our neuropsychological assessment could be explained by the fact that regions responsible for performance of the TMT and the Stroop-test are especially vulnerable to perfusion changes by ICA stenosis. Indeed, task-related fMRI data on TMT suggest that, among others, parietal and motor association areas are activated during its performance (Varjacic et al. 2018). Since these areas are partly located in the media border zone, their subtle functional impairment by chronic hypoperfusion might be a possible explanation for the worse performance of subjects with ICA stenosis. Similarly, the areas activated during the Stroop task (e.g. Zysset et al. 2007) are partly located in the media boarder zone. Alternatively, worse cognitive performance could be an indirect effect of a higher degree of minor – MRI-negative – microstructural ischemic changes in the patient group. These questions await investigation by a task-related study.

4.2. Changes in functional connectivity

Before and after treatment of the stenosis, intrahemispheric FC was neither different between hemispheres ipsi- and contralateral to stenosis, nor between patients and controls. After treatment, we observed an increase of FC within patients. This effect was significant across thresholds from 0 to 0.2 contralateral to stenosis and in interhemispheric FC and showed a trend to significance ipsilateral to stenosis. If this represents a true physiological process, it would suggest a non-lateralized general effect on FC. However, it could as well just be a coincidental finding due to the limited sample size, especially since we do not observe a difference to the control group before or after intervention. An analysis of graph-theoretical parameters did not show any additional topological change.

Most previous studies on influence of unilateral ICA stenosis on FC focus on connectivity in the classic resting-state networks: the fronto-parietal network (FPN), the default-mode network (DMN) and the dorsal attention network (DAN). A study in 17 patients described reduced connectivity ipsilateral to the stenosis as well as interhemispheric connectivity in the FPN and bilaterally impaired connectivity in the DMN (Cheng et al. 2012). In 30 patients, of which 12 showed mild cognitive impairment, especially reduced long-range connections in DMN, DAN and FPN were reported (Lin et al. 2014). Another study focusing on DMN, FPN and DAN described reduced interhemispheric connectivity in these networks and a bilaterally reduced FC in some connections in patients. Some connections showed reduction of intrahemispheric FC ipsilateral to the stenosis in comparison to the contralateral hemisphere (Avirame et al., 2014). However, this study included mainly patients with unilateral ICA occlusion, which is likely to cause more severe perfusion changes and a higher risk of consecutive functional impairment than high-grade stenosis. To our knowledge, only one study assessed graph-theoretical changes on whole-brain level in patients with unilateral ICA stenosis and observed reduced degree and higher global

efficiency ipsilateral to stenosis (Chang et al., 2016). In this study, however, patients with previous stroke affecting up to one-third of the MCA territory were not excluded, which might explain the difference to our observations of normal FC at baseline in carefully selected patients without MRI lesions.

One of the studies mentioned examined connectivity changes in a subgroup of patients after stenting and observed a slight increase of FC in the DMN ipsilateral to stenosis after stenting (Cheng et al. 2012). Another study with 21 patients without a control group observed an increase of connectivity in DAN and FPN contralateral to stenosis after ICA stenting (Lin et al. 2016), which is compatible with our finding of a significant connectivity change contralateral to the stenosis on whole-brain level.

In a subgroup of 12 of our patients, resting-state electroencephalogram (EEG) was recorded and FC defined by mean alpha- and beta-band imaginary. FC ipsilateral to stenosis, contralateral to stenosis and interhemispheric FC were reduced at baseline and normalized after revascularization (Quandt et al., 2019). These diverging results from coherence analysis of EEG data and rsfMRI are remarkable but do not question the validity of each of the two approaches. Network metrics based on EEG or fMRI capture different aspects of intrinsic neural activity. Networks defined by phase-based connectivity of oscillatory electrophysiological signals are responsible for the dynamic, state- and task-dependent formation of neural assemblies on short timescales. The BOLD-signal has been shown to be closely related to amplitude envelopes of oscillatory brain activity, which are modulated at lower frequencies and within networks which are relatively robust to state changes (Engel et al. 2013).

The BOLD signal represents a convolution of low-frequency components of neural activity with the hemodynamic response function (Drew 2019), which shows regional variances across different brain areas (Amemiya et al. 2020). It has been suggested that besides neural connectivity, rsfMRI FC might to a certain extent reflect vascular anatomy even in healthy subjects (Tong et al. 2015). Therefore, in patients with vascular pathologies of the brain it cannot be said with certainty whether changes in the BOLD signal and fMRI FC represent changes in neural activity, changes in the hemodynamic response function due to the vascular pathology, or a mixture of both. In patients with chronic occlusion of the middle cerebral artery as well as with chronic stroke, it has been shown the temporal shift of the BOLD signal of each voxel to the averaged whole brain signal corresponds well to the temporal shift observed in contrast-enhanced perfusion imaging (Amemiya et al. 2014). In patients with ICA stenosis, apparent changes in BOLD FC network architecture have been shown to normalize after correction for the hemodynamically caused time lag in the regions downstream of the stenosis (Christen et al. 2015). Concerning our study population, cerebral perfusion before and after revascularization of ICA stenosis has been examined in a majority of the subjects who's fMRI data we report here using perfusion MRI by Schröder et al. 2019. They found hypoperfusion limited to the MCA boarder zone ipsilateral to carotid stenosis which normalized after revascularization. Considering the data mentioned above, it is possible that the increase of FC we observe after revascularization does not reflect a true change in neural network architecture, but is the effect of this alteration of perfusion and a resulting change in neurovascular coupling which shift the fMRI representation of a stable underlying neural network. Furthermore, as a limitation to the lack of any pathological finding before revascularization, we cannot exclude that for methodological reasons we do not detect minor physiological changes because the variance of our metrics is too large.

Taken together, our resting-state FC results match well with the rather subtle neuropsychological deficits of patients. They suggest that in our study population there is no major effect of chronic perfusion changes on functional connectivity and clinical performance. The subtle increase of connectivity within patients after revascularization is difficult to interpret, since we observe no difference to the control group before or after intervention. This might be a coincidental finding due to limited sample size or be due to altered neurovascular coupling caused by restoration of perfusion rather than to a change of underlying FC. If it is a true physiological effect, it might either represent a normalization of a subtle FC reduction at baseline or indicate the presence of compensatory mechanisms with an excessive upregulation after restoration of perfusion. In future, analysis of longer rsfMRI recordings with dynamic FC methods (Hutchison et al. 2013; Filippi et al. 2019) might provide further insight in the effects of ICA stenosis on FC. Our results await confirmation in a larger study population.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: B. Cheng, J. Fiehler, F. Fischer, M. Heinze, A. Larena-Avellaneda, C. Malherbe, E. Schlemm, M. Schulz and J. Schröder report no competing interests related to this work. C. Gerloff reports personal fees from Amgen, personal fees from Boehringer Ingelheim, Daiichi Sankyo, Abbott, Prediction Biosciences, Novartis, and Bayer outside the submitted work. G. Thomalla has received fees as consultant or lecturer from Acandis, Bayer, Boehringer Ingelheim, BristolMyersSquibbb/Pfizer, Daiichi Sankyo, Portola, and Stryker outside the submitted work.

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Appendix A. Supplementary data

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