Differential Impact of Brain Network Efficiency on Poststroke Motor and Attentional Deficits

Giorgia G. Evangelista, PhD; Philip Egger, PhD; Julia Brügger, PhD; Elena Beanato, MS; Philipp J. Koch, MD; Martino Ceroni, MS; Lisa Fleury, PhD; Andéol Cadic-Melchior, MS; Nathalie H. Meyer, MS; Diego de León Rodríguez, PhD; Gabriel Girardi, PhD; Bertrand Léger, PhD; Jean-Luc Turlan, MD; Andreas Mühlehl, MD; Philippe Vuadens, MD; Jan Adolphsen, MD; Caroline E. Jagella, MD; Christophe Constantin, MD; Vincent Alvarez, MD; Diego San Millán, MD; Christophe Bonvin, MD; Takuya Morishita, PhD; Maximilian J. Wessel, MD; Dimitri Van De Ville, PhD; Friedhelm C. Hummel, MD

BACKGROUND: Most studies on stroke have been designed to examine one deficit in isolation; yet, survivors often have multiple deficits in different domains. While the mechanisms underlying multiple-domain deficits remain poorly understood, network-theoretical methods may open new avenues of understanding.

METHODS: Fifty subacute stroke patients (7 ± 3 days poststroke) underwent diffusion-weighted magnetic resonance imaging and a battery of clinical tests of motor and cognitive functions. We defined indices of impairment in strength, dexterity, and attention. We also computed imaging-based probabilistic tractography and whole-brain connectomes. To efficiently integrate inputs from different sources, brain networks rely on a rich-club of a few hub nodes. Lesions harm efficiency, particularly when they target the rich-club. Overlaying individual lesion masks onto the tractograms enabled us to split the connectomes into their affected and unaffected parts and associate them to impairment.

RESULTS: We computed efficiency of the unaffected connectome and found it was more strongly correlated to impairment in strength, dexterity, and attention than efficiency of the total connectome. The magnitude of the correlation between efficiency and impairment followed the order attention ≈ dexterity > strength (strength: |r| = 0.03, P = 0.02, dexterity: |r| = 0.30, P = 0.05, attention: |r| = 0.55, P < 0.001). Network weights associated with the rich-club were more strongly correlated to efficiency than non-rich-club weights.

CONCLUSIONS: Attentional impairment is more sensitive to disruption of coordinated networks between brain regions than motor impairment, which is sensitive to disruption of localized networks. Providing more accurate reflections of actually functioning parts of the network enables the incorporation of information about the impact of brain lesions on connectomics contributing to a better understanding of underlying stroke mechanisms.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: attention ■ connectivity ■ motor ■ stroke ■ structural MRI

It has long been acknowledged that different brain regions are linked together in complex patterns, making networks a natural mathematical model for the brain, with regions of the brain serving as nodes and edges being weighted according to structural characteristics.1–4 Furthermore, neuroimaging evidence in humans suggests that stroke is a network disease, indicating that using network theory as the basis of a model for stroke5–7 might significantly enhance the understanding of stroke, its deficits and the recovery therefrom. It is useful to think of networks on a spectrum between regularity and randomness. Connectivity in regular networks...
tends to feature well-defined local communities, while in random networks it tends to feature one global community with costly long-distance connections; brain networks occupy the zone on the spectrum in which the tradeoff between global integration and local segregation is optimal. They optimize the tradeoff with an architecture featuring a small set of hub nodes called a rich-club (RC). These hubs are rich because they are strongly connected to nearby nodes, and form a club because they are strongly connected to each other. The RC can be thought of as a backbone for global connectivity, and therefore attacks (eg, stroke lesions) against it will have a greater impact on global connectivity than random attacks of similar magnitude.

When brain networks are attacked by a stroke, the effect on global integration can be considerable, particularly when the attack focuses on the RC. Likewise, the effect on behavioral function can be significant, particularly on cognitive functions, such as attention, that rely heavily on global integration as opposed to those functions whose neurological substrate is more localized, such as sensorimotor functions.

Structural connectomics relies on models of white matter (WM) tractography computed from diffusion-weighted imaging (DWI). In areas with high axon density, water molecule diffusion has a strong preference for the direction of the axons, that is, high anisotropy. By chaining together high-anisotropy voxels in the relevant directions, one can extract a model for WM tracts. Typically, stroke-lesioned brain tissue undergoes significant changes including liquefactive necrosis, reducing the anisotropy with consequences on the modelled WM tracts. Nonetheless, many paths pass through lesioned tissue, although they might not correspond to a functioning axon bundle.

We set out to answer 2 questions. First, is the understanding of connectomics significantly enhanced by the lesion structure information derived from DWI? To answer this question, we defined the structural connectome with and without explicit lesion information, respectively, and compared the data to behavioral metrics.

Second, how strongly are network-theoretic notions of global connectivity or RC integrity associated with stroke-induced impairment in different behavioral domains? We hypothesized that global connectivity and RC integrity will be associated with these behavioral functions, but that this association will be stronger in the less-localized attentional domain than in the more-localized motor domain. To test this hypothesis, we defined indices of impairment in motor and attentional functioning, and correlated them with a mathematically-defined notion of global efficiency (GE).

METHODS
This manuscript follows the STROBE reporting guidelines (Supplemental Material).

Data Availability
Data will be made available upon reasonable request.

Patients
We recruited 85 patients with stroke admitted between 2018 and 2021 to the stroke unit of the Hospital of Valais in Sion, Switzerland, of which N=50 (48 ischemic, 2 hemorrhagic strokes) completed both imaging sessions and behavioral tests and were therefore included in the study (Figure 1B). The inclusion criteria included being older than 18 years, presence of a motor deficit. Exclusion criteria included requests not to be informed in case of incidental findings, inability to provide informed consent, severe neuropsychiatric or medical disease, history of seizures, pregnancy, regular use of narcotic drugs, presence of implanted devices incompatible with magnetic resonance imaging or transcranial magnetic stimulation, use of medication that interacts with noninvasive brain stimulation, severe sensory, musculoskeletal or cognitive deficit incompatible with understanding instructions or performing experiments. For detailed patient characteristics, please see Table 1. The lesion locations were representative of the overall stroke patient population as shown in the lesion heatmap (Figure 1A) and were not used as a selection criterion. All patients gave written informed consent at the time of enrolment. The current data was acquired in the framework of a larger project (TiMeS project work package_1) and all research was approved by the local ethical committee swisethics (approval number 2018-01355).

Clinical Assessment
Each patient underwent magnetic resonance imaging at the subacute stage in addition to a battery of clinical tests of motor and cognitive function. The focus of this work was on motor and attentional functions. Motor strength was measured by performing the fist, grip, and pinch strength test on both hands, motor dexterity by performing the Box&Block and Purdue pegboard tests. Attentional functions were measured using the test of attentional performance, the color trail test parts A and B, and the Bells test. These tests were selected for fitting in the Sohlberg-Mateer model, which involves the use of 5 types of attention of increasing difficulty.

Magnetic Resonance Imaging Data Acquisition
All images were acquired using a 3T MAGNETOM Prisma (Siemens Healthcare, Erlangen, Germany) with a 64-channel head and neck coil.

T1-weighted anatomic images were acquired using 3D magnetization-prepared, rapid acquisition gradient-echo sequence with the following parameters: 192 axial slices, response time=2300 ms, echo time=2.96 ms, flip angle=9°, voxel size=1×1×1 mm, field of view=256×256 mm.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description                           |
|--------------|---------------------------------------|
| DWI          | diffusion-weighted imaging            |
| GE           | global efficiency                     |
| NMF          | nonnegative matrix factorization      |
| RC           | rich-club                             |
| WM           | white matter                          |

956 April 2023
For the DWI, diffusion gradients with 5 different gradient strengths (b-values=[300, 700, 1000, 2000, 3000]s/mm²; shell-samples=[3, 7, 16, 29, 46]) were obtained in 101 noncolinear directions distributed equally over the brain in 84 axial slices. The images were acquired using the pulsed gradient spin echo technique with the following parameters: repetition time=5000 ms, echo time=77 ms, field of view=234×234 mm, voxel resolution=1.6×1.6×1.6 mm, readout bandwidth=1630 Hz/pixel, GRAPPA acceleration factor=3.

Seven T2-weighted images without diffusion weighting (b=0 s/mm²) were acquired, including one in opposite phase encoded direction.

Lesion Segmentation
All the lesion masks were hand-drawn using MRview from MRtrix321 and subsequently verified by a neurologist. This enabled us to also compute, for each streamline, the binary value indicating whether or not the streamline passed through the lesion as described in previous work.10

Image Analysis
Tissue partial volume maps were estimates from the T1-weighted image and registered to the average b0 image using FSL.22 FreeSurfer was used to obtain a brain parcellation including 74 cortical areas per hemisphere (Destrieux atlas), subcortical areas (thalamus, caudate, putamen, hippocampus, amygdala), the cerebellum, and a subdivision of the brainstem (midbrain, pons, medulla), yielding 163 brain areas.23 The voxels corresponding to the lesion were stamped out and replaced by the mirrored voxels of the contralateral side.

The DWI were preprocessed using MRtrix3, 21 and FSL 22 (Gibbs ringing, motion, field inhomogeneity, susceptibility-induced off-resonance field, eddy currents and bias-field correction). Multi-shell multitissue constrained spherical deconvolution24 was used to estimate the fiber orientation distributions within each voxel. Whole-brain probabilistic tractography was performed using the MRtrix3 second-order integration over fiber orientation distribution method, 21 initiating streamlines in all voxels of the WM. Streamline tracking parameters were set to default values, except the minimum streamline length of 1.6 mm. For each dataset, 1 million streamlines were selected with both end points in the individual cortical or subcortical mask using the Dipy software package. 25 Every streamline was weighted fitting the underlying diffusion compartment model using a Stick-Ball-Zeppelin26 model using Convex Optimization Modeling for Microstructure Informed Tractography (COMMIT), a practice designed to boost the anatomical accuracy of the tractography mainly by avoiding or down-weighting false positives.27 Thus, rather than counting streamlines, we count COMMIT-weighted streamlines. Taken together, the COMMIT weighting and the large number of streamlines ensure that the estimated diffusion connectivity stabilizes, mitigating the pitfalls by improving the robustness and reproducibility of diffusion connectivity estimations.27 28

**Table 1. Patient Characteristics**

|                           | Value* | Unit   |
|---------------------------|--------|--------|
| Sex                       | 38 male/12 female | Patients |
| Age                       | 65.2±13.7 | Years |
| Time of MRI               | 4±2    | Days poststroke |
| Time of behavioral tests  | 7±3    | Days poststroke |
| Paretic side              | 28 left/22 right | Patients |
| Thrombolysis              | 17 yes/33 no | Patients |
| NIHSS                     | 5.8±4  | Points |
| FMUE                      | 53.6±18.1 | Points |
| Fist-grip strength        | 28.1±15.8 | Kg force |
| Pinch-grip strength       | 3.6±2.2 | Kg force |
| Key-grip strength         | 5.8±3.3 | Kg force |
| Box & Block test          | 34.6±18.6 | Blocks |
| Purdue pegboard test      | 6.7±4.4 | Pegs |
| CTT part A                | 77±56  | Seconds |
| CTT part B                | 143±78 | Seconds |
| RT on alertness test of TAP | 342±130 | Milliseconds |
| RT on divided attention test (single condition) of TAP | 1012±205 | Milliseconds |

CTT indicates Color Trail Test; FMUE, Fugl-Meyer Upper Extremity score; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; RT, reaction time; and TAP, Test of Attentional Performance.

*Categorical values are given as breakdowns by level of the category, separated by forward slashes. Numeric values are given with mean and standard deviation, separated by ±.
Total and Unaffected Connectome

For each patient, a structural connectome was built with 13,202 pairs of areas obtained through the parcellation. Here, we used for further analyses the unaffected connectome defined as the connectome consisting only of streamlines not affected (passing through) the lesion. To do this, we used binary maps indicating whether or not the streamline passed through the lesion to split the full connectome $C_{\text{total}}$ into the sum

$$C_{\text{total}} = C_{\text{unaffected}} + D$$

(1)

$$C_{\text{total}}[i,j] = \sum_{\text{streamline } k \text{ goes from } i \text{ to } j} w_k$$

(2)

$$C_{\text{unaffected}}[i,j] = \sum_{\text{streamline } k \text{ goes from } i \text{ to } j \text{ and does not pass through the lesion}} w_k$$

(3)

$$D[i,j] = \sum_{\text{streamline } k \text{ goes from } i \text{ to } j \text{ and passes through the lesion}} w_k$$

(4)

In this way, the lesion is incorporated more explicitly by only considering streamlines which are not lesioned, simultaneously encode true structural connectivity and mitigate the potential for artifacts of, for example, Wallerian degeneration.

Rich-Club, Edge Weight, and Node Weight

We considered the same set of nodes as found by van den Heuvel and Sporns to form the RC, namely the bilateral precuneus, superior frontal cortex, superior parietal cortex, hippocampus, putamen, and thalamus. Finally, we split the edges into 3 groups (Figure 2): pure RC connections (between RC nodes); feeder connections (between a RC and a non-RC node); and local connections (between non-RC nodes).

Each edge has a weight; each node has a weight, defined to be the sum of the weights of all edges linked to that node.

Dimensionality Reduction

The behavioral metrics of strength, dexterity, and attention all were represented by multiple features, which implies a need for dimensionality reduction. Popular methods include principal component analysis and non-negative matrix factorization (NMF); because our data are non-negative by nature and distance from zero impairment has a relevant meaning, we chose NMF. The amount of information that is lost by reducing features is captured by calculating the proportion of variance accounted for by the low-dimensional representation.

Figure 2. Connectome nodes and edges on glass brain.

Our parcellation contains 163 nodes, depicted as dots on the brain. Eighteen of these nodes, shown as enlarged dots, are the Rich-Club (RC) nodes. The edges are partitioned into pure RC (A, red), feeder (B, green), and local (C, blue) types.
Behavioral Metrics

To measure strength impairment, we consider the average force in 3 trials exerted by the patients on both hands, and calculate a normalized impairment metric as follows:

$$F_{norm} = \frac{F_{\text{nonparetic}} - F_{\text{paretic}}}{F_{\text{nonparetic}} + F_{\text{paretic}}}$$  

(5)

in a fist grip, a pinch grip and a key grip,\textsuperscript{15} giving the 3 features $F\text{IST}_{n}\text{orm}$, $P\text{INCH}_{n}\text{orm}$, and $K\text{EY}_{n}\text{orm}$. These features are bounded between $-1$ and 1, where $-1$ means only the paretic hand exerts force, 0 means both hands exert equal force, and 1 means only the nonparetic hand exerts force. While mildly negative values are possible, they are unlikely to be clinically meaningful, so we set negative values to zero in order for the features to be non-negative. Patients missing all 3 of $F\text{IST}_{n}\text{orm}$, $P\text{INCH}_{n}\text{orm}$ and $K\text{EY}_{n}\text{orm}$ were excluded; those who were missing some but not all were replaced by the mean of all non-missing data in the respective field. Finally, we used NMF (VAF = 97%) to reduce the 3 features into one strength impairment index

$$\text{strength} = 1.39 \times F\text{IST}_{n}\text{orm} + 1.43 \times P\text{INCH}_{n}\text{orm} + 1.53 \times K\text{EY}_{n}\text{orm}. \quad (6)$$

To measure dexterity impairment, we consider the number of fine motor tasks performed by the patient with both hands in a given time limit. As before, we calculate the normalized functional metric

$$N_{norm} = \frac{N_{\text{nonparetic}} - N_{\text{paretic}}}{N_{\text{nonparetic}} + N_{\text{paretic}}} \quad (7)$$

in the box-and-block test\textsuperscript{32} and the Purdue pegboard test,\textsuperscript{16} set negative values to zero, impute missing data, and use NMF (VAF = 97%) to reduce the 2 features into one dexterity impairment index

$$\text{dexterity} = 1.43 \times B & B_{n}\text{orm} + 1.53 \times P\text{urdue}_{n}\text{orm}. \quad (8)$$

To measure functional deficits in attention, we began with the widely used model of Sohlberg-Mateer,\textsuperscript{20} which suggests measuring 5 tasks of increasing difficulty, as described in Table 2:

Table 2. Sohlberg-Mateer Attention Model

| Component | Type of task | Metric | Unit |
|-----------|--------------|--------|------|
| Focused   | Response to discrete stimuli | Mean RT on alertness test (no warning) of TAP | Milliseconds |
| Sustained | Ability to work in a quiet environment | Completion time of CTT part A | Seconds |
| Selective | Ability to ignore distractors | Completion time of Bells test* | Seconds |
| Alternating | Shifting attention between tasks | Completion time of CTT part B | Seconds |
| Divided   | Response to multiple stimuli | Mean RT on divided attention test of TAP | Milliseconds |

CTT indicates Color Trail Test; RT, reaction time; and TAP, Test of Attentional Performance.

*A penalty of 0.7 s was added for every omission in the Bells test.

Global Efficiency

Most networks lie on a spectrum between local segregation and global integration. Many biological networks are small-world networks, which have both the clustered nature of locally segregated networks and the short path length of globally integrated networks.\textsuperscript{33,34} The GE of a network with $n$ nodes is defined by Rubinov and Sporns\textsuperscript{34} as

$$\text{GE} = \frac{1}{n(n-1)} \sum_{i \neq j} d_{ij},$$  

(10)

where $d_{ij}$ is the length of the shortest path between nodes $i$ and $j$, that is, the smallest sum of reciprocal edge weights in any path from $i$ to $j$. GE of the brain networks were computed using MATLAB’s Brain Connectivity Toolbox.\textsuperscript{34}

RESULTS

We computed the weighted GE of each patient’s total connectome $C_{\text{total}}$ and unaffected connectome $C_{\text{unaffected}}$ and then correlated these with strength, dexterity and attention impairment.

All correlations were estimated using bootstrap resampling\textsuperscript{35} with 10,000 iterations, that is, at each iteration, we drew 50 patients from our sample of 50 (with replacement) and computed the respective correlations on the subsample. We computed the Pearson correlation between $\text{GE}_{\text{total}}$ and impairment (Figure 3 blue; strength: $r = -0.20$, $P = 0.07$, dexterity: $r = -0.11$, $P = 0.25$, attention: $r = -0.41$, $P = 0.0001$); and between $\text{GE}_{\text{unaffected}}$ and impairment (Figure 3 green; strength: $r = -0.30$, $P = 0.02$, dexterity: $r = -0.30$, $P = 0.05$, attention: $r = -0.55$, $P < 0.001$). The negative correlations are expected, given that GE is known to contribute to better functional outcomes\textsuperscript{11,36}. $P$ values are proportions of bootstrap correlations that were non-negative. Here, we focused our analyses on few hypothesis-driven questions, thus not performing all comparisons possible, which would make a correction for multiple comparisons necessary.

We computed effect sizes for the difference between $r(\text{GE}_{\text{unaffected}}, \text{impairment})$ and $r(\text{GE}_{\text{total}}, \text{impairment})$ across bootstrap iterations using Cohen’s $d$ statistic rather than Student’s $t$ due to the latter showing inflated effect sizes with large datasets\textsuperscript{37}; $P$ values were computed by probability of superiority\textsuperscript{28}. $\text{GE}_{\text{unaffected}}$ was more strongly correlated with impairment than $\text{GE}_{\text{total}}$ (strength: $d = -0.73$, $P = 0.07$, dexterity: $d = -0.73$, $P = 0.07$, attention: $d = -1.1$, $P = 0.006$, attention: $d = -1.5$, $P = 0.004$). We did not control for age, as age was found not to be a meaningful covariate in previous studies of older healthy subjects.\textsuperscript{11}

It is known from work of van den Heuvel and Sporns\textsuperscript{9} that attacks on pure RC edges result in more loss of GE than attacks of similar magnitude on feeder or local edges. Conversely, we expected that greater integrity of pure RC edges should correspond to greater GE in the network, and this is the case (Figure 4A, left: 1-way ANOVA $F = 82.1$, $P < 0.001$). Greater integrity of RC...
nodes also corresponds to greater GE in the network (Figure 4B; left: 2-sample t test $T=2.6, P=0.009$).

It has been shown that among healthy older subjects, when considering correlations to attention, which requires integration of inputs from across the brain, pure RC edges are strongest, then feeder, then local. However, no such order exists for correlations to visual processing, which is more localized.11 The same holds when considering RC nodes as opposed to non-RC nodes.

We have found analogous results to those reported by Baggio et al11 in healthy older adults. Pure RC edge weights have more negative (ie, stronger) correlations to behavior than feeder and local edges, and this gap is smallest for strength and largest for attention (Figure 4A, right: 1-way ANOVA. Strength: $F=6.5, P<0.001$; dexterity: $F=19.7, P<0.001$; attention: $F=89.4, P<0.001$). Similarly, RC node weights have stronger correlations to behavior than non-RC node weights, and this gap is smallest for strength and the largest for attention (Figure 4B, right: 2-sample t test. Strength: $T=0.7, P=0.474$; dexterity: $T=2.0, P=0.048$; attention: $T=3.0, P=0.003$).

**DISCUSSION**

Given the complex interactions between different brain areas, mathematical tools for complex network analyses offer an exciting opportunity to better understand mechanisms underlying neurological disorders, especially when current findings strongly support the maxim that many neurological disorders, including stroke, are network disorders.5,39 Therefore, by evaluating the patient’s specific brain connectivity, connectomics has great potential to yield important insights into poststroke impairment and recovery mechanisms.

Our data suggest there are considerable differences in the mechanisms underlying deficits in the motor and attentional domains. These differences provide justified optimism that while treatments designed to promote more globally efficient brain networks are likely to have benefits in treating many deficits, this is particularly true for attentional deficits.

---

**Figure 3.** Bootstrapped correlations between connectome global efficiency (GE) and impairment.
Boxplots show bootstrapped Pearson correlations on the ordinate between GE and the 3 types of impairment on the abscissa. Blue plots refer to GE$_{total}$, while green plots refer to GE$_{unaffected}$. Note that all correlations tend to be negative and that correlations with GE$_{unaffected}$ tend to be stronger (ie, more negative) than those with GE$_{total}$. Note also that GE tends to be more strongly correlated to attention impairment than to strength or dexterity impairment, while it seems to be equally strongly correlated to strength and dexterity impairment.

**Figure 4.** Correlations between connectome global efficiency (GE), graph weights, and impairment.
Plots show mean and SD. **A**, left, Correlations between edge weight and GE$_{unaffected}$. Please note that the order pure Rich-Club (RC)>feeder>local holds. **A**, right, Correlations between edge weight and impairment. Please note that the order pure RC<feeder<local holds in all domains, and that the gap is largest in the attentional domain. **B**, left, Correlations between node weight and GE$_{unaffected}$. Please note that RC nodes have stronger correlation to GE$_{unaffected}$ than non-RC nodes. **B**, right, Correlations between node weight and impairment. Please note that RC nodes have stronger correlations to behavior than non-RC nodes and that the gap increases between strength, dexterity, and attention.
While the patients in stroke in this study were selected for their motor deficit, many also showed cognitive/attentional deficits (eg, 39/50 pathological on MOCA). It has been suggested from studies of older healthy subjects and patients with stroke that cognitive functions, such as attention, memory or language functions, are more heavily reliant on integration of inputs from different parts of the brain than functions such as motor or visual ones, which reside in more specialized local brain networks. This important assumption has been confirmed by our findings that $GE_{\text{unaffected}}$ is more strongly correlated to attention than to motor strength or dexterity, highlighting the reliance of the attentional domain on larger-scale emergent dynamics. Note that the correlation between $GE_{\text{unaffected}}$ and strength does not differ significantly from that between $GE_{\text{unaffected}}$ and dexterity, highlighting the fact that the motor domain, whether for pure strength production or for more fine motor skills, is less reliant on emergent (larger-scale) dynamics than attention is, but still residual motor functions rely on the efficiency of the unaffected connectome. Mathematical modeling conducted by Sporns and van den Heuvel has found that the resilience of brain networks to attack varies depending on the place of attack, indicating that attacks on pure RC edges result in greater drops in GE than other (non-RC) attacks of similar magnitude. Accordingly, we found that RC node weight and pure RC edge weight were more strongly correlated to attention than to motor functions, suggesting that the importance of the RC is derived from its disproportionate impact on GE.

Our approach adds personalization to traditional connectomics by separating fibers according to whether or not they are impacted by the patient’s particular lesion. This approach has borne fruit, as the unaffected connectome is more strongly associated with behavior than the traditional total connectome. From a hypothesis-driven perspective, the importance of including a lesion profile in the measurement of brain networks is obvious as WM tracts can be detected by DWI-derived tractography, though probably with more diffusivity inhomogeneities, even if they are interrupted by a lesion (particularly in the early poststroke period). Such tractography by itself fails to acknowledge that if tracts are interrupted by the lesion, their ability to transmit information is compromised and they will not contribute to the normal functioning of the network. From a data-driven perspective, it has been found that $GE_{\text{total}}$ does not differ significantly either over time, or even between stroke patients and healthy controls, casting doubt on the value of $GE_{\text{total}}$ as a biomarker. By contrast, we provide evidence that $GE_{\text{unaffected}}$ differs significantly from $GE_{\text{total}}$, and that in stroke patients $GE_{\text{unaffected}}$ is more strongly correlated to behavior than $GE_{\text{total}}$ is. In the present manuscript, we did not consider global efficiency of the disconnectome, but focused on the unaffected connectome, because while efficiency of a network roughly means how easy it is to get from one place to another using the functional pathways of the network, the disconnectome represents non-functional pathways, which conceptually thus does not allow to determine global efficiency.

Consequently, we find that explicitly discarding tracts that pass through the lesion as inoperative ensures that the unaffected connectome is a more accurate reflection of true patterns of connectivity than the traditional structural connectome, and thus a better candidate as a stroke-related biomarker.

**Limitations**

The primary drawback of our approach is that splitting the total connectome into its affected and unaffected parts requires that one draw lesion masks and overlay them onto the tractography. This imposes considerable additional work; yet, we are convinced that the benefits in terms of relevance to behavior and understanding of mechanisms are worth the cost. In addition to being time-consuming and labor intensive, they require substantial anatomical expertise, which might introduce a considerable source of variability; both on an interrater and (to a lesser extent) test-retest basis. While the use of machine learning algorithms to delineate lesions holds some promise, it is a sufficiently difficult task that at the time of writing, human-drawn lesions remain the gold standard, with even the best available algorithms failing to come close to interrater levels of agreement with humans. The present work does not address in detail the relationship between lesion volume and GE in regard of impairment, functional deficit and recovery. Which of the factors, one of them or the 2 together, might be most informative is an important open question that has to be addressed in more detail in upcoming studies focused on specifically on it.

**Future Work**

This study was conducted cross-sectionally; however, longitudinal evaluation of parameters of network efficiency in the affected and unaffected parts of the network will open novel opportunities to study the mechanisms underlying recovery of multidomain (eg, motor and attention) poststroke deficits. It will provide novel insights into the reorganization of structural brain networks, how these reorganizational patterns relate to recovery of behavioral functions, and whether they allow prediction of outcome or treatment stratification. In particular, it would be worth investigating whether among our cohort, patients’ increase in GE over time was associated with recovery from their impairment, particularly attentional impairment.

There are biological reasons to expect that this might occur. Reparative axonal sprouting is characterized by growth of long-distance connections, the precise type...
of connections that contribute most to GE. It has also been found to be clearly associated with poststroke behavioral recovery.43

Conclusions

While the patients in our cohort were selected for motor deficits, most of them also had an attention deficit, which can have an additional impact on the recovery process. This considerable overlap between motor and attentional deficits implies the need for finer-grained discriminators between multidomain deficits and their underlying mechanisms.

Here, we suggest structural connectivity analyses of RC properties with a focus on affected and unaffected parts of the network to better characterize these multidomain deficits in the subacute stage after stroke. These analyses allow the following conclusions: First, current structural connectome approaches use DWI to trace axon fiber bundles and simply rely on lesion-induced tract inhomogeneities. However, this implicit consideration of the lesion is suboptimal, particularly in the acute and subacute phase as it might lead to the tractography finding tracts that are no longer functional. Therefore, the results support the importance of explicitly overlaying lesion masks onto the tractography to be able to split the structural connectome into its unaffected (well-functioning) and affected (non-functional) parts to determine which parts of the brain network are actually relevant to residual functions and impairment. Second, based on this approach, the results suggest that in patients with stroke, attention is more sensitive to non-integrity of the connectome (especially the RC) and the resulting deficiency of GE than motor functions, strongly underscoring the differential importance of RC network properties for different behavioral functions. The results further confirm and are consistent with reports in healthy subjects that the neural substrate underlying motor functions is rather localized, while that underlying attention is based on a more global representation in terms of RC organization.

REFERENCES

1. Bassett DS, Bullmore E. Small-world brain networks. Neuroscientist. 2006;12:523–534. doi: 10.1177/1073858405283182
2. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009;10:186–198. doi: 10.1038/nrn2575
3. Sporns O. Networks of the brain. MIT Press; 2011.
4. Sporns O. Discovering the human connectome. MIT Press; 2012.
5. Guggisberg AG, Koch PJ, Hummel FC. Biutrofisch CM. Brain networks and their relevance for stroke rehabilitation. Clin Neurophysiol. 2019;130:1098–1124. doi: 10.1016/j.clinph.2019.04.004
6. Aben HR, Biessels GJ, Weaver NA, Spikman JM, Visser-Meijer JMA, de Kort PLM, Reijmer YD. PROCRAST Study Group. Extent to which network hubs are affected by ischemic stroke predicts cognitive recovery. Stroke. 2019;50:2768–2774. doi: 10.1161/STROKEAHA.119.025637
7. Ktena SI, Schirmer MD, Etherton MR, Giese A-K, Tuozzo C, Mills BB, Rueckert D, Wu O, Rost NS. Brain connectivity measures improve modeling of functional outcome after acute ischemic stroke. Stroke. 2019;50:2761–2767. doi: 10.1161/STROKEAHA.119.025798
8. Watts DJ, Strogatz SH. Collective dynamics of “small-world” networks. Nature. 1998;393:440–442. doi: 10.1038/30918
9. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. J Neurosci. 2011;31:15775–15786. doi: 10.1523/JNEUROSCI.3539-11.2011
10. Egger P, Evangelista GG, Koch PJ, Park C-H, Levin Gleba L, Girard G, Beanato E, Lee J, Choirat C, Guggisberg AG, et al. Disconnectomics of the rich club impacts motor recovery after stroke. Stroke. 2021;52:2115–2124. doi: 10.1161/STROKEAHA.120.031541
11. Baggio HC, Segura B, Junque C, de Reus MA, Sala-Llonch R, Baggio HC, Segura B, Junque C, de Reus MA, Sala-Llonch R, van den Heuvel MP. Rich-club organization and cognitive performance in healthy older participants. J Cogn Neurosci. 2015;27:1801–1810. doi: 10.1162/jocn_a_00892
12. Vandenburgroucke JP, van Elst E, Altman DG, Gatzche PC, Mulrow CD, Pocock SJ, Poole C, Schmiegelow KJ, Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12:1500–1524. doi: 10.1016/j.ijsu.2014.07.014
13. Choi YM. Comparison of grip and pinch strength in adults with dexterity limitations to normative values. Pocedia Manuf. 2015;5:532–533. doi: 10.1016/j.promfg.2015.07.037
14. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am. 1984;9:222–226. doi: 10.1016/s0363-5023(84)80146-x
15. Tiffin J, Asher EJ. The Purdue pegboard: norms and studies of reliability and validity. J Appl Psychol. 1948;32:234–247. doi: 10.1037/h0061266

ARTICLE INFORMATION

Received May 18, 2022; final revision received December 1, 2022; accepted December 15, 2022.

Affiliations

Defitech Chair of Clinical Neuroengineering, NeuroX Institute (INX), École polytechnique fédérale de Lausanne (EPFL), Geneva, Switzerland (G.G.E., P.E., J.B., E.B., M.C., L.F., A.C.-M., D.d.L.R., T.M., M.J.W., F.C.H.). Departement of Neurology, University Hospital Würzburg, Germany (M.J.W.). Medical Image Processing Laboratory, Institute of Biomedical Imaging (CIBM), Switzerland (G.G.). Department of Radiology and Medical Informatics, University of Geneva (UNIGE), Switzerland (D.V.D.V.). Clinical Neurosciences, Geneva University Hospital (HUG), Switzerland (F.C.H.).

Acknowledgments

We thank Silvia Avanzi for her excellent support during the recruitment and data acquisition process.

Sources of Funding

Partially supported by No. 2017-205 Personalized Health and Related Technologies (FHT-RT-205) of the ETH Domain, Defitech Foundation (Strike-the-Stroke project, Morges, Switzerland), Bartarelli Foundation (Catalyst Deep-MCI-T project), FreeNovation Program of the Novartis Research Foundation and the Wys Center for Bio and Neuroengineering. We acknowledge access to the facilities and expertise of the Neuroradiology Center of the HVS (Sion) and the Center for Biomedical Imaging and of the MRI facilities of the Human Neuroscience Platform of the Fondation Campus Biotech Geneva.

Disclosures

Dr Adolfsen discloses Talk for Biogen Schweiz 2020; participation advisory board for the drug Fampryra for Biogen Schweiz 2019 and participation advisory board for the drug Sativex for Almirall Schweiz 2018. Dr Hummel reports funding from Fondation Bartarelli and Novartis Foundation. The other authors report no conflicts.
16. Zimmermann P, Fimm B. Test of attentional performance manual (version 2.3). 3rd ed. Psytest; 2012; Herzogenrath.
17. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol. 1955;19:393–394. doi: 10.1037/h0044509
18. Messinis L, Malegiannaki A-C, Christodoulou T, Panagiotopoulos V, Papathanasopoulos P, Color trails test: normative data and criterion validity for the Greek adult population. Arch Clin Neuropsychol. 2011;26:322–330. doi: 10.1093/acn/act027
19. Gauthier L, Dehaut F, Joanette Y. The bells test: a quantitative and qualitative test for visual neglect. Int J Clin Neuropsychol. 1989;1:1–95.
20. Scholzberg MM, Mateer CA. Cognitive rehabilitation: an integrative neuropsychological approach. Cognitive rehabilitation: An integrative neuropsychological approach 2001; Guilford Press.
21. Tournier J-D, Smith R, Tuch DS. Multibody fractional anisotropy: a new tool for studying the microstructure of multi-compartmental tissues. Magn Reson Med. 2012;68:1857–1865. doi: 10.1002/mrm.24576
22. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, De Luca M, Dobbins IJ, Fitzgibbons DE, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:S208–S219. doi: 10.1016/j.neuroimage.2004.07.051
23. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage. 2010;53:1–15. doi: 10.1016/j.neuroimage.2010.06.010
24. Jeurissen B, Tournier J-D, Dhimant D, Connelly A, Sijbers J. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. Neuroimage. 2014;103:411–426. doi: 10.1016/j.neuroimage.2014.07.061
25. Garyfallidis E, Brett D, Wernick N, Desikan RS, Katiyar G, et al. FLAME: a fast and accurate multi-subject registration algorithm. Neuroimage. 2014;90:112–121. doi: 10.1016/j.neuroimage.2013.12.073
26. Alexander DC. A general framework for experiment design in diffusion MRI and its application in measuring direct tissue-microstructure features. Magn Reson Med. 2008;60:439–448. doi: 10.1002/mrm.21646
27. Madhu M, Bai H, Liao X, Yan H, Zhang J, et al. A novel approach for diffusion MRI segmentation using deep learning. Neuroimage. 2019;197:30–40. doi: 10.1016/j.neuroimage.2018.09.003
28. Smith RE, Tournier J-D, Calamante F, Connelly A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. Neuroimage. 2012;62:1924–1938. doi: 10.1016/j.neuroimage.2012.06.005
29. Koch P, Park C-H, Giraud G, Beanato E, Eggert P, Evangelista GG, Lee J, Wessel MJ, Morishita T, Koch G, et al. The structural connectome and motor recovery after stroke: predicting natural recovery. Brain. 2021;144:2107–2119. doi: 10.1093/brain/awab082
30. Jones DK. Challenges and limitations of quantifying brain connectivity in vivo with diffusion MRI. Imaging Med. 2010;2:341–355. doi: 10.2217/im.10.21
31. Lee DD, Seung HS. Learning the parts of objects by non-negative matrix factorization. Nature. 1999;401:788–791. doi: 10.1038/44565
32. Mathiowitz V, Volland G, Kashman N, Weber K. Adult norms for the box and block test of manual dexterity. Am J Occup Ther. 1985;39:386–391. doi: 10.5014/ajot.39.6386
33. Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett. 2001;87:198701. doi: 10.1103/PhysRevLett.87.198701
34. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010;52:1059–1069. doi: 10.1016/j.neuroimage.2009.10.003
35. Efron B. Bootstrap methods: another look at the jackknife. Ann Statist. 1979;7:1–26. doi: 10.1214/aos/1176344552
36. van den Heuvel MP, Sporns O, An anatomical substrate for integration among functional networks in human cortex. J Neurosci. 2013;33:14489–14500. doi: 10.1523/JNEUROSCI.2128-13.2013
37. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 2013.
38. Ruscio J. A probability-based measure of effect size: robustness to base rates and other factors. Psychol Methods. 2008;13:19–30. doi: 10.1037/1082-989X.13.1.19
39. Grefkes C, Fink GR. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 2014;13:206–216. doi: 10.1016/S1474-4422(13)70264-3
40. Siegel JS, Siegel JS, Ramsey LE, Ortega M, Gordon EM, et al. Advances in diffusion MRI data analysis. Neuroimage. 2014;90:112–121. doi: 10.1016/j.neuroimage.2014.07.061
41. Liew S-L, Anglin JM, Banks NW, Sondag M, Ito KL, Kim H, Chan J, Ito J, Jung C, Khoshabeh N, et al. A large, open source dataset of stroke anatomical brain images and manual lesion segmentations. Sci Data. 2018;5:180011. doi: 10.1038/sdata.2018.11
42. Maier O, Schröder C, Forkert ND, Martinez T, Handels H. Classifiers for ischemic stroke lesion segmentation: a comparison study. PLoS One. 2015;10:e0145118. doi: 10.1371/journal.pone.0145118
43. Carmichael ST, Kothariu B, Schveppe CA, Nie EHT. Molecular, cellular and functional events in axonal sprouting after stroke. Exp Neurol. 2017;287:384–394. doi: 10.1016/j.expneurol.2016.02.007