Combining function and structure in a single macro-scale connectivity model of the human brain

A Preprint

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Abstract

Combining the macro-scale functional and structural connectivity matrices of the human brain could provide useful information on how various diseases and conditions affect the brain. However, it is not a simple task to combine such information as they are derived usually in very different ways with functional information typically gathered using fMRI, EEG, or MEG whereas structural information relies on robust diffusion-weighted MRI tractography methods. This work proposes a solution to this problem using an analogy to an electric circuit with the functional information being the voltage sources and the structural information resistance of the elements in the circuit. The voltage sources and resistances can be used to solve the current in the circuit using Modified Nodal Analysis, for example. In the proposed analogy, the solved electric current represents how the functional information flows in the structural brain network. This work demonstrates a connection-specific example of such analysis

as well as whole-brain analysis using data from the Human Connectome Project. Another dataset of functional and structural data from healthy brains is used to demonstrate that the proposed method can be used to study the aging of the human brain. The main motivation for the proposed analysis method is that it could provide new information on various conditions and diseases such as Alzheimer's that affect the human brain. In a sense, the proposed functio-structural current (FSC) analysis is a macro-scale version of the classical Hodkin-Huxley model.

Keywords brain connectivity · structure · function · diffusion MRI · resting-state fMRI · conductance

1 Introduction

Understanding the human brain and its macro-scale connections or 'the brain connectome' (Sporns et al., 2005) is a challenge with likely far-reaching benefits in brain sciences and medicine. This challenge is often divided into two parts that either study the brain function or the brain structure. While both parts alone are readily difficult to study, it seems that linking them is an even more elusive task (Damoiseaux and Greicius, 2009; Greicius et al., 2009; Hermundstad et al., 2013; Huang and Ding, 2016; Sporns, 2013; Suárez et al., 2020). However, it is reasonable to assume that such a link must exist as the brain could not support functions without the structure.

The functional connectome or functional networks can be derived from statistical patterns (Rubinov and Sporns, 2010) detected in the brain using functional magnetic resonance imaging (fMRI) time series, electroencephalography (EEG), or magnetoencephalography (MEG), for example. (Sporns, 2013). The derived functional connectome depicts only the correlations between activities in different brain regions which means that this information alone cannot be used to imply causal relationships (Smith et al., 2011). Yet, functional connectome has provided insights into the behavior, aging, and how various diseases and conditions can affect the human brain.

The structural connectome of the living human brain is derived using diffusion-weighted magnetic resonance imaging (dMRI) and tractography (Basser et al., 1994; Behrens and Sporns, 2012; Johansen-Berg and Rushworth, 2009; Le Bihan et al., 2001). The derived connectome depicts pathways in which water molecules can travel in the brain and is often assumed to remain relatively stable during short time periods. These pathways are often referred to as tractography streamlines. While streamlines do not directly imply that there would be a white matter tract or fiber, many studies have demonstrated that streamlines indeed can be used to infer orientations and trajectories of white matter bundles. (Sporns, 2013) However, tractography has a tendency to produce many false positive streamlines (Maier-Hein et al., 2016) due to e.g., noise, measurement methods, and processing (Sairanen and Andersson, 2023) which complicate deductions from the results. Despite these complications, the structural connectome has provided new insights into the organization of the human brain in various conditions.

Combining the functional and structural connectomes is a difficult task as both techniques depend heavily on the chosen data acquisition and processing methods which can set various limitations on how data could be merged. In many cases, functional correlations may be found between two brain regions that do not share a direct structural connection (Damoiseaux and Greicius, 2009). In such cases, finding the optimal indirect connection between regions can be challenging. Especially, with the dMRI tractography providing large numbers of false positive streamlines (Maier-Hein et al., 2016).

An interesting proposal to join these two connectomes is to use an electrical circuit as an analogy for the human brain on the macro scale. Recent studies (Chung et al., 2017; Frau-Pascual et al., 2021, 2019) used voxel-wise structural model to derive the analogue for electric conductance from the structural information and then used a fixed current of one ampere to solve the voltage from the partial differential equations related to electrical circuit laws. The authors showed that the ensuing voltage matrix correlated well with the functional connectivity matrices obtained using fMRI.

This study takes the electrical circuit analogy a step further. Instead of using a fixed current, we propose that the analogy could be defined as the structural connectome being the resistance (or conductance) and the functional connectome being the potential (or independent voltage sources) in the electrical circuit. In this formulation, the current would be the unknown element of interest, and it can be readily solved following Ohm's and Kirchhoff's laws using the modified nodal analysis (MNA) (Ho et al., 1975; Wedepohl and Jackson, 2002). Please, note that this study does not aim to improve or even comment on how structural or functional connectivity matrices should be derived.

In the proposed analogy, the current depicts how the functional information flows through the brain structures similar to how electrical current flows through elements of resistance in an electric circuit. The proposed analogy provides a way to naturally combine the two brain connectomes while taking into account direct and indirect structural connections simultaneously. The ensuing novel connectivity matrix depicts the functio-structural current (FSC) in the brain which hopefully can be used to deepen the understanding of the living brain. The following sections detail how FSC is calculated in theory and demonstrate how it can be applied to general connectivity matrices as well as studying the aging brain. To facilitate further implementations, a Python function that calculates FSC matrix from a given functional and structural connectome is provided in GitHub [1].

2 Results

Two real healthy human datasets were used in this study. The first dataset consists of an unrelated cohort of 207 healthy adult subjects from the Human Connectome Project (Larivière et al., 2021; Van Essen et al., 2012). Average high-resolution functional and structural connectivity matrices based on diffusion-weighted tractography and resting-state functional MRI from this sample were used to evaluate the general feasibility of the proposed FSC model.

[1] https://github.com/vilsaira/FSC

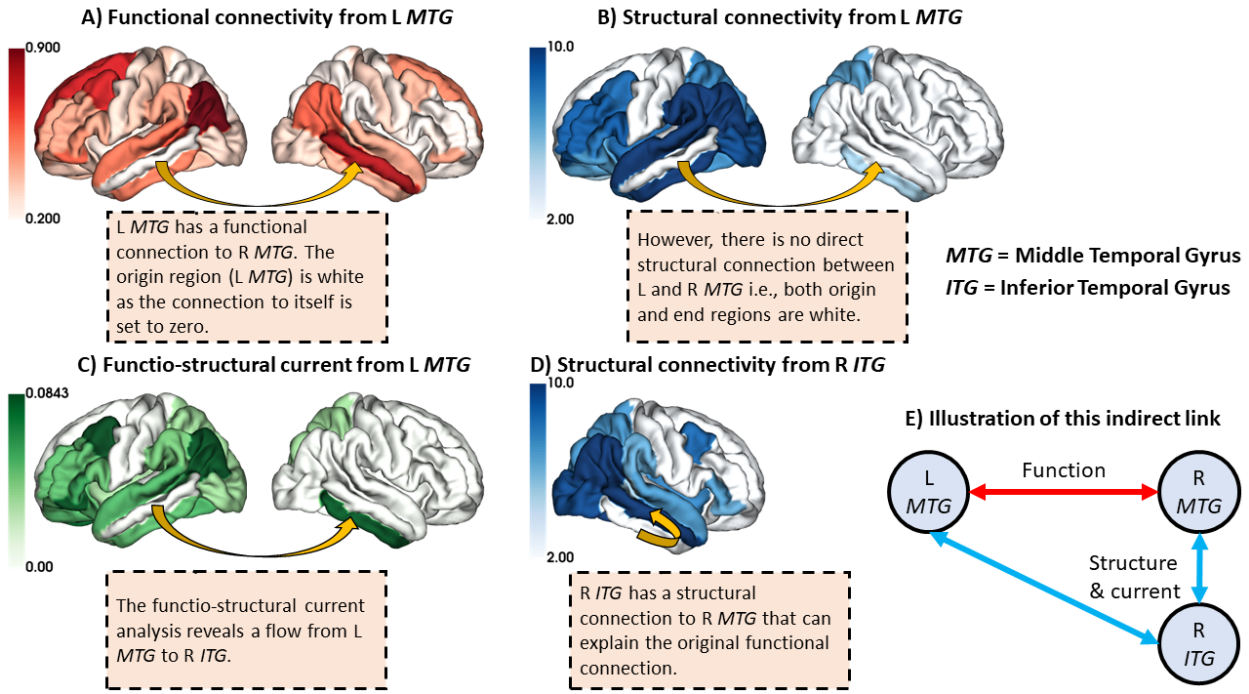

Figure 1: A demonstration of the functio-structural current analysis. Using an analogy to an electric circuit with (**A**) functional connectivity being voltage sources, (**B**) structural connectivity being resistance, (**C**) the functio-structural current, an equivalent for electrical current, can be derived. An example: There is no current between L and R MTG because they have no structural connection (**B**). However, the FSC shows a high current through R ITG and by analyzing the structural connections from R ITG, a link to R MTG is found explaining (**D**) the original functional connection shown in (**A**). A simple schematic illustration of this indirect link is shown in (**E**).

The second dataset consists of another unrelated sample of 171 healthy subjects with varying ages from the UCLA multimodal connectivity database (Brown et al., 2012). Subject-wise functional and structural connectivity matrices (based on diffusion-weighted tractography and resting-state functional MRI, correspondingly) were used to demonstrate how the proposed FSC could reveal new information in studying the aging of healthy human brain that is not observable from the functional and structural data alone.

Further details on how datasets were processed are available in the Methods section.

2.1 General feasibility of the proposed method

Functional and structural connectivity matrices from 207 unrelated healthy adults from the Human Connectome Project (Van Essen et al., 2012) were used to calculate average functional and structural matrices using the ENIGMA Toolbox (Larivière et al., 2021). These average connectivity matrices were used to demonstrate the general feasibility of the proposed functio-structural current (FSC) analysis. Two different examples of the potential applications for FSC are demonstrated: The first is an example of mapping an indirect functional connection and the second is an example of calculating the whole-brain connectivity matrices and investigating their correlations.

The first example in figure 1 demonstrates how an indirect functional connection could be facilitated by the structural network. This example starts with a functional connection found between (the source) at the left middle temporal gyrus (L_MTG) and (the target) at the right middle temporal gyrus (R_MTG). The structural connectivity matrix does not show a direct link between the source and the target therefore this functional connection is likely established via an indirect link or links.

By applying the proposed FSC analysis, a current flowing from the source (L_MTG) to a proxy at the right inferior temporal gyrus (R_ITG) is found. The structural connections from the proxy (R_ITG) onwards show a link to the original target (R_MTG) completing the circuit. While this was a simple example of how the proposed FCS analysis and easily evaluated manually, more complex network structures could be studied by following the different current branches in the network with more automated approaches.

The first example is repeated using Chord plots in figure 2 to summarize all connections from the source (L_MTG). The logic of following FSC connections remain the same but this visualization could help identify more complex paths. This kind of brain region-specific analysis could be helpful when investigating some specific brain diseases or conditions.

The second example of whole-brain connectivity demonstrates that the proposed FSC analysis is not limited to any specific brain regions. The same analysis approach can be applied to the whole-brain functional and structural connectivity matrices as shown in figure 3. This kind of whole-brain connectivity analysis could be helpful in the mapping of how aging affects the healthy brain, for example.

Figure 4 shows the correlations between the three connectivity matrices were calculated using ordinary linear least squares regression (OLS). A statistically significant ($p<0.05$) correlation (Pearson $r\approx 0.5$) between the average structural and functional connectivity matrices is found which is expected based on previous research e.g., (Brown et al., 2012). A more interesting part is to see how the proposed functio-structural current correlates with the two parts from which it is derived.

The two other subplots of figure 4 show that functio-structural current has a statistically significant ($p<0.05$) negative correlation (Pearson $r\approx -0.45$) with structural connectivity. This indicates that weak structural connections seem to carry the highest currents. No correlation is found between functio-structural current and functional connectivity ($p \approx 0.83$ and Pearson $r\approx -0.01$) which could indicate that the majority of the functional brain connections are carried by indirect structural connections and they become dispersed across the macro-scale structural network.

2.2 Aging of the healthy human brain

This example demonstrates how FSC could uncover information that is not available in the functional and structural connectivity matrices alone. The functional and structural connectivity matrices from 171 unrelated healthy subjects from a previous study by Brown et al. (2012) were used to obtain FSC connectivity matrices. The edge weights from these matrices were averaged and plotted against the age data in figure 5.

A statistically significant ($p<0.05$) correlation between age and functional connectivity is found. Age and structural connectivity did not correlate in our test (unless using a non-robust regression model that is heavily affected by four extreme outliers). When

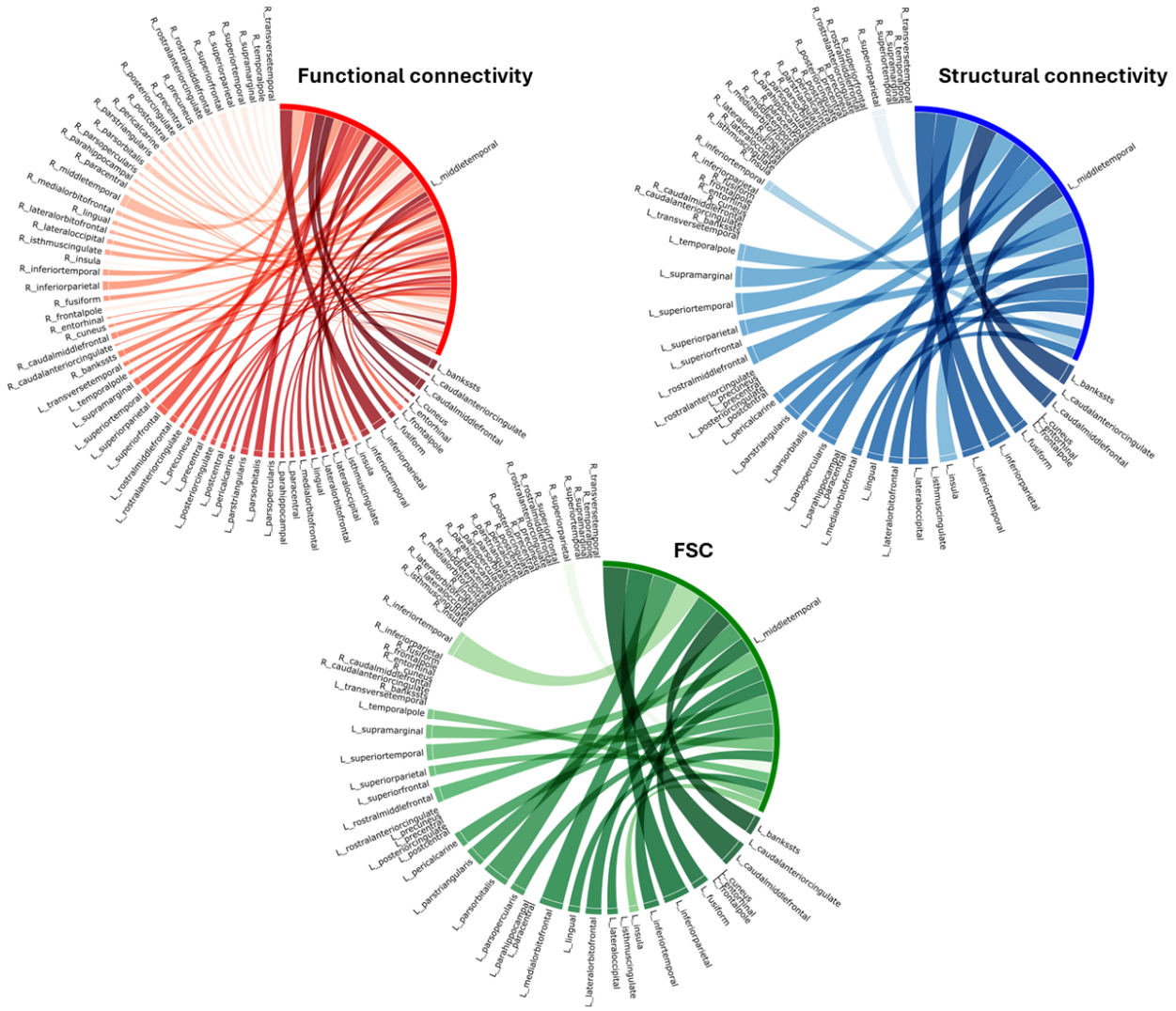

Figure 2: Connections from the left middle temporal gyrus (source). Red shows the functional connectivity, blue structural connectivity, and green functio-structural current (FCS). For example, the second strongest functional link with the source is the right middle temporal gyrus (target). However, there is no direct structural link between them, but there is a weak structural connection between the source and right inferior temporal gyrus which is known to have a structural link with the target. Despite the weak structural connection, the FSC from the source to the right inferior temporal gyrus is high to facilitate this functional connection between the source and target.

the previous two are combined using the proposed model, a statistically significant ($p<0.05$) correlation between age and FSC is found and it has a steeper slope than the regression model with age and functional connectivity. This suggests that the

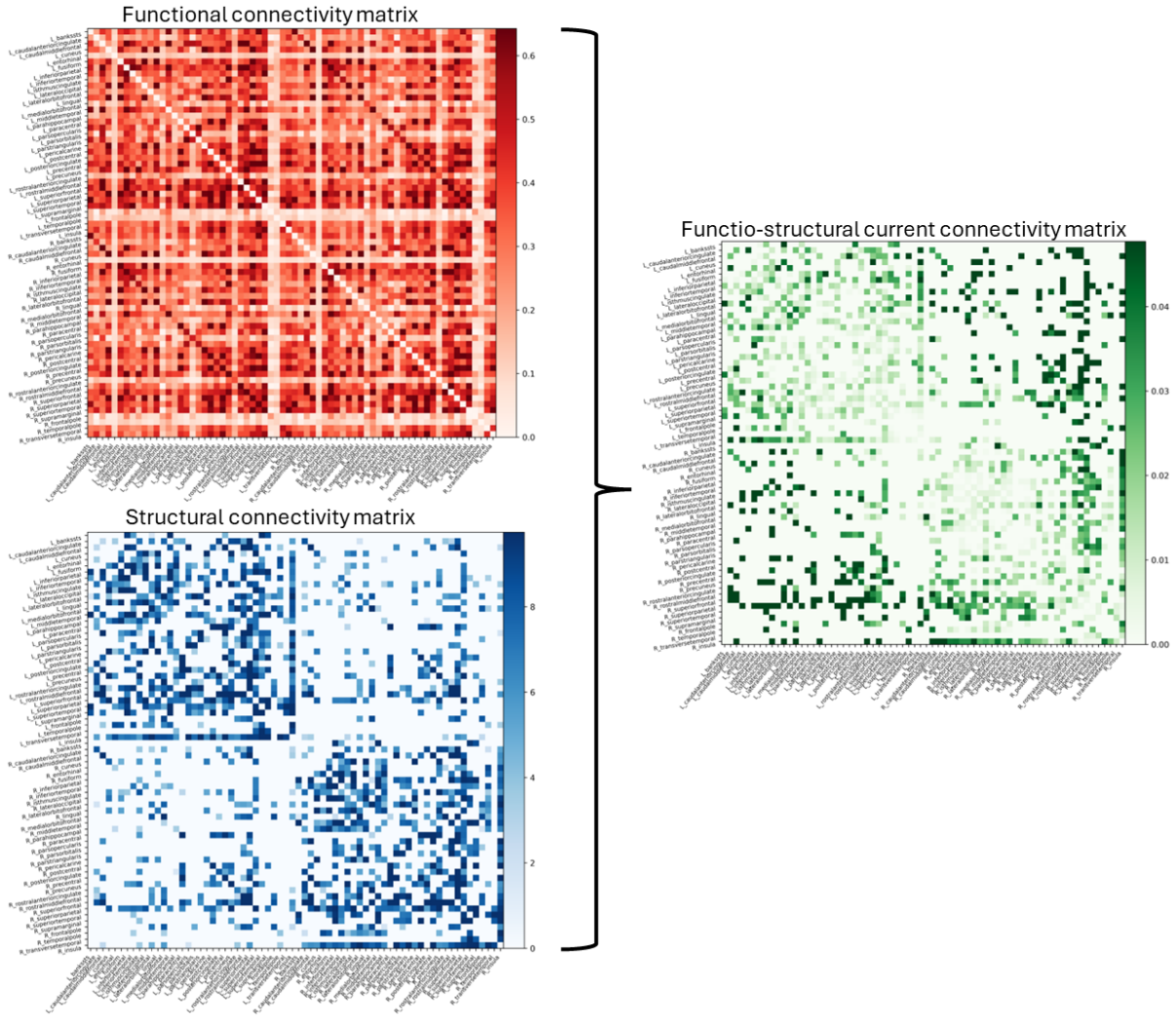

Figure 3: The proposed functio-structural current analysis is not limited to any one specific connection. Functional (red) and structural (blue) connectivity matrices from the whole brain or sub-networks can be used as a basis to calculate the corresponding FSC (green) matrices.

proposed FSC analysis could uncover information that is not directly available in the original connectivity matrices alone.

3 Discussion

This study set out to investigate if an analysis method used to study electrical circuits (Modified Nodal Analysis, MNA) (Ho et al., 1975; Wedepohl and Jackson, 2002) could

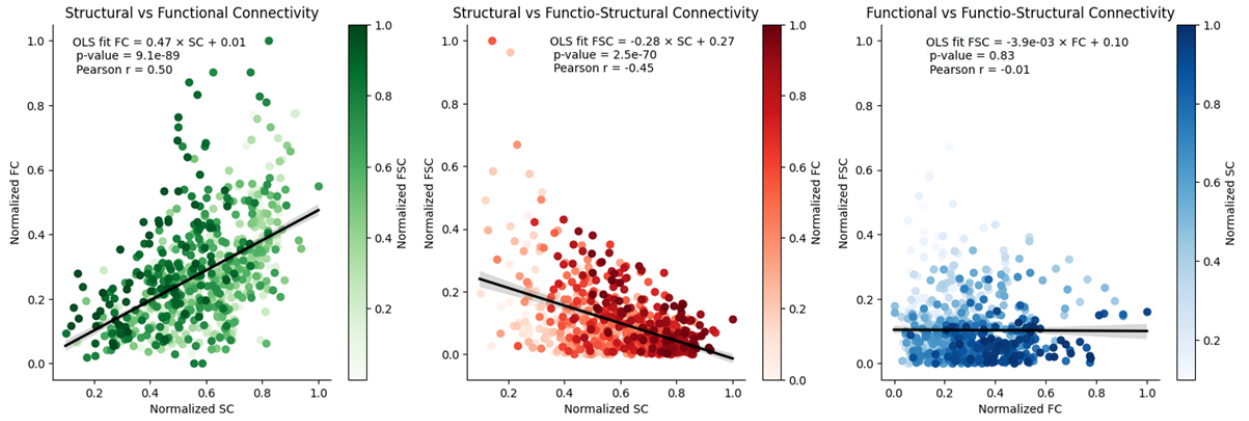

Figure 4: Correlations between the normalized connectivity matrices from HCP dataset. SC against FC is shown on the left with the colormap indicating FSC (green), SC against FSC is shown in the middle with the colormap indicating FC (red), and FC against FSC is shown on the right with the colormap indicating SC (blue). SC and FC demonstrate a positive correlation whereas SC and FSC demonstrates a negative correlation. FC and FSC do not correlate. Only non-zero edges based on the SC connectivity matrix were used for this analysis.

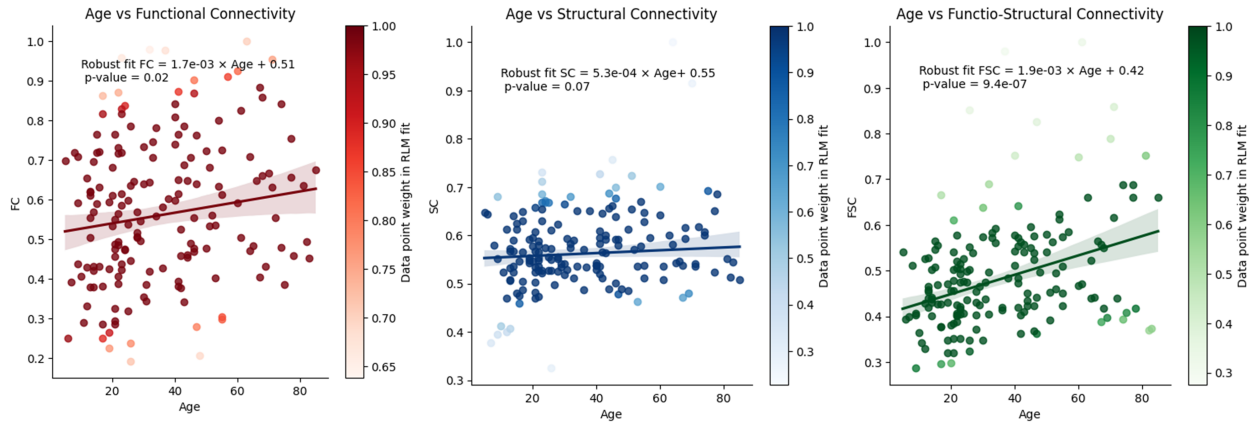

Figure 5: An example of how FSC could be used in studying the healthy human brain aging. Here subject age is shown on x-axes and normalized average edge weights from functional (red), structural (blue), functio-structural (green) connectivity matrices on y-axes. Functional data indicates a very weak but statistically significant positive correlation with age. Structural data does not indicate any correlation. In combination with the previous two using the FSC model, a correlation that is stronger than just the functional connectivity is found. The color scale on each plot indicates the weight of the corresponding data point on the robustly weighted linear model fit (RLM)

be used to study the macro-scale connectivity of the living human brain. While this can sound like an outrageously simplifying model for a such complex organ, the aim is not to say that this model holds on a small scale but only on macro-scale

connectivity. Similar to the classical Hodkin-Huxley model (Hodgkin and Huxley, 1952) it is reasonable to assume that this model too needs to be adjusted for further accuracy. However, this study already demonstrates that the approach is plausible and the proposed functio-structural current (FSC) analysis could potentially uncover information that is not available directly using only functional or structural connectivity data alone.

In the proposed FSC analysis, the analogy between the human brain and an electric circuit is used to combine functional and structural connectivity matrices. This is achieved by using the functional connectivity as independent voltage sources in the circuit and the structural connectivity as resistances of the elements in the circuit. Node-wise voltages are solved by applying the Modified Nodal Analysis (Ho et al., 1975; Wedepohl and Jackson, 2002). Ohm's law is then applied to the voltage differences between the nodes and resistances to obtain the currents flowing in the circuit.

Two unrelated datasets (Brown et al., 2012; Larivière et al., 2021) of functional and structural connectivity matrices obtained from healthy human brains are used to demonstrate how the proposed FSC analysis could be applied in practice. Figure 1 demonstrates how FSC can be used to map how functional connections could traverse indirect pathways in the structural brain network using data from the Human Connectome Project (Larivière et al., 2021). One benefit of the proposed analysis method is that it is capable of calculating all possible pathways simultaneously and applying weights to them based on how much that pathway is needed to carry the corresponding functional signal.

The Human Connectome Project data was further used to study the cross-correlation of the different connectivity matrices in figure 4. Similar to a previous study (Brown et al., 2012), a positive correlation between the average edge weights of functional and structural connectivity matrices was found. A negative correlation between structural and FSC connectivity matrices was found indicating that with the used brain parcellation (Desikan-Killiany) the highest functional currents are carried via

weaker structural links. If this is a correct finding, it suggests that even weak structural links can play significant parts in the human brain.

The dataset from the UCLA multimodal connectivity database (Brown et al., 2012) provided subject-wise connectivity matrices and age data which were used to demonstrate that the FSC analysis could uncover information that is not directly available in functional and structural data alone. When the average edge weights of all three connectivity matrices were plotted against the subject's age, the strongest correlation was found between the FSC and age. No correlation was found with the structure and age and the correlation between function and age was weaker than with FSC and age. This indicates in sense of modelling that FSC could enhance the information that is available in the functional and structural data in a useful way. What this correlation indicates in sense that the human brain is more complex but could be interpreted as the older the *healthy* brain gets it gets also better in functional processing enabling higher currents in the structural network.

As the FSC is effectively an adjacency matrix, many existing network analysis tools can be readily applied to study it further (Sporns, 2013). Additional applications for FSC that are not investigated in this study could be the filtering of possible structural connections (Sairanen et al., 2021) which are known to contain large numbers of false positive findings (Maier-Hein et al., 2016). If there are structural connections that do not carry any currents, those could be pruned as false connections. Another application could be to study if these currents are somehow affected by various diseases. E.g. as a biomarker for early Alzheimer's disease. Alzheimer's might cause a lower information flow overall in their brain or some specific regions or connections. A similar hypothesis could be set for any disease or condition that affects the brain.

The proposed analogy could be used to model the causality of brain functions to some extent as well. This is because the modified nodal analysis can be used to analyze circuits containing dependent voltage sources (Ho et al., 1975). In the brain, such dependencies or causalities are likely more complex to model but in some cases, they could be identified. However, this discussion of causality delves towards effective

connectivity (Friston, 2011) which is beyond the topic and data used in this study. In the future, with a suitable data set for causality modelling, this could be studied further.

The proposed FSC is limited by all the inaccuracies and assumptions that affect the functional and structural connectivity analyses. However, as it is based on the analysis of the connectivity matrices it is a relatively freely adaptable method. If new progress is made on functional or structural connectivity analyses, results from them can readily be used in the FSC to evaluate the changes.

Network-related applications beyond neuroscience could also be solved with the proposed analog. As long as the network can be divided into potential and resistance. For example, a delivery route could be modelled with income as potential and round length, traffic, or speed limit as resistance. It could be a quite rapid way to solve such problems as systems of linear equations which can be scaled from very large to small subnetworks easily. The FSC can be used to find the shortest path in the network similar to Dijkstra's algorithm. Additionally to the shortest path, the FSC provides all possible paths. This can be done by setting the voltage source between two nodes and getting resistances from the (weighted) network edges which provides the shortest route as the route with the highest current, for example. However, it remains to be demonstrated if the FSC would be beneficial in such applications.

In summary, this work combined functional and structural brain connectomes using an analogy to an electric circuit. This method provided a novel brain connectivity matrix that represents how the functional information flows in the structural brain network. As this work is a proof-of-concept study, it considers only data from healthy human brains with the proposed method and demonstrates how it can be applied to any pair of functional and structural connectivity matrices. Future studies with patients affected by various diseases or conditions are needed to evaluate, if the proposed functio-structural current has a place in neuroscience.

4 Methods

This section describes 1) the theoretical framework used in the proposed functio-structural current analysis, 2) data processing for the general feasibility demonstration, and 3) data processing for the aging brain demonstration.

4.1 Functio-Structural Current Analysis

This section demonstrates how the modified nodal analysis is applied to study the living brain. First, a voltage source matrix $\mathbf{V}$ is defined as a copy of the functional connectivity matrix. This means that voltage source matrices can be defined in as many ways as the functional connectivity matrix e.g., as a resting state network or a task-specific activity in fMRI, EEG, or MEG. Second, a resistance matrix $\mathbf{R}$ is defined as a copy of the structural connectivity matrix. This means that the resistance matrix can also be defined with various tractography algorithms and be based on e.g., the streamline length, average fractional anisotropy, or degree of myelination. The main restriction is that both the functional and structural connectivity matrices should be generated using the same brain segmentations or atlas and therefore have the same number of parcellations.

The proposed nodal analysis aims to first calculate the nodal voltages $\mathbf{u}$ which are then used to solve the functio-structural current matrix $\mathbf{FSC}$. The voltage source matrix obtained from the functional connectivity should not be confused with the nodal voltages. Setting up the system of linear equations for solving these nodal voltages using MNA requires the following six steps.

First, the definition of a conductance matrix $\mathbf{G}$ with the conductance being the reciprocal of the resistance. The diagonal elements $\mathbf{G}_{ii}$ are the sum of all conductances connected to node i. All other elements ij with $i \neq j$ are the opposite of the sum of all conductances connected between nodes i and j.

Second, the definition of a $\mathbf{B}$ matrix that holds the information of positive and negative terminals in the circuit and has dimensions of the number of nodes N in the connectivity matrices times the number of voltage sources M. The number of

voltage sources is the number of non-zero elements in the voltage matrix. While it is an arbitrary choice of which direction is positive or negative in the $\mathbf{B}$ matrix, in all cases $B_{ij} = -B_{ji}$.

Third, since the proposed model does not take into account any dependent voltage sources, the next matrices $\mathbf{C}$ and $\mathbf{D}$ needed for MNA are simply defined as $\mathbf{C} = \mathbf{B}^T$ and $\mathbf{D}$ is an M times M zero matrix. If dependent voltage sources would be of interest in future applications, these can readily be modified for them according to MNA rules (Ho et al., 1975; Wedepohl and Jackson, 2002).

Fourth, these matrices are concatenated into one $\mathbf{A} = \left[\begin{smallmatrix} \mathbf{G} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{smallmatrix}\right]$.

Fifth, a vector $\mathbf{z}$ with elements of N independent current sources and M independent voltage sources is defined. Note that the proposed model does not include independent current sources therefore the first N elements are zeros in $\mathbf{z}$. The rest M elements are the independent voltage sources from the functional connectivity matrix.

Sixth, a ground node is selected. This is an arbitrary decision therefore selecting the first node as ground is as good as any other selection. Practically, this sixth step is done by removing the ground node from both $\mathbf{A}$ (the first row) and $\mathbf{z}$ (the first element). The nodal voltages $\mathbf{u}$ are then solved from the system of linear equations $\mathbf{Ax} = \mathbf{z}$ where the first $N - 1$ (-1 because the ground node was removed) elements of $\mathbf{x}$ are the nodal voltages of interest $\mathbf{u}$ and the rest M elements are the currents associated with the voltage sources (which are not considered in the proposed model but could be useful in future applications). The ground node with zero voltage is prepended as the first element into $\mathbf{u}$.

At this point, the MNA is completed and analysis continues to calculate the voltage difference or potential matrix $\mathbf{U}$ between the N nodes. The elements in this difference matrix are obtained from the nodal voltage vector as follows $U_{ij} = |u_i - u_j|$. Lastly, the functio-structural current matrix is calculated by applying Ohm's law $\mathbf{FSC} = \frac{\mathbf{U}}{\mathbf{R}}$.

4.2 General feasibility of the proposed method

The same subgroup of unrelated healthy adults ($n = 207$, with 83 males, ages ranging from 22 to 36 years with mean $\pm$ std being 28.73$\pm$3.73) from the HCP (Van Essen et al., 2012) that was used in previous studies (Larivière et al., 2021, 2020) was utilized in this study. The average structural and functional connectivity matrices of this sample were accessed using the ENIGMA Toolbox (Larivière et al., 2021) functions $load_fc()$ and $load_sc()$. For the complete details on how these matrices were calculated, please see the "Connectivity data for macroscale connectome models" section by Larivière et al. (2021). For the demonstration purposes, the default parcellation scheme (Desikan-Killiany) was selected resulting in 68 times 68 connectivity matrices.

The first example demonstrating indirect connection mapping was done using a masked functional connectivity matrix. The masking was done by selecting the left middle temporal gyrus as the seed region as shown in figure 1 A. The right middle temporal gyrus was selected as the target as it did not have a direct structural connection to the seed region (figure 1 B). The masked functional connectivity matrix was used as voltage sources with the non-masked structural connectivity matrix as the resistance in the FSC analysis. This resulted in the functio-structural current map seeding from the left middle temporal gyrus (figure 1 C) from which a current to the right inferior temporal gyrus was identified. Going back to the structural connectivity data starting from the right inferior temporal gyrus, it was identified as the needed link between the original indirect connection from left to right middle temporal gyrus (figure 1 D).

The second example was done using the whole functional connectivity matrix as the voltage sources for the FSC analysis. The full functional and structural connectivity matrices were used to calculate the FSC connectivity matrix. All connectivity matrices were normalized by dividing them by their maximum value. However, to study the correlations between the matrices, all edges that had zero weight in the structural connectivity matrix were removed. This is a sensible choice as the structure is necessary for the current to flow therefore any edge with zero weight in the structural connectivity

matrix would have also zero weight in the FSC connectivity matrix. Ordinary linear regression and Pearson correlation analysis were performed on the resulting matrices.

4.3 Aging of the healthy human brain

An another set of healthy human brain data ($n = 171$, with 97 males, ages raging from 5 to 85 years with mean $\pm$ std being 38.5 ± 19.9) was obtained from the UCLA multimodal connectivity database (Brown et al., 2012). For the complete details on how the connectivity matrices were calculated, please see the previous study by Brown et al. (2012). The brain parcellations for this data were based on the spatially constrained spectral clustering method (Craddock et al., 2012) to obtain 188 times 188 connectivity matrices. The only difference between the data in the current study compared to the previous one is that in this study the analysis was limited to subjects that had both functional and structural connectivity matrices. The main benefit from this dataset was that it enabled the analysis across the ages of the subjects.

Subject-wise functional and structural connectivity matrices were used to calculate corresponding FSC connectivity matrices. An average over subject-wise edge weights for each matrix was calculated to study how they would correlate with the subject's age. A robust linear regression model (Huber's M-estimator) was used to fit a line to find out if there is a linear correlation between age and the average edge weights. The robust estimator was used as structural data contained outliers. If outliers were left in place, all correlations would be enhanced therefore this approach provides a conservative estimate for the correlations.

References

Basser, P., Mattiello, J., and LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1):259–267.

Behrens, T. E. J. and Sporns, O. (2012). Human Connectomics. *Current Opinion in Neurobiology*, 22(1):144–153.

Brown, J. A., Rudie, J. D., Bandrowski, A., Van Horn, J. D., and Bookheimer, S. Y. (2012). The UCLA multimodal connectivity database: a web-based platform for brain connectivity matrix sharing and analysis. *Frontiers in Neuroinformatics*, 6. Publisher: Frontiers.

Chung, M. K., Hanson, J. L., Adluru, N., Alexander, A. L., Davidson, R. J., and Pollak, S. D. (2017). Integrative Structural Brain Network Analysis in Diffusion Tensor Imaging. *Brain Connectivity*, 7(6):331–346.

Craddock, R. C., James, G. A., Holtzheimer, P. E., Hu, X. P., and Mayberg, H. S. (2012). A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Human Brain Mapping*, 33(8):1914–1928.

Damoiseaux, J. S. and Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure and Function*, 213(6):525–533.

Frau-Pascual, A., Augustinack, J., Varadarajan, D., Yendiki, A., Salat, D. H., Fischl, B., and Aganj, I. (2021). Conductance-Based Structural Brain Connectivity in Aging and Dementia. *Brain Connectivity*, 11(7):566–583. Publisher: Mary Ann Liebert, Inc., publishers.

Frau-Pascual, A., Fogarty, M., Fischl, B., Yendiki, A., and Aganj, I. (2019). Quantification of Structural Brain Connectivity via a Conductance Model. *NeuroImage*, 189:485–496.

Friston, K. J. (2011). Functional and effective connectivity: a review. *Brain*, 1(1):13–36. MAG ID: 2061564920.

Greicius, M. D., Supekar, K., Menon, V., and Dougherty, R. F. (2009). Resting-State Functional Connectivity Reflects Structural Connectivity in the Default Mode Network. *Cerebral Cortex*, 19(1):72–78. MAG ID: 2106396500.

Hermundstad, A. M., Bassett, D. S., Brown, K. K., Brown, K. S., Aminoff, E., Clewett, D., Freeman, S., Frithsen, A., Johnson, A., Tipper, C. M., Miller, M. B., Grafton, S. T., and Carlson, J. M. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proceedings of the National*

Academy of Sciences of the United States of America, 110(15):6169–6174. MAG ID: 2002807356.

Ho, C.-W., Ruehli, A., and Brennan, P. (1975). The modified nodal approach to network analysis. *IEEE Transactions on Circuits and Systems*, 22(6):504–509. Conference Name: IEEE Transactions on Circuits and Systems.

Hodgkin, A. L. and Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, 117(4):500–544.

Huang, H. and Ding, M. (2016). Linking Functional Connectivity and Structural Connectivity Quantitatively: A Comparison of Methods. *Brain*, 6(2):99–108. MAG ID: 2229937548.

Johansen-Berg, H. and Rushworth, M. F. (2009). Using Diffusion Imaging to Study Human Connectional Anatomy. *Annual Review of Neuroscience*, 32(1):75–94. _eprint: https://doi.org/10.1146/annurev.neuro.051508.135735.

Larivière, S., Paquola, C., Park, B.-y., Royer, J., Wang, Y., Benkarim, O., Vos de Wael, R., Valk, S. L., Thomopoulos, S. I., Kirschner, M., Lewis, L. B., Evans, A. C., Sisodiya, S. M., McDonald, C. R., Thompson, P. M., and Bernhardt, B. C. (2021). The ENIGMA Toolbox: multiscale neural contextualization of multisite neuroimaging datasets. *Nature Methods*, 18(7):698–700. Number: 7 Publisher: Nature Publishing Group.

Larivière, S., Rodríguez-Cruces, R., Royer, J., Caligiuri, M. E., Gambardella, A., Concha, L., Keller, S. S., Cendes, F., Yasuda, C., Bonilha, L., Gleichgerrcht, E., Focke, N. K., Domin, M., von Podewills, F., Langner, S., Rummel, C., Wiest, R., Martin, P., Kotikalapudi, R., O'Brien, T. J., Sinclair, B., Vivash, L., Desmond, P. M., Alhusaini, S., Doherty, C. P., Cavalleri, G. L., Delanty, N., Kälviäinen, R., Jackson, G. D., Kowalczyk, M., Mascalchi, M., Semmelroch, M., Thomas, R. H., Soltanian-Zadeh, H., Davoodi-Bojd, E., Zhang, J., Lenge, M., Guerrini, R., Bartolini, E., Hamandi, K., Foley, S., Weber, B., Depondt, C., Absil, J., Carr, S. J. A., Abela, E., Richardson, M. P., Devinsky, O., Severino, M., Striano, P., Tortora, D., Hatton,

S. N., Vos, S. B., Duncan, J. S., Whelan, C. D., Thompson, P. M., Sisodiya, S. M., Bernasconi, A., Labate, A., McDonald, C. R., Bernasconi, N., and Bernhardt, B. C. (2020). Network-based atrophy modeling in the common epilepsies: A worldwide ENIGMA study. *Science Advances*, 6(47):eabc6457. Publisher: American Association for the Advancement of Science.

Le Bihan, D., Mangin, J.-F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., and Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4):534–546. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1002/jmri.1076.

Maier-Hein, K. H., Neher, P. F., Jean-Christophe Houde, Houde, J.-C., Côté, M.-A., Garyfallidis, E., Jidan Zhong, Zhong, J., Jidan Zhong, Chamberland, M., Fang-Cheng Yeh, Yeh, F.-C., Lin, Y.-C., Qing Ji, Ji, Q., Reddick, W. E., Glass, J. O., David Chen, David Qixiang Chen, David Qixiang Chen, Chen, D., Chen, D., Yuanjing Feng, Feng, Y., Chengfeng, G., Wu, Y., Ma, J., Renjie, H., Li, Q., Carl-Fredrik Westin, Westin, C.-F., Samuel Deslauriers-Gauthier, Deslauriers-Gauthier, S., Gonzalez, J. O. O., Paquette, M., St-Jean, S., Gabriel Girard, Girard, G., François Rheault, Rheault, F., Sidhu, J., Chantal M. W. Tax, Tax, C. M. W., Fenghua Guo, Guo, F., Mesri, H. Y., Szabolcs Dávid, David, S., Froeling, M., Heemskerk, A. M., Alexander Leemans, Leemans, A., Boré, A., Pinsard, B., Christophe Bedetti, Bedetti, C., Desrosiers, M., Brambati, S. M., Brambati, S. M., Doyon, J., Sarica, A., Vasta, R., Cerasa, A., Aldo Quattrone, Quattrone, A., Yeatman, J. D., Khan, A. R., Hodges, W., Wes Hodges, Wes Hodges, Alexander, S. P., Simon Alexander, Simon Alexander, Alexander, S., David Romascano, Romascano, D., Barakovic, M., Auria, A., Esteban, O., Lemkaddem, A., Thiran, J.-P., Jean-Philippe Thiran, Jean-Philippe Thiran, Jean-Philippe Thiran, Cetingul, H. E., Cetingul, H. E., Odry, B. L., Mailhe, B., Nadar, M. S., Mariappan S. Nadar, Nadar, M. S., Pizzagalli, F., Prasad, G., Villalon-Reina, J. E., Galvis, J., Thompson, P. M., De Santiago Requejo, F., Laguna, P. L., Lacerda, L., Rachel Barrett, Barrett, R., Flavio Dell'Acqua, Dell'Acqua, F., Catani, M., Petit, L., Caruyer, E., Daducci, A., Dyrby, T. B., Holland-Letz, T., Hilgetag, C. C., Stieltjes, B., Bram Stieltjes, and Descoteaux, M. (2016). Tractography-based

connectomes are dominated by false-positive connections. *bioRxiv*, page 084137. MAG ID: 2550828940.

Rubinov, M. and Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3):1059–1069.

Sairanen, V. and Andersson, J. (2023). Outliers in diffusion-weighted MRI: Exploring detection models and mitigation strategies. *NeuroImage*, 283:120397.

Sairanen, V., Ocampo-Pineda, M., Granziera, C., Schiavi, S., and Daducci, A. (2021). Incorporating outlier information into diffusion MR tractogram filtering for robust structural brain connectivity and microstructural analyses. Technical report. Company: Cold Spring Harbor Laboratory Distributor: Cold Spring Harbor Laboratory Label: Cold Spring Harbor Laboratory Section: New Results Type: article.

Smith, S. M., Miller, K. L., Salimi-Khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., Ramsey, J. D., and Woolrich, M. W. (2011). Network modelling methods for FMRI. *NeuroImage*, 54(2):875–891.

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues in Clinical Neuroscience*, 15(3):247–262.

Sporns, O., Tononi, G., and Kötter, R. (2005). The Human Connectome: A Structural Description of the Human Brain. *PLOS Computational Biology*, 1(4). MAG ID: 2146693559.

Suárez, L. E., Markello, R. D., Betzel, R. F., and Misic, B. (2020). Linking Structure and Function in Macroscale Brain Networks. *Trends in Cognitive Sciences*, 24(4):302–315.

Van Essen, D. C., Ugurbil, K., Auerbach, E. J., Behrens, T. E., Bucholz, R. D., R. Bucholz, Chang, A., Chen, L., Maurizio Corbetta, Corbetta, M., Della Penna, S., Curtiss, S. W., Della Penna, S., Feinberg, D. A., Glasser, M. F., Heath, A. C., Harel, N., Heath, A. C., Larson-Prior, L. J., Marcus, D. S., Michalareas, G., Moeller, S., Oostenveld, R., Petersen, S., Petersen, S. E., Prior, F. W., Schlaggar, B. L., Smith, S. M., Snyder, A. Z., Xu, J., and Yacoub, E. (2012). The Human Connectome

Project: A data acquisition perspective. *NeuroImage*, 62(4):2222–2231. MAG ID: 2020519533.

Wedepohl, L. M. and Jackson, L. (2002). Modified nodal analysis: an essential addition to electrical circuit theory and analysis. *Engineering Science & Education Journal*, 11(3):84–92. Publisher: IET Digital Library.

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