Jamalabadi, H., Zuberer, A., Kumar, V. J., Li, M., Alizadeh, S., Moradi, A. A., Gaser, C., Esterman, M., & Walter, M. (2020). The missing role of gray matter in studying brain controllability. *Network Neuroscience*. Advance publication. https://doi.org/10.1162/netn_a_00174

The missing role of gray matter in studying brain controllability

Hamidreza Jamalabadi[1*], Agnieszka Zuberer[1,2,3,7*], Vinod Jangir Kumar[6], Meng Li[6], Sarah Alizadeh[1], Ali Amani Moradi[8], Christian Gaser [7], Michael Esterman [2,3,9,10], Martin Walter [1,4,5,6,7]

[1] Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany

[2] Boston University School of Medicine, Department of Psychiatry, Boston, USA

[3] Boston Attention and Learning Laboratory, VA Boston Healthcare System, Boston, USA

[4] Clinical Affective Neuroimaging Laboratory, Magdeburg, Germany

[5] Leibniz Institute for Neurobiology, Magdeburg, Germany

[6] Max Planck Institute for biological cybernetics, Tübingen, Germany

[7] Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany

[8] School of Engineering, RMIT university, Melbourne, Victoria, Australia

[9] Neuroimaging Research for Veterans Center (NeRVe), Veterans Administration, Boston Healthcare System, Boston, USA

[10] National Center for PTSD, VA Boston Healthcare System, USA

* equal contribution

Corresponding Authors: Hamidreza Jamalabadi (hamidreza.jamalabadi@uni-tuebingen.de), Department of Psychiatry and Psychotherapy, Division for Translational Psychiatry, University of Tübingen, Calwerstr. 14, 72076; Agnieszka Zuberer (azuberer@bu.edu), National center for PTSD, VA Boston Healthcare System, USA

1 Abstract

Brain controllability properties are normally derived from the white matter fiber tracts in which the neural substrate of the actual energy consumption, namely the gray matter, has been widely ignored. Here, we study the relationship between gray matter volume of regions across the whole cortex and their respective control property derived from the structural architecture of the white matter fiber tracts. The data suggests that the ability of white fiber tracts to exhibit control at specific nodes not

only depends on the connection strength of the structural connectome but additionally strongly depends on gray matter volume at the host nodes. Our data indicates that connectivity strength and gray matter volume interact with respect to the brain's control properties. Disentangling effects of the regional gray matter volume and connectivity strength, we found that frontal and sensory areas play crucial roles in controllability. Together these results suggest that structural and regional properties of the white matter and gray matter provide complementary information in studying the control properties of the intrinsic structural and functional architecture of the brain.

Key words: Network control theory, Gray matter, Brain controllability

2 Introduction

Network control theory, as recently applied to white matter (WM) fiber tracts in the human brain, provides a novel mechanistic framework to describe the ease of switching between different dynamical functional brain states, and the regions that best drive these dynamics (Bassett & Sporns, 2017; John D Medaglia, 2019; John Dominic Medaglia, Pasqualetti, Hamilton, Thompson-Schill, & Bassett, 2017). This approach has the potential to inform theories of dynamic cognitive processes, clinical neuroscience, neurodegeneration, and brain reserve. Specifically, there is evidence that these global brain state transitions are impaired in clinical populations (Braun et al., 2019; Jeganathan et al., 2018; Kenett, Beaty, & Medaglia, 2018) and that such impairments can be traced back to specific driver nodes (Jeganathan et al., 2018; Yoed N Kenett et al., 2018; Muldoon et al., 2016; Zoeller et al., 2019). However, this far, these control properties have been exclusively derived from WM fiber tracts without the consideration of gray matter (GM) properties. Given the importance of GM properties for cognitive functioning and brain health, and the established interrelationships between white and gray matter, it has been suggested that regional gray matter integrity may be a critical contributor and proxy for network and node controllability (John Dominic Medaglia et al., 2017; J. D. Medaglia, Zurn, Sinnott-Armstrong, & Bassett, 2017).

Several lines of research suggest that GM may be essential to understanding brain controllability. First, GM is a proxy for the quantity of neurons and synaptic densities in a particular region (Lüders, Steinmetz, & Jäncke, 2002), and metabolic energy expenditure is primarily realized through the gray matter cell bodies that scaffold white matter tracts (Zhu et al., 2012). In neurodegenerative disorders, region specific lesions of GM only partially agrees with corresponding lesions in WM in some neurodegenerative disorders (Agosta et al., 2011; Bodini et al., 2009; Douaud et al., 2007; Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000; Villain et al., 2008), suggesting that GM reserve and WM may provide independent additional information with respect to controllability properties of the structural connectome. Taken together, these studies motivated the hypothesis that the controllability properties suggested by the WM should be partially related to or even predicted by GM integrity. Critically, it has been argued that including GM metrics in control theory will extend traditional volumetrics into network neuroscience (John Dominic Medaglia et al., 2017). Nevertheless, to our knowledge the nature of the interdependency between controllability properties and GM properties has not been addressed empirically.

To tackle this issue, we used two independent data sets to investigate whether, and if so, how control properties extracted from the structural connectome relate to properties of the gray matter, i.e. GM volume which engenders other GM metrics e.g. surface and thickness (Kong et al., 2015; Winkler et al., 2010). Since previous studies have shown that brain controllability can be largely explained by the connectivity strength of the structural connectome, we also considered whether GM volume could explain additional variance in controllability not accounted for by white matter connectivity. Initially, we investigated how WM and GM factors affect brain controllability on a whole brain level. In a further step, we identified the brain regions for which controllability was most sensitive to GM and/or WM properties. We discuss our findings with respect to their potential relevance to cognitive and clinical neuroscience.

3 Methods and Materials

3.1 Data acquisition

The structural and diffusion datasets are from 65 healthy subjects with the age range of 22 to 36 (28 M, mean age 29.2) which were taken from the Human Connectome Project (HCP, Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657; Van Essen et al., 2012). While HCP offers more than 1100 subjects, the data in the present study is limited by the resources necessary for preprocessing. We have tried to lift the potential bias by including an independent dataset (see replication study).

3.1.1 MRI Data Specification

Structural images were acquired with the following specification: T1w MPRAGE, TR 2400 ms, TE 2.14 ms, TI 1000 ms, flip angle 8 degrees, Field of View (FOV) 224x224, 256 slices, voxel size 0.7 mm isotropic, Bandwidth 210 Hz/Px, IPAT 2, acquisition time 7:40 min.

Diffusion weighted imaging (DWI) data were acquired by using a Spin-echo EPI sequence with TR 5520 ms, TE 89.5 ms, flip angle 78 degrees, voxel size, 1.25 mm isotropic, 111 slices, multiband factor, 3, echo spacing, 0.78 ms, b-values 1000, 2000, and 3000 s/mm2. For details, see (Glasser et al., 2013; Van Essen et al., 2012).

3.1.2 AAL mask definitions and native space transformation

The 3-D anatomy atlas of the AAL2 was acquired from the neurofunctional imaging group (http://www.gin.cnrs.fr/en/tools/aal-aal2/) (Tzourio-Mazoyer et al., 2002). It contains 120 regions, which include subcortical structures i.e. thalamus, caudate, putamen, pallidum, etc. However, it misses the brainstem. The 12-parameter affine transformation (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) was computed for each volunteer's T1 and non-diffusion image and the MNI spaced standard brain. The resulted transformation matrix was applied to the left and right AAL brain regions to transform them into the native structural and diffusion space.

3.1.3 Structural volume analysis

The tissue type segmentation employed SPM12 unified segmentation approach. The process resulted in segmented gray, white, and cerebro-spinal fluid (CSF) volumes. In the next step, we determined the volume of the brain, gray matter, and under each AAL atlas region for all subjects. The skull extracted AC-PC aligned native spaced NIFTI structural scans were obtained from the Human Connectome database. In the next step, the tissue type segmentation was applied to delineate the gray matter within the brain using the SPM12 unified segmentation approach (Ashburner & Friston, 2005). This segmentation approach employs a generative model that combines non-linear registration, tissue classification, and bias correction.

3.1.4 Preprocessing and Diffusion-Fit

The obtained HCP diffusion data were reconstructed using a SENSE1 algorithm (Sotiropoulos et al. 2013). The DWI data was corrected for motion and distortion (Andersson et al. 2003; Andersson and Sotiropoulos 2015, 2016). Furthermore, pre-processing included unringing, denoising, and tensor analysis implemented in MRtrix (Tournier, Calamante, & Connelly, 2012).

The data were reconstructed using the multi-shell multi-tissue constrained spherical deconvolution (Jeurissen, Tournier, Dhollander, Connelly, & Sijbers, 2014). The resulted Orientation Distribution Function (ODF) was registered to the structural space. The initial tractogram was generated using mrtrix-tckgen, resulting in 100 million streamlines within each subject. In the next step, we applied spherical deconvolution informed filtering of tractograms (SIFT) to reduce the streamline count to 10 million. In the final step, the number of streamlines was determined between AAL brain regions to produce a connectome. The analysis steps in more details are documented at the mrtrix docs i.e. (https://mrtrix.readthedocs.io/en/latest/quantitative_structural_connectivity/structural_connectome.html).

3.2 Network control framework

Controllability is one of the fundamental concepts in the control theory. The notion of controllability of a dynamical system was first introduced in (Kalman, 1963). State (output) controllability of a

dynamical system is defined as the possibility of driving states (outputs) of the system from an arbitrary initial condition to any desired values in finite time by applying appropriate control signals (Kailath, 1980). The most famous classic method to ensure state controllability of a dynamical system defined by the noise-free linear discrete-time and time-invariant network model says that the system

$$x(k+1) = Ax(k) + Bu(k) \quad (1)$$

$$y(k) = Cx(k) + Du(k) \quad (2)$$

is full state controllable if and only if the Kalman's controllability matrix [B, AB, …, $A^{n-1}B$] has full rank (Kailath, 1980). In the system represented in equations 1-2, $\boldsymbol{x} \in \mathbb{R}^n$ and $\boldsymbol{u} \in \mathbb{R}^p$ are state and input signals, respectively. A, B, C and D are matrices with appropriate dimensions where A and B are called state and input matrices, respectively. When applied in the context of brain controllability, $\boldsymbol{x}$ describes the activity of brain regions. A is an adjacency matrix that represents the interactions between brain regions and its elements are often the strength of the white tracts connecting two areas (see section 3.3 for details). The input matrix B identifies the control nodes in the brain which may be confined to one or more brain areas whose activities are denoted by the corresponding elements of $\boldsymbol{x}$. While the controllability matrix is a valuable metric to study the overall character of asystem, it does not directly quantify potential ability of different nodes of the system to act as driver nodes. To achive this, a common practice is to use $Tr(W_k)$ which is the trace of the controllability Gramian $W_k = \sum_{i=0}^{\infty} A^i B B^T (A^T)^i$ when the system is controlled from node k. Referred to as average controllability (AC), this metric is the most commonly used controllability measure in the neuroimaging literature (Gu et al., 2015; John D Medaglia, 2019) and is a measure of the average energy required for node k to steer the brain into all possible output states (see Tang & Bassett, 2018 a formal definition). In addition to AC that quantifies the ability of the nodes to drive the who system into all potential target states, Modal Controllability (MC) is another commonly used metric which is a measure of the ability of the nodes to push the system toward difficult-to-reach states. Formally defined as $\phi_k = \sum_j^N [1 - \xi_j^2(A)] v_{kj}^2$ MC is a scaled measure of difficulty of driving the system toward all N modes of A from node k (Pasqualetti, Zampieri, & Bullo, 2014).

3.3 Statistical analysis

Linear mixed effect (LME) regression (Baayen, Davidson, & Bates, 2008) allows to model the interrelation among multiple variables and has the ability to accommodate various experimental designs including repeated measurements, subject variability, and grouping structures in one unified implementation (Boisgontier & Cheval, 2016). In this paper, we model the interrelation between brain controllability (AC and MC), GM volume, and connectivity strength, for which we train multiple LMEs for different tasks. In these models, the elements A_{ij} of the structural connectivity matrix (i.e. A in equation 1) represent the number of streamlines between regions i and j. To ensure robustness, we keep only 10% of strongest connections using brain connectivity toolbox (Rubinov & Sporns, 2010). Within this scheme, i^{th} node degree is estimated by the sum of all elements of A in the i^{th} row. GM volume is estimated from the unified segmentation approach within SPM 12 (see section 3.1.3 for details). In particular, we include regional gray matter (rGM) and total intracranial volume (TIV) in the LMEs.

3.3.1 LME formulation and statistical model comparison

To predict brain controllability metrics based on structural measures of the brain we built a linear mixed-effects (LME) regression (Baayen et al., 2008) using a step-wise approach retaining an effect only if there was a significant difference between the log-likelihood ratio of the two models, based on an ANOVA ($p < 0.05$). Statistical analysis was performed using the lme4 package in R (Bates, Maechler, Bolker, & Walker, 2014). Specifically, we used two models. The first model is defined by controllability (AC/MC) ~ TIV+ Regions + Nodal degree * rGM + (1|participants) where "*" denotes the interaction where we are interested in quantifying the contribution of regional gray matter and nodal degree in explaining AC after controlling for the regional differences of AC. In a second model which is defined as AC/MC ~ TIV+ Regions * Nodal degree + Regions * rGM + (1| participants) we investigate the contribution of regional differences of regional gray matter and regional differences of nodal degree onto AC.

On the models, the volume of the entire brain (TIV) was added as a covariate because of the evidence that it is related to properties of the GM (Lüders et al., 2002). In these models all the variables are centered around zero within each subject and normalized using z-transformation. Furthermore, we statistically tested different models explaining the same outcome measure using the lme4 package in R (Bates et al., 2014).

3.3.2 Null models

To further test our hypothesis, similar to (Lee, Rodrigue, Glahn, Bassett, & Frangou, 2020), we built random null models by randomizing the structural connectivity matrix (i.e. A in equation 1) and estimated the interrelation between controllability, gray matter, degree distribution as explained in section 3.3.1. Specifically, preserving its degree distribution, we randomized matrix A 1000 times using the brain connectivity toolbox (Rubinov & Sporns, 2010) and compared the beta values of rGM in the randomized networks to that obtained in the original network.

4 Results

4.1 Effects of gray matter on brain controllability

In a first step, we investigated if we could replicate previously reported findings that higher nodal degree relates to higher AC (see Figure 1A). We built a linear mixed effects model to predict AC based on nodal degree with subjects as a random intercept (for details see Supplementary Material-Model comparisons Table C1). Our results, summarized in Figure 1A replicates previous findings (Gu et al., 2015) suggesting that structural connectivity strength quantified in terms of nodal degree across the whole brain is positivity associated with nodal AC. In the second step we investigated if, beyond this positive association between degree and AC, rGM explains additional variance of AC. To this aim, we extended our model by including regional GM volume and TIV as additional predictors to nodal degree Our results show that rGM and nodal degree are both critical to explain AC and their respective sizes of effect are comparable (β_{degree}= 0.36 [p-value < 0.001], β_{rGM} = 0.44 [p-value < 0.001]). Next, we

included regions as additional predictors to further explain AC and to improve the fitness of the model. Our results show, that rGM and AC are significantly positively associated (see Figure 1B) and interact with nodal degree (β=0.04, 95% CI:[0.01 0.07], p_{bonf} = 0.01), suggesting that highest levels of average controllability were best explained with concurrent high rGM and high node degree (see Figure 1C). To verify that the AC cannot not be explained with simpler models, we compared competing models (see Supplementary Material-Model comparisons Table C1). The results show that the full model (for details, see the competing models Supplementary Material-Model comparisons Table C1 and the full outcomes of the winning model in Table S1) outperformed all alternatives Finally, we used randomized null networks (for details see section 3.3.2) to investigate if rGM would remain a significant factor. Our results show that the contribution of rGM in the randomized networks is significantly lower than those in the original networks (p-value < 0.001). Taken together, our results stress the interdependency between nodal connectivity strength and GM volume for brain controllability.

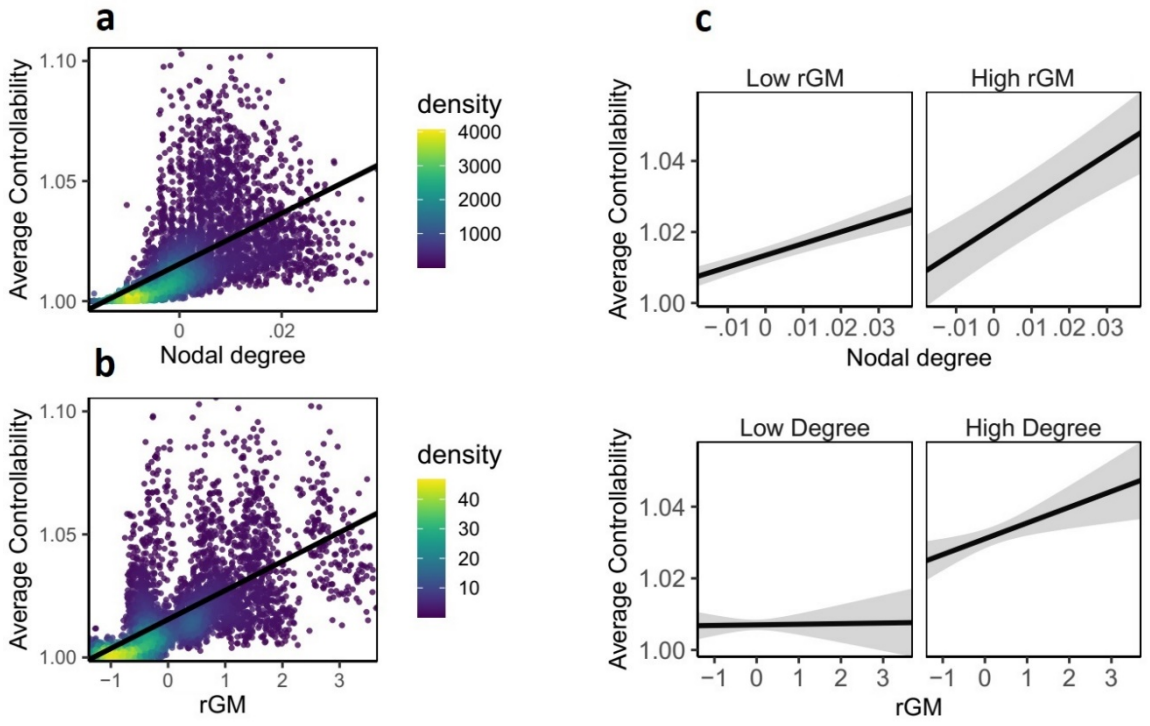

Figure 1: Visualization of interaction effect of nodal degree and rGM in the mixed effects model predicting average controllability (AC). This effect was controlled for by the TIV and regional differences of average controllability. Figure shows that AC is best explained by WM structure and rGM together. Each dot represents one region from one subject. The density bar shows where the majority of the data is located. (A) Association between nodal degree and AC. (B) Association between

rGM and AC. (C) Interaction between rGM and degree on AC suggesting that highest levels of AC are reached when both degree and rGM are high together. For visualization, median split was used to classify rGM and Degree into high and low respectively. In the original model, both effects were preserved as continuous variables.

Finally, in a further step, we used the same model to assess the relation between MC, rGM, and nodal degree (see Supplementary Material-Modal controllability, Figure B1). Replicating previously reported findings that MC and nodal degree relates are negatively correlated (see Supplementary Material-Modal controllability, Figure B1-a), we find that rGM explains a large part of MC variance and that the combination of nodal degree, rGM, and their interaction is necessary.

4.2 Regional distribution of Average Controllability based on gray matter volume

Further, we investigated if this global interdependency between WM and rGM (see previous section) differs on a regional level. Given our previous results that MC and AC are strongly negatively correlated and that this is reflected in the LMEs, here we focus on the AC.

Our results (see the competing models Supplementary Material-Model comparisons Table C2 and the full outcomes of the winning model in Table S2) show that, higher rGM and nodal degree concomitantly are associated with higher AC (see Figure 2; Table S2). Notably, highest AC levels with higher nodal degree were exhibited in the left frontal middle gyrus (β=15.11, 95% CI:[4.09 26.13], p_{bonf} =0.007) left superior frontal gyrus (β=3.01, 95% CI:[.24 5.78],p_{bonf}=0.033), which agrees with previous research also locating driver nodes for AC in the frontal lobes. Further, higher levels of AC were linked to higher levels of nodal degree in the left Calcarine (β=1.78, 95% CI:[.69 2.86],p_{bonf}=0.001). There were also regions where higher levels of nodal degree exacerbated AC, with strongest effects located in the right and left cuneus (right cuneus: β=-1.34, 95% CI:[-2.11 -0.57], p_{bonf}=0.001; left cuneus: β=-2.70, 95% CI:[-3.33 -2.08],p_{bonf}<0.001). When turning to the relation of rGM and AC, higher rGM associated with higher AC levels in the right Calcarine (β=5.61, 95% CI:[4.50 6.73],p_{bonf}<0.001), right lingual area (β=2.98, 95% CI:[2.63 3.33],p_{bonf}<0.001) and the left and right anterior cingulate (left anterior

cingulate: β= 3.76, 95% CI:[2.61 4.91],p_{bonf}<0.001; right anterior cingulate: β= 2.88, 95% CI:[2.28 3.48],p_{bonf}<0.001).

There were several regions exhibiting lower AC levels with higher rGM. Strongest effects were found in the right cuneus (β=-16.17, 95% CI:[-18.46 -13.88],p_{bonf}<0.001) and the left frontal middle gyrus (β=-3.34, 95% CI:[-6.62 -0.07],p_{bonf}= 0.045). The finding suggests that, although on a whole brain level nodal degree and rGM are concomitantly associated with increased AC, for some regions, most notably the left frontal middle gyrus, higher nodal degree and lower rGM together exhibit higher AC (see Table S2).

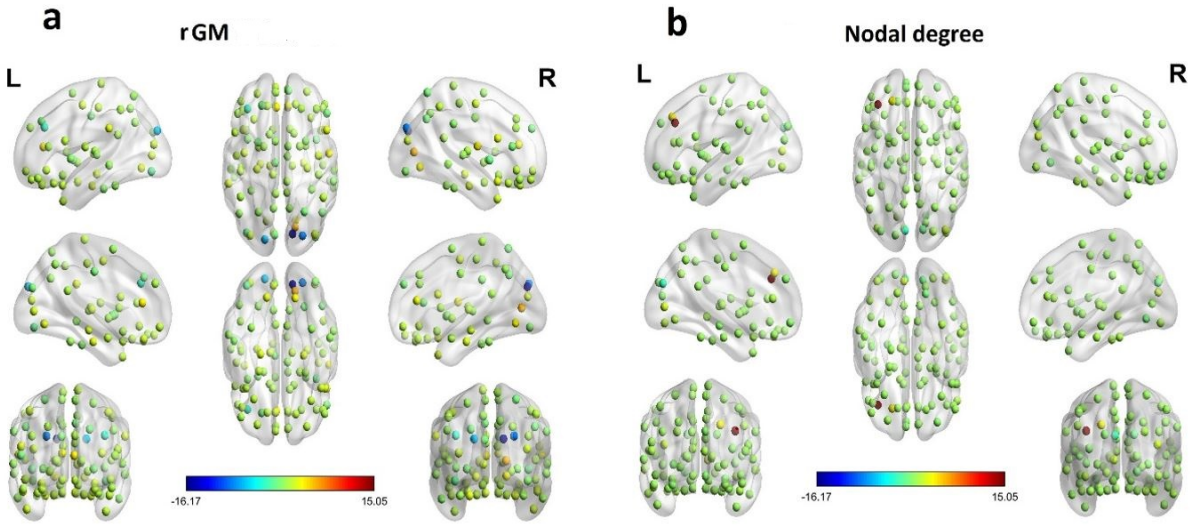

Figure 2: Visualization of interaction effects of mixed effects model predicting average controllability (AC) based on regional GM (A) and regional nodal degree (B). For visualization, colors represent standardized Beta coefficients for effects of rGM and nodal degree respectively for each brain region. Higher values indicate a beneficial and lower values indicate an impeding effect of rGM /nodal degree onto AC.

4.3 Replication study

To investigate if the results in section 3.1. (complementary effects of rGM and nodal degree and AC and MC) are replicable, we used data from a cohort of 48 subjects from another publicly available dataset where we also used a slightly different preprocessing pipeline (see Supplementary Material-Replication study methods for details). Also, in this data set nodal degree and rGM increased AC (see Figure 3; for details see Table S3), while highest AC levels were achieved when both nodal degree and higher rGM were high together (β=0.08, 95% CI:[0.04 0.12], p_{bonf} =0.01). Furthermore, rGM and nodal

degree both decrease MC and the lowest values of MC were achieved only for the lowest levels of rGM and nodal degree (Supplementary Material - Modal controllability, Figure B2). Taken together, these results suggest that this association between rGM and nodal degree is robust and not driven by individual differences in different data sets.

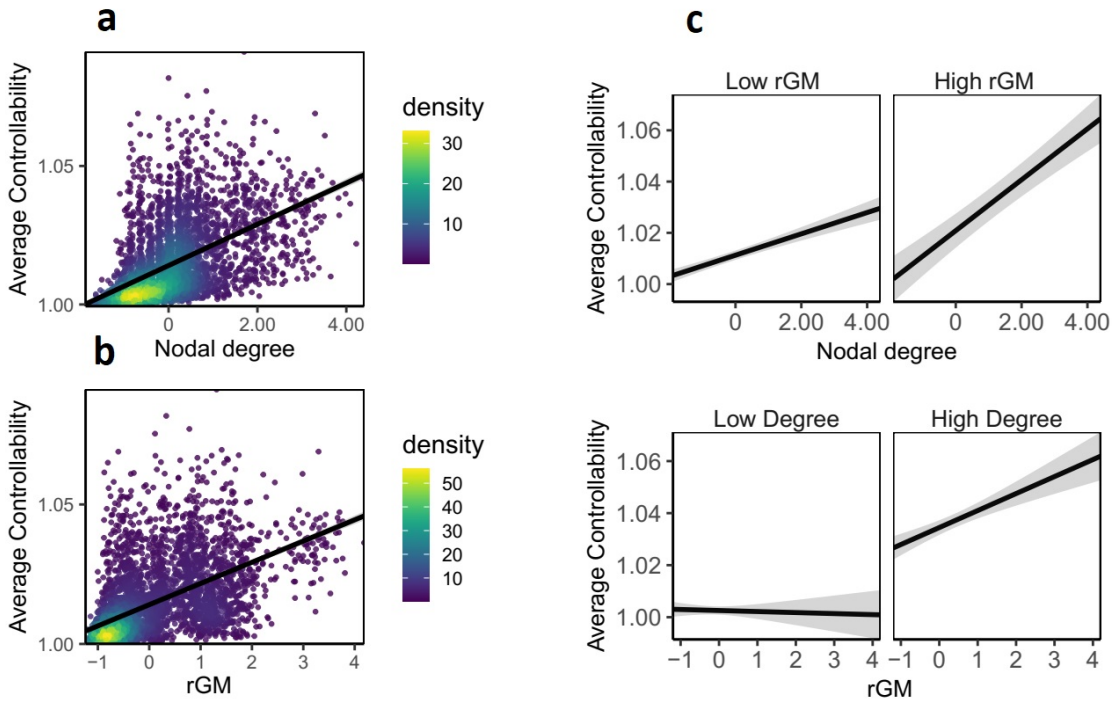

Figure 3: Replication sample. AC is estimated based on WM structure but strongly relates to rGM. Each dot represents data from one region of one subject and density bar shows where the majority of data is located. (A) Effect of nodal degree on AC. (B) Effect of rGM on AC. (C) Interaction effect between rGM and nodal degree suggests that highest levels of AC are reached when both degree and rGM are high together. For visualization, median split was used to classify rGM and degree into high and low respectively. In the original model, both effects were preserved as continuous variables.

5 Discussion

In this work, we investigated how brain volumetrics contribute to global network control properties derived from the structural connectome composed of the white matter fiber tracts. In line with (John Dominic Medaglia et al., 2017), we hypothesized that large-scale network dynamics derived from the structural connectome (here quantified by average and modal brain controllability) would be further

explained by GM structural properties. This work is, to our knowledge, the first attempt to map the interdependency of both metrics, and we discuss findings with respect to their clinical relevance.

We show that on average, the amount of rGM directly affects the brain's availability to dynamically transition between brain states and to adopt new modes of activity. However, levels of brain controllability were best explained when combining information from structural properties of both WM and rGM, suggesting that volumetric might provide additional information in relating brain controllability to understanding cognition, neurological and neuropsychiatric disorders, and the concept of brain reserve.

5.1 Mediating role of GM on the relation between WM and brain controllability

Our finding that nodal degree is highly predictive of brain controllability agrees with previous works (Gu et al., 2015; John D Medaglia, 2019), suggesting that the brain's ability to traverse into easy and difficult-to-reach brain states relies on strength of structural connectivity, which might reflect the degrees of freedom to steer the transition of brain states. However, our findings suggest that this picture is incomplete. Structural connectivity relies on sufficient support from GM reserves. Highest effects of AC were reached with enhanced nodal degree within frontal regions, which support the rich literature showing that frontal brain networks play a central role in initiating dynamic reconfigurations during executive cognition. However, increased rGM within that very region was negatively related to brain controllability. While within clinical populations reduced rGM is generally related to neuropathology, there is research suggesting that within healthy subjects, rGM decreases with increases of WM density throughout development from adolescence to adulthood. This finding has been related to reduced quantity of synapses resulting from synaptic pruning (Giorgio et al., 2010) which has been predominantly found in primary visual (calcarine sulcus) and prefrontal cortex (middle frontal gyrus) (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997). In our data, average brain controllability was maximal when exactly these regions showed reduced rGM and increased connectivity of the white matter connectome. One could speculate that this finding reflects more

efficient and developmentally advanced brain functioning in a broad range of tasks potentially related to synchronizing the actions with intentions in a goal directed way.

5.2 Potential contribution of sensory regions to brain controllability

On a functional level, we find several key visual areas to stand out with respect to both average as well as modal controllability. Enhanced rGM in the right cuneus has previously been reported to predict higher error rates in a response inhibition task in bipolar (Haldane, Cunningham, Androutsos, & Frangou, 2008) and has also been related to motor response in functional imaging studies (Booth et al., 2005; Matthews, Simmons, Arce, & Paulus, 2005). We believe that these findings suggest that the function of those primary visual areas goes far beyond unimodal information processing. Closely related, recent work suggests that primary sensory cortices might occupy more "hub-like" positions in the brain through enhanced long-distance connectivity across brain-wide communities (Esfahlani, Bertolero, Bassett, & Betzel, 2020). Taken together, we speculate that sensory regions could be ideal hot spots for brain controllability nodes. Given their high global inter-connectivity, these sensory nodes act potentially as the controllers with respect for the afferent inputs while the other regions act as controllers for efferent demands.

5.3 Linking GM and WM in the context of controllability

Cognitive functioning arises from complex re-configurations across metabolically expensive large-scale networks, facing a trade-off between wiring cost (topological efficiency) and efficient adaptation patterns between multiple neuronal populations (topological value; Bullmore & Sporns, 2012). Recent studies have suggested that the behavioral relevance of this tradeoff between topological efficiency and topological value can be described by the brain's energy expenditure to exhibit control along large-scale structural networks. The ratio of neuronal signaling to non-signaling related metabolic energy expenditure has shown opposite directionalities for white and gray matter (Yu et al, 2018, Zhu et al 2012). Here, we speculate that energy expenditure could be one of the key factors linking GM and WM in the framework of controllability analysis. AC relates to the average energy a brain region needs to

exert to steer the brain dynamics into all possible brain states (Gu et al., 2015; Y. N. Kenett et al., 2018; Liu, Slotine, & Barabasi, 2011) and therefore, more regional gray matter volume is more likely to provide the sufficient energy. In contrast, in absence of sufficient WM tracts i.e. lower nodal degree, rGM cannot fully force the transitions since the energy cannot be exerted. This conception has to be expressed on a behavioral level, in that the brain system's control capacity is especially sensitive to rGM. Indeed, a range of studies have suggested that rGM but not white matter changes relate to abnormal behavioral conditions, such as in antisocial personality disorder (Raine et al., 2000), medication-naive high-functioning children with autism spectrum disorder (Palmen et al., 2005), and alcohol dependent individuals (Fein et al., 2002). Closely related, MC is strongest when nodal degree and rGM are simultaneously low. MC is related to the ability to drive the brain dynamics toward difficult to reach states by change the modes of activity on the whole brain level. It is therefore conceivable to propose that similar to the relevance of nodal sparsity to enable optimal MC (Gu et al., 2015), scarcity of rGM enhances the ability of the host node by exerting more fine-grained effects that affect only a minimal set of others nodes.

5.4 Limitations: beyond linear full controllability

Our results in the current study warrant the conclusion that the interplay of gray matter and controllability has a complex nature. Different kinds of controllability are best practiced for different values of gray matter volume. While this seems to be a satisfying first insight on the potential missing role of gray matter in studying brain controllability, there are important aspects which remain yet to be explored. The choice of nonlinear dynamics to define the range of controllability metrics could have considerable effects on our findings. For instance, it is suggested that importance of nodal geometry could actually follow opposite trends when nonlinear and control models are compared (Jiang & Lai, 2019). How the nonlinearity might (re)define the role of rGM for control is an interesting question to ask. Relatedly, brain controllability metrics considered in the current paper are trajectory unspecific. This approach, although theoretically interesting and widely practiced, is of limited practical relevance. Studies of dynamical functional and structural connectivity and analysis of structural covariance have

reliably shown that brain state trajectories are not random, but rather follow general rules (see Gu et al., 2017; Tang & Bassett, 2018 for recent attempts to accommodate trajectory dependence within in the broader context of network control theory). Taken together, we believe that the role of GM should be further studied and possibly updated accounts of controllability introduced. An updated version can incorporate the nonlinearity of controllability indices and the rGM relevance by introducing novel metrics which are simultaneously dependent on structural connectivity and regional gray matter.

6 Acknowledgements

HJ was supported by Fortüne grant of Medical Faculty of University of Tübingen (No. 2487-1-0). AZ was supported by the Swiss National Science Foundation (P2ZHP1_181435). MW was supported by EU-ERA-Net: Neuromarket, EU-WIDESPREAD: Fat4BBrain, DFG Wa2673/10, and Neurobiologie motivierten Verhaltens (TPA06). The authors declare no conflict of interest.

7 Author contribution statement

Conceptualization: HJ, AZ, MW, SA. Methodology: HJ, SA, AM, AZ. Validation: HJ, AZ. Statistical analysis: AZ, HJ. Resources: MW, ME. Supervision: MW, ME, CG. Data Curation: VK, ML. Writing-Original Draft: AZ, HJ. Writing-Review: AZ, HJ, ME, MW, CG.

8 Data availability statement

The data used in the current study publicly available online. See Methods for detail.

9 References

Agosta, F., Pievani, M., Sala, S., Geroldi, C., Galluzzi, S., Frisoni, G. B., & Filippi, M. (2011). White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology, 258*(3), 853-863.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839-851.

Baayen, R. H., Davidson, D. J., & Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *Journal of memory and language, 59*(4), 390-412.

Bassett, D. S., & Sporns, O. (2017). Network neuroscience. *Nature Neuroscience, 20*(3), 353.

Bates, D., Maechler, M., Bolker, B., & Walker, S. (2014). lme4: Linear mixed-effects models using Eigen and S4. *R package version, 1*(7), 1-23.

Bodini, B., Khaleeli, Z., Cercignani, M., Miller, D. H., Thompson, A. J., & Ciccarelli, O. (2009). Exploring the relationship between white matter and gray matter damage in early primary progressive multiple sclerosis: an in vivo study with TBSS and VBM. *Human Brain Mapping, 30*(9), 2852-2861.

Boisgontier, M. P., & Cheval, B. (2016). The anova to mixed model transition. *Neuroscience & Biobehavioral Reviews, 68*, 1004-1005.

Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D., . . . Marsel Mesulam, M. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry, 46*(1), 94-111.

Braun, U., Harneit, A., Pergola, G., Menara, T., Schaefer, A., Betzel, R. F., . . . Chen, J. (2019). Brain state stability during working memory is explained by network control theory, modulated by dopamine D1/D2 receptor function, and diminished in schizophrenia. *arXiv preprint arXiv:1906.09290*.

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience, 13*(5), 336.

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., . . . Matthews, P. M. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain, 130*(9), 2375-2386.

Esfahlani, F. Z., Bertolero, M. A., Bassett, D. S., & Betzel, R. F. (2020). Space-independent community and hub structure of functional brain networks. *Neuroimage*, 116612.

Fein, G., Di Sclafani, V., Cardenas, V., Goldmann, H., Tolou-Shams, M., & Meyerhoff, D. J. (2002). Cortical gray matter loss in treatment-naive alcohol dependent individuals. *Alcoholism: Clinical and Experimental Research, 26*(4), 558-564.

Giorgio, A., Watkins, K. E., Chadwick, M., James, S., Winmill, L., Douaud, G., . . . Johansen-Berg, H. (2010). Longitudinal changes in grey and white matter during adolescence. *Neuroimage, 49*(1), 94-103.

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., . . . Polimeni, J. R. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage, 80*, 105-124.

Gu, S., Betzel, R. F., Mattar, M. G., Cieslak, M., Delio, P. R., Grafton, S. T., . . . Bassett, D. S. (2017). Optimal trajectories of brain state transitions. *Neuroimage, 148*, 305-317. doi:10.1016/j.neuroimage.2017.01.003

Gu, S., Pasqualetti, F., Cieslak, M., Telesford, Q. K., Yu, A. B., Kahn, A. E., . . . Bassett, D. S. (2015). Controllability of structural brain networks. *Nature Communications, 6*. doi:ARTN 8414

10.1038/ncomms9414

Haldane, M., Cunningham, G., Androutsos, C., & Frangou, S. (2008). Structural brain correlates of response inhibition in Bipolar Disorder I. *Journal of Psychopharmacology, 22*(2), 138-143.

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex-developmental changes and effects of aging. *Brain Res, 163*(2), 195-205.

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of comparative Neurology, 387*(2), 167-178.

Jeganathan, J., Perry, A., Bassett, D. S., Roberts, G., Mitchell, P. B., & Breakspear, M. (2018). Fronto-limbic dysconnectivity leads to impaired brain network controllability in young people with bipolar disorder and those at high genetic risk. *NeuroImage: Clinical, 19*, 71-81.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical image analysis, 5*(2), 143-156.

Jeurissen, B., Tournier, J.-D., Dhollander, T., Connelly, A., & Sijbers, J. (2014). Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *Neuroimage, 103*, 411-426.

Jiang, J., & Lai, Y.-C. (2019). Irrelevance of linear controllability to nonlinear dynamical networks. *Nature Communications, 10*(1), 1-10.

Kailath, T. (1980). *Linear systems* (Vol. 156): Prentice-Hall Englewood Cliffs, NJ.

Kalman, R. E. (1963). Mathematical description of linear dynamical systems. *Journal of the Society for Industrial and Applied Mathematics, Series A: Control, 1*(2), 152-192.

Kenett, Y. N., Beaty, R. E., & Medaglia, J. D. (2018). A computational network control theory analysis of depression symptoms. *Personality neuroscience, 1*.

Kenett, Y. N., Medaglia, J. D., Beaty, R. E., Chen, Q., Betzel, R. F., Thompson-Schill, S. L., & Qiu, J. (2018). Driving the brain towards creativity and intelligence: A network control theory analysis. *Neuropsychologia*. doi:10.1016/j.neuropsychologia.2018.01.001

Kong, L., Herold, C. J., Zöllner, F., Salat, D. H., Lässer, M. M., Schmid, L. A., . . . Schad, L. R. (2015). Comparison of grey matter volume and thickness for analysing cortical changes in chronic schizophrenia: a matter of surface area, grey/white matter intensity contrast, and curvature. *Psychiatry Research: Neuroimaging, 231*(2), 176-183.

Lee, W. H., Rodrigue, A., Glahn, D. C., Bassett, D. S., & Frangou, S. (2020). Heritability and cognitive relevance of structural brain controllability. *Cereb Cortex, 30*(5), 3044-3054.

Liu, Y. Y., Slotine, J. J., & Barabasi, A. L. (2011). Controllability of complex networks. *Nature, 473*(7346), 167-173. doi:10.1038/nature10011

Lüders, E., Steinmetz, H., & Jäncke, L. (2002). Brain size and grey matter volume in the healthy human brain. *Neuroreport, 13*(17), 2371-2374.

Matthews, S. C., Simmons, A. N., Arce, E., & Paulus, M. P. (2005). Dissociation of inhibition from error processing using a parametric inhibitory task during functional magnetic resonance imaging. *Neuroreport, 16*(7), 755-760.

Medaglia, J. D. (2019). Clarifying cognitive control and the controllable connectome. *Wiley Interdisciplinary Reviews: Cognitive Science, 10*(1), e1471.

Medaglia, J. D., Pasqualetti, F., Hamilton, R. H., Thompson-Schill, S. L., & Bassett, D. S. (2017). Brain and cognitive reserve: translation via network control theory. *Neuroscience & Biobehavioral Reviews, 75*, 53-64.

Medaglia, J. D., Zurn, P., Sinnott-Armstrong, W., & Bassett, D. S. (2017). Mind control as a guide for the mind. *Nature Human Behaviour, 1*(6). doi:UNSP 0119

10.1038/s41562-017-0119

Muldoon, S. F., Pasqualetti, F., Gu, S., Cieslak, M., Grafton, S. T., Vettel, J. M., & Bassett, D. S. (2016). Stimulation-based control of dynamic brain networks. *PLoS computational biology, 12*(9), e1005076.

Palmen, S. J., Pol, H. E. H., Kemner, C., Schnack, H. G., Durston, S., Lahuis, B. E., . . . Van Engeland, H. (2005). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. *Psychological Medicine, 35*(4), 561-570.

Pasqualetti, F., Zampieri, S., & Bullo, F. (2014). Controllability metrics, limitations and algorithms for complex networks. *IEEE Transactions on Control of Network Systems, 1*(1), 40-52.

Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry, 57*(2), 119-127.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059-1069.

Tang, E., & Bassett, D. S. (2018). Colloquium: Control of dynamics in brain networks. *Reviews of Modern Physics, 90*(3), 031003.

Tournier, J. D., Calamante, F., & Connelly, A. (2012). MRtrix: diffusion tractography in crossing fiber regions. *International journal of imaging systems and technology, 22*(1), 53-66.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.

Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T., Bucholz, R., . . . Curtiss, S. W. (2012). The Human Connectome Project: a data acquisition perspective. *Neuroimage, 62*(4), 2222-2231.

Villain, N., Desgranges, B., Viader, F., De La Sayette, V., Mézenge, F., Landeau, B., . . . Chételat, G. (2008). Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. *Journal of Neuroscience, 28*(24), 6174-6181.

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., . . . Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage, 53*(3), 1135-1146.

Zhu, X.-H., Qiao, H., Du, F., Xiong, Q., Liu, X., Zhang, X., . . . Chen, W. (2012). Quantitative imaging of energy expenditure in human brain. *Neuroimage, 60*(4), 2107-2117.

Zoeller, D., Sandini, C., Schaer, M., Eliez, S., Bassett, D., & Van De Ville, D. (2019). Structural control energy of resting-state functional brain states reveals inefficient brain dynamics in psychosis vulnerability. *bioRxiv*, 703561.