All Whole-Brain Models developed during SGA2 and Comparison with Experiments (D4.5.1 – SGA2)

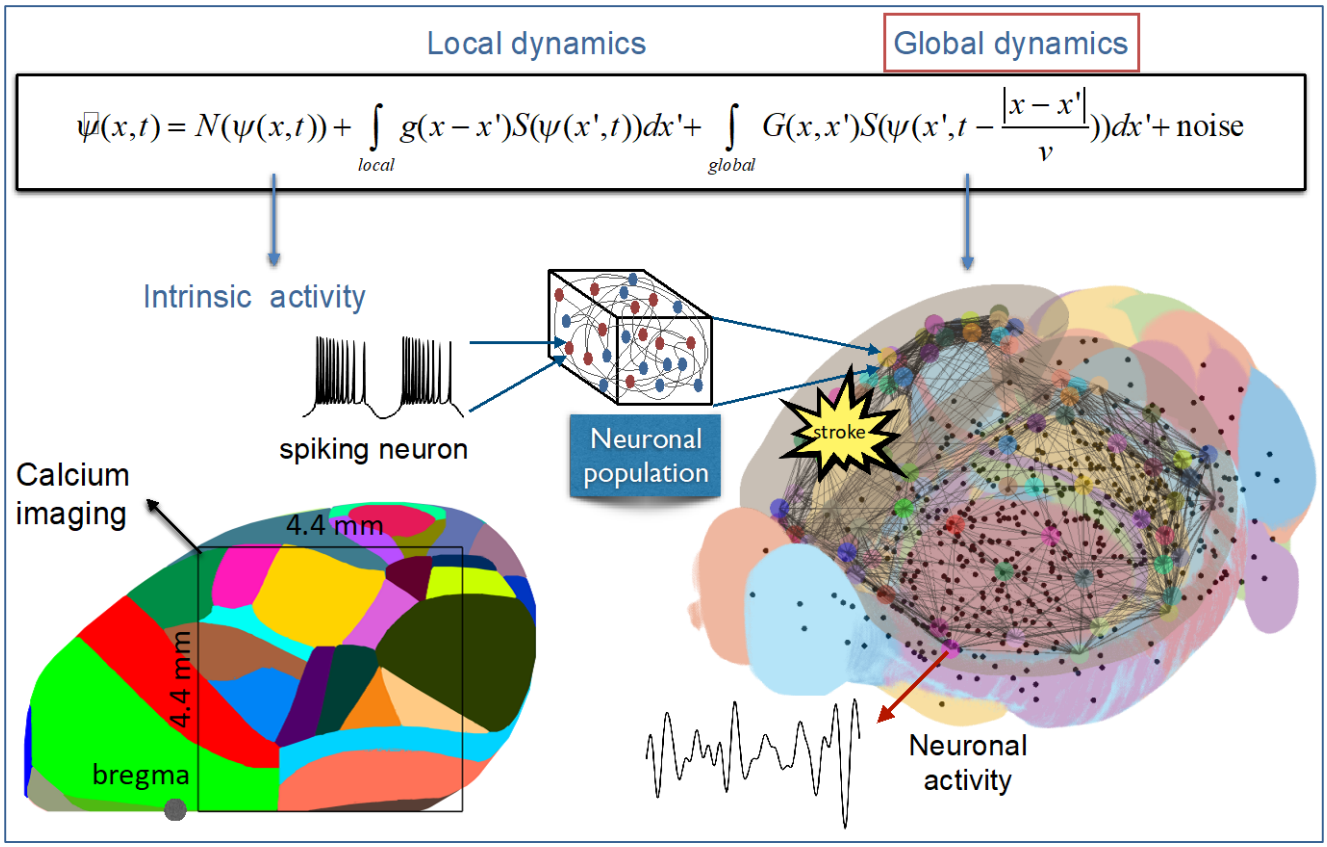

Figure 1: Mouse brain network model for stroke and the general TVB equation about the spatiotemporal brain activity.

The brain network is reconstructed from the Allen mouse connectome, and the model is validated against wide-field calcium imaging (see more details in Output 2 of KR4.11).

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Author(s):	Viktor JIRSA, AMU (P78), Gustavo DECO, UPF (P77)
Compiled by:	Spase PETKOSKI, AMU (P78)
Contributor(s):	Viktor JIRSA, AMU (P78), Gustavo DECO, UPF (P77)
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Description in GA:	For consistent presentation of HBP results, SGA2 M24 Deliverables describing the accomplishments of an entire SP, WP or CDP have been prepared according to a standard template, which focuses on Key Results and the outputs that contribute to them. Project management elements such as Milestones and Risks will be covered, as per normal practice, in the SGA2 Project Periodic Report.
Abstract:	This report describes the progress made on the various models developed in WP4.5 Whole Brain Models in SGA2 together with related outputs and publications.
Keywords:	brain network models, connectome, functional connectivity, personalized models, epilepsy, Bayesian inference, stroke, resection
Target Users/Readers:	Scientific community, Neuroscience Researcher

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History of Changes made to this Deliverable (post Submission)

Date	Change Requested / Change Made / Other Action
20 May 2020	Deliverable submitted to EC
28 Sep 2020	Revised draft sent by SP4 to PCO. Main changes made, with indication where each change was made: • Change 1: Figure 4 • Change 2: Figure 8
28 Sep 2020	Revised version resubmitted to EC by PCO via SyGMa
1 Oct 2020	Minor editorial change by PCO
1 Oct 2020	Revised version resubmitted to EC by PCO via SyGMa

1. Overview

The theoretical and computational models developed in SP4 occupy a central position in the HBP. On the one hand, they are derived from experimental data produced in the HBP. On the other hand, models are implemented in the HBP platforms, where they serve as "first users". These models also constitute the building blocks of work that will be continued in SGA3, such as bridging scales, network models, models of plasticity, models of cognitive processes and whole-brain models.

The main aim of the WP was to use neural masses and mean fields to build models of mouse and humans brain that will demonstrate the predictive value of the structural brain connectivity. This was achieved for personalized models, which were shown to have predictive value for the seizure propagation in epilepsy, and which allow improved identification of the epileptogenic zone. The predictive value of the personalized connectome was also demonstrated for the resting state in mouse, together with the applicability of the state of the art generic tracer connectivity data by the Allen Institute, which was validated against the gold standard fMRI data. Further on, the predictability of the connectome dysfunction in the context of stroke was also demonstrated, even though the work as part of CDP1 will continue for 3 more months.

The past few years have seen the discovery of novel methods in personalised medicine; in particular, resulting in improvements in epilepsy surgery success rates (a clinical trial is on-going in this area). In light of these, the results of the WP4.5 using The Virtual Brain offer a framework for fusion of an individual's brain structure derived from brain Imaging (anatomical MRI, diffusion tensor imaging - DTI) with computational neuroscience modelling, allowing neuro-electric stimulation and surgery, mimicking brain mapping including fMRI, EEG, MEG for hypothesis testing and treatment discovery.

2. Introduction

Linking model activity and function to experimental data at the large scale, has been the main achievement of the WP4.5 in SGA2. Up to now, functional analysis of brain models has been used as biomarkers for identification of epileptogenic zones, without the proper analysis of the impact of the personalized brain networks. Similarly, in case of network dysfunction such as stroke, the impaired structural and functional connectivity has been described mainly for regions adjacent to the stroke-affected tissue, but not systematically on large-scale network level.

In line with the state of the art, a part of the results in WP4.5 has been related to improving the current methods for epilepsy focus prediction based on entropy measures of the oscillatory activity in the brain electrodes. However, the main contribution was in generating new theoretical insights into network dynamics that demonstrate the explanatory value of large-scale brain network models in activity propagation such as in the cases of stimulation and seizure propagation in epilepsy, as well as in pathologies with impaired connectivity and dysfunctional network node, such as stroke. These were the two key results of the WP, which allowed us to build individual whole-brain network models for mimicking pathologies including epilepsy and stroke.

The findings in WP4.5 have resulted in improved identification of the epileptogenic zone and the mechanisms underlying the propagation of epileptic seizures. Thousands of patients with drug resistant focal epilepsy undergo resective brain surgery with the aim of achieving seizure freedom. Despite technical advances, the success rate of epilepsy surgery has not greatly improved, remaining at around 50%. Epilepsy surgical failure can be due to the non-resection or insufficient modulation of the important nodes and pathways that characterize the epileptogenic network. Demonstration that personalization of network models has predictive value for epileptogenic zones of individual patients has enabled translation, leading to the first large-scale clinical trial in epilepsy.

More specifically, personalized structural connectivity and information about the excitability of different regions is now used in generative models to predict the location of the epileptogenic zone and the propagation patterns of patients with epilepsy. The results allow the personalized models to serve as *in-silico* platforms. Virtual surgeries can be performed, helping to identify the least invasive strategies either in the epileptogenic zone, or out of it. Finally, including the Bayesian frameworks offer powerful and principled methods for parameter inference and model prediction from the epileptic seizures propagation. TVB connectome-based approach with the mathematical model and data fitting strategies give rise to the Virtual Epileptic Patient (VEP). VEP simulations, data fitting and mathematical analysis pipeline result in the prediction of the most likely seizure propagation patterns through the patient's brain and allow the exploration of personalized brain intervention strategies.

The work on mouse is closely related to models on human brains, since it was this work that showed in more detail how individual structural features constrain the functional connectome. The validation of the state-of-art mice tracer data has led to stroke model which allows systematic exploration and discovery of the changes of network dynamics due to structural impact of the stroke and the subsequent recovery. Similarly, the implementation of this connectome has allowed systematic in-silico exploration of mouse brain dynamics by stimulation, which largely explains the activated functional networks and sensory processing, as observed by the experimental data.

At the very end, we report part of the results that do not directly contribute to the any of the KRs, but are in line with the objectives of the WP. They show the impact that the spatio-temporal structure has over the emergent network dynamics, which is of underlying importance for the both key results achieved by WP4.5.

Also note that part of the results from T4.5.1 is reported in D4.2.1 in the KR4.5.

Note that most of the models will be available in the Knowledge Graph and are in the process of being transfered, the final list of the links will be given in due time.

3. Key Results KR4.10 Demonstration that brain personalized network models have predictive value for epileptogenic zones of individual patients.

3.1 Outputs

3.1.1 Overview of Outputs

Within the task T4.5.3 Human brain function from Structure, AMU group has completed work on minimally invasive network interventions for stopping the seizure propagation in epileptic patients, and developed a probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread, the so-called Bayesian Virtual Epileptic Patient (BVEP). These resulted in 2 different outputs, which utilized human whole-brain network models based on personalized DTI-derived connectome data using Epileptor neural mass model, the so-called Virtual Epileptic Patient (VEP). The output of the UPF group consists of a new method for automated epilepsy focuxs prediction, where a low entropy map of brain oscillatory activity is used to identify spatially localized events related to the ictal and pre-ictal epochs of the measured time-series.

3.1.1.1 List of Outputs contributing to this KR

- Output 1: Minimally invasive network interventions for stopping the seizure propagation in epileptic patients
- Output 2: Bayesian Virtual Epileptic Patient
- Output 3: Low entropy map of brain oscillatory activity identifies spatially localized events: A new method for automated epilepsy focus prediction

3.1.1.2 How Outputs relate to each other and the Key Result

The Outputs 1 and 2 apply the same validated modelling approach to the human for epilepsy patients with intracranial electrodes. Both outputs rely on the same data feature of seizure propagation pattern in their analysis for different epileptogenic zones. Output 1 designs network interventions to stop seizure propagation, whereas Output 2 uses the seizure propagation pattern to better estimate the Epileptogenic Zone (EZ). Both generate new theoretical insights into network dynamics and the mechanisms underlying the propagation of epileptic seizures. Also, both outputs demonstrate that personalization of network models have predictive value for EZ of the individual patients and can be used as in-silico platforms for patient evaluation. Output 3 considers a different data feature for the estimation of the EZ and develops biomarkers thereof that have the potential to be used in the BVEP technology used in Output 2.

3.1.2 Output 1: Minimally invasive network interventions for stopping the seizure propagation in epileptic patients

We constructed and simulated a patient-specific brain network model comprising phenomenological neural mass models at the nodes, and patient-specific structural brain connectivity using the neuroinformatics platform The Virtual Brain (TVB). Next, we performed virtual surgeries to identify the least invasive strategies. Two different approaches were analyzed for network interventions for stopping the seizure propagation in epileptic patients: 1) the most invasive lesion of the direct links to the epileptogenic zone (EZ), and 2) targeting nodes or links outside the EZ, the so-called target zone (TZ).

For the first approach, linear stability analysis was applied to the reduced Epileptor, uncovering significant reduction of the necessary lesions needed to stop the seizure compared to other possible strategies. In addition, the importance of the individualized connectome was also demonstrated. The second approach is relevant for a considerable number of patients who have EZs that are distributed across multiple brain regions and may involve eloquent areas that cannot be removed due to the risk of neurological complications. Based on the clinically identified EZ, we employed modularity analysis to identify target brain regions and fibre tracts involved in seizure propagation. In addition, we assessed safety via electrical stimulation for pre- and post-surgical condition to quantify the impact on the signal transmission properties of the network.

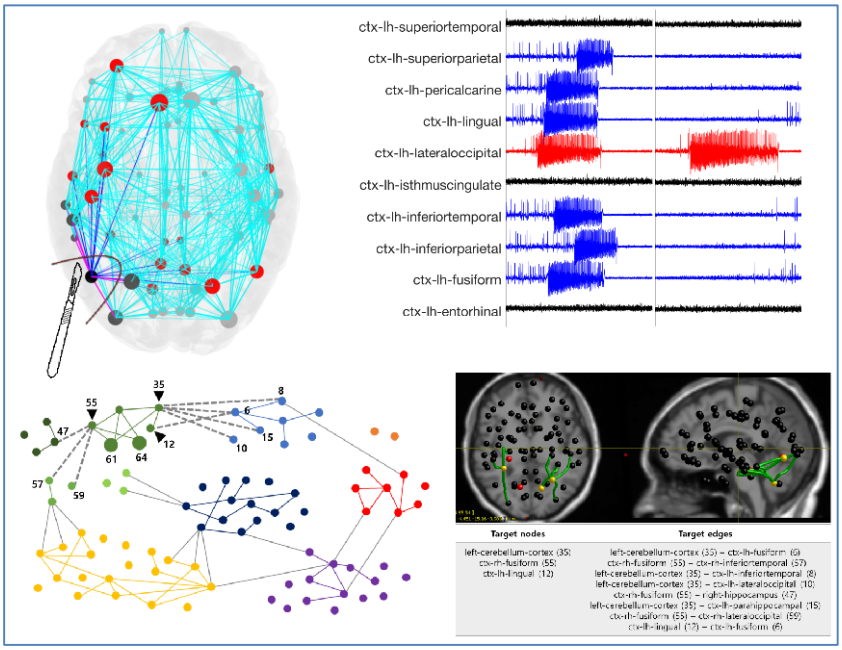

Figure 2: Minimally invasive resections for epileptic patients.

(top) Scheme of standard resection (removal of the entire EZ versus lesioning minimal number of links (left) and the epileptic activity before and after the intervention (right). (bottom) TZs derived from the modularity analysis when setting EZs to inoperable zones. The brain network is divided into seven modules and the EZ (nodes 61 and 64, large circles), based on which three nodes (triangles) and eight edges (dotted lines) are derived as target nodes and edges. Anatomical locations and list of the newly obtained TZs are shown on the bottom right.

3.1.3 Output 2: Bayesian Virtual Epileptic Patient

Model inversion i.e., finding a set of model parameters that yields the best possible fit to the observed data is a challenging task in statistical inference. Bayesian frameworks offer powerful and principled methods for parameter inference and model prediction from experimental data with a broad range of applications, and hence we have employ it to the personalized large-scale brain network modelling of epileptic seizures propagation. The Bayesian Virtual Epileptic Patient is a probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. It establishes a link between the probabilistic modelling and personalized brain network modeling in order to systematically predict the location of seizure initiation in a virtual epileptic patient. We demonstrated step by step, how the proposed framework allows one to infer the spatial map of epileptogenicity based on large-scale brain network models that are derived from noninvasive structural data of individual patients. The approach rests on advanced efficient sampling algorithms that provide accurate and reliable estimates validated by the posterior behavior analysis and convergence diagnostics. In summary, with the help of probabilistic programming languages, the use of personalized brain network models offers a proper guidance for development of comprehensive clinical hypothesis testing and novel surgical intervention.

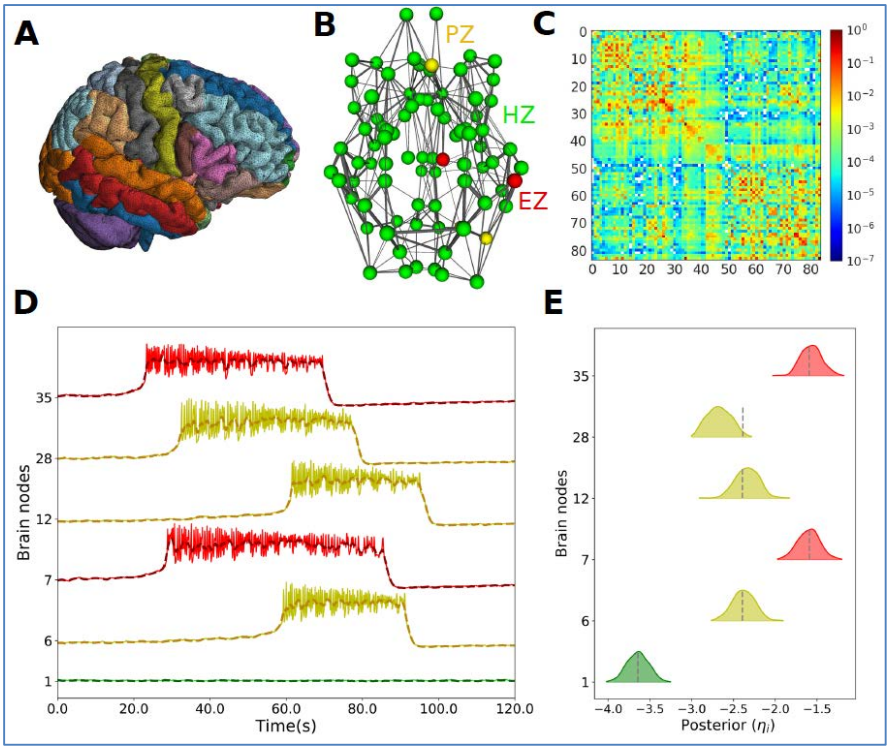

Figure 3: The result of workflow in the BVEP model to estimate the spatial map of epileptogenicity across different brain regions.

(A) Parcellation of reconstructed brain of the patient. (B) Brain network of the patient consisting of 84 regions (green: HZ, yellow: PZ, red: EZ). Thickness of the lines indicates the strength of the connections. For illustration purposes, only connections with weight above 10% of the maximum weight are shown. (C) Structural connectivity matrix. (D) Exemplary simulation of full VEP model at the source-level brain activity versus the predicted envelope (dashed line). (E) The estimated densities of the excitability parameters for different brain node types. The vertical dashed lines indicate the true values.

3.1.4 Output 3: Low entropy map of brain oscillatory activity identifies spatially localized events: A new method for automated epilepsy focus prediction

In the context of epilepsy research, a number of different electrophysiological patterns have been associated with epileptogenic activity. For example, determining the spatial mapping of pathological patterns of activity in drug-resistant epilepsy patients undergoing pre-surgical stereo-electroencephalography (SEEG) is a crucial step to delineate the seizure onset zone (SOZ) and plan a successful surgery. Motivated by the need to define automated seizure focus detectors, we propose a novel data-driven algorithm for the spatial identification of localized events that is based on the following rationale: the distribution of emerging oscillations during confined events across all recording sites is highly non-uniform and can be mapped using a spatial entropy function.

By applying this principle to EEG recording obtained from 67 distinct seizure epochs, our method successfully identified the seizure focus on a group of ten drug-resistant temporal lobe epilepsy patients (average sensitivity: 0.94, average specificity: 0.90) together with its characteristic electrophysiological pattern signature. Cross-validation of the method outputs with postresective information revealed the consistency of our findings in long follow-up seizure-free patients. Overall, our methodology provides a reliable computational procedure that might be used as in both experimental and clinical domains to identify the neural populations undergoing an emerging functional or pathological transition.

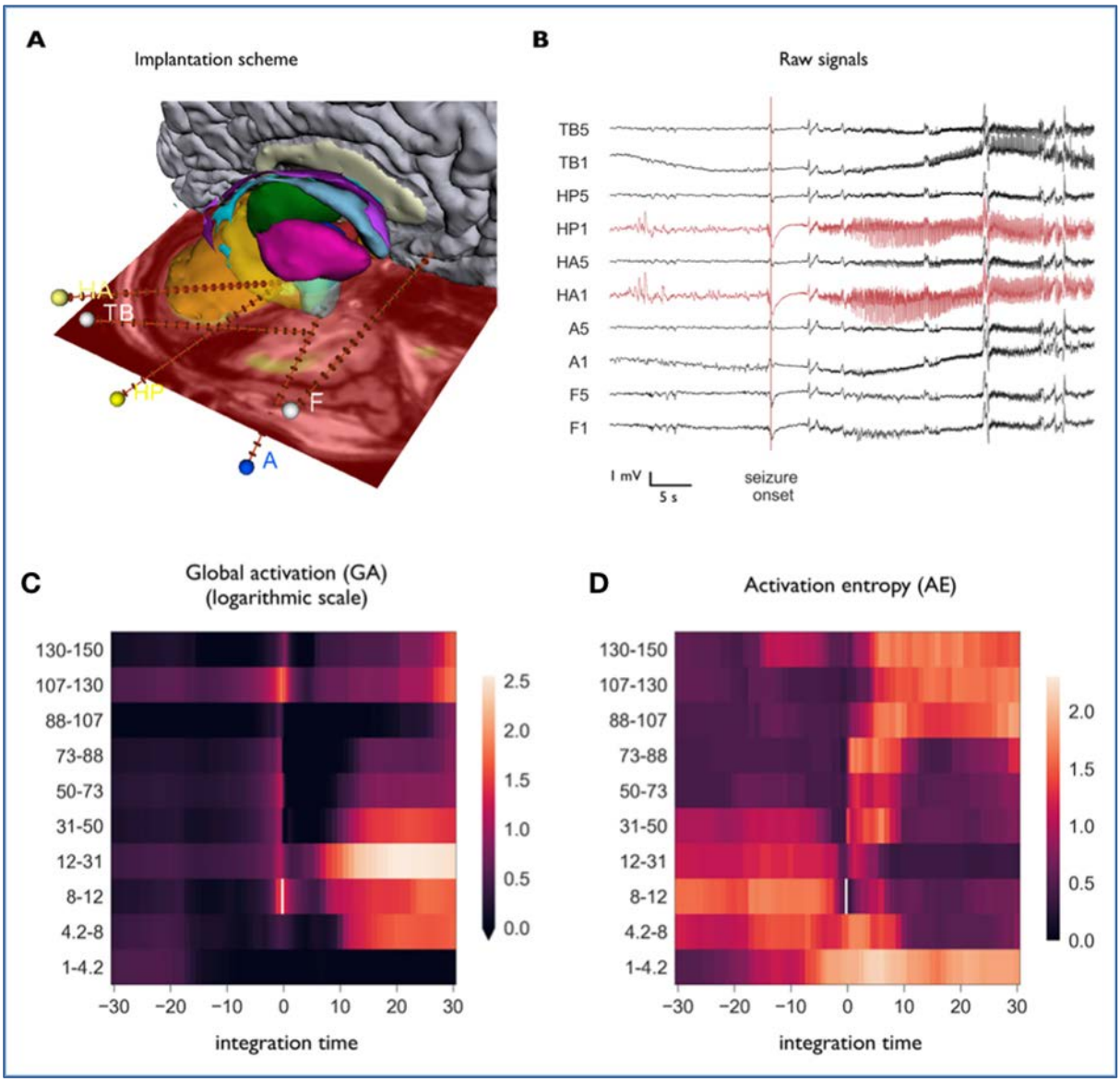

Figure 4 Localization of brain oscillatory activity

A Medial view of the brain showing the trajectories of the five electrodes and their target regions. B SEEG recordings from a selection of contacts (two per electrode) around the seizure onset Clinically identified SOZ contacts are marked in red. C Global activation (GA) across all possible combinations of time and frequency windows of interest in the peri-ictal period. Positive and negative times denote time windows spanning from seizure onset into the ictal and pre-ictal epochs, respectively. D Activation entropy (AE) across all possible combinations of time and frequency windows of interest in the peri-ictal period.

3.2 Validation and Impact

The outputs 1-3 offer together a framework with clear potential for translation towards clinical application.

The newly developed resection techniques (Output 1) demonstrate the potential and capacity of minimally invasive surgical procedures for epileptic patients as compared to the current procedures. Moreover, they can be applied for patients who have EZs that involve areas that cannot be removed due tothe risk of neurological complications. For the latter, a safety assessment procedure involving electrical stimulation has been also developed. This technology has not yet been validated against empirical data, but applied to simulated data only.

Our results in Output 2 indicate that the BVEP procedure accurately estimates the degree of epileptogenicity of brain regions, therefore, the hypothetical brain areas responsible for the seizure initiation and propagation. The convergence diagnostics and posterior behaviour analysis validate the

reliability of the estimations. The suggested Bayesian framework proposes an appropriate patient-specific strategy for estimating the epileptogenicity of the brain regions to improve outcome after epilepsy surgery. This technology has been validated on synthetic data on the source and sensor level, and against empirical data on the sensor level for a retrospective cohort of 50 patients. The performance values are very good and reported in the preprint.

Despite many efforts, the gold standard in clinical practice to identify seizure onset zones still remains visual inspection of EEG recordings due a number of reasons. For instance, the heterogeneity of electrophysiological patterns associated with seizure onset represents a major drawback to design SOZ detection algorithms that are universally valid for all seizure typologies and individual patients. The method in Output 3 allows to find time-frequency windows where the most relevant sites can be optimally discriminated.

3.2.1 Actual and Potential Use of Output(s)

The results of the Outputs 1-3 will be used by the computational and theoretical neuroscience community, as well by clinicians working with epileptic patients.

3.2.2 Publications

Output 1

Controlling seizure propagation in large-scale brain networks. Plos CB 15(2): e1006805. Olmi et al. 2019. PLUS ID : P1853

Optimization of surgical intervention outside the epileptogenic zone (EZ) in the Virtual Epileptic Patient (VEP); Plos CB 15(6): e1007051. An et al. 2019. PLUS ID: P1956

Output 2

The Bayesian Virtual Epileptic Patient: a probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. Hashemi et al. [in press, Neuroimage doi.org/10.1016/j.neuroimage.2020.116839].

https://kg.ebrains.eu/search/?facet_type[0]=Model&q=petkoski#Model/efbc12fff29147b8a0d23216712212ac

Output 1

Vila-Vidal M, Pérez Enriquez C, Principe A, Rocamora R, Deco G, & Tauste Campo A (2020) Low entropy map of brain oscillatory activity identifies spatially localized events: A new method for automated epilepsy focus prediction. NeuroImage 208, 116410. (P2472)

4. Key Results KR4.11 Demonstration of explanatory value of large-scale brain network mouse models with impaired connectivity and dysfunctional network.

4.1 Outputs

4.1.1 Overview of Outputs

Within the task T4.5.2 Mouse Brain Function from Structure, AMU group has has worked on a whole brain mouse models of spontaneous resting state activity, which were validated against mouse recordings in

3 different modalities: fMRI, calcium imaging, and voltage sensitive dye imaging VSDI. All the work was built on the state of the art open source mice tracer dataset of the Allen Institute (Oh et al., 2014) that AMU partner has implemented in The Virtual Brain (TVB) (Sanz-Leon et al. 2015), thus allowing detailed Structural Connectivity (SC) to be obtained (Melozzi et al 2017). This is then used to build large-scale brain network models for the resting state Functional Connectivity (FC). For the network nodes we have used different neural masses depending on the activity that is modelled.

The first output is significant because, besides showing that the individual structural features constrain the mouse functional connectome, it validates the Allen Mouse Brain Connectivity Atlas (AMBCA). This then allows the other two outputs to use this dataset for building mice brain network models for: 1) stroke and recovery, and 2) stimulation.

4.1.1.1 List of Outputs contributing to this KR

- Output 1: Individual structural features constrain the mouse functional connectome
- Output 2: Mouse stroke Brain network model
- Output 3: In-silico Exploration of Mouse Brain Dynamics by Stimulation explains Functional Networks and Sensory Processing

4.1.1.2 How Outputs relate to each other and the Key Result

The first output validates the AMBCA demonstrating that it has the highest predictive value for the resting state. This allows for it to be used for modelling the experimental data in the cases when the individual structural data is missing to accomplish the large-scale functional imaging. As a result, the AMBCA is used in the other two models (outputs). The second output demonstrates that the large-scale brain network mouse model has predictive value for impaired connectivity, while the third one shows that the subsequently emerging brain function (and dysfunction) is shaped by the brain structure through the network interactions and, hence, the local response can be highly specific to a brain area though the areas are equally parameterized.

4.1.2 Output 1: Individual structural features constrain the mouse functional connectome

Whole brain dynamics intuitively depend upon the internal wiring of the brain; but to which extent the individual structural connectome constrains the corresponding functional connectome is unknown, even though its importance is uncontested. After acquiring structural data from individual mice, we virtualized their brain networks and simulated in silico functional MRI data. Theoretical results were validated against empirical awake functional MRI data obtained from the same mice. We demonstrate that individual structural connectomes predict the functional organization of individual brains. Using a virtual mouse brain derived from the AMBCA, we further show that the dominant predictors of individual structure-function relations are the asymmetry and the weights of the structural links. Model predictions were validated experimentally using tracer injections, identifying which missing connections (not measurable with diffusion MRI) are important for whole brain dynamics in the mouse. Individual variations thus define a specific structural fingerprint with direct impact upon the functional organization of individual brains, a key feature for personalized medicine.

In conclusion, we identified key individual structural features (fibre directionality, connection strength and patterns, and interhemispherical asymmetry), which are relevant to predict the emergence of the functional patterns during a resting state in mice. Our results strongly suggest the existence of a causal relation between the structural and the functional connectome. Although the detailed structural results presented here are species specific, our conceptual framework is species invariant and can now be exploited in humans for individual diagnosis and clinical decision making.

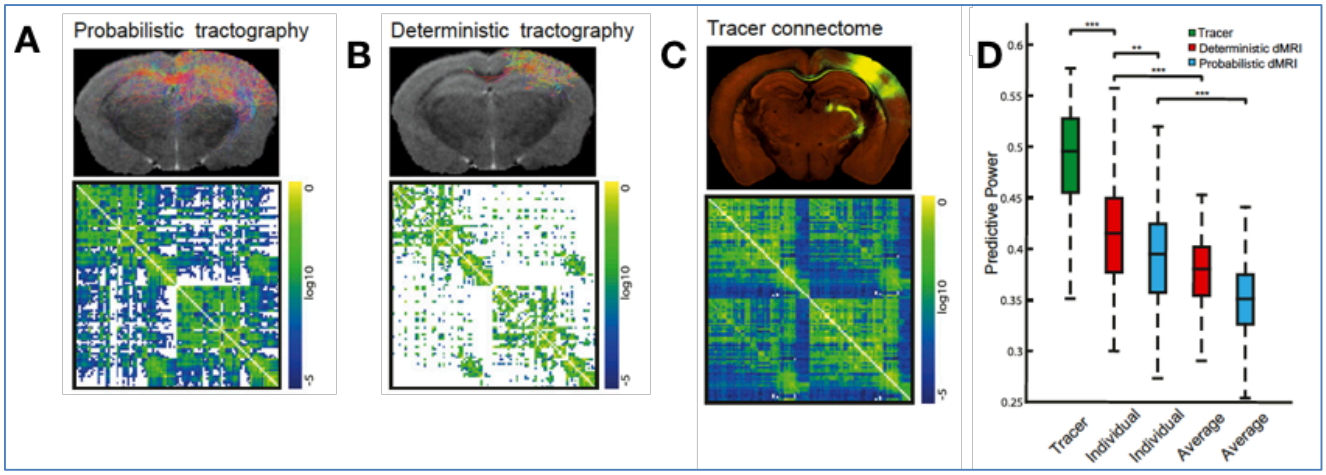

Figure 5: Comparison of the predictive power of different connectomes.

(A) Probabilistic and (B) deterministic connections for the right barrel-related primary somatosensory cortex (SSp-bfd, Top) and for the whole brain (Bottom) of an individual mouse. (C) Tracer-based connections from SSp-bfd (Top) and group tracer-based SC matrix (the Allen SC, Bottom). (D) Predictive power of simulations using different types of tracer- and dMRI-based SCs. dMRI-based simulations were performed using individual or group-averaged dMRI (AVG).

4.1.3 Output 2: Mouse stroke Brain network model

The large-scale Mouse Brain Model for simulating the stroke and rehabilitation allows modeling of the results of the experiment defined in CDP1: calcium analysis for a single mouse in the first and in the fourth week after stroke, compared with its healthy activity. Experimental calcium data are used in a close loop validation system to model the cortical activity of the mouse. The top-down model systematically exploits the effects of the SC constraints upon network dynamics, and was compared with empirical cortical activation maps in SP1, in healthy, stroke and rehabilitation. The model allows systematic analysis of the structural impact of the stroke and of the recovery. This leads to the best fit for parameters which were in agreement with the experimental results for the structural damage during the stroke and the recovery. Data analysis and modelling were performed for recordings of one hemisphere of one animal (SP1 data), and further recordings from both hemispheres are expected from 4 more animals.

In this work we have focused on fitting the structural changes due to stroke and recovery in order to validate the usage of AMBCA even in the cases when there are significant changes in SC as compared to the healthy state. Results from the model help to identify the route of the stroke and the recovery in the parameter space that can be related to neurophysiological quantities, such as the white matter tracts. We could thus identify which are the most important links that need to be restored, or prevented from occurring, for a successful recovery.

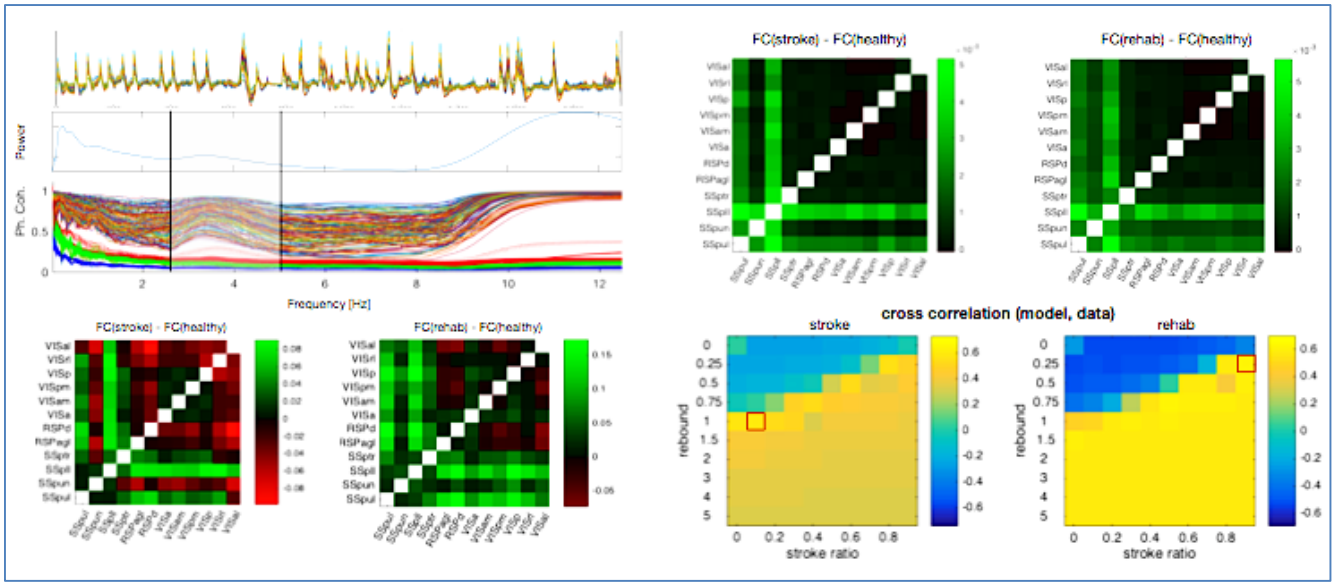

Figure 6: Comparison of empirical and simulated FC.

Time-series, phase coherence and FC from calcium imaging empirical data (left), and FC from the model and cross-correlation between the model and the data (right). Relative changes of the FC are shown at stroke and after the rehabilitation compared to the healthy control for frequency band f=2.5-5Hz. (C) Cross correlation of the model upper triangles of FC between the model and the data for fixed global coupling K = 4:3 and different levels of stroke (0 for complete damage and 0.9 for damage of 10% of the links) and rebound connectivity (0 for no rewiring and 5 for overall rewiring with strength of 5 times of the damaged links). Parameters: frequency f = 2Hz, noise strength D = 1. (D) Simulated relative changes of the FC at stroke and rehabilitation relative to the healthy control for the working points marked with red squares in the parameters space in the panel (C).

4.1.4 Output 3: In-silico Exploration of Mouse Brain Dynamics by Stimulation explains Functional Networks and Sensory Processing

Sensory and direct stimulation of the brain probes its functional repertoire and the information processing capacity of networks. However, a systematic exploration can only be performed in silico. Stimulation takes the system out of its attractor states and samples the environment of the flow to gain insight into the stability and multiplicity of trajectories. It is the only means of obtaining a complete understanding of the healthy brain network's dynamic properties. We built a whole mouse brain model with connectivity derived from tracer studies. We systematically varied the stimulation location, the ratio of long- to short-range interactions, and the range of short connections. Functional networks appeared in the spatial motifs of simulated brain activity. Several motifs included the default mode network, suggesting a junction of functional networks. The model explains processing in sensory systems and replicates the in vivo dynamics after stimulation without parameter tuning, emphasizing the role of connectivity.

Resting state stimulated and propagation patterns due to connectivity have been analysed in line with the experimental data from voltage-sensitive dyes imaging. The propagation of activation patterns was systematically studied, thus helping to describe the excitability of different cortical areas of the mouse brain and to mathematically and computationally investigate the non-stationary properties and capacity of the models to propagate activations through the network.

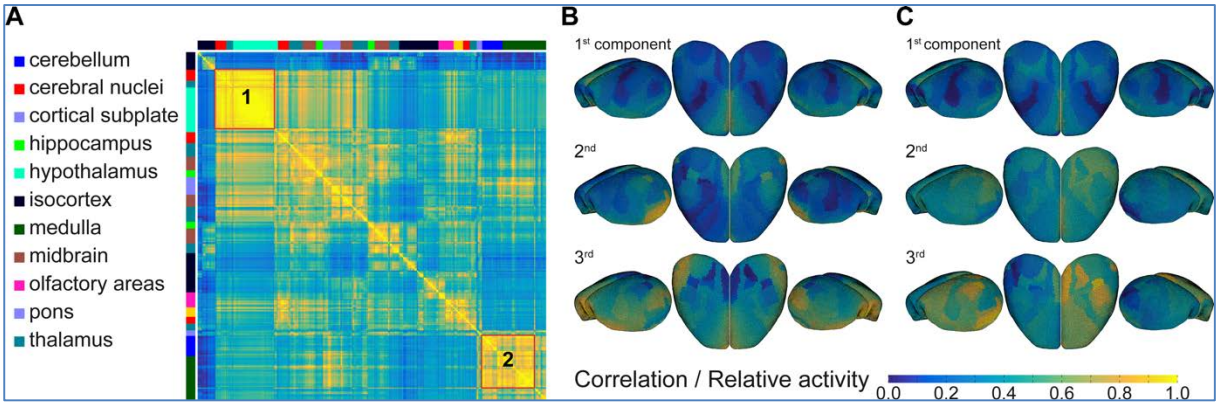

Figure 7: Specific focal stimulations activate similar networks.

Panel A is the similarity matrix of stimulation with the clusters 1 and 2. Panels B and C show the responsive networks (isocortex) of cluster 1 and of cluster 2.

4.2 Validation and Impact

Output 1 provides so far the strongest evidence in the literature for our capacity to individualize brain network models. On the one hand side, the approach has been validated against functional MRI data in the mouse, which establishes only a derived measure of cerebral activity, on the other hand a large range of structural connectomes (AMBCA connectome, individual DTI-based derived connectomes using different tractography methods, and various surrogates) has been applied, allowing detailed analysis of the structural constraints placed upon the dynamics. Besides validating AMBCA against the gold standard structural and functional MRI data, our results strongly suggest the existence of a causal relation between the structural and the functional connectome, here captured by the brain network model. We have essentially mapped out all the network signal propagation pathways supported by the mouse brain. Although the detailed structural results presented here are species specific, our conceptual framework is species invariant and can now be exploited in humans for individual diagnosis and clinical decision-making. The other two outputs take advantage of the knowledge generated by Output 1 and apply it in a stroke model (Output 2) and stimulation paradigm (Output 3). Both applications have demonstrated first proof of concept and feasibility of these application use cases and laid the seed for further research in this domain.

4.2.1 Actual and Potential Use of Output(s)

The full-brain network decomposes the brain into a system composed of nodes and links, which is capable of spatiotemporal pattern formation. This view allows us to ask fundamental questions about stimulated pattern propagation, which is at the heart of information processing in the brain.

As part of CDP1, the output of the stroke model is planned to be integrated with the Neurorobotic Platform together with the experiment, thus building a closed-loop for validation of different hypothesis regarding the stroke. It could also be used for novel and improved strategies for rehabilitation after stroke. In future, combined with individualized connectome data during the recovery, a therapy could be proposed targeting specific parts of the brain, depending on the location and the size of the stroke.

4.2.2 Publications

Output 1

Individual structural features constrain the mouse functional connectome. PNAS 15(2): e1006805. Melozzi et al. 2019. PLUS ID : P1893

Output 3

In-silico Exploration of Mouse Brain Dynamics by Stimulation explains Functional Networks and Sensory Processing. Spiegler A et al. [in press Network Neuroscience]. https://www.biorxiv.org/content/10.1101/512871v1

Output 2

Mouse stroke Brain network model, Petkoski S & Jirsa V.

https://github.com/esaps/AllenMouse_strokeKuramoto
https://kg.ebrains.eu/search/?facet_type[0]=Model&q=petkoski#Model/2b9158547b4c0f15dc59d176081c1525

Experimental and computational study on motor control and recovery after stroke: towards a constructive loop between experimental and virtual embodied neuroscience, Allegra Mascaro AL, Falotico E, Petkoski S, et al. [in press Frontiers of Systems Neuroscience] https://www.biorxiv.org/content/10.1101/2020.04.22.019661v1

5. Other outputs/publications contributing to the general WP objectives.

5.1 Outputs

5.1.1 Overview of Outputs

Here we list two outputs that are not directly related to specific Key results of this work-package, but are still contributing to the general WP objectives and to the SGA2 SP Objective SO4.2 Comparative assessment of brain data and different modelling approaches (analytical models, large-scale network models, neuromorphic computing systems, neurorobotics experiments). In fact they are analytical models that analyze the impact of the spatio-temporal structure, over the emergent network dynamics. Importantly, the same principle of the impact of the structure over the dynamics is underlying the findings related to the both key results achieved by WP4.5, namely, demonstration that brain personalized network models have predictive value for epileptogenic zones of individual and for impaired connectivity and dysfunctional network in mice.

5.1.1.1 List of Outputs contributing to this KR

- Output 1: Spatio-temporal structure of the brain shapes its large scale dynamics
- Output 2: Natural rhythms of periodic temporal attention

5.1.1.2 How Outputs relate to each other and the Key Result

The first output is directly in line with WP objectives to: “investigates mathematical principles and theoretical methods required for integrating neuroscience data (both anatomical and physiological) into models, and for comparing the results of the models with the existing data“. It is theoretical work that describes how the structural network connectivity constrains obtained dynamics over it, for oscillatory activity.

The second output shows that the same mathematical principles of the network topology, more specifically the time delays and the coupling strengths, also shape the natural rhythms of periodic temporal attention, which same as with rhythms of the brain networks, can be represented as delay-coupled self-sustained oscillators.

5.1.2 Output 1: Spatio-temporal structure of the brain shapes its large scale dynamics

The timing of activity across brain regions can be described by its phases for oscillatory processes, and is of crucial importance for brain functioning. The structure of the brain constrains its dynamics through the delays due to propagation and the strengths of the white matter tracts. We have used phenomenological model of delay-coupled oscillators with increasing degree of topological complexity to identify underlying principles by which the spatio-temporal structure of the brain governs the phase lags between oscillatory activities at distant regions. Besides in-phase, we have shown that clustered delays can induce anti-phase synchronization for certain frequencies, while the sign of the lags is determined by the natural frequencies and by the inhomogeneous network interactions. Faster oscillators always phase lead, while stronger connected nodes lag behind the weaker during frequency depression, which consistently arises for in-silico results.

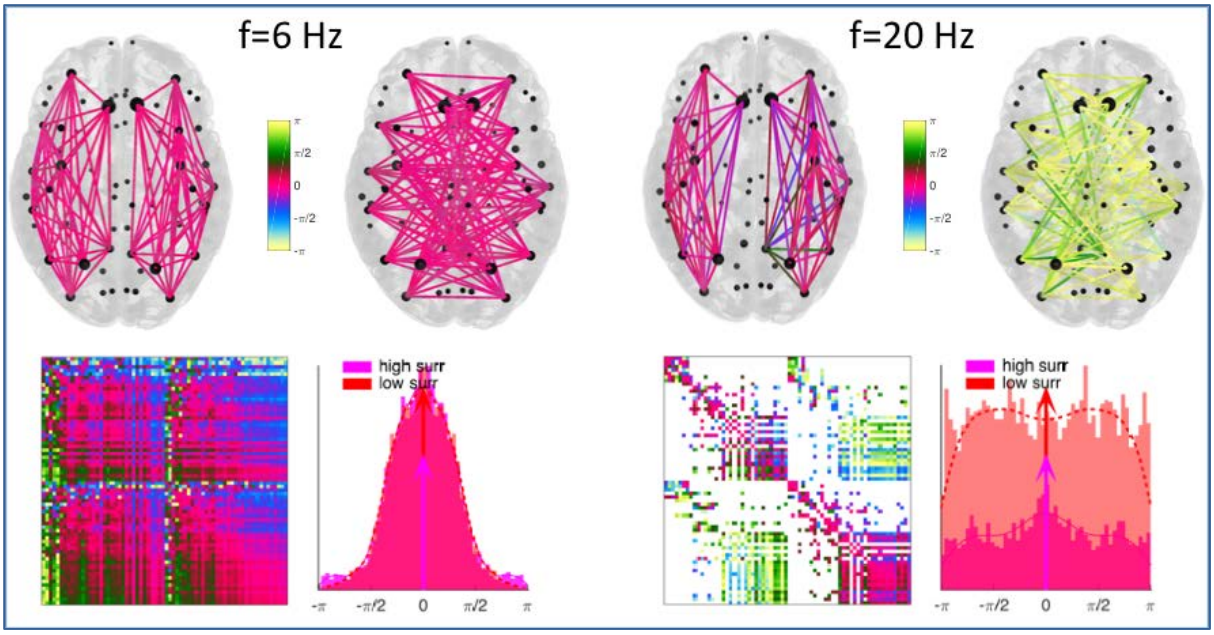

Figure 8: In- and anti- phase synchronization between brain hemispheres.

Upper plots show subnetworks of 10 strongest regions of each hemisphere, with their internal and external links (left and right). Bottom plots are matrices of phase lags between brain regions ordered by strength within hemisphere, and the overall distribution of phase lags, using two different levels of significance.

We have also showed that the choice of surrogates do not affects the mean of the observed phase lags, but higher significance levels decrease their variance and might fail to detect the generally weaker coherence of the interhemispheric links. Our results uncover mechanisms through which the spatio-temporal structure of the brain renders phases to be distributed around 0 and π. These results indicate specific features in the phase relationships within the brain that need to hold for a wide range of local oscillatory dynamics, given that the time delays of the connectome are proportional to the lengths of the structural pathways.

5.1.3 Output 2: Natural rhythms of periodic temporal attention

That attention is a fundamentally rhythmic process has recently received abundant empirical evidence. The essence of temporal attention, however, is to flexibly focus in time. Whether this function is constrained by an underlying rhythmic neural mechanism is unknown. In six interrelated experiments, we behaviourally quantify the sampling capacities of periodic temporal attention during auditory or visual perception. Critically, motor modulation is beneficial to auditory but detrimental to visual temporal attention. These results are captured by a computational model of coupled oscillators, which reveals the underlying structural constraints governing the temporal alignment between motor and attention fluctuations.

To understand the specific motor contribution to auditory and visual periodic temporal attention, each having its own optimal sampling rate, we implemented a model in which sensory-specific temporal attention behaves like a self-sustained oscillator (a structure with an intrinsic rhythm capable of being entrained coupled to a motor oscillator and entrained by an external beat. In its simplest realisation, this results in a model of three coupled phase oscillators (stimulus (S), attention (A) and motor (M) oscillators) with time-delays and noise.

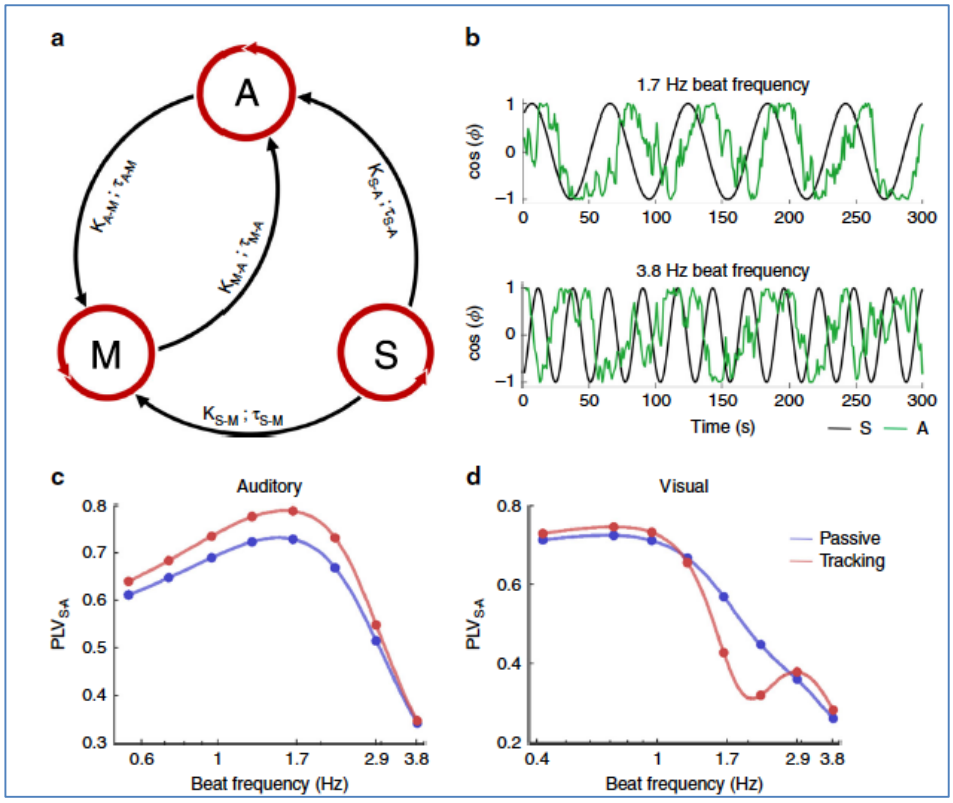

Figure 9: A model of coupled oscillators to for the periodic temporal attention.

Model of three delay-coupled phase oscillators approximating the selective coupling between the external beat (stimulus S), sensory-specific temporal attention (A), and natural motor dynamics (M). The external oscillator (S) influences attention and motor oscillators with a specific strength K and delay τ, and attention and motor oscillators reciprocally influence each other. The phase locking value (PLV) between the external beat (S) and the sensory-specific temporal attention oscillator (A) reflects the capacity of A to entrain to S and thus is used as an approximation of behavioural performance. b Example of dynamics of the auditory temporal attention oscillator (A; green) during presentation of an external beat (S; black) at 1.7 Hz or 3.8 Hz. c, d Replication of the (c) auditory and (d) visual passive (blue) and tracking (red) experiments. Difference between conditions was obtained by adjusting three key parameters: the natural frequency of the sensory-specific temporal attention oscillator (A) and the time-delay between the stimulus (S) and the motor oscillator (M).

5.2 Validation and Impact

The theoretical findings of the first output should allow further work on renormalization of the connectome that will specifically take into account the impact of time-delays for oscillatory activity at different frequencies.

The model of the second output is directly validated by the experimental results with visual and audio attention, qualitatively describing the mechanisms for the impact of the motor contribution to the periodic temporal attention.

5.2.1 Actual and Potential Use of Output(s)

As one of the objectives of the WP, the model predictions of the first output can be used to suggest new experiments to test the spectral dependent activation patterns in the brain, and to extend the current graph theoretical metrics to account for the oscillatory activity over delayed networks.

As for the second output, it remains to be investigated whether the structural constraints of the motor contribution are specific to periodic temporal attention or generalise to other forms of temporal attending.

5.2.2 Publications

Output 1

Phase-lags in large scale brain synchronization: Methodological considerations and in-silico analysis. PloS CB. 14(7): e1006160. Petkoski et al. 2018. PLUS ID: P1364

Transmission time delays organize the brain. Phil. Trans. R. Soc. A 377 : 20180132. Petkoski et al. 2019. PLUS ID : P1928

Output 2

Natural rhythms of periodic temporal attention. Nat Commun, 11:1. Zalta et al. 2020. PLUS ID : P2367.

6. Conclusion and Outlook

During the SGA2, the WP4.5 has achieved its main goals in linking model activity and function to experimental data. The new theoretical insights into network dynamics from our work have manifested that the large-scale brain network models have explanatory value for the macroscopic activity propagation in the brain. The results on mice strongly suggest the existence of a causal relation between the structural and the functional connectome, establishing currently the strongest evidence of our capacity of tailoring individual brain network models based on specific connectomes; while simulation of personalised brain network models of epilepsy patients has demonstrated the potential to improve the outcome of surgical interventions in patients with drug-resistant epilepsy (a clinical trial is on-going).

The fusion of an individual's brain structure derived from brain Imaging (anatomical MRI, diffusion tensor imaging - DTI) with computational neuroscience modelling allows creating one model per patient. Model functions are governed by neuro-electric and vascular processes, allowing neuro-electric stimulation and surgery, mimicking brain mapping including fMRI, EEG, MEG for hypothesis testing and treatment discovery. The Virtual Epileptic Patient brain model is therefore a strong candidate for exploitation, with possible future application in hospitals and epilepsy-oriented clinics. Collaborations could be explored with hospitals that are diagnosing and treating epilepsy.

This modelling approach also allows performing virtual surgeries and testing different hypothesis, such as different network manipulations for stopping the seizure propagation in epileptic patients. For this we have developed two minimally invasive strategies that can be tested with the novel resection technologies such as laser surgeries via thermal ablations and gamma knives surgeries.

Even though the results that we have obtained span across species, our conceptual framework is species invariant and can be exploited in humans for individual diagnosis and clinical decision making. We have hence individual whole-brain network models for mimicking pathologies including epilepsy and stroke, as well as resting state and different sensory stimuli. More importantly, the data used to validate our models spans several imaging modalities, such as implanted EEG electrodes, BOLD fMRI, wide-field calcium, and voltage sensitive dye imaging.

The spatio-temporal structure of the connectome is implied to shape the emergent network dynamics on the brain demonstrate by both key results achieved by WP4.5. On a slightly wider aspect of the objectives of the WP, we have theoretically and computationally explained the impact that the spatio-temporal structure has over the emergent synchronization over the brain network. For this we have used phenomenological model of delay-coupled oscillators to identify the underlying principles by which the spatio-temporal structure of the brain governs the phase lags between distant brain regions. As a direct consequence, in the future work this will lead to renormalization of the connectome to account for the impact of time-delays due to propagation over links, besides their weights. The same mechanism

is also responsible for the impact of the motor contribution to the periodic temporal attention, as was demonstrated experimentally.

The only still on-going work of SGA2 in this WP at the time of writing of this report, is the work on integrating the validated mean-field and population models developed in 4.1.3 and extending them towards pathological conditions including stroke and epilepsy. This work includes validating neuronal mass models against high-dimensional neuronal network models, enabling parameter space explorations to guide high performance computations (SP7). This has become much more crucial and far-reaching for bridging the scales of different levels of description, and as a such it will be of central impotance in SGA3. Related to this is linking theoretical models at different levels of description to cross-bridge neuroscience and models implemented in various Platforms of the HBP, which will be integrated in EBRAINS. Not less important is the contribution of our results in CDP1, which in the further period should also lead to closed loop including the experiment on one side, and the neurorobotic platform on the other. Closing this loop also implies bridging different levels of description for the brain activity, hence converging towards the main goals of SGA3.

The general modelling framework in SGA3 will strongly endorse the multi-scale approach, for which the TVB framework for the large-scale brain network modelling is well positioned. The emphasis on model validation will be on the Bayesian framework for the model inversion and the probabilistic programming languages applied on personalized brain network models, a concept that we have already introduced. With the primary disease data target in SGA3 expected to shift to epilepsy, this approach should offer a proper guidance for development of comprehensive clinical hypothesis testing and novel surgical intervention.

Finally, our modelling and data validation framework, as well as the obtained key results, should allow us in SGA3 to continue the work towards further incorporating intersubject variability of multiscale and connectomics data reflected in relevant structural and functional data features. The workflow should hence proceed along two complementary dimensions, first, integrating intra- and intersubject variability; and second, inferring their capacity for personalization. This includes constructing personalized brain models using structural and functional brain data and estimating their mutual predictive capacity across modalities, paradigms and tasks.