Short Thesis for the Degree of Doctor of Philosophy (PhD)

Application of functional MRI–based brain network analysis and hemodynamic model calculation in various pathologies

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The Examination takes place at the Directors's office, Dept. of Biophysics and Cell Biology, Division of Biophysics, Faculty of Medicine, University of Debrecen, at 11:00 am, on 16th January, 2025.

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1. Background and objectives

Neuroscience is one of the fastest growing fields of research, closely intertwined with other disciplines such as mathematics, engineering, computer science and psychology. The main goal of neuroscience is to understand the operation of the brain, to systematically study the functions of the central nervous system and to determine the functionally active areas.

Functional magnetic resonance imaging (fMRI) is developed to track regional changes in brain metabolism over time. These metabolic changes may be the result of the cognitive state changes caused by the task or the processes taking place in the brain during the resting test. Neural activity is linked to many complex physiological processes, in which metabolic by–products, cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral meatbolic rate of oxygen ($CMRO_2$) and blood oxygenation create together Blood Oxygen Level Dependent (BOLD) response in fMRI. The transient and delayed changes observed in the BOLD contrast are called the hemodynamic response. After a short period of neural activity, this localized response follows a clear and reproducible time course called the hemodynamic response function (HRF). HRF describes the local changes in cerebral blood flow, blood volume and oxygen supply related to neural activity, and models the spatial course of the BOLD signal expected during the examination. Accurate modeling of the hemodynamic response induced by a neural event plays an important role in the analysis of fMRI data.

1.1. Estimation of hemodynamic parameters

1.1.1. Balloon model

The Balloon model is a hemodynamic model suitable for characterizing the BOLD signal based on blood volume and deoxyhemoglobin (dHb) concentration. The first part of the model describes the relationship between neural activity and regional cerebral blood flow (rCBF). The second part depends on the change in blood volume and dHb content induced by the BOLD signal rCBF. This is the so–called „Balloon model", which describes the behavior of the postcapillary venous space by analogy with an inflated „balloon". With the hemodynamic model, the „neuronal efficacy", „signal decay" and „transit time" parameters can be estimated for the smallest units (voxels) of the created image.

1.1.2. Blind deconvolution

Reconstruction of brain activity from an fMRI signal involves several challenges. For example, the measured signals may contain components from non–neural hemodynamic sources that may influence connectivity estimates. We know two methods that, in addition to analyzing the connections between brain regions, are also suitable for estimating hemodynamic parameters, these are blind deconvolution and dynamic causal modeling (DCM).

Deconvolution is a method that treats the image as an estimate of the true intensity of the sample, performing the mathematical inverse of the imaging process by applying a point spread function to obtain a better approximation of the image intensity. For fMRI data processing, this means estimating the hemodynamic response that best predicts the measured fMRI signal by convolving the impulse response with the neural response. Blind deconvolution is based on the problem of separating two convolutional signals if both signals are unknown or only partially known.

HRF is characterized by three parameters: (1) response height/intensity (H), (2) response length/full width at half maximum (FWHM), and (3) time to peak/response delay (time to peak) (T2P). The height of the response is the amplitude of the HRF, the T2P measures the latency, and the FWHM is related to the duration of the BOLD response.

1.2. Brain network analysis methods on a macroscopic scale

Our brain is a very complex organ consisting of anatomically distinct but closely interconnected regions. These areas form a complex system of connections in which information flows continuously: this is how the brain network is created.

The analysis of human brain networks (i.e. mapping the connectivity patterns of the human brain) has attracted increasing interest in the field of neuroscience, as network science and graph theory have provided researchers with new methods. During network analysis, structural connections or functional connections are analyzed in the case of predetermined brain region pairs (region of interest – ROI).

1.2.1. Effective connectivity–based brain network analysis using the DCM method

DCM is a model–based approach to studying brain connectivity that incorporates a biophysical model of the BOLD response. It uses a Bayesian framework to simultaneously estimate parameters characterizing neural activity (and connectivity) and vascular changes following activity.

1.2.2. Model selection

Traditionally, DCM is used to test hypotheses that describe networks containing a few regions and compare them with Bayesian model selection. It is a procedure that „predicts" the most likely of hypotheses (or models).

1.2.3. Graph–theoretic analysis of adjacency matrices

The use of graph–based network analyzes enables the determination of general patterns of connectivity between all ROIs, the exploration of differences in global network structure, and the investigation of how different modules (i.e., connected clusters of ROIs) communicate with each other. In neuroscience, graph theory is usually used to study topological patterns of functional or effective connectivity. Graph–based network analysis provides useful information about the topological architecture of human brain networks, such as small–world structure, modular architecture, and highly connected or highly important nodes. Small–world nature is a property of networks in which most nodes are not neighbors of each other, but are reachable from every other node by a small number of steps.

The use of network analysis techniques enables the comparison of brain connectivity patterns obtained during structural and functional studies. For example, the discovery of small–world features in functional connectivity patterns from fMRI, Electroencephalography (EEG), and Magnetoencephalography (MEG) studies raises the question of how closely functional connections match structural connections.

1.3. An overview of the literature related to the patient groups examined in the research

1.3.1. Brain networks

Large–scale brain networks are collections of extensive regions of the brain that can be studied by analyzing the fMRI BOLD signal. Various brain areas are responsible for executing movements: the primary motor cortex (M1), the supplementary motor area (SMA) and the premotor cortex (PM). M1 controls the execution of movement by generating nerve impulses, and PM controls the initiation of various movement patterns.

Resting fMRI allows us to examine the organization and connectivity of multiple brain networks that cannot be easily mapped using other techniques.

The default mode network (DMN) is a large resting network consisting of the medial prefrontal cortex, posterior cingulate cortex/precuneus and the angular gyrus.

The dorsal attention network (DAN), i.e. the dorsal attention network, is also a large network consisting of the superior and inferior parietal gyrus and the frontal visual fields.

The salience network (SN), i.e. the midcingulo–insular network, consists primarily of the anterior insula and the posterior anterior cingulate cortex (dACC).
The sensorimotor network (SMN), also known as the somatomotor network, includes the somatosensory (postcentral gyrus) and motor (precentral gyrus) regions and extends to the supplementary motor areas (SMA).
The visual network (VN) processes information and is located in the medial part of the occipital lobe.
The auditory network (AN), i.e. the network responsible for hearing, includes the primary and secondary auditory cortex, including Heschl's gyrus, the planum polare and planum temporale, the lateral superior temporal gyrus and the posterior insular cortex.
The executive control network includes the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC).

1.3.2. Examination of upper and lover limb movements in stroke patients with activation fMRI

A stroke means the death of brain tissue, which can occur as a result of inadequate blood supply and lack of oxygen to a brain area, or brain hemorrhage. In the literature, many research groups have used fMRI to examine the connections and connection patterns between motor areas after a stroke during the movement of the paretic upper limb compared to a healthy control group. The consistent finding of the studies is that compared to healthy controls, patients with chronic motor deficits often show increased activity, especially in the contralateral primary motor cortex (M1), the bilateral ventral and dorsal premotor cortex (PMv, PMd), and the supplementary motor area (SMA). In contrast to the rich literature dealing with the restoration of the motor functions of the hand and the underlying neural mechanisms, the reorganization processes leading to the functional restoration of the lower limbs are less well known. It is very likely that the recovery of lower extremity function involves different mechanisms than the recovery of motor function of the hand, given that the upper and lower extremity play different roles in everyday life.

1.3.3. Resting fMRI studies in diabetic and obese patients

According to the definition of the World Health Organization (WHO), diabetes mellitus (DM) is a chronic metabolic disease caused by an inherited and/or acquired lack of insulin production by the pancreas or the ineffectiveness of the produced insulin.

Previous resting–state fMRI studies have demonstrated subtle brain changes in widespread cortical and subcortical regions observed in T2DM patients, but these studies have reported relatively conflicting results. Based on findings from previous studies of T2DM, we hypothesize that brain connectivity patterns may differ between diabetics and obese individuals.

1.3.4. Obesity

Previous studies have explored functional brain connectivity in obese subjects and reported decreased connectivity in the right anterior cingulate cortex and left insula, and increased connectivity in the bilateral precuneus, putamen, and posterior cingulate cortex. Increased BOLD signals were observed in the insula and orbitofrontal cortex.

1.4. Objectives

During the research work, we investigated the clinical applicability of activation and resting brain network analysis, with the following objectives formulated:

1. Comparative analysis of the BLD and DCM methods developed for the parameter estimation of the models describing the hemodynamic response following brain neural activity using resting fMRI measurements of healthy individuals.
2. Analysis of the sensorimotor network in the stroke patient group based on activation fMRI measurements:
   a) Selection of the sensorimotor network topology that best describes the measurement data, including the external stimulus triggered by passive leg movement.
   b) Characterization of the differences between the networks activated during the stimulation of the paresis and non–paresis side in the defined network topology.
3. Using effective connectivity methods, we are looking for differences between the resting brain connections of T2DM and the connection system of obese people, assuming that obesity precedes the prediabetic state.

2. Materials and methods

2.1. Comparison of DCM and BLD techniques

50 healthy, young, right–handed individuals (mean age: 28.15 years (SD=3.58); female/male distribution: 26/24) were selected from the Human Connectome Project (HCP) database.

Functional and structural images were obtained at Washington University in St. Louis using a 3T Siemens Skyra MR unit. After the 3D T1–weighted MP–RAGE structural imaging (TE=2.14 ms, TR=2400 ms, TI=1000 ms, FA=8, voxel size 0.7x0.7x0.7 mm), a BOLD contrast–sensitive gradient echo series was also prepared (TE=33.1 ms, TR=2400 ms, FA=52, resolution=3x3 mm).

We worked with resting–state fMRI data, which were taken on two separate occasions in four series of approximately 15 minutes each. The subjects lay in the MR machine in a relaxed state with their eyes open. During each MR image acquisition, oblique axial data acquisition alternated between right to left (RL) phase coding in one series and left to right (LR) phase coding in the other series.

The fMRI images from the HCP database were processed according to a minimal preprocessing protocol, which included spin echo field map–based gradient distortion correction, motion correction, spatial standardization for the 2 mm isovoxel brain template created by the Montreal Neurological Institute (MNI152 space), and global intensity normalization. Before performing blind deconvolution, additional noise filtering steps were performed. After region selection based on independent component analysis (ICA), regional time series were obtained using two techniques: 1) DCM 1 and BLD 1, and cross–spectral DCM (CSD) methods were obtained based on the first principal component calculated from the voxel–level time series and 2) based on averaged voxel–level time series in the case of the BLD mean method.

In order for the hemodynamic parameters calculated by the methods to be comparable, the Balloon model parameters estimated by DCM were converted to HRF parameters.

In the course of our work, we examined the comparability of the hemodynamic response estimated by different methods. An important aspect of the comparability of the methods for estimating regional hemodynamic parameters was that the parameters show an almost normal distribution, with few outliers. Furthermore, we stipulated that the variability of the investigated parameters should be nearly homogeneous. The distribution of the parameters was examined with the Shapiro–Wilk test. Their deviation depending on the method used was characterized with the Wilcoxon test.

2.2. Analysis of passive leg movements in stroke patients with activation fMRI

We selected 10 stroke patients (average time since stroke onset: 18.2 days (SD=11.4); average age: 64 years (SD=7.2); male/female: 5/5) from the patient group of our previous therapeutic study.

The functional and structural MR images were taken at the Central Radiology Diagnostics Department of the University of Debrecen Clinical Center, Kenézy Gyula Campus, with a 1.5T Siemens Magnetom Essenza MR device. 3D T1–weighted MR–RAGE structural (TE=4.73 ms, TR=1.540 ms, TI=800 ms, FA=15, voxel size 0.9x0.9x0.9 mm) images were taken. The two functional series were made with a BOLD contrast–sensitive gradient echo pulse sequence (TE=42 ms, FA = 90, resolution=3x3 mm; TR=4000 ms, slice thickness = 3.3 mm). The two series represent passive movement of the left or right ankle separately. Both sets consisted of 100 functional images lasting 400 s, with 40 s active and inactive blocks following each other throughout the session. During the inactive blocks, no stimulus was applied, while in the active blocks, the physical therapist performed a slow (~1Hz) passive movement of the left or right ankle. In order to reduce movement artifacts, the legs and hips of the patients were attached to the bed.

Before preprocessing, the left and right sides of the structural and functional recordings of patients with lesions in the left hemisphere were mirrored. This step facilitated population–level statistical analysis for all patients and thus prevented us from dividing the population into two groups depending on the side of the stroke. Our image processing process followed the steps used in previous DCM studies on motor control of stroke patients.

Independent component analysis (MELODIC ICA) implemented in the FSL software was used to determine motor network components. By visual evaluation of the thus obtained independent components and their characteristic time series, we selected the components corresponding to the motor network areas (M1, PM and SMA). The component search was completed by identifying the primary somatosensory cortex (S1).

In our analysis, we used the stochastic version of DCM, which models the endogenous or random fluctuation of hidden neural activity.

To construct the DCM model space, we created bilateral models for both fMRI series in relation to the contralateral and ipsilateral brain hemispheres of the moved limb. Based on the measured data, in order to find the most probable connection architectures in the motor network, we defined a bilateral basic model: the extrinsic (i.e. inter–regional) directed connection between the PM, SMA and M1 regions connected to each region in both hemispheres, and the M1 and SMA regions between the hemispheres we connected. To investigate the connections between S1 and other regions, we defined four possible network models on both sides: (1) S1 is not connected to PM, SMA and M1, (2) S1 is connected only to M1, (3) S1 is connected only to PM, (4) S1 is connected to PM and M1.

To check the target areas of the external stimulus on the side opposite to the movement, three functional variations were taken into account: (1) the stimulus to PM and S1, (2) the stimulus to PM, S1 and M1, (3) to S1 and Stimulus directed to M1.

We evaluated the 12 model variants for all the examined subjects, and then selected the winning model family according to the relationship between stimulation and S1 using two different group–level Bayesian model comparisons (BMC).

DCM not only examines the connection system during model fitting, but also estimates the hemodynamic parameters of the brain areas included in the calculation using the Balloon model: hemodynamic signal attenuation (D), transit time (T) and the ratio of the intra– and extravascular components of the gradient echo signal (E).

In our study, we examined the hemodynamic parameters of subacute stroke patients, which were calculated using the DCM of the winning model for statistical analysis.

Since the continuous passive movement of the non–paretic and paretic ankle (right–left or left–right depending on the patient) induced lateralized brain activations, we had to relabel the names of the brain regions in terms of laterality before the statistical analysis. Therefore, we used the ipsi– and contralateral nomenclature (denoted with the prefixes i and c, respectively) to indicate the position of the brain regions for the two types of stimuli, i.e. cM1, cSMA, cPM, cS1 and iM1, iSMA, iPM, iS1. This made it possible to compare the connection strength and hemodynamic parameters of the activated (or passive) regions during continuous passive movement (CPM) of paretic and non–paretic ankles.

The normality of the data was checked with Shapiro–Wilk tests. Since these tests showed a non–normal distribution, Monte–Carlo–based permutation tests were performed to characterize the stimulus–related differences of paretic and non–paretic ankles in the elements of the endogenous connectivity matrix (matrix A), respectively. in the parameters of the modulation effects (matrix B). Similarly, neither the strength of the external stimulus (matrix C) nor the hemodynamic parameters showed a normal distribution, so we applied the same comparison technique to these data.

To correct multiple comparisons, we used the false discovery rate (FDR) method to correct p–values calculated with statistical tests.

2.3. Comparative analysis of resting fMRI studies in diabetic and obese patients

We selected the data used for our research from the materials of ninety–six people. The examination materials of the patients were prepared at the Internal Medicine Clinic of the University of Debrecen. We analyzed a total of 70 subjects who had T1–weighted and 10–minute resting fMRI recordings. Forty–three patients diagnosed with type 2 diabetes (17 women, 26 men) and 27 obese subjects (19 women, 8 men) make up the two patient groups.

The structural and functional images were taken at the Clinical Center of the University of Debrecen with the Philips Achieva 3T MR device of the radiology service company Diagnoscan. 3D T1 weighted turbo field echo (TFE) structural (TE=3.7 ms, TR=8 ms, FA=8, slice

0.5x0.5x1 mm voxel size) recordings were made. Resting functional MR images covered the entire brain and were made with the field–echo echo–planar imaging (FE_EPI) sequence (TE=35 ms, TR=2300 ms, FA=90, resolution=1.25x1.25 mm, slice thickness=4 mm).

We used the nipype framework for preprocessing. Preprocessing of T1–weighted images consisted of brain and tissue segmentation and spatial normalization. The software fits the brain images to the MNI152 space by combining linear and non–linear transformations during spatial normalization.

We started the preprocessing of the functional images with motion correction, for which we used the FMRIB Software Library MCFLIRT utility. To reduce movement artifacts, 24 regression variables were generated from the head movement parameters of the six rigid bodies (translation and rotation along three axes). In order to reduce the impact of outliers on the analysis, we limited their size. Functional images were registered to structural images using the FSL FLIRT tool. The fMRI recordings were then transformed into MNI152 space. In this step, the first four volumes were deleted from the timeline. After the brain segmentation with FSL BET, the anatomical CompCor method was used to calculate the components of the fMRI time series measured in the white matter and cerebrospinal fluid, which are not considered relevant for the analysis. Spatial filtering was performed using the SUSAN FSL application, with a Gaussian kernel with a half–value width of 6 mm. Further correction of motion artifacts appearing in the fMRI signal was performed with ICA–AROMA based on independent component analysis. We removed the 24 motion parameters and five components that showed the greatest variation. With temporal band filtering between 0.009 Hz and 0.08 Hz, only the signal frequencies related to the nervous fluctuations of the resting state were analyzed.

We identified 36 regions (ROIs) in seven resting state networks (RSN): default mode network (DMN), dorsal attention network (DAN), the control executive network (CEN), salience network (SN), sensorimotor network (SMN), the visual network (VN) and auditory network (AN). To take into account the variability between neural fluctuations per subject, the coordinates were modified based on the results of the independent component analysis. Matlab's GIFT module was used to calculate ICA in both groups. The components corresponding to the synchronous fluctuations of each resting network were selected as follows: first, we counted how many resting network regions with a T statistic value greater than 3 were found in the Student–t statistical image of each component. Then we selected the component with the most matches. In cases where more than one component was found, the one with the highest average T value was used. The individual coordinates were set by finding the peak T value on the reconstructed ICA images within a circle with a radius of 8 mm from the original location.

Effective connectivity calculations within the large–scale resting brain network were performed using the DCM method, which is freely available in the Statistical Parametric Mapping (SPM12 v6906) Matlab toolbox. The effective connectivity was estimated using the cross–spectral DCM method optimized for resting data.

We determined the parameters that fit a fully connected network in cross–spectral DCM with 36 regions yielding 1296 endogenous connectivity parameters for all 70 subjects.

With the latest developments of the DCM framework, we can model the relationships between subjects or at a higher level using the parametric empirical Bayes (PEB) method. We performed our analysis at the group level in two separate ways. First, we assessed the main effect of the estimated DCM parameters in both T2DM and obese groups in two separate PEB models. Second, we designed a between–subjects PEB analysis with all subjects to explore relationship differences between the study groups. PEB analysis combined with Bayesian model reduction (BMR) created a group–level effective connectivity matrix (ECM) for both groups, as well as a group–level connectivity differences matrix (dECM). In further analysis, we used these three matrices to characterize resting network topology differences between the T2DM and obese groups.

The structure of ECMs and dECM are similar: they define 36x36 connection matrices, the elements of which are organized into seven RSNs.

With the help of the presented graph models, three levels of graph analysis were performed: global (brain), modular (RSN) and regional.

One important global feature that can be extracted from the weighted undirected connectivity matrix (WUCM) during brain–level analysis is the small–world property. In the case of brain networks, the small–world characteristic is used to describe both strong local clustering (connection) and strong average interaction between any two regions.

We used „small–world propensity” (SWP) to measure the small–world nature of weighted networks. This method ignores density dependence and preserves basic network characteristics such as link strength. SWP is a quantitative metric to measure the extent to which regions in a network participate in small–world model formation.

In the graph theory approach, RSNs were treated as network modules, so it became possible to use the metrics developed for endpoint groups (modules) of graph theory. To describe the topological differences of RSNs, we used intra–network properties of individual RSNs and inter–network properties of pairs of RSNs. We generated a 7x7 RSN matrix according to the connections within and between networks from all the graph properties we calculated at the global level, corresponding to the seven RSNs under investigation.

Regional differences between the two groups can be measured from the dECM matrix.

We have separately calculated the average increase and decrease in connectivity of each region. We only report significant connectivity differences, i.e., regions below the 5% quantile of mean decrease and above the 95% quantile of mean increase in connectivity among the 36 regions.

3. New scientific results

3.1. Comparison of DCM and BLD techniques

In the comparison of the hemodynamic parameters describing the shape of the HRF curves calculated with the BLD and DCM techniques, we considered it an advantage if they show an almost normal distribution in all regions in the examined healthy population. Among the HRF characteristics, the time parameters were found to be comparable, since the methods using BLD determine the Height parameter on a different scale than the DCM versions.

There are significant differences between the BLD and DCM methods for both T2P and FWHM in all DMN regions. While HRF is 4.96 and 4.47 seconds on average according to the BLD 1 and BLD mean methods, it peaks after 6.48 and 6.03 seconds in DCM 1 and DCM CSD. Furthermore, a faster breaking of the curve can be observed in the two BLD methods with an average half–value width of 3.99 and 3.56 seconds compared to 6.3 and 6.32 seconds in the DCM methods.

The normality of the parameters was tested with the Shapiro–Wilk test. In all 4 regions of T2P, the CSD–based DCM method approaches the normal distribution. In the examination of the FWHM, the DCM CSD estimates follow the normal distribution the best, with the exception of the rIPL region.

Among the four HRF estimation methods, no variance was found in the curve parameters for DCM 1. However, the disadvantage of DCM is that we can only perform calculations at the regional level, i.e. hemodynamic parametric maps cannot be prepared with this procedure.

3.2. Analysis of passive leg movements in stroke patients with activation fMRI

In our research work, we examined the connection topology of the motor network extended with the S1 region and the differences in the effective connectivity related to passive movement between paretic and non–paretic ankles during CPM in subacute stroke patients. Since the exact effective connectivity structure of the motor network in stroke is not completely known, we used an fMRI–based model search procedure to identify the model family that best fits the motor network.

In our study, we used the DCM–based effective connectivity technique to describe the properties of the motor network during the applied CPM stimulations. We chose this method because it helps to understand the cause–effect relationships of the activation of the modeled network regions and takes into account the temporal change of the neural activity estimated by the BOLD signal. During the model selection, we defined two model families, which contain four and three models, respectively, according to the model combinations of the S1 connections and the effect of the external stimulus. The applied BMC selection showed that external sensory stimulation was bound to the S1 and PM regions, and S1 was bound only to the M1 and PM regions.

Using BMC selection, we found that during the continuous passive leg movement task, the S1 connection with M1 and PM (F_4^{S1} family) was the most likely network topology with an expected probability of 0.784 and an „exceedance" probability of 0.998. When choosing the model family describing the stimulus effect, we observed that stimulation of S1, M1 and PM (F_2^{stim} family) was the most likely with an expected probability of 0.845 and an „exceeding" probability of 0.999. Based on these results, model 11, the so–called we chose the winning model for the statistical analysis of the model parameters.

After statistical comparison of external connections of the winning model during non–paretic and paretic CPM, we concluded that three contralateral self–inhibitions (cM1, cS1 and cSMA), one contralateral interregional connection (cSMA→cM1) and one interhemispheric connection (cM1→iM1) was significantly different.

The strength of the contralateral SMA→M1 connection was different during the two CPMs: SMA increased M1 neural activity by 0.085 Hz (SD=0.049 Hz) during movement on the non–paretic side. This effect changed to −0.0053 Hz (SD=0.084 Hz) during contralateral CPM, implying that this interaction occurs only in the non–paretic case.

The 50% stronger cM1→iM1 interaction (0.276 Hz and 0.170 Hz) during paretic CPM may indicate that after the stroke, the unaffected M1 partially compensates the function of the damaged motor cortex.

Our results show that stroke can affect the functional connectivity of areas remote from cerebral infarction, especially S1, which can further reduce motor performance.

We showed that the hemodynamic parameters of the regions of the motor networks (Balloon model parameters: D, T and E) were statistically similar during the two stimulations. This result suggests that the observed differences in connection strengths originate from real neural activity and that hemodynamic changes did not have a confounding effect during the measurements.

3.3. Comparative analysis of resting fMRI studies in diabetic and obese patients

In our research work, we tried to distinguish effective connectivity patterns in a large brain network between groups containing obese and diabetic individuals. We found that the new developments of the DCM framework can be useful in the analysis of effective connectivity changes in a sufficiently complex system, and the graph–theoretic characterization of group–level PEB models can reveal significant topological differences between the connection points of groups.

In both groups we examined, reduced connectivity between the posterior cingulate cortex (PCC) and the right middle temporal gyrus (rMTG) was detected. The PCC has a high metabolic rate, extensive functional and structural connections with other nodes, and plays a key role in higher–order cognitive functioning and complex information processing.

Reduced connectivity was observed in the rIPL in the diabetic group. As the region of the rIPL, similar to the rMTG, is a brain region associated with dementia, we hypothesize that altered connectivity in this region may be a promising indicator of potential future cognitive decline associated with T2DM. However, in order to confirm our hypothesis, future studies involving patients with dementia are warranted.

On a global scale, different graph analysis was observed in diabetic patients, with a lower clustering coefficient and a larger characteristic path length than in obese patients.

For dECM, positive values indicate a greater association with T2DM, and negative values indicate a reduced association with obesity.

We found that the overall connection strength of the regions is higher in T2DM (6.01 Hz) than in obesity (4.11 Hz), and this was also observed in the diagonal (S_{diag}) values for diabetes (0.25) and obesity (0.19). This means that regions are generally more connected and regional self–inhibition is stronger in diabetics.

The SWP of the network of the T2DM group was higher (mean=0.75, SD=0.006) than that of the obese group (mean=0.72, SD=0.007), which means that the network of diabetic patients is slightly shifted towards regular networks as expected from random networks due to an increased mean short path length (dL), which had a mean value of 0.32 (SD=0.009) in diabetes and 0.27 (SD=0.01) in obesity. However, diabetes shows a smaller difference in the level of clustering (dC) than obesity (0.28, SD=0.011 in the obese group and 0.17, SD=0.007 in diabetes).

We used „selectivity” to measure how strongly regions from the same RSNs are generally connected to each other. We found that RSNs are less „selective” in T2DM (0.063) than in obesity (0.127).

The RSN–level characteristic calculated from the weighted directed connectivity matrices (WDCM) is presented in the 7x7 RSN–matrices, where the parameters within the network are summed up in the main diagonal, and the off–diagonal values represent the parameters between the networks. We found that both „selectivity” and the strength of connectivity between networks are higher in T2DM. These changes are mainly due to the connectivity of the DMN, DAN and SN. We found significant inter–network imbalance in diabetes (negative $\log_{10}(p)>3$), with the DMN associated with most deviations from connectivity balance ($-\log_{10}(p) = 7.725$).

For region–level analysis, dECM was used to examine connectivity differences between individual regions. Among all regions, the most striking decrease in connectivity, exceeding the lower quantile of 0.05%, is found in the right middle temporal gyrus (rMTG) with an average decrease of 0.013 Hz and in the right inferior parietal lobe (rIPL) with a decrease of 0.01 Hz. On the other hand, in the left anterior prefrontal cortex, the SN (lAPFC2) and the medial dorsal thalamus (MDT) have the highest increase in T2DM, with 0.01 Hz and 0.009 Hz, respectively.

One of our main findings was that network connectivity was generally increased in T2DM compared to the obese group. Interestingly, overall connectivity strength increased in diabetes, particularly in SN.

We hypothesize that hyperglycemia–induced glucotoxicity may contribute to changes in brain networks, resulting in reduced connectivity. Since the glucose levels of our diabetic patients were adequately controlled and they did not show cognitive symptoms, we came to the conclusion that hyperconnectivity may be a kind of compensatory mechanism in the early stages of disease progression. Increased connectivity between networks was mainly seen between DMN, DAN and SN.

Network analysis may be a sensitive tool in the assessment of subclinical brain changes caused by T2DM and obesity, which may precede cognitive clinical symptoms. Based on the relationship between network impairments and cognitive function, we hypothesize that connectivity analysis in a large–scale resting network may serve as a potential biomarker for cognitive dysfunction and neurodegeneration.

The large number of different connections and their connections suggests that T2DM may be associated with large–scale, global changes in brain connectivity.

4. Summary

Examining the functional connectivity of the human brain is essential to gaining insight into the organization of the human brain. In our research project, we examined the clinical applicability of neurobiological parameters that can be determined with resting–state and task–based fMRI. The procedures developed for estimating the hemodynamic parameters that can be calculated from the fMRI measurement data were examined with a comparative analysis, and brain network characteristics were calculated for patients with stroke and diabetes mellitus.

4.1. Comparison of DCM and BLD methods

We know two methods based on the literature that can be used to determine the parameters characterizing hemodynamic changes, these are blind deconvolution (BLD) and Dynamic Causal Modeling (DCM). In order to compare algorithms based on different mathematical models, the Balloon model parameters estimated by DCM were converted to HRF parameters. An important aspect of the comparability of the methods was that the parameters showed an almost normal distribution, with few outliers. We obtained the result that only the time parameter (T2P) can be used for comparison. After performing the statistical analysis, we came to the conclusion that, among the examined techniques, the DCM calculation is the acceptable method for determining the hemodynamic parameters. However, the disadvantage of the method is that we can only perform calculations at the regional level, and hemodynamic parametric maps cannot be prepared with this procedure.

4.2. Analysis of passive leg movements in stroke patients with task–based fMRI

During our research, we studied the connectivity changes observed in the sensorimotor network of 10 stroke patients as a result of passive leg movement. For the analysis, we processed the patients' activation fMRI data. For the analysis, we defined model families that can be connected to the sensorimotor network depending on the external stimulus and the connectivity patterns of the primary sensory cortex (S1). We defined a total of 12 model families, of which we chose model 11 as the best. During the passive leg movement task, the S1 connection with M1 and PM showed the most probable network topology. When choosing the model family describing the effect of the stimulus, we observed that stimulation of S1, M1 and PM was the most likely. We also showed that paretic passive leg movement caused stronger self–inhibition in the contralateral M1 and S1 and weaker self–inhibition in SMA. The relationship between the contralateral SMA and M1 changed significantly: during non–paretic leg movement, the contralateral SMA stimulated the neural activity of M1, which in turn inhibited the paretic stimulus. The interhemispheric contralateral M1 → ipsilateral M1 connection showed stronger excitation during paretic movement compared to non–paretic ankle movement.

4.3. Comparative analysis of T2DM and obese patients based on resting state fMRI

The aim of our work was to examine the brain effective connectivity changes that occur in diabetes in a large–scale model of resting networks. We included 70 people in the research, of which 43 subjects were diagnosed with type 2 diabetes mellitus, and 27 individuals were obese patients. We identified 36 regions in 7 quiescent networks. The advantage of using DCM is that it can be used to estimate causal interactions between underlying neural states. Using this framework together with graph theory methods, we revealed topological differences between type 2 diabetes and obesity, and also managed to highlight regions whose effects on each other can cause functional changes in the brain. We have shown that the use of this type of more complex analysis can help to further understand the neural mechanisms of the disease, or perhaps to find biomarkers that can predict the causes leading to the development of type 2 diabetes.

By applying the DCM method, in addition to connection parameters, hemodynamic parameters can also be estimated. By using it in stroke and T2DM, we were able to determine the regions and the relationships between regions that change as a result of the disease.

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Registry number: DEENK/433/2024.PL
Subject: PhD Publication List

Candidate: Marianna Nagy
Doctoral School: Doctoral School of Molecular Medicine
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List of publications related to the dissertation

1. Aranyi, S. C., Képes, Z., **Nagy, M.**, Opposits, G., Garai, I., Káplár, M., Emri, M.: Topological dissimilarities of hierarchical resting networks in type 2 diabetes mellitus and obesity.
   J. Comput. Neurosci. 51 (1), 71-86, 2023.
   DOI: http://dx.doi.org/10.1007/s10827-022-00833-9
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2. **Nagy, M.**, Aranyi, S. C., Opposits, G., Papp, T., Lánczi, L., Berényi, E., Vér, C., Csiba, L., Katona, P., Spisák, T., Emri, M.: Effective connectivity differences in motor network during passive movement of paretic and non-paretic ankles in subacute stroke patients.
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List of other publications

3. Winkler-Ferenczi, Z., Pelyvás, B., **Nagy, M.**, Marosi, M., Béres, M., Varga, R., Bencze, J., Szűcs, P., Berényi, E., Englohner, A., Meszár, Z., Papp, T.: Repeated diagnostic ultrasound exposure modifies the structural properties of CA1 dendrites and alters the hippocampal transcriptome.
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5. Payette, K., de Dumast, P., Kebiri, H., Ezhov, I., Paetzold, J. C., Shit, S., Iqbal, A., Khan, R., Kottke, R., Grehten, P., Ji, H., Lánczi, L., **Nagy, M.**, Béres, M., Nguyen, T. D., Natalucci, G., Karayannis, T., Menze, B., Cuadra, M. B., Jakab, A.: A comparison of automatic multi-tissue segmentation methods of the human fetal brain using the FeTA Dataset.
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   IF: 1.953

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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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