

Aberrant change in brain network flexibility during the performance of Theory of Mind task in schizophrenia patients

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1 Introduction

Theory of Mind (ToM) is the ability to "see the others as intentional beings, to see their actions as motivated by mental states." and "the realization that the mental states of others may differ from one's own" [25]. Or in other words, "the ability to infer intentions, dispositions, and beliefs of others" [10, 9, 2].

In the following research, we explore if the difference in ToM between schizophrenia and control group is reflected in the flexibility of brain functional network detected by the template flexibility method introduced in [5]. The analysis is done in 3 different scales: whole brain, groups of regions and single regions.

The results are then used to test if an accurate classification of the subjects into the two groups of patients and controls is possible employing the flexibility-based features.

64 healthy controls and 64 schizophrenia patients were matched and selected from the IntegraMent (Integrated Understanding of Causes and Mechanisms of Mental Disorders) multi-centric study at Charité Universitätsklinikum Berlin and the Zentrum für Seelische Gesundheit in Mannheim.

The part of the multi-centric study data used in the present study contains Blood-Oxygen-Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) collected during the performance of the cartoon ToM paradigm first introduced by Schnell and colleagues and later used in further studies [23, 26, 19, 18]. Subjects were presented short cartoon stories of 3 images per trial and they were asked to evaluate either the change in the main character's affective state of mind (options: better/equal/worst) compared to the preceding image in the ToM condition or changes in the number of living beings (options: more/equal/less) in the control condition. The two conditions were presented in alternating blocks of approximately 30 seconds. Pre-processing was done using a similar pipeline from Erk et al [7] in SPM8. It included realignment to mean image (movement parameters 3mm and 1.7 degrees between volumes), slice-time correction, normalization to the standard MNI (Montreal Neurological Institute) space with $3 \times 3 \times 3$ mm voxel size and Gaussian kernel smoothing with a 9 mm Full Width at Half Maximum (FWHM).

Mean time courses were extracted for 246 Brainnetome atlas regions belonging to 15

a-priori modules⁴ The method for the calculation of flexibility introduced in [5] is applied to the time series. This method finds the deformation of a-priori modules in the brain by comparing the connection weights of the weighted adjacency matrix and pre-defined affiliation of the nodes to an a-priori module (each node belongs to an a-priori module by default). In each weighted adjacency matrix, the absolute value of functional connections between every single node and all the members of every a-priori group is calculated and then normalized to the size of each a-priori group. The resulting weights are compared to choose a “winner” affiliation. The winner affiliation can be the same or different from the a-priori affiliation. Assigning winner affiliations to every node, a new set of affiliations for all nodes in each window is achieved. The ratio of nodes in the brain that change their affiliation between two subsequent windows is called the whole-brain-flexibility (WBF) between those windows. A time serie of WBF is achieved via concatenation of between-window ratios. In addition to the whole brain, one can look at the changes of affiliations in a module level. The population of modules will increase and decrease as a result of nodes changing their affiliations. Finally, on a node level, the affiliation changes that a selected node experiences over the course of the experiment rises the possibility to investigate the behaviour in a selected set of nodes.

2 Results

2.1 Scale Results

Schizophrenia patients and healthy controls show significantly different variance and range in their whole-brain flexibility (WBF) time series (see figure 4) while their mean WBFs are not significantly different. Figure 3 shows all WBF time series in one frame. The schizophrenia group subjects (left, yellow column) are more likely to show an aberrant increase or decrease in their WBF time series compared to the control group on the right (reflected in the variance) at irregular intervals (reflected in give/take measure).

Our investigations on the module population (nodes that belong to an a-priori module by their winner-affiliation at a given window) dynamics suggests that there are significantly different behaviours in modules population dynamics of Auditory, High Visual, Left Executive Control (LECN), sensorimotor, ventral Default Mode Network (vDMN) and the 15th undefined module (see [5] for the definition of this 15th module and figure 13 for the list of regions in it). The differences are observed using the 3 measures (average, variance and range) on the module population time series (see figures 5, 6 and 7). Abnormalities in the Default Mode and Executive Control Networks have

⁴The module used in this context is equivalent to a group of nodes that are put in the same group based on a-priori knowledge of researchers. A module is defined as a subnetwork that is dedicated to a specific brain function or located in a specific spatial region and is of interest to the area of research. It does not follow the mathematical definition for module and modularity as in the mathematical literature [20]. In the current study, a module refer to the 14 well-known Independent Component Analysis (ICA) -based subnetworks introduced by Findlab [24] (see table 1) plus one module that includes the rest of the nodes not belonging to the 14 known ones as in [5].

been extensively reported in the resting state fMRI studies of schizophrenia patients [4, 22, 17]. Our findings suggest that the different behaviours of Default Mode (DM) and Executive Control (EC) Networks extend to the mentalizing tasks. To study the level of synchrony between brain time series and task design, a give/take measure is defined as modules which have the peak of losing or gaining members at the frequency of task. An overall decrease in give/take changes associated with the task time-pattern of 30 s in schizophrenia is observed (height of all bars in figure 8). This in turn agrees with the lower contrast between ToM and control conditions observed by several studies. The contrast is explained by either hypometabolization during ToM or hypermetabolization during the control condition [1, 8, 16, 6]. The results suggest that the schizophrenic brain distinguishes less between TOM and control stimuli than a healthy brain regardless of whether hyper- or hypo-mentalizing is the source of this change in the contrast.

In addition, some columns in figure 8 show a different trend between the 2 groups. Module 2 [Auditory] and module 5 [High Visual], are dominantly giver modules in the control group while they act as stronger takers in the schizophrenia patients. This suggests that these modules are receiving reinforcement from other modules and expanding in a frequency corresponding to the task-blocks. Several schizophrenia studies in fact suggest that the deficits occurring at the stage of sensory processing and perception are the bottom-up reasons for the dysfunction in higher cognitive levels in the patients suffering from schizophrenia [14, 13, 15, 3].

The different trends observed by our method in the auditory, visual and sensorimotor modules could be interpreted as a further sign of perception-related abnormalities associated with schizophrenia.

On the node scale, a mask of ToM-associated areas generated by Neurosynth⁵ engine from 181 studies was overlaid by a Brainnetome atlas map of regions. 9 shows Brainnetome regions and ToM associated area. Brainnetome regions with higher than 50% overlap with ToM areas were marked and selected to be investigated. These were 5 regions in total listed in 9. The violin plot for the total number of switches for these 5 regions in schizophrenia patients and healthy controls is shown in figure 9.

2.2 Classification of Control Subjects and Schizophrenia Patients

A Generalized Linear Model (GLM) model with L2 (ridge regression) penalties ($\alpha = 0^6$), a gradient descent solver and logistic regression (binomial family) [21] from h2o python package [12] was used on vectors with all the three level values (whole brain, modules and nodes) listed in figure 2 as elements. The giver/taker elements were filtered to contain only columns with at least 10 non-zero values. The total number of elements after this filtering was 81. The mean accuracy in 10 fold for the classification was 0.74 (see figure 11 for the cross-validation metrics summary). The relatively

⁵<https://neurosynth.org/>

⁶The alpha parameter controls the distribution between the l1 (LASSO) and l2 (ridge regression) penalties. The penalty is defined as [21]:

$$P(\alpha, \beta) = (1 - \alpha)/2\|\beta\|_2^2 + \alpha\|\beta\|_1 = \sum_j [(1\alpha)/2\beta_j^2 + \alpha|\beta_j|]$$

small dataset for training and test results in considerable fluctuation in accuracy (each prediction moves the accuracy by around 8%) within different folds but the classification distinguishes between the two groups with a significant margin. The contribution of columns as the coefficients in the classification are shown in figure12. The classification can be improved by using bigger datasets for training and testing purposes.

3 Summary

The flexibility-based measures of brain network obtained from fMRI data collected during the theory of mind (ToM) cognitive task for 2 groups of schizophrenia patients and healthy controls were calculated and compared. Based on these measures, the two groups were distinguished with an average accuracy of 74% while the algorithm relied heavily on the information from population of modules 13 (vDMN) and 15 (untagged) and variance of whole-brain flexibility together with the member exchange of modules 7 (Left Executive Control (LECN)) and 15 and modules 2 [Auditory] and 7 [Left Executive Control (LECN)].

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Table 1. Number and Name of modules.

Module Number (Short Name)	Module Name
Module 1 (M1)	Anterior Salience
Module 2 (M2)	Auditory
Module 3 (M3)	Basal Ganglia
Module 4 (M4)	Dorsal Default Mode Network (dDMN)
Module 5 (M5)	High Visual
Module 6 (M6)	Language
Module 7 (M7)	Left Executive Control (LECN)
Module 8 (M8)	Posterior Salience
Module 9 (M9)	Precuneus
Module 10 (M10)	Primary Visual
Module 11 (M11)	Right Executive Control (RECN)
Module 12 (M12)	Sensorimotor
Module 13 (M13)	Ventral Default Mode Network (vDMN)
Module 14 (M14)	Task Positive
Module 15 (M15)	Undefined (untagged nodes listed in 13)

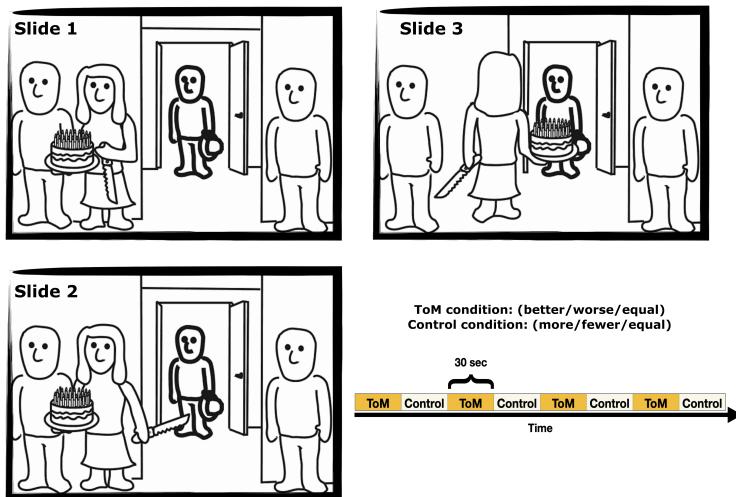


Fig. 1. Sample cartoons from Theory of Mind (ToM) task

During ToM condition, The protagonist's (character in bold line) change in affective state should be described by participants as better, worse or equal. During the control condition, the number of living beings should be counted (more/fewer/equal). Each condition takes 30 s including the instruction.

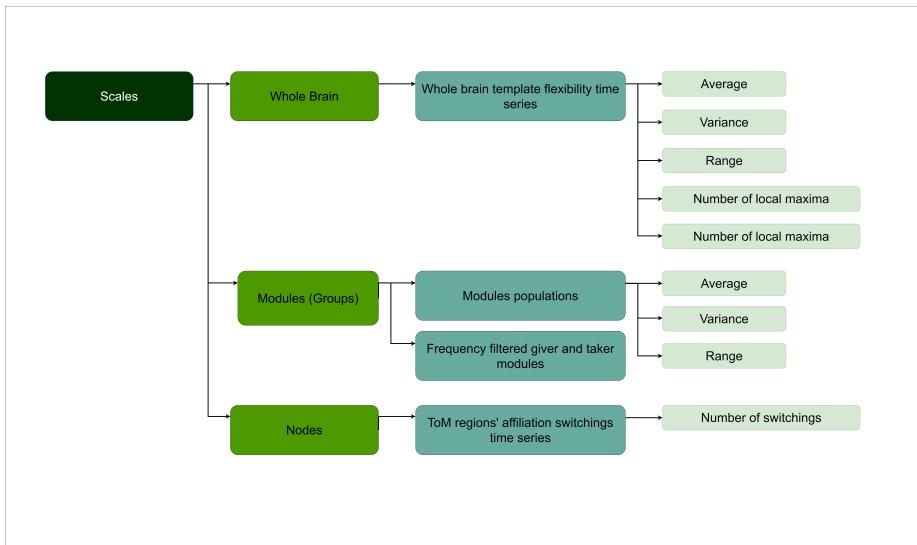


Fig. 2. A summary of flexibility-based values calculated for each subject

On the whole brain scale, the WBF time series are calculated and average, variance, range, number of maxima and number of minima for each time serie are extracted and saved. On the module scale, the population time series for all 15 Findlab modules are extracted and average, variance and range are calculated and saved. In addition, modules that had a dominant pattern of giving or taking members from or to other modules in the frequency associated with the task are marked and saved. Finally, on node scale, 5 regions associated with ToM task are selected and the the number of affiliation-switching for each of them is counted.

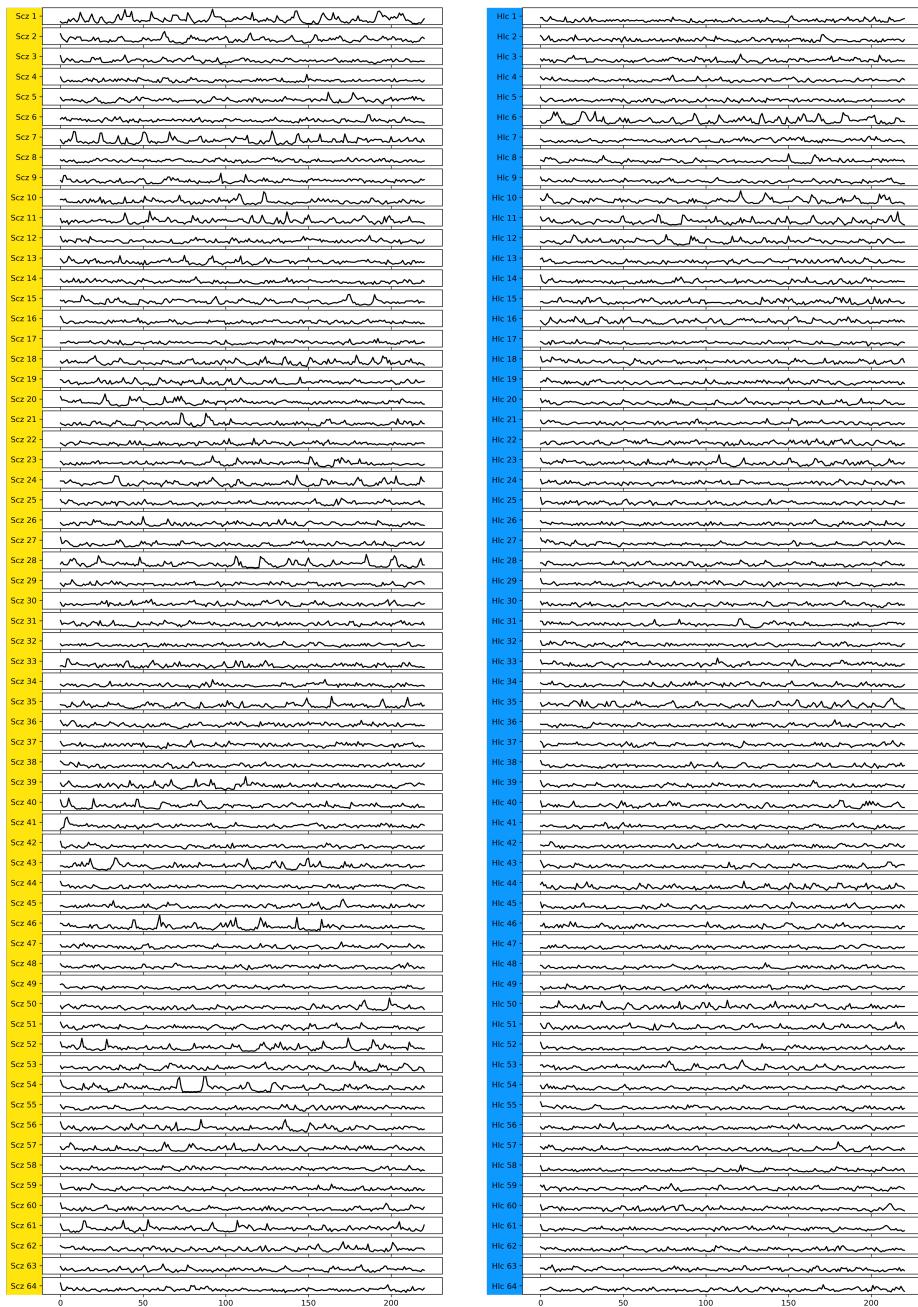


Fig. 3. All whole-brain flexibility time series for schizophrenia patients and healthy controls
 Right column shows all healthy controls and left column the schizophrenia patients (each row is a single participant). Y axis is WBF value and X axis is time.

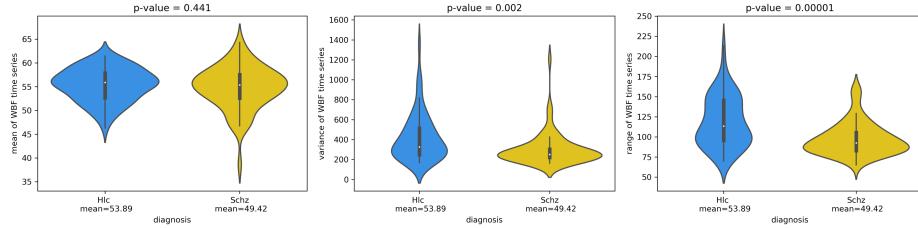


Fig. 4. WBF (whole-brain flexibility) comparison

Average, variance and range of every WBF time serie is calculated and the 2 subject groups are compared based on these measures. Average, in contrast to the other two measures, is not showing a significant difference.

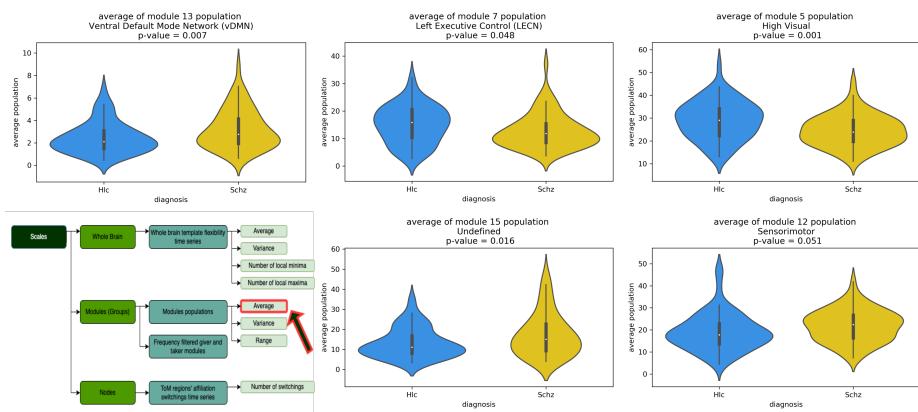


Fig. 5. Significantly different module population averages

Blue and gold violin plots respectively show the control group and schizophrenia patients average module populations. The 5 modules (high visual, LECN, vDMN, sensorimotor and undefined [regions not associated with Findlab modules]) show considerably small p-values (≤ 0.051).

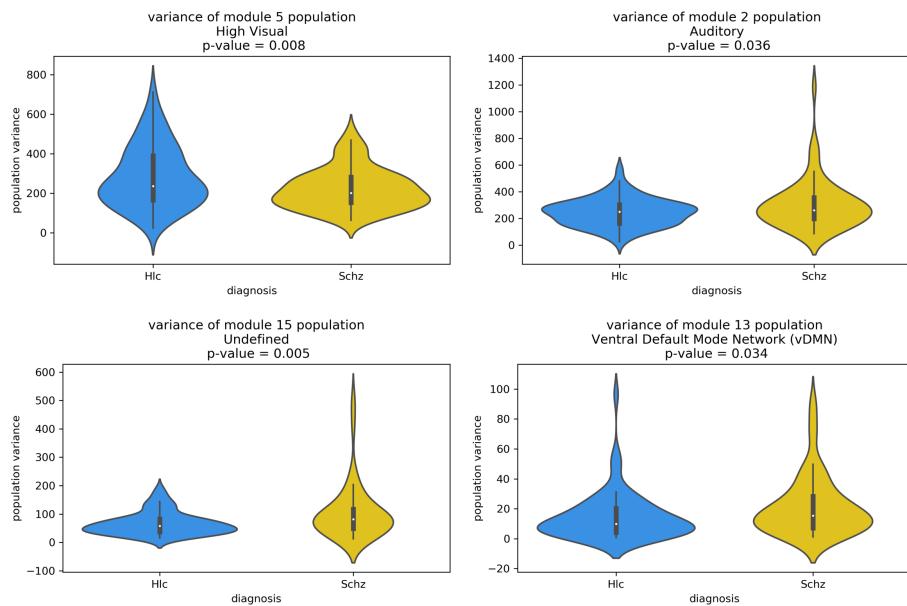


Fig. 6. Significantly different module population variances

Blue and gold violin plots respectively show the control group and schizophrenia patients variance of module populations. The 4 modules (high visual, Auditory, vDMN, and undefined [regions not associated with Findlab modules]) show considerably small p-values (≤ 0.036).

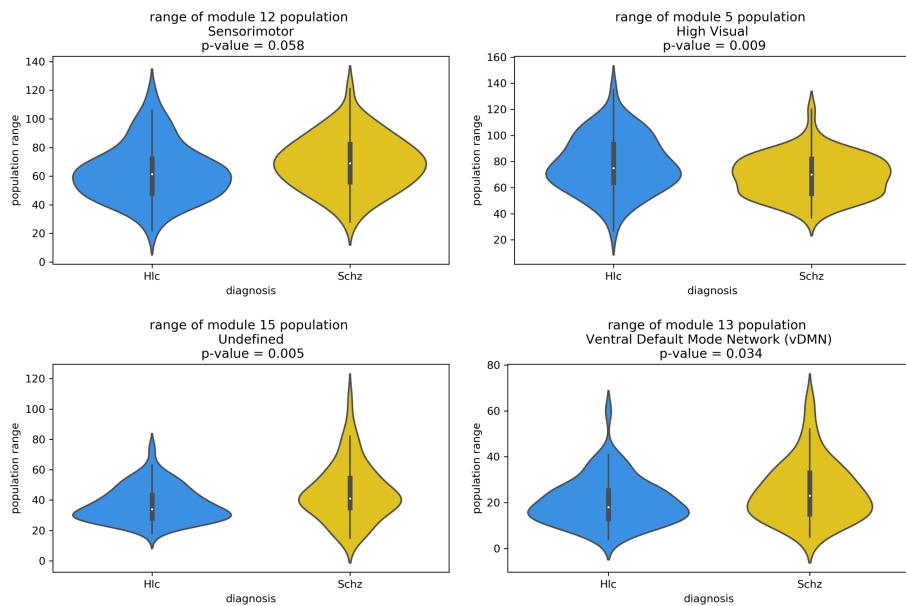


Fig. 7. Significantly different module population ranges

Blue and gold violin plots respectively show the control group and schizophrenia patients range of module populations. The 4 modules (high visual, vDMN, sensorimotor and undefined [regions not associated with Findlab modules]) show considerably small p-values (≤ 0.058).

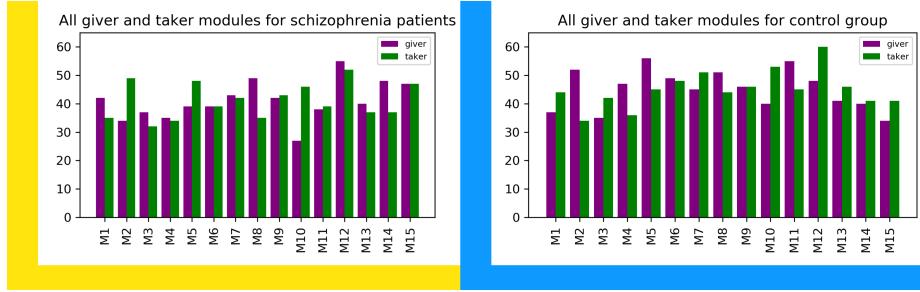


Fig. 8. All non-unique giver and taker modules for both groups When a node moves from one module to another between two consecutive time windows, one module loses a member and another gains one. We call these modules the “giver” [the module which loses a member] and “taker” [the module which gains a member] modules respectively. For each time step t between two windows, a 15×15 non-symmetric matrix called D_t with elements $D_{t,ij}$ showing the number of nodes that move from module i to module j in t is calculated. Extracting the information of a fixed i and j through time dimension, a time serie of giving-taking between module i and j is achieved. If this time serie shows a peak in the frequency value close to our change of task conditions frequency, the giving-taking behaviour is associated with the performance of the ToM task. The task-associated giver and taker modules of each subject that show a repetitive behaviour in the range of ± 5 seconds from the task period were extracted and recorded to generate these plots. Each bar shows how many times a module was found as a giver (purple) or taker(green) Right plot shows healthy controls and left plot the schizophrenia patients.

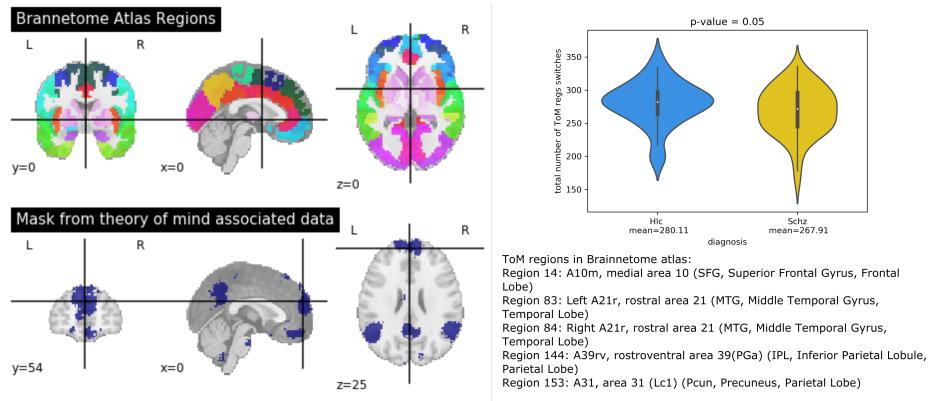


Fig. 9. Brainnetome and ToM regions

There are 5 regions from Brainnetome atlas that have higher than 50% overlap with ToM mask.

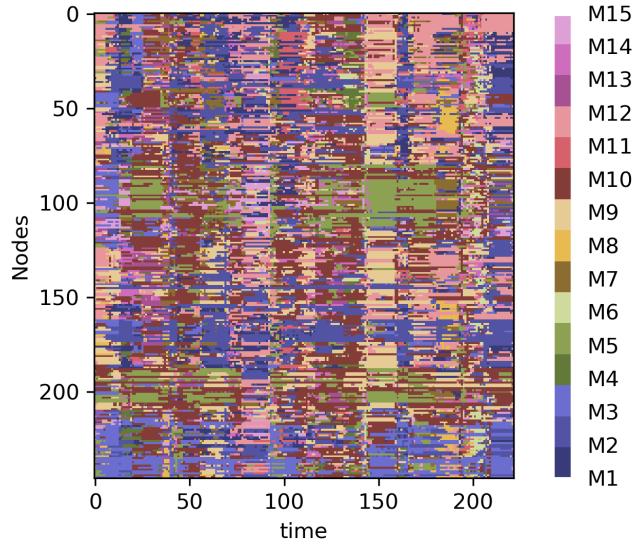


Fig. 10. All 246 nodes affiliations over time for one sample subject
Visualization of affiliation change over time for all nodes in one subject.

	mean	sd	cv_1_valid	cv_2_valid	cv_3_valid	cv_4_valid	cv_5_valid	cv_6_valid	cv_7_valid	cv_8_valid	cv_9_valid	cv_10_valid
accuracy	0.742608	0.090405	0.666667	0.800000	0.875000	0.750000	0.583333	0.692308	0.666667	0.842105	0.750000	0.800000
auc	0.706121	0.115547	0.745455	0.777778	0.933333	0.666667	0.656250	0.650000	0.512500	0.769231	0.750000	0.600000
err	0.257392	0.090405	0.333333	0.200000	0.125000	0.250000	0.416667	0.307692	0.333333	0.157895	0.250000	0.200000
err_count	3.400000	2.065591	7.000000	3.000000	1.000000	1.000000	5.000000	4.000000	6.000000	3.000000	2.000000	2.000000
f0points	0.699137	0.120361	0.642857	0.735294	0.862069	0.555556	0.500000	0.729167	0.625000	0.869565	0.714286	0.757576
f1	0.760537	0.103100	0.720000	0.769231	0.909091	0.666667	0.615385	0.777778	0.625000	0.888889	0.800000	0.833333
f2	0.842195	0.094967	0.818182	0.806452	0.961538	0.833333	0.800000	0.833333	0.625000	0.909091	0.909091	0.925926
lift_top_group	1.428654	1.084548	2.100000	2.500000	1.600000	0.000000	3.000000	1.625000	0.000000	1.461538	2.000000	0.000000
logloss	0.605597	0.122935	0.606646	0.565684	0.309346	0.720407	0.679225	0.692103	0.693523	0.567010	0.535866	0.686156
max_per_class_error	0.426768	0.133408	0.545455	0.222222	0.333333	0.333333	0.625000	0.600000	0.375000	0.333333	0.500000	0.400000
mcc	0.522010	0.149175	0.391965	0.600099	0.745356	0.577350	0.408248	0.317543	0.325000	0.622532	0.577350	0.654654
mean_per_class_accuracy	0.748187	0.075251	0.677273	0.805556	0.833333	0.833333	0.687500	0.637500	0.662500	0.794872	0.750000	0.800000
mean_per_class_error	0.251813	0.075251	0.322727	0.194444	0.166667	0.166667	0.312500	0.362500	0.337500	0.205128	0.250000	0.200000
mse	0.213540	0.047916	0.211321	0.192809	0.105944	0.263545	0.243125	0.249442	0.250165	0.190718	0.181579	0.246754
null_deviance	17.928375	7.712128	29.132708	20.964321	11.159250	5.610740	16.925781	18.187233	25.031984	27.318438	11.090355	13.862944
pr_auc	0.656512	0.198501	0.747247	0.702518	0.963536	0.306853	0.584491	0.739754	0.437974	0.848301	0.735552	0.498895
precision	0.666516	0.130398	0.600000	0.714286	0.833333	0.500000	0.444444	0.700000	0.625000	0.857143	0.666667	0.714286
r2	0.073469	0.252445	0.152796	0.198629	0.547974	-0.405572	-0.094060	-0.053894	-0.013169	0.117317	0.273684	0.012983
recall	0.915641	0.119620	0.900000	0.833333	1.000000	1.000000	1.000000	0.875000	0.625000	0.923077	1.000000	1.000000
residual_deviance	15.626870	7.392748	25.479120	16.970522	4.949533	5.763259	16.301400	17.994690	24.966812	21.546385	8.573858	13.723117

Fig. 11. Cross-validation metrics summary
10 fold cross-validation metrics summary. For more information on how each value is calculated see [11]

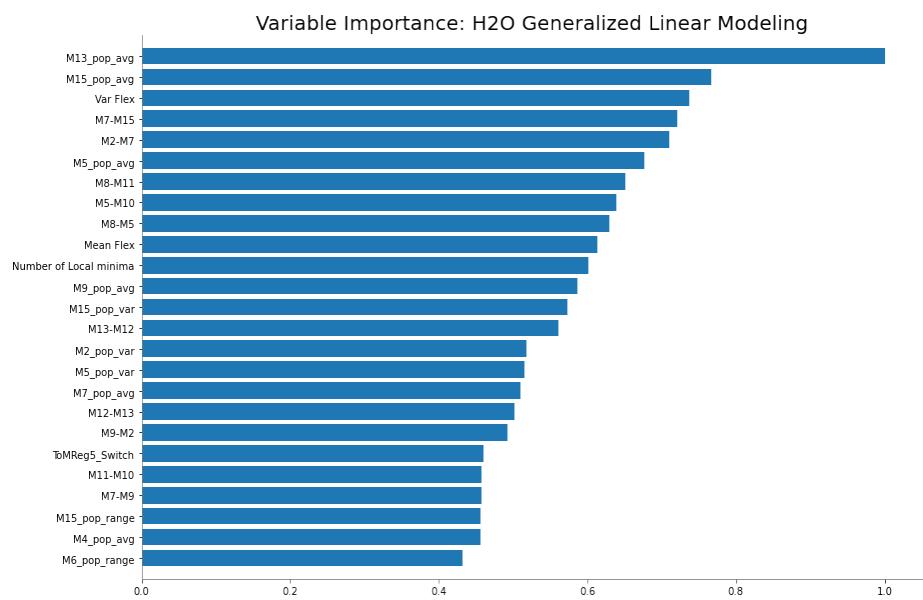


Fig. 12. GLM variable importance

Variable coefficients sorted based on their importance in the GLM model.

Lobe	Gyrus	Left and Right Hemisphere	Label ID.L	Label ID.R
Frontal Lobe	OrG, Orbital Gyrus	OrG_L(R)_6_3	45	46
		OrG_L(R)_6_5		50
Temporal Lobe	STG, Superior Temporal Gyrus	STG_L(R)_6_1	69	70
	MTG, Middle Temporal Gyrus	MTG_L(R)_4_1		82
		MTG_L(R)_4_2		84
	ITG, Inferior Temporal Gyrus	ITG_L(R)_7_1	89	90
		ITG_L(R)_7_3	93	94
		ITG_L(R)_7_4		96
		ITG_L(R)_7_6		100
		ITG_L(R)_7_7	101	102
	PhG, Parahippocampal Gyrus	PhG_L(R)_6_1	109	110
		PhG_L(R)_6_4	115	116
		PhG_L(R)_6_5	117	118
		PhG_L(R)_6_6		120
Insular Lobe	INS, Insular Gyrus	INS_L(R)_6_1		164
		INS_L(R)_6_5	171	172
Subcortical Nuclei	Amyg, Amygdala	Amyg_L(R)_2_1	211	212
		Amyg_L(R)_2_2	213	214
	BG, Basal Ganglia	BG_L(R)_6_3		224

Fig. 13. Module 15 membersRegions in the 15th module and where they belong to.