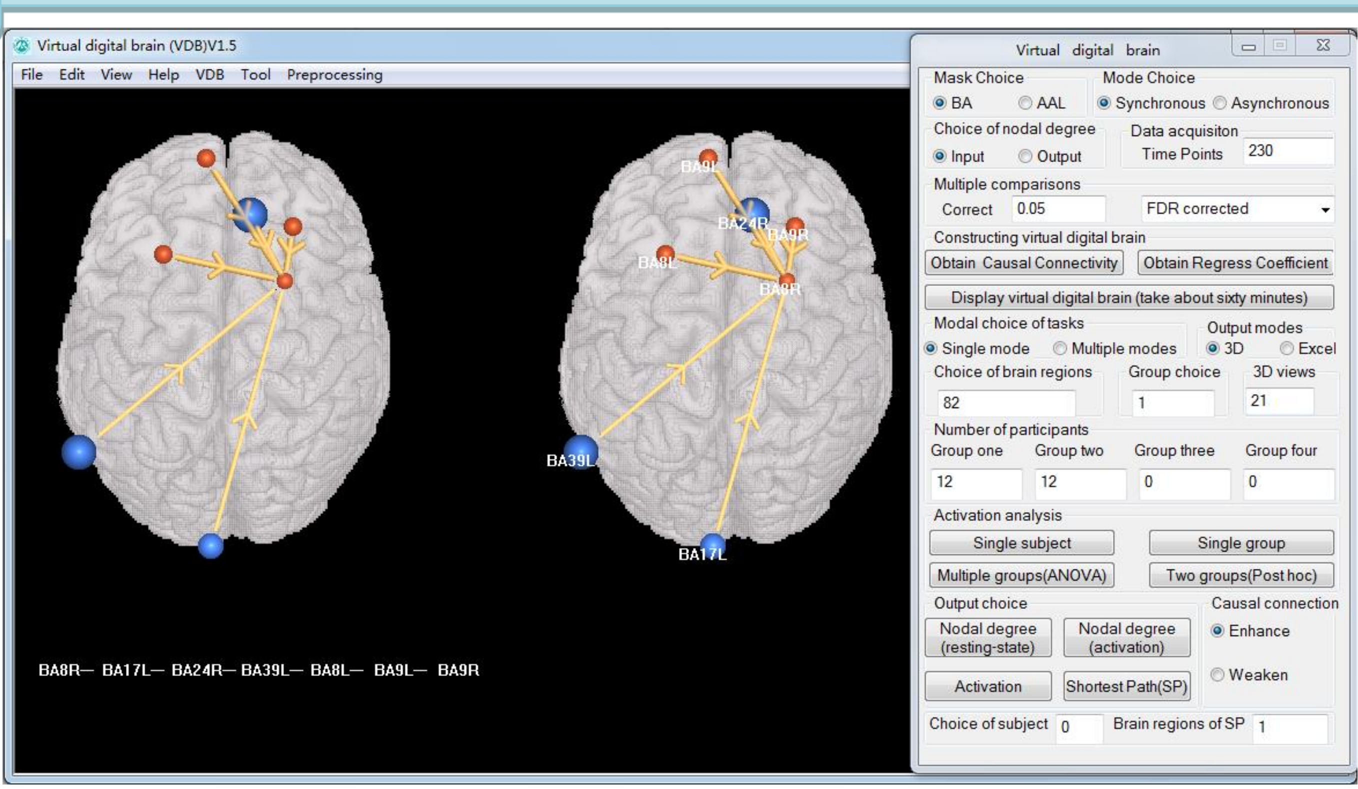
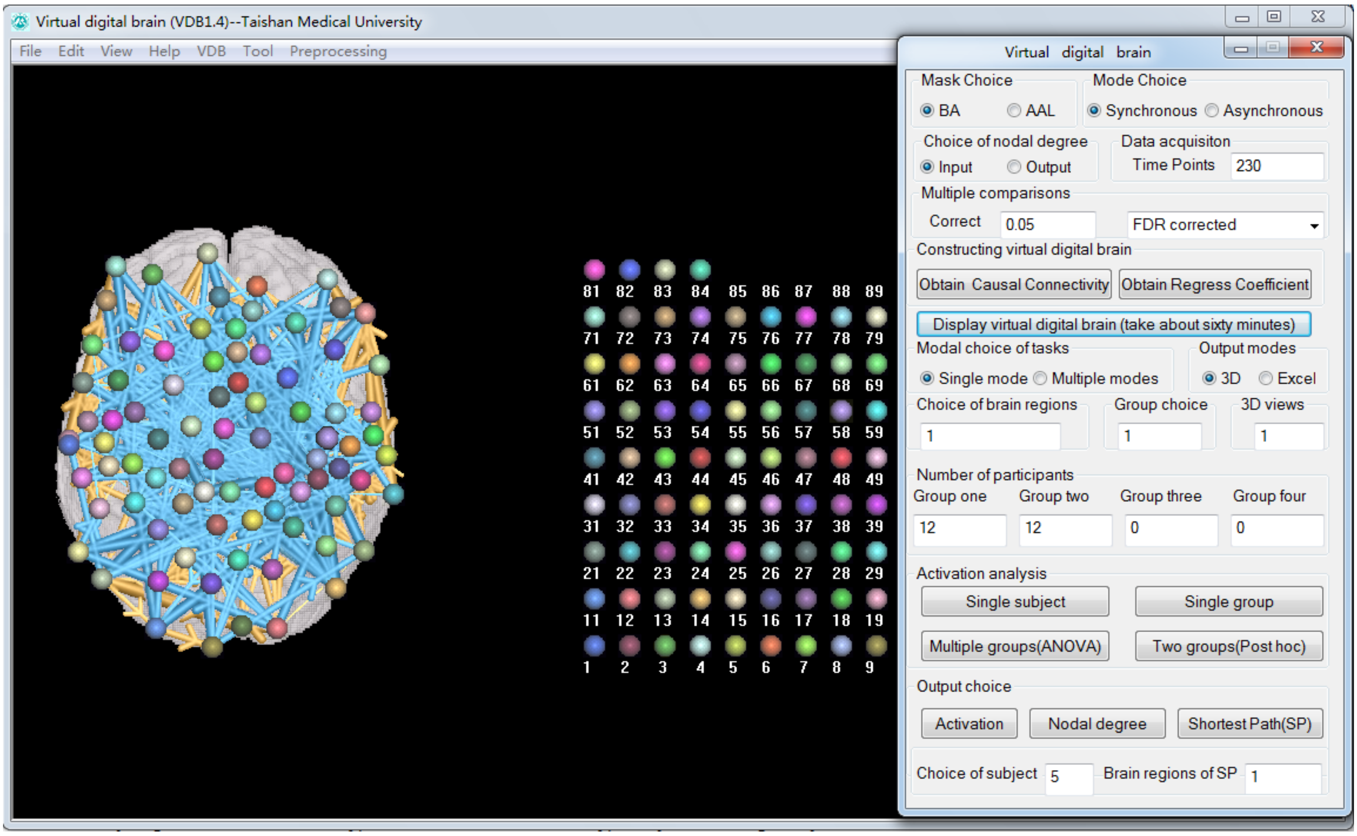
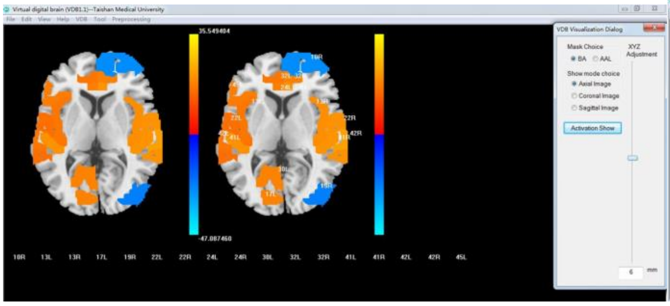
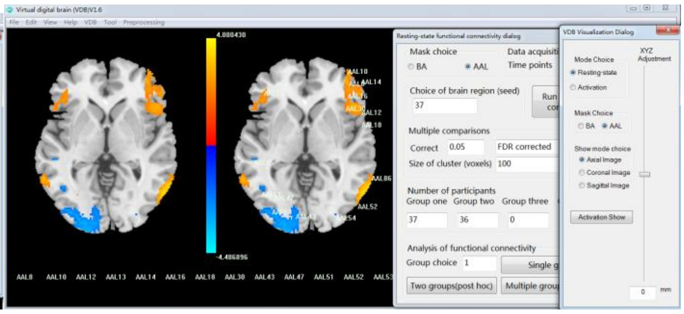
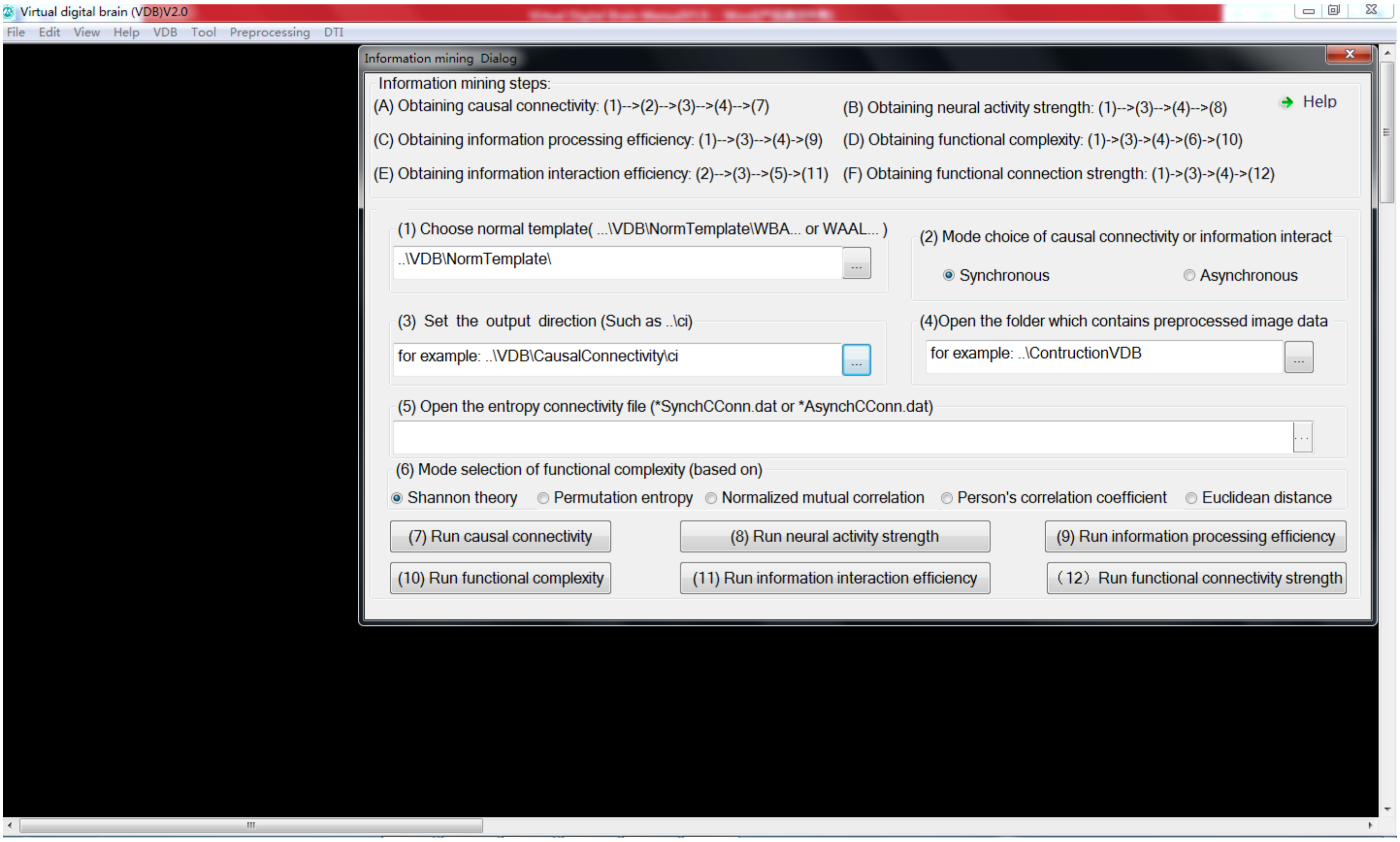
Virtual Digital Brain Manual











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Contents

1. Introduction

Please cite as '... was/were performanced using the virtual digital brain software package VDBV2.0 (https://www.nitrc.org/projects/vdb/) while using the software to make publicized paper.

We have improved the procedure and have added some functions，such as the functional complexity of brain region (including functional complexity based on Shannon theory, functional complexity based on Pearson's correlation coefficient, functional complexity based on Permutation entropy, etc.), the information interaction efficiency of brain region, functional connectivity strength of the brain region, in the software package VDBV2.0. Several bugs on entropy connectivity in VDBV1.9 have been modified, and this version is more convenient for constructing and displaying task signals (i.e. designing fMRI experimental paradigms). In addition, we have added several functions including 3D visualization of resting-state nodal degree, and activated state nodal degree. VDB V1.5 is a 3D visualization tool of human brain, which is used to construct the virtual digital brain and research neural activities of brain regions evoked by the virtual stimulating signal (or the stimulating signal of task). The virtual digital brain is a human brain model (i.e. a causal connectivity network). Every node of the human brain model denotes a Brodmann's area (or AAL area) of human brain. We can exert the stimulating signal of task to some brain areas of the virtual digital brain and observe activation of brain regions. In addition, this tool V1.5 can also be used to obtain the stimulating signal of task, design task (i.e. design fMRI experimental paradigm), and study interregional causal connectivity and the shortest causal connectivity path (i.e. the strongest causal interactive path) from one brain area to another in the virtual digital brain.

The individualized virtual digital brain can be constructed by using VDBV1.5 based on resting-state fMRI data of every participant. The virtual digital brain technique is similar to virtual reality. To investigate activation of brain regions, the stimulating signal of task is firstly processed, and then translated into an input signal of brain regions. Finally, the input signal is directly exerted to some brain regions of the individualized virtual digital brain instead of exerting to real human brain of every participant. Researchers can exert the stimulating signal of task to any brain area of the virtual digital brain and observe activation of brain regions.

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2. Installation

Firstly, you need to download the software package from (https://www.nitrc.org/projects/vdb/) and unzip downloaded file. Copy all files that are contained in the folder “VDB2.0” to the directory: D: \\VDB, and then add the executable file ‘fMRISoft.exe’ in the folder “Bin” to the desktop shortcut.

3. Construct and display the virtual digital brain

3.1. Data preprocessing

Data were preprocessed using spm8(http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The performance is described as follows.

(1) Slice timing and motion corrections are first executed, and then processed functional images, structural images, and Brodmann Area (BA) or AAL mask are normalized to the standard brain template from the Montreal Neurological Institute (MNI 152) by applying nonlinear registration. The parameters of bounding box (in mm) are described as follows: [-90 -126 -72; 90 90 108]. Copy normalized BA or AAL mask to the folder “NormTemplate ”(the directory :D: \\VDB \\NormTemplate). It is worth noting that normalized BA mask must be named as WBA.nii or WBAxxx...nii, and normalized AAL mask must be named as WAAL.nii or WAALxxx....nii.

(2) Spatial smoothing with a Gaussian kernel of a specified width is applied to the normalized functional images.

(3) Normalized structural images are registered to the normalized functional images by applying rigid registration.

(4) Those registered structural images are segmented into the white matter, gray matter, and cerebrospinal fluid images.

(5) Preprocessed functional images of every subject are placed in a folders named as Subxxx(such as Sub001). All folders (Sub001, Sub002,…Subxxx) are combined into a big destination folder(for example, Detrend).

Preprocessed data mentioned above are further preprocessed using the following procedures.

(1) The removal of linear and quadratic trends. Open the software (i.e. run the fMRISoft.exe file in the folder “VDB” or the desktop) and click on the menu “Preprocessing”, and then click on the option “Detrend”, select the

folder “Detrend” in the opened dialog. Finally, click on the button “Ok”, the procedure will run and execute Detrend. Processed functional image files with the prefix “D” are stored in the folder “Detrend” (Figure 1).

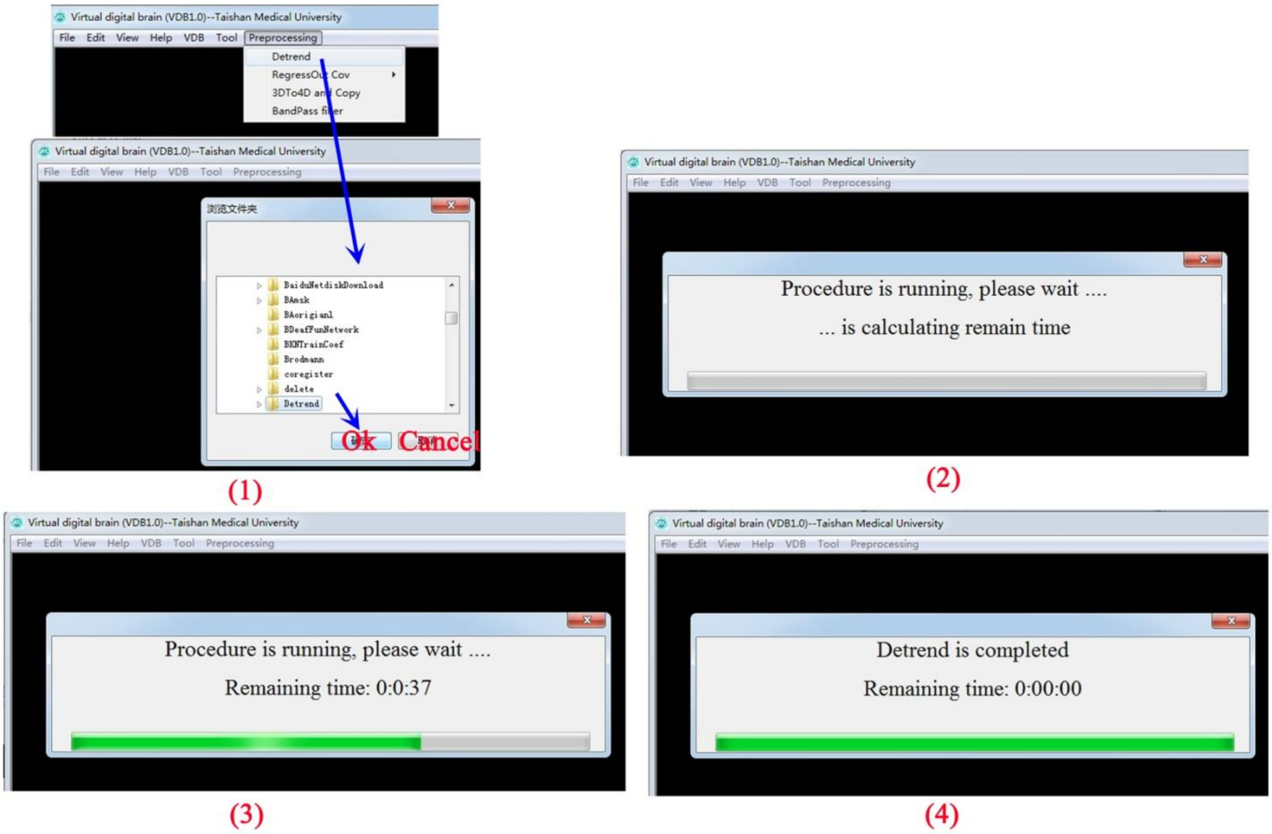


Figure 1. Detrend

(2) Copy the white matter, cerebrospinal fluid and motion parameter image files of every subject to those folders Subxxx(such as Sub001, Sub002,…)in the folder “Detrend ”.

(3) Regress out covariates including realignment parameters (motion parameters), the global mean signal, mean white matter signal, and the mean cerebrospinal fluid signal. Click on the option “RegressOut Cov” in the menu “Preprocessing”. Click on the button “Starting regression” in the covariate regression dialog and select the folder “Detrend” in the opened dialog. Finally, click on the button “Ok”, the procedure will run and execute covariate regression. Processed functional image files with the prefix “C ” are stored in the directory : D:\\DetrendCoved (Figure 2).

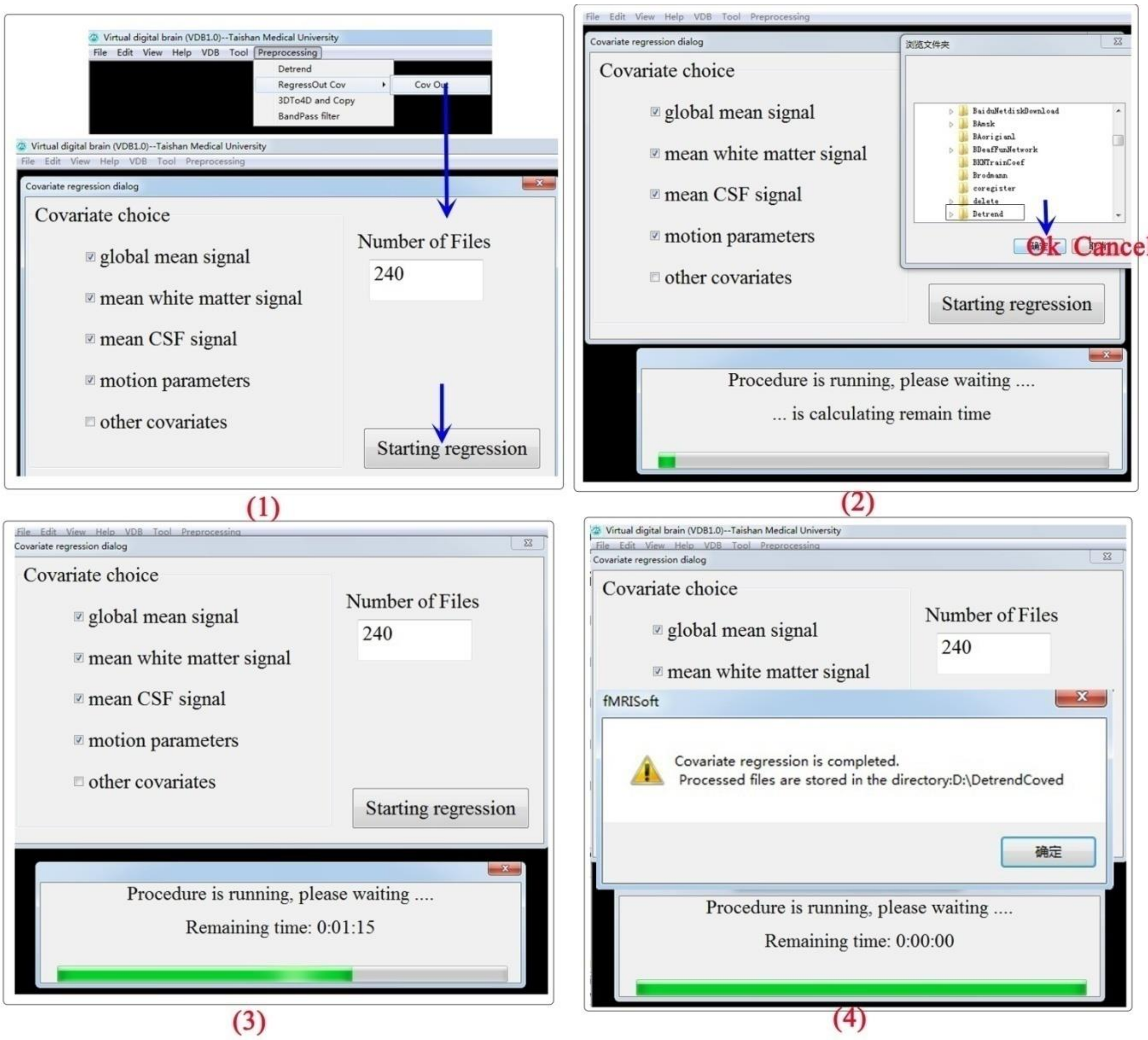


Figure 2.　Covariate regression

(4) Integrating 3D images to 4D.　As shown in Figure 3, firstly, click on the menu "Preprocessing", and then click on the option "3DTo4D and Copy".　Select the folder "DetrendCoved" in the opened dialog, finally, click on the button "Ok", the procedure will run and execute data transform. Constructed 4D data are stored in the folder "DetrendCoved4D "(the directory :D: \\DetrendCoved4D).

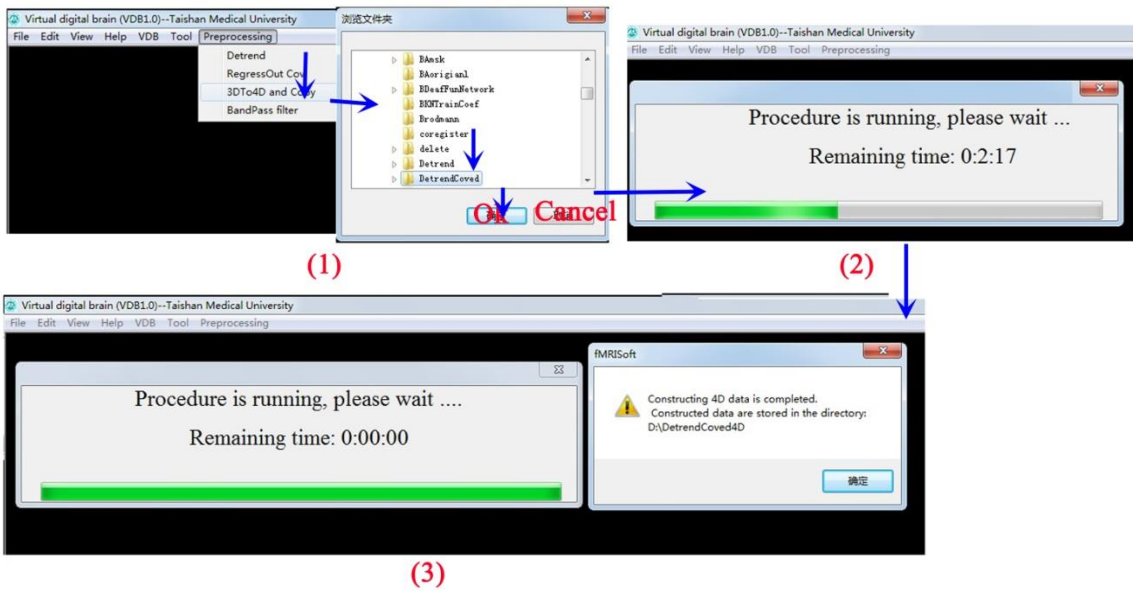


Figure 3. Integrating 3D images to 4D

(5) Band-pass temporal filter. As shown in Figure 4, firstly, click on the menu "Preprocessing", and then click on the option "Bandpass filter". Select the folder "DetrendCoved4D" in the opened dialog, finally, click on the button "Ok", the procedure will run and execute filtering. Filtered 4D data are stored in the folder "ConstructionVDB"(the directory :D: \\ConstructionVDB).

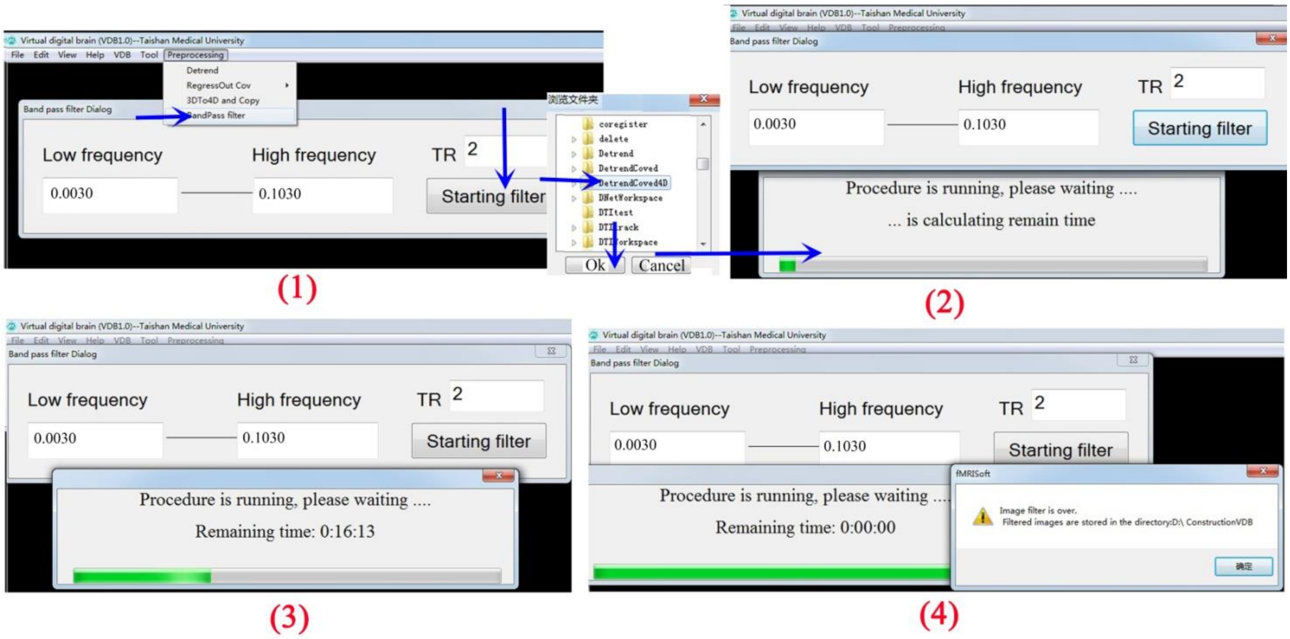


Figure 4. Band-pass temporal filter

3.2. Calculate interregional causal connectivity and regress coefficients

The steps of construction are described as follows:

1. Firstly, open the software and click on the menu VDB, and then start the construction of the brain causal network (Figure 5).

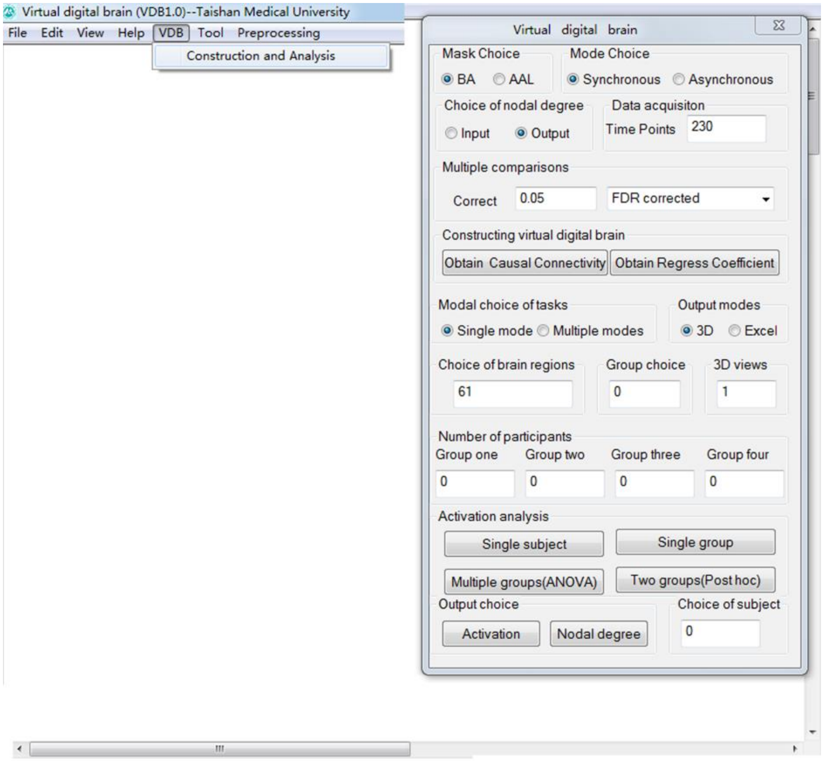


Figure 5.Construction of the brain causal network.

2. Select "BA" or "AAL" in the mask choice, "Synchronous" in the mode choice, "Time Points" in the data acquisition, and then click on the button "Obtain Causal Connectivity" and open the destination folder (Figure 6).

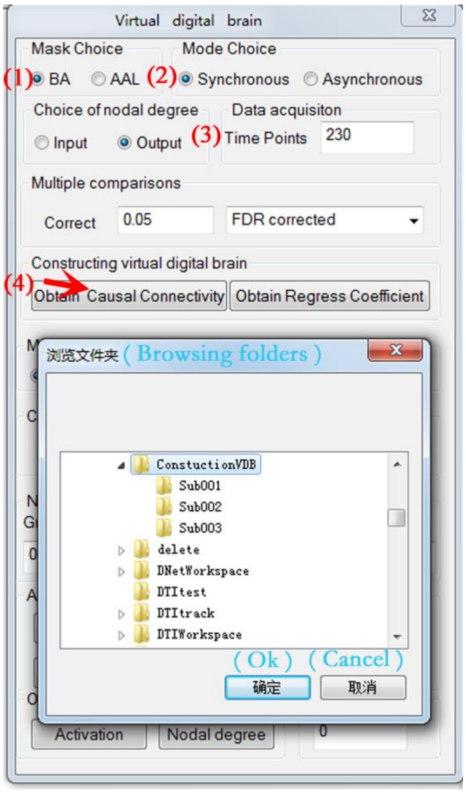


Figure 6. Opening the destination folder

3. Run the procedure and obtain the matrix of synchronous causal connectivity. The result is automatically stored in the directory: D: \\VDB\\CausalConnectivity(Figure 7).

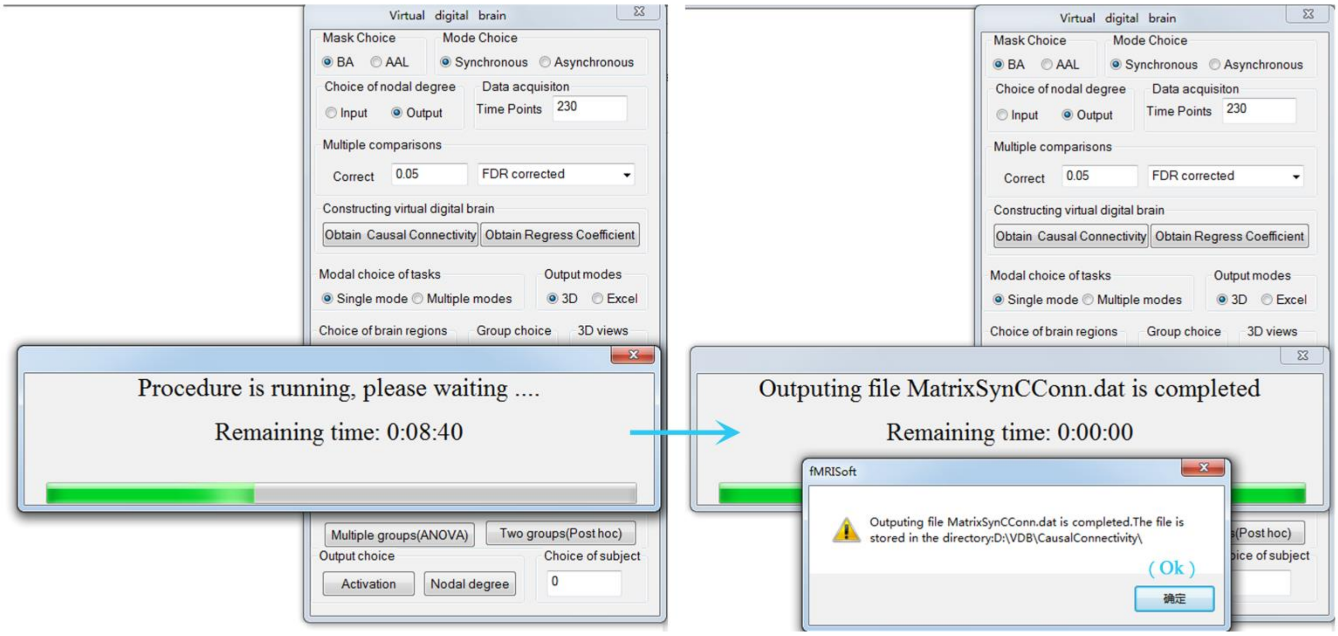


Figure 7.Obtaining the matrix of synchronous causal connectivity.

4. Select “Asynchronous” in the mode choice and repeat the steps 2and 3. The matrix of asynchronous connectivity is also stored in the directory: D: \\VDB\\CausalConnectivity.

5. Obtain causal connectivity between ROIs (regions of interesting). Select “Excel” in the output modes, and input the number of ROIs in the control “3D views”, others are similar with step 2-4.

6. Select “BA” or “AAL” in the mask choice, “Time Points” in the data acquisition, corrected parameter in the multiple comparisons, and then click on the button “Obtain Regress Coefficient” and open the destination folder. Run the procedure and obtain the regress coefficient. The result is automatically stored in the directory: D:\\VDB\\RegressCoefficient.(Figure 8).

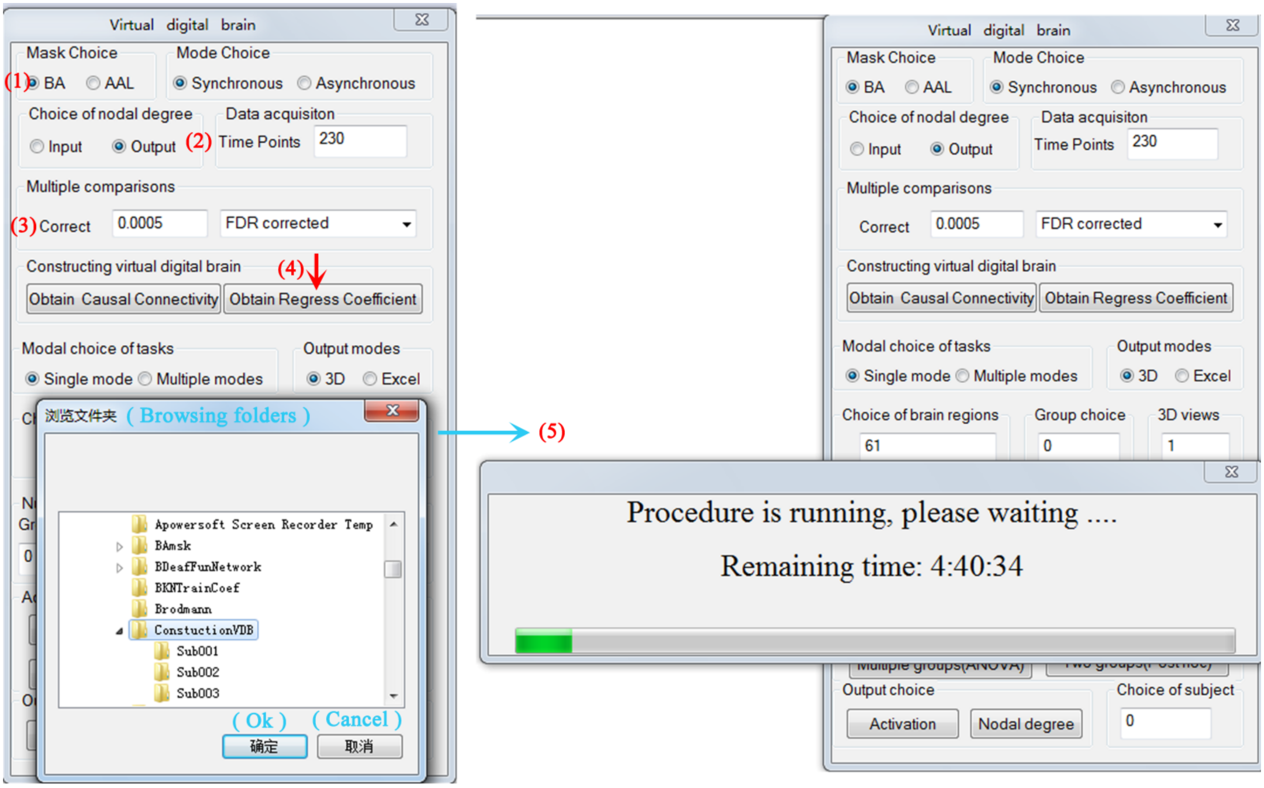


Figure 8.Obtaining the regress coefficient

3.3. Display the virtual digital brain

1. Display the individualized virtual digital brain. Firstly, open the software and click on the menu VDB, and then input the code of subject (for example,"1" or "2", …) in the edit control "Choice of subject". Click on the button "Display virtual digital brain" (Figure 8A). The result is displayed in Figure 8B.

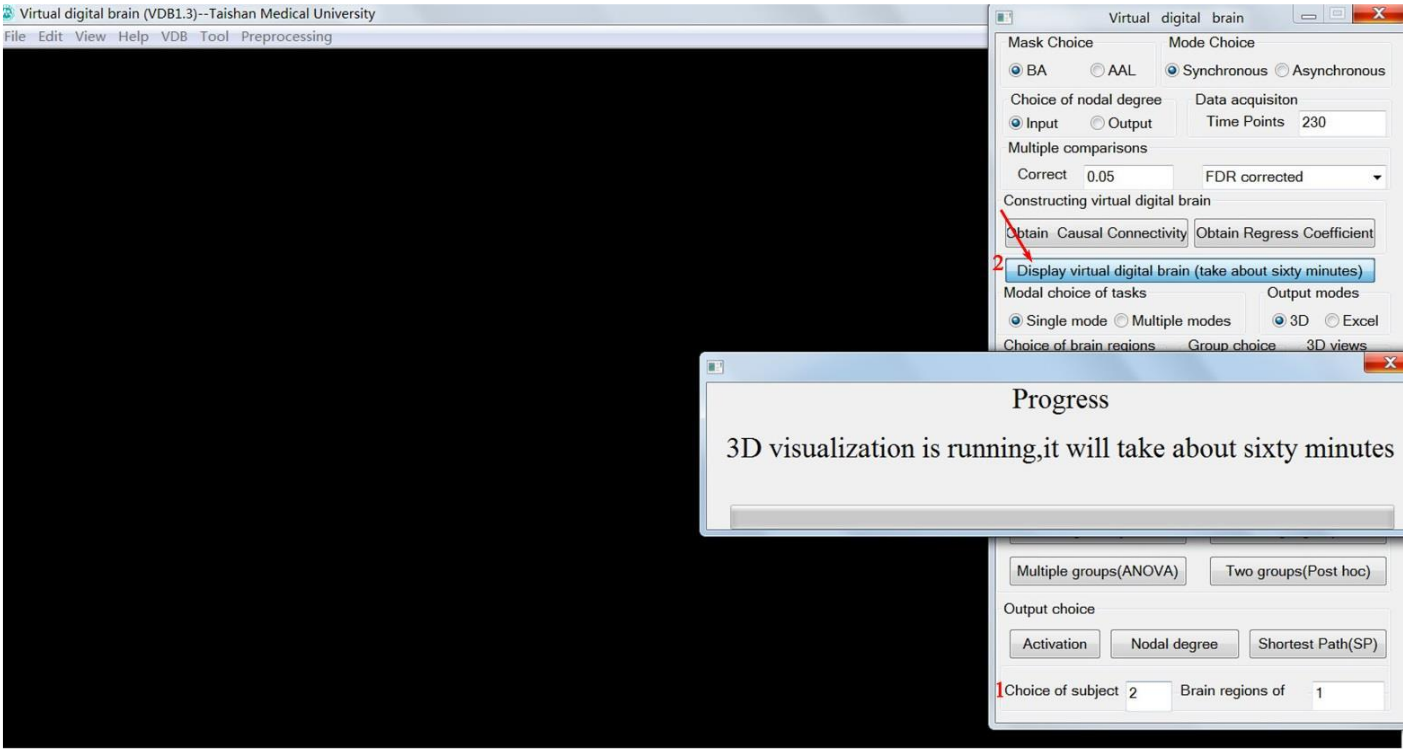


Figure 8A. Display the individualized virtual digital brain.

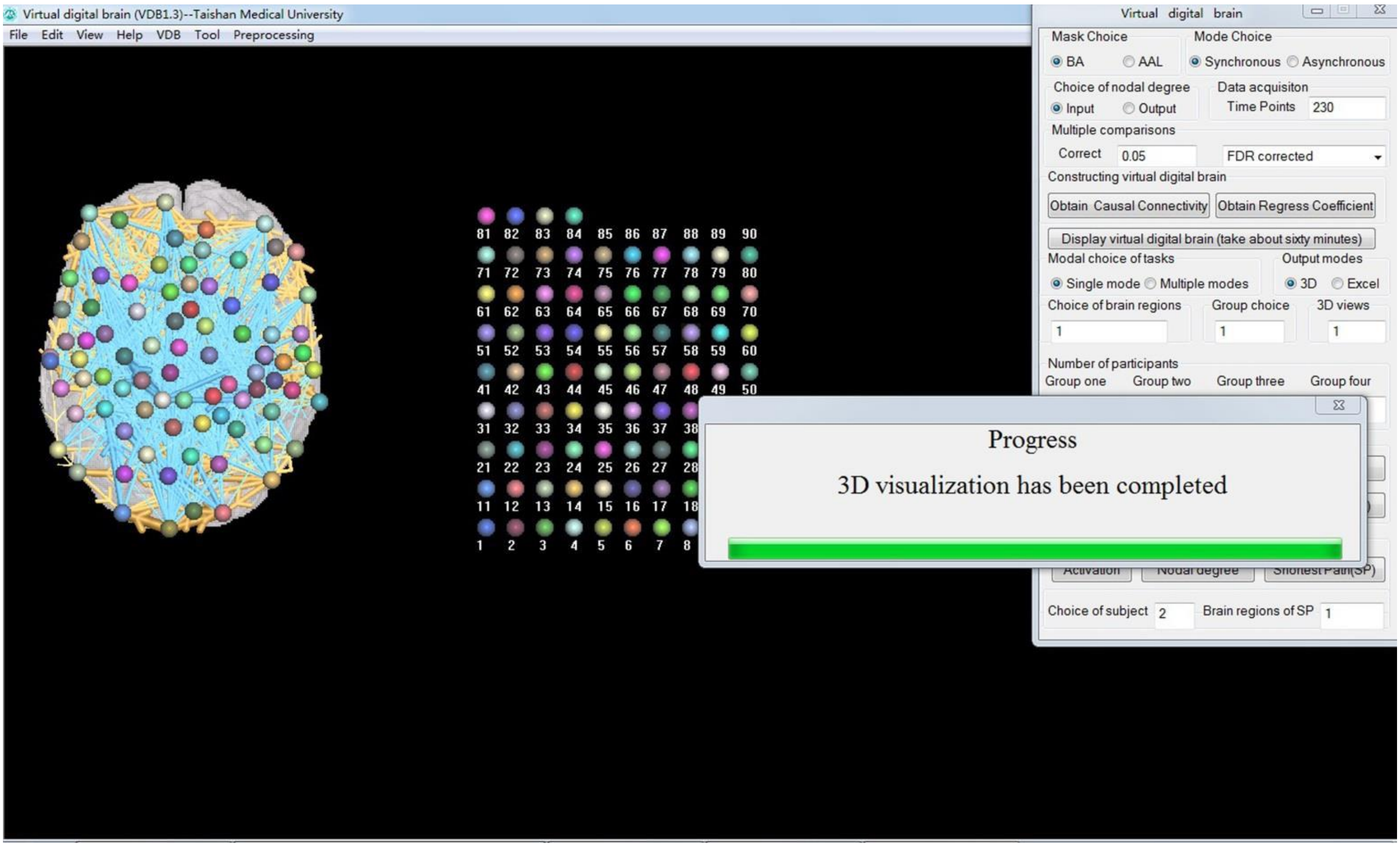


Figure 8B. Result of the individualized virtual digital brain display.

2. Display the virtual digital brain of each group. Firstly, open the software and click on the menu VDB, and then input the code of group (for example,“1” or “2”, …) in the edit control “Group choice”, input “0” in the edit control “Choice of subject”. Click on the button “Display virtual digital brain”. (Figure 8C). The result is displayed in Figure 8D.

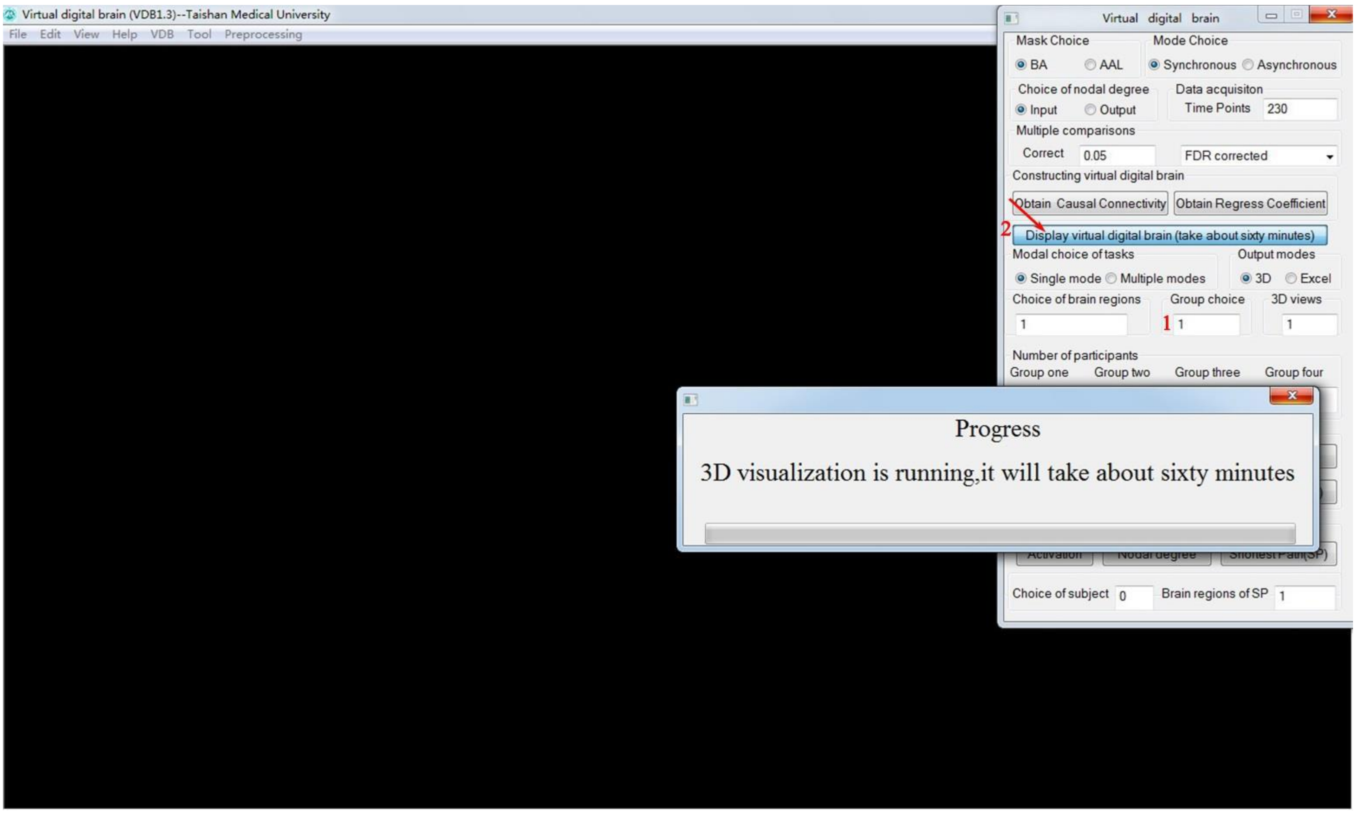


Figure 8C. Display the virtual digital brain.

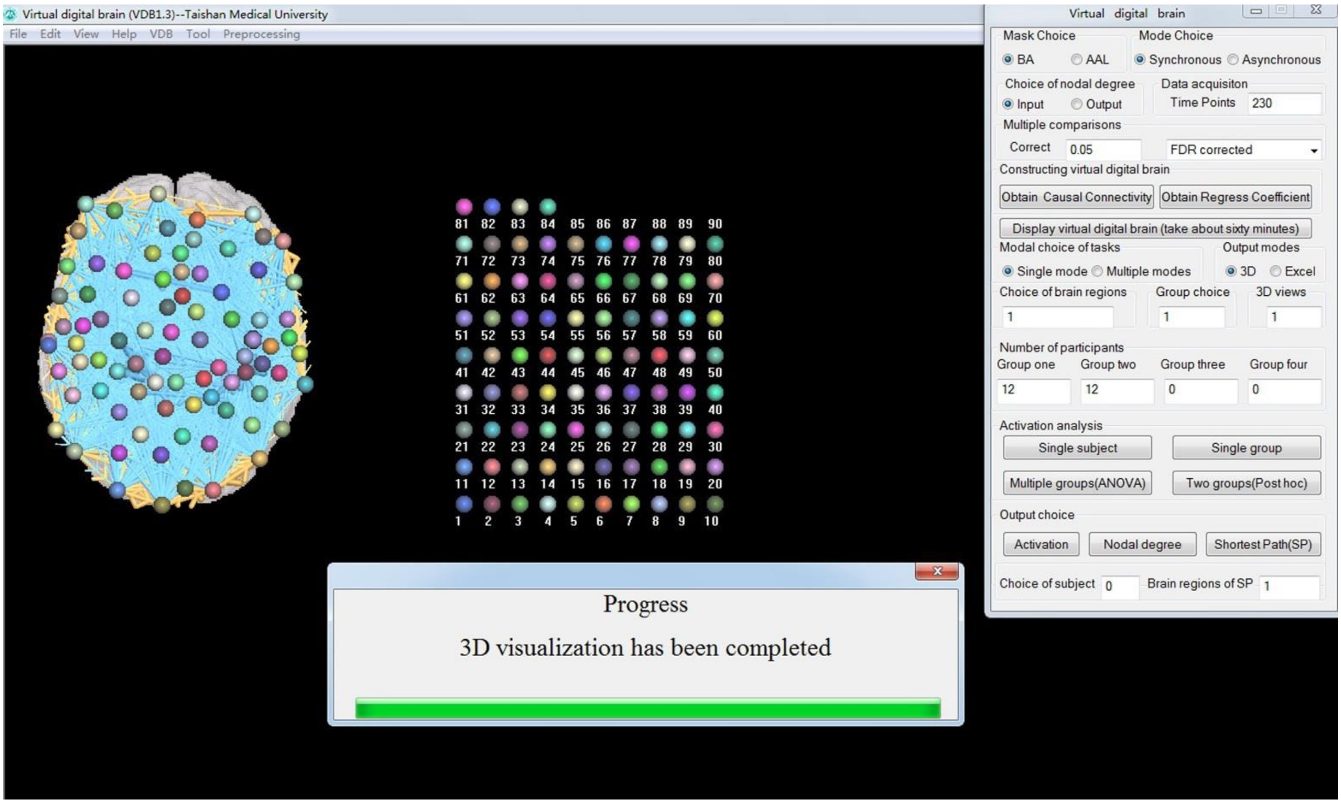


Figure 8D. Result of the virtual digital brain display.

4. Analysis of nodal degrees

4.1. Nodal degrees of the causal connectivity network (resting-state)

1. Nodal degrees of all subjects. Select “BA” or “AAL” in the mask choice, “Synchronous” or “Asynchronous” in the mode choice, “Input” or “Output” in the choice of nodal degree, corrected parameter in the multiple comparisons (this parameter must be equal to the value that has been used in the “Obtain Regress Coefficient” step), “Excel” in the output modes, and then fill “0” in the editor control “Group choice”. In addition, the number of participants must be filled in these editor controls (Group one to four). Click on the button “Nodal degree (resting-state)” and obtain the nodal degrees of all subjects. The result is showed in an excel file (Figure 9). In addition, if you fill “00” in the editor control “Choice of brain regions”, you will obtain the causal connectivity between ROIs.

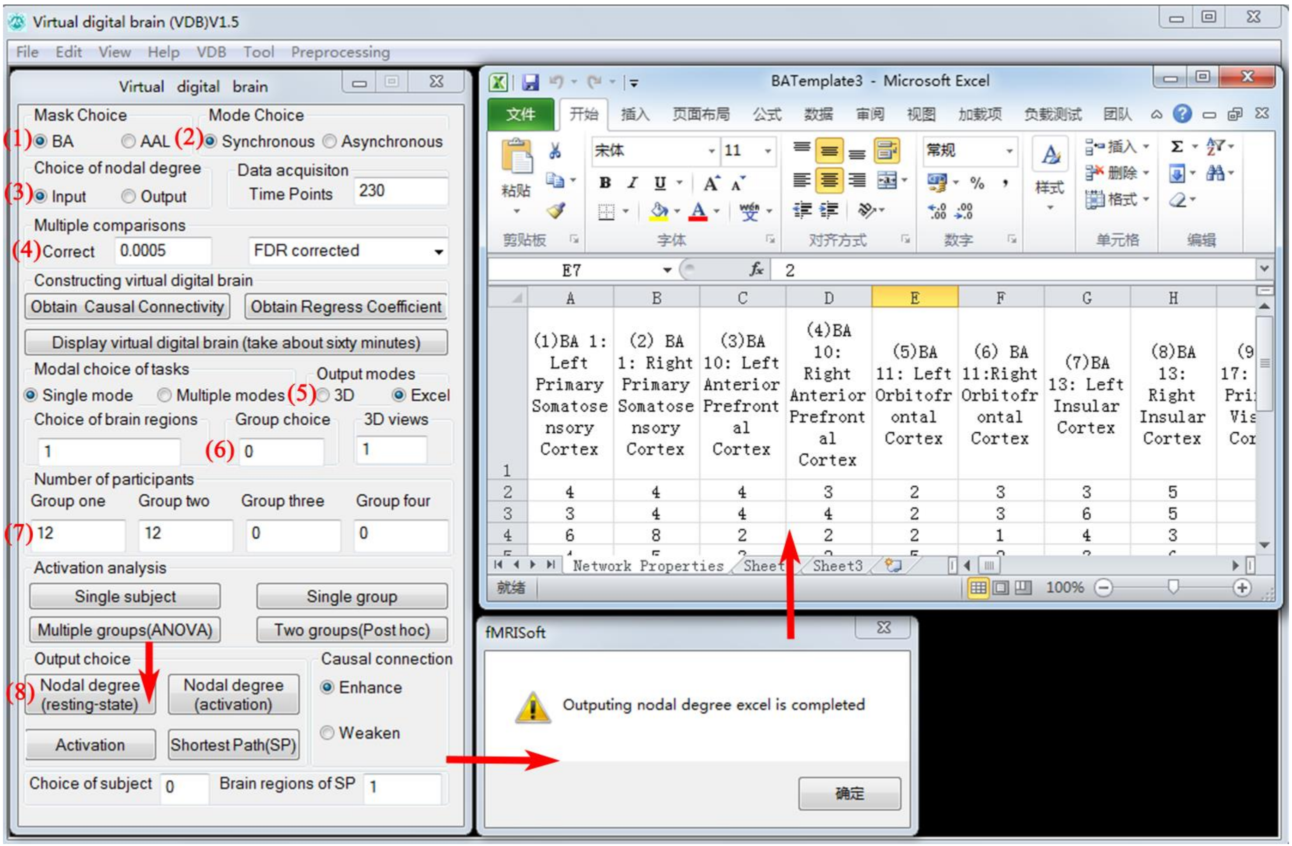


Figure 9. Nodal degrees of all subjects

2. Nodal degrees of the group (causal connectivity of every brain region).Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons, “Excel” in the output modes, and then fill the code of group such as “1”or others (2-4) in the editor control “Group choice”. In addition, the number of participants must be filled in these editor controls (Group one to four). Click on the button “Nodal degree (resting-state)” and obtain the nodal degrees of the group. The result is showed in an excel file (Figure 10). Positive real numbers indicate the strengths of synchronous causal connectivity, and negative real numbers indicate the strengths of asynchronous causal connectivity. The real numbers of every row indicate the strengths of output causal connectivity corresponding to every node, and the real numbers of every column indicate the strengths of input causal connectivity corresponding to every node.

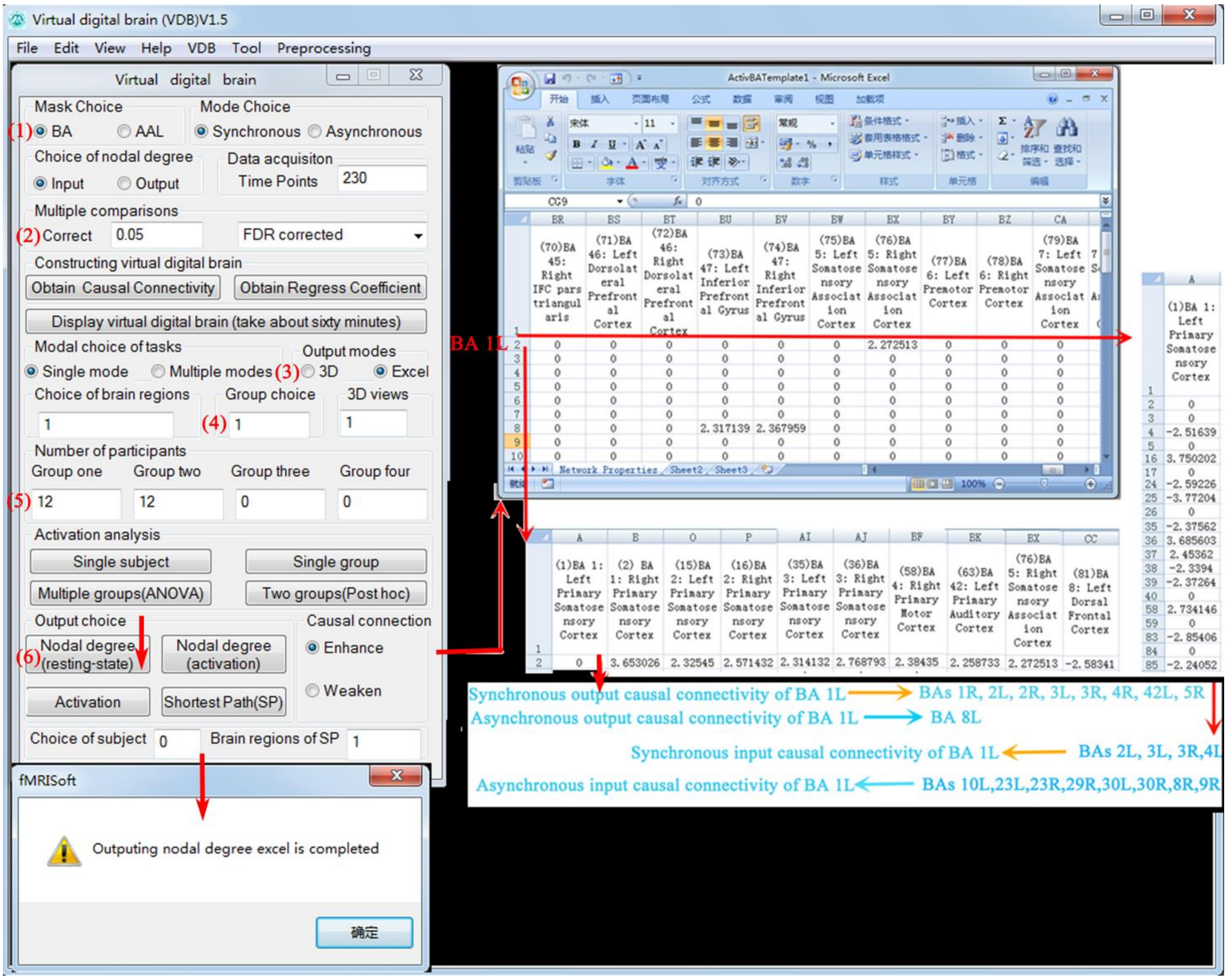


Figure 10. Nodal degrees of the group

3.Nodal degree of one brain region in the single group (3D visualization). Select “BA” or “AAL” in the mask choice, “Synchronous” or “Asynchronous” in the mode choice, “Input” or “Output” in the choice of nodal degree, corrected parameter in the multiple comparisons, and “3D” in the output modes, fill the index of displayed brain region in the “Choice of brain regions ” control, and then fill the code of group such as “1”or others (2-4) in the editor control “Group choice”, the index of 3D view in the editor control “3D views” (the index “1” indicates the superior view, “2” indicates the inferior view,“3” indicates the left view,“4” indicates the right view,“21” indicates the superior view with marks of brain regions), and the index of brain region in the editor control “Choice of brain regions ” see also table 1 and table 2 for details. In addition, the number of participants must be filled in these editor controls (Group one to four). Click on the button “Nodal degree (resting-state)”, and 3D visualization will run. The result is showed in the left of client area (Figure 11A). The size of bar indicates the strength of causal connectivity, and the arrow indicates the direction of causal connectivity. The light blue bar denotes synchronous causal connectivity, and the gold bar denotes asynchronous causal connectivity.

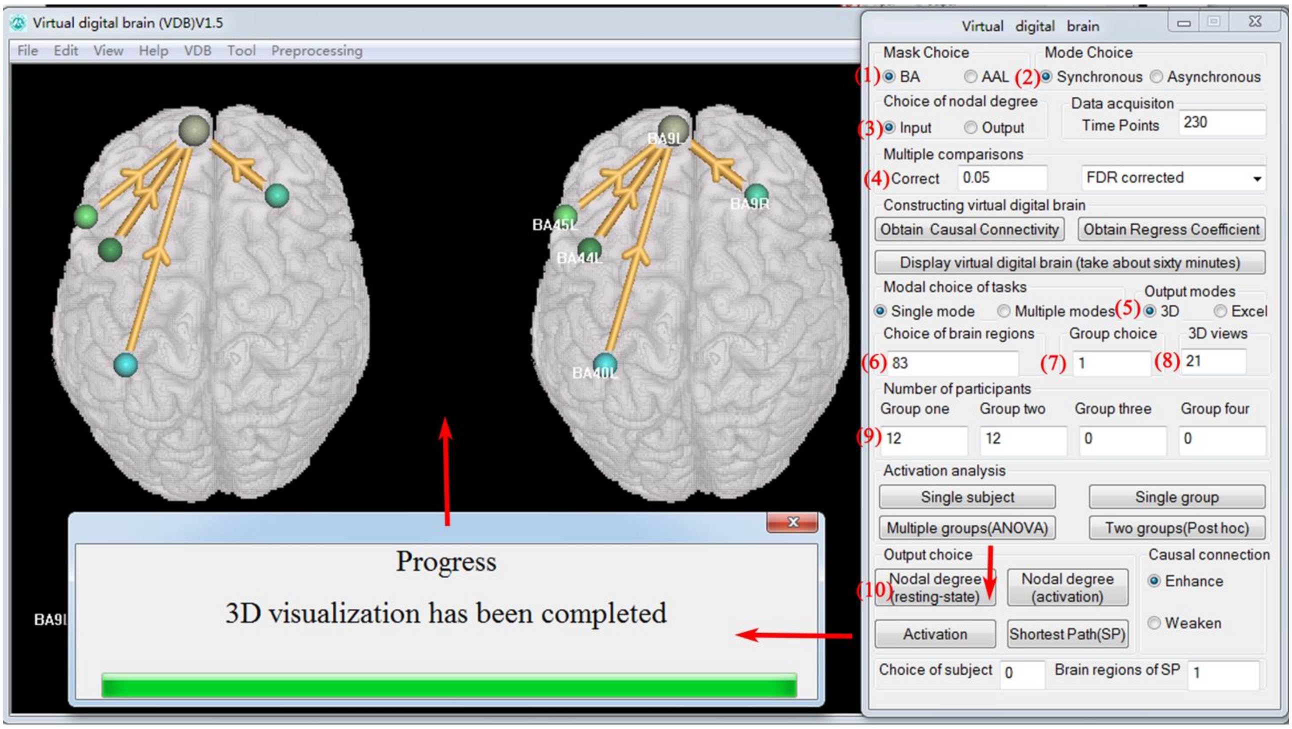


Figure 11A . 3D visualization of the nodal degree.

Table 1 Indexes of brain regions and corresponding Brodmann areas

Indexes	Index of Brodmann Areas
1	1 (L). Primary Somatosensory Cortex
2	1 (R). Primary Somatosensory Cortex
3	10 (L). Anterior Prefrontal Cortex
4	10 (R). Anterior Prefrontal Cortex
5	11 (L). Orbitofrontal Cortex
6	11 (R). Orbitofrontal Cortex
7	13 (L). Insular Cortex
8	13 (R). Insular Cortex
9	17 (L). Primary Visual Cortex
10	17 (R). Primary Visual Cortex
11	18 (L). Secondary Visual Cortex
12	18 (R). Secondary Visual Cortex
13	19 (L). Associative Visual Cortex
14	19 (R). Associative Visual Cortex
15	2 (L). Primary Somatosensory Cortex
16	2 (R). Primary Somatosensory Cortex
17	20 (L). Inferior Temporal Gyrus

18	20 (R). Inferior Temporal Gyrus
19	21 (L). Middle Temporal Gyrus
20	21 (R). Middle Temporal Gyrus
21	22 (L). Superior Temporal Gyrus
22	22 (R). Superior Temporal Gyrus
23	23 (L). Ventral Posterior Cingulate Cortex
24	23 (R). Ventral Posterior Cingulate Cortex
25	24 (L). Ventral Anterior Cingulate Cortex
26	24 (R). Ventral Anterior Cingulate Cortex
27	25 (L). Subgenual cortex
28	25 (R). Subgenual cortex
29	27 (L). Piriform Cortex
30	27 (R). Piriform Cortex
31	28 (L). Posterior Entorhinal Cortex
32	28 (R). Posterior Entorhinal Cortex
33	29 (L). Retrosplenial Cingulate Cortex
34	29 (R). Retrosplenial Cingulate Cortex
35	3 (L). Primary Somatosensory Cortex
36	3 (R). Primary Somatosensory Cortex
37	30 (L). Cingulate Cortex
38	30 (R). Cingulate Cortex
39	31 (L). Dorsal Posterior Cingulate Cortex
40	31 (R). Dorsal Posterior Cingulate Cortex
41	32 (L). Dorsal anterior Cingulate Cortex
42	32 (R). Dorsal anterior Cingulate Cortex
43	33 (L). Anterior Cingulate Cortex
44	33 (R). Anterior Cingulate Cortex
45	34 (L). Anterior Entorhinal Cortex
46	34 (R). Anterior Entorhinal Cortex
47	35 (L). Perirhinal cortex
48	35 (R). Perirhinal cortex
49	36 (L). Parahippocampal cortex
50	36 (R). Parahippocampal cortex
51	37 (L). Fusiform gyrus
52	37 (R). Fusiform gyrus
53	38 (L). Temporopolar Area
54	38 (R). Temporopolar Area
55	39 (L). Angular gyrus
56	39 (R). Angular gyrus

57	4 (L). Primary Motor Cortex
58	4 (R). Primary Motor Cortex
59	40 (L). SupramarginalGyrus
60	40 (R). SupramarginalGyrus
61	41 (L). Primary Auditory Cortex
62	41 (R). Primary Auditory Cortex
63	42 (L). Primary Auditory Cortex
64	42 (R). Primary Auditory Cortex
65	43 (L). Subcentral Area
66	43 (R). Subcentral Area
67	44 (L). IFC pars opercularis
68	44 (R). IFC pars opercularis
69	45 (L). IFC pars triangularis
70	45 (R). IFC pars triangularis
71	46 (L). Dorsolateral Prefrontal Cortex
72	46 (R). Dorsolateral Prefrontal Cortex
73	47 (L). Inferior Prefrontal Gyrus
74	47 (R). Inferior Prefrontal Gyrus
75	5 (L). Somatosensory Association Cortex
76	5 (R). Somatosensory Association Cortex
77	6 (L). Premotor Cortex
78	6 (R). Premotor Cortex
79	7 (L). Somatosensory Association Cortex
80	7 (R). Somatosensory Association Cortex
81	8 (L). Dorsal Frontal Cortex
82	8 (R). Dorsal Frontal Cortex
83	9 (L). Dorsolateral Prefrontal Cortex
84	9 (R). Dorsolateral Prefrontal Cortex

Table 2 Indexes of brain regions and corresponding AALareas

Indexes	AAL Areas
1	Precentral (L)
2	Precentral (R)
3	Frontal Sup (L)
4	Frontal Sup (R)
5	Frontal Sup Orb (L)
6	Frontal Sup Orb (R)
7	Frontal Mid (L)

8	Frontal Mid (R)
9	Frontal Mid Orb (L)
10	Frontal Mid Orb (R)
11	Frontal InfOper (L)
12	Frontal InfOper (R)
13	Frontal Inf Tri (L)
14	Frontal Inf Tri (R)
15	Frontal Inf Orb (L)
16	Frontal Inf Orb (R)
17	RolandicOper (L)
18	RolandicOper (R)
19	Supp Motor Area (L)
20	Supp Motor Area (R)
21	Olfactory (L)
22	Olfactory (R)
23	Frontal Sup Medial (L)
24	Frontal Sup Medial (R)
25	Frontal Med Orb (L)
26	Frontal Med Orb (R)
27	Rectus (L)
28	Rectus (R)
29	Insula (L)
30	Insula (R)
31	Cingulum Ant (L)
32	Cingulum Ant (R)
33	Cingulum Mid (L)
34	Cingulum Mid (R)
35	Cingulum Post (L)
36	Cingulum Post (R)
37	Hippocampus (L)
38	Hippocampus (R)
39	ParaHippocampal (L)
40	ParaHippocampal (R)
41	Amygdala (L)
42	Amygdala (R)
43	Calcarine (L)
44	Calcarine (R)
45	Cuneus (L)
46	Cuneus (R)

47	Lingual (L)
48	Lingual (R)
49	Occipital Sup (L)
50	Occipital Sup (R)
51	Occipital Mid (L)
52	Occipital Mid (R)
53	Occipital Inf (L)
54	Occipital Inf (R)
55	Fusiform (L)
56	Fusiform (R)
57	Postcentral (L)
58	Postcentral (R)
59	Parietal Sup (L)
60	Parietal Sup (R)
61	Parietal Inf (L)
62	Parietal Inf (R)
63	SupraMarginal (L)
64	SupraMarginal (R)
65	Angular (L)
66	Angular (R)
67	Precuneus (L)
68	Precuneus (R)
69	Paracentral Lobule (L)
70	Paracentral Lobule (R)
71	Caudate (L)
72	Caudate (R)
73	Putamen (L)
74	Putamen (R)
75	Pallidum (L)
76	Pallidum (R)
77	Thalamus (L)
78	Thalamus (R)
79	Heschl (L)
80	Heschl (R)
81	Temporal Sup (L)
82	Temporal Sup (R)
83	Temporal Pole Sup (L)
84	Temporal Pole Sup (R)
85	Temporal Mid (L)

86	Temporal Mid (R)
87	Temporal Pole Mid (L)
88	Temporal Pole Mid (R)
89	Temporal Inf (L)
90	Temporal Inf (R)
91	Cerebelum Crus1 (L)
92	Cerebelum Crus1 (R)
93	Cerebelum Crus2 (L)
94	Cerebelum Crus2 (R)
95	Cerebelum 3 (L)
96	Cerebelum 3 (R)
97	Cerebelum 4 5 (L)
98	Cerebelum 4 5 (R)
99	Cerebelum 6 (L)
100	Cerebelum 6 (R)
101	Cerebelum 7b (L)
102	Cerebelum 7b (R)
103	Cerebelum 8 (L)
104	Cerebelum 8 (R)
105	Cerebelum 9 (L)
106	Cerebelum 9 (R)
107	Cerebelum 10 (L)
108	Cerebelum 10 (R)
109	Vermis 1 2
110	Vermis 3
111	Vermis 4 5
112	Vermis 6
113	Vermis 7
114	Vermis 8
115	Vermis 9
116	Vermis 10

4. Changes of interregional causal connectivity between two groups (3D visualization). Select “BA” or “AAL” in the mask choice, “Synchronous” or “Asynchronous” in the mode choice, “Input” or “Output” in the choice of nodal degree, corrected parameter in the multiple comparisons, and “3D” in the output modes, fill the index of displayed brain region in the “Choice of brain regions ” control, and then fill the code of group such as “1,2”

in the editor control “Group choice”, the index of 3D view in the editor control “3D views” (the index “1” indicates the superior view, “2” indicates the inferior view,“3” indicates the left view,“4” indicates the right view,“21” indicates the superior view with marks of brain regions), and the index of brain region in the editor control “Choice of brain regions ” see also table 1 and table 2 for details. In addition, the number of participants must be filled in these editor controls (Group one to four). Select “Enhance” or “Weaken” in the causal connection, and click on the button “Nodal degree (resting-state)”, and 3D visualization will run. The result is showed in the left of client area (Figure 11B). The size of bar indicates the strength of causal connectivity, and the arrow indicates the direction of causal connectivity. The red bar denotes enhanced interregional causal connectivity between two groups, and the blue bar denotes weakened interregional causal connectivity between two groups.

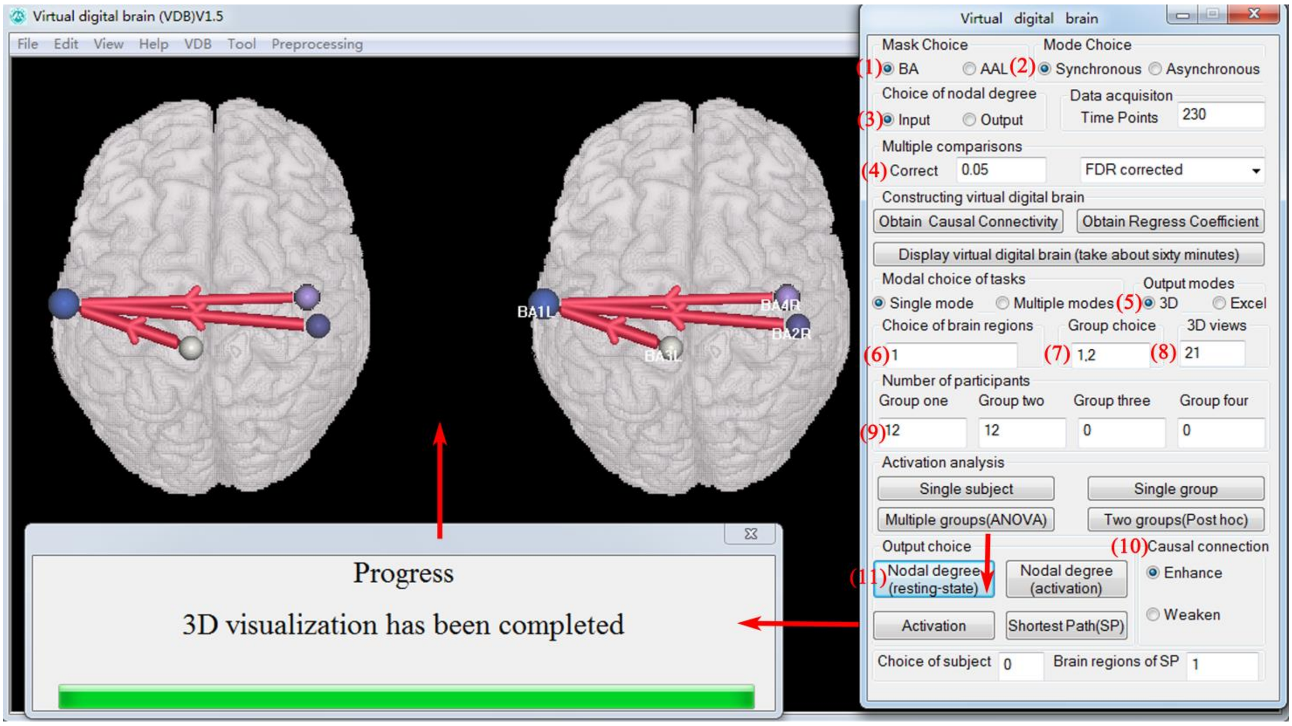


Figure 11B. 3D visualization of interregional causal connectivity changes between two groups

5. Changes of interregional causal connectivity between two groups. Select “BA” or “AAL” in the mask choice, “Synchronous” or “Asynchronous” in the mode choice, corrected parameter in the multiple comparisons, and “Excel” in the output modes, and then fill the code of group such as “1,2” in the editor control “Group choice”. In addition, the number of participants must be filled in these editor controls (Group one to four). Click on the button “Nodal degree (resting-state)”, and the procedure will run. The result is showed in an excel table (Figure 11C). Positive real numbers indicate the strengths of enhanced interregional causal connectivity, and negative

real numbers indicate the strengths of weakened interregional causal connectivity. The real numbers of every row indicate the change of output causal connectivity strength of every brain area, and the real numbers of every column indicate the change of input causal connectivity strength of every brain area.

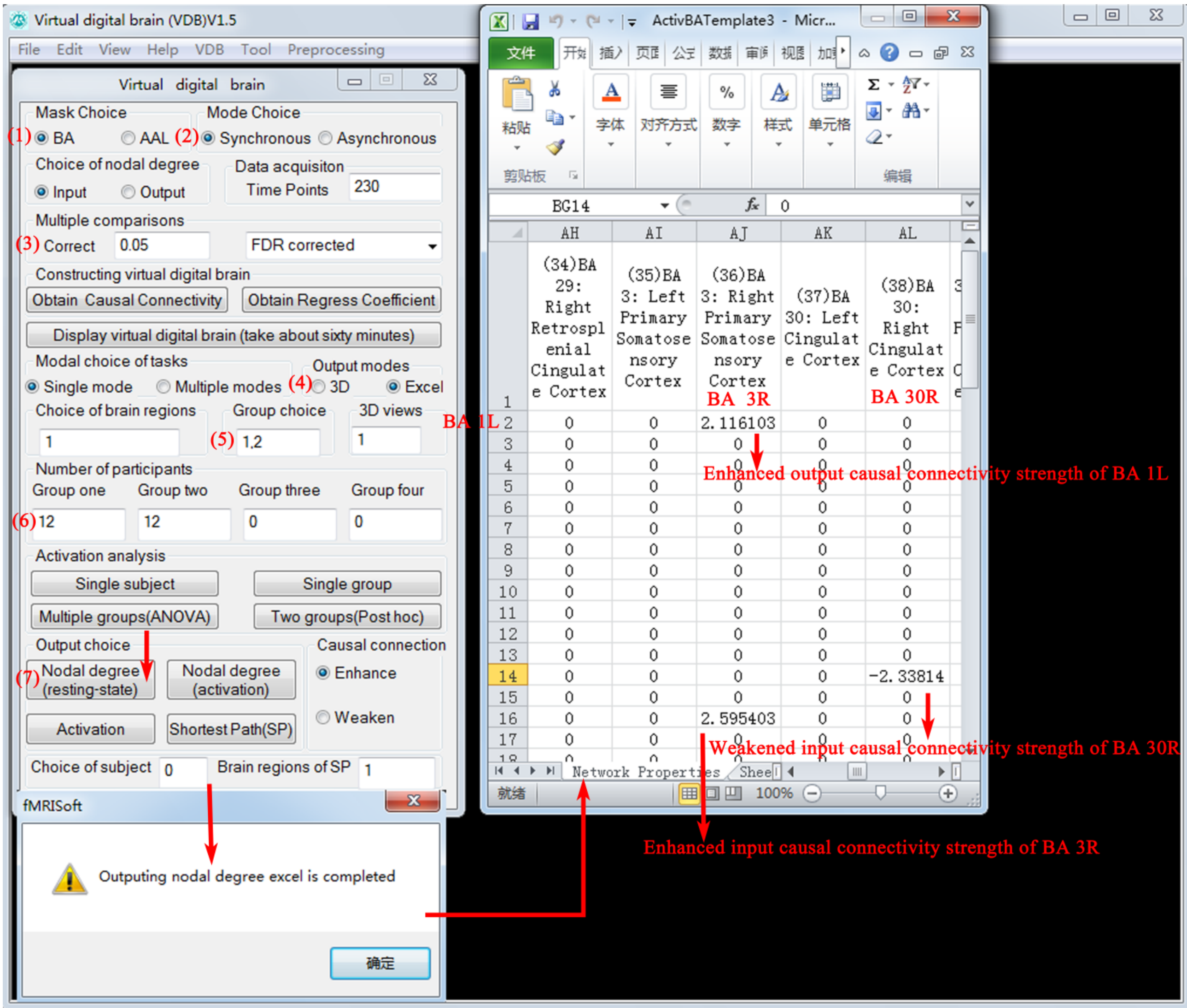


Figure 11C. Changes of interregional causal connectivity strengths between two groups

4.2. Nodal degrees of the causal connectivity network (Activation)

1. Nodal degree of one brain region in the single group (3D visualization). Select “BA” or “AAL” in the mask choice, “Synchronous” or “Asynchronous” in the mode choice, “Input” or “Output” in the choice of nodal degree, corrected parameter in the multiple comparisons, and “3D” in the output modes, fill the index of displayed brain region in the “Choice of brain regions ” control, and then fill the index of 3D view in the editor control “3D views” (the index “1” indicates the superior view, “2” indicates the inferior view,“3” indicates the left view,“4”

indicates the right view,"21" indicates the superior view with marks of brain regions), and the index of brain region in the editor control "Choice of brain regions " see also table 1 and table 2 for details. In addition, the number of participants must be filled in these editor controls (Group one to four). Click on the button "Nodal degree (activation)", and 3D visualization will run. The result is showed in the left of client area (Figure 11D). The size of bar indicates the strength of causal connectivity, and the arrow indicates the direction of causal connectivity. The light blue bar denotes synchronous causal connectivity, and the gold bar denotes asynchronous causal connectivity. Red spheres denote positively activated brain regions, and blue spheres denote negatively activated brain regions. The size of sphere is corresponding to the strength of activation.

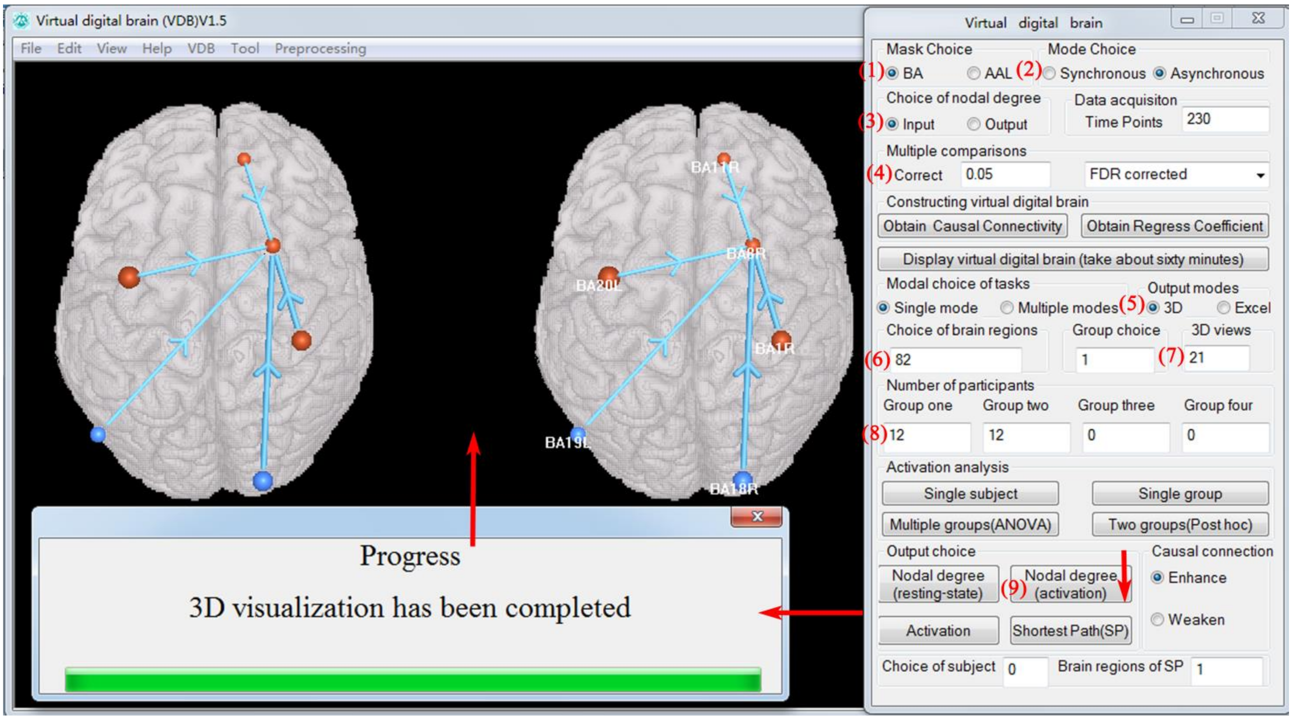


Figure 11D. 3D visualization of nodal degree in the activation network

5. Task design

The procedure "TaskDesign" in the folder VDB (D: \\VDB\\TaskDesign) is an example of designing task. The integrated development environment of this procedure is Microsoft Visual studio 2013 or above. Several functions have been built in the class "TaskConstruction", and these functions are responsible for constructing tasks or reading constructed signals. VDB 1.4 adds several functions that can construct auditory and visual task signals (Figure 12 A and B). The auditory signal one is generated by sampling an audio signal, which is obtained by reading the stroop color-word test B. The auditory signal two was composed of the sum of sines and cosines of various frequencies, and this frequency range was from 500Hz to 2000Hz. The amplitude of the auditory signal was modulated by using random values. The visual signal one is obtained by sampling a stroop color-word test B card. The visual signal two is obtained by sampling four different checkerboard patterns.

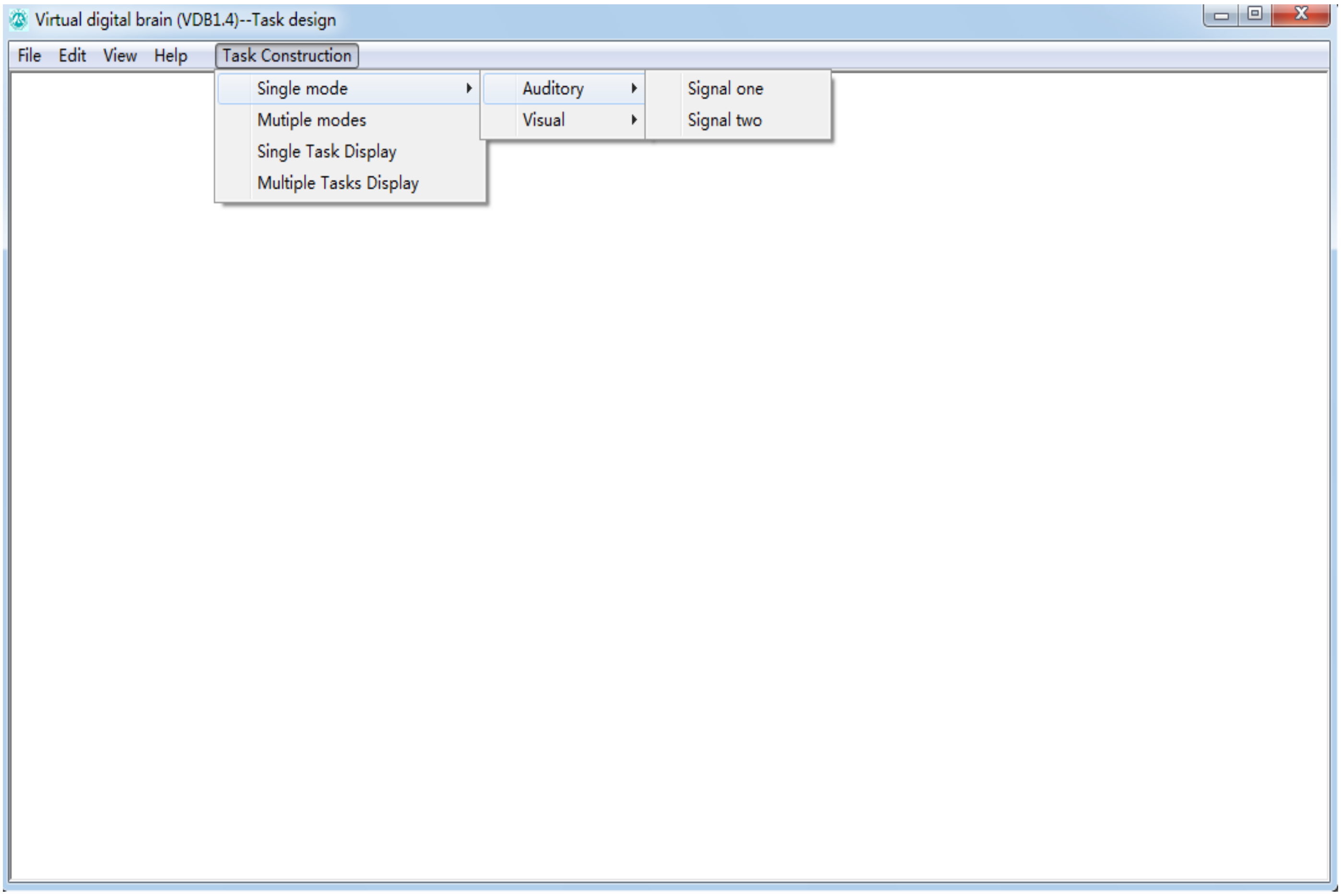


Figure12 A Auditory signal construction of single mode

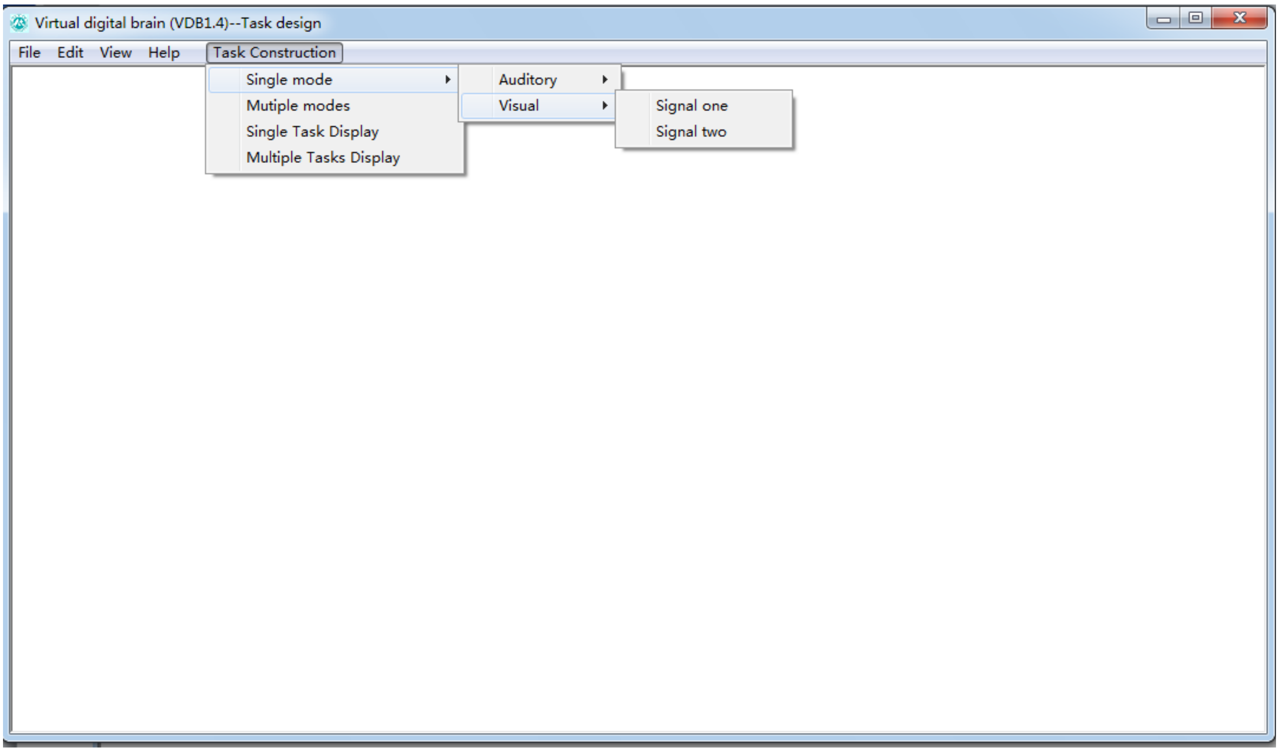


Figure12 B Visual signal construction of single mode

The testing functions have been built in the classes “CTaskDesignDoc” and “CTaskDesignView”, and these functions are responsible for displaying the waveforms of the stimulating signal of task, BOLD signal, event-related design and input signal of brain regions (Figure 12 C and D). Users can add member functions in these classes to achieve task design (experimental paradigm) and waveform display. The software “VDBV1.5” can be used to analysis brain region activations evoked by these constructed task signals.

Figure 12 C. Task design and waveform display (Mode One)

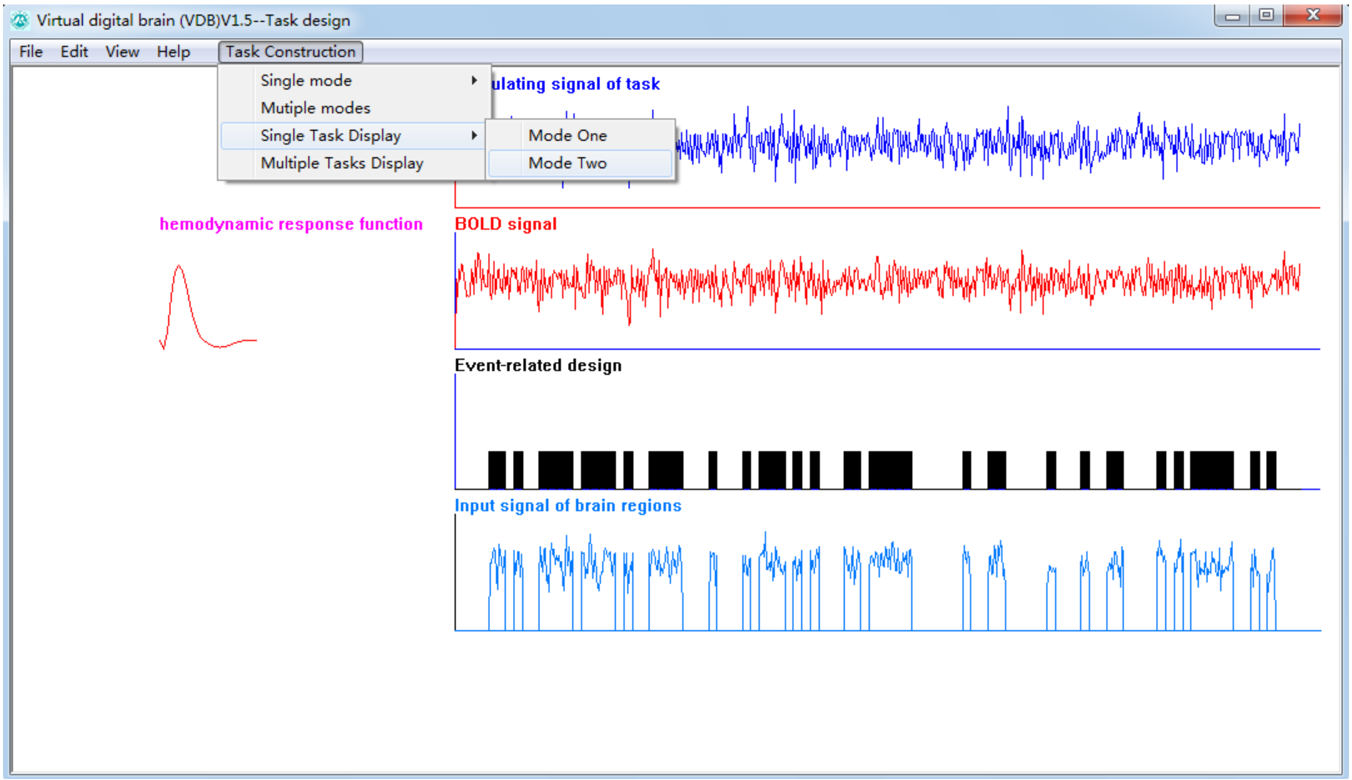


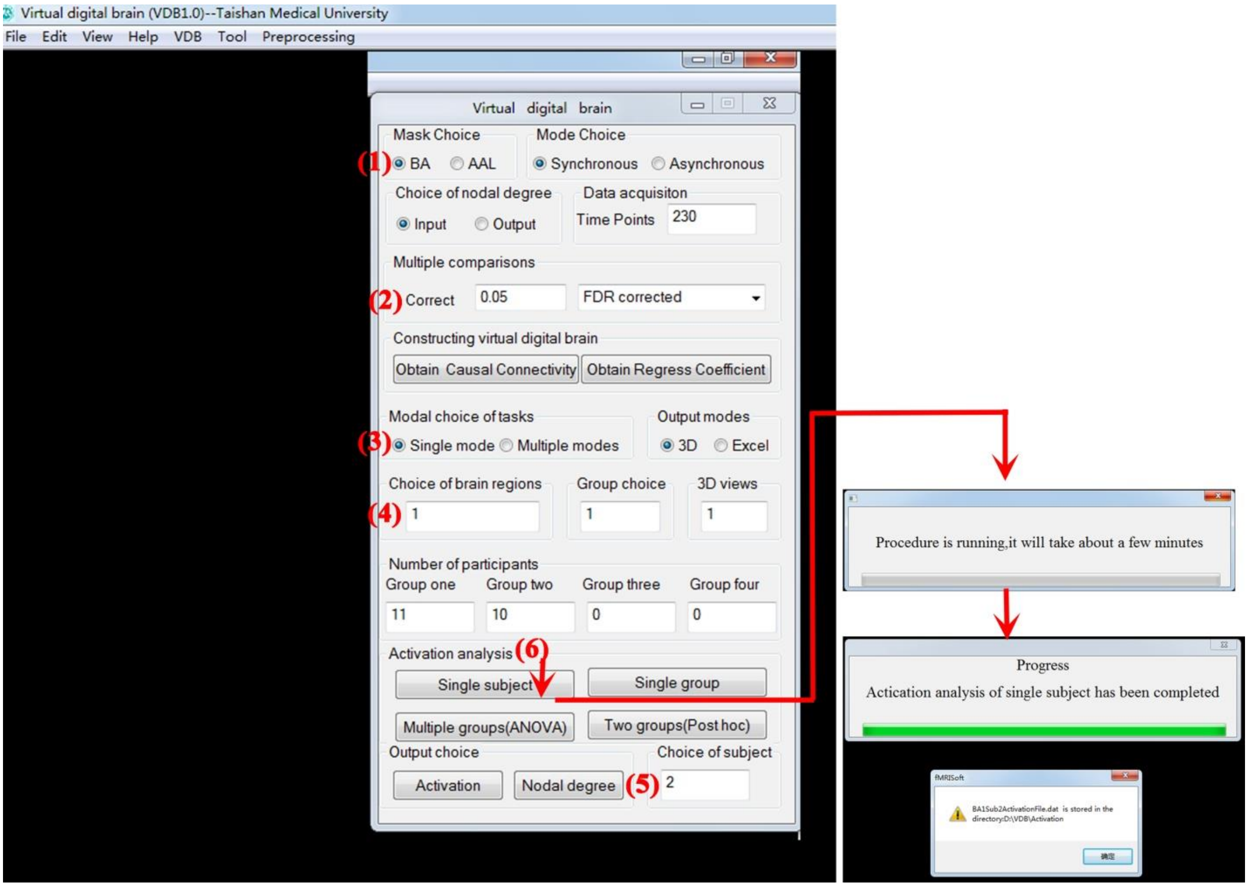
Figure 12 D. Task design and waveform display (Mode Two)

6. Task-based activation analysis

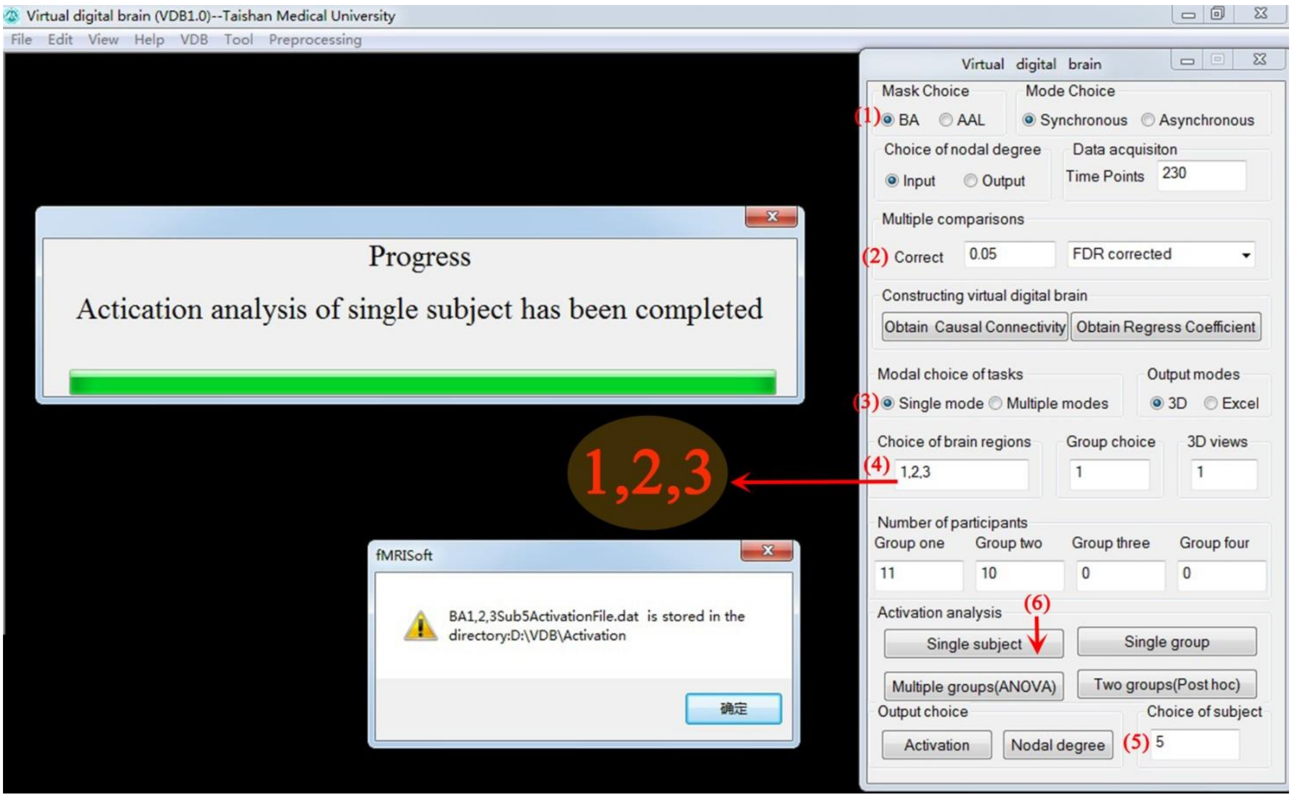
6.1. Activation analysis of single subject

1. Activation of single subject. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons (correction is for the results of activations), “Single mode or Multiple modes” in the modal choice of tasks, and then fill the index of brain region (if need to fill multiple brain regions, the format is as follows: brain region A, B, C, D,…. For example, 1, 2, 3. The string “1, 2, 3” indicates that the task stimulating signal will be exerted to 3 brain regions, and the indexes of these brain regions are 1, 2 and 3. When select “Multiple modes” in the modal choice of tasks, the format is as follows: brain region A, B; C, D; E, F. For example, 61, 62; 1, 2; 9, 10. The string “61, 62” indicates that the first task stimulating signal will be exerted to brain regions 61 and 62; the string “1, 2” indicates that the second task stimulating signal will be exerted to brain regions 1 and 2; the string “9, 10” indicates that the third task stimulating signal will be exerted to brain regions 9 and 10) in the editor control “Choice of brain regions”. In addition, the number of participants must be filled in these editor controls (Group one to four). Fill the index of subject in the editor control “Choice of subject”. Finally, click on the button “Single subject” and the procedure starts to run (Figure 13). The result of analysis is named as

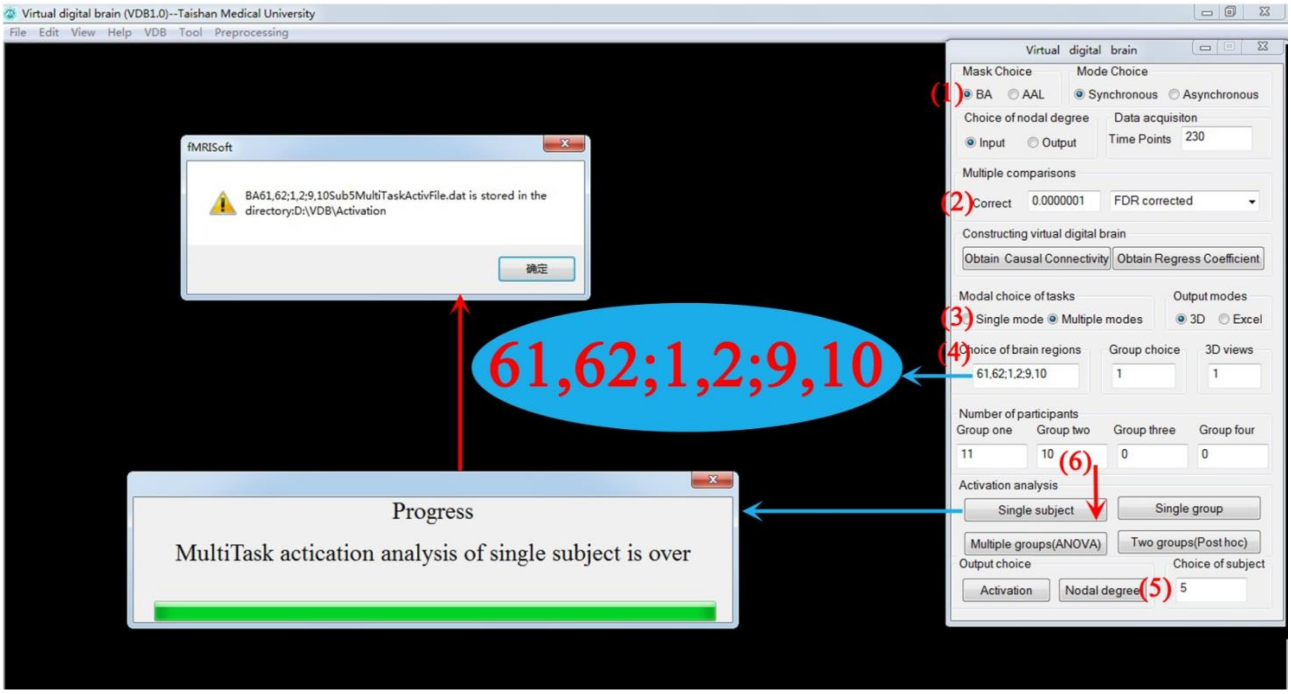
"BAxSubxActivationFile.dat or AALxSubxActivationFile.dat" and is automatically stored in the folder "Activation" (the directory: D: \\VDB\\Activation).



(a)



(b)



(c)

Figure 13. Activation analysis of single subject

2. Activation results of single subject. (1) Output the activation results through the excel table. Select corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), “Excel” in the “Output modes”, and then click the button “Activation”. Select one file in the folder “Activation” (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click the button “Open” and then the result is displayed in an excel table (Figure 14). In this table, the numbers in the column “CH” indicate the index of activated brain regions, and the column “CG” is the strength of activation. Positive real numbers indicate positive strengths of activation. On the contrary, negative real numbers indicate negative strengths of activation. Positive real numbers in every row indicate the strengths of synchronous causal connectivity among activated brain regions, and negative real numbers indicate the strengths of asynchronous causal connectivity. The real numbers of every row indicate the strengths of output causal connectivity corresponding to every node, and the real numbers of every column indicate the strengths of input causal connectivity corresponding to every node. It is worth noting that the values in the excel table are actual values of activation strengths and causal connectivity.

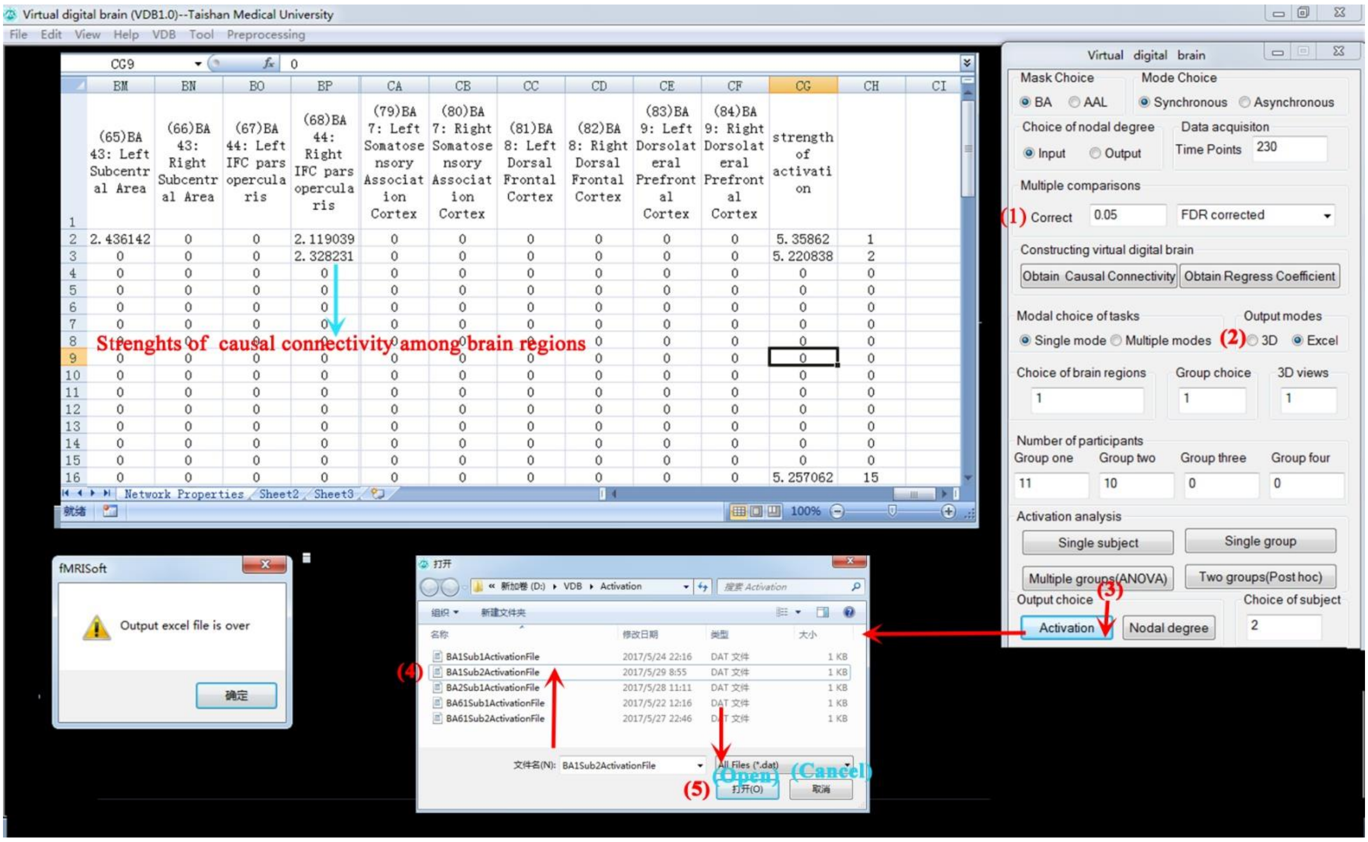


Figure 14. Activation result of single subject

(2) Output the activation results through 3D visualization. Select "BA" or "AAL" in the mask choice, "Synchronous" or "Asynchronous" in the mode choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), and "3D" in the output modes, and then fill the index of 3D view in the editor control "3D views" (the index "1" indicates the superior view, "2" indicates the inferior view, "3" indicates the left view, and "4" indicates the right view. In these views, every color sphere indicates an activated brain region. The size of the sphere indicates the strength of the brain region activation (It is worth noting that the sizes are not responding to actual strengths of brain region activations, these sizes are responding to standardized strengths of activations. The actual strengths of activations can be displayed through the excel table), every bar among spheres indicates the casual connectivity among these brain regions, and the diameter of the bar denotes the strength of the interregional causality connectivity (It is worth noting that the diameters are not responding to actual strengths of interregional causality connectivity, these diameters are responding to standardized strengths of interregional causality connectivity. The actual strengths of causality connectivity can be obtained through the excel table). The gold bar denotes the synchronous causality

connectivity, and the light blue bar denotes the asynchronous causality connectivity. The direction of the arrow denotes the direction of causality connectivity. Especially, when the index of 3D view is bigger than 4, we display activated brain regions by using color areas. Different colors indicate distinct strengths of brain region activations. Blue is corresponding to weaker activated strength and yellow indicates stronger activated strength. Color changes of the color bar are corresponding to changes of activated strengths of brain regions. The index "5" of 3D view indicates that the activated brain regions are projected to this view from superior to inferior; "6" indicates that the activated brain regions are projected to this view from left to right ; "7" indicates that the activated brain regions in the superior cerebral hemisphere are projected to this view from inferior to superior; "8" indicates that the activated brain regions in the inferior cerebral hemisphere are projected to this view from superior to inferior; "9" indicates that the activated brain regions in the left cerebral hemisphere are projected to this view from right to left; "10" indicates that the activated brain regions in the right cerebral hemisphere are projected to this view from left to right). Click on the button "Activation". Select one file in the folder "Activation" (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click on the button "Open" and then the result is showed in the left of client area (Figure 15).

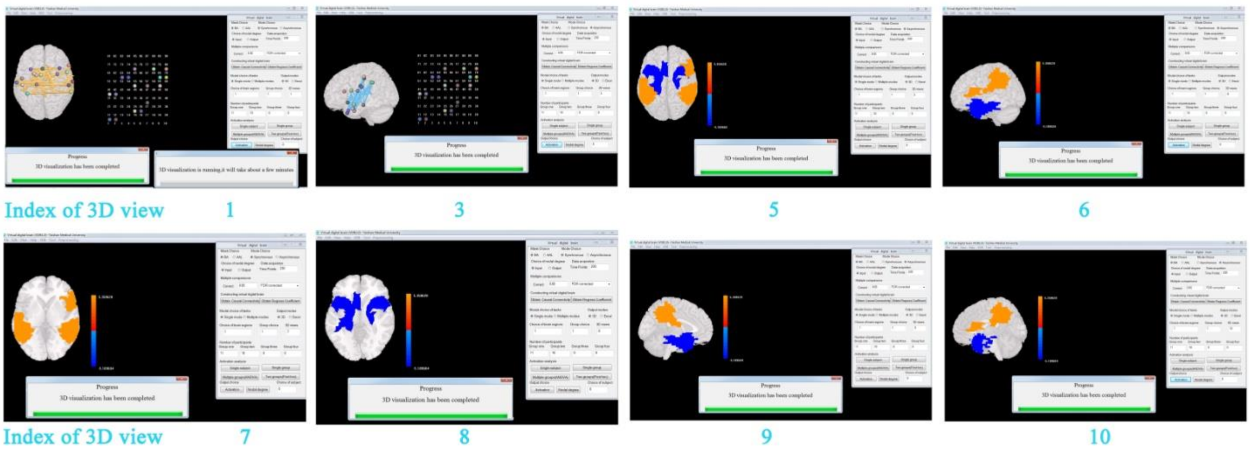


Figure 15. 3D visualization of brain region activations of single subject

6.2. Activation analysis of single group

1. Activation analysis of single group. Select "BA" or "AAL" in the mask choice, corrected parameter in the multiple comparisons (correction is for the results of activations), "Single mode or Multiple modes" in the modal choice of tasks, and then fill the index of brain region (if need to fill multiple brain regions, the format is as

follows: brain regions A, B, C, D,…. For example, 61, 62. The string "61, 62" indicates that the task stimulating signal will be exerted to 2 brain regions, and the indexes of these brain regions are 61 and 62) in the editor control "Choice of brain regions". In addition, the number of participants must be filled in these editor controls (Group one to four). Fill the index of group in the editor control "Group choice". Finally, click on the button "Single group" and the procedure starts to run (Figure 16). A file named as "BAxGrpxActivationFile.dat or AALxGrpxActivationFile.dat" is automatically stored in the folder "Activation" (the directory: D: \\VDB\\Activation).

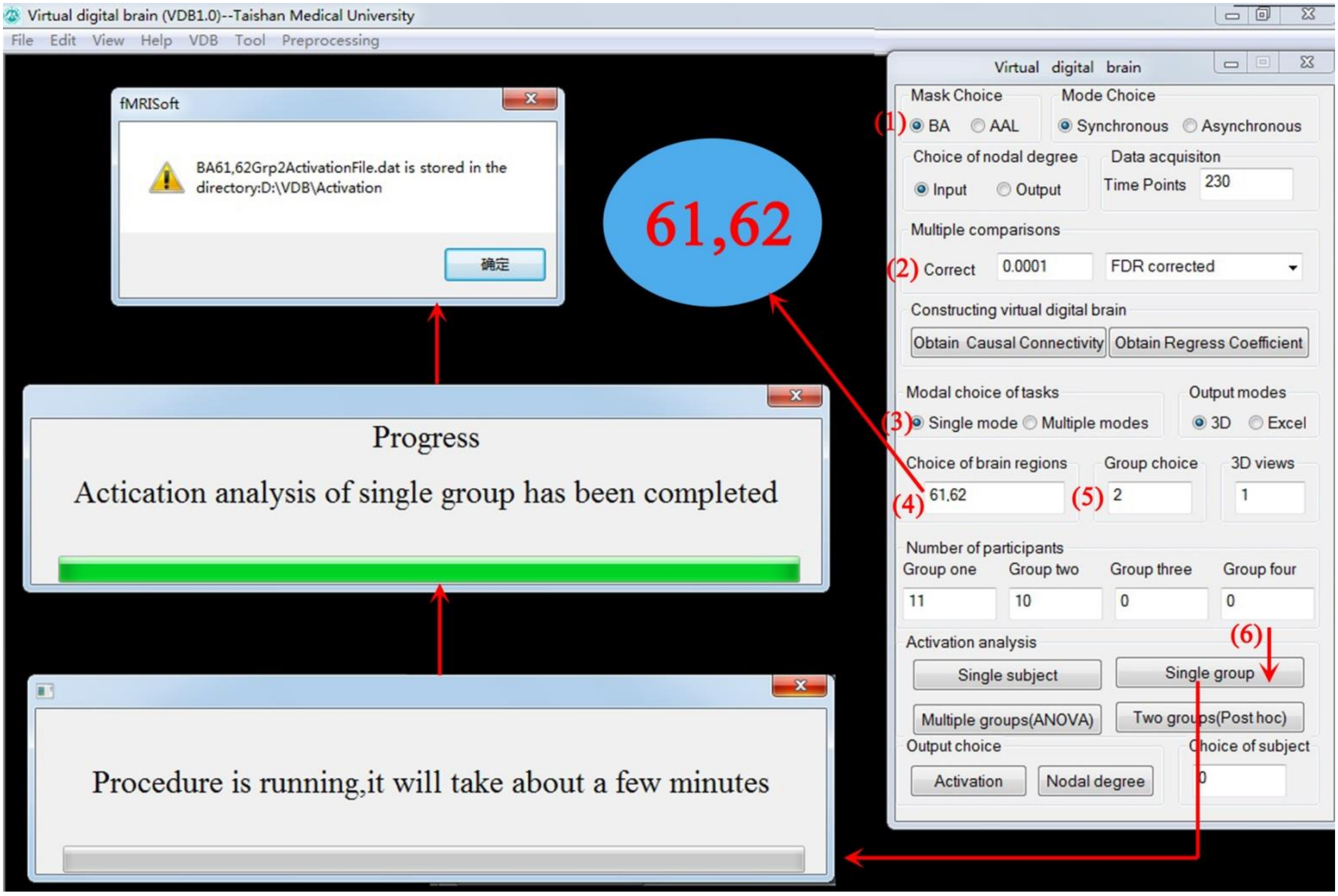


Figure 16. Activation analysis of single group

2. Activation results of single group. (1) Output the activation results through the excel table. Select "BA" or "AAL" in the mask choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), "Excel" in the "Output modes", and then click on the button "Activation". Select one file in the folder "Activation" (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click on the button "Ok" and then the result is displayed in an excel table (Figure 17). In this table, the numbers in the column "CH" indicate the index of

activated brain regions, and the column "CG" is the strength of activation. Positive real numbers indicate positive strengths of activation. On the contrary, negative real numbers indicate negative strengths of activation. Positive real numbers in every row indicate the strengths of synchronous causal connectivity among activated brain regions, and negative real numbers indicate the strengths of asynchronous causal connectivity. The real numbers of every row indicate the strengths of output causal connectivity corresponding to every node, and the real numbers of every column indicate the strengths of input causal connectivity corresponding to every node (see also Figure 14 for details). In addition, the number of participants must be filled in these editor controls (Group one to four).

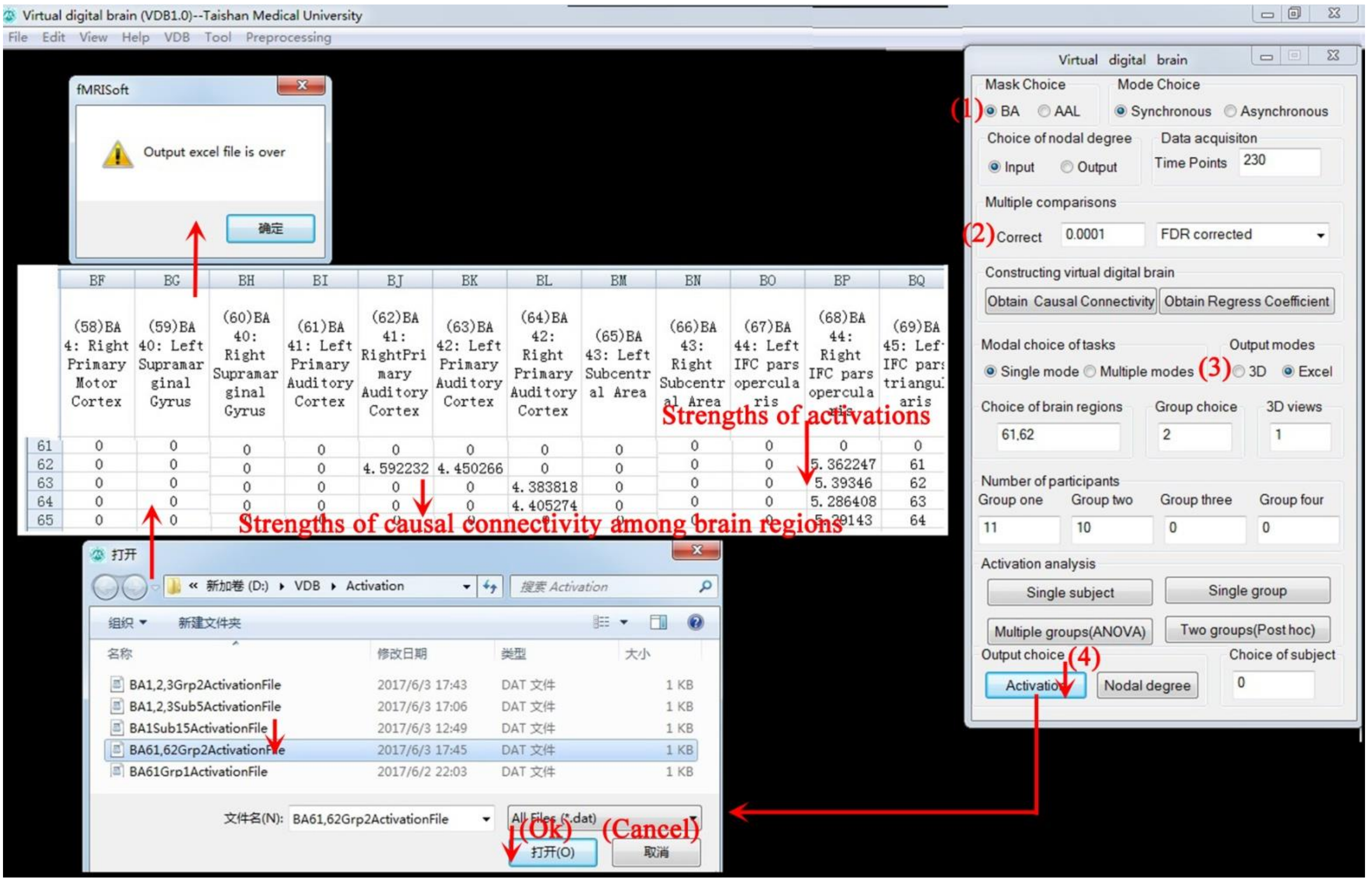


Figure 17. Activation result of single group

(2) Output the activation results through 3D visualization. Select "BA" or "AAL" in the mask choice, "Synchronous" or "Asynchronous" in the mode choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), and "3D" in the output modes, and then fill the index of 3D view in the editor control "3D views" (the index "1" indicates the superior view, "2" indicates the inferior view, "3" indicates the left view, and "4" indicates the right view. In these views,

every color sphere indicates an activated brain region. The size of the sphere indicates the strength of the brain region activation, every bar among spheres indicates the casual connectivity among these brain regions, and the diameter of the bar denotes the strength of the interregional causality connectivity. The gold bar denotes the synchronous causality connectivity, and the light blue bar denotes the asynchronous causality connectivity. The direction of the arrow denotes the direction of causality connectivity. Especially, when the index of 3D view is bigger than 4, we display activated brain regions by using color areas. Different colors indicate distinct strengths of brain region activations. Blue is corresponding to weaker activated strength and yellow indicates stronger activated strength. Color changes of the color bar are corresponding to changes of activated strengths of brain regions. The index "5" of 3D view indicates that the activated brain regions are projected to this view from superior to inferior; "6" indicates that the activated brain regions are projected to this view from left to right; "7" indicates that the activated brain regions in the superior cerebral hemisphere are projected to this view from inferior to superior; "8" indicates that the activated brain regions in the inferior cerebral hemisphere are projected to this view from superior to inferior; "9" indicates that the activated brain regions in the left cerebral hemisphere are projected to this view from right to left ; "10" indicates that the activated brain regions in the right cerebral hemisphere are projected to this view from left to right). Click on the button "Activation". Select one file in the folder "Activation" (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click on the button "Open" and then the result is showed in the left of client area (Figure 18). In addition, the number of participants must be filled in these editor controls (Group one to four).

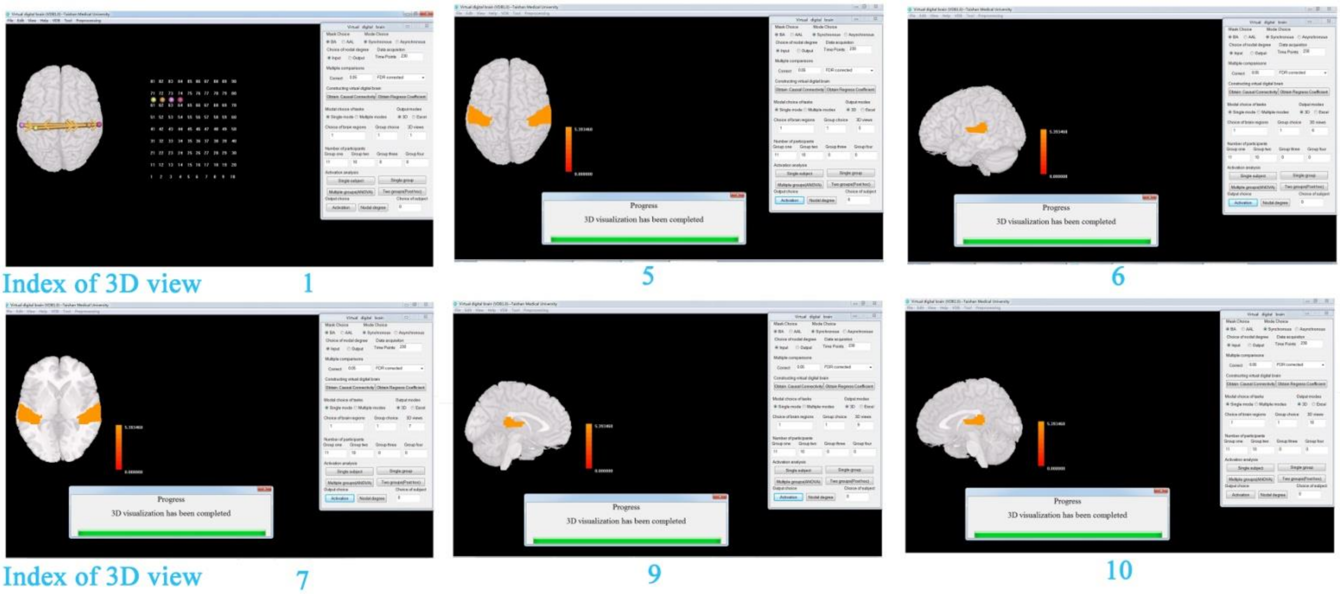


Figure 18. 3D visualization of brain region activations of single group

(3) Output the activation results of all subjects through the excel table. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons (correction is for the strengths of brain region activation), “Single mode or Multiple modes” in the modal choice of tasks, “Excel” in the “Output modes”, and then fill the index of brain region (if multiple brain regions need to be filled in the editor control, then the format is as follows: brain regions A, B, C, D,…. For example, 61, 62. The string “61, 62” indicates that the task stimulating signal will be exerted to 2 brain regions, and the indexes of these brain regions are 61 and 62) in the editor control “Choice of brain regions”. Fill “0” in the editor control “Group choice” and the number of participants in editor controls (Group one to four). Finally, click on the button “Activation”, and then the result is displayed in an excel table (Figure 18A). In this table, the numbers in the column are the strengths of activation of each brain region. Positive real numbers indicate positive strengths of activation. On the contrary, negative real numbers indicate negative strengths of activation. Every row is corresponding to one subject.

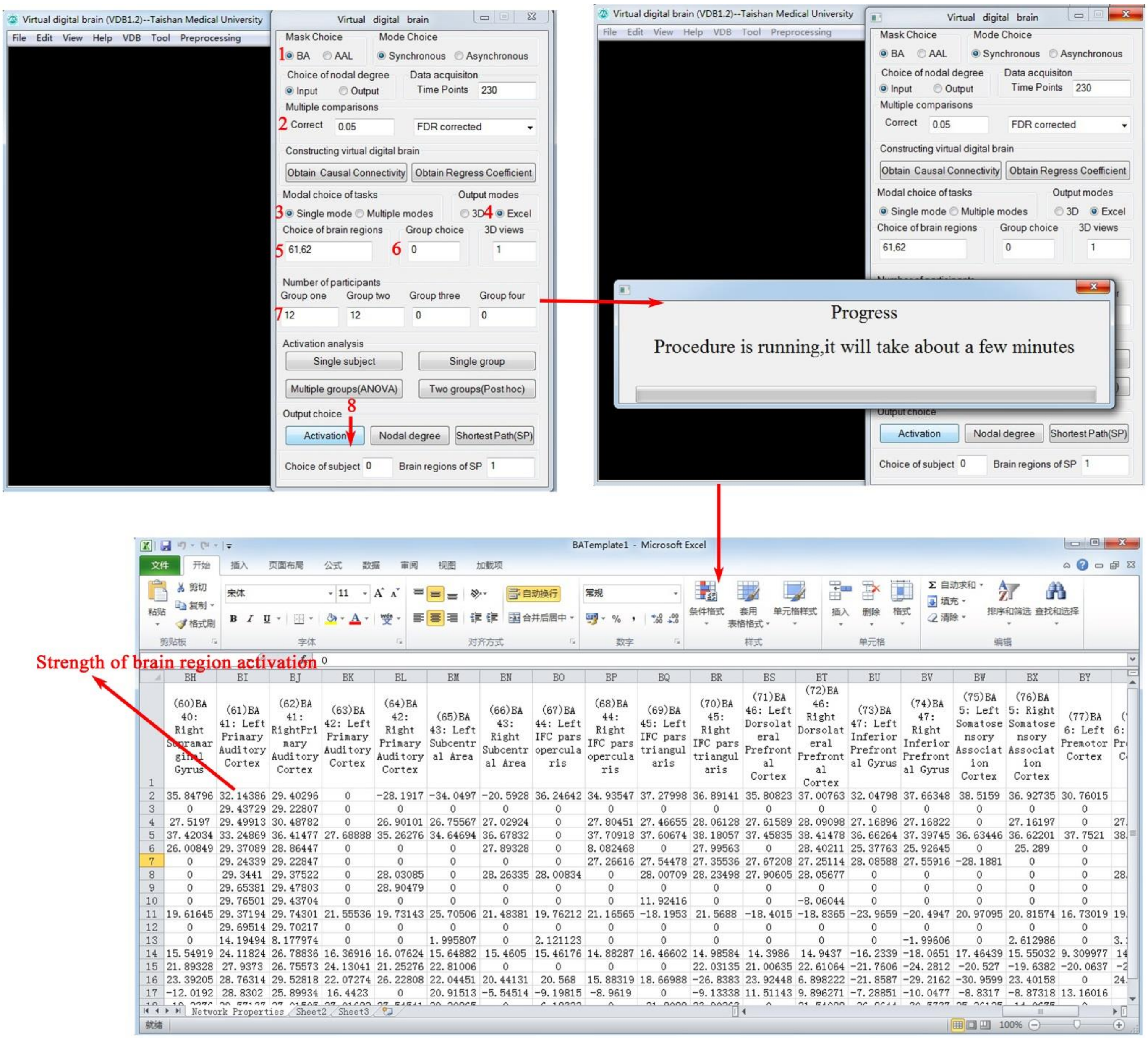


Figure 18A Activation result of all subjects

6.3. Activation analysis of two groups

1. Activation analysis of two groups. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons (correction is for the results of activations), “Single mode or Multiple modes” in the modal choice of tasks, and then fill the index of brain region (if multiple brain regions need to be filled in the editor control, then the format is as follows: brain regions A, B, C, D,…. For example, 61, 62. The string “61, 62” indicates that the task stimulating signal will be exerted to 2 brain regions, and the indexes of these brain regions are 61 and 62) in the editor control “Choice of brain regions”. In addition, the number of participants must be filled in these editor controls (Group one to four). Fill the indexes of groups in the editor control “Group choice” (The format is as follows: Groups A, B. For example, 1, 2. The string “1, 2” indicates that the groups 1 and 2

participate in the test. Two-sample t-test will be implemented to compare activation results of group 1 to 2.). Finally, click on the button “Two groups” and the procedure starts to run (Figure 19). The result of analysis is named as “BAxTrpxActivationFile.dat or AALxTrpxActivationFile.dat” and is automatically stored in the folder “Activation” (the directory: D: \\VDB\\Activation).

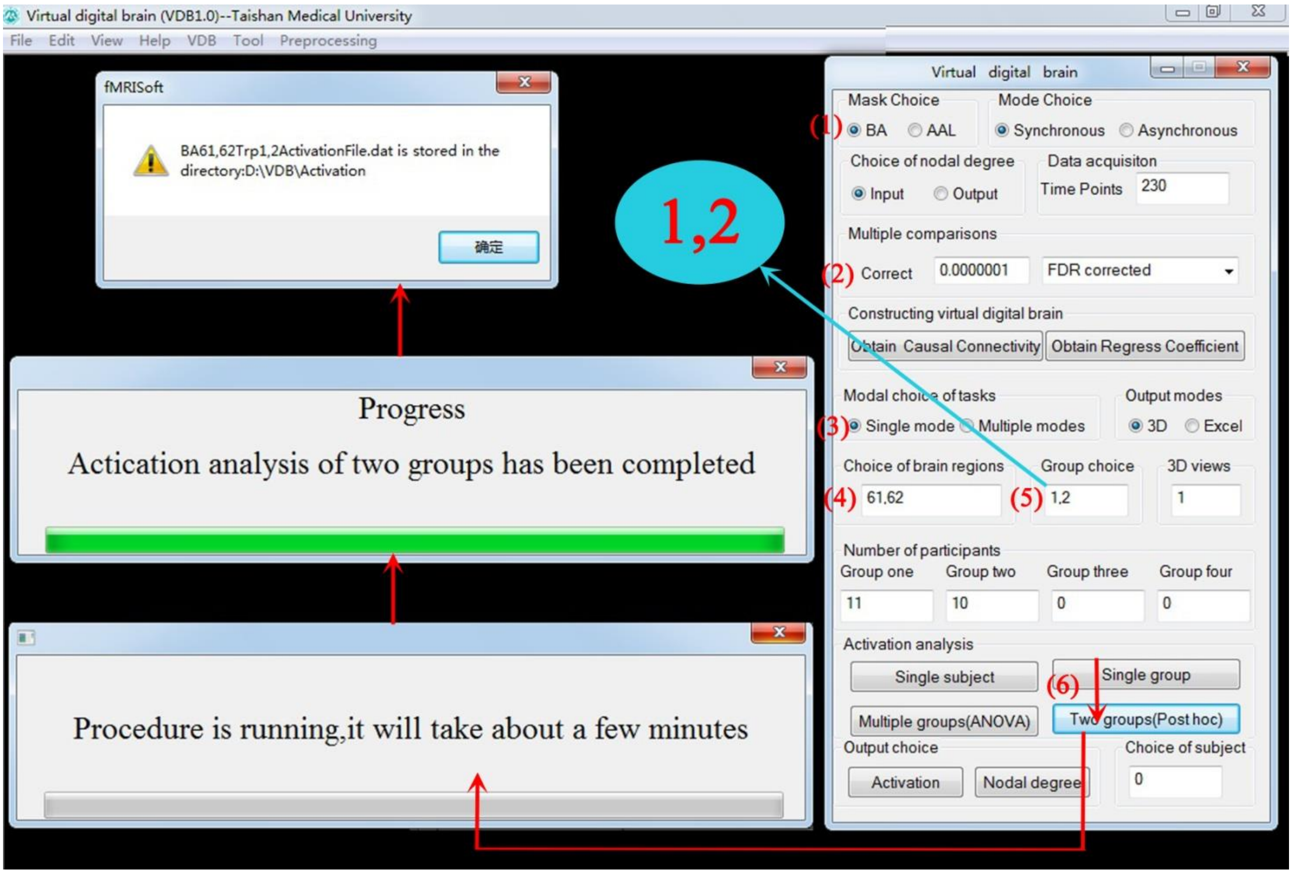


Figure 19. Activation analysis of two groups

2. Activation results of two groups. (1) Output the activation results through the excel table. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), “Excel” in the “Output modes”, and then click on the button “Activation”. Select one file in the folder “Activation” (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click on the button “Ok” and then the result is displayed in an excel table (Figure 20). In this table, the numbers in the column “CH” indicate the index of activated brain regions, and the column “CG” is the strength of activation. Positive real numbers indicate positive strengths of activation. On the contrary, negative real numbers indicate negative strengths of activation. Positive real numbers in every row indicate the strengths of synchronous causal connectivity among activated brain

regions, and negative real numbers indicate the strengths of asynchronous causal connectivity. The real numbers of every row indicate the strengths of output causal connectivity corresponding to every node, and the real numbers of every column indicate the strengths of input causal connectivity corresponding to every node (see also Figure 14 and 17for details). In addition, the number of participants must be filled in these editor controls (Group one to four).

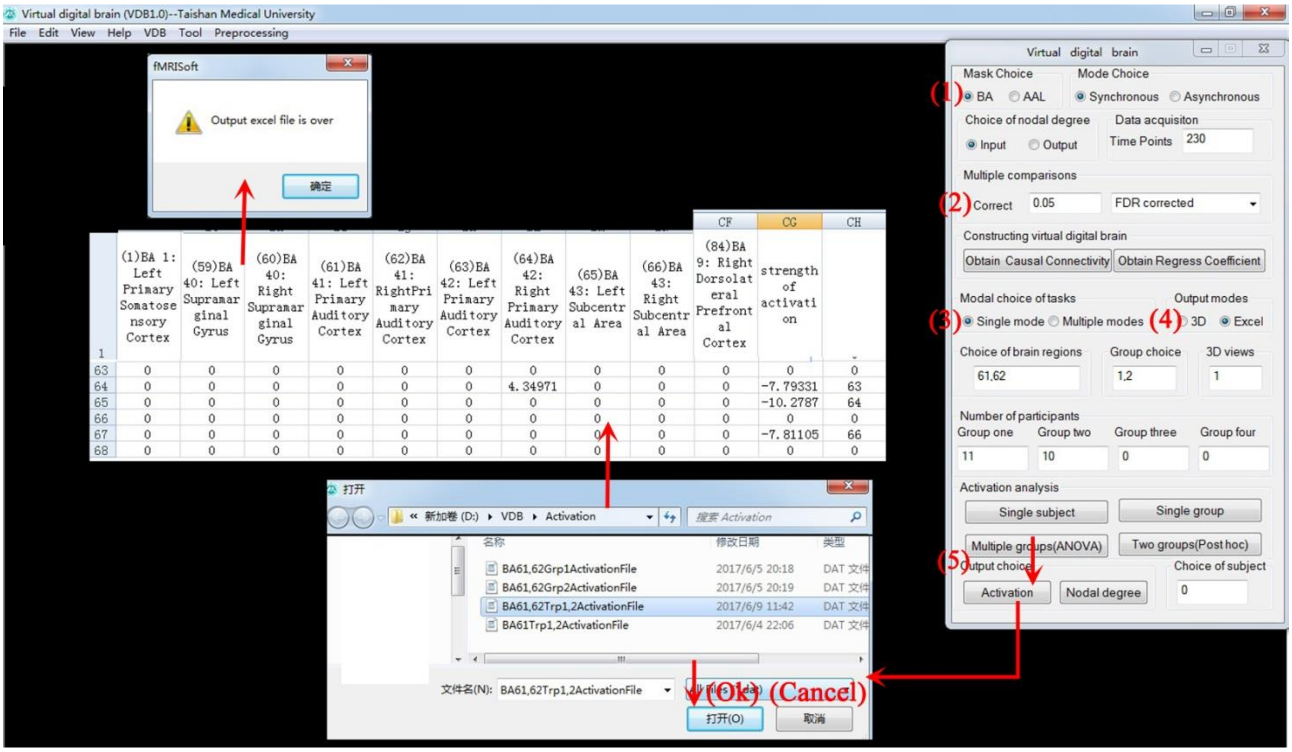


Figure 20. Activation result of two groups

(2) Output the activation results through 3D visualization. Select “BA” or “AAL” in the mask choice, “Synchronous” or “Asynchronous” in the mode choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), and “3D” in the output modes, and then fill the index of 3D view in the editor control “3D views” (the index “1” indicates the superior view, “2” indicates the inferior view, “3” indicates the left view, and “4” indicates the right view. In these views, every color sphere indicates an activated brain region. The size of the sphere indicates the strength of the brain region activation, every bar among spheres indicates the casual connectivity among these brain regions, and the diameter of the bar denotes the strength of the interregional causality connectivity. The gold bar denotes the synchronous causality connectivity, and the light blue bar denotes the asynchronous causality connectivity. The direction of the arrow denotes the direction of causality connectivity. Especially, when the index of 3D view is

bigger than 4, we display activated brain regions by using color areas. Different colors indicate distinct strengths of brain region activations. Blue is corresponding to weaker activation strength and yellow indicates stronger activation strength. Color changes of the color bar are corresponding to changes of activated strengths of brain regions. The index “5” of 3D view indicates that the activated brain regions are projected to this view from superior to inferior; “6” indicates that the activated brain regions are projected to this view from left to right ; “7” indicates that the activated brain regions in the superior cerebral hemisphere are projected to this view from inferior to superior; “8” indicates that the activated brain regions in the inferior cerebral hemisphere are projected to this view from superior to inferior; “9” indicates that the activated brain regions in the left cerebral hemisphere are projected to this view from right to left; “10” indicates that the activated brain regions in the right cerebral hemisphere are projected to this view from left to right). Click on the button “Activation”. Select one file in the folder “Activation” (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click on the button “Open” and then the result is showed in the left of client area (Figure 21). In addition, the number of participants must be filled in these editor controls (Group one to four).

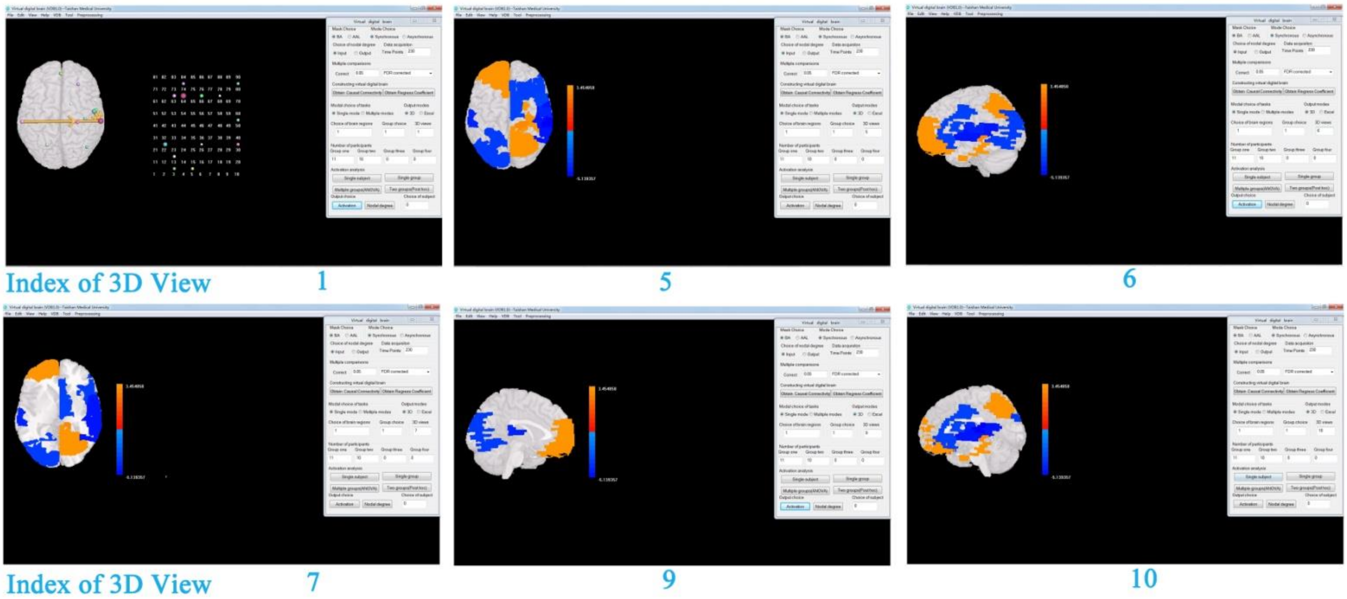


Figure 21. 3D visualization of brain region activations of two groups

In order to obtain 3D view of brain regions, we can implement following steps: Select “BA” or “AAL” in the mask choice, “3D” in the output modes, fill the index of brain region in the editor control “Choice of brain regions”, then fill “20” in the editor control “3D views”. Click the button “Activation”. Select one file in the folder "Activation" (the directory: D: \\VDB\\Activation) through an opened dialog box. These files have been generated in previous step. Click on the button "Open" and then the result is showed in the left of client area (Figure 22). In addition, the number of participants must be filled in these editor controls (Group one to four).

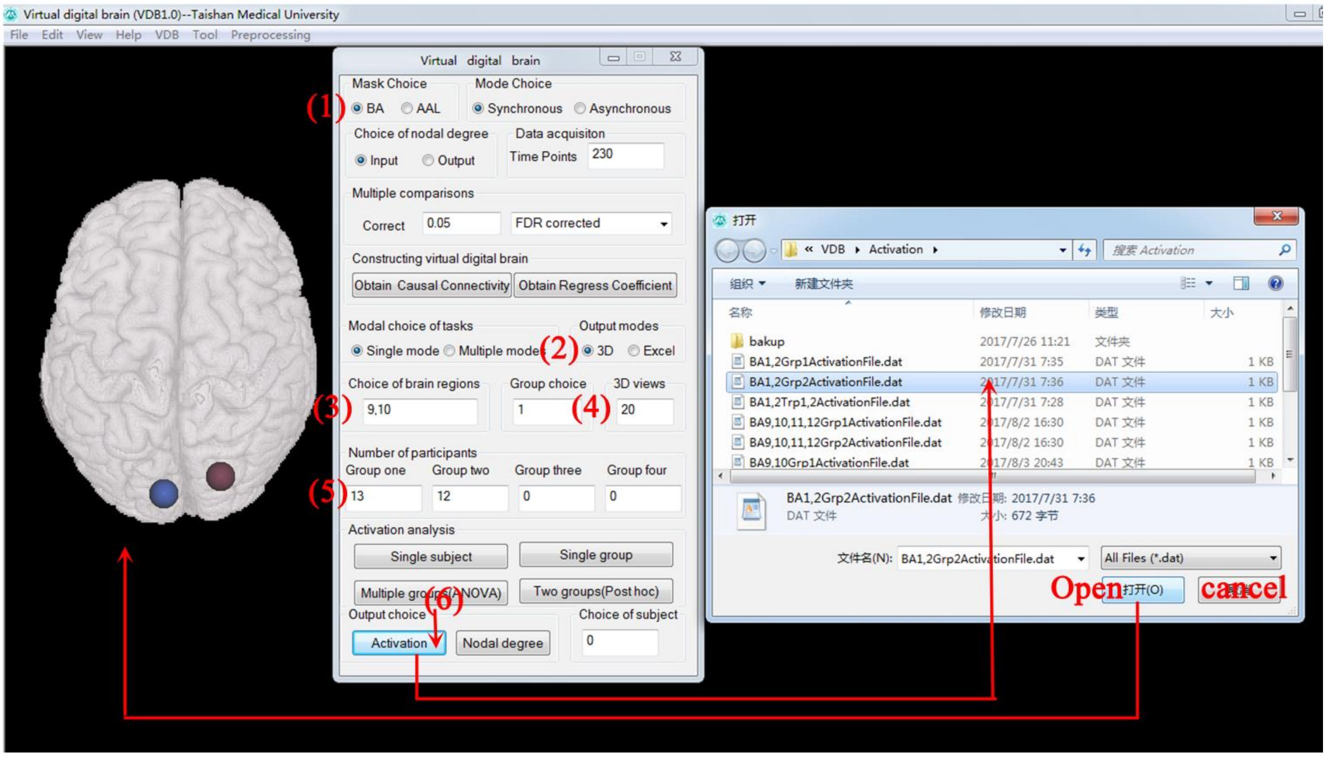


Figure 22. 3D visualization of selected brain regions

6.4. Activation visualization

1. Firstly, click on the menu VDB, and then select the "Visualization" in the drop-down menu. As shown in Figure 23.

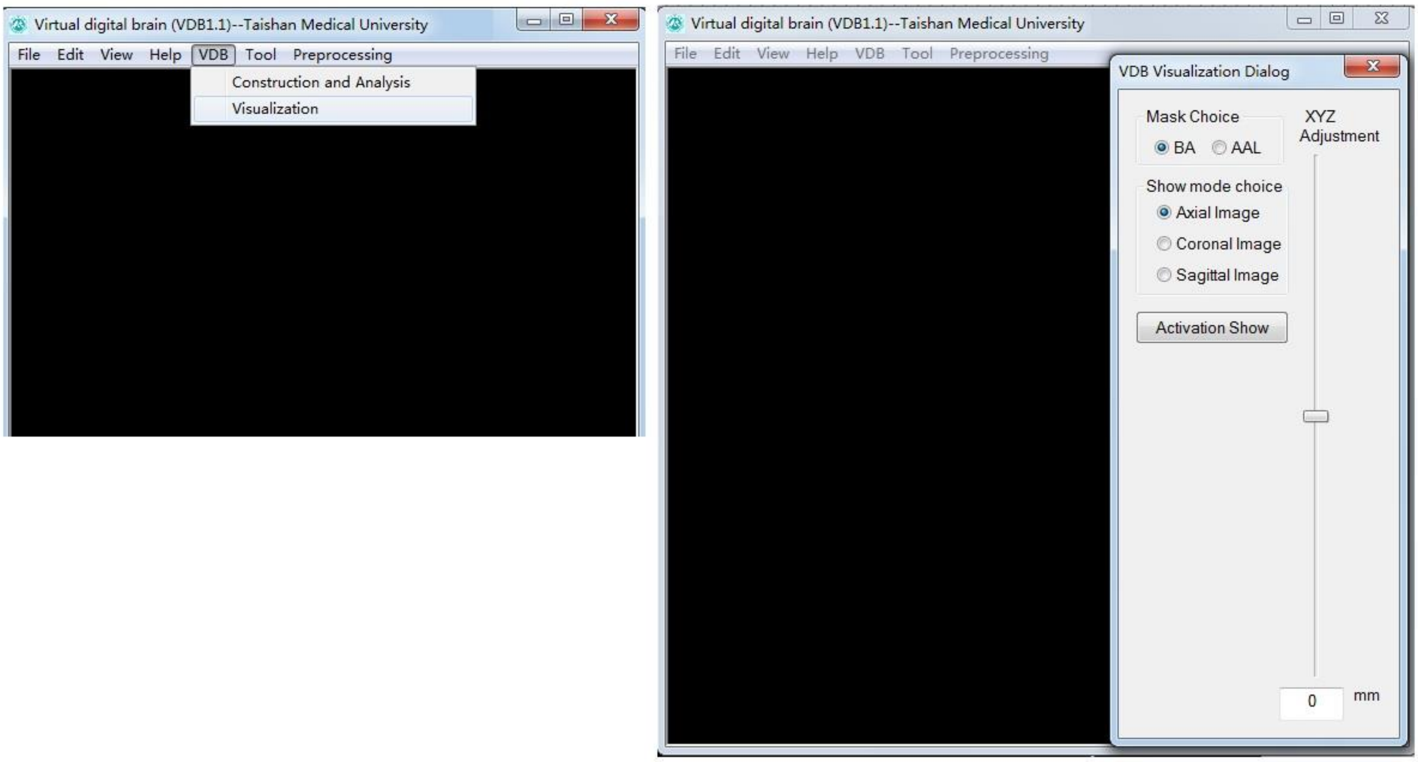


Figure 23. Diagram of opening visualization dialog.

2. Select “BA” or “AAL” in the mask choice, “Axial Image” or “Coronal Image” or “Sagittal Image” in the show mode choice, and then click on the button “Activation Show” and open the destination folder “Activation”. Select a file in the opened folder and click on the button “Open”, and then the axial image is displayed in the client area, as shown in figure 24. The color bar indicates the strengths of activation, the negative value denotes the strength of negative activation, and the positive value denotes the strength of positive activation. The numbers beside the activated regions indicate the index of Brodmann Area (BA), the “L” denotes the left, and the “R” denotes the right.

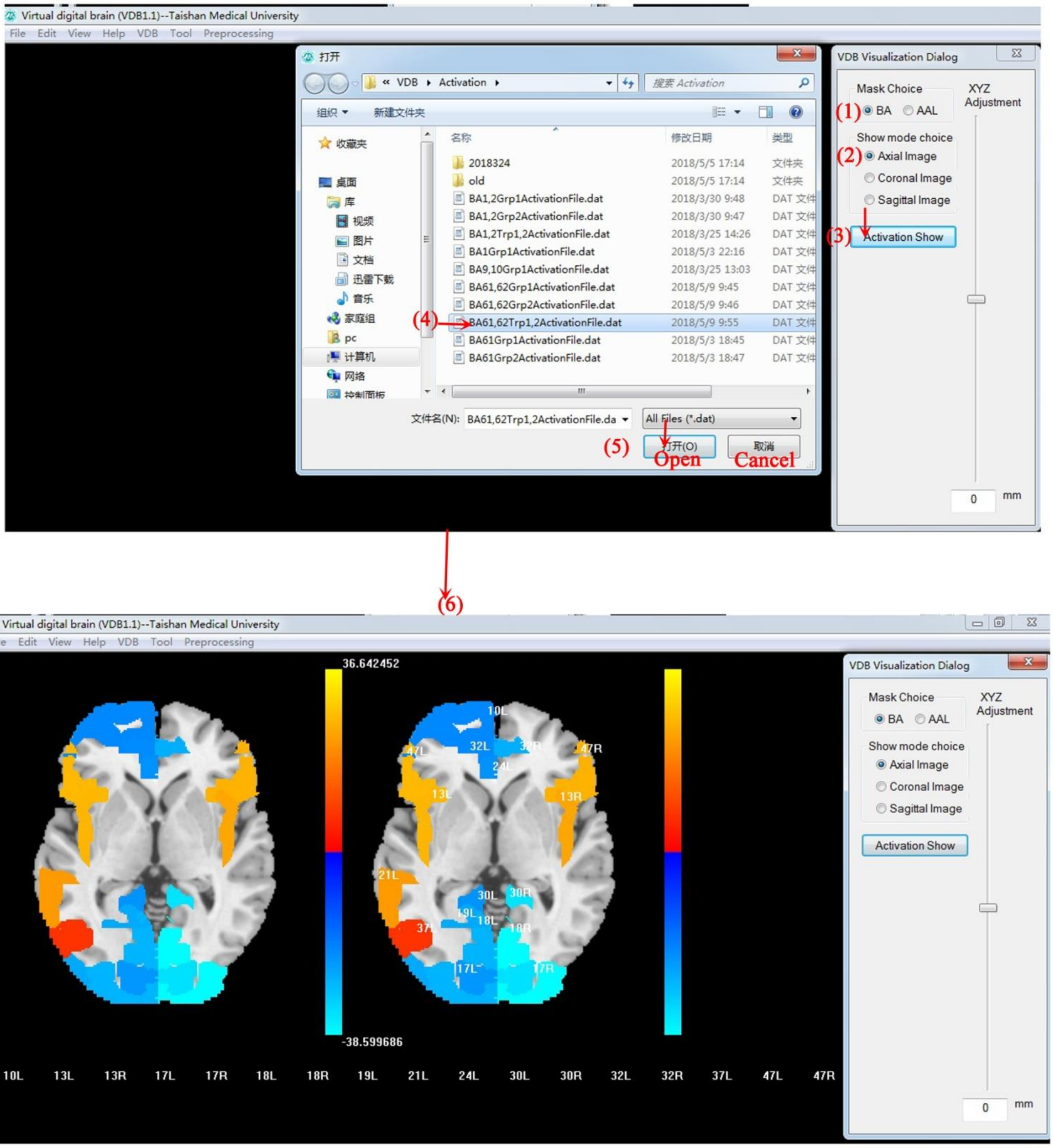


Figure 24. Diagram of the axial image display

3. Remove the slider and alter the location of the activated images (for example, the axial image), as shown in figure 25.

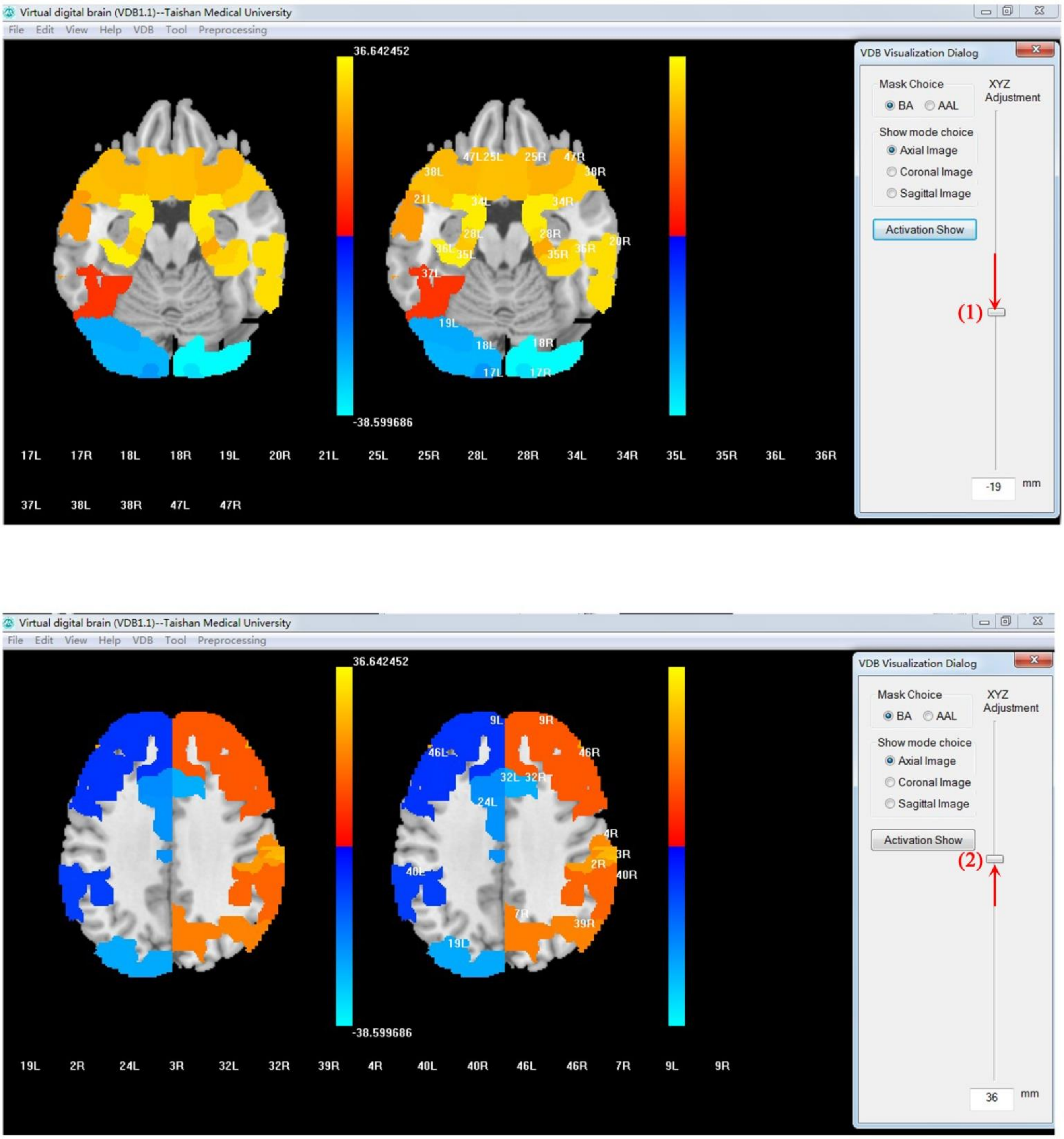


Figure 25. Diagram of the axial image change

7. The shortest path

1. The resting-state shortest path between brain regions. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), “3D” in the output modes, fill the index of group in the editor control “Group choice”, and then fill “A,B” in the editor control “Brain regions of SP”(“A,B” denotes the direction of the shortest path is from the

brain region A to B). Click on the button "Shortest Path (SP) (resting-state)" and obtain the 3D view of the resting-state shortest path between brain regions A and B. The result is showed in figure 26A.

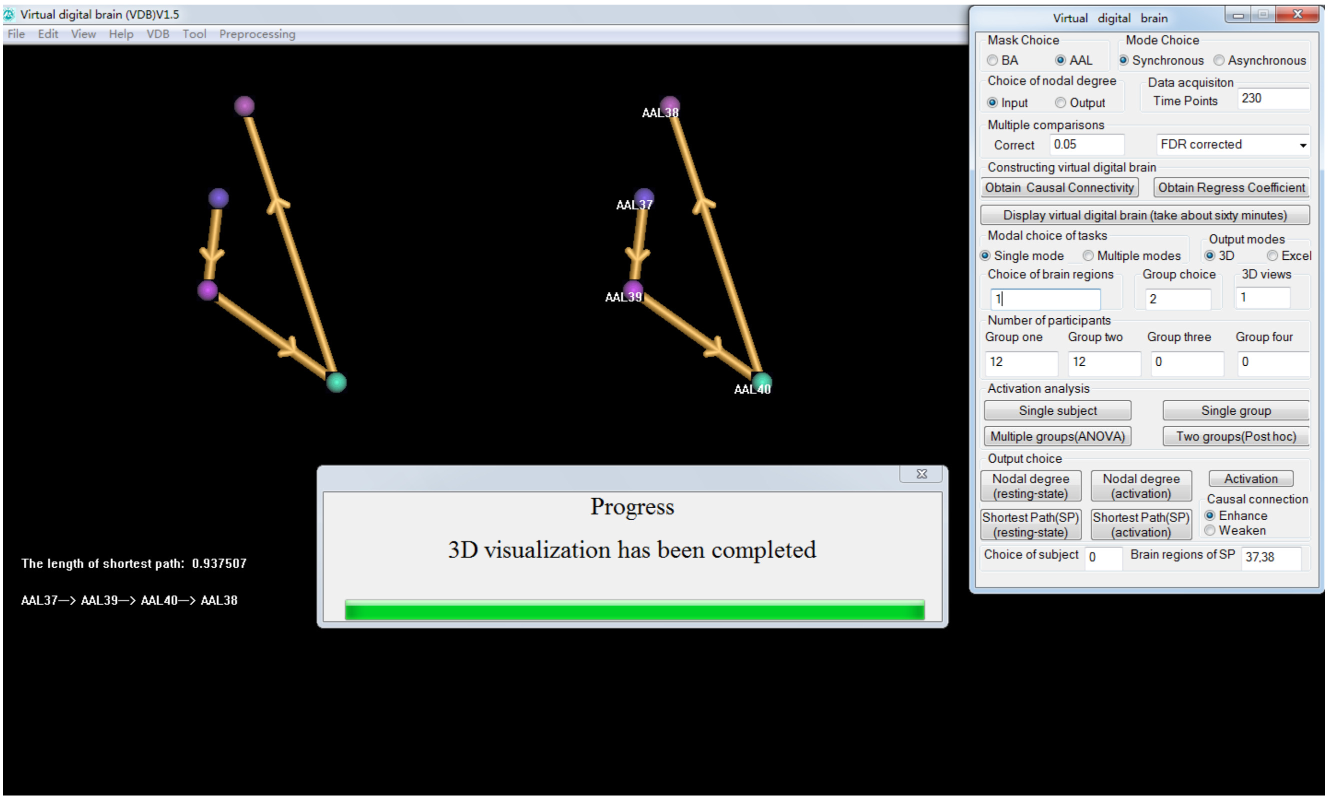


Figure 26A. 3D view of the resting-state shortest path between brain regions

In figure 26A, the gold bar denotes the synchronous causality connectivity, and the light blue bar denotes the asynchronous causality connectivity. The direction of the arrow denotes the direction of causality connectivity, and the diameter of the bar denotes the strength of the interregional causality connectivity.

2. The shortest path between brain regions in the activation brain network. Select "BA" or "AAL" in the mask choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), "3D" in the output modes, and then fill "A,B" in the editor control "Brain regions of SP"("A,B" denotes the direction of the shortest path is from the brain region A to B). Click on the button "Shortest Path (SP) (activation)" and select the activation file in the folder "Activation" through the opened dialog. Click on the button "Open" and obtain the 3D view of the shortest path between brain regions A and B in the activation brain network. The result is showed in figure 26B.

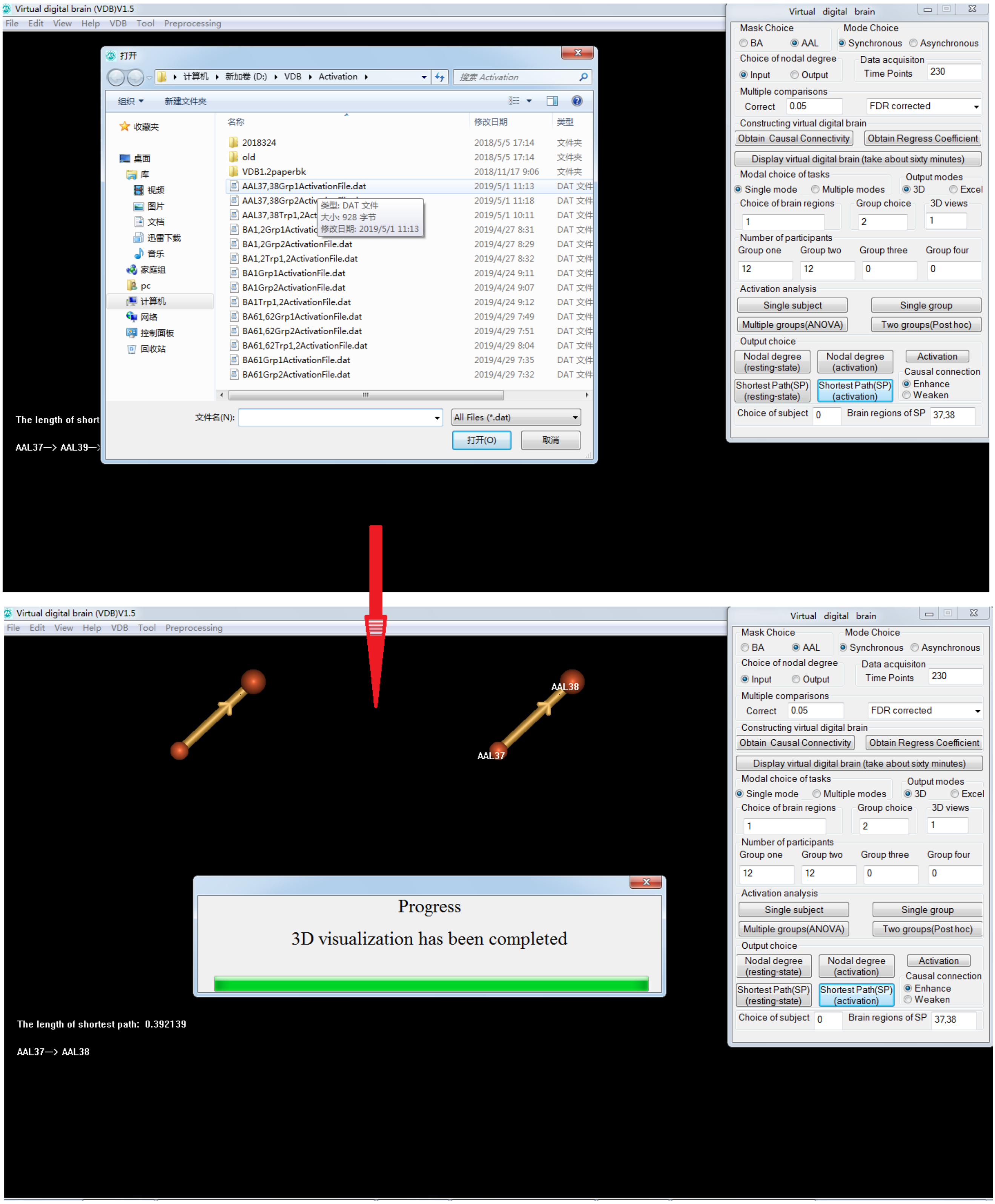
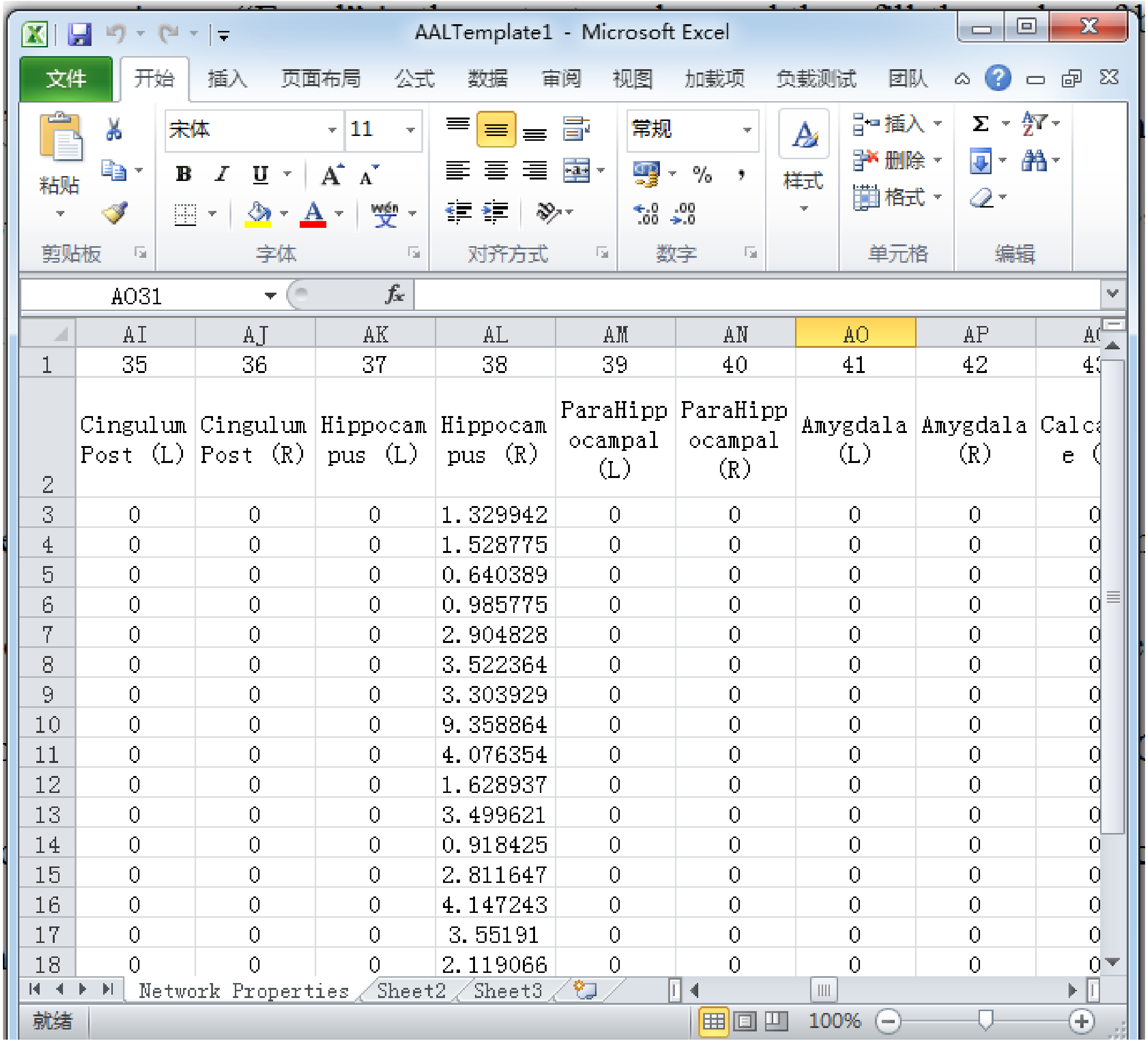


Figure 26B. 3D view of the shortest path between brain regions in the activation brain network

In figure 26B , the red sphere denotes positive activation, and the blue sphere denotes negative activation. The size of sphere is corresponding to the strength of activation. The gold bar denotes the synchronous causality connectivity, and the light blue bar denotes the asynchronous causality connectivity. The direction of the arrow denotes the direction of causality connectivity, and the diameter of the bar denotes the strength of the interregional causality connectivity.

3. The resting-state shortest path lengths of all subjects. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons, “Excel” in the output modes, and then fill the codes of brain regions in the “Brain regions of SP”(such as “61,62”, “1,61”). In addition, the number of participants must be filled in these editor controls (Group one to four). Click on the button “Shortest path(SP) (resting-state) ” and obtain the shortest path lengths of all subjects. The result is showed in an excel file (Figure 27).

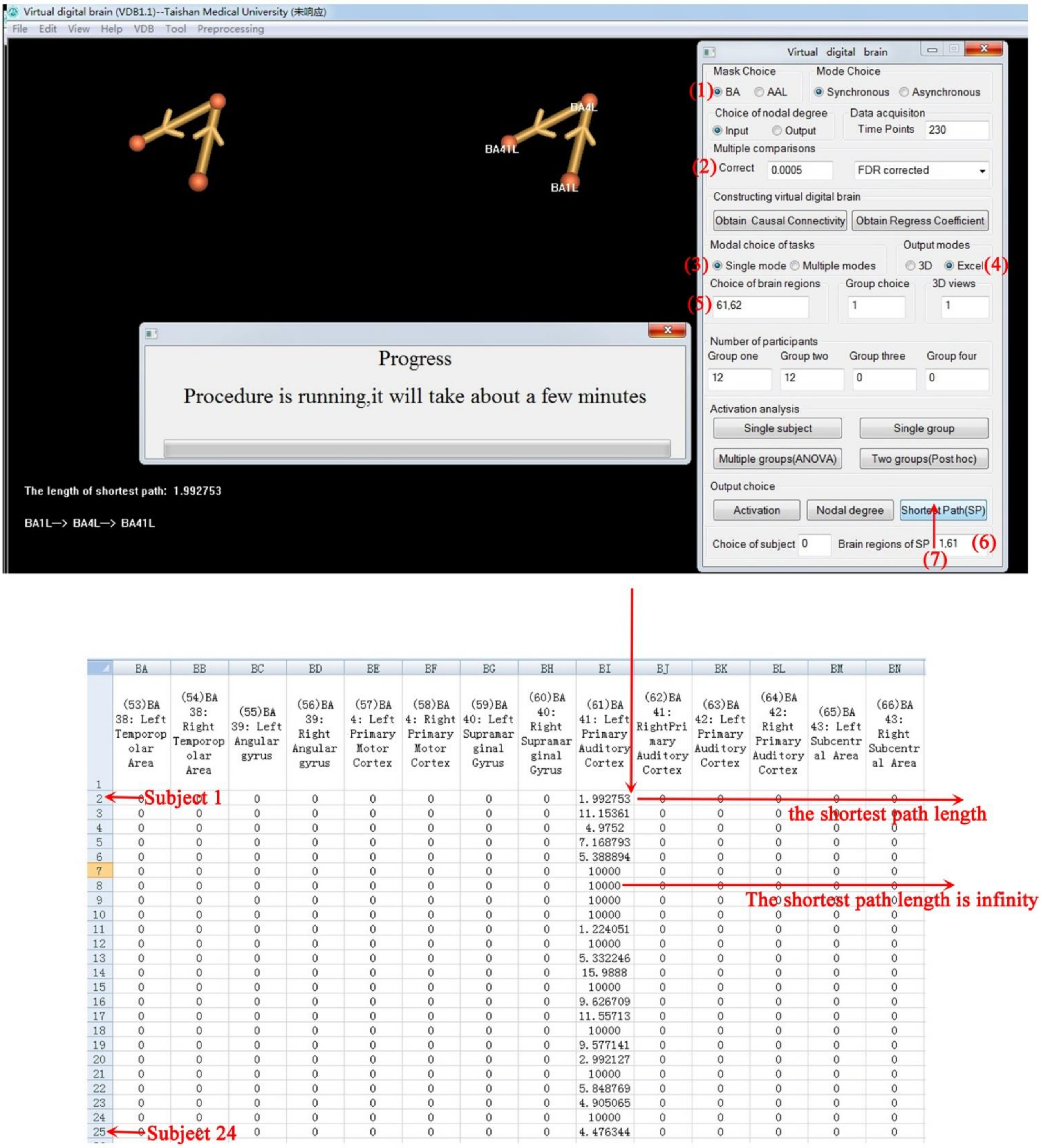


	AI	AJ	AK	AL	AM	AN	AO	AP	A
1	35	36	37	38	39	40	41	42	4
2	Cingulum Post (L)	Cingulum Post (R)	Hippocampus (L)	Hippocampus (R)	ParaHippocampal (L)	ParaHippocampal (R)	Amygdala (L)	Amygdala (R)	Calca e (
3	0	0	0	1.329942	0	0	0	0	0
4	0	0	0	1.528775	0	0	0	0	0
5	0	0	0	0.640389	0	0	0	0	0
6	0	0	0	0.985775	0	0	0	0	0
7	0	0	0	2.904828	0	0	0	0	0
8	0	0	0	3.522364	0	0	0	0	0
9	0	0	0	3.303929	0	0	0	0	0
10	0	0	0	9.358864	0	0	0	0	0
11	0	0	0	4.076354	0	0	0	0	0
12	0	0	0	1.628937	0	0	0	0	0
13	0	0	0	3.499621	0	0	0	0	0
14	0	0	0	0.918425	0	0	0	0	0
15	0	0	0	2.811647	0	0	0	0	0
16	0	0	0	4.147243	0	0	0	0	0
17	0	0	0	3.55191	0	0	0	0	0
18	0	0	0	2.119066	0	0	0	0	0

Figure 27. The resting-state shortest path lengths of all subjects

4. The shortest path lengths of all subjects in the brain activation networks . Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons, “Single mode” or “Multiple modes” in the modal choice of tasks, “Excel” in the output modes, and then fill the codes of brain regions in the editor controls “Choice of brain regions” and “Brain regions of SP”(such as “61,62”, “1,61”). In addition, the number of participants must

be filled in these editor controls (Group one to four). Click on the button "Shortest path(SP) (activation)" and obtain the shortest path lengths of all subjects. The result is showed in an excel file (Figure 28). Here, the codes of brain regions in the editor controls "Choice of brain regions" denote those brain regions which the virtual task signal will be exerted to.



	BA	BB	BC	BD	BE	BF	BG	BH	BI	BJ	BK	BL	BM	BN
1	(53)BA 38: Left Temporopolar Area	(54)BA 38: Right Temporopolar Area	(55)BA 39: Left Angular gyrus	(56)BA 39: Right Angular gyrus	(57)BA 4: Left Primary Motor Cortex	(58)BA 4: Right Primary Motor Cortex	(59)BA 40: Left Supramarginal Gyrus	(60)BA 40: Right Supramarginal Gyrus	(61)BA 41: Left Primary Auditory Cortex	(62)BA 41: RightPrimary Auditory Cortex	(63)BA 42: Left Primary Auditory Cortex	(64)BA 42: Right Primary Auditory Cortex	(65)BA 43: Left Subcentral Area	(66)BA 43: Right Subcentral Area
2	0	0	0	0	0	0	0	0	1.992753	0	0	0	0	0
3	0	0	0	0	0	0	0	0	11.15361	0	0	0	0	0
4	0	0	0	0	0	0	0	0	4.9752	0	0	0	0	0
5	0	0	0	0	0	0	0	0	7.168793	0	0	0	0	0
6	0	0	0	0	0	0	0	0	5.388894	0	0	0	0	0
7	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
8	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
9	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
10	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
11	0	0	0	0	0	0	0	0	1.224051	0	0	0	0	0
12	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
13	0	0	0	0	0	0	0	0	5.332246	0	0	0	0	0
14	0	0	0	0	0	0	0	0	15.9888	0	0	0	0	0
15	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
16	0	0	0	0	0	0	0	0	9.626709	0	0	0	0	0
17	0	0	0	0	0	0	0	0	11.55713	0	0	0	0	0
18	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
19	0	0	0	0	0	0	0	0	9.577141	0	0	0	0	0
20	0	0	0	0	0	0	0	0	2.992127	0	0	0	0	0
21	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
22	0	0	0	0	0	0	0	0	5.848769	0	0	0	0	0
23	0	0	0	0	0	0	0	0	4.905065	0	0	0	0	0
24	0	0	0	0	0	0	0	0	10000	0	0	0	0	0
25	0	0	0	0	0	0	0	0	4.476344	0	0	0	0	0

Figure 28. The shortest path lengths of all subjects in the activation networks of brain regions

8. Resting-state functional connectivity

1. The resting-state shortest path between brain regions. Select “BA” or “AAL” in the mask choice, corrected parameter in the multiple comparisons (correction is for the strengths of causal connectivity among activated brain regions), “3D” in the output modes, fill the index of group in the editor control “Group choice”, and then fill “A,B” in the editor control “Brain regions of SP”(“A,B” denotes the direction of the shortest path is from the brain region A to B). Click on the button “Shortest Path (SP) (resting-state)” and obtain the 3D view of the resting-state shortest path between brain regions A and B. The result is showed in figure 26A.

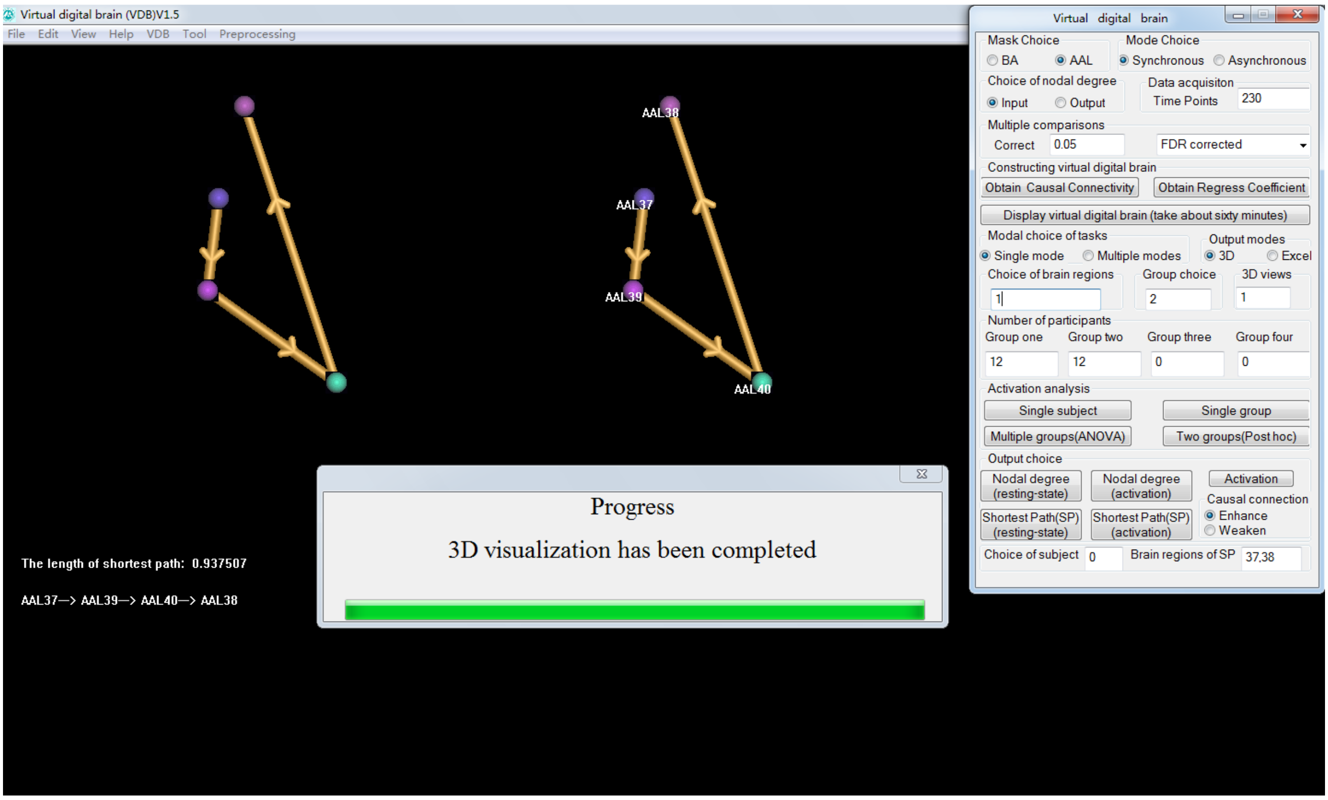


Figure 26A. 3D view of the resting-state shortest path between brain regions

In figure 26A, the gold bar denotes the synchronous causality connectivity, and the light blue bar denotes the asynchronous causality connectivit

9. Obtain causal connectivity and nodal topological properties

1. Steps are shown in Figure 27.

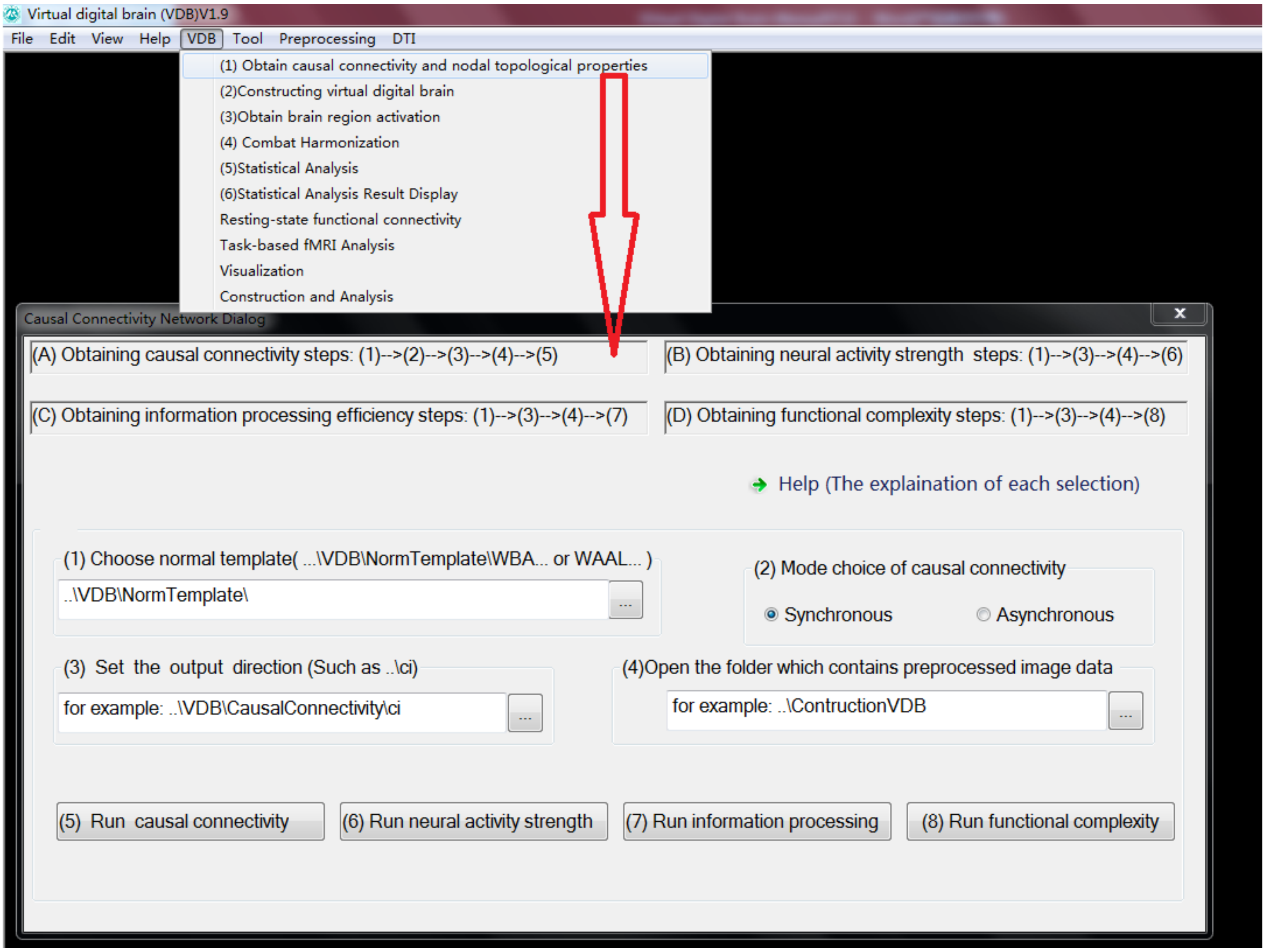


Figure 27 Dialog of obtaining causal connectivity and nodal topological properties

10. Constructing virtual digital brain

2. Steps are shown in Figure 28.

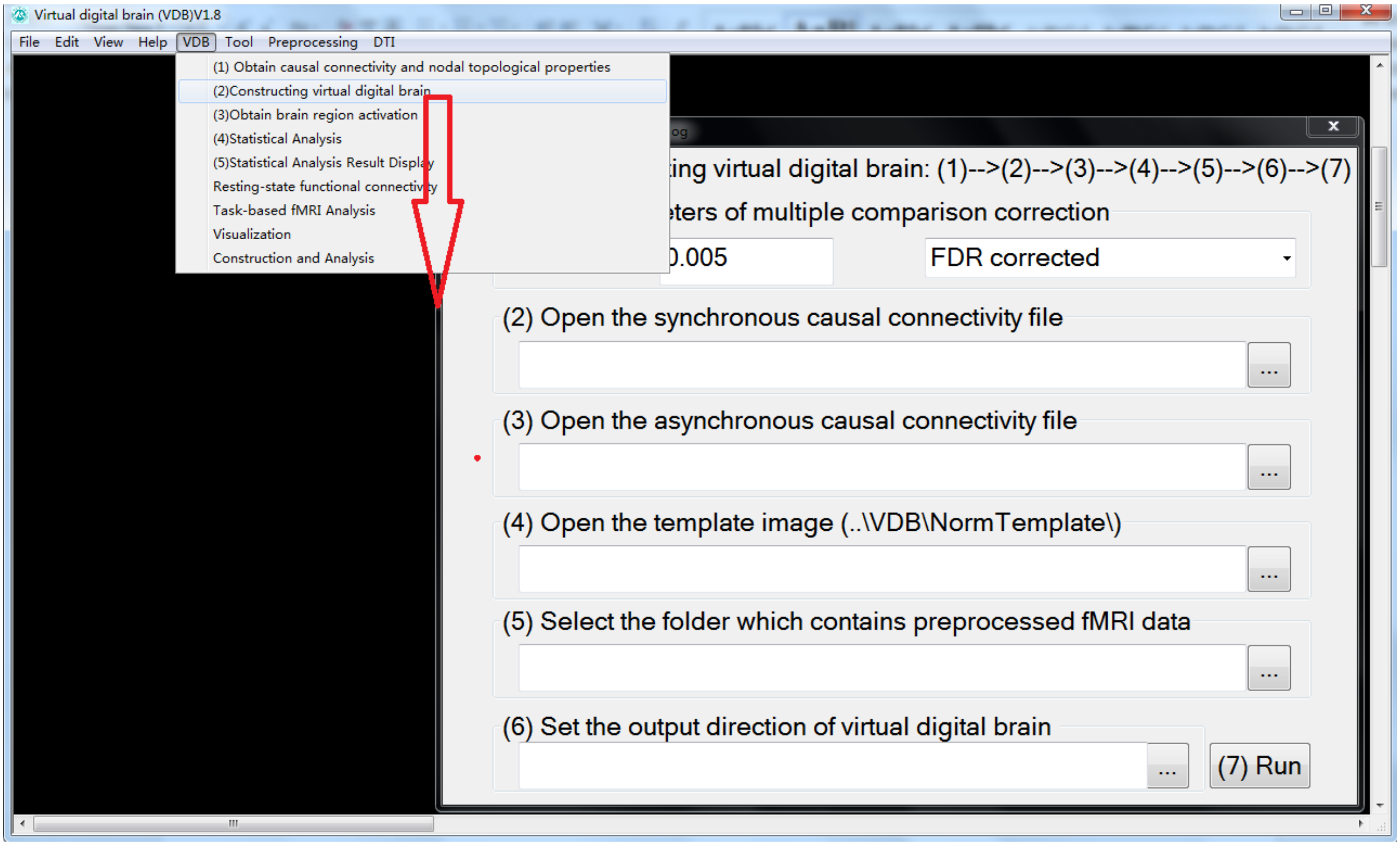


Figure 28 Dialog of constructing virtual digital brain

11. Obtain brain region activation

3. Steps are shown in Figure 29.

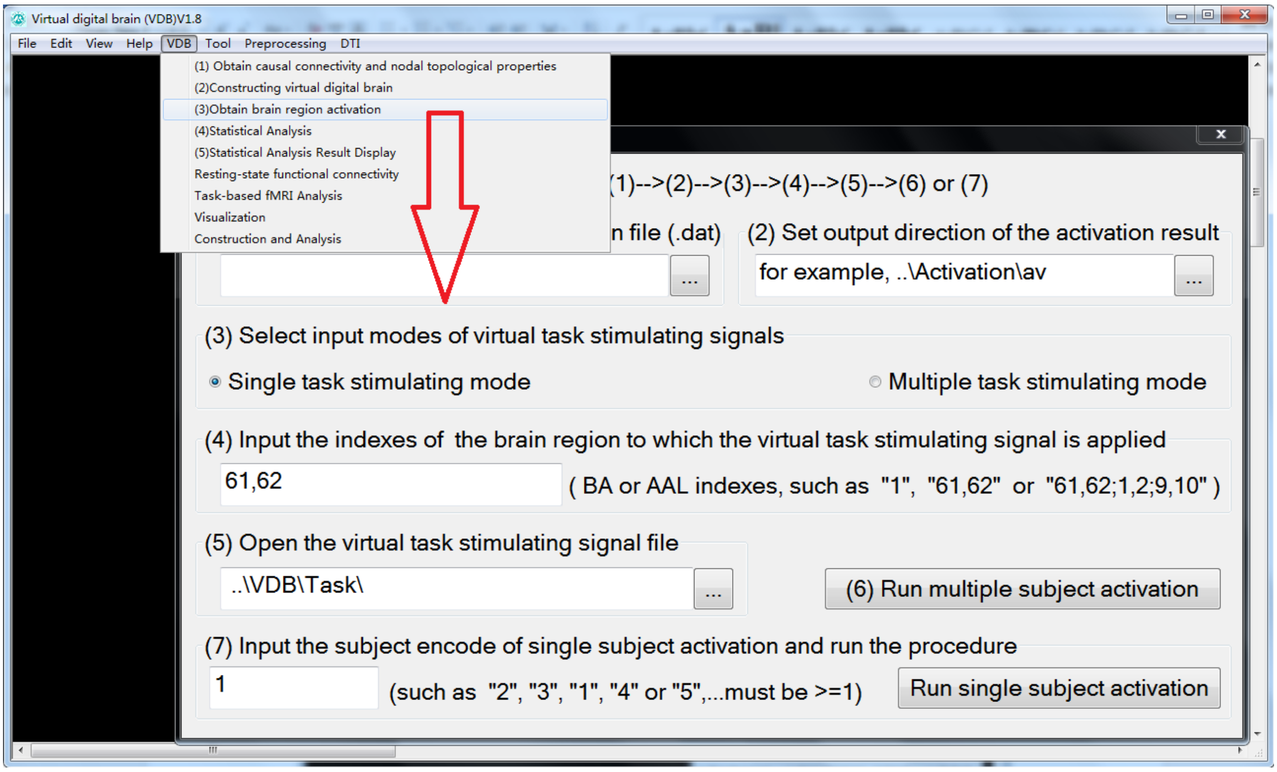


Figure 29 Dialog of obtaining brain region activation

12. Statistical Analysis

4. Steps are shown in Figure 30.

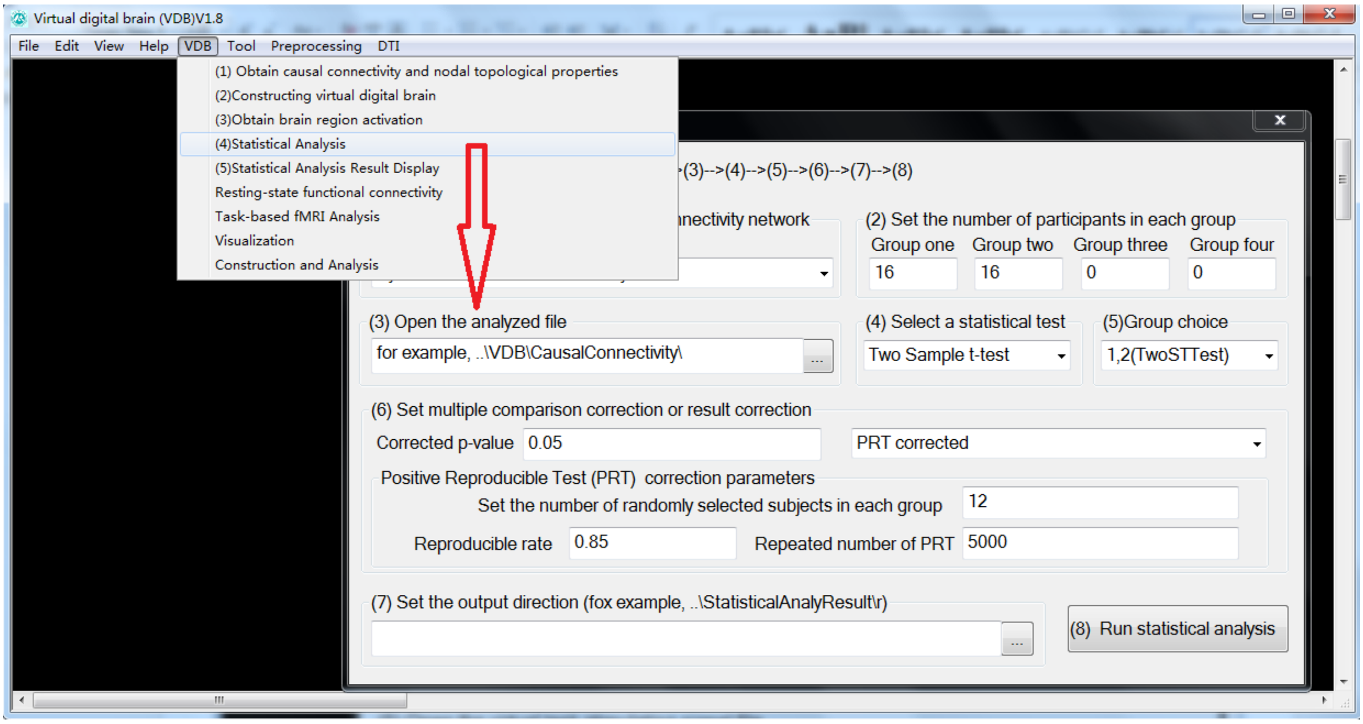


Figure 30 Dialog of statistical analysis

13. Statistical analysis result display

5. Steps are shown in Figure 31.

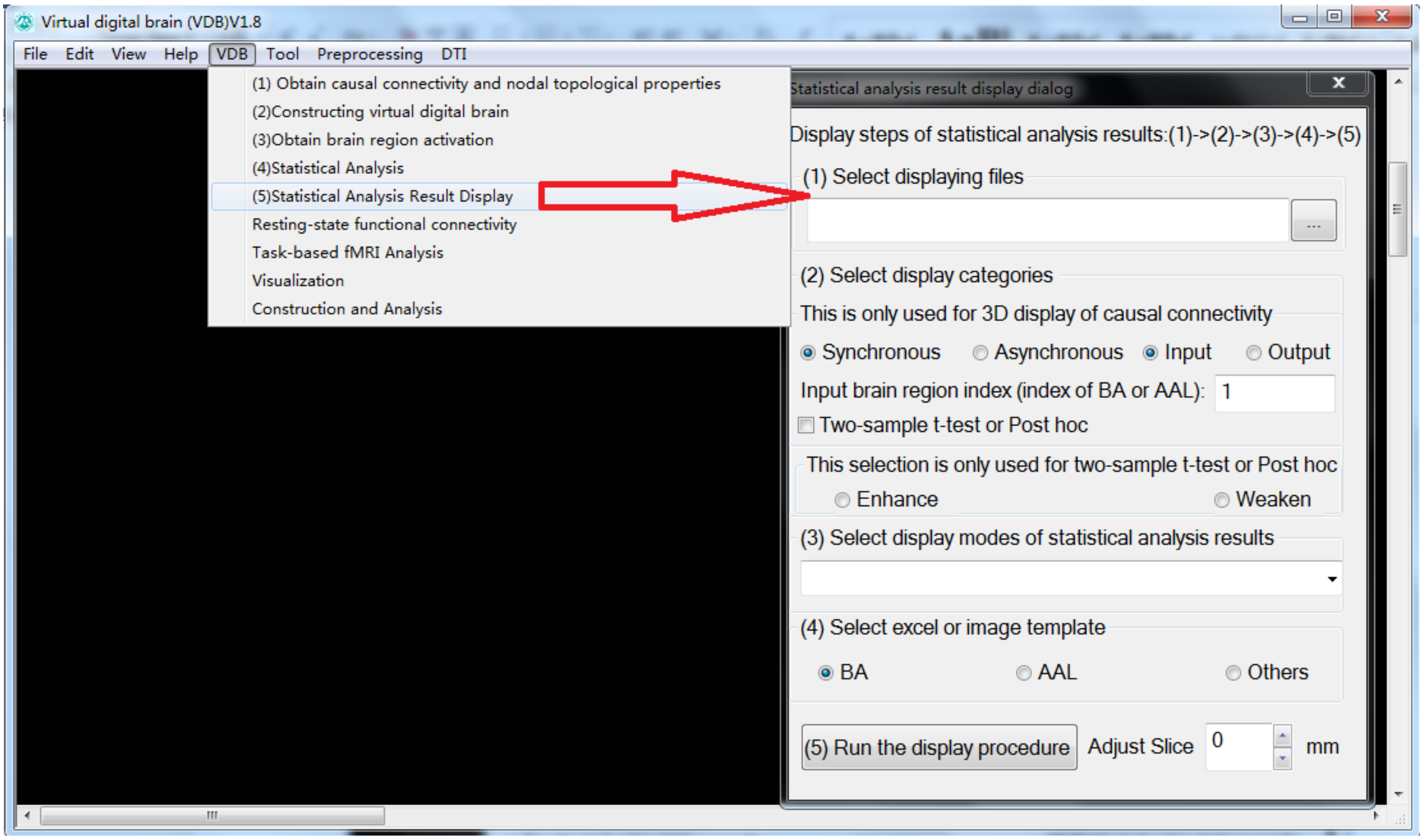


Figure 31 Dialog of statistical analysis result display