Online Appendix to

Alteration of individual metabolic network of brain based on Jensen-Shannon Divergence Similarity Estimation in the elderly with type 2 diabetes mellitus

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Supplemental Figure 1. Flow diagram showing images quality control. *PET*, positron emission tomography. *T2DM*, type 2 diabetes mellitus. *HCs*, healthy controls.

Supplemental Table 1. Baseline characteristics of all participants.

Baseline characteristics	elderly T2DM (n = 37)	elderly HCs (n = 32)	middle-aged T2DM (n = 34)	middle-aged HCs (n = 34)	<i>F</i>	<i>P</i>
HbA _{1c} (%)	7.20 ± 0.48	4.79 ± 0.51	6.99 ± 0.30	4.74 ± 0.48	312.078	< 0.001
HbA _{1c} (mmol/mol)	55.23 ± 5.21	28.81 ± 5.52	52.83 ± 3.32	28.26 ± 5.22	312.078	< 0.001

T2DM, type 2 diabetes mellitus. HCs, healthy controls.

Supplemental Table 2. The post-hoc analysis of SUV in the left triangle of inferior frontal gyrus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	<i>P</i>	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	3.282	0.213	0.076	0.219	-0.046	0.198
		T2DM	34	3.205	0.247				
	elderly	HCs	32	3.262	0.238	0.312	< 0.001	0.190	0.433
		T2DM	37	2.950	0.299				
aging	HCs	middle old	34	3.282	0.213	0.020	0.750	-0.104	0.144
		old	32	3.262	0.238				
	T2DM	middle old	34	3.205	0.247	0.256	< 0.001	0.136	0.375
		old	37	2.950	0.299				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 3. The post-hoc analysis of the strength of metabolic connectivity between the left triangle of inferior frontal gyrus and the left anterior cingulate cortex.

Factors	Levels	Contrasts	n	mean	SD	mean difference	<i>P</i>	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.035	0.008	-0.002	0.394	-0.008	0.003
		T2DM	34	0.037	0.010				
	elderly	HCs	32	0.033	0.007	-0.011	< 0.001	-0.016	-0.006
		T2DM	37	0.044	0.017				
aging	HCs	middle old	34	0.035	0.008	0.001	0.666	-0.004	0.007
		old	32	0.033	0.007				
	T2DM	middle old	34	0.037	0.010	-0.007	0.007	-0.013	-0.002
		old	37	0.044	0.017				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 4. The post-hoc analysis of the strength of metabolic connectivity between the left triangle of inferior frontal gyrus and the left middle cingulate cortex.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.034	0.009	-0.004	0.150	-0.009	0.001
		T2DM	34	0.038	0.011				
	elderly	HCs	32	0.035	0.009	-0.014	< 0.001	-0.019	-0.008
		T2DM	37	0.049	0.013				
aging	HCs	middle	34	0.034	0.009	-0.001	0.715	-0.006	0.004
		old	32	0.035	0.009				
	T2DM	middle	34	0.038	0.011	-0.011	< 0.001	-0.016	-0.006
		old	37	0.049	0.013				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 5. The post-hoc analysis of the strength of metabolic connectivity between the left triangle of inferior frontal gyrus and the right middle cingulate cortex.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.038	0.009	-0.005	0.136	-0.011	0.001
		T2DM	34	0.043	0.014				
	elderly	HCs	32	0.039	0.010	-0.014	<0.001	-0.020	-
		T2DM	37	0.053	0.016				
aging	HCs	middle	34	0.038	0.009	-0.001	0.744	-0.007	0.005
		old	32	0.039	0.010				
	T2DM	middle	34	0.043	0.014	-0.010	0.001	-0.016	-
		old	37	0.053	0.016				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 6. The post-hoc analysis of the strength of metabolic connectivity between the left triangle of inferior frontal gyrus and the left angular gyrus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.034	0.010	-0.001	0.628	-0.006	0.004
		T2DM	34	0.035	0.011				
	elderly	HCs	32	0.033	0.007	-0.009	< 0.001	-0.014	-0.004
		T2DM	37	0.042	0.011				
aging	HCs	middle	34	0.034	0.010	0.001	0.628	-0.004	0.006
		old	32	0.033	0.007				
	T2DM	middle	34	0.035	0.011	-0.007	0.004	-0.011	-0.002
		old	37	0.042	0.011				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 7. The post-hoc analysis of the strength of metabolic connectivity between the left triangle of inferior frontal gyrus and the left Heschl's gyrus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.051	0.014	-0.012	0.004	-0.020	-0.004
		T2DM	34	0.063	0.014				
	elderly	HCs	32	0.052	0.014	-0.031	< 0.001	-0.039	-0.023
		T2DM	37	0.083	0.023				
aging	HCs	middle	34	0.051	0.014	-0.001	0.850	-0.009	0.007
		old	32	0.052	0.014				
	T2DM	middle	34	0.063	0.014	-0.020	< 0.001	-0.028	-0.012
		old	37	0.083	0.023				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 8. The post-hoc analysis of the strength of metabolic connectivity between the left triangle of inferior frontal gyrus and the right Heschl's gyrus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.032	0.011	-0.010	0.002	-0.017	-0.004
		T2DM	34	0.042	0.014				
	elderly	HCs	32	0.035	0.014	-0.020	< 0.001	-0.026	-0.013
		T2DM	37	0.055	0.015				
aging	HCs	middle	34	0.032	0.011	-0.003	0.394	-0.009	0.004
		old	32	0.035	0.014				
	T2DM	middle	34	0.035	0.014	-0.012	< 0.001	-0.019	-0.006
		old	37	0.055	0.015				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 9. The abbreviations and full names of 90 AAL brain regions.

Number	Abbreviations	Full names
1	PreCG.L	Precentral gyrus
2	PreCG.R	Precentral gyrus
3	SFG.L	Superior frontal gyrus, dorsolateral
4	SFG.R.	Superior frontal gyrus, dorsolateral
5	SFGorb.L	Superior frontal gyrus, orbital part
6	SFGorb.R	Superior frontal gyrus, orbital part
7	MFG.L	Middle frontal gyrus
8	MFG.R	Middle frontal gyrus
9	MFGorb.L	Middle frontal gyrus, orbital part
10	MFGorb.R	Middle frontal gyrus, orbital part
11	IFGoper.L	Inferior frontal gyrus, opercular part
12	IFGoper.R	Inferior frontal gyrus, opercular part
13	IFGtri.L	Inferior frontal gyrus, triangular part
14	IFGtri.R	Inferior frontal gyrus, triangular part
15	IFGorb.L	Inferior frontal gyrus, orbital part
16	IFGorb.R	Inferior frontal gyrus, orbital part
17	ROL.L	Rolandic operculum
18	ROL.R	Rolandic operculum
19	SMA.L	Supplementary motor area
20	SMA.R	Supplementary motor area
21	OLF.L	Olfactory cortex

22	OLF.R	Olfactory cortex
23	SFGmed.L	Superior frontal gyrus, medial
24	SFGmed.R	Superior frontal gyrus, medial
25	SFGmorb.L	Superior frontal gyrus, medial orbital
26	SFGmorb.R	Superior frontal gyrus, medial orbital
27	REG.L	Gyrus rectus
28	REG.R	Gyrus rectus
29	INS.L	Insula
30	INS.R	Insula
31	ACC.L	Anterior cingulate and paracingulate gyri
32	ACC.R	Anterior cingulate and paracingulate gyri
33	MCC.L	Median cingulate and paracingulate gyri
34	MCC.R	Median cingulate and paracingulate gyri
35	PCC.L	Posterior cingulate gyrus
36	PCC.R	Posterior cingulate gyrus
37	HIP.L	Hippocampus
38	HIP.R	Hippocampus
39	PHIP.L	Parahippocampal gyrus
40	PHIP.R	Parahippocampal gyrus
41	AMYG.L	Amygdala
42	AMYG.R	Amygdala
43	CAL.L	Calcarine fissure and surrounding cortex
44	CAL.R	Calcarine fissure and surrounding cortex
45	CUN.L	Cuneus
46	CUN.R	Cuneus
47	LING.L	Lingual gyrus
48	LING.R	Lingual gyrus
49	SOG.L	Superior occipital gyrus
50	SOG.R	Superior occipital gyrus
51	MOG.L	Middle occipital gyrus
52	MOG.R	Middle occipital gyrus
53	IOG.L	Inferior occipital gyrus
54	IOG.R	Inferior occipital gyrus
55	FG.L	Fusiform gyrus
56	FG.R	Fusiform gyrus
57	PoCG.L	Postcentral gyrus
58	PoCG.R	Postcentral gyrus
59	SPG.L	Superior parietal gyrus

60	SPG.R	Superior parietal gyrus
61	IPG.L	Inferior parietal, but supramarginal and angular gyri
62	IPG.R	Inferior parietal, but supramarginal and angular gyri
63	SMG.L	Supramarginal gyrus
64	SMG.R	Supramarginal gyrus
65	ANG.L	Angular gyrus
66	ANG.R	Angular gyrus
67	PCUN.L	Precuneus
68	PCUN.R	Precuneus
69	PCL.L	Paracentral lobule
70	PCL.R	Paracentral lobule
71	CAU.L	Caudate nucleus
72	CAU.R	Caudate nucleus
73	PUT.L	Lenticular nucleus, putamen
74	PUT.R	Lenticular nucleus, putamen
75	PAL.L	Lenticular nucleus, pallidum
76	PAL.R	Lenticular nucleus, pallidum
77	THA.L	Thalamus
78	THA.R	Thalamus
79	HES.L	Heschl gyrus
80	HES.R	Heschl gyrus
81	STG.L	Superior temporal gyrus
82	STG.R	Superior temporal gyrus
83	STGp.L	Temporal pole: superior temporal gyrus
84	STGp.R	Temporal pole: superior temporal gyrus
85	MTG.L	Middle temporal gyrus
86	MTG.R	Middle temporal gyrus
87	MTGp.L	Temporal pole: middle temporal gyrus
88	MTGp.R	Temporal pole: middle temporal gyrus
89	ITG.L	Inferior temporal gyrus
90	ITG.R	Inferior temporal gyrus

Supplemental Table 10. The main effects of aging and T2DM on the topological properties of global network.

Topological properties of the global network	T2DM		aging	
	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
Clustering coefficient	-1.358	0.177	-1.209	0.229
Characteristic path length	1.643	0.103	0.455	0.650
Sigma	0.200	0.842	-1.563	0.120
Global efficiency	-1.893	0.060	-0.296	0.768
Local efficiency	-0.564	0.574	-1.442	0.151
Assortativity	4.452	< 0.001	-1.935	0.055
Synchronization	-0.559	0.577	-1.645	0.102
Hierarchy	-1.935	0.055	0.116	0.908

T2DM, type 2 diabetes mellitus.

Supplemental Table 11. The main effect of T2DM on the global assortativity.

Factors	Levels	n	mean	SD	mean difference	<i>P</i>	95% CI	
							Upper	Lower
T2DM	HCs	66	-9.309	1.406	1.366	< 0.001	0.759	1.973
	T2DM	71	-10.675	2.092				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 12. The post-hoc analysis of the degree centrality of the left putamen.

Factors	Levels	Contrasts	n	mean	SD	mean difference	<i>P</i>	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	5.553	1.715	-0.565	0.196	-1.424	0.295
		T2DM	34	6.118	2.316				
	elderly	HCs	32	5.357	1.854	0.750	0.085	-0.105	1.605
		T2DM	37	4.607	1.133				
aging	HCs	middle	34	5.553	1.715	0.196	0.658	-0.677	1.069
		old	32	5.357	1.854				
	T2DM	middle	34	6.118	2.316	1.511	0.001	0.699	2.353
		old	37	4.607	1.133				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 13. The post-hoc analysis of the efficiency of the left anterior cingulate cortex.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.244	0.022	0.004	0.391	-0.006	0.015
		T2DM	34	0.240	0.016				
	elderly	HCs	32	0.240	0.021	-0.015	0.004	-0.025	-0.005
		T2DM	37	0.255	0.025				
aging	HCs	middle	34	0.244	0.022	0.005	0.355	-0.005	0.015
		old	32	0.240	0.021				
	T2DM	middle	34	0.240	0.016	-0.015	0.004	-0.025	-0.005
		old	37	0.255	0.025				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 14. The post-hoc analysis of the local efficiency of the right medial superior frontal gyrus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.327	0.028	0.008	0.348	-0.008	0.024
		T2DM	34	0.320	0.039				
	elderly	HCs	32	0.323	0.032	-0.016	0.051	-0.032	0
		T2DM	37	0.338	0.033				
aging	HCs	middle	34	0.327	0.028	0.005	0.568	-0.012	0.021
		old	32	0.323	0.032				
	T2DM	middle	34	0.320	0.039	-0.019	0.019	-0.034	-0.003
		old	37	0.338	0.033				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 15. The post-hoc analysis of the local efficiency of the left calcarine.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.314	0.027	0.012	0.128	-0.003	0.027
		T2DM	34	0.303	0.033				
	elderly	HCs	32	0.312	0.030	-0.012	0.120	-0.027	0.003
		T2DM	37	0.324	0.036				
aging	HCs	middle	34	0.314	0.027	0.002	0.777	-0.013	0.018
		old	32	0.312	0.030				
	T2DM	middle	34	0.303	0.033	-0.022	0.005	-0.036	-0.007
		old	37	0.324	0.036				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 16. The post-hoc analysis of the local efficiency of the right precuneus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.328	0.034	0.008	0.367	-0.009	0.024
		T2DM	34	0.320	0.031				
	elderly	HCs	32	0.323	0.039	-0.016	0.059	-0.032	0.001
		T2DM	37	0.338	0.034				
aging	HCs	middle	34	0.328	0.034	0.005	0.530	-0.011	0.022
		old	32	0.323	0.039				
	T2DM	middle	34	0.320	0.031	-0.018	0.029	-0.034	-0.002
		old	37	0.338	0.034				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Table 17. The post-hoc analysis of the local efficiency of the left thalamus.

Factors	Levels	Contrasts	n	mean	SD	mean difference	P	95% CI	
								Lower	Upper
T2DM	middle-aged	HCs	34	0.299	0.038	0.003	0.768	-0.019	0.026
		T2DM	34	0.295	0.058				
	elderly	HCs	32	0.294	0.040	-0.035	0.002	-0.057	-0.013
		T2DM	37	0.329	0.047				
aging	HCs	middle	34	0.299	0.038	0.005	0.658	-0.018	0.028
		old	32	0.294	0.040				
	T2DM	middle	34	0.295	0.058	-0.034	0.003	-0.055	-0.012
		old	37	0.329	0.047				

T2DM, type 2 diabetes mellitus. HCs, healthy controls. SD, standard deviation. CI, confidence interval.

Supplemental Figure 2. Negative correlations between the glucose metabolism in the left triangle of the inferior frontal gyrus and age, fasting plasma glucose. The glucose metabolism in the left triangle of the inferior frontal gyrus was negatively correlated with (A) age ($r = -0.198$, $P = 0.021$) and (B) FPG ($r = -0.412$, $P < 0.001$), respectively. IFGtri, triangle of inferior frontal gyrus. L, left.

Supplemental Figure 3. Positive correlation between the strength of metabolic connectivity and fasting plasma glucose. The strength of metabolic connectivity between IFGtri.L and six brain regions including (A) MCC.L; (B) MCC.R; (C) HES.L; (D) HES.R; (E) ACC.L; (F) ANG.L had positive correlations with fasting plasma glucose (all $P < 0.001$). *IFGtri*, triangle of inferior frontal gyrus. *ACC*, anterior cingulate cortex. *MCC*, middle cingulate cortex. *ANG*, angular gyrus. *HES*, Heschl's gyrus. *L*, left. *R*, right.

Supplemental Figure 4. Positive correlation between the strength of metabolic connectivity and age. The strength of metabolic connectivity between IFGtri.L and four brain regions including (A) MCC.L; (B) MCC.R; (C) HES.L; (D) HES.R had positive correlations with age (all $P < 0.05$). And the strength of metabolic connectivity between IFGtri.L and two brain regions including (E) ACC.L and (F) ANG.L had no correlation with age. *IFGtri*, triangle of inferior frontal gyrus. *ACC*, anterior cingulate cortex. *MCC*, middle cingulate cortex. *ANG*, angular gyrus. *HES*, Heschl's gyrus. *L*, left. *R*, right.