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

Yu-Lin Li, M.D.¹*, Jia-Jia Wu, M.D., Ph.D.²*, Jie Ma, M.D.¹, Si-Si Li, M.D.¹, Xin Xue, M.D.¹, Dong Wei, M.D.¹, Chun-Lei Shan, M.D., Ph.D.¹²⁴, Xu-Yun Hua, M.D., Ph.D.³#, Mou-Xiong Zheng, M.D., Ph.D.³#, Jian-Guang Xu, M.D., Ph.D.^{1,2}#

- School of Rehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, China.
- Department of Rehabilitation Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.
- Department of Traumatology and Orthopedics, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.
- 4. Engineering Research Center of Traditional Chinese Medicine Intelligent Rehabilitation, Ministry of Education, Shanghai, China.

* First author

Corresponding authors



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

Baseline characteristics	elderly T2DM (n = 37)	elderly HCs (n = 32)	middle-aged T2DM (n = 34)	middle-aged HCs (n = 34)	F	Р
HbA _{1c} (%)	7.20 ± 0.48	4.79 ± 0.51	6.99 ± 0.30	4.74 ± 0.48	312.078	< 0.001
HbA _{1c}	55 23 + 5 21	28 81 + 5 52	52 83 + 3 32	28 26 ± 5 22	312 078	< 0.001
(mmol/mol)	33.23 ± 3.21	20.01 ± 3.32	52.05 ± 5.52	20.20 ± 3.22	512.078	< 0,001

Supplemental Table 1. Baseline characteristics of all participants.

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	T	s Contrasts			SD	mean	מ	95% CI	
	Levels		n	mean		difference	Ρ	Lower	Upper
T2DM	middle-	HCs	34	3.282	0.213	0.076	0.210	0.046	0.198
	aged	T2DM	34	3.205	0.247	0.070	0.219	-0.040	
	elderly	HCs	32	3.262	0.238	0.312	< 0.001	0 100	0 422
		T2DM	37	2.950	0.299			0.190	0.433
		middle	34	3.282	0.213	0.020	0.750	0 104	0 1 4 4
aging	HCS	old	32	3.262	0.238		0.750	-0.104	0.144
	T2DM	middle	34	3.205	0.247	0.256	< 0.001	0.126	0 275
		old	37	2.950	0.299			0.130	0.5/5

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	C			CD	mean	מ	95% CI		
	Contrasts	n	mean	5D	difference	P	Lower	Upper	
midd T2DM	middle-	HCs	34	0.035	0.008	0.002	0.204	0.000	0.003
	aged	T2DM	34	0.037	0.010	-0.002	0.394	-0.008	
	elderly	HCs	32	0.033	0.007	-0.011	< 0.001	-0.016	-0.006
		T2DM	37	0.044	0.017				
	ЦСа	middle	34	0.035	0.008	0.001	0 666	-0.004	0.007
aging T	пся	old	32	0.033	0.007		0.000		
		middle	34	0.037	0.010	-0.007	0.007	0.012	0.002
	12DM	old	37	0.044	0.017			-0.013	-0.002

						mean		95% CI	
Factors	Levels	Contrasts	n	mean	SD	differen ce	Р	Lower	Upper
	middle-	HCs	34	0.034	0.009				
T2DM	aged	T2DM	34	0.038	0.011	-0.004	0.150	-0.009	0.001
	11 1	HCs	32	0.035	0.009	-0.014	< 0.001	-0.019	-0.008
	elderly	T2DM	37	0.049	0.013				
	ЧСа	middle	34	0.034	0.009	0.001	0.715	0.006	0.004
aging	HUS	old	32	0.035	0.009	-0.001	0.713	-0.000	0.004
	T2DM	middle	34	0.038	0.011	-0.011	< 0.001	0.016	0.006
		old	37	0.049	0.013			-0.010	-0.000

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.

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 Lev	Lavala	Contrasts	n	maan	SD	mean	D	95%	6 CI
	Levels		Π	mean		difference	Γ	Lower	Upper
	middle-	HCs	34	0.038	0.009	0.005	0.136	0.011	0.001
тэрм	aged	T2DM	34	0.043	0.014	-0.003	0.130	-0.011	0.001
	elderly	HCs	32	0.039	0.010	-0.014	< 0.001	-0.020	-
		T2DM	37	0.053	0.016				0.008
	HCs	middle	34	0.038	0.009	-0.001	0 744	0.007	0.005
aging		old	32	0.039	0.010		0.744	-0.007	0.005
aging	T2DM	middle	34	0.043	0.014	-0.010	0.001	-0.016	-
		old	37	0.053	0.016				0.004

Factors Levels	т1.	C	n		CD	mean	л	95% CI	
	Levels	Contrasts		mean	5D	difference	P	Lower	Upper
mid T2DM	middle-	HCs	34	0.034	0.010	0.001	0.628	0.000	0.004
	aged	T2DM	34	0.035	0.011	-0.001	0.028	-0.000	
	elderly	HCs	32	0.033	0.007	-0.009	< 0.001	-0.014	-0.004
		T2DM	37	0.042	0.011				
	UСа	middle	34	0.034	034 0.010	0.628	0.004	0.006	
aging	пся	old	32	0.033	0.007	0.001	0.028	-0.004	0.006
	T2DM	middle	34	0.035	0.011	-0.007	0.004	0.011	0.002
		old	37	0.042	0.011			-0.011	-0.002

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.

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	Controata			CD	mean	ת	95% CI		
	Contrasts	n	mean	5D	difference	Р	Lower	Upper	
middle T2DM	middle-	HCs	34	0.051	0.014	0.012	0.004	0.020	-0.004
	aged	T2DM	34	0.063	0.014	-0.012	0.004	-0.020	
	elderly	HCs	32	0.052	0.014	-0.031	< 0.001	-0.039	-0.023
		T2DM	37	0.083	0.023				
	ЧСа	middle	34	0.051	0.014	-0.001	0.850	0.000	0.007
aging T	nes	old	32	0.052	0.014			-0.009	0.007
		middle	34	0.063	0.014	-0.020	< 0.001	0.020	0.012
	I ZDIVI	old	37	0.083	0.023			-0.028	-0.012

Factors Levels	τ1.				CD	mean	מ	95% CI	
	Contrasts	n	mean	5D	difference	Ρ	Lower	Upper	
middle T2DM	middle-	HCs	34	0.032	0.011	0.010	0.002	0.017	-0.004
	aged	T2DM	34	0.042	0.014	-0.010	0.002	-0.017	
	aldarly	HCs	32	0.035	0.014	-0.020	< 0.001	-0.026	-0.013
	elderly	T2DM	37	0.055	0.015				
	ЦСа	middle	34	0.032	0.011	-0.003	0.394	0.000	0.004
aging T2D	пся	old	32	0.035	0.014			-0.009	
		middle	34	0.035	0.014	-0.012	< 0.001	0.010	0.006
	I 2DM	old	37	0.055	0.015			-0.019	-0.000

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.

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					
(1		Inferior parietal, but supramarginal and					
01	IPG.L	angular gyri					
(2)		Inferior parietal, but supramarginal and					
62	IPG.K	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					

Topological properties	T2	DM	agi	ng
of the global network	F	Р	F	Р
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

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

T2DM, type 2 diabetes mellitus.

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

Factors	Lavala	12		SD	mean	מ	95% CI	
Factors	Levels	11	mean	SD	difference	Γ	Upper	Lower
T2DM	HCs	66	-9.309	1.406	1 266	< 0.001	0.750	1 072
	T2DM	71	-10.675	2.092	1.300	< 0.001	0.739	1.9/3

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

Supplement	al Table 12. '	The post-hoc a	analysis of the o	degree centrality	v of the left i	outamen.
~ approntent			•••••••••••••••••••••••••••••••••••••••		,	

						mean		95% CI	
Factors	Levels	Contrasts	n	mean	SD	differen	Р	Lower	Unnor
						ce		Lower	Opper
	middle-	HCs	34	5.553	1.715	0 565	0 106	1 424	0.205
T2DM	aged	T2DM	34	6.118	2.316	-0.363	0.190	-1.424	0.293
	elderly	HCs	32	5.357	1.854	0.750	0.085	-0.105	1.605
		T2DM	37	4.607	1.133				
	UC.	middle	34	5.553	1.715	0.107	0.658	0 (77	1.070
aging	HCS	old	32	5.357	1.854	0.190		-0.077	1.009
		middle	34	6.118	2.316	1.511	0.001	0.000	0 0 5 0
	12DM	old	37	4.607	1.133		0.001	0.099	2.355

Factors	T1.	Carterate	n	mean	SD	mean	ת	95% CI	
	Levels	Contrasts	n	mean	5D	difference	Ρ	Lower	Upper
n T2DM	middle-	HCs	34	0.244	0.022	0.004	0.201	0.006	0.015
	aged	T2DM	34	0.240	0.016	0.004	0.391	-0.000	
	elderly	HCs	32	0.240	0.021	0.015	0.004	-0.025	-0.005
		T2DM	37	0.255	0.025	-0.015			
	ИСа	middle	34	0.244	0.022	0.005	0 255	0.005	0.015
aging	псs	old	32	0.240	0.021	0.005	0.333	-0.003	
		middle	34	0.240	0.016	0.015	0.004	0.025	0.005
	12DM	old	37	0.255	0.025	-0.015	0.004	-0.023	-0.003

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

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

						mean		95%	6 CI
Factors	Levels	Contrasts	n	mean	SD	differen	Р	Lower	Unnor
						ce		Lower	Opper
	middle-	HCs	34	0.327	0.028	0.008	0 2 4 8	0.008	0.024
T2DM	aged	T2DM	34	0.320	0.039	0.008	0.340	-0.008	0.024
	elderly	HCs	32	0.323	0.032	-0.016	0.051	0.022	0
		T2DM	37	0.338	0.033			-0.032	0
		middle	34	0.327	0.028	0.005	05(0	0.010	0.021
aging	HCS	old	32	0.323	0.032	0.005	0.368	-0.012	0.021
		middle	34	0.320	0.039	0.010	0.010	0.004	0.002
	T2DM	old	37	0.338	0.033	-0.019	0.019	-0.034	-0.003

						mean		95% CI	
Factors	Levels	Contrasts	n	mean	SD	differen	Р	Louvon	Linnon
						ce		Lower	Opper
	middle-	HCs	34	0.314	0.027	0.012	0 1 2 9	0.003	0.027
T2DM	aged	T2DM	34	0.303	0.033	0.012	0.128	-0.003	0.027
	elderly	HCs	32	0.312	0.030	0.012	0.120	-0.027	0.003
		T2DM	37	0.324	0.036	-0.012			
	HCs	middle	34	0.314	0.027	0.002	0.777	0.012	0.010
aging		old	32	0.312	0.030	0.002		-0.015	0.018
		middle	34	0.303	0.033	0.022	0.022 0.005	0.026	0.007
	12DM	old	37	0.324	0.036	-0.022		-0.030	-0.007

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

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

		Contract				mean		95% CI	
Factors	Levels	Contrast	n	mean	SD	differen	Р	Tarran	I I.e.e.e.e.
		S				ce		Lower	Opper
	middle-	HCs	34	0.328	0.034	0.009	0 267	0.000	0.024
T2DM	aged	T2DM	34	0.320	0.031	0.008	0.307	-0.009	0.024
	elderly	HCs	32	0.323	0.039	-0.016	0.059	0.022	0.001
		T2DM	37	0.338	0.034			-0.032	0.001
		middle	34	0.328	0.034	0.005	0.520	0.011	0.022
aging	HCS	old	32	0.323	0.039	0.003	0.550	-0.011	0.022
	TODM	middle	34	0.320	0.031	0.019	0.020	0.024	0.002
	12DM	old	37	0.338	0.034	-0.018	018 0.029	-0.034	-0.002

						mean		95% CI	
Factors	Levels	Contrasts	n	n mean	SD	differen	P	Lower	Upper
_						ce			
	middle-	HCs	34	0.299	0.038	0.002 0.7(0		0.010	0.02(
T2DM	aged	T2DM	34	0.295	0.058	0.005	0.708	-0.019	0.020
	elderly	HCs	32	0.294	0.040	-0.035	0.002	-0.057	-0.013
		T2DM	37	0.329	0.047				
	HCs	middle	34	0.299	0.038	0.005	0 (50	0.010	0.029
aging		old	32	0.294	0.040	0.003	0.038	-0.018	0.028
		middle	34	0.295	0.058	0.024	0.002	0.055	0.010
	12DM	old	37	0.329	0.047	-0.034	0.003	-0.033	-0.012

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



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 (D) ACC.L and (E) 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.*