

Müller et al.

## **Increased thalamic resting state connectivity as a core driver of LSD-induced hallucinations**

### **Supporting Information**

#### **Supporting material and methods**

##### Participants

24 Subjects were recruited by advertisement and word of mouth. Exclusion criteria were age <25 or >65 years, pregnancy (as determined by urine test), nursing, hypertension (>140/90 mmHg) or hypotension (SBP<85 mmHg), cardiac or neurological disorders, use of contraindicated medication or medication that could interfere with effects of the study medication (as determined by medical history and general medical examination including ECG, blood chemistry and haematology), use of illicit drugs (except cannabis) >10 times or any time within the previous two months (as assessed by history and urine tests), smoking >10 cigarettes/day, history of drug dependence, personal or first degree relative with an axis I major psychiatric disorder (as determined by general medical history and a semi-structured interview for DSM-IV). Subjects received monetary compensation for their participation.

##### Study procedure

The study included a screening visit, two 25-hour test sessions and an end of study visit. The experimental sessions took place in a quiet standard patient room at the University Hospital of Basel, Switzerland. Study session dates were between December 2014 (first subject screened) and September 2015 (last end of study visit). Participants were monitored for adverse events during the study sessions and the end of study visit. Participants were instructed to abstain from any illicit drugs during the whole study period and additionally to

abstain from caffeine, chocolate and alcohol for at least 8 h before the sessions. Urine drug tests were performed before every study session. In women, pregnancy tests were performed prior to every session. Except for tetrahydrocannabinol, which can be detected for several weeks, detection of any other drug resulted in study exclusion. A light standardised breakfast was served at both sessions.

Table S1: Cumulative lifetime use by the included subjects of legal and illicit drugs

Nicotine		Stimulants	
No. of subjects with regular use	7/20	No. subjects with any use	5/20
Cigarettes per day (mean/SD/range)	1.85/3.44/0-10	Lifetime occasions (mean/SD/range)	0.45/0.83/0-2
Caffeine		Sedatives	
No. of subjects with regular use	19/20	No. subjects with any use	0/20
Units per day (mean/SD/range)	2.60/1.88/0-8	Lifetime occasions (mean/SD/range)	0/0/0
Alcohol		Psychedelics	
No. of subjects with regular use	20/20	No. subjects with any use	2/20
Units per week (mean/SD/range)	4.20/2.75/1-10	Lifetime occasions (mean/SD/range)	0.10/0/0-1
Cannabis		Opioids	
No. subjects with any use	14/20	No. subjects with any use	1/20
Lifetime occasions (mean/SD/range)	7.05/12.42/0-50	Lifetime occasions (mean/SD/range)	0.05/0.23/0-1
MDMA		Others	
No. subjects with any use	7/20	No. subjects with any use	0/20
Lifetime occasions (mean/SD/range)	0.85/1.44/0-3	Lifetime occasions (mean/SD/range)	0/0/0

## Drugs and randomisation

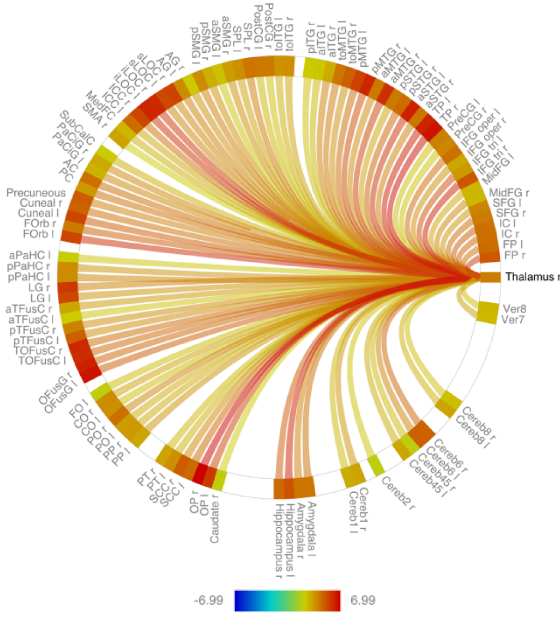
Gelatin capsules containing 100 µg D-lysergic acid diethylamide (Lipomed AG, Arlesheim, Switzerland) and identical capsules containing mannitol were prepared. Each subject received either placebo or LSD on two study sessions in a balanced manner. Only the person dispensing the capsules (who was not further involved in conducting the study) was aware of the treatment assignment. Subjects and study personnel monitoring the sessions were blind to the treatment order.

## Assessments of subjective drug effects and plasma levels

The 5D-ASC consists of 94 items, that measure the following five major dimensions and their corresponding subscales (in brackets): “Oceanic boundlessness” (“experience of unity”, “spiritual experience”, “blissful state”, “insightfulness”), “anxious ego dissolution” (“disembodiment”, “impaired control” and “cognition”, “anxiety”), “visionary restructuralization” (“complex imagery”, “elementary imagery”, “audio-visual synthaesia”, “changed meaning of percepts”), “auditory alterations”, and “reduction of vigilance” (both without subscales).

# Supporting results

**A**  
LSD > Placebo



**B**  
LSD > Placebo

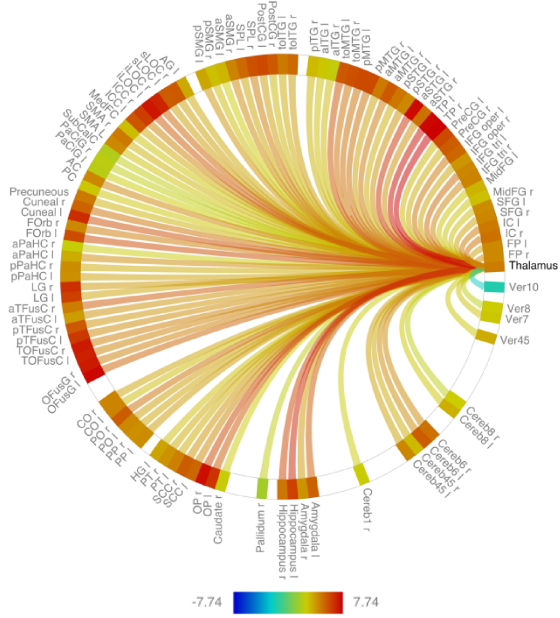


Figure S1: Connectome ring showing the results of the ROI-to-ROI-analysis using the right (A) and left (B) thalamus as sources and ROIs covering the whole brain as targets (see Table S2 for ROI labels). Results are corrected for multiple comparisons across all ROI-pairs ( $p < 0.05$ , FDR). The colour bar represents the t value.

Table S2: Results of the ROI-to-ROI analysis using the right and left thalamus as seeds and ROIs covering the whole brain as targets. Results are corrected for multiple comparisons across all ROI-pairs (2x130,  $p < 0.05$ , FDR).

		Right thalamus		Left thalamus	
Abbreviation	Full description	t	p, FDR	t	p, FDR
AC	Cingulate Gyrus, anterior division	4.62	0.0009	4.46	0.0011
Accumbens l	-	-	-	-	-
Accumbens r	-	-	-	-	-
AG l	Angular Gyrus Left	4.13	0.0018	3.57	0.0041
AG r	Angular Gyrus Right	3.75	0.0031	-	-
aITG l	Inferior Temporal Gyrus, anterior division Left	2.95	0.013	2.99	0.0121
aITG r	Inferior Temporal Gyrus, anterior division Right	4.14	0.0018	3.16	0.0088
aMTG l	Middle Temporal Gyrus, anterior division Left	3.84	0.0027	3.72	0.0032
aMTG r	Middle Temporal Gyrus, anterior division Right	5.64	0.0003	4.73	0.0008
Amygdala l	-	4.54	0.001	5.53	0.0003
Amygdala r	-	4.14	0.0018	3.91	0.0024
aPaHC l	Parahippocampal Gyrus, anterior division Left	2.61	0.0237	4.26	0.0015
aPaHC r	Parahippocampal Gyrus, anterior division Right			2.49	0.0302
aSMG l	Supramarginal Gyrus, anterior division Left	2.64	0.0225	2.66	0.0221
aSMG r	Supramarginal Gyrus, anterior division Right	3.78	0.003	4.31	0.0014
aSTG l	Superior Temporal Gyrus, anterior division Left	5.91	0.0002	6.52	0.0001
aSTG r	Superior Temporal Gyrus, anterior division Right	4.2	0.0017	4.12	0.0018
aTFusC l	Temporal Fusiform Cortex, anterior division Left	2.63	0.023	4.15	0.0017
aTFusC r	Temporal Fusiform Cortex, anterior division Right	3.62	0.0038	5.53	0.0003
Brain-Stem	-	-	-	-	-
Caudate l	-	-	-	-	-
Caudate r	-	2.44	0.0331	2.65	0.0223
Cereb1 l	Cerebellum Crus1 Left	2.89	0.0144	-	-
Cereb1 r	Cerebellum Crus1 Right	3.66	0.0035	-	-
Cereb10 l	Cerebellum 10 Left	-	-	-	-
Cereb10 r	Cerebellum 10 Right	-	-	-	-
Cereb2 l	Cerebellum Crus2 Left	-	-	-	-
Cereb2 r	Cerebellum Crus2 Right	2.63	0.0229		
Cereb3 l	Cerebellum 3 Left	-	-	-	-
Cereb3 r	Cerebellum 3 Right	-	-	-	-
Cereb45 l	Cerebellum 4 5 Left	3.19	0.0085	3.72	0.0032

Cereb45 r	Cerebellum 4 5 Right	2.87	0.0149	3.47	0.005
Cereb6 l	Cerebellum 6 Left	4.12	0.0018	4.28	0.0014
Cereb6 r	Cerebellum 6 Right	4.72	0.0008	4.35	0.0013
Cereb7 l	Cerebellum 7b Left	-	-	-	-
Cereb7 r	Cerebellum 7b Right	-	-	-	-
Cereb8 l	Cerebellum 8 Left	3.05	0.0108	2.8	0.0169
Cereb8 r	Cerebellum 8 Right	2.74	0.0188	2.24	0.0484
Cereb9 l	Cerebellum 9 Left	-	-	-	-
Cereb9 r	Cerebellum 9 Right	-	-	-	-
CO l	Central Opercular Cortex Left	2.81	0.0169	3.07	0.0105
CO r	Central Opercular Cortex Right	3.34	0.0062	3.65	0.0035
Cuneal l	Cuneal Cortex Left	4.97	0.0006	5.83	0.0002
Cuneal r	Cuneal Cortex Right	4.54	0.001	4.9	0.0007
FO l	Frontal Operculum Cortex Left	2.8	0.0169	-	-
FO r	Frontal Operculum Cortex Right	-	-	-	-
FOrb l	Frontal Orbital Cortex Left	6.02	0.0002	5.9	0.0002
FOrb r	Frontal Orbital Cortex Right	4.92	0.0006	4.71	0.0008
FP l	Frontal Pole Left	4.54	0.001	3.77	0.0031
FP r	Frontal Pole Right	5.83	0.0002	4.33	0.0014
HG l	Heschl's Gyrus Left	-	-	-	-
HG r	Heschl's Gyrus Right	-	-	-	-
Hippocampus l	-	6.37	0.0001	6.88	0.0001
Hippocampus r	-	4.98	0.0006	5.97	0.0002
IC l	Insular Cortex Left	4.88	0.0007	4.68	0.0009
IC r	Insular Cortex Right	4.75	0.0008	4.99	0.0006
ICC l	Intracalcarine Cortex Left	3.25	0.0074	3.5	0.0048
ICC r	Intracalcarine Cortex Right	4.44	0.0011	-	-
IFG oper l	Inferior Frontal Gyrus, pars opercularis Left	4.7	0.0008	-	-
IFG oper r	Inferior Frontal Gyrus, pars opercularis Right	3.82	0.0028	3.61	0.0038
IFG tri l	Inferior Frontal Gyrus, pars triangularis Left	5.24	0.0004	5.11	0.0005
IFG tri r	Inferior Frontal Gyrus, pars triangularis Right	6.28	0.0001	4.46	0.0011
iLOC l	Lateral Occipital Cortex, inferior division Left	5.87	0.0002	5.51	0.0003
iLOC r	Lateral Occipital Cortex, inferior division Right	5.77	0.0002	5.23	0.0004
LG l	Lingual Gyrus Left	3.76	0.0031	3.68	0.0034
LG r	Lingual Gyrus Right	4.17	0.0017	3.98	0.0022
MedFC	Frontal Medial Cortex	3.06	0.0107	2.86	0.0153
MidFG l	Middle Frontal Gyrus Left	3.33	0.0064	2.94	0.0134
MidFG r	Middle Frontal Gyrus Right	4.06	0.0019	2.83	0.0163
OFusG l	Occipital Fusiform Gyrus Left	4.96	0.0006	5.26	0.0004
OFusG r	Occipital Fusiform Gyrus Right	4.81	0.0007	4.62	0.0009
OP l	Occipital Pole Left	5.47	0.0003	5.53	0.0003
OP r	Occipital Pole Right	6.99	0.0001	5.96	0.0002
PaCiG l	Paracingulate Gyrus Left	4.03	0.002	2.62	0.0233

PaCiG r	Paracingulate Gyrus Right	4.02	0.002	2.36	0.0386
Pallidum l	-	-	-	2.32	0.0418
Pallidum r	-	-	-	-	-
PC	Cingulate Gyrus, posterior division	4.51	0.001	2.78	0.0173
pITG l	Inferior Temporal Gyrus, posterior division Left	-	-	-	-
pITG r	Inferior Temporal Gyrus, posterior division Right	2.71	0.02	3.35	0.0061
pMTG l	Middle Temporal Gyrus, posterior division Left	4.61	0.0009	4.98	0.0006
pMTG r	Middle Temporal Gyrus, posterior division Right	5.31	0.0004	5.02	0.0006
PO l	Parietal Operculum Cortex Left	3.18	0.0085	3.83	0.0028
PO r	Parietal Operculum Cortex Right	4.06	0.0019	4.99	0.0006
PostCG l	Postcentral Gyrus Left	2.92	0.0138	3.79	0.003
PostCG r	Postcentral Gyrus Right	2.74	0.0188	3.25	0.0075
PP l	Planum Polare Left	3.75	0.0031	3.92	0.0024
PP r	Planum Polare Right	3.15	0.0089	3.66	0.0035
pPaHC l	Parahippocampal Gyrus, posterior division Left	4.09	0.0019	3.74	0.0031
pPaHC r	Parahippocampal Gyrus, posterior division Right	3.71	0.0032	3.45	0.0052
PreCG l	Precentral Gyrus Left	2.69	0.0209	3.24	0.0075
PreCG r	Precentral Gyrus Right	2.63	0.0229	3.48	0.0049
Precuneous	Precuneous Cortex	4.17	0.0017	3.34	0.0062
pSMG l	Supramarginal Gyrus, posterior division Left	4.17	0.0017	4.03	0.002
pSMG r	Supramarginal Gyrus, posterior division Right	3.71	0.0033	3.06	0.0108
pSTG l	Superior Temporal Gyrus, posterior division Left	3.27	0.0072	3.39	0.0058
pSTG r	Superior Temporal Gyrus, posterior division Right	4.81	0.0007	4.11	0.0018
PT l	Planum Temporale Left	3.03	0.0114	3.44	0.0053
PT r	Planum Temporale Right	2.89	0.0146	3.48	0.0049
pTFusC l	Temporal Fusiform Cortex, posterior division Left	3.93	0.0024	4.29	0.0014
pTFusC r	Temporal Fusiform Cortex, posterior division Right	3.86	0.0026	4.01	0.002
Putamen l	-	-	-	-	-
Putamen r	-	-	-	-	-
SCC l	Supracalcarine Cortex Left	4.64	0.0009	4.33	0.0014
SCC r	Supracalcarine Cortex Right	3.97	0.0022	4.03	0.002
SFG l	Superior Frontal Gyrus Left	3.65	0.0035	3.02	0.0114
SFG r	Superior Frontal Gyrus Right	4.64	0.0009	3.75	0.0031
sLOC l	Lateral Occipital Cortex, superior division Left	4.06	0.0019	3.84	0.0027
sLOC r	Lateral Occipital Cortex, superior division Right	4.05	0.0019	3.82	0.0028
SMA l	Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex- Left	-	-	2.92	0.0138

SMA r	Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex -Right	2.44	0.0334	3.36	0.0061
SPL l	Superior Parietal Lobule Left	3.39	0.0058	3.66	0.0035
SPL r	Superior Parietal Lobule Right	4.25	0.0015	4.66	0.0009
SubCalC	Subcallosal Cortex	3.06	0.0107	2.25	0.0484
Thalamus l	-	-	-	-	-
Thalamus r	-	-	-	-	-
TOFusC l	Temporal Occipital Fusiform Cortex Left	4.7	0.0008	4.53	0.001
TOFusC r	Temporal Occipital Fusiform Cortex Right	4.58	0.0009	4.6	0.0009
toITG l	Inferior Temporal Gyrus, temporo-occipital part Left	3.17	0.0086	3.49	0.0048
toITG r	Inferior Temporal Gyrus, temporo-occipital part Right	3.37	0.006	3.9	0.0025
toMTG l	Middle Temporal Gyrus, temporo-occipital part Left	4.28	0.0014	5.62	0.0003
toMTG r	Middle Temporal Gyrus, temporo-occipital part Right	3.7	0.0033	4.95	0.0006
TP l	Temporal Pole Left	6.31	0.0001	7.35	0.0001
TP r	Temporal Pole Right	6.73	0.0001	7.74	0.0001
Ver10	Vermis 10	-	-	-2.32	0.0422
Ver12	Vermis 1 2	-	-	-	-
Ver3	Vermis 3	-	-	-	-
Ver45	Vermis 4 5			2.79	0.0173
Ver6	Vermis 6	-	-	-	-
Ver7	Vermis 7	3.44	0.0053	2.92	0.0137
Ver8	Vermis 8	2.79	0.0172	2.24	0.0487
Ver9	Vermis 9	-	-	-	-



Table S3: Results of the ROI-to-voxel using the bilateral thalamus as seed (cluster-size corrected ( $p < 0.05$ , FDR) on the basis of a cluster-forming threshold of  $p < 0.05$ , FDR).

Cluster	Size (voxels)	MNI <sub>max</sub>	cluster p-FDR	Regions (percent coverage of cluster, cluster size)
1	25333	-32, -84, 0	0	iLOC r (61, 1254), sLOC r (25, 1216), OP r (49, 1214), sLOC l (23, 1128), OP l (4, 1055), iLOC l (5, 1026), TP r (38, 907), LG r (47, 816), OFusG r (77, 681), TP l (28, 661), OFusG l (63, 586), Precuneous (09, 500), pMTG l (36, 499), TOFusC r (58, 474), pMTG r (3, 408), FOrb l (24, 400), ICC r (5, 379), FP r (05, 369), Cuneal r (55, 350), LG l (21, 318), TOFusC l (49, 317), Cuneal l (61, 315), Hippocampus l (41, 310), toMTG r (27, 308), IFG tri Right) (52, 286), toMTG l (31, 268), AG l (26, 250), Cereb6 r (16, 249), aSTG l (8, 225), IFG oper Left) (29, 222), FOrb r (15, 222), pTFusC l (25, 216), IFG tri Left) (32, 211), Hippocampus r (28, 193), IC l (14, 191), pTFusC r (26, 185), aMTG r (43, 175), FP l (02, 173), IC r (11, 150), aMTG l (31, 139), AG r (09, 131), Amygdala r (34, 117), pSMG l (1, 105), Cereb6 l (08, 104), Amygdala l (31, 103), toITG r (13, 102), PC (Cingulate (04, 100), ICC l (15, 95), aSTG r (33, 91), PP l (25, 89), pSTG r (21, 87), toITG l (12, 85), aTFusC r (28, 81), SCC r (55, 79), pSTG l (2, 78), PP r (2, 74), pPaHC r (2, 64), IFG oper Right) (08, 57), alTG r (17, 56), Cereb45 l (06, 51), aSMG l (05, 47), pPaHC l (11, 43), pITG r (04, 41), pSMG r (03, 40), Cereb45 r (06, 38), Cereb1 r (01, 32), PO l (05, 30), SCC l (38, 28), MidFG l (01, 27), alTG l (07, 25), FO l (06, 23), Thalamus l (02, 22), pITG l (02, 21), CO r (02, 21), CO l (02, 19), MidFG r (01, 18), Cereb1 l (01, 18), Thalamus r (01, 17), Putamen r (01, 10), aPaHC r (01, 8), aPaHC l (01, 8), PT l (01, 8), PreCG l (0, 7), Brain-Stem (0, 4), HG l (01, 3), Ver45 (Vermis (0, 3), SubCalC (Subcallosal (0, 2), Putamen l (0, 1), not-labelled (01, 4174)
2	820	36, -42, 60	0	PostCG r (12, 383), SPL r (21, 309), sLOC r (01, 37), PreCG r (0, 3), pSMG r (0, 2), not-labelled (0, 86)
3	684	-50, 0, 48	0	PreCG l (07, 298), PostCG l (05, 196), MidFG l (06, 183), aSMG l (0, 1), not-labelled (0, 6)

4	626	-26, 68, -2	0	FP I (04, 245), MedFC (Frontal (17, 165), FP r (01, 109), PaCiG r (0, 4), PaCiG I (0, 4), not-labelled (0, 99)
5	562	-28, -42, 52	0	PostCG I (07, 256), SPL I (1, 152), PreCG I (01, 31), not-labelled (0, 123)
6	442	40, -2, 56	0	PreCG r (07, 287), MidFG r (01, 33), SFG r (01, 26), PostCG r (01, 17), not-labelled (0, 79)
7	432	54, -20, 26	0	aSMG r (21, 169), PO r (29, 155), PostCG r (01, 41), PT r (04, 16), CO r (01, 12), not-labelled (0, 39)
8	278	18, 54, 36	0.000002	FP r (01, 92), PaCiG r (06, 88), SFG r (02, 64), SFG I (0, 4), not-labelled (0, 30)
9	241	-8, 74, 12	0.00001	FP I (02, 119), FP r (01, 49), PaCiG I (01, 9), not-labelled (0, 64)
10	209	-18, 18, -12	0.000033	FOrb I (02, 42), SubCalC (Subcallosal (01, 7), Caudate I (0, 2), Accumbens I (01, 1), not-labelled (0, 157)
11	158	-20, 4, -44	0.000298	TP I (02, 57), aPaHC I (09, 50), aTFusC I (09, 27), not-labeled (0, 24), pSMG r (0, 2), not-labelled (0, 86)
12	134	-4, -38, 44	0.000875	PC (Cingulate (03, 73), Precuneous (01, 33), PreCG I (0, 9), PostCG I (0, 7), not-labelled (0, 12)
13	131	-2, -20, 10	0.000939	Thalamus I (03, 46), Thalamus r (02, 29), not-labelled (0, 56)
14	126	16, 68, 16	0.001122	FP r (01, 118), not-labelled (0, 8)
15	118	62, -2,	0.00158	CO r (04, 37), HG r (06, 18), PP r (04, 15), PT r (03, 12),

		6		aSTG r (01, 2), PreCG r (0, 1), not-labelled (0, 33)
16	109	-8, 66, -42	0.00238	Cereb8 l (02, 38), Ver8 (Vermis (06, 14), Cereb8 r (0, 10), Cereb9 r (01, 8), Cereb7 r (0, 2), Cereb7 l (0, 1), Ver9 (Vermis (01, 1), not-labelled (0, 35)
17	91	16, 38, 48	0.006024	PC (Cingulate (01, 26), Precuneous (0, 25), PostCG r (0, 11), PreCG r (0, 7), not-labelled (0, 22)
18	89	56, 8, 36	0.006375	PreCG r (01, 53), MidFG r (01, 35), not-labelled (0, 1)
19	85	-30, 52, -62	0.007603	Cereb8 l (0, 6), not-labelled (0, 79)
20	72	-12, 62, 28	0.015672	FP l (01, 71), not-labelled (0, 1)
21	70	2, 8, 38	0.016114	AC (Cingulate (02, 64), PaCiG r (0, 6)
22	70	8, -6, 32	0.016114	not-labelled (0, 70)
23	64	-10, 0, 26	0.022466	not-labelled (0, 64)
24	60	-36, 14, 20	0.02786	IFG oper Left) (0, 1), not-labelled (0, 59)
25	51	44, 30, 4	0.048828	pSTG r (02, 9), pMTG r (01, 9), not-labelled (0, 33)

Table S4: Correlation between functional connectivity measures and the tenth item (“ I felt sleepy” ) of 5D-ASC

Analysis	Placebo		LSD	
	r	p	r	p
ROI-to-voxel	-0.30	0.20	-0.20	0.40
Global correlation	-0.09	0.71	-0.14	0.56
Thalamus -right insula	0.02	0.93	0.01	0.97
Thalamus – right fusiform gyrus	0.08	0.74	-0.13	0.58