**PATHOLOGICAL ANATOMICAL CONNECTIONS OF ASSOCIATIVE AND LIMBIC CORTICO-BASAL-GANGLIA CIRCUITS IN OBSESSIVE-COMPULSIVE DISORDER**

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**SUPPLEMENTARY MATERIAL**

# **Contents**

Supplementary methods

 Statistical analyses: topography of the connections

Supplementary tables

* Supplementary Table 1: FreeSurfer labels
* Supplementary Table 2: Patient Characteristics
* Supplementary Table 3: PVox
* Supplementary Table 4: Density
* Supplementary Table 5: Topography

**SUPPLEMENTARY METHODS**

*Statistical analyses: topography of the connections*

We investigated whether the topography of the connections was conserved in patients compared to the literature in healthy controls (i.e. whether OFC connections were more ventral and medial than DPFC ones). Conserved topography is an essential prerequisite to interpret modifications in segregation.

In each patient, for each of the connections (3 seeds x 4 targets, bilateral), we constructed a connectivity map and calculated its center-of-gravity (barycentre). For each sead, all barycentres being in the same coordinate system, we fitted a 3D line to the four barycentres. We then projected the four barycentres onto the line using the geom3d toolbox (<http://www.pfl-cepia.inra.fr/index.php?page=geom3d>). This yielded an estimate of the points' linear order in space. Finally, we investigated whether this order of the barycentres was robust across subjects by correlating (linear regression) the rank of the barycentre in space with the nature of the associated target. This analysis was performed separately for patients and controls.

**SUPPLEMENTARY TABLES**

|  |  |
| --- | --- |
| ROI | FreeSurfer Labels |
| Left ACC | 11106 11132 11167 |
| Right ACC | 12106 12132 12167 |
| Left DLPFC | 11112 11113 11114 11115 11116 11139 11140 11153 11154 11155 |
| Right DLPFC | 12112 12113 12114 12115 12116 12139 12140 12153 12154 12155 |
| Left OFC | 11124 11131 11163 11164 11165 |
| Right OFC | 12124 12131 12163 12164 12165 |
| Left Fpole | 11101 11105 |
| Right Fpole | 12101 12105 |
| Left Caudate Nucleus | 11 26 |
| Right Caudate Nucleus | 50 58 |
| Left Putamen | 12 |
| Right Putamen | 51 |
| Left Thalamus | 10 |
| Right Thalamus | 49 |

# STable 1: FreeSurfer labels used in the segmentation of seed and target masks

| Patient ID | Age(yrs) | Durationof Illness (yrs) | YBOCS(0-40) | YBOCS-O(0-20) | YBOCS-C(0-20) | Padua1 | Padua2 | Padua3 | Padua4 | Medications |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 29 | 10 | 29 | 14 | 15 | 46 | 9 | 23 | 5 | SSRI, buspirone |
| 2 | 45 | 38 | 30 | 15 | 15 | 38 | 27 | 26 | 4 | SNRI, thymoregulator, lithium |
| 3 | 44 | 30 | 16 | 9 | 7 | 25 | 2 | 21 | 2 | SSRI |
| 4 | 50 | 23 | 16 | 6 | 10 | 17 | 13 | 12 | 0 | / |
| 5 | 45 | 31 | 18 | 8 | 10 | 38 | 27 | 26 | 4 | SSRI, tricyclical antidepressant |
| 6 | 22 | 3 | 18 | 8 | 10 | 91 | 2 | 20 | 6 | SSRI, benzodiazepine |
| 7 | 34 |  | 29 | 17 | 12 | 15 | 27 | 16 | 0 | SSRI |
| 8 | 32 | 24 | 18 | 9 | 9 | 46 | 2 | 26 | 0 | SSRI |
| 9 | 44 | 24 | 16 | 8 | 8 | 23 | 7 | 17 | 1 | / |
| 10 | 52 | 8 | 19 | 9 | 10 | 18 | 11 | 13 | 2 | / |
| 11 | 33 | 17 | 25 | 13 | 12 | 44 | 9 | 27 | 5 | Thymo-regulator |
| 12 | 47 | 31 | 28 | 14 | 14 | 51 | 33 | 31 | 4 | SNRI, atypical neuroleptic, thymoregulator, amytryptilline |
| 13 | 44 | 24 | 21 | 9 | 12 | 36 | 12 | 9 | 4 | SSRI |
| 14 | 53 | 25 | 25 | 11 | 14 | 35 | 7 | 27 | 4 | SNRI, benzodiazepine |
| 15 | 33 | 27 | 23 | 12 | 11 | 26 | 13 | 18 | 3 | / |
| 16 | 50 | 43 | 22 | 10 | 12 | 37 | 33 | 13 | 1 | / |
| 17 | 23 | 11 | 26 | 13 | 13 | 43 | 29 | 29 | 5 | / |
| 18 | 29 | 23 | 25 | 11 | 14 | 53 | 38 | 19 | 12 | SSRI, sodium valproate, atypical neuroleptic, hydroxyzine |
| 19 | 39 | 15 | 30 | 14 | 16 | 43 | 22 | 22 | 0 | SSRI |
| 20 | 33 |  | 24 | 10 | 14 | 32 | 14 | 28 | 4 | SSRI |
| 21 | 23 | 10 | 19 | 13 | 6 | 19 | 29 | 13 | 3 | / |
| 22 | 37 | 31 | 17 | 8 | 9 | 16 | 1 | 10 | 0 | / |
| 23 | 35 | 29 | 16 | 4 | 12 | 27 | 22 | 23 | 3 | / |
| 24 | 30 | 6 | 25 | 12 | 13 | 31 | 0 | 15 | 0 | SSRI, neuroleptic, benzodiazépine |
| 25 | 33 | 5 | 25 | 12 | 13 | 25 | 2 | 11 | 0 | / |
| 26 | 55 | 16 | 29 | 14 | 15 | 51 | 14 | 26 | 0 | SSRI, benzodiazepine, neuroleptic |
| 27 | 39 | 24 | 20 | 10 | 10 | 30 | 15 | 20 | 0 | / |
| 28 | 35 | 16 | 17 | 7 | 10 | 24 | 21 | 4 | 1 | SSRI, benzodiazepine |
| 29 | 27 | 16 | 24 | 13 | 11 | 41 | 28 | 20 | 8 | SSRI, benzodiazepine |
| 30 | 38 | 18 | 18 | 10 | 8 | 11 | 4 | 15 | 1 | / |
| 31 | 22 | 6 | 29 | 14 | 15 | 43 | 8 | 23 | 7 | atypical neuroleptic, clomipramine |
| 32 | 31 | 24 | 23 | 14 | 9 | 38 | 24 | 19 | 6 | / |
| 33 | 56 | 22 | 17 | 9 | 8 | 25 | 11 | 10 | 3 | neuroleptic, clomipramine, benzodiazepine |
| 34 | 26 | 10 | 20 | 8 | 12 | 40 | 4 | 23 | 5 | / |
| 35 | 53 | 35 | 33 | 18 | 15 | 26 | 6 | 19 | 0 | SSRI, atypical neuroleptic, benzodiasepine, antihistaminic H1, meprobamate |
| 36 | 33 | 10 | 17 | 7 | 10 | 27 | 20 | 17 | 1 | SNRI, valproate |
| 37 | 35 | 27 | 24 | 8 | 16 | 16 | 36 | 20 | 4 | / |

# **STable 2: Detailed Patient characteristics.** SSRI: selective serotonin reuptake inhibitor, SNRI: serotonin-noradrenalin reuptake inhibitor. Padua 1-4: factors of the Padua Inventory. 1: Impaired control over mental activity, 2: contamination/washes, 3 checking, 4 impulsion phobia.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Connection** | **Mean (SD) (%)****OCD** | **Mean (SD) (%)****Controls** | **Uncorrected****P-value** | **FDR adjusted****P-value** |
| **Left Caudate to ACC** | 84.38 (16.03) | 90.94 (13.62) | **0.031** | **0.049** |
| **Left Caudate to DPFC** | 95.88 (8.50) | 98.56 (3.18) | **0.033** | **0.049** |
| **Left Caudate to OFC** | 92.97 (13.57) | 97.09 (8.36) | **0.062** | **0.078** |
| **Left Caudate to Fpole** | 94.24 (8.59) | 98.94 (2.15) | **0.000** | **0.003** |
| **Left Putamen to ACC** | 67.62 (20.77) | 79.28 (18.61) | **0.007** | **0.018** |
| **Left Putamen to DPFC** | 97.55 (4.54) | 99.43 (1.88) | **0.009** | **0.022** |
| **Left Putamen to OFC** | 89.54 (17.25) | 96.14 (5.22) | **0.005** | **0.018** |
| **Left Putamen to Fpole** | 86.97 (13.81) | 93.58 (8.61) | **0.006** | **0.018** |
| **Left Thalamus to ACC** | 90.91 (10.86) | 95.43 (5.86) | **0.012** | **0.024** |
| **Left Thalamus to DPFC** | 96.23 (5.57) | 99.07 (1.56) | **0.000** | **0.003** |
| **Left Thalamus to OFC** | 91.70 (12.67) | 96.57 (4.78) | **0.011** | **0.024** |
| **Left Thalamus to Fpole** | 90.13 (12.80) | 96.57 (3.98) | **0.001** | **0.005** |
| **Right Caudate to ACC** | 84.23 (16.34) | 94.35 (6.80) | **0.000** | **0.003** |
| **Right Caudate to DPFC** | 98.10 (4.10) | 98.81 (3.61) | 0.227 | 0.247 |
| **Right Caudate to OFC** | 90.50 (15.24) | 93.74 (11.80) | 0.162 | 0.185 |
| **Right Caudate to Fpole** | 97.73 (5.95) | 99.15 (1.61) | 0.087 | 0.105 |
| **Right Putamen to ACC** | 73.84 (21.64) | 82.23 (15.08) | **0.028** | **0.049** |
| **Right Putamen to DPFC** | 97.80 (7.30) | 98.90 (2.95) | 0.264 | 0.264 |
| **Right Putamen to OFC** | 88.83 (18.90) | 95.10 (6.28) | **0.027** | **0.049** |
| **Right Putamen to Fpole** | 89.95 (11.80) | 95.84 (6.00) | **0.003** | **0.013** |
| **Right Thalamus to ACC** | 89.23 (14.11) | 95.75 (6.30) | **0.004** | **0.018** |
| **Right Thalamus to DPFC** | 97.32 (4.03) | 98.50 (2.19) | **0.062** | **0.078** |
| **Right Thalamus to OFC** | 89.47 (15.35) | 91.66 (9.90) | 0.236 | 0.247 |
| **Right Thalamus to Fpole** | 91.92 (11.57) | 95.78 (5.44) | **0.035** | **0.049** |

# **STable 3: PVox** represents the spatial spread of a connection, and was lower in OCD patients than in controls for 19 of 24 connections studied. The criterion p-value was 0.0618 for an FDR of 10% (bold), 0.0349 for an FDR of 5% (bold red). Uncorrected P-values were significant if inferior to criterion, adjusted P-values were significant if below the FDR.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Connection** | **Mean (SD)****OCD** | **Mean (SD)****Controls** | **uncorrected****P-value** | **FDR adjusted****P-value** |
| **Left Caudate to ACC** | 213.5 (92.3) | 204.2 (84.8) | 0.326 | 0.356 |
| **Left Caudate to DPFC** | 251.3 (131.1) | 358.1 (177.7) | **0.002** | **0.018** |
| **Left Caudate to OFC** | 466.7 (408.8) | 411.4 (251.9) | 0.244 | 0.321 |
| **Left Caudate to Fpole** | 406.6 (262.7) | 578.0 (290.6) | **0.005** | **0.029** |
| **Left Putamen to ACC** | 105.9 (78.3) | 108.5 (74.8) | 0.443 | 0.443 |
| **Left Putamen to DPFC** | 545.1 (242.8) | 672.6 (215.4) | **0.009** | **0.038** |
| **Left Putamen to OFC** | 494.1 (369.4) | 450.8 (266.2) | 0.283 | 0.323 |
| **Left Putamen to Fpole** | 339.7 (162.9) | 465.4 (163.6) | **0.001** | **0.018** |
| **Left Thalamus to ACC** | 53.5 (46.4) | 82.2 (73.9) | **0.024** | **0.072** |
| **Left Thalamus to DPFC** | 543.9 (182.9) | 681.9 (208.5) | **0.002** | **0.018** |
| **Left Thalamus to OFC** | 165.1 (142.1) | 146.7 (87.3) | 0.254 | 0.321 |
| **Left Thalamus to Fpole** | 167.6 (99.1) | 208.2 (86.2) | **0.032** | **0.077** |
| **Right Caudate to ACC** | 251.3 (106.7) | 197.2 (77.5) | **0.007** | **0.033** |
| **Right Caudate to DPFC** | 381.5 (180.5) | 430.9 (295.7) | 0.197 | 0.316 |
| **Right Caudate to OFC** | 390.3 (380.1) | 302.4 (290.4) | 0.135 | 0.248 |
| **Right Caudate to Fpole** | 594.1 (340.0) | 766.4 (385.4) | **0.022** | **0.072** |
| **Right Putamen to ACC** | 100.4 (74.0) | 114.2 (83.9) | 0.230 | 0.321 |
| **Right Putamen to DPFC** | 655.0 (264.9) | 731.6 (291.2) | 0.120 | 0.248 |
| **Right Putamen to OFC** | 567.9 (425.6) | 508.4 (322.0) | 0.250 | 0.321 |
| **Right Putamen to Fpole** | 495.9 (215.6) | 598.6 (245.1) | **0.030** | **0.077** |
| **Right Thalamus to ACC** | 60.7 (48.5) | 64.8 (39.6) | 0.345 | 0.360 |
| **Right Thalamus to DPFC** | 651.9 (179.1) | 676.8 (166.9) | 0.269 | 0.323 |
| **Right Thalamus to OFC** | 123.6 (132.3) | 98.2 (93.4) | 0.174 | 0.299 |
| **Right Thalamus to Fpole** | 215.2 (101.8) | 242.8 (110.7) | 0.134 | 0.248 |

# **STable 4: Density** represents the density of connections in connected voxels. It was reduced in 10 of 24 connections in OCD patients. The criterion p-value was of 0.0322 for a 10% FDR (bold), 0.0095 for a 5% FDR (bold red).

|  |
| --- |
| Patients |
| Connection | **Regression** | **R2** | **F statistic** | **P-value** |
| Left Caudate | F = 2.92 -1.86\*A +1.08\*D -0.89\*O | 0.95 | 874.92 | p<10-3 |
| Left Putamen | F = 2.41 -0.76\*A +1.22\*D -0.08\*O | 0.40 | 32.61 | p<10-3 |
| Left Thalamus | F = 1.14 +2.62\*A +1.22\*D +1.62\*O | 0.71 | 115.30 | p<10-3 |
| Right Caudate | F = 2.03 +1.86\*A -1.03\*D +1.05\*O | 0.95 | 907.12 | p<10-3 |
| Right Putamen | F = 3.24 -0.16\*A -1.95\*D -0.86\*O | 0.47 | 42.61 | p<10-3 |
| Right Thalamus | F = 3.97 -2.73\*A -1.41\*D -1.76\*O | 0.77 | 157.86 | p<10-3 |
|  |  |  |  |  |
|  |  |  |  |  |
| Controls |
| Connection | **Regression equation** | **R2** | **F statistic** | **P-value** |
| Left Caudate | F = 3.00 -1.86\*A +1.00\*D -1.14\*O | 0.95 | 978.75 | p<10-3 |
| Left Putamen | F = 2.57 -1.32\*A +1.30\*D -0.24\*O | 0.70 | 109.66 | p<10-3 |
| Left Thalamus | F = 1.03 +2.78\*A +1.22\*D +1.89\*O | 0.83 | 227.64 | p<10-3 |
| Right Caudate | F = 2.03 +1.81\*A -1.03\*D +1.11\*O | 0.93 | 672.53 | p<10-3 |
| Right Putamen | F = 3.03 +0.05\*A -1.41\*D -0.76\*O | 0.29 | 19.41 | p<10-3 |
| Right Thalamus | F = 3.92 -2.78\*A -1.14\*D -1.76\*O | 0.81 | 210.30 | p<10-3 |

# **STable 5: Topography of cortico-subcortical connections** was assessed, for each seed, by extracting the barycentre of the connectivity map for each target, fitting a 3D line to the 4 barycentres and correlating the order of the barycentres on that line to the target (cf Methods). We present the regression equations where F is the rank of a barycentre as a function of the cortical targets A, D and O (ACC, DPFC and OFC; Fpole is not included as the information is redundant).