**SUPPLEMENTARY MATERIAL**

**Supplementary Table S1:** The pre- and post-surgical clinical and cognitive psychometric scores which were available for 30 patients. Subjects not in surgical date order.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measures** | **Subjects** | | | | | | | | | | | | | | |
|  | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** |
| BDI-Pre | 40 | 15 (HADS) | 17 (HADS) | 49 | 42 | 59 | 23 | 32 | 38 | 42 | 49 |  | 51 | 43 | 56 |
| BDI-Post | 24 | 13 (HADS) | 4 (HADS) | 14 | 18 | 9 | 3 | 6 | 39 | 29 | 9 | 39 | 5 | 1 | 53 |
| MADRS-Pre |  |  |  |  |  |  |  |  | 22 |  |  |  |  |  |  |
| MADRS-Post |  | 24 |  |  | 14 | 12 | 5 | 9 | 4 |  |  |  |  | 18 | 40 |
| BAI-Pre |  | 15 (HADS) | 13 (HADS) | 30 | 26 | 14 | 25 | 35 | 25 | 17 | 28 |  |  |  |  |
| BAI-Post |  | 16 (HADS) | 15 (HADS) | 29 | 17 | 1 | 2 | 4 | 26 | 27 | 15 |  |  |  | 23 |
| V-IQ | 118 |  | 97 |  |  |  | 126 | 91 |  | 95 |  |  | 129 | 76 |  |
| P-IQ | 89 |  | 91 |  |  |  | 133 | 108 |  | 108 |  |  | 84 | 63 |  |
| FS-IQ |  |  | 94 |  |  |  | 133 | 90 |  | 102 |  |  |  | 69 |  |
| VF-Pre |  | 37 | 58 | 21 | 23 | 13 | 57 | 41 | 36 | 24 | 34 |  |  |  |  |
| VF-Post |  | 24 | 42 | 12 | 28 | 23 | 56 | 35 | 34 | 29 | 15 | 28 | 42 |  | 21 |
| S-Pre | 13 | 7 |  | 10 |  | 6 | 15 | 11 |  | 9 |  |  | 15 | 5 |  |
| S-Post | 9 | 6 |  |  |  | 17 |  |  |  |  |  | 11 |  |  | 8 |
| SP-Pre |  |  |  | 48 | 5 | 30 | 42 |  | 33 | 41 | 31 |  |  |  |  |
| SP-Post |  |  |  | 43 |  | 60 | 58 | 50 | 28 | 29 | 30 | 36 | 47 | 35 | 41 |
| IP-Pre |  |  |  | 50 | 29 | 35 | 79 | 44 | 28 | 38 | 23 |  |  |  |  |
| IP-Post |  |  |  | 60 | 30 | 54 | 101 | 46 | 30 | 40 | 10 | 65 | 60 | 33 | 34 |
| DS-Pre | 12 | 5 | 7 | 6 |  | 10 |  |  |  |  |  |  | 6 | 6 |  |
| DS-Post |  | 5 | 9 |  |  | 11 |  |  |  |  |  | 13 |  |  | 8 |
| DSy-Pre | 6 | 6 | 7 |  |  |  |  |  | 5 |  |  |  |  | 2 |  |
| DSy-Post | 5 | 6 | 9 |  |  |  |  |  |  |  |  |  |  |  |  |
| LL-Pre |  |  |  | 39 |  | 29 | 56 | 49 | 36 | 38 |  |  |  | 20 |  |
| LL-Post |  |  |  | 30 | 43 | 35 | 40 | 35 | 34 | 40 |  |  | 40 | 30 | 37 |
| S\_IR-Pre | 36 | 29 | 28 | 32 | 5 | 10 | 35 | 24 | 18 | 24 | 26 |  | 30 | 34 |  |
| S\_IR-Post | 39 | 19 | 32 | 14 | 38 | 30 | 22 | 44 | 26 | 25 | 10 | 39 | 23 | 29 | 35 |
| S\_DR-Pre | 31 | 21 | 24 | 22 | 3 | 3 | 35 | 16 | 16 | 16 | 15 |  | 21 | 23 |  |
| S\_DR-Post | 36 | 6 | 30 | 0 | 37 | 20 | 25 | 38 | 24 | 21 | 2 | 36 | 25 | 21 | 26 |
| F\_IR-Pre | 49 | 75 | 38 | 67 | 3 | 55 | 90 | 75 | 41 | 96 | 26 |  | 51 | 56 |  |
| F\_IR-Post | 33 | 90 | 53 | 63 | 70 | 65 | 97 | 84 | 34 | 92 | 21 | 61 | 80 | 38 | 48 |
| F\_DR-Pre | 59 | 43 | 38 | 63 | 0 | 60 | 90 | 59 | 42 | 93 | 25 |  | 36 | 38 |  |
| F\_DR\_Post | 33 | 38 | 44 | 0 | 70 | 61 | 97 | 68 | 34 | 95 | 18 | 50 | 81 | 33 | 56 |
| **Measures** | **Subjects** | | | | | | | | | | | | | | |
|  | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** |
| BDI-Pre | 42 |  | 26 | 32 | 56 | 37 | 37 | 25 | 47 | 29 | 52 | 34 | 30 |  | 42 |
| BDI-Post | 23 | 40 | 36 | 24 | 54 | 42 | 25 |  | 5 | 5 | 25 | 25 | 1 |  | 4 |
| MADRS-Pre |  | 40 |  |  |  |  |  |  |  |  |  | 25 |  |  | 23 |
| MADRS-Post | 11 | 21 | 21 | 11 |  |  |  |  | 13 |  | 22 |  |  | 12 | 6 |
| BAI-Pre | 50 |  | 35 |  |  | 41 |  | 0 | 40 | 12 |  |  |  |  | 18 |
| BAI-Post | 2 |  | 23 | 36 | 17 | 18 | 25 |  |  | 4 |  |  |  |  | 11 |
| V-IQ | 82 |  |  |  |  | 107 |  |  |  | 111 |  |  | 72 |  |  |
| P-IQ | 102 |  |  |  |  | 97 |  |  |  | 110 |  |  | 80 |  |  |
| FS-IQ | 88 |  |  |  |  | 102 |  |  |  | 113 |  |  | 74 |  |  |
| VF-Pre | 19 |  | 11 | 39 |  | 45 |  | 17 |  | 51 |  |  | 18 |  | 47 |
| VF-Post | 22 |  | 12 | 36 | 24 | 21 | 38 |  |  | 44 |  | 23 | 33 |  | 51 |
| S-Pre | 9 |  | 4 |  |  | 12 |  | 6 | 12 | 38 |  |  | 4 |  |  |
| S-Post |  | 11 |  |  |  | 11 |  |  |  |  |  |  | 6 |  |  |
| SP-Pre |  |  |  |  |  |  | 40 | 54 |  | 25 |  |  |  |  | 40 |
| SP-Post |  |  |  |  |  |  | 44 |  |  | 47 |  |  |  |  | 46 |
| IP-Pre | 61 |  |  |  |  |  | 65 | 44 |  | 38 |  |  |  |  | 60 |
| IP-Post | 50 |  |  |  |  |  | 53 |  |  | 45 |  |  |  |  | 62 |
| DS-Pre | 8 |  | 6 |  |  | 14 |  | 8 |  |  |  |  | 4 |  |  |
| DS-Post |  | 13 |  |  |  | 15 | 6 |  |  |  |  |  | 6 |  |  |
| DSy-Pre | 10 |  | 4 |  |  | 6 |  | 2 |  |  |  |  | 6 |  |  |
| DSy-Post |  |  | 4 |  |  | 6 | 6 |  |  |  |  |  | 8 |  |  |
| LL-Pre | 43 |  | 33 |  |  |  |  | 39 |  | 50 | 49 |  |  |  | 60 |
| LL-Post | 32 |  | 24 |  |  |  |  |  |  | 55 | 42 |  |  |  | 63 |
| S\_IR-Pre | 20 |  | 25 | 44 |  | 36 |  | 17 |  | 36 |  |  | 32 |  | 42 |
| S\_IR-Post | 21 | 39 | 18 |  | 10 | 25 | 24 |  |  | 41 |  |  | 40 |  | 47 |
| S\_DR-Pre | 14 |  | 18 |  |  | 28 |  | 16 |  | 37 |  |  | 25 |  | 41 |
| S\_DR-Post | 6 | 36 | 15 | 44 | 7 | 23 | 26 |  |  | 38 |  |  | 35 |  | 45 |
| F\_IR-Pre | 95 |  | 18 |  |  | 53 |  | 97 |  |  |  |  | 84 |  | 83 |
| F\_IR-Post | 94 |  | 27 | 75 | 30 | 46 | 59 |  |  |  |  |  | 67 |  | 85 |
| F\_DR-Pre | 95 |  | 18 |  |  | 58 |  | 89 |  |  |  |  | 78 |  | 84 |
| F\_DR\_Post | 95 |  | 28 | 83 | 26 | 46 | 59 |  |  |  |  |  | 67 |  | 80 |

**Footnote: Footnote:** BDI = Beck Depression Inventory; HADS = Hospital anxiety and depression scale (these scores were available for 2 patients and replace the BDI (HADS depression scale) and BAI (HADS anxiety scale) where indicated); MADRS = Montgomery Asberg Depression Rating Scale; BAI = Beck Anxiety Inventory; I = Imputed; V = Verbal; P = Performance; FS = Full Scale; VF = Verbal Fluency; S = Similarities; SP = Speed Processing; IP = Information Processing; DS = Digit Span; DSy = Digit Symbol; LL = List Learning; S = Story; F = Figure; IR= Immediate Recall; DR = Delayed Recall.

**Diffusion Tensor Imaging:**

**The potential use of DTI-based fibre tracking**

Diffusion Tensor Imaging (DTI)-based fibre-tracking enables the *in vivo* reconstruction of connection pathways of the human brain (Catani *et al.* 2002).Previous research suggests that white matter microstructure of the medial forebrain bundle (MFB) and the anterior thalamic radiation (ATR), pathways that are likely to be interrupted during anterior capsulotomy, are altered in depression (Jia et al. 2014; Bracht et al. 2014). Based on a recent review these changes are most pronounced in MDD patients with severe/ treatment-resistant depression (Bracht et al. 2015). Thus the MFB and ATR may be of particular relevance regarding the clinical effects of anterior capsulotomy. Pre-operative DTI-based identification of target fibre tracts that may underlie depression symptomatology may therefore potentially represent an important step forward in psychiatric surgery. Furthermore, DTI fibre tracking may be used for evaluation of surgical outcome, and to link side effects to the lesioning of specific pathways. In three patients pre- and postoperative DTI data were available and analyzed.

**Methods:**

*Diffusion Tensor Imaging (DTI):*

Data were acquired on a clinical GE Medical System 1·5 Tesla scanner with the following parameters: 24 diffusion encoding directions with a b-value of 1000 s/mm2, 1B0 image without diffusion weighting, 30 slices, voxel size 2x2x5 mm. Pre and post diffusion-MRI data were available for three patients.

*Imaging Analysis:*

Data were pre-processed and analysed using the software package *ExploreDTI (*Leemans *et al.* 2009).Regions of interest of connection pathways were chosen from the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer *et al.* 2002), implemented in *ExploreDTI (*Leemans *et al.* 2009). We hypothesized the thalamo-orbitofrontal cortex (OFC) connection pathway to be interrupted by the operation. For reconstruction of this pathway the thalamus and Brodmann areas 10 and 11 were chosen as seed regions. The thalamo-primary motor cortex (PMC) connection was reconstructed as a comparison tract which we did not expect to be affected by the operation. These two connection pathways were separately reconstructed for individual pre-surgical and post-surgical datasets.

***Results:*D:\Neurosurgery_24022015\Psychological Medicine\Response to reviewers\Final\Final\Final\Final\Second revision\Final\Final\Final\Final\DLinden_Figure 1S_Other supplementary material.tif**

**Supplementary Figure S1**: **Fibre connections between the thalamus and orbitofrontal cortex pre and post-surgery (left panel) and fibre connections between the thalamus and primary motor cortex pre and post-surgery (right panel). BDI clinical scores for the 3 patients: Row 1: Pre-42, Post-4, 90% change; Row 2: Pre-42, Post-29, 31% change; Row 3: Pre-49, Post-9, 82% change.**

In all pre-surgery DTI scans both bilateral thalamo-OFC connection pathways travelling through the anterior limb in the internal capsule and bilateral thalamo-PMC pathways running through the cortico-spinal tract could be identified reliably.

In the post-operative DTI scans in one participant no fibres connecting thalamus and OFC could be identified (row 1, Figure 1B). In two participants DTI-fibre-tracking revealed sparse unilateral connection pathways between the OFC and the thalamus running through the external capsule (row 2 and row 3, Figure 1B). These fibres had not been reconstructed before the operation. Bilateral thalamo-PMC connections remained unchanged in comparison to the pre-operative DTI scan.

***Discussion***

At present diffusion MRI is the only available method for in vivo reconstruction of fibre pathways and thus offers unique opportunities in psychiatric surgery and stimulation studies. Our DTI-fibre tracking results support the assumption that pathways connecting the thalamus and OFC have been successfully interrupted. DTI fibre tracking results of the thalamo-PMC comparison pathway remained unchanged after the operation, indicating that the surgical intervention had no effect on more posterior thalamo-cortical connections.

We suggest that DTI-fibre tracking will find more widespread use in future applications of psychiatric surgery. It may be used to reconstruct pathways before the operation and serve as guidance to specifically modulate pathways of interest; postoperative DTI-fibre tracking may validate surgery outcome; follow-up studies could link the lesioning of specific pathways to treatment outcome and side effects. This may contribute to the development of more specific and less invasive surgery, potentially being associated with fewer side effects. DTI-based tractography has already informed new protocols for DBS (Coenen *et al.* 2011)and is being used to localize stimulation targets (Schlaepfer *et al.* 2013).

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