**Supplementary File – Isobe et al.**

**Imaging: technical scan details**

Regarding sample set 1, data were acquired with a 1.5 T GE Signa system (General Electric, Milwaukee, USA). Axial three-dimensional T1-weighted images were obtained using a spoiled gradient recall sequence (slice thickness: 2mm; TR: 33 msec; TE: 3 msec; FOV: 256 × 240 mm). For sample set 2, data were acquired with a Siemens Trio 3T MRI Scanner (Siemens, Munich, Germany). Anatomical three-dimensional T1-weighted images were obtained using a magnetization prepared rapid gradient echo (MPRAGE) sequence (slice thickness: 1mm; inversion time (TI), 1,100 ms, FOV: 176 × 240 mm).

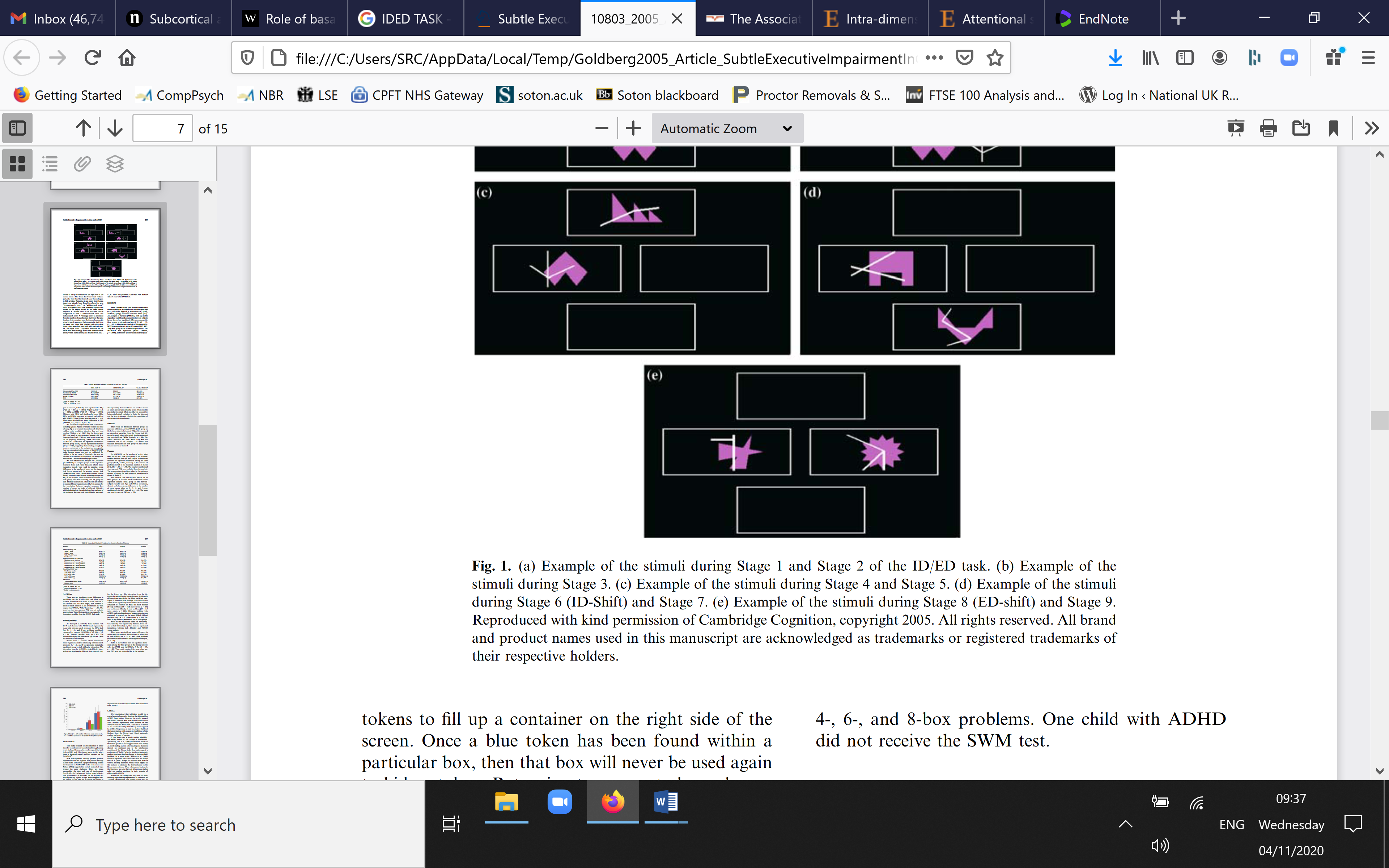
**Imaging: pre-processing steps**

The T1-weighted images of each subject were individually preprocessed. Bias-field correction was automatically performed and images were non-linearly registered to the MNI 152 standard space. We employed FMRIB's Integrated Registration and Segmentation Tool (FIRST) implemented in FSL 5.0.9 to identify subcortical structures in an automatic manner. Shape models with structural boundaries obtained from 336 manually segmented images were identified for segmentation, resulting in a deformable surface mesh of each subcortical structure consisting of vertices. The meshes were then reconstructed into MNI space, and boundary corrected. Then, the segmented images were transformed back into original space. We visually checked all segmented images to avoid registration errors.

**Cognitive task: more detailed description**

The Intra-Dimensional/Extra-Dimensional Set-Shift task (IDED) from the CANTAB battery was used in this study. This is a standardised task examining different stages of rule acquisition and flexible responding. On the task, participants view two stimuli presented on the computer screen at a time (Figure S1). They have to make a choice regarding which of the two stimuli they believe to be “correct” according to an underlying rule they must work out through trial and error. After each choice, visual feedback is provided (the word “correct” or “incorrect” on-screen) so that participants can learn the underlying rule the computer has determined, over time. Once a participant has learnt the underlying rule about which stimulus is correct, the computer then introduces a different rule, which must then be learnt. The crucial stage of the task is the so-called ED shift: here, the stimulus dimension that was previously always relevant to learn the rule (e.g. number of lines) becomes irrelevant; and the previously irrelevant stimulus dimension (e.g. shape of blobs) becomes relevant. As such, ED shift requires individuals to flexibly adapt their learnt pattern of responding, and to shift attention away from a previously relevant aspect of the environment to a different one.

Figure S1. Sample screenshot from the IDED task. Volunteers view two compound stimuli; each stimulus has two dimensions (blobs and lines). Through trial and error, individuals attempt to learn the underlying ‘rule’ about what stimulus is correct.



**Cognitive task: group comparisons**

Groups differed significantly in terms of ED errors on the IDED task (F=11.06, p<0.001), but not on errors prior to the ED stage (F=2.70, p=0.07). The overall group difference in ED errors was due to OCD patients making significantly more errors than controls (p<0.001); and relatives of OCD patients making more errors than controls (p<0.001). Patients did not differ significantly from relatives on ED error task performance (p=0.366). The mean (standard deviation) number of ED errors in each group were as follows: OCD patients (11.92 [11.47]), patient relatives (13.81 [11.26]), controls (5.60 [7.07]).

**Supplementary Table 1. Demographic and other key characteristics of the groups**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | OCD | Relatives | HC | Statistic | p-value | Post-Hoc analysis |
| Total | (N=76) | (N=32) | (N=75) |  |  |  |
| Age (mean, SD) | 34.79 (10.95) | 37.03 (13.37) | 35.96 (11.78) | 0.45† | 0.64 |  |
| Gender (N, %) |  |  |  |  |  |  |
| Male | 30 (39.5%) | 9 (28.1%) | 34 (45.3%) |  |  |  |
| Female | 46 (60.5%) | 23 (71.9%) | 41 (54.7%) | 2.78‡ | 0.25 |  |
| Estimated verbal IQ, NART | 113.02 (7.04) | 114.40 (8.42) | 115.46 (6.17) | 2.33† | 0.10 |  |
| MADRS (mean, SD) | 7.16 (5.87) | 1.69 (2.83) | 0.67 (1.23) | 52.74† | < 0.001 | OCD > HC\*  OCD > Relatives\* |
| Receiving psychotropic medication (N, %) | 51 (67.1%) | N/A | N/A | N/A | N/A |  |

†One-way analysis of variance (ANOVA); ‡Chi-square tests. \*Significant p value (p<0.01) for the Tukey HSD post-hoc analysis

Abbreviations: SD = standard deviation; NART = National Adult Reading Test; MADRS = Montgomery-Asberg Depression Rating Scale.

**Supplementary Table 2. Cognitive performances of the groups on the Intra-/Extra Dimensional Set Shift task**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | OCD | Relatives | HC | ANOVA | | Post-Hoc analysis |
| Total | (N=76) | (N=32) | (N=75) | Statistic | p-value |  |
| Pre-extra dimensional errors (mean SD) | 6.39 (4.02) | 7.65 (6.52) | 5.40 (4.12) | 2.70 | 0.07 |  |
| Extra-dimensional errors (mean, SD) | 11.92 (11.47) | 13.81 (11.26) | 5.60 (7.07) | 11.06 | < 0.001† | OCD > HC\*  Relatives >HC\* |

†One-way analysis of variance (ANOVA).

\*Significant p value (p<0.01) for the Games-Howell post-hoc analysis

Abbreviations: SD = standard deviation.

**Supplementary Table 3. Details of psychotropic medication among OCD patients**

|  |  |
| --- | --- |
| (Dose range, mg) | Number |
| Receiving psychotropic medication |  |
| Antidepressants |  |
| Citalopram (16-60) | 7 |
| Clomipramine (75-200) | 2 |
| Escitalopram (10-20) | 2 |
| Fluoxetine (20-100) | 9 |
| Fluvoxamine (300) | 4 |
| Mirtazapine (30-45) | 2 |
| Paroxetine (30-60) | 4 |
| Sertraline (50-250) | 20 |
| Sulpiride (800) | 1 |
|  |  |
| Antipsychotics | 5 |
| Clotiapine (50-150) | 2 |
| Quetiapine (25) | 1 |
| Risperidone (0.5-2.0) | 2 |
|  |  |
| Others | 2 |
| Tramadol (100) | 1 |
| Gabapentin (660) | 1 |