The Role of Serotonin in Compulsive Behavior in Humans: Underlying Brain Mechanisms

NCT Number: 04336228

Document Date: July 8, 2024

Statistical Analysis Plan

1 Data Collection

Data collection took place between May 15, 2020, and June 20, 2024. This pre-registration analysis plan is completed before breaking the blinding code.

2 Main Hypotheses

1. In participants with high obsessive-compulsive (OC) traits (including those diagnosed with OCD), there is a positive correlation between striatal/prefrontal cortex (PFC) 5-HT4R binding and the severity of OC traits.

2. Enhanced OC traits relate to alterations in fMRI BOLD responses associated with the goal-directed and habit systems, consistent with a bias towards habitual control.

3. High baseline levels of 5-HT4R binding in the PFC and striatum are positively related to a bias towards habitual behaviour.

3 Other Hypotheses

4. Compared to placebo, escitalopram treatment reduces 5-HT4R binding in the striatum, PFC and possibly other brain areas both in healthy controls (HC) and in individuals with OC traits.

5. Compared to HCs, individuals with OC traits show larger reductions in 5-HT4R binding with escitalopram treatment.

6. Escitalopram treatment compared with placebo in individuals with OC traits improves symptoms in a manner that is associated with reduced 5-HT4 binding.

7. Compared with HCs, individuals with OC traits show impairments in certain aspects of cognition such as goal-directed behaviour, cognitive flexibility and inhibitory response control.

8. Cognitive impairments in individuals with OC traits improve with escitalopram treatment.

4 Key Dependent Variables

1. One key dependent variable is the 5-HT4 binding potential with cerebellum as a reference tissue (BPND). Measurements are obtained using dynamic PET imaging, kinetic modeling and automatic delineation of brain regions with T1-weighted magnetic resonance imaging.

2. Another key dependent variable is the BOLD signal, which is expected to change in response to tasks manipulating the balance between the goal-directed and the habitual systems, particularly within the cortico-striatal networks.

3. At the behavioural level, aspects of cognition such as goal-directed behaviour, cognitive flexibility and inhibitory response control will be assessed.

5 Analysis Plan

We will use a latent variable model (LVM) for the analyses, including covariates age, sex, and injected mass, to evaluate the statistical effects. The specifics of our analysis are as follows:

5.1 Baseline Analysis

- Correlation with OC Traits: Conduct a one-sided test to evaluate the positive correlation between striatal and PFC 5-HT4R binding and the severity of OC traits.

5.2 Treatment Effect Analysis

- Interaction Effects: Evaluate the interaction effect of treatment (escitalopram vs. placebo) by time (baseline vs. follow-up) and group (individuals with OC traits vs. HC).

- Group and Treatment Effects: Examine main effects of group (individuals with OC traits vs. HC) and treatment (escitalopram vs. placebo) on 5-HT4R binding.

- Reduction in 5-HT4R Binding: Compare the reduction in brain 5-HT4R binding between the escitalopram and placebo groups.

- Symptom Improvement: Analyze the correlation between reductions in 5-HT4R binding and symptom improvement within the escitalopram and placebo groups.

6 Analysis Sample Size

A total of 46 participants will be included in the analysis, consisting of 23 healthy controls and 23 individuals with high OC traits (including patients with OCD). Participants are screened using the Padua Inventory (PI) and Obsessive-Compulsive Inventory (OCI), to enable recruitment of individuals with high OC trait scores (PI >15, OCI >20) and healthy controls defined as individuals with low OC scores (PI <15, OCI <20).