Effects of Sertraline on Brain Connectivity in Adolescents with OCD

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Specific Aims:

Obsessive-compulsive disorder (OCD) is a debilitating anxiety disorder that afflicts 1-3% of youth,[1,2] often causing incapacitation by obsessions and compulsions. Although effective treatments are available, not all patients respond.[3] This highlights the need for research to develop new treatments. The groundwork for such developments will require neurobiological research that will (a) further elucidate the neural mechanisms of disease, (b) characterize the specific changes that underlie response to established treatments, and (c) demonstrate the specific neurobiology in patients who do not respond to established treatments. Previous research has suggested that dysregulation of the frontal-striatal-thalamic circuitry (FSTC) is associated with OCD.[4] Functional magnetic resonance imaging (fMRI) studies in children and adults with OCD compared to controls have shown decreased activation in FSTC regions during tasks involving cognitive control.[5-13] Also, emerging research in OCD using resting-state functional magnetic resonance imaging (R-fMRI)[14-16] and diffusion imaging (DI) has begun to identify alterations in connectivity (i.e., connections within networks) within FSTC and points to alterations in connectivity between the frontal cortex and striatum (caudate and putamen).

In our pilot study of 15 adolescents with OCD (mostly medicated) and 12 controls, we examined 22 specific connections within FSTC (11 per hemisphere) using R-fMRI. Findings demonstrated that in comparison with controls, adolescents with OCD show significantly lower connectivity and high effect sizes in 11 links. Lower functional connectivity in 10 of these segments was associated with significantly higher severity on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).[17] Furthermore, we examined how specific dimensions of OCD would map onto this circuitry. We found that bilaterally, for cortical-subcortical connections, the ordering/repeating dimension correlates with orbitofrontal cortex (OFC)-subcortical connections, the hoarding dimension correlates with rostral anterior cingulate cortex (ACC)-subcortical connections, and the forbidden thoughts dimension correlates with caudal ACC-subcortical connections. These data were obtained using advances in brain imaging acquisition and analysis that were developed at the University of Minnesota (UMN) for the NIH-funded Human Connectome Project (HCP). We have also begun to show that our imaging tools can reliably and accurately measure structural connectivity within deep FSTC white matter connections of interest. Earlier imaging research had limitations (low spatial and temporal resolution, limited ability to resolve crossing white matter fibers, and OFC signal drop) that can be addressed with advances at our site. Since our pilot study included mostly medicated OCD adolescents, it is unclear to what extent the findings reflect effects of disease, treatment, or both. For example, it may be that prior to medication treatment, group differences are even larger than what we detected, and are then mitigated by treatment. Furthermore, treatment may alter some parts of FSTC more than others and key changes may underlie treatment response, which are not seen in non-responders.

Selective serotonin reuptake inhibitors (SSRIs) are the pharmacological treatment of choice for pediatric OCD.[18] Twelve weeks of sertraline, an SSRI, was found to be moderately effective in decreasing OCD symptoms in the NIMH-funded Pediatric OCD Treatment Study (POTS).[3] There is some fMRI evidence that SSRIs reduce brain abnormalities in patients with OCD.[19] We propose to comprehensively evaluate FSTC using a multi-modal neuroimaging approach [R-fMRI and high angular resolution diffusion imaging (HARDI)] in 25 unmedicated adolescents with OCD and 25 matched healthy controls to confirm our pilot findings at baseline in unmedicated adolescents with OCD. We will examine how treatment with sertraline for 12 weeks impacts FSTC in this OCD sample.

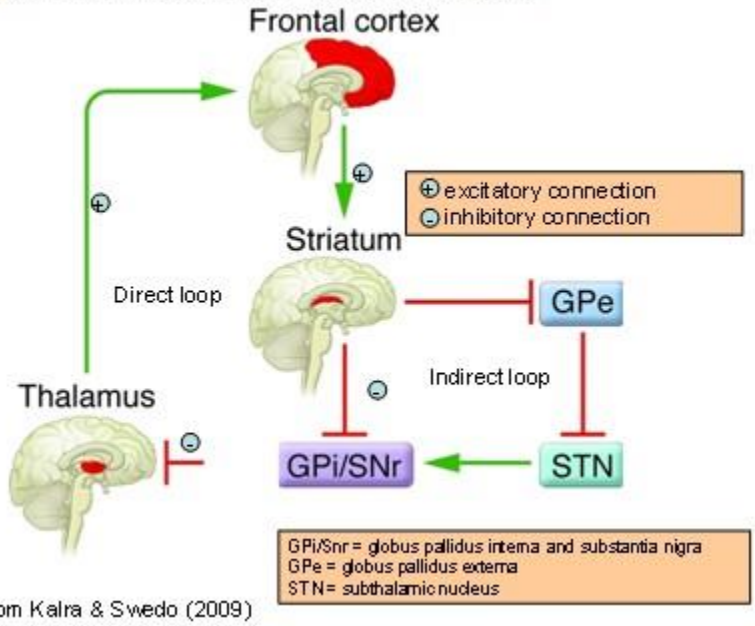
Specific Aim #1: To examine FSTC using advanced multi-modal imaging techniques (R-fMRI, HARDI) in 25 medication-free youths with OCD (ages 8-17) in comparison with 25 matched healthy controls. Hypotheses: (A) *Based on our pilot data, youths with OCD will show lower functional connectivity in FSTC at baseline when compared with controls, and , lower functional connectivity in FSTC will correlate with greater severity on CY-BOCS.* (B) *Youths with OCD will also show abnormalities in structural connectivity in FSTC at baseline when compared with controls, and structural and functional connectivity will be related. (C) We will explore relations between OCD dimensions and functional connectivity measures, and predict that the repeating/ordering dimension will correlate with OFC connections, hoarding will correlate with rostral ACC connections, and forbidden thoughts will correlate with caudal ACC connections.*

Specific Aim #2 (Exploratory): To investigate how sertraline impacts functional connectivity in FSTC in adolescents with OCD. Hypothesis: *After 12 weeks of sertraline treatment, functional connectivity measures within FSTC for the OCD group will (on average) increase compared to baseline and will no longer be*

significantly different when compared with controls. Non-responders may show a different pattern (i.e. failure to show these changes).

A. Background and Significance: OCD is a debilitating anxiety disorder with a prevalence rate of 1% to 3% in youth.[1,2] Children and adolescents with OCD are often incapacitated by obsessions and compulsions. Up to 80% of OCD cases may begin in childhood or adolescence.[20] Studying youths with OCD (rather than adults) offers the advantage of identifying brain differences early in development when confounding factors of chronicity of symptoms and interventions (i.e., psychotropic medications and cognitive-behavioral therapy [CBT]) are less likely to be present. ***FSTC in OCD:*** Neuroimaging research has implicated FSTC in OCD. This network connects neurons in the frontal cortex, striatum (i.e., caudate, putamen), thalamus, and back to the frontal cortex.[4,21] See basic diagram of FSTC in Figure 1. Task fMRI studies demonstrate that participants with OCD compared to matched healthy controls exhibit lower levels of activation of brain regions in FSTC regions.[5-13] A review of neuroimaging studies concluded that results from a variety of imaging techniques converge to implicate abnormalities in FSTC in pediatric OCD.[22] Theory suggests that abnormalities in the FSTC result in obsessional thoughts and compulsive behaviors.[4]

Figure 1. Frontal-Striatal-Thalamic Circuitry



Adapted from Kalra & Swedo (2009)

Developmental Framework for Pediatric OCD: There are clinical and neuroimaging differences between childhood- and adult-onset OCD. Pediatric OCD has male predominance and is commonly comorbid with tic disorders (30%),[23] whereas adult-onset is predominantly female and often comorbid with depression.[22] Childhood OCD is viewed as a neurodevelopmental subtype of OCD based on similarity of its symptoms to developmentally normal childhood rituals,[24,25] and comorbidity with Tourette's disorder (a neurodevelopmental condition). It is thought to be related to prefrontal-striatal abnormalities that are neurodevelopmentally mediated.[26] Striatal structures mature earlier than prefrontal regions which continue to mature into early adulthood.[27] During development, white matter changes are primarily due to increases in myelination which fine-tune the connectivity between prefrontal and subcortical regions.[27] Meta-analysis of fMRI studies show involvement of OFC and caudate in adults with OCD,[28] whereas pediatric OCD studies indicate involvement of other basal ganglia areas (e.g., putamen) and thalamus.[29-31] Medication-naïve youth with OCD compared with controls demonstrate greater ACC gray matter.[30] These differences highlight the importance of utilizing a developmental approach to studying FSTC in pediatric OCD.

Advanced Neuroimaging Technologies for Connectivity: Recent advances in neuroimaging that assess brain "connectivity" allow for a sophisticated understanding of neural networks. Several studies have demonstrated significant differences in connectivity in the corticostriatal link of this circuit in adults[14-16] and in youths with OCD.[14] We have identified specific connections within this network that show significantly lower functional connectivity in adolescents with OCD compared with controls (see Pilot Data). We plan to evaluate brain connectivity in adolescents using two advanced, noninvasive technologies. First, ***R-fMRI*** measures the covariance of blood-oxygen-level-dependent (BOLD) signals between brain areas ("functional connectivity").[32] Second, ***HARDI***[33] is a rapidly developing technology that includes a number of alternative approaches to inferring fiber orientations in white matter. Unlike traditional diffusion tensor imaging (DTI),[34] HARDI techniques can resolve complex fiber architecture within a single voxel and permit assessment of microstructural integrity of white matter fiber tracts,[33] indexing the anatomical strength of connections between brain areas ("structural connectivity"). Recently-developed acquisition schemes at UMN[35] enable rapid collection of both types of connectivity data to reduce long acquisition times and minimize motion artifacts.

Neuroimaging Studies Evaluating Connectivity in OCD: *Functional Connectivity*: Harrison and colleagues[15] found reduced functional connectivity between the lateral prefrontal cortex and dorsal striatum and between the ventral striatum and the midbrain ventral tegmental area in 21 adults with OCD (mostly medicated) and 21 matched healthy controls. Sakai and associates[16] used R-fMRI to study 20 medication-free

adults with OCD and 23 matched healthy controls. Significantly greater positive functional connectivity was found between regions of the frontal cortex and the ventral striatum in OCD participants. Fitzgerald et al. examined connectivity between OCD and controls in four developmental age groups [children 8-12 years (n = 11), adolescents 13-17 (n = 18), young adults 18-25 (n = 18), and older adults 26-40 (n = 13)].[14] Half of the OCD participants were on psychotropic medications. Across all age groups, OCD patients compared with controls showed increased connectivity between ventral medial frontal cortex and dorsal striatum. However, children with OCD showed reduced connectivity between rostral ACC and dorsal striatum (associated with greater OCD severity), and also between dorsal ACC and medial dorsal thalamus. No studies have reported R-fMRI results on medication-free youths with OCD. *Structural Connectivity:* A handful of studies have used DI to examine white matter connectivity in OCD, with somewhat mixed findings. The first DI study in OCD found that adult patients had lower fractional anisotropy (FA) in the white matter of several cortical regions including ACC, parietal cortex, posterior cingulate gyrus, and occipital cortex. No areas of significantly higher FA were found in patients compared with healthy controls.[36] Similarly, another study found significantly increased FA in the genu and body of corpus callosum and white matter of right superior frontal gyrus and corpus callosum in OCD compared with control subjects, and no areas of significantly decreased FA.[37] However, one study found reduced fronto-callosal fiber integrity in unmedicated OCD adults versus controls.[38] No DI studies have focused on FSTC connections, and none have been conducted in pediatric OCD.

SSRI Effects in OCD: Treatment-naïve adults with OCD (n = 13) exhibited smaller putamen volume which normalized following 12 weeks of SSRI treatment.[39] Treatment-naïve children with OCD (N = 21) showed greater thalamic volume which normalized after 12 weeks of an SSRI.[31] No studies were found of SSRI effects on connectivity in pediatric OCD. SSRIs have been demonstrated to be efficacious in reducing pediatric OCD symptoms in multiple randomized placebo-controlled trials.[18,40] In POTS, 12 weeks of sertraline was effective in reducing OCD symptoms (ES = 0.67).[3] Sertraline was selected because it was used in POTS, is FDA approved for pediatric OCD, and Dr. Bernstein has years of experience treating OCD youths with sertraline.

B. Innovation: Given that OCD may have a neurodevelopmental etiology and that the networks of interest in OCD undergo considerable refinement throughout childhood and adolescence, examination of OCD circuitry in youth is critical. Furthermore, studying unmedicated youth allows for identifying brain differences without the confound of current pharmacological treatment. The proposed study is cutting edge because we will use innovative advanced data acquisition methods for fMRI and HARDI that have been developed at the UMN as part of the NIH-funded HCP. These tools allow us to collect data with much higher temporal and spatial resolution than has been standard. These advantages are important for OCD, a disease that involves a complex circuitry involving deep brain areas and orbitofrontal regions that have been difficult to study using standard techniques. We will look at change in functional connectivity measures in OCD participants compared with controls after OCD participants receive 12 weeks of sertraline. This innovative approach will allow us to examine sertraline treatment effects on neural circuitry in OCD. To our knowledge, this has never been done and will represent an important advance. We hope to identify specific connections in the FSTC that normalize with response to SSRI treatment and identify links that do not change in treatment refractory participants. We will also explore OCD dimensions and their relations with functional connectivity links to identify possible differences in FSTC in OCD subtypes.

C. Pilot Data: ***Functional and Structural Connectivity in Adolescents with OCD*** Seventeen adolescents with OCD and 13 controls were scanned using a 32 channel head coil on the 3T Human Connectome scanner (http://www.humanconnectome.org/about/project/MR-hardware.html). Three scans were eliminated (1 subject terminated the scan early and 2 were excluded during the "scrubbing" process.[41] Anatomic Acquisition: Whole brain anatomical data with T1 contrast were acquired in 5 minutes using an MP-RAGE sequence with 1 mm isotropic resolution (TR=2530 ms, TE=3.52 ms, TI=1100 ms, flip angle=7 degrees). Processing and Analysis: The T1 images were processed using FreeSurfer. Regions of interest (ROIs) for each structure within FSTC were identified and later aligned to both functional and diffusion images.

R-fMRI: Acquisitions: Resting state BOLD data were collected using a novel multi-band EPI pulse sequence that allows for the simultaneous acquisition of multiple slices.[35,42] Resting scans lasting 12 minutes were acquired (TR=1.15 seconds, TE=30 ms, voxel size=2 mm isotropic, 60 slices, multiband=4, echo spacing 0.57ms, 600 volumes) to assess functional connectivity. The subjects were instructed to close their eyes, remain awake, and not think about anything in particular. A field map scan with identical voxel parameters to the BOLD acquisition was also acquired to allow for correction of geometric distortion. Processing and Analysis: FSL tools were used to conduct standard preprocessing steps, including skull removal, distortion

correction, motion correction, and registration to MNI space. MELODIC was applied to each dataset to identify and remove noise components using *fsl regfilt*. To further remove confound due to transient head motion, we utilized the "scrubbing" procedure advocated by Power and colleagues,[41] computing their frame-wise displacement (FD) and derivative variance (DVARS) metrics. Volumes with FD>0.5mm and/or DVARS>8 were excluded from analysis along with the previous volume and the two following volumes. Two subjects had more than 33% of volumes removed with "scrubbing" and were eliminated from analyses. There was no significant difference between the number of volumes excluded from remaining OCD subjects (n = 15, mean = 68.5, SD = 70.2) and control subjects (n = 12, mean = 60.5, SD = 70.7) (F = .16, p = 0.76). Twelve FreeSurfer ROIs from the FSTC circuit, implicated in OCD, were selected for further investigation. Frontal regions included bilateral OFC, rostral ACC, and caudal ACC. Subcortical ROIs were bilateral caudate, putamen, and thalamus. The mean time series within each ROI was computed from the scrubbed data and cross-correlated. These r values were converted to z scores using the fisher transformation. The resulting z scores were used to investigate group differences in functional connectivity and in correlation analyses with measures of OCD severity (CY-BOCS) and impairment [Child Obsessive-Compulsive Impact Scale-Revised (COIS-R)].[43]

Results: There were no significant differences between OCD and control groups on IQ, age, gender, SES, or ethnicity. Adolescents with OCD showed lower functional connectivity compared with controls on 19 of 22 connectivity comparisons (11 per hemisphere) within FSTC. Eleven of 22 connectivity comparisons were significant at $p < .05$ (Table 1). Cohen's d effect sizes for significant group differences were large (0.82 to 1.10). Our results are consistent with findings of Fitzgerald et al.[14] that show significantly lower functional connectivity between ACC and striatum and between ACC and thalamus in children with OCD compared with controls. Correlations between age and connectivity measures in the OCD sample were not significant. Using data from OCD participants, the CY-BOCS (OCD severity) demonstrated significant negative correlations with 10 of 11 connectivity segments. Parent COIS-R and child COIS-R (OCD functional impairment) showed significant negative correlations with 5 of 11 and 3 of 11 of the connectivity measures, respectively.

Table 1. Functional Connectivity Measures

	Mean Scores (SD)						
Region	**OCD (n = 15)**	**Control (n = 12)**	**P**	**Cohen's D**	**CY-BOCS r, p**	**Parent COIS-R r, p**	**Child COIS-R r, p**
R. OFC – R. Caudate	0.31 (0.14)	0.46 (0.23)	.040	0.82	---	---	-.41, p=.04
R. Caudal ACC – R. Caudate	0.54 (0.16)	0.71 (0.21)	.023	0.93	-.44, p=.02	---	-.41, p=.04
R. Rostral ACC – R. Caudate	0.44 (0.09)	0.61 (0.23)	.013	0.99	-.48, p=.01	-.41, p=.05	-.48, p=.02
R. Caudal ACC – R. Putamen	0.56 (0.18)	0.77 (0.24)	.017	0.98	-.46, p=.02	-.43, p=.04	---
L. Caudal ACC – L. Putamen	0.57 (0.16)	0.76 (0.25)	.024	0.91	-.41, p=.04	-.44, p=.03	---
R. Caudal ACC – R. Thalamus	0.60 (0.21)	0.81 (0.18)	.010	1.10	-.48, p=.01	---	---
L. Caudal ACC – L. Thalamus	0.59 (0.19)	0.75 (0.16)	.030	0.90	-.41, p=.04	-.60, p<.01	---
R. Rostral ACC – R. Thalamus	0.49 (0.17)	0.65 (0.20)	.042	0.82	-.42, p=.03	-.48, p=.02	---
R. Caudate – R. Thalamus	0.60 (0.16)	0.81 (0.22)	.010	1.07	-.51, p<.01	---	---
R. Putamen – R. Thalamus	0.57 (0.19)	0.75 (0.20)	.026	0.92	-.42, p=.03	---	---
L. Putamen – L. Thalamus	0.55 (0.17)	0.72 (0.19)	.020	0.95	-.44, p=.02	---	---

HARDI: Acquisition: DI data were collected using a novel multi-band EPI pulse sequence that allows for the simultaneous acquisition of multiple slices.[35,42] DI scans with left-right and right-left phase encoding were acquired on each subject (128 volumes with b=3000 and 9 volumes with b=0, TR=2300ms, TE=70ms, 2mm isotropic voxel, 60 slices, MB = 3, 5 minutes each). Preprocessing: Data were corrected for eddy currents and the skull was removed. FSL's *topup* program was used to correct the DI for geometric distortions. The corrected data were then submitted to FSL's *bedpost* and probabilistic tractography was then conducted between ROIs using FSL's probtractx.

Results: We demonstrate rudimentary examples of tracking within FSTC in one subject in Figures 2-4. Refinements to the tracking procedure are currently underway prior to group analyses.

Figure 2: Caudate-ACC tract
Blue: Left caudate
Red: Left ACC
Pink: White matter tract

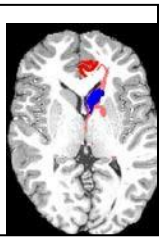


Figure 3: Caudate-pallidum tract
Blue: Left caudate
Red: Left pallidum
Pink: White matter tract

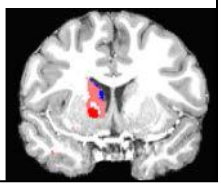
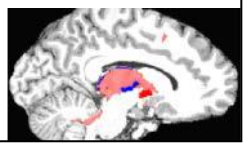


Figure 4: Caudate-pallidum
Blue: Left caudate
Red: Left ACC
Pink: White matter tract



Pediatric OCD Dimensions and Functional Connectivity: We completed an exploratory factor analysis (EFA) of CY-BOCS in 77 youths with OCD that revealed 4 OCD dimensions (58% of variance): ordering/repeating, contamination/cleaning, hoarding, and forbidden thoughts. Dimensional structure was similar to previous factor analyses of CY-BOCS.[44-47] Based on the CY-BOCS Checklist, adolescents with OCD (n = 15) were given a score on each of 4 dimensions identified in EFA. Dimensional scores were the sum of the number of items currently endorsed in each of the CY-BOCS categories that loaded most strongly on the given dimension. Significant correlations were found between (1) ordering/repeating dimension scores and 3 OFC-subcortical connections, (2) hoarding scores and 3 rostral ACC-subcortical connections, and (3) forbidden thoughts scores and 4 caudal ACC-subcortical connections. We plan to explore relations between OCD dimensions and functional connectivity in FSTC in this project.

D. Approach: The aims of this protocol are to examine connectivity in FSTC using R-fMRI and HARDI in medication-free adolescents with OCD in comparison to controls and to investigate how sertraline impacts FSTC connectivity. Our pilot studies focus on functional connectivity. ***Participants:*** We will include 25 youths (males and females) with OCD ages 8-17 years and 25 age- and gender-matched healthy controls with no psychiatric disorders and without a family history of OCD. ***Inclusion Criteria*** for OCD participants: (1) OCD as the primary DSM-IV diagnosis based on the Anxiety Disorders Interview Schedule (ADIS) for DSM-IV, Child Version,[48] and (2) CY-BOCS[49] score of greater than 15. ***Exclusion Criteria:*** (1) lifetime diagnosis of bipolar disorder, schizophrenia, or substance abuse/dependence on ADIS, (2) IQ < 80 on Wechsler Abbreviated Scales of Intelligence (WASI),[50] (3) positive urine drug screen, (4) MRI-incompatible features (e.g., metal implants, claustrophobia), (5) current or recent trial of psychotropic medication (within the past 4 weeks or past 6 weeks for fluoxetine), (6) non-response in > 2 SSRI trials of adequate dose/duration, (7) positive pregnancy test, (8) history of seizure disorder or serious head injury. **Rationale for Inclusion/Exclusion Criteria:** OCD participants will have CY-BOCS score above 15 because greater OCD severity correlated with lower functional connectivity in our pilot data. With CY-BOCS score above 15, all participants will have moderate or severe OCD. While I originally suggested excluding MDD and ADHD due to connectivity differences in youth with MDD and ADHD that might confound the differences due to OCD, these comorbidities are so common that it is extremely difficult to find subjects with "pure" OCD. A more heterogeneous sample with respect to comorbidity will be more generalizable to all youth with OCD. Further, recently published neuroimaging studies of youth with OCD have not excluded participants with lifetime MDD, ADHD, or autism (e.g., Weber AM, Soreni N, & Noseworthy MD, 2014, *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 53:129-136). I plan to include participants with lifetime diagnoses of ADHD, MDD, and autism/pervasive developmental disorder.

Recruitment: For our pilot study, we scanned 30 teenagers (17 OCD and 13 controls) in 6 months. Of 30 scans, one was excluded because the subject could not complete the scan and 2 were excluded due to excessive motion artifacts[41] (10% excluded). In addition, we will factor in an attrition rate of 10% during sertraline treatment. Therefore, to have 40 sets of scans for full data analyses, we will plan to scan 50 participants. Participants will be recruited from Dr. Bernstein's Child and Adolescent Anxiety Disorders Clinic

that has evaluated and treated over 800 youths with anxiety disorders over a 9-year period. Review of 24 months of Anxiety Clinic records indicate approximately 9 new anxiety cases per month, of which 2 cases per month have OCD. Approximately 50% of new cases with OCD are medication-free. Therefore, approximately 1 case per month or 12 new cases per year are diagnosed with OCD and are medication-free. To meet our necessary enrollment of 1-2 OCD cases per month, we will e-mail recruitment information to several hundred mental health providers and pediatricians in the Minneapolis/St. Paul metropolitan area. We will also use local newspapers, Craig's List, and Facebook which were successful methods of recruitment in our pilot study. Additional participants will be recruited via posters in the community and in clinics. To facilitate enrollment of minorities, we will actively recruit from Northpoint Clinic and Children's Hospitals and Clinics of Minnesota that serve underrepresented youths. See letters of support.

Procedure: After written informed consent and assent are obtained, a 2-3 hour diagnostic assessment Including Interviews and rating scales as described in the Assessment Instruments section will be administered by a trained interviewer with a master's degree or above. Participants meeting inclusion/exclusion criteria based on diagnostic assessment will undergo neuroimaging at the CMRR within the following week. Assessment instruments and neuroimaging will be obtained at baseline and 12 weeks later in all participants (OCD and controls). Families will be offered $30 for completion of the diagnostic assessment and $45 for imaging studies at baseline and again at 12 weeks. Before the scans, participants will (1) provide a urine sample for drug screening and (for females who have begun their menstrual periods) pregnancy testing; and (2) complete a screening questionnaire to ensure MRI safety (e.g., to exclude subjects with metal implants). After baseline assessment and scans, OCD participants will receive 12 weeks of treatment with sertraline. See Medication Management section.

Assessment Instruments: (1) *ADIS,* semistructured interview, will confirm OCD diagnosis and define comorbid diagnoses. Psychometric properties are good to excellent.[51-53] (2) *CY-BOCS and CY-BOCS Checklist,* clinician-rated semistructured instrument to assess types and severity of obsessions and compulsions. Psychometric properties are satisfactory.[17,54] (3) *Tic Questionnaire*, assesses the presence and severity of motor and vocal tics. (4) *CDI-II, evaluates depressive symptoms in children and* self-report scale to document severity of depression symptoms. (5) *Tanner Staging* will be obtained for participants using drawings of Tanner pubertal stages.[56,57] (6) *COIS-R*[43] measures functional impairment due to OCD and has good psychometric properties.[43] (7) *WASI* provides an abbreviated measure of cognitive functioning to ensure participants have IQs > 79. (8) *Family Interview for Genetic Studies (FIGS)*[58] documents family history of OCD. (9) *MASC-II,* assesses the presence of symptoms related to anxiety disorders in youth aged 8 to 19 years. (10) *Side Effects Checklist* will be completed at medication management appointments. (11) *Services Questionnaire* will be completed at the final assessment in order to assess the presence of any therapy or medications sought by participants throughout the course of the study.

Washout Period for Participants on Psychiatric Medications: For participants on psychiatric medications for OCD (SSRI or clomipramine) who have not had an adequate response to treatment (i.e., CY-BOCS score of greater than 15), Dr. Bernstein will recommend a safe schedule to gradually lower the medication dose and then stop it. The washout period (no medication) will be 4 weeks for most psychiatric medications and 6 weeks for fluoxetine. During the period of lowering and stopping the medication for OCD, there is a potential risk of discontinuation symptoms (for example, headaches or flu-like symptoms) which should be prevented by the gradual lowering of medication dose. There is also a risk of OCD symptoms worsening during the washout. If this occurs, Dr. Bernstein may recommend withdrawal from the study and re-starting the original psychiatric medication.

Medication Management: After baseline assessment and scans**,** OCD participants will receive sertraline which will be titrated using a flexible dosing schedule and individualized based on maximizing efficacy and minimizing side effects. As in POTS, we will aim to achieve target dose by week 6 of the 12-week trial. Target dose will be 100-200 mg/day, based on age and weight of the participant, given as a single dose. Sessions will be 30 minutes every week for the first 4 weeks then every other week with Dr. Bernstein who may provide support and encouragement but no CBT. Sessions will include vital signs, monitoring of side effects with a checklist, and safety evaluation. Human Subjects section includes discussion of potential side effects and their management. Compliance will be monitored with pill counts. Sertraline level will be obtained at week 12 to further document compliance with taking sertraline. Independent evaluators (blind to study hypotheses) will obtain the CY-BOCS with parent and teenager together at baseline, week 6, and week 12.

No concurrent therapies (e.g., CBT, family therapy) are permitted during medication trial. At the end of 12 weeks, participants can choose to stay on sertraline with follow up in Dr. Bernstein's Anxiety Clinic or see another physician (we will provide a referral letter), or taper off the medication. Non- or partial-responders can be referred to the Anxiety Clinic for CBT and/or crosstaper to another SSRI or clomipramine.

Neuroimaging Data Acquisition and Procedures: MRIs will be obtained at baseline and 12 weeks later in all participants (OCD and controls). The MRIs will take place at the CMRR using a standard Siemens 3T TIM Trio because the Human Connectome scanner (used for pilot data collection) has moved to Washington University. The HCP multi-band fMRI and DI sequences are available for the TIM; fMRI and HARDI data acquisition for this new study will use the multiband sequence,[35,59] advances to which have recently been developed in CMRR for the HCP. The major advantage of the new sequences includes substantially accelerating whole brain image acquisition times. For fMRI acquisitions, TRs for comparable acquisitions are 1.24 seconds for the Trio, 1.15 seconds for the Human Connectome Scanner, and 4 seconds for the Trio without multi-band acquisition. We are currently running subjects using these modified sequences (i.e., Cullen 1R21 MH094558) and obtaining excellent quality data of similar caliber to the HCP study and our pilot data. To ease anxiety, participants will have the option of practicing in the mock scanner, will be able to communicate with staff between acquisition periods, and will listen to music during parts of the scan.

First, a high-resolution structural image will be collected (parameters as in Pilot Data). These data will be processed using FreeSurfer to yield ROIs within FSTC. A field map will be collected to correct for geometric distortions in the fMRI scans. *R-fMRI:* Subjects will be instructed to keep eyes open instead of closed, which is becoming more standard in the field. EPI images with whole brain coverage will be collected with TR=1.32 seconds, multiband factor=4, voxel size=2 mm isotropic resolution, TE=30 ms, 64 contiguous AC-PC aligned axial slices (12 minutes). Such dramatic reduction of TR in comparison to standard TRs (4 sec) can substantially improve statistical significance of resting networks.[35] *HARDI:* Diffusion encoding will be performed along 128 non-collinear directions (single shell) with single shot EPI, multiband factor=3, TR=3800ms, TE=90ms, 2 mm isotropic resolution, 106 matrix, 212mm FOV, 66 contiguous slices, b value=3000, total acquisition time 9 min per scan (one PE left-to-right and one PE right-to-left). The number of directions and the high b value here are optimal for enhancing the capacity for resolution of crossing fibers. In addition, during part of the scan, the participant will be asked to complete a task. The participant will be shown a set of three numbers on a projector, and be asked to press one of three buttons depending on the numbers he or she sees. This scan will provide information about areas of the brain that are activated in OCD versus control participants during the task.

If the quality of the baseline or 12-week scan is poor due to motion artifacts from small head movements, the participant and his/her parents will be asked to consider returning for a repeat scan. This is optional.

Imaging Data Analysis: *Specific Aim #1: Functional and Structural Connectivity Analysis:* The objective of the neuroimaging data analysis is to test the hypothesis that youth with OCD have abnormal functional and structural connectivity within FSTC. Functional Connectivity: First, pre-processing steps will be conducted as described in Pilot Data, to remove effects due to physiological noise and motion and to correct for geometric distortions. Freesurfer seed regions (medial OFC, rostral ACC, caudal ACC, caudate, putamen, and thalamus) will be aligned to the fMRI data. Mean time series for spontaneous fluctuations in BOLD signal of ROI will be calculated, correlations will be determined between these time series, and correlation values will be normalized using an r-z transformation. Normalized values are then used for group comparison using age as a covariate. Analysis of covariance (ANCOVA) will be applied to the data. Correlations will be calculated to examine the relations between functional connectivity in FSTC and severity on CY-BOCS. Structural Connectivity: The structural connectivity analysis will be designed to supplement the functional connectivity analysis by investigating identical connections. The same Freesurfer ROIs as above will be aligned to the data. Following the methods of Lenglet and colleagues[60] at UMN who have mapped human basal ganglia and thalamic connectome in healthy adults, we will delineate FSTC tracts in all participants with FSL software. We will first estimate fiber orientations with a maximum number of 3 crossing fibers using *bedpostx* and then probabilistic tractography (*probtrackx)* will be used to estimate the connectivity distribution of pathways within FSTC. We will then use connectivity measures (i.e., FA, mean diffusivity, and radial diffusivity within tracts, and number of samples passing from seed to target) to examine effects of group, accounting for the size of the seed region for each individual. ANCOVA will be applied to the baseline connectivity data to test the main effect of group using age as a covariate. Correlation coefficients will be calculated to examine the relations between functional and structural connectivity. Relations between OCD dimensions and functional connectivity will also be explored using correlations. *Specific Aim #2: Effects of Sertraline on Connectivity:* Change in connectivity

data from baseline to 12 weeks will be compared between OCD and control groups using repeated-measures ANCOVA with group as between-subject main effect, time as within-subject main effect, group x time interaction effect and covariate effects of age. Group differences in connectivity at 12 weeks will be examined using t- tests. An OCD responder will be defined as a participant with a decrease of 35% in total CY-BOCS score from baseline to 12 weeks because the average decrease in OCD symptoms with SSRI treatment is 30-40%.[40] Secondary repeated measures ANCOVA will be conducted including responder groups as a between-subject main effect to explore how change over time differs between these groups. Finally, baseline connectivity differences will be compared between OCD responders and non-responders using t-tests and chi-square tests to explore connectivity differences that are associated with response to sertraline in youth with OCD (i.e. response predictors).

Power Analyses/Sample Size: *Specific Aim #1:* The study design is powered to accomplish Specific Aim #1. (a) Functional Connectivity: Pilot data from 15 OCD adolescents and 12 controls provided effect sizes for the functional connectivity power calculation. Effect sizes for significant group differences between OCD and controls ranged from 0.82 and 1.10 (Table 1). Thus, the effect size of 0.82 can be considered a conservative estimate or "upper bound" of sample size needed, while the effect size of 1.10 can be considered a "lower bound" estimate of sample size needed. For the upper bound estimate, a sample size of n = 25 per group is needed to detect significant group differences with power of 80% at alpha = .05. Using the lower bound estimate, we would require a sample size of n = 15 per group to detect significant group differences with power of 80% at alpha =.05. (b) Structural Connectivity: Feasibility of finding significant group differences in structural connectivity with the proposed sample size is based on a study with smaller sample size (14 depressed adolescents and 14 healthy controls).[61,62] Depressed adolescents had lower FA in the fiber tract of interest (tract connecting sgACC to amygdala) (p = 0.03, effect size d = 0.89), standard error of difference = 0.01125. Based on this, minimum difference required to show a difference in FA for the OCD sample using a similar approach (tractography to delineate a desired tract and measuring FA) would be at least 0.2205 units of FA. Therefore, we will require a sample of 20 per group to have power of 80% to detect a group difference at alpha =0.05. *Specific Aim #2* (Exploratory) will generate data (means, SDs and test statistics) that will inform effect sizes to calculate power and sample size for a R01 study. In the larger trial, impact of sertraline treatment on the abnormalities in functional and structural connectivity will be formally tested in youths with OCD.

Risks to Human Subjects:

Human Subjects Involvement and Characteristics:

Twenty-five participants will meet criteria for OCD on the ADIS. We will also enroll 25 healthy controls without a family history of OCD who are matched on age and gender to participants with OCD. All participants (OCD and controls) will have two scanning sessions, one at baseline and the second 12 weeks later. OCD participants will be treated with 12 weeks of sertraline, an SSRI medication.

Inclusion Criteria:

1. Ages 8-17 years.
2. Female or male.
3. Meets DSM-IV criteria for OCD as the primary diagnosis based on ADIS.
4. CY-BOCS score greater than 15.

Exclusion Criteria:

1. Lifetime diagnosis of bipolar disorder, schizophrenia, or substance abuse/dependence on ADIS.
2. IQ < 80 on WASI.
3. Positive urine drug screen.
4. History of seizure disorder or significant head injury.
5. MRI-incompatible features (e.g., metal implants other than dental fillings, claustrophobia).
6. Fluoxetine treatment within the past 6 weeks or treatment with a different psychotropic drug within the past 4 weeks.
7. Non-response to 2 previous SSRI trials of adequate dosage and duration.
8. Positive pregnancy test.
9. Presence of any psychiatric disorder on ADIS (for control subjects only).
10. Family history of OCD (for control subjects only).
11. Females with OCD who are unwilling to use an acceptable method of birth control if they are sexually active will be excluded.

Sources of Research Materials:

Research materials obtained from human participants include clinical interviews and rating scales. In addition, neuroimaging studies (HARDI and fMRI) will be obtained. These materials will be collected for the purposes of the research study.

Potential Risks:

Potential risks of participating in the study include:

1. Issues related to confidentiality.
2. Gathering of sensitive information during interviews and on rating scales.
3. Anxiety about having MRI scans.
4. Sertraline side effects.

SSRIs are the pharmacological treatment of choice for pediatric OCD.[18] They are the first-line standard medication treatment for OCD in children and adolescents. Sertraline, an SSRI, is generally well tolerated~~,~~; however, side effects can occur. Potential side effects of sertraline include stomachaches, insomnia, headaches, and sexual side effects. In addition, there are psychiatric side effects including motor activation, suicidal ideation/suicidal behaviors, and precipitation of manic symptoms. All antidepressant (including sertraline) have an FDA black box warning for children, adolescents, and young adults. The black box warning is for the rare possibility of suicidal ideation or suicidal behavior while on an antidepressant. This is based on a

meta-analysis of 24 short-term, placebo-controlled randomized trials of antidepressants for treatment of pediatric anxiety disorders (including OCD) or depressive disorders. The meta-analysis included >4,500 children and adolescents and showed a 2% risk of suicidal ideation or behavior on placebo and 4% on antidepressants.[63] There were no completed suicides in the 24 studies.

Adequacy of Protection Against Risks:

Recruitment Methods and Informed Consent:

Recruitment of participants with OCD will be through the Principal Investigator's Child and Adolescent Anxiety Disorders Clinic at the University of Minnesota Medical School. Dr. Bernstein and her colleagues have evaluated and treated over 800 youths with anxiety disorders over a 9-year period. Referrals to the Clinic are from school personnel, pediatricians, child psychiatrists, and psychologists. We have strong connections to school personnel, community primary care physicians, and mental health practitioners. Thus, recruitment for the proposed study will be through well-established referral sources. OCD is one of the most common anxiety diagnoses in our Clinic. Approximately 2 new OCD patients are evaluated in the Clinic each month including approximately one who is unmedicated.

In addition, we have e-mail and address lists for several hundred pediatricians and mental health providers in the Minneapolis/St. Paul metropolitan area that will be used for recruiting children with OCD. Families with a child with OCD and healthy controls will also be recruited through flyers on bulletin boards in the community and in clinics, radio advertisements, and advertisements in newspapers. In our pilot study, we used advertising in Facebook which was an effective method of recruiting. A description of the study will be posted on the OCD Twin Cities Chapter and International OCD websites.

If the potential participant is being seen in the Child and Adolescent Anxiety Disorders Clinic, the parents and child will be asked if they would be interested in being included in the study at the conclusion of their Clinic visit. Documentation will be presented at that time, and parents will have time to ask any questions about the proposed study. Parents will be encouraged to take documentation materials with them to consider their child's participation, and will be allowed to bring back or mail back the signed documentation. If the potential participant is a healthy adolescent, interested parents will be asked to contact research personnel through ads in local newspapers or Facebook, or via flyers posted on bulletin boards.

Written informed consent from parents and written informed assent from adolescents will be obtained. Gail Bernstein, MD, PI, Kathryn Cullen, MD, Co-I, and Alexandra Zagoloff, Ph.D., Co-PI will be obtaining informed consent from participants and their parents. The project coordinator will also be obtaining informed consent after undergoing training from the PI in obtaining informed consent.

Protections Against Risk:

1. Issues Related to Confidentiality: All study staff will complete the U of MN HIPAA training. All data will be identified with subject number and will be stored in locked file cabinets with access only to designated study personnel. Other than research staff directly interfacing with participants (e.g., independent evaluators), only PI and Co-I will have access to subject data and subject identities. This approach is very likely to be effective in achieving protection of confidentiality.
2. Gathering of Sensitive Information: The study personnel will be trained to be sensitive to the early signs of distress, to provide support, and to allow the participant the opportunity to stop at any time should he/she become uncomfortable or have questions. The PI or Co-I will always be available for consultation if necessary and the subject will be allowed to withdraw from the study at any time.
3. Anxiety about Scanning: The MRIs will take place at the CMRR, where a mock scanner is available. The mock scanner is a practice scanner that can be used to prepare the participants for the MRI. Participants who are anxious about the MRI will have the option of practicing in the mock scanner. They will be able to communicate with the scanners throughout the scanning session. The participants will have the opportunity to listen to music for relaxation during most parts of the scan. In the event that they are too uncomfortable with the procedure, the subjects will not be scanned.

4. Sertraline Side Effects: All participants and their parents will receive psychoeducation about sertraline and the potential risks and benefits. They will be encouraged to ask questions and will be engaged in a dialogue about sertraline and potential risks and benefits. Participants will be seen for 30 minutes every week for the first 4 weeks then every other week by Dr. Bernstein for medication management. Weight and vital signs will be obtained at each visit. There is no need for EKGs, laboratory studies, and blood levels when treating with sertraline on a short-term basis. Side Effects Checklist will be administered by Dr. Bernstein at each appointment. Dr. Bernstein will assess for suicidal ideation at each appointment. To minimize the potential for side effects, treatment will be initiated with a low dose of sertraline followed by systematic increases based on side effects and clinical response. We will use a flexible dosing schedule which is individualized based on minimizing side effects and maximizing efficacy. We aim to reach target dose by week 6. Minor side effects may be managed by dose adjustments. If ~~any~~ any adverse medication reactions occur, the sertraline will be withdrawn and Dr. Bernstein will follow the patient closely until the adverse reaction remits. At the end of the 12 weeks, participants can choose to stay on sertraline and follow up in Dr. Bernstein's Anxiety Clinic for medication management or with another physician (we will provide a referral letter), or taper off the medication. Non- or partial-responders can be referred to Dr. Bernstein's Clinic for CBT and/or crosstaper to another SSRI or clomipramine. If the family would like to taper off the medication, Dr. Bernstein will supervise a gradual taper down in order to avoid withdrawal effects and will monitor for potential recurrence of OCD symptoms. Dr. Bernstein has years of experience treating children and adolescents with sertraline. She teaches and supervises residents and fellows who are prescribing this medication in the Child and Adolescent Anxiety Clinic at the UMN.

In order to protect against risk of harm to youths, several steps will be taken. Consent will be obtained from parent(s) and assent from adolescents. Youths and parents will be allowed to discontinue participation at any time. We believe that adequate protections against risks are in place as documented earlier in this section.

Potential Benefits of the Proposed Research to Human Subjects and Others:

The results of the psychiatric interviews and rating scales can be shared with families. This information could be beneficial in the care of children and adolescents with OCD. The findings will advance knowledge in the area of neuroimaging for pediatric OCD. In addition, the study will contribute to the knowledge about underlying mechanisms of obsessions and compulsions and site of action of SSRIs.

Participants with OCD will receive 12 weeks of treatment with sertraline. They will attend medication management appointments with a child and adolescent psychiatrist. Potential benefits include relief of OCD symptoms from the sertraline.

Importance of Knowledge to be Gained:

If our proposed model of dysfunction in FSTC is supported by the neuroimaging findings, this will represent an important step in the effort to understand the neurobiology of pediatric OCD. We hope to delineate specific neural changes that underline response to sertraline. The findings of this study will inform future studies about the neurobiology of OCD and treatment response to SSRI medications. This study will yield information regarding the connectivity in the FSTC related to OCD and will move the field closer to understanding the etiology of pediatric OCD.

Data and Safety Monitoring Plan:

Data and safety monitoring will take place continuously throughout the course of the study. The PI will be responsible for coordinating and overseeing all data and safety monitoring efforts which include (but are not limited to) supervising all recruitment efforts; evaluating risks versus benefits for participants; and monitoring the quality, validity, and reliability of data gathered. Some data monitoring efforts will be delegated to research staff; however, the PI will oversee all monitoring activities through regularly scheduled meetings and review of data summaries. The PI has selected two University of Minnesota faculty members (Andrew Barnes, M.D., Department of Pediatrics, and Suma Jacob, M.D., Ph.D., Department of Psychiatry) uninvolved with the present study to serve on a Data and Safety Monitoring Board. The Board will review the data and safety of the study approximately once per year.

All data collected will remain confidential and will be in file folders which will be stored in locked file cabinets in a locked room. File folders will contain only subject identification numbers. Only the PI, Dr. Cullen, Co-I, and Project Coordinator will have access to the master file containing names, identification numbers, and addresses. The master file will be kept separate from the data collection instruments and from the data file on the computer system protected by password. Information given to persons other than project personnel will occur only with written parental consent and for the specific purpose documented on the release of information form. The imaging data will be completely de-identified. All imaging data will be stored in the CMRR which is highly secure. All processing will be conducted using the Minnesota Supercomputing Institute resources.

Potential Adverse Events:

The possibility of the following adverse events is low. We will monitor for:

1. Suicidal or homicidal ideation or behavior.
2. Worsening of clinical condition of children with OCD (i.e., symptoms become severe so that assessment for possible psychiatric hospitalization is needed).
3. Suspected child abuse.

Protocols for Managing Adverse Events:

Project staff (including project coordinator and independent evaluators) will be trained by Drs. Bernstein and Cullen about how to assess for suicidal and homicidal ideation, how to identify deterioration of an adolescent's clinical condition, and what clinical situations raise concern about suspected child abuse or neglect:

1. If a child is identified as suicidal or homicidal, this will be reported to Dr. Bernstein, PI, or Dr. Cullen, Co-I, who will evaluate the patient and provide psychiatric care as needed. If suicidal ideation or suicidal behavior is determined to be secondary to sertraline, the sertraline will be discontinued and psychiatric care will be provided by the PI or Co-I. If necessary, the adolescent will be referred to the Emergency Room**,** or Behavioral Evaluation Center at the University of Minnesota Medical Center – Fairview, as deemed appropriate, based on clinical information. If evaluation results in recommendation for inpatient hospitalization, this can be arranged at the Child and Adolescent Psychiatry Inpatient Unit at the University of Minnesota Medical Center – Fairview.

2. If worsening of clinical condition is noted by a research staff member, it will be reported to Dr. Bernstein, PI or Dr. Cullen, Co-I. They will provide psychiatric care as needed and/or facilitate the child being evaluated in a local mental health clinic**,** the Emergency Room**,** or Behavioral Evaluation Center at the University of Minnesota Medical Center – Fairview, as deemed appropriate, based on clinical information. If the evaluator recommends inpatient hospitalization, admission to the Child and Adolescent Psychiatric Unit at the University of Minnesota Medical Center – Fairview can be arranged.

3. If child abuse is suspected, the research staff member will immediately report to Dr. Bernstein or Dr. Cullen who will then assist the staff member in reporting to Child Protection and/or police immediately.

Parents will be given office phone numbers for the Project Coordinator, Dr. Bernstein and Dr. Cullen to call during office hours in case any of the clinical situations described above occur and they will be given Dr. Bernstein's cell phone number for after hours and weekends.

Reporting Adverse Events:

All serious adverse events (e.g., psychiatric hospitalization) that occur during the study will be reported within 24 hours by the PI to the Institutional Review Board (IRB) at the University of Minnesota. Yearly written reports regarding data and safety monitoring will be provided to the University of Minnesota IRB and the NIMH Project Officer.

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