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Effects of ondansetron in obsessive-compulsive and tic disorders

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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1 Purpose of the Study and Background

1.1 Purpose of the Study

The overall objective of this study is to test the use of 4 weeks of 24 mg daily ondansetron as compared to placebo on symptoms and brain functioning in patients with obsessive-compulsive disorder (OCD) and tic disorders (TD). This is the second phase (R33 phase) of a 2-phase R21/R33 project. In the first (R21) phase, we found that single doses of 24-mg ondansetron significantly reduced activation of insula and sensorimotor brain regions in healthy volunteers.

Despite extensive research, 30-60% of OCD patients do not respond adequately to first-line treatments (1,2), with similarly disappointing rates in TD3. Treatment presents a particular challenge because these disorders are heterogeneous, with clusters of symptoms likely derived from differing neural etiologies. The Research Domain Criteria (RDoC) approach seeks to address this problem by investigating transdiagnostic components of behavior that more closely align with brain circuitry (4,5). This application focuses on sensory phenomena (SP) as a critical component of both OCD and TD with a discrete neural circuitry centered on the insula and somatosensory cortex. Consistent with the experimental therapeutic approach, the current project will test the ability of ondansetron, a 5-HT3 antagonist acting on sensory pathways, to engage this neural circuitry in order to modulate sensory phenomena.

Sensory phenomena are uncomfortable or aversive sensations that precede compulsions in OCD and tics in TD (6-10). They are highly prevalent, occurring in up to 70% of OCD patients (7-9) and 93% of TD patients (11,12). In the majority of cases, SP may actually drive the repetitive behavior (7,13,14) and are experienced as highly distressing (7,12,13,15), yet these symptoms are not well addressed by standard treatment approaches in OCD or TD (6,16-19). The current project will address this issue by investigating the novel use of ondansetron as a means to target neural systems underlying symptoms of SP. Much research points to a discrete circuit involved in detecting sensory information from the body, with activation of the insula and somatosensory cortex associated with the conscious perception of visceral and somatic sensation (20-25).

Our group (26-28) and others (29-35) have found hyperactivation and hyperconnectivity of insula and somatosensory cortex in OCD and TD. Furthermore, “urges-for-action” – everyday sensory experiences in healthy individuals (such as the urge to blink) that share phenomenological similarity with abnormal urges in OCD and TD – are linked to activation of the insula, somatosensory cortex, and adjacent motor regions (36-40). Taken together, these data provide strong rationale for targeting insula and somatosensory cortex as a means to treat SP in OCD and TD.

FDA-approved for nausea and vomiting (41), ondansetron is a promising novel candidate for the modulation of neural circuits related to SP. Ondansetron has been shown to decrease overall symptom severity in both OCD and TD (42-48), although the neural mechanisms associated with these effects are unknown. Ondansetron is an antagonist at 5-HT3 receptors, which are ligand-gated ion channels located abundantly throughout the peripheral and central nervous system (Wilde & Markham 1996; Ye et al., 2001; Farber et al. 2004; Jakab et al., 2000). The highest density of central nervous system (CNS) 5-HT3 receptors are located in subcortical regions of the interoceptive circuit, including the dorsal horn of the spinal cord, the NTS, and area postrema (Ye et al., 2001; Farber et al., 2004; Bloom & Morales 1998). In addition, 5-HT3 receptors are located in limbic (hippocampus and amygdala) and cortical regions (Jakab & Goldman-Rakic 2000; Bloom & Morales 1998; Tecott et al., 1993; Tuerke et al., 2012), with receptor transcripts identified throughout the cortex including in insula and somatosensory areas (Bloom & Morales 1998; Hawrylycz et al., 2012). Data from the R21 phase showed that single 24 mg doses decreased activity in the insula and somatosensory cortex in healthy subjects, raising the possibility that ondansetron may reduce disorder severity by targeting sensory circuits. Building on these promising findings, this proposal will investigate the effects of 4 weeks of ondansetron on neural targets and SP in a sample of OCD and TD patients.

1.2 Hypotheses

Aim 1 of the study (the R21 phase) has been completed. This application applies only to the R33 phase (Aim 2).

Aim 2 (R33): Further validate neural targets in a sample of OCD and TD patients with sensory phenomena. Employing a placebo-controlled parallel group design, we will measure the effects of 4 weeks of optimal dose ondansetron (that with the greatest effect on neural targets in the R21 phase: 24 mg) on activation and connectivity of insula and somatosensory cortex in patients with at least moderate SP (measured with the Sensory Phenomena Scale7). Hyp. 2: Compared to placebo, ondansetron will be associated with greater decreases in the activation and connectivity of insula and somatosensory cortex from baseline to week 4.

Aim 3 (R33): Examine the relationship between target engagement and clinical symptoms. Hyp. 3a: Compared to placebo, ondansetron will be associated with greater reductions of SP from baseline to week 4, Hyp. 3b: Decreases in overall symptom severity (measured with Y-BOCS and Yale Global Tic Severity Scale) from baseline to week 4 will be mediated by reductions in SP, Hyp. 3c: Decreases in SP between baseline and week 4 will be mediated by reduced activation and connectivity of insula and somatosensory cortex.

1.3 Background

Many psychiatric disorders are associated with altered sensory experiences arising from within the body (Rosario et al, 2009). Examples include increased experience of sensations or urges in muscles, skins, joints or visceral organs in tic disorders, OCD patients with symptoms of “not just right experiences” or disgust sensitivity, and impulse control disorders (ICDs) such as trichotillomania or skin-picking. In OCD, sensory phenomena occur in approximately half of patients, are associated with earlier age of onset (Ferrão et al., 2012), and may be harder to treat with classic cognitive-behavioral approaches to OCD (Summerfeldt, 2004). Of interest, sensory phenomena in OCD are associated with Tourette’s syndrome (Ferrão et al., 2012) and respond to pharmacological treatments primarily used for tics (Shavitt et al., 2006). As such, abnormal sensory processing may be a basic mechanism that links various psychiatric disorders.

The process of attending to body sensations is referred to as interoception, and broadly includes the detection of, or attention to, experiences arising from the viscera and soma (Cameron 2001). In healthy individuals, research has revealed a cortical interoceptive network involving insula, anterior cingulate cortex (ACC), and somatomotor cortex (Simmons et al., 2012; Paulus & Stein, 2010; Cameron 2001, Khalsa et al., 2009; Critchley et al., 2004). Furthermore, our group (Stern et al., unpublished data) has obtained pilot data indicating that sensory phenomena in OCD are associated with activity in this interoceptive network (insula and somatosensory cortex).

Ondansetron (OND) is a good candidate for modulation of the interoceptive circuit. It is a selective 5-HT3 (serotonin) receptor antagonist that acts on both peripheral and central receptors (Ye et al., 2006; Haus et al., 2004). OND has long been used to treat nausea and vomiting due to chemotherapy, radiation therapy, anesthesia, and opioid-induced emesis. The mechanism of action of OND for the treatment of nausea is thought to be its action on both peripheral enterochromaffin cells of the intestine as well as on the area postrema (chemoreceptor trigger zone) and the nucleus of the solitary tract (a key node of the interoceptive network). OND has also been used in a variety of conditions other than nausea and vomiting, including irritable bowel syndrome, pruritus, alcohol and substance dependence, and psychosis (Ye et al., 2006; Farber et al., 2004; Haus et al., 2004). Particularly relevant for the current application, OND has been used alone or as adjunctive therapy for the treatment of both OCD and Tourette’s disorder, showing some efficacy in small clinical trials (Toren et al., 1999; 2005; Soltani et al., 2010; Hewlett et al., 2003; Pallanti et al., 2009). The mechanisms by which ondansetron improves symptoms in OCD and tic disorders are unknown, but a recent study found that OND application directly into the insula decreased disgust reactions in rats (Tuerke et al.,

2012). These data suggest that ondansetron's clinical efficacy in OCD and tic disorders could be related to effects on interoceptive circuit activity in the insula, a possibility that is being explored in the current protocol.

The current project has two parts (R21 and R33 phases). We completed the first, R21 phase of the project, which was a dose-response investigation of 8, 16, and 24 mg of ondansetron on brain function in healthy volunteers, in May of 2017. From this study, we determined that the optimal dose for modulation of brain circuits of interest is 24 mg. The R33 phase uses a randomized double-blind parallel group design to compare the use of this dose (24 mg) vs. placebo taken daily for 4 weeks to reduce sensory symptoms and alter brain functioning in patients with OCD and tic disorders.

1.3.1 References

For references, please see pages 14-22 in the R21/R33 application.

2 Characteristics of the Research Population

2.1 Number, Gender, Age and Racial/Ethnic Origin of Subjects

2.1.1 Number

It is expected that approximately 45 participants will be enrolled at NYU Langone Medical Center in order to produce 30 eligible participants at this site. Approximately 45 participants will also be enrolled at Nathan Kline Institute to produce 30 evaluable participants at that site. Participants enrolled at NYU will primarily be recruited from flyers throughout the NYU campus, internet advertisements, newspaper advertisements, recruitment emails to university mailing lists and previous studies from prior studies conducted by the lab and will directly contact the Research Coordinator for more information.

2.1.2 Gender

Subjects would include both male and female volunteers.

2.1.3 Age

Subjects will be recruited between the ages of 18 to 60.

2.1.4 Racial/Ethnic Origin

Subjects will be of any racial or ethnic origin.

2.2 Inclusion Criteria

<u>Criteria for all participants</u>

- Ages between 18 and 60 years
- Fluent (speaking and writing) in English.
- Diagnosis of obsessive-compulsive disorder (OCD) or tic disorder (OCD) according to DSM-5 criteria as determined with the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998; J Clin Psychiatry, 59 Suppl 20, 22-33)
- Moderate or greater disorder severity: ≥ 16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) or ≥ 20 on the Yale Global Tic Severity Scale (YGTSS)
- Moderate or greater severity of sensory phenomena (≥ 6 on the Sensory Phenomena Scale, SPS)
- Stable on psychotropic medication for at least 6 weeks or unmedicated.

<u>Additional criteria for all participants who are screened remotely</u>

- access to a computer or phone with a camera

2.3 Exclusion Criteria

- Present or previous diagnosis of psychosis, bipolar disorder, or major developmental disorder (autism spectrum disorder with intellectual disability, intellectual developmental disorder) based on DSM-5 criteria
- Present diagnosis of alcohol or substance use disorder (moderate or severe) based on DSM-5 criteria
- Current moderate or higher suicidality as assessed through the C-SSRS with clinician assessment that there is significant risk for the subject if they participate
- Major neurological illness (e.g., self-reported history of organic mental syndromes, head trauma with sequelae, chronic and severe migraines, history of seizures, or other significant medical illness that would make participation unsafe or unfeasible as determined by a licensed clinician on the team)
- Any disability or health problem that prevents them from completing study procedures (e.g. back problems, severe carpal tunnel syndrome, impaired vision that is not corrected with glasses or contact lenses, etc.).
- Pregnant or nursing women
- Positive urine toxicology (except for currently prescribed medications or cannabis) or positive pregnancy test
- MRI contraindications such as claustrophobia, ferrous implants, braces, or pacemakers
- Subjects with a medical condition or other predisposition that increases the risk of adverse effects when taking ondansetron (by self-report or medical clearance testing). These include, but are not limited to, individuals with drug allergies or known hypersensitivity to ondansetron (or other 5-HT3 antagonists), heart disease, congestive heart failure, heart rhythm disorder, congenital long QT syndrome, electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia) or hepatic impairment.
- All subjects will have a thorough review of their medical history and concomitant medications to evaluate for potential interaction effects that may impact serum ondansetron concentrations. Participants felt to be at risk of having a significantly reduced effective serum ondansetron concentration (e.g., due to concomitant carbamazepine or phenytoin) or elevated effective serum ondansetron concentration (e.g. due to liver disease, significant potential P450 isoenzyme inhibitors, or known P450 isoenzyme deficiencies) may be excluded at the determination of the study physician
- Subjects who report taking apomorphine (which is a contraindication to ondansetron)
- Subjects taking a 5-HT3 antagonist (as cross-reactivity with other 5-HT3 antagonists has been reported)
- Subjects with abnormal (with clinical significance) EKG including abnormal QT will either be excluded from participation or, if eligibility is unclear, will be referred to a cardiologist for further determination of safety for participation. Subjects with QT prolongation (QTc>450 ms for men and >470 ms for women) will be excluded.
- Subjects with abnormal liver function, electrolytes, or other lab results (as determined by CBC/CMP) will be excluded from participation if the study team physician determines these abnormalities make it is unsafe for them to participate
- Present diagnosis of Phenylketonuria (PKU).
- Excess ginger consumption (consumption in meal or with supplements > once per week)

2.4 Vulnerable Subjects

No member of vulnerable groups such as children, pregnant women, prisoners, institutionalized individuals, or others members of vulnerable populations will be recruited. However, Illiterate subjects are being excluded from enrollment as it is important that subjects understand the procedures and concepts involved in the research and the implications of taking the medication. The capacity to provide informed consent will be performed by a licensed physician at the screening visit. If there is any question regarding whether a participant has the capacity to consent, we will not enroll them in the study.

Participation in our study requires a high degree of comfort with the English language both in oral and written form. The study procedures involve extensive in-person interviews involving regarding complex psychological concepts that will be difficult to explain to someone who does not have a fluent understanding of the English language. Furthermore, subjects fill out multiple English-language questionnaires and perform fMRI and behavioral tasks that require a good understanding of English.

3 Subject Identification, Recruitment and Consent/Assent

3.1 Method of Subject Identification and Recruitment

Participants will be identified through the following methods:

1. Flyers - We will put up flyers in different high-traffic, approved areas around NYU (pharmacies, libraries, coffee shops) and on the NYU Langone Medical Center campus.
2. Internet Advertisements - We have "internet advertisement" language (included as attachment in this application) that we will use on Internet sites such as Craigslist, Research Match, Facebook, the International OCD Foundation (IOCDF) website, as well as Google Ads. With regard to social media, we have a dedicated lab Facebook page where we will be posting our approved ads. On this webpage we also occasionally post links to popular science articles about OCD and treatments for OCD. People are able to like and comment on our posts, and the posts would be made visible to the public, that is, anyone who visits our page. Although we do not currently, we may in the future wish to use the paid advertising feature that involves promoting our Facebook page so that a specified number of people see it per day. We will also google adwords that will be linked to our Facebook page and/or to our NYU webpage when it is set up with the approved language as submitted in the IRB application. We may wish to use a recruitment service called StudyKik to advertise our study as well. Our approved ad will be listed on the StudyKik website where potential participants can sign up to learn more about and participate in research studies.
3. Websites - We will upload details of the study and how to participate on the webpage of our lab (Psychiatric Neurocognition Lab). On this website, on a “How to Participate” page, we would like to include a description of the study and an optional entry form for individuals interested in participating in our research to complete. Individuals would be asked to enter their name and contact information. This entry form is powered by surveymonkey.com, and will be embedded into the webpage. To protect subjects’ privacy, all content submitted through the survey will be encrypted with SSL protection. Responses will only be accessible to study personnel through a password-protected surveymonkey account.
4. We may reach out to participants from the lab’s own prior studies at Mount Sinai. We will only contact participants who have agreed to be recontacted during the initial consent.
5. Reach out to physicians and psychologists in the community for referrals into the study via email or letter. If we solicit referrals, we will submit the email or letter text to NYULH IRB for prior approval. We would then e(mail) this approved text to clinics and clinicians with publicly available contact info (i.e. those clinics that provide their contact information on a webpage or in psychology/psychiatric newsletters/journals).
6. Sending recruitment emails to the mailing list of different universities in New York.
7. Place advertisements in local newspapers.
8. This study will utilize EPIC to identify potentially eligible subjects in the NYU health system. For patients who have a recorded diagnosis of Obsessive-Compulsive Disorder or Tic Disorder/Tourette’s Disorder, the study team will review age and other psychiatric and medical diagnoses to determine initial eligibility. If the patient appears eligible based on the EPIC search, an email (if email address is available) or written letter (if email address not available or if the email address is defunct) will be sent to them that briefly describes the study and provides the study team contact information (see letter included in application).

   We will also utilize DataCore to assist in the management and procurement of search queries and reports which will be used to execute EPIC searches. The research team will provide DataCore with

the study eligibility requirements. DataCore will generate a report of individuals who meet those eligibility requirements. This report will be replicated in EPIC which will allow the study team to identify those individuals and view their health and contact information. For patients who have a recorded diagnosis of obsessive-compulsive disorder or tics/Tourette's disorder, the study team will review age and other psychiatric and medical diagnoses to determine initial eligibility. If the patient appears eligible based on the EPIC search, an email (if email address is available) or written letter (if email address not available or if the email address is defunct) will be sent to them that briefly describes the study and provides the study team contact information (see letter included in application). Additionally, an approved message may be sent via the MyChart message portal. Any recruitment information sent by email will utilize Send Safe email.

All study team members (Stern, Iosifescu, Brown, Shahab) are seeking approval to access the EPIC search results. Although Brown and Shahab will be doing the initial searches, they may have questions they will want to ask the PI (Stern) or study team physician (Iosifescu) to clarify information they view and/or to further determine whether something in the chart affects eligibility. Searches will be run to first look for diagnosis codes for OCD or Tic Disorders, and then, within that group, for subsets of patients who do not meet exclusionary criteria. To this end, PHI including name, contact information, age, and medical and psychiatric diagnoses will be viewed. The study team will search the EPIC database multiple times over the course of a year; the exact number of times that the team searches will depend on how many results each query produces (i.e. highly successful queries with a lot of eligible subjects will lead to less frequent searching).

Once potential subjects have been identified through the above method, the study team will notify the treating physician that they have patients eligible to participate and that the study team would like to contact potential subjects directly, either by letter or email. Once contact is made with the potential subject, approved recruitment language (attached letter) will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

9. If the patient reports that they have a sibling (SIB) during the administration of the Family History Questionnaire at the baseline visit, the experimenter will attempt to recruit the SIB for our other project, (#17-01606) "Neurobiology of sensory phenomena in obsessive-compulsive disorder". The experimenter will provide an IRB-approved letter that explains the study and will ask for permission to contact their SIB to tell them about the study. If the patient agrees, he/she will indicate that on the letter and write down the SIB's contact information.
10. We will utilize the service BuildClinical's online ads, landing page, and screening questions. We have entered into a contract with the online study recruitment company, BuildClinical LLC. BuildClinical is a data-driven software platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. BuildClinical has worked with IRBs in the US to ensure they adhere to all the appropriate guidelines and procedures. On our behalf, BuildClinical has creating several study-specific advertisements (submitted as "BuildClinical R33 Online Ads) designed to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On this landing page (submitted as "BuildClinical Landing Page") the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform and is to be reviewed by the study team.

3.2 Process of Consent

Informed consent will be obtained either remotely or in-person by a member of the research team authorized to obtain consent. The decision to conduct remote vs. in-person visits will be made according to NYU Langone rules and procedures for research participant contact during the COVID crisis. As long as the study team determines in-person contact presents an unecessary risk for the

participant and study staff, screening procedures will be conducted remotely via video conferencing.

A) Remote e-consent processes: To reduce the need for in-person contact during the COVID-19 pandemic, we may collect consent via Webex video conferencing. A trained member of the study team will schedule a time with interested participants to go over the written consent via Webex. The researcher will email or mail a copy of the consent to participants in preparation for the remote e-consent. After going over the written consent via Webex, the researcher will send the consent via a REDCap link where the participant has the opportunity to read a copy of the written consent and sign electronically, confirming that they read and understood the consent. The researcher will also document on REDCap the time and date of the consent and note that the consent process was done via Webex due to COVID-19. The researcher will also review the Nathan Kline Institute (NKI) Scanning Consent Addendum, which provides information on the research procedures conducted at the Nathan Kline Institute.

The individual obtaining consent will provide an oral explanation of the research study during the Webex meeting. The individual obtaining consent will be responsible for assessing the subject's comprehension of the information presented and the risks/benefits of participating in the study. Individuals obtaining consent will follow HIPAA guidelines in protecting privacy. A digital version of the signed form will be stored on the REDCap server. A member of the research team will print a copy of the signed/dated consent form and it will be filed as documentation of informed consent in locked file cabinets at NYU Langone Medical Center.

B) In-person consent processes: When it is determined to be safe to resume in-person appointments due to the COVID-19 pandemic, in-person informed consent processes will be done in a quiet room in the psychiatry department offices at One Park Avenue at NYU Langone. Access to the facility is limited to authorized personnel. The individual obtaining consent will provide an oral explanation of the research study and allow the subject to read the consent form. The individual obtaining consent will be responsible for assessing the subject's comprehension of the information presented and the risks/benefits of participating in the study. Individuals obtaining consent will follow HIPAA guidelines in protecting privacy. Subjects will receive a copy of their signed/dated consent form. The original signed/dated consent form will be filed as documentation of informed consent in locked file cabinets at NYU Langone Medical Center.

4 *Methods and Procedures*

4.1 Study Procedures

All procedures described below (see schedule of events on the next page for overview) will be done for research purposes and are not part of standard clinical care.

A) Initial Contact and Phone screening (Phone, email, in person) (20-30 minutes)
All potential subjects will first come into contact with a research team member via phone, email, or in person. Either the potential subject will contact the research team member of his or her own accord, or the research team member will initiate first contact. Team members will initiate first contact only if the subject has previously signed a document (such as consent form) agreeing to be re-contacted. At this time, the potential subject will be told what the experiment generally involves, including time commitment and compensation.

All subjects who are interested in participating in the study will be asked a series of initial screening questions to determine initial eligibility (see attached phone screen), including questions about physical and mental health and MRI safety. Verbal consent is obtained prior to asking questions on the phone screen (see introduction in phone screen). The Sensory Phenomena Scale (SPS) may also be administered during the phone screen to

determine whether patients' sensory symptoms are severe enough to be eligible for the protocol. Participants who encounter our BuildClinical advertising may elect to answer screening questions prior to the phone screen with a member of the research team. These questions are not a substitute for a comprehensive eligibility screening, and only ask about broader inclusion/exclusion criteria in significantly less detail. If a subject meets eligibility recruitments based upon the phone screen, they will be scheduled for a screening visit on Webex or in-person at the NYU Langone Medical Center with a psychiatric evaluation and medical screening will be conducted. If the subject declines participation, the phone screening questionnaire will be destroyed and no protected health identifiers for the potential subject will be retained.

Schedule of Events:

Overview: If a patient is eligible based on the phone screen and wishes to participate, they will be asked to complete four study visits including: one screening visit online via Webex videoconferencing or in-person at NYU Langone Medical Center (Psychiatry department offices at One Park Avenue) or the Nathan Kline Institute (NKI) in Orangeburg, NY; one baseline scan visit at NKI; one mid-trial visit online via Webex or in-person at NYU Langone or NKI; one final (exit) scan visit including medical screening at NKI. They will also complete 2 phone calls during the trial and one follow-up phone call after the trial has ended.

(B) Screening Visit (1-2 visits, 3-4 hours)

1. Informed Consent (30 minutes)
At the Screening Visit, a member of the research team present participants with the consent form. The individual obtaining consent will review the form and answer any questions the subjects may have. This will be done through Webex for remote visits.

2. Psychiatric and Symptom Evaluation (90-180 minutes): If consent is acquired, we will perform a longer screening for psychiatric history using the Mini International Neuropsychiatric Interview (M.I.N.I., Sheehan et al. 1998). This tool contains diagnostic modules for the assessment of several psychiatric conditions including mood, substance use, anxiety, psychotic, and eating disorders. The Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) will be used to determine risk for suicide. Sensory phenomena will be assessed using the Sensory Phenomena Scale (SPS, Rosario et al., 2009). This semi-structured scale assesses the presence and severity of different types of SP preceding or occurring at the same times as repetitive behaviors in OCD. The SPS contains a checklist with examples of different types of SP encompassing all previous descriptions in the literature, including physical sensations, "just right" sensations, incompleteness, general energy or inner tension buildup, and urges. OC symptoms in OCD patients will be assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS, Goodman et al., 1989), while tics symptoms in TD patients will be assessed using Yale Global Tic Severity Scale (YGTSS, Leckman et al., 1989). Psychiatric symptoms including suicidality will be confirmed by a licensed clinician on the protocol to ensure participant safety. If the clinician determines that the subject is at an immediate and significant health risk, they will be sent to the nearest Emergency Department. If the visit is conduted remotely via videoconferencing and no study clinician is available at that moment to speak with the participant, a member of the study team will direct the participant to call 911 or go to the nearest psychiatric emergency department. We will also have subjects complete several self-rated scales or questionnaires to assess a variety of other symptoms: Beck Depression and Anxiety Inventories (Beck et al. 1996), Dimensional Obsessive-Compulsive Scale (Abramowitz et al. 2010), Penn State Worry Questionnaire (Meyer et al. 1990), Multidimensional Assessment of Interoceptive Awareness (Mehling et al., 2012), Adolescent/Adult Sensory Profile Scale (Brown and Dunn., 2002), the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011), Frost Multidimensional Perfectionism scale (Frost et al., 1990), Obsessive-Compulsive Trait Core Dimensions Questionnaire (Pietrefesa et al., 2009), Resilience Scale (Wagnild et al., 1993), Not Just Right Experiences Questionnaire, Revised (Coles et al., 2003), Obsessive-Compulsive Inventory (Foa et al., 1998), Quick Inventory of Depressive Symptomatology (Rush et al., 2003).

2a. Family History Assessment (15-30 minutes): A member of the research team will administer the Family History Questionnaire to the participant. This tool will be used to ask more detailed questions related to family psychiatric and medical history.

3. Medical Screen (30-60 minutes)
Some portions of the medical screen (3a, 3b, 3c) may be performed in a separate in-person visit if the psychiatric and symptom evaluation portion of the screening visit is conducted remotely due to COVID-19 safety concerns. In this case, participants will be transported to Clinical Research Center at Bellevue Hospital or the NKI Outpatient Clinical Research Division (OPRD) using a car service paid for by the study. The participant may drive themselves if they have a car available. A researcher will ask questions about the participant's recent medical history, including inquiring about any surgeries, hospitalizations, or significant illness. This will include over-the-counter commercially-available urine drug and pregnancy tests purchased from Fisher Scientific or other approved vendors. Questions will again be asked to assess for the presence of exclusionary medical conditions (allergies to ondansetron or other 5-HT3 antagonists, heart disease, congestive heart failure, heart rhythm disorder, congenital Long QT syndrome, electrolyte abnormalities, and hepatic impairment). Any subject meeting these conditions will be excluded from participation (see 3a and b). Additionally, subjects who report taking apomorphine will also be excluded from participating in the study. Those with lab results (see 3a) or EKG abnormalities (see 3b) that would make participation unsafe will be excluded.

3.a. Blood Tests: During the Screening Visit, Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP) tests will be run to ensure lack of major medical illness or abnormalities that would increase risk. For participants screened through NYU, these blood tests will be performed at either the Clinical Research Center at Bellevue Hospital through the resources of the CTSI or the blood will be collected by a nurse practitioner at NYU Langone Medical Center (One Park Ave, 8th floor) and processed at Clinical Laboratories, located at Tisch Hospital. Subjects undergoing medical procedures at NKI will have blood drawn and processed through the NKI Outpatient Clinical Research Division. Subjects with electrolyte abnormalities, hepatic impairment, or any other major medical illness that would increase risk will be excluded from further participation.

3.b. EKG: During the Screening Visit, an EKG will also be performed either at Clinical Research Center at Bellevue Hospital through the CTSI, on the 8th floor of One Park Avenue (Psychiatric department testing rooms), or the NKI OPRD, The results from the EKG will be read by a licensed study team physician or nurse practitioner regardless of where the EKG is acquired, to determine that it is safe for the subject to continue in the study. If the EKG results are abnormal, the patient may be referred to a cardiologist for follow-up and a repeat EKG may be conducted. If safety cannot be established, the subject will be excluded from further participation.

Subjects with QT prolongation will be excluded for safety. For the purposes of the study, QT prolongation is defined as a QTc>450 ms for men and >470 ms for women. Should this be identified at screening, a repeat EKG will be obtained immediately as a confirmation and, if confirmed, the participant will be excluded from the study. If the QTc at screening is greater than 430 but less than 450 for a man or greater than 450 but less than 470 for a woman, we will enroll pending other safety assessments and additionally perform two surveillance EKGs at week 1 and at week 2. While numerous psychotropic medications can prolong QT intervals, we do not determine that a participant being prescribed another medication known to prolong QT intervals prior to enrollment in the study constitutes additional risk assuming the pre-randomization EKG shows no evidence for QT prolongation. Should a participant have, for any clinical reasons, a medication change by their primary clinical outpatient team during the randomization period, this will be reviewed by a study physician and an EKG may be performed, if indicated.

3.c. Vital Signs: The medical screening would also involve administering Vital Signs by a licensed CTSI or study team physician or nurse practitioner to ensure safety to participate.

3d. Medical history: The coordinator will obtain information regarding the participant's medical history which may involve administering the Patient-Rated Inventory of Side Effects (PRISE). This information will be reviewed by a licensed study clinician and discussed with the participant during a remote meeting between the clinician and the participant via phone or Webex. At that time, and after reviewing results from the bloodwork, EKG, and vital signs, the study clinician will determine whether a physical exam is required to determine safety. If the physical exam is required, it will be conducted during the baseline visit at Nathan Kline Institute, which already requires an in-person visit, prior to randomization.

4. Picture Ratings and practice trials on task (10-30 minutes): Subjects will be asked to rate a series of 72 images. These images include 24 OCD images from the Berlin Obsessive-Compulsive Disorder Picture Set (Simon et al., 2012), as well as 24 threat-related and 24 neutral images. Threat-related images are from the standardized IAPS database and include pictures of snarling or ferocious looking animals, weapons, and injured or distressed-looking people. Neutral images are also taken from the IAPS database and include non-ferocious looking animals, people with neutral facial expressions, and objects such as books or tables. The images (OCD, threat and neutral) will be presented in random order. After viewing each image they will make two ratings: 1. how generally negative or positive the image makes them feel and 2. how much the image evokes their OCD symptoms. This task will be performed on REDCap if the visit is remote. Ratings made during this task will be used by the research team to pick images relevant to each subject's symptoms for the SP provocation task in the scanner (see below). Subjects may also be asked to perform practice trials of the fMRI tasks during the Experiment Visits.

The entire screening procedure is expected to take from 3-4 hours, depending on the pace of the subject in answering questions, the timeliness of the medical screen appointment, and whether practice trials for the task are performed. After the Screening Visit, if the subject is deemed safe and fit to participate in the study, they will be given the option to schedule an appointment for the Baseline Visit.

Study Group Assignment after Screening Visit:
After the Screening Visit, eligible subjects will be randomly assigned into two groups: one group will receive 24 mg of ondansetron and the other group will receive placebo daily for 4 weeks. Participants will receive a 40-day supply of drug at the Baseline Visit (Day 0) and instructed to take the first dose on the following day in the morning (Day 1). The 40-day supply includes a buffer so that participation in the trial is not disrupted in the rare case that a patient needs to reschedule the Mid-Trial or Final Visits at the last minute.

Drug and placebo will be compounded and physically matched to each other by a pharmacy located near to the Nathan Kline Institute (Miller's Pharmacy). Blister packs containing 40-day supplies of blinded drug or placebo will be provided to the study team for each patient and stored in a secure locked room located at NKI. Drug will be ordered in bulk to cover 5-10 patients at a time (depending on expiration date and enrollment pace), and can be delivered directly to NKI or picked up by NKI staff at Miller's Pharmacy. Randomization will be conducted by Miller's Pharmacy, who will hold the link between subject code and active/placebo drug. They have experience doing this for other clinical trials at NKI. Study drug for patients recruited at both NKI and NYU sites will be provided through this method. The NYU site will only screen patients, while scanning and drug dispensation will be done for all patients at the NKI location, regardless of whether they are screened at NYU or NKI, and thus no coordination of randomization between sites is needed.

Packs will be stored with a code number and will not identify whether they contain active drug or placebo. Dissemination of study drug will be logged in paper form located in the secure room and follow a two-step authentication procedure requiring signatures from two different NKI staff members confirming that the correct blister pack is being selected to provide to the patient. The logs will be reviewed by the PI on a regular basis to ensure there are no errors.

(C) Baseline Visit (Day 0), 3-4 hours
The baseline and final visits take place at the Nathan Kline Institute (NKI) for Psychiatric Research, a New York State Office of Mental Health research institute affiliated with NYU Langone. Subjects will meet a member of the research team at the offices of the study team at the Nathan Kline Institute (NKI) approximately 30-60 minutes prior to the scheduled time for the scan. The following procedures will occur during the Baseline Visit:

1. Physical Exam
A licensed study team physician or nurse practitioner may perform a physical exam to ensure safety to participate. The physical exam will be determined to be necessary at the discretion of the licensed study clinician based on evaluation of the medical history, lab results, EKG results, and vital signs.

2. Symptom review

The experimenter will review the patient's current symptoms (using Y-BOCS/YGTSS, SPS and PRISE) to determine if there have been any changes since the Screening Visit, and explain the cognitive tasks with them. An MRI safety screen will be performed to ensure that the individual is safe to enter the scanning environment.

3. Practice trials on task/pre-task ratings of stimuli (optional, 10-20 minutes)
Participants may be asked to perform practice trials of the task or answer questions about task stimuli.

4. MRI set up and scanning (90 minutes)
When it is time for subjects to be set up in the MRI scanner, they will be introduced to the MRI technician, who will prepare them. The technician is highly trained in participant safety protocols. The technician will run through a checklist with the subject to ensure that no metal objects are on the subject's body. Once cleared, the technician will set up the subject in the scanner and make sure they are comfortable and ready to begin the experiment.

4.a. Eye tracking and Physiological measurements (e.g., respiratory rate, pulse oximetry) may be taken while subjects perform the task inside the scanner. All physiological measurements are non-invasive (e.g., pulse is measured by attachment of device to finger). During the set-up of physiological equipment, participants will be asked to confirm that they are comfortable with the attachments. If they are not comfortable after or during the set-up: 1) the placement will be altered to achieve comfort, or 2) the equipment will be removed. Subjects will never be required to wear the equipment if they are uncomfortable. Physiological measurements will be collected with commercially available BIOPAC equipment.

4.b. MRI scanning
The MRI scanning session will be no more than 90 minutes in total and may include a resting-state fMRI scan (subjects fixate on a crosshair with eyes open, 10 min), 3-4 brief fMRI tasks (35-45 min), diffusion-weighted MRI (10-15 min), and a structural T1-weighted scan (5-10 min).
This may include the following tasks:
1. "Urges-for-action" (UFA) task: This task examines neural activity during the buildup of the urge to blink. Blocks of eyes-open rest (30 s) alternate with blink suppression (60 s). During rest blocks, subjects fixate on the screen and are permitted to blink normally. During blink suppression blocks, subjects see the instruction "HOLD" and attempt to withhold blinking for the next 60 seconds. After 60s, subjects see a cue letting them know they are now permitted to blink (the word "OK" for 3 s), following which they rate the subjective urge experienced during the prior suppression block on a 5-point scale (1="none at all", 5="extreme") (3.5 s). Subjects are instructed to return to blink suppression should any accidental blinks occur. Eyes blinks are monitored (via eye tracking system connected to the scanner) to obtain rates of spontaneous blinking during rest as well as to identify accidental blinking during suppression blocks using an eyetracking device. Eight blocks of blink suppression and eight blocks of rest are presented over 2 runs. Each run lasts approximately 7 minutes, for a total task length of 14 minutes.

2. "Body-focused videos" (BFV) task: In the task, subjects view "body-focused" or control videos for 15 s. The body-focused videos depict 3 different scenarios: a brush stroking the underside of a hand, a close-up of a person's throat while swallowing, and a medical illustration of a heart beating. The event depicted in each scenario repeats several times, with the number of repetitions varying between blocks (e.g., videos depict the brush stroking the hand 3, 4, or 5 times). Each body-focused video has an associated control video showing repeating non-body-related events: a pen moving across a table, a ball sliding through a tube, and a colored rectangle changing in height. After watching the video, subjects report the number of repetitions using a 5-point scale (3.5 s) in order to ensure that attention is focused on the videos throughout the task (better accuracy leads to a small monetary bonus). A jittered ITI consisting of a fixation cross is then displayed for 2-6 s, after which a new video begins. In total, there are 27 body-focused and 27 control blocks (each of the 3 scenarios presented 9 times) over 3 runs. Each run lasts approximately 7 minutes, for a total task length of 21 minutes.

3. SP provocation task: During the training session, the participant will rate images from the Berlin Obsessive-Compulsive Disorder Picture Set (Simon et al., 2012) on how much they evoke their OCD symptoms or not (tic disorder patients will also complete this task, but if they do not have OCD symptoms they will rate that none are evoked from the task stimuli). They will also rate threat-related images and neutral images from the based on

how negative they are or not. Threat-related images are from the standardized IAPS database and include pictures of snarling or ferocious looking animals, weapons, and injured or distressed-looking people. Neutral images are also taken from the IAPS database and include non-ferocious looking animals, people with neutral facial expressions, and objects such as books or tables. During the SP task in the scanner, patients view the OCD images that have been selected based on their ratings during the screening visit to trigger their OCD symptoms. Three different images of each type (SP, threat-related, neutral) are presented 6 times each in pseudorandom order over 2 runs. Each image is shown for 5 s, after which patients rate their current severity of SP on a 5-point scale ("none at all" to "very severe", 4 s), followed by a 2-6 s jittered ITI. Each run lasts approximately 4 min, for a total task time of 8 min.

There may be minor changes to the content or timing of these tasks and the scanning protocol as the experiment is prepared and in the early stages of implementation. Specifically, if problems are encountered along the way regarding the length of the protocol or the utility of the tasks (e.g., if the total length of the scanning session appears to be too long for subjects), we may remove or alter some tasks or scans to address these issues. In no case will the risks to the subjects be increased by any changes, and the total time of the scanning session will never be increased above 90 minutes.

5. Questionnaires: At the end of MRI scanning, subjects will be asked to fill out questionnaires about their emotions and beliefs, including: Beck Depression and Anxiety Inventories (Beck et al. 1996); Dimensional Obsessive-Compulsive Scale (Abramowitz et al. 2010); Multidimensional Assessment of Interoceptive Awareness (Mehling et al., 2012); Adolescent/Adult Sensory Profile Scale (Brown and Dunn., 2002); Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011); Frost Multidimensional Perfectionism scale (Frost et al., 1990); Obsessive-Compulsive Trait Core Dimensions Questionnaire (Pietrefesa et al., 2009); Resilience Scale (Wagnild et al., 1993); Not Just Right Experiences Questionnaire, Revised (Coles et al., 2003); Premonitory Urges for Tics Scale (Woods et al., 2005); The Psycho-Sensory hAllucinations Scale (PSAS) for Schizophrenia and Parkinson's disease (Chéreau-Boudet et al., 2013); Quick Inventory of Depressive Symptomatology (QIDS, Rush et al. 2003).

We will also ask participants to answer a few debriefing questions about the task stimuli, their subjective experience, and memory of the study. These inquiries may help illuminate flaws in study design.

6. Drug dispensation
At the end of the visit, patients will be given a 40-day supply of drug (ondansetron or placebo, blinded to study participant and investigator) and instructed to take the first dose on the following day in the morning with food (Day 1). There will be some flexibility with the timing of the first dose and the subject will be permitted to start within the first 3 days following the scan on a date that is convenient for them.

7. Subject ID Card:
Patients will be given a Subject ID Card that they will be asked to carry for the duration of the study. This Subject ID Card will indicate that they are enrolled in a clinical trial and may be taking 24mg of ondansetron and will include the research team's contact information. The research team will advise the patient to keep the card with them in case of any medical event or emergency during which a medical professional may need to know that they are enrolled in a clinical trial and/or may need to contact the research team for more information.

8. Journaling Sheet:
At the end of the visit, the patient will be given a "Journaling Sheet" where they will rate the severity of their OCD and sensory symptoms twice (afternoon and evening) during Week 1 (Days 1 to 7) and Week 4 (Days 21 to 28). The purpose of the sheet is to track any changes over the course of the day related to the time that they took the study drug.

(D and F) Phone Calls (Approximately Days 7 and 21, 30-60 minutes each call)
The experimenter will call the subject on the phone at pre-arranged times to ask about study compliance, evaluate any side effects patients might be experiencing, and assess symptoms. This will involve administering the Patient-Rated Inventory of Side Effects (PRISE), the Y-BOCS or YGTSS (for OCD and TD patients,

respectively), the SPS, and also assessing suicidal ideation in patients with QIDS item #12. During the Day 21 Phone Call session, the study team member will remind the subject to start filling out the Journaling Sheet.
For patients with EKG at screening within the normal range but within 430-450 ms for men or 450-470 ms for women, we will have them come into the lab at NYU or NKI at week 1 (approximately 7 days) instead of doing a phone call to perform a surveillance EKG to determine continued safety to participate. If the visit is remote, participants will be transported to CTSI or OPRD using a car service paid for by the study in order to complete the EKG. They may also drive themselves. All other non-medical procedures listed for this visit will be conducted over the phone.

(E) Mid-Trial Visit (Approximately "Day 14", 2 hours)
For the Mid-Trial visit, the patient will meet with the study team remotely via Webex or come in-person to NYU or NKI to repeat symptom and side effects assessment (YBOCS/YGTSS, SPS, PRISE, and suicidal ideation) and fill out self-report questionnaires. In addition, the patient will meet with the licensed study team physician to ensure safety. This will be conducted in a separate, in-person visit if the first part of the visit is online. We will perform a repeat EKG during the mid-trial visit. The Mid-Trial Visit will ideally be scheduled for Day 14; realistically, we will allow patients to complete the procedures within a window of +/- 7 days. Participants will be transported to CTSI using a car service paid for by the study or using their own vehicles.

(F) Final (Exit) Visit (Approximately Day 28, 4-6 hours)
Participants will return to NKI to repeat MRI scanning (see Baseline Visit for procedures). In addition, they will fill out the same questionnaires as during the Baseline Visit and have their symptoms re-assessed with the Y-BOCS/YGTSS and SPS. Side effects will again be evaluated using the PRISE. Suicidal ideation will be assessed using the QIDS item # 12. Repeat EKG and Bloodwork will be performed at the NKI Outpatient Research Department (OPRD; Director: Dr. Russell Tobe, co-investigator on the approved IRB protocol at the NKI site) and the subject will meet with a study team physician. The Final Visit will ideally be scheduled for Day 28; realistically, we will allow patients to come into the lab within a window of +/- 7 days.

In the rare instance that the patient wishes to break up the final visit, which is long, into two shorter appointments (scanning one day and medical testing on another day), we will try to accommodate their schedule. If the patient is from the NYC area and will be transported up to NKI via car service provided by the study, the repeat EKG and bloodwork and physician appointment may occur at the Bellevue CTSI instead of at the NKI OPRD.

At the end of the Final Visit, subjects will be provided with psychiatric referral if desired. Arrangements will be made to compensate subjects for their time.

Total time for participation, including the Screening Visit, Baseline Visit, Mid-Trial Visit and the Final Visit, and the 2 phone calls will be approximately 16-20 hours.

Approximately one week after the Final Visit, the study coordinator will make a follow-up phone call with the patient to ask how they are functioning after completing the study and provide referral if necessary.

4.2 Data Analysis and Data Monitoring

(See R21/R33 application for section references)
The primary endpoints of the study are clinical symptoms and fMRI data. The specific analyses (independent and dependent variables) will be unique to each task, as described below. Safety and tolerability of 4 weeks of 24 mg ondansetron will also be evaluated.

Alpha level will be set at 0.05 for all analyses. Task-based fMRI analysis will focus on brain activation in an a priori ROI consisting of bilateral insula and somatosensory cortex, although exploratory whole-brain analyses will also be conducted. Primary group-level analyses for the R33 phase will be performed on a modified intent to treat sample consisting of participants completing at least 2 weeks of treatment. Missing data values are expected to amount to 10% or less of the data. We will consider them as MAR and impute based on a regression model. The degrees of freedom of t-tests will be adjusted appropriately. Secondary per-protocol analyses will also be conducted.

Task-based and symptoms analyses for R33:
First-level fMRI analysis: For each fMRI task, image analysis at the first (subject) level will specify separate regressors for baseline and week 4 for conditions of interest (e.g., for the “urges-for-action” task: blink suppression at baseline, blink suppression at week 4, rest at baseline, rest at week 4) to examine contrasts between baseline and week 4 (e.g., blink suppression vs. rest for baseline vs. week 4). For each task, contrasts will also examine activation during the baseline scan only (e.g., blink suppression vs. rest at baseline scan). These latter contrasts will be performed in order to measure and adjust for any baseline differences in ROI activation between ondansetron and placebo groups.
Group-level fMRI analysis: Testing for Hypothesis 2: Two-sample t-tests will compare ondansetron and placebo groups on change in activation over the 4-week trial (using first-level contrasts comparing baseline with week 4). However, if there are significant baseline differences between the groups within the insula and somatosensory ROI (using two-sample t-tests on baseline scan contrasts), standardized parameter estimates will be extracted from these regions for each subject. These parameter estimates will then be specified as covariates in follow-up one-way ANOVAs comparing ondansetron and placebo groups on change in activation from baseline to week 4 after adjusting for baseline differences.

Relationships with clinical symptoms: Testing for Hypothesis 3a: A change score will be computed between SPS score at baseline and after 4 weeks for each subject. Two-sample t-tests will compare ondansetron and placebo groups on SPS change scores to determine whether the intervention reduces SP significantly more than placebo. In addition, change scores from baseline to week 4 will be computed for measures of overall symptom severity (using Y-BOCS and YGTSS) and compared between ondansetron and placebo groups. If there are baseline differences between the groups in any of the symptom scales (SPS, Y- BOCS, or YGTSS), follow-up one-way ANOVAs will compare change scores between ondansetron and placebo groups after adjusting for baseline scores. Testing for Hypothesis 3b: If there are significant differences between ondansetron and placebo groups in (1) SPS change scores and (2) Y-BOCS or YGTSS change scores, a Sobel test of mediation205,206 will investigate whether group differences in Y-BOCS/YGTSS changes are mediated by SPS changes. Briefly, mediation analyses perform a series of regressions in order to determine whether the relationship between an independent and dependent variable (e.g., treatment group and Y-BOCS/YGTSS scores) reduces significantly after including a third mediator variable (e.g., SPS score). Testing for Hypothesis 3c: If there are significant differences between ondansetron and placebo groups in (1) SPS change scores and (2) change in ROI activation or connectivity from baseline to week 4, a Sobel test will investigate whether group differences in SPS change are mediated by changes in activation or connectivity.

Resting-state functional connectivity analysis: After heart rate and respiratory signals are removed from resting-state data using “RETROICOR”207, analysis will proceed using the “conn” toolbox (www.nitrc.org/projects/conn) following our previous protocol26. Timecourses of the BOLD signal for each rest scan will be extracted from four seeds (6-mm radius spheres) in bilateral insula (two seeds in anterior and two seeds in mid-posterior insula, coordinates taken from prior work26,208). Partial correlations will be conducted between these timecourses and whole-brain gray matter, controlling for several factors. Timecourses from the top three principle components within white matter and CSF will be determined using the “CompCor” method209 and included as covariates to control for noise without having to regress out global signal210,211. Additionally, the inclusion of 12 motion variables (6 realignment parameters and first derivatives) as covariates will control for movement. Because movement is a major concern for connectivity analysis212, we will exclude from resting-state analyses any subject moving > 1 mm or 0.5 degrees. Data will be filtered between 0.01 and 0.10 Hz213. At the first level, partial correlation coefficient images between each seed’s timecourse and the whole brain will be z-transformed and compared in contrasts between baseline and week 4. For Hypotheses 2 and 3c (R33), two-sample t-tests will compare ondansetron and placebo groups in change in connectivity between baseline and week 4. As with task analyses, baseline differences will be probed using t-tests and included as covariates in follow-up ANOVAs if necessary.

Additional post-hoc analyses: Exploratory whole-brain analyses will be conducted for all contrasts of interest, correcting for multiple comparisons using cluster-level false discovery rate. For the R33 phase, we will probe for correlations between SPS score and whole-brain activation and connectivity in order to identify other future targets for treatment. We will also examine associations between other clinical measures (DOCS, PUTS, GAF)

and ondansetron treatment as well as brain functioning. Investigation of symptom trajectories over the duration of the trial will use ANOVAs with time (baseline, week 1, 2, 3, 4) as a repeated measure. Any clinical or demographic differences remaining between the groups after randomization including age, gender, illness duration, and medication dosage (using fluoxetine equivalence) will be statistically controlled for in all analyses. For illness duration and medication, follow-up analyses will investigate the relationship between these variables and study measures (brain functioning and symptoms), not only to control for confounding but also to interrogate these variables as factors of interest.

A Data Safety Monitoring Board consisting of external scientists was assembled in August of 2015 for the R21 phase. This DSMB met every 6 months (February, August of 2016, and March 2017) via teleconference to review aggregate safety data. The board will continue to meet at this same schedule during the R33 phase. The DSMB meeting in March 2017 approved continuation to the R33 phase using the procedures described in this protocol. The board last met on December 20, 2017 (6 months after the start of the R33 phase in June of 2017) and approved the continuation of the R33 phase.

i. The primary safety measure discussed at DSMB meetings is the incidence of adverse events, which are assessed weekly throughout the trial using the Patient-Rated Inventory of Side effects (Rush et al., 2004, Control Clin Trials, 25, 119-142). The PRISE consists of a checklist of side effects in the categories of: Gastrointestinal, Heart, Skin, Nervous System, Eyes/Ears, Genital/Urinary, Sleep, Sexual Functioning, and Other (which includes symptoms related to energy and mood). Patients endorse items and indicate whether they are tolerable or distressing. Secondarily, safety outcomes related to results from medical surveillance tests (EKG, blood test) occurring during Mid-trial and Final visits will be discussed.
ii. There are no predetermined stopping rules for the study. Every 6 months the DSMB will review side effects and determine whether the study may continue for the next 6 months. Critically, if any SAEs occur at any time during the trial, the study team will report this to the NYU Langone IRB and the DSMB within 48 hours and the determination regarding continuation of the study will be made at that time by both entities. In addition to the DSMB meetings, a study physician (Dr. Dan Iosifescu) will review side effects for each patient at the Mid-Trial and Final Visits. If there are any unexpected or severe side effects that the study physician determines pose a safety risk, this will be communicated immediately to the study team and the PI and a determination regarding continuation of the patient in the trial will be made.
iii. Following the DSMB meetings, the Chair (Dr. Chris Pittenger, Yale University) discusses the safety data with the other board members, and together they make a determination about continuation of the study. This information is communicated both verbally to the PI (informally at the end of the teleconference), as well as in a written report prepared by the Chair and sent to the PI following the meeting.

In addition to safety data, the DSMB also reviews any proposed amendments to the study protocol, performs ongoing monitoring of drop-outs, determines whether study procedures should be changed or the study should be halted, and performs periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB also ensures subject privacy and research data confidentiality.

The Board comprises the following individuals:

Chris Pittenger, MD, PhD
Associate Professor of Psychiatry and in the Child Study Center
Director, Yale OCD Research Clinic
Co-Director, Neuroscience Research Training Program
Yale University

Dr. Pittenger is the Chair of the DSMB. He is an expert in neuroscience and obsessive-compulsive disorder. He has considerable experience in running clinical trials in OCD and related disorders, as well as conducting experimental studies in both animal and human subjects. Dr. Pittenger's research and clinical work have been acknowledged by a number of prestigious awards, including grant funding from the National Institutes of Health,

NARSAD, the Tourette Syndrome of America, and the Doris Duke Charitable Trust, and awards from the National Institute of Mental Health, the Society for Neuroscience, the American College of Neuropsychopharmacology, the American Psychiatric Association, and the American College of Psychiatrists. He is a member of the Scientific Advisory Board of the International OCD Foundation and an active member of the Society for Neuroscience, the American College of Neuropsychopharmacology, the Society of Biological Psychiatry, the American Neurological Association, the American Psychiatric Association, and other groups.

Ted Satterthwaite, MD, MA
Assistant Professor of Psychiatry
University of Pennsylvania Perelman School of Medicine

Dr. Satterthwaite is a psychiatrist and researcher with expertise in functional neuroimaging and its applications to psychiatric disorders. His research uses multi-modal neuroimaging to describe both normal and abnormal patterns of brain development, in order to better understand the origins of neuropsychiatric illness, and he has published extensively on data integrity and statistics in fMRI. He joined the faculty in 2014 and has served as the Director of Imaging Analytics of the Brain Behavior Laboratory since 2015. His work has been recognized with the Brain and Behavior Research Foundation's Klerman Prize for Clinical Research, the NIMH Biobehavioral Research Award for Innovative New Scientists (BRAINS) award, as well as several clinical teaching awards.

Katherine Kirkwood
Senior Biostatistician, Parexel

Ms. Kirkwood is a biostatistician with experience in clinical trial methodology. Her primary research focuses on clinical trials, censored survival analysis, Bayesian inference, and methods for handling missing data. She has been a member of the DSMB for approximately 2 years when she was a staff member at the Icahn School of Medicine at Mount Sinai. As of April of 2020, she has left Mount Sinai for a position as Senior biostatistician at Parexel,

4.3 Data Storage

Subject names and contact information will be entered into a log sheet in a password-protected Excel document that is located on a password-protected network attached storage device behind a firewall at NYU Langone Medical Center. Only the research team members will have access to the passwords that will allow them to view this document. In this document, alongside the subject's name and contact information, a unique identifying code will be placed, which will be used for all other documents for the study. This information will not be carried outside the lab or left on flash drives. Paper consent forms containing identifying information (subject names) will be stored in locked filing cabinets at NYU Langone Medical Center. Digital consent forms will be stored on the REDCap server. Research data and files containing health information (such as files resulting from psychiatric evaluation) will not contain subject names and will only be labeled with subject ID numbers. De-identified paper documents (e.g., questionnaires and forms) will be stored in locked cabinets at NYU Langone Medical Center. All electronic files including MRI data are securely stored on a password protected network attached storage device protected behind a firewall that only study personnel have access to. The password protected worksheet that links the identifying information (name, contact) with subject ID will be kept until the study is closed and all data analysis has been completed. Anonymized MRI and clinical data (without any identifying information) will be stored indefinitely.

If potential participants locate our study information through a BuildClinical advertisement, they may be redirected to our study-specific landing page, and can elect to answer some screening questions prior to contact with a member of our research team. The potential participant's questions will be shared with the study team via a password-protected BuildClinical online account, and the data entered by potential participants gets routed into BuildClinical's platform. This platform utilises Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps this information private and HIPAA compliant. This data is stored in BuildClinical's

backend servers, which are stored in the USA at some of the most secure data centers in the world. Only the study team will have access to the login information to access our BuildClinical screening question data.

4.3.1 Confidentiality

If a subject calls or emails about participation, and a screening date is scheduled, then the subject's name and contact information will be entered into a log sheet in a password-protected Excel document that is located on a password protected network attached storage device protected behind a firewall. Only the research team members will have access to the passwords that will allow them to view this document. In this document, alongside the subject's name and contact information, a unique identifying code will be placed, which will be used for all other documents for the study. This information will not be carried outside the lab or left on flash drives. Participant names will not be submitted to the funding agency or used in any presentations of the data (posters, publications, reports). Paper consent forms containing identifying information (subject names) will be stored in locked filing cabinets. Only the PI and personnel employed by the PI will have access to these cabinets. MRI data are stripped of names and other identifiers and are only stored with a code number. De-identified paper documents (e.g., questionnaires and forms) will be stored in locked cabinets, separately from consent forms. Electronic files other than MRI data are also de-identified (labeled with code number only) and securely stored on a password protected network attached storage device protected behind a firewall that only study personnel have access to. Regular access to research records will be limited to NYU Langone Medical Center research staff employed by the PI and working on the project. However, fully de-identified data (e.g., MRI images, demographics) may be submitted to international neuroimaging consortia and/or publicly accessible neuroimaging databanks, as is encouraged by the funders of this project (NIH).

Webex will be the platform used for remote screening visits. Webex is a HIPAA compliant platform that enables parties to communicate using a webcam. The study team member conducting the remote visits will be located in a private room to ensure confidentiality.

4.3.2 Data Sharing

These are the following institutions that data will be shared with:

- NKI collaborators: Identifiable data may be shared with collaborators at the Nathan Kline Institute who are on the IRB-approved protocol at the NKI site, as it may be necessary to share this information for safety reasons.
- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety.
- The sponsoring government agency and/or their representative who need to confirm the accuracy of the results submitted to the government or the use of government funds, as required by law: National Institute of Health
- The United States Food and Drug Administration as required by law
- The United States Department of Health and Human Services and the Office of Human Research Protection as required by law
- De-identified clinical and neuroimaging data, and associated files (e.g. behavioral response data generated during tasks), may be provided for use by other researchers. De-identified data may also be shared with public databanks and scientific consortia as it becomes available.
- If requested, we will provide participants with a summary of the results from the study, without providing any names or individual level data from other participants. We also may provide subjects with images (jpegs) of their brain scan if they request it.

The monitors, auditors, the IRB, the Office of Human Subjects Protection (OHRP) of the Department of Health and Human Services as well as the Food and Drug Administration (FDA) will be granted access to the data as required by law for the verification of the research procedures and integrity. Sharing de-identified data with other researchers/uploading to appropriate databases might help to expand upon and improve this research in the

future. All shared clinical and neuroimaging data will be de-identified. De-identification will include removal of sensitive and identifying data (e.g. name, date of birth, contact information). The anonymized final data set will be made available upon request, with an announcement on the lab website providing information on how to obtain the data. In addition, final data may be uploaded to an appropriate database, such as the Open fMRI project, for broad availability. Data sharing will comply with local, state, and federal laws and regulations, including the Health Insurance Portability and Accountability Act (HIPPA), as well as institutional policies and review.

Any shared data, whether it contains PHI or not, will be shared using secure methods including encryption and password protection. Shared external drives will be password protected and encrypted (using TrueCrypt or StorageCrypt). Alternatively, data may be transmitted over a secure network connection between two encrypted password-protected NAS devices or computers. If paper documents are shared, they will either be hand delivered to the recipient by a member of the study team or sent via certified mail. Data will not be shared using unsecured cloud-based methods or unencrypted USB drives.

5 Equipment

None of the equipment to be used in the study is investigational, and all have either received FDA approval or are exempt from FDA requlations. The list of equipment (located at NKI) includes:

- Siemens 3T MAGNETOM Trio scanner with head coil (FDA approved; see attached documentation)
- BIOPAC pulse oximeter transducer (clip on finger) and respiration transducer (belt placed across chest). These are commercially available, non-significant risk devices that are MR-safe (see attached documentation).
- SR Research Eyelink 1000 Eye tracker, which is a video camera mounted outside of the MRI scanner that monitors eye blinks and eye movements. This is a Class 1 non-significant risk device that is commercially available and MR-safe (see attached documentation).

Several various types of software will be used to analyze the data, including AcqKnowledge software to analyze BIOPAC pulse and respiration data (https://www.biopac.com/product/acqknowledge-software), Microsoft Excel and SAS (https://www.sas.com/en_us/software/stat.html) to analyze behavioral data, and MATLAB (https://www.mathworks.com/products/matlab.html) to analyze MRI data. As these products do not interact with subjects and are only used for data analysis, they pose no risk and are not subject to FDA regulations.

6 Risk/Benefit Assessment

6.1 Risk

Screening and evaluation: There are no serious risks associated with the screening and evaluation phases of this study. Participants may become uncomfortable when asked personal questions, and experience feeling embarrassed or nervous. However, they may refuse to answer individual questions. Interviewers will strive to help subjects feel as comfortable as possible.

Medical Tests (Blood Test, EKG, Urine Test, Vital Signs, History & Physical): Mild temporary discomforts such as bleeding, bruising, or fainting may occur when blood samples are obtained. Rarely, an infection develops at the site of the blood draw. If an infection does occur, it can be treated. There are no known risks to the EKG and urine tests. A subject may find these tests uncomfortable.

Rating scales and surveys: All are non-invasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality have been

effective in previous research, and only patients' code numbers will be recorded on the forms themselves to protect confidentiality.

Paradigms: There is minor risk that subjects will feel uncomfortable or bored performing the tasks. Subjects may refuse to do any task, and research team members will seek to make sure they are not in psychological distress both during and after the task. There is very little risk associated with performing the tasks, which are similar to the risks posed by playing a computer or video game.

Physiological measurement: There are no known risks associated with the physiological measurements taken using the BIOPAC system. There is a risk that subjects may feel uncomfortable with the placement of the equipment. If subjects are uncomfortable, the equipment will be altered or removed entirely.

Ginger Consumption: Ginger is a 5HT3 antagonist and since it acts through a similar biological mechanism as ondansetron, high ginger consumption could pose a risk for patients receiving active drug by potentially increasing the overall amount of serotonin antagonism experienced. We will ask patients both during phone screen and the study doctor visit in the screening appointment how much ginger they consume and will ask them to limit ginger consumption during the length of the trial (to ginger consumption in food or with supplement to once or less per week).

MRI scanning: Risks associated with the MRI imaging are minimal and include: (1) discomfort or anxiety from being in the confined space of the MRI scanner. The MRI scanner makes loud, vibrating noises. Sometimes, subjects report a temporary, slight dizziness or light-headedness when they come out of the scanner; (2) the MRI may reveal an abnormality that is already in the brain, such as a cyst or tumor. Many such abnormalities are not clinically significant, but may require further investigation. Such a finding might require additional tests, and maybe even treatment, neither of which would be paid for by the investigators, the sponsor, or NYU Langone Medical Center; (3) the strong magnetic field of the MRI scanner could disturb a foreign metallic body in the patient and cause injury. We have taken several steps to minimize these risks, including excluding subjects with metals in their body that would pose a risk; (4) A small number of people with tattoos have reported feeling mild tingling or heating during MRI scanning. If a patient has tattoos and reports an unpleasant tingling or heating during the scan, we will stop the scan immediately. The risks that MRI imaging may pose to an embryo or fetus are unknown as a result, pregnant subjects will be excluded.

Ondansetron: Ondansetron hydrochloride is an FDA approved drug that has been used clinically in adult populations. Ondansetron has a high therapeutic index, and accidental ingestion of ten times the recommended daily dose with no fatality has been reported (Ye et al., 2006).

Most adverse effects are rare and resolve after cessation of drug. They are most frequently reported after IV administration, in patient groups also receiving chemotherapy, are dose-dependent, and are more pronounced over repeated administration.

Short-term dosing:

Most commonly, ondansetron has been used as a single dose or multiple doses for a short period of time for the treatment of nausea and vomiting related to chemotherapy, radiation, or surgery.

In a randomized clinical trial of 300 patients receiving a single 24 mg dose of ondansetron to treat nausea associated with highly-emetogenic cisplatin-based chemotherapy, the only side effect occurring in greater than 5 % of patients was headache (at 11 %, reference: Zofran prescribing information). In a randomized clinical trial of 550 patients receiving 16 mg ondansetron and 531 patients receiving placebo for post-operative nausea, only headache had a higher rate of incidence in the ondansetron group (9 vs. 5 %) (reference: Zofran prescribing information).

Among patients taking ondansetron for chemotherapy or surgery-related nausea, the most commonly reported side effects (> 5 %) include:

- headache

- dizziness
- fatigue or drowsiness
- diarrhea or constipation

Rare but reported side effects, mostly with IV administration in patients receiving other medications, that have not been determined to be causally related to ondansetron include:

- Neurological (acute reversible chorea, tonic-clonic seizure, grand mal seizure, extrapyramidal signs, oculogyric crisis)
- Skin (paresthesia, hot and cold sensations)
- Psychiatric (depression)
- Cardiovascular (including angina, atrial fibrillation, cardiac dysrhythmia, hypotension, atrioventricular block, ST segment depression, syncope, tachycardia, Torsades de points, QT prolongation)
- Endocrine (hypokalemia)
- Hepatic (liver failure, hepatic necrosis, hepatitis, transient increases in liver enzymes)
- Gastrointestinal (bowel obstruction)
- Immunological (Anaphylactic and hypersensitivity reactions, fever)
- Ophthalmologic (blurred vision and transient blindness)

The FDA has issued a warning for the emergence of serotonin syndrome for ondansetron particularly when used in combination with other serotonergic drugs (serotonin-reuptake inhibitors (SSRI/SNRI), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The likelihood of experiencing serotonin syndrome is very small. Patients will be monitored for the emergence of symptoms related to serotonin syndrome, especially with concomitant use of ondansetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, they will immediately discontinue ondansetron and be referred for treatment.

In the R21 phase of the study, healthy volunteers were administered single doses of ondansetron (8, 16, or 24 mg) prior to MRI scanning. Side effects were evaluated approximately 3 hours after drug administration using the PRISE. A table showing reported side effects across the 3 groups (n=56) is included with this submission. A significantly greater percentage of subjects reported ringing in the ears for the ondansetron (5/56) than placebo (1/56) session (McNemar's test statistic (S)=4.0, p=0.05). When looking within each dose group separately, for the 8-mg dose group, a significantly greater percentage of subjects reported fatigue for the placebo (9/56) than ondansetron (4/56) session (S=5, p=0.03). For the 16-mg dose group, there was trend for a greater percentage of subjects to report ringing in the ears for the ondansetron (4/56) than placebo (1/56) session (S=3, p=0.08). For the 24-mg dose group, there was a trend for a greater percentage of subjects to report blurred vision for the placebo (4/56) than ondansetron (1/56) session (S=3, p=0.08). As can be seen, the most commonly reported side effects for both sessions were fatigue and poor concentration, which is likely due to the fact that subjects had just completed the MRI scan.

Longer-term (i.e., multiple weeks) repeated dosing:

Previous studies in psychiatric disorders have used ondansetron over the course of multiple weeks. To our knowledge, no prior study has investigated the use of single 24 mg doses of ondansetron over multiple weeks. However, there are multiple published research studies using 24 mg over a 24-hour period (typically given as 8 mg t.i.d.) for up to 4 weeks (Faris et al., 2000, The Lancet, 355, 792-797; Faris et al., 1998, Pain, 77, 297-303; Muller et al., 1998, European Journal of Gastroenterology and Hepatology, 19, 865-870; Toren et al., 2005, Journal of Clinical Psychiatry, 66, 499-503), with no reported safety concerns or adverse events except mild and transient abdominal pain, which was reported by 1 out of 15 patients in the ondansetron group and 1 out of 15 patients in the placebo group in the study by Toren et al. (2005). Adverse effects in this same study also included general gastrointestinal complaints leading to dropout of 1 patient in the ondansetron group.

In an 8-week trial using 8 mg of daily ondansetron plus an antidepressant (fluvoxamine) (23 patients) vs. fluvoxamine only (23 patients) in OCD patients (Heidari et al., 2014), the frequency of adverse events was not significantly different between the groups. Adverse events reported in both groups included: headache (13-21 %), dry mouth (13 %), constipation (17 %), dizziness (13-26 %), muscle cramps (8-17 %), insomnia (8-13 %), diarrhea (8 %), and nervousness (17-21 %).

6.2 Protection Against Risks

We plan to protect participants from adverse effects of ondansetron by excluding individuals predisposed to risk caused by allergies to ondansetron or other 5-HT3 antagonists, heart disease, congestive heart failure, heart rhythm disorder, congenital Long QT syndrome, known electrolyte imbalance, and hepatic impairment. Additionally, subjects who report taking apomorphine, and pregnant and nursing women will also be excluded. We will assess for the above conditions by evaluating medical history (via self-report during the phone screen and again during the Screening Visit), and conducting pregnancy testing during the Screening Visit. We will obtain a History & Physical, Vital Signs, and EKG during the Screening visit and will exclude for any cardiac abnormalities that the study physician (Dr. Dan Iosifescu) judges to pose a safety risk. Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP) tests will also be run to ensure lack of major medical illness or abnormalities that would increase risk. We will exclude subjects with electrolyte abnormalities, hepatic impairment, or any other major medical illness that the study physicians believe would increase risk. We will be carefully monitoring the subject during the experiment to ensure that any drug effects experienced are noted and medical intervention provided, if necessary. All side effects will be assessed weekly, and patients will have a surveillance EKG at the week 2 visit. Higher-risk patients (those with normal QTc within the range of 430-450 ms for men and 450-470 ms for women) will have surveillance EKGs at both week 1 and week 2. The EKG, blood testing, and physician meeting conducted at the Screening Visit will be repeated at the Final (exit) Visit and the study coordinator will also call the patients approximately one week after the Final Visit to ensure safety.

At any point should a medical emergency arise, a study physician or other licensed medical provider will be available. Other facilities at NYU and NKI will be made available if the need arises.

There could be a breach of confidentiality regarding participants study participation or research records, but there are measures in place to limit this risk (see above).

6.3 Potential Benefits to Subjects

There may be no direct benefits to a subject for participation in this study. However, it is possible that some patients will experience a reduction of symptom severity when taking the study drug. This research will contribute to the body of knowledge in psychiatric neuroscience by elucidating the neural mechanisms of OCD and tic disorders and the effects of ondansetron on brain function in these patient populations.

6.4 Alternatives to Participation

There are several medications for OCD that subjects can take as an alternative and can also seek therapy for symptom reduction. Another alternative is to not participate in the study.

6.5 Costs to the Subject

There are typically no additional costs to subjects for participating in this study. However, if the MRI identifies an abnormality, it may lead to extra medical costs for the subject. The cost of any extra tests would be billed to the subject's insurance provider and will not be reimbursed by the research project or NYU.

6.6 Payment for Participation

Subjects will be compensated at a rate of 25 dollars per hour for their time and effort. In our prior experience running this trial for the past 5 months at the PI's prior institution, we estimate that the maximum that they will end up being paid is $600. Most participants receive less than this (between 400 and 500) but since we pay at

an hourly rate the subject compensation varies based on a number of factors including the complexity of the clinical presentation, the wait time (i.e. to see a study clinician or delays at the scanner), and if the subject withdraws from the study early. We will additionally pay for travel time to and from NKI for scanning visits (up to 1 hour each way) and will compensate the patient for the costs of transportation to and from NKI. If a subject is revealed to be ineligible to participate during the screening process, they will receive compensation for time already spent, or 25 dollars, whichever is greater. Subjects who participate in remote screening procedures but are found to be ineligible for the study will receive an electronic Amazon gift card worth 25 dollars for each hour of time spent rounded up to the nearest hour. Eligible participants who continue on in the study will be paid for remote study visits at their next in-person study visit.The study drug will be paid for through a grant to the PI from the National Institutes of Health, and is at no cost to the subject.

7 Investigator's Qualifications & Experience

Please find attached to the submission the CV/resume of the investigators of this protocol.

8 Attachments

1) Clinical Trial Consent Form_Clean
2) Clinical Trial Consent Form_TrackChanges
3) Phone Screen Form_Clean
4) Phone Screen Form_TrackChanges
5) Summary of Modifications
6) Family History Questionnaire
7) NYU Protocol_ Clean