Locating Biomarkers of Obsessive-Compulsive Disorder Through the Use of Behavioral Tasks: Protocol Development

By
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Vita

Connor Ray Lohman was born to Sabrina Wells and Sean Lohman, and raised in Louisville, Kentucky. He attended Brown University for his undergraduate studies, where he completed his degree in in May of 2017. He received a Bachelor of Arts in Health and Human Biology with a focus on the Social Context of Health and Disease, and was also a member of the Varsity Men's Swimming and Diving team for four years. He then continued his studies at Brown University, entering the Master's Program in Biotechnology Management. While at Brown he worked on a multi-center collaborative effort to develop a provocation study in patients with Obsessive Compulsive Disorder (OCD). After this year, he will participate in the co-op program, working as a Research and Development Engineer at Becton Dickinson in the Surgical Specialties Department. After graduation, Connor hopes to continue working in the biotechnology industry.

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Abstract:

Patients who undergo deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) for intractable Obsessive-Compulsive Disorder (OCD) have approximately a 60% reduction in symptom severity in general (B. D. Greenberg et al. 2010). However, there are still negative DBS-induced behavioral side effects. One of the most important areas in which current DBS treatment is lacking is the inability to quickly react to phasic changes in both positive (hypomania) and negative (OCD-triggered distress) valence states. Adaptive (or "closed loop") DBS systems would solve this problem by recording, stimulating, and using predetermined signals from the brain to make adjustments to patients' behavior as it happens in real time. The only issue is the lack of reliably known biomarkers that can indicate these changes (or other physiological correlates of OCD and associated symptoms) are happening. The goal of this study is to accurately classify the acute fluctuations in OCD-related distress that will help to locate the biomarkers of change during the negatively valenced state. We plan to locate these biomarkers through a series of tests during which we record patients' affective states through neural and video recordings while provoking their OCD symptoms. This should help us to distinguish such states from other affective states which might not require any changes in stimulation levels. Along with OCD-related distress, we will also be looking for state changes related to elevated or depressed mood and nonspecific anxiety which may also require an adjustment in stimulation. This paper describes the process of developing a unique provocation task intended to delineate such biomarkers, using EEG, as well as the experimental protocol and materials used to measure the relevant state changes.

Intro:

Background, OCD:

Obsessive-compulsive disorder (OCD) is common anxiety disorder, with a lifetime prevalence affecting 2-3% of the US population, with an estimated prevalence of 1.2% last year (Ruscio et al. 2010; "NIMH » Obsessive-Compulsive Disorder (OCD)" n.d.). OCD is persistent, and often disabling for those affected due to the disturbing and unwanted thoughts or mental images (obsessions) and irresistable overly repetitive behaviors (compulsions) which cause anxiety (Rasmussen and Eisen 1992; "NIMH » Obsessive-Compulsive Disorder" n.d.). Although 2-3% is the official affected population, it is believed that this number is even larger due to patients' reluctance to admit that they have obsessions and/or compulsions, as well as a lack of OCD screening questions in routine mental health examinations (Rasmussen and Eisen 1992). This is important because while many may not meet the full requirements for OCD, even sub-threshold patients have reduced QOL from their symptoms, making an argument to lower the threshold and include these patients as well (Rasmussen and Eisen 1992). OCD affects children, adolescents, and adults all over the world, and most people affected are usually diagnosed by age 19, with symptoms often coming and going throughout patients' lives ("NIMH » Obsessive-Compulsive Disorder" n.d.).

Comorbidities:

The public health burden from OCD is probably higher than previously thought, not only because of a lack of inclusion of sub-threshold patients, but also due to misdiagnosis with the many comorbidities. It ranks highly among causes of years lived with a disability in developed

countries because of its severity, as it is the anxiety disorder with the highest percentage (50.6%) of severe cases (Dickel et al. 2006; Veale D 2014). Depression and anxiety also frequently co-occur for OCD patients, which possibly contributes to misdiagnosis (Rasmussen and Eisen 1992). Compared with the general population, those with schizophrenia, eating disorders, and Tourette's syndrome have a greater comorbid risk as well (Rasmussen and Eisen 1992).

Obsessive compulsive disorder is often differentially diagnosed as specific phobia, generalized anxiety disorder, hypochondriasis, panic disorder, and compulsive personality disorder (Rasmussen and Eisen 1992). These are distinguishable from OCD in that while many of them have intrusive thoughts, most do not have associated rituals (Rasmussen and Eisen 1992). There is also significant overlap between the neurological pathways and symptoms of Tourette's syndrome and OCD, which can cause the complex tics associated with Tourette's to be difficult to distinguish from the compulsions in OCD (Rasmussen and Eisen 1992). Along with anxiety, mood disorders, and Tourette's, OCD is also shares a substantial comorbidity with substance use and impulse-control disorders (Ruscio et al. 2010). Even sub-threshold patients are associated with increased odds of also having mood, anxiety, and somatoform disorders, as well as substance abuse or dependence, and even stronger connections with possible psychotic and bipolar disorder (Adam et al. 2012).

QOL/Functional Impairment:

OCD can cause substantial functional impairment for those affected (Norberg, Calamari, and Cohen 2008; Adam et al. 2012). It is ranked in the top ten most disabling conditions as measured by quality of life decrease and income loss according to the world health organization

(Veale D 2014). This is true even for sub-threshold patients who along with obsessive-compulsive patients show substantial impairment, comorbidity, and healthcare spending (Adam et al. 2012). OCD has also been connected to increased risk of mortality, as both natural and unnatural death rates have been found to be higher in OCD patients than the general population (Meier et al. 2016). While comorbid disorders like anxiety, depression, and substance use increased the likelihood of death, significantly higher than average death rates were still true of OCD patients after excluding people with comorbid disorders (Meier et al. 2016). Most of the causes for early death in people with OCD were linked to accidents and suicide, showing the need for improvement in long-term OCD treatment outcomes (Meier et al. 2016).

Proposed Pathophysiology:

When looking for biomarkers of change, it is important to have an idea of what pathways are already known to be involved in the underlying causes of OCD. The general consensus is that OCD stems from a dysfunction in cortico–striato–thalamo–cortical circuits (CSTC), consistent with specific neuropsychological impairments in, e.g., executive function observed in OCD (Saxena and Rauch 2000). Genes affecting and interacting between the serotonergic, dopaminergic, and glutamatergic systems have been implicated both in OCD and in the functioning of these networks (Haber and Heilbronner 2013; Pauls et al. 2014). The expression of these risk genes can be modified by environmental factors, such as adverse perinatal events, psychological, and neurological trauma, which could potentially trigger the manifestation of these OC behaviors (Pauls et al. 2014).

The most widely accepted model of OCD indicates that there is an imbalance between the direct/indirect pathways that are located within the ventral and dorsal frontal-striatal circuits (van den Heuvel et al. 2010; Kwon et al. 2009). Excessive activity of direct relative of the indirect pathways in the ventral circuit would be expected to lead to enhanced activation in the ventral striatum, the orbitofrontal cortex, and the mediodorsal thalamus (van den Heuvel et al. 2010). Failure in the dorsal frontal-striatal circuits, mainly the caudate nucleus, has been shown to cause impaired executive functioning and enhanced error monitoring (van den Heuvel et al. 2010; A. Del Casale et al. 2011). Dysfunction in the caudate nucleus can result in inefficient thalamic gating, which leads to intrusive thoughts because of hyperactivity within the orbitofrontal cortex, and anxiety from hyperactivity in the anterior cingulate cortex (A. Del Casale et al. 2011). This can cause the patient's frequent and unnecessary feeling that something is wrong. Impairment in the ventral frontal-striatal circuits often noted in OCD patients seems to be a cause of their inability to stop cognitions and behaviors (van den Heuvel et al. 2010). Normal inhibitory processes are often lost in most patients with OCD, as shown in experimental settings where altered activation of the frontal-striatal circuit was co-occurring with a diminished performance in response inhibition (van den Heuvel et al. 2010).

Another study found that the patients' overall symptom severity could be predicted by the connectivity strength between the ventral caudate/nucleus accumbens and the anterior orbitofrontal cortex (Harrison et al. 2009). Specifically, aggressive obsessions were linked to an increase of connectivity between the ventromedial frontal cortex, ventral striatum, and amygdala, and sexual/religious symptoms also caused heightened connectivity in ventral striatal-insular connectivity when compared to controls (Harrison et al. 2013). In general, OCD patients were

also found to have lower functional connectivity of the dorsal striatum and lateral prefrontal cortex compared to controls (Harrison et al. 2009). This was also true of the ventral striatum with the region of the midbrain ventral tegmental area, supporting the hypothesis that all forms of OCD are connected to functional changes of brain corticostriatal networks, specifically heightened and abnormal functional connectivity of ventrolimbic corticostriatal regions (Harrison et al. 2009, 2013).

Subtypes:

There are many subtypes of OCD, each with distinct neural correlates, part of the reason that effectively treating it remains so difficult (Sookman et al. 2005). The data from various symptom subtype research has been consistent in identifying the same group of subtypes despite varying methodologies (Sookman et al. 2005). The commonly listed subtypes are hoarding, obsessions without overt compulsive rituals, contamination/decontamination, and checking (Sookman et al. 2005). A more recent study by Pinto et al looked to develop a multidimensional model of OCD symptoms, and found five-factor solutions: symmetry/ordering; contamination; taboo thoughts; hoarding; and doubt/checking, which are all consistent with the long held beliefs of the widely accepted OCD themes (Pinto et al. 2008). Although hoarding is now its own distinctive subtype in DSM-V, it is still closely enough related to OCD historically to be included for the purposes of this study. More and more, research is showing that each subtype might have a tendency to respond differently to different psychosocial treatments.

Within these subtypes there are often more subtypes, complicating the matter even further. Obsessions related to contamination and corresponding rituals related to

washing/cleaning have been the main focus of OCD studies over the years (Ball, Baer, and Otto 1996). Patients with these symptoms can be further subdivided into two separate categories: people who fear harm will come to themselves or others as a result of contamination; and people who have a feeling of contamination from specific substances but report no related feelings of harm (Ball, Baer, and Otto 1996). The latter group has fewer obsessions causing their compulsions, which are more often driven by the need to alleviate discomfort caused by a feeling of being contaminated (Sookman et al. 2005). Because of this, these patients are notable in their strong disgust reactions (Sookman et al. 2005).

Within the checking subtype, it is possible to find a range of triggers that lead to the checking compulsion, including harming, sexual, or aggressive obsessions (Feinstein et al. 2003). Compulsions for these people are often driven by the need to reduce stress caused by uncertainty or doubt that something bad will happen to themselves or others around them. Checking can be cued by tangible situations and stimuli, such as leaving the house or flipping a light switch (Sookman et al. 2005). For some, however, the compulsions are in reaction to spontaneously intrusive thoughts, as a way to rid themselves of them because they're seen as dangerous (Sookman et al. 2005).

Hoarders are unique within the OCD spectrum because of their excessive emotional attachment to objects, heightened concerns about memory, difficulties with decision making, and problems with organization and categorization (Sookman et al. 2005). This often leads to greater anxiety and depression than is seen in other OCD patients, as well as poorer insight and worse psychosocial functioning (Sookman et al. 2005). Those who suffer from obsessional fear with compulsive urges attached are often related to the following cognitive domains: overestimation

of threat, beliefs regarding the over importance of and need to maintain control over intrusive thoughts, as well as an intolerance of uncertainty, responsibility, and perfectionism (Sookman et al. 2005).

Core Features: A Two-Factor Proposal (Harm Avoidance and Incompleteness)

Obsessive compulsive disorder has several distinct subtypes of obsessions and compulsions, but they are all marked by three core features: incompleteness, pathological doubt, and abnormal risk assessment (Rasmussen and Eisen 1992). These features can be important in distinguishing between subgroups with distinct treatment outcomes. The core features can be different even within the same type of compulsion or ritual- a checker may check because of a feeling of incompleteness that the act they just performed wasn't done "just right," or they may do it out of fear that if they don't do it a certain way or that they didn't do it at all it may cause a harmful outcome in the future.

Some studies suggest that incompleteness (INC) and harm avoidance (HA) have almost completely separate OCD subtypes attached to each (Ecker and Gonner 2008). INC is often related to symmetry and ordering, while HA is most often attached to obsessional thoughts (Ecker and Gonner 2008). Those thoughts are often focused on the fear of harm coming to oneself or others, and how to prevent that from happening, and could be related to anything from spreading disease to going to hell (Salkovskis, McGuire, and web 2003). Checking, however, is motivationally heterogeneous and has been found to be almost equally caused by INC and HA (Ecker and Gonner 2008). Contamination/washing OCD patients did not show many (if any at all) unique associations with HA or INC, and symptom severity was noted to be uniquely

contributing to INC in several analyses (Ecker and Gonner 2008). Knowing the intricacies of what specifically causes one's obsessions and/or compulsions is very important for clinicians during treatment, as certain forms of therapy benefit certain subtypes of OCD more effectively than others. The ability to connect the action and mechanism of the neural pathways with a specific phenotype can help to treat patients as efficiently as possible from the beginning rather than having to continuously search for the best treatment method. Understanding details such as whether the patient's motivations are caused by INC or HA could help clinicians to individually tailor their therapy to the most effective method for that root cause. This is especially important for improving the response prediction for neurosurgery (Benjamin D. Greenberg, Rauch, and Haber 2009).

This has been shown to be true, especially in DBS, where clinical observations after treatment of the ventral anterior limb of the internal capsule/ventral striatum (VC/VS) suggests that patients motivated by a feared consequence respond better than those whose symptoms are associated with incompleteness (Benjamin D. Greenberg, Rauch, and Haber 2009). Patients with otherwise intractable depression also respond better to DBS of the VC/VS, which could show some improved treatment for hoarders who often have higher depressive symptoms related to their OCD (Benjamin D. Greenberg, Rauch, and Haber 2009).

Because some forms of therapy are more effective for specific subtypes of OCD than for others, this is something that must be taken into account when coming up with an adaptive DBS system. We have to ask ourselves, "who will this be suited for best, and can we reconfigure its placement so that we can equally improve the conditions across all forms of OCD?" To know that, we have to understand the specific biomarkers of change during OCD symptom

provocation. The neurobiology of these disorders cut across the phenomenological subtypes, and may make assessing the core feature groups more relevant than the subtypes in leading to effective treatments for OCD. There is a theory that VS DBS changes the bias between Positive and Negative Valence States in the direction of reward/approach over HA (W. K. Goodman et al. 2010; Figee et al. 2013). This is backed by the pattern and time course normally seen in OCD symptom improvement, wherein mood usually improves first, followed by a reduction in symptoms. This idea supports a focus on HA over INC patients, as they would benefit most from VS DBS.

Testing:

The most widely used OCD severity measure is the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), developed by Wayne Goodman. The scale asks patients to report the amount of obsessions and compulsions they currently spend time thinking about or doing, as well as those that they have experienced in the past (W. K. Goodman et al. 1989). This method of rating severity allows clinicians to measure response to treatments (Ruscio et al. 2010). Severity as measured by the Y-BOCS is associated with high functional impairment, high comorbidity, poor insight, and high probability of seeking treatment (Ruscio et al. 2010). There is also a Y-BOCS symptom checklist which is complementary to the Y-BOCS and asses OCD symptom subtypes.

Treatment Methods:

Behavior Therapy:

Behavioral therapies represent one of only two established first-line treatments, the other being medication management. The best known behavioral approach is a variant of

cognitive-behavioral therapy (CBT), exposure and response prevention (ERP) (Deacon and Abramowitz 2004). Cognitive therapy is effective, although not as much as CBT that utilizes ERP (Deacon and Abramowitz 2004). Exposure is a key element in reduction of OCD symptoms, a reason that it will be included in our testing protocol. When coming up with a treatment plan, it is very important to take all factors into account, including specifics like fear vs incompleteness, comorbidities, and family history (Koran et al. 2007). Other factors like the patient-doctor relationship, the social/environmental factors, and the patient's beliefs about the nature of the illness can help to determine things like whether inpatient or outpatient therapy would be more effective, as it works well for some but can be detrimental to others' therapeutic success (Koran et al. 2007).

While CBT can be an effective form of therapy for some, up to 25% of OCD patients have reported difficulty tolerating CBT (Mancebo et al. 2011). The most common reasons for dropping out of therapy early include fears about participation in treatment as well as perceived environmental barriers and financial costs of CBT (Mancebo et al. 2011). Some patients never try CBT after its recommendation by a clinician, or never receive treatments that are intense enough to be effective (Mancebo et al. 2011). Even after a full course of therapy (20 CBT sessions), the probability of full remission (35% reduction in Y-BOCS score) is only about 12%, and the probability of partial remission (25% reduction in Y-BOCS score) is less than 50% (Eisen et al. 1999; P. Alonso et al. 2001). Of those who achieve full remission from OCD symptoms, there is still a 48% chance of relapse within 2 years, with religious and sexual obsessions potentially causing worse long-term outcomes (Eisen et al. 1999; P. Alonso et al. 2001).

More recent studies show that fear extinction may be impaired in addition to behavioral inhibition, due to neuroimaging evidence indicating the involvement of the lateral and medial orbitofrontal cortices, the dorsal anterior cingulate cortex and amygdalo-cortical circuitry, on top of the cortico-striatal circuitry (Milad and Rauch 2012; Kwon et al. 2009). This has been confirmed by several studies, but there have been different findings regarding whether or not the magnitude of symptom severity is correlated with the level of extinction recall (ER) (Milad et al. 2013; McLaughlin et al. 2015). In a study by McLaughlin et al, the only differences were seen in people who had been diagnosed with OCD at some point in their lives when compared to control subjects (McLaughlin et al. 2015). However, a prior study found that symptomatology was directly linked with ER, although both showed a large heterogeneity across OCD patients, warranting further research looking into the connection between OC symptoms and extinction memory (Milad et al. 2013; McLaughlin et al. 2015).

ERP as a treatment method is based on the patient's ability to engage in fear extinction, and discontinue the use of rituals to reduce anxiety in certain situations, which is done through exposure to those specific triggers in therapy settings (Mancebo et al. 2011; McLaughlin et al. 2015). Part of the reason for the long-term ineffectiveness of CBT is the reduced ability for OCD patients to maintain the ER after fear extinction, but is something that could be improved long-term with more invasive treatment methods (McLaughlin et al. 2015).

Providing patients and their families with education on the complexities of OCD can help to increase adherence to treatment, and should be done before the first line of treatment begins, whether it's CBT, serotonin reuptake inhibitors (SRIs), or both (Koran et al. 2007). Initial adherence and treatment success can be critical to a patient's long-term recovery, because with

every failed treatment method comes increased hopelessness and despair, as is the case with a majority of patients who come in for deep brain stimulation (DBS) (Koran et al. 2007).

Unfortunately, even with proper patient education and the choice of the best individual treatment method, 30-40% of patients don't respond to CBT or SRIs (Öst et al. 2015; Romanelli et al. 2014). CBT has been found to be significantly better than SRIs, although a combination of the two, or the use of selective serotonin reuptake inhibitors (SSRIs) instead of SRIs is often even more effective (Öst et al. 2015; Romanelli et al. 2014).

Medication Therapy:

Some studies have found up to a 70% success rate using first-line serotonin reuptake inhibitor (SRI) antidepressants (Pittenger and Bloch 2014). Other classes of antidepressants are typically ineffective. SRIs used for OCD are typically used for longer periods and at higher doses than in treatment for depression (Pittenger and Bloch 2014). Effective SSRIs in treating OCD include fluoxetine, sertraline, paroxetine, citalopram, and escitalopram (Pigott and Seay 1999). Clomipramine has been found to be about as or more effective, however, because of frequent negative side effects it is not often used as a first-line treatment (Pittenger and Bloch 2014; Pigott and Seay 1999).

For SRI partial responders, the addition of antipsychotics like haloperidol and risperidone can be beneficial (McDougle et al. 1994; Bloch et al. 2006). Only one-third of these patients show a meaningful response to the addition of antipsychotics, almost all of which are patients with concomitant tics (McDougle et al. 1994; Bloch et al. 2006). Reviews have pointed out that

for the 30% of patients who don't respond to pharmaceutical treatments for OCD, there is a dearth of established treatment options to fall back on (Pittenger and Bloch 2014).

Notably, responders to SRI treatment as measured by Y-BOCS score reduction showed lower central nervous system (CNS) arousal, which was seen by using EEG-based arousal markers (Dohrmann et al. 2016). The study concluded that EEG-based markers could be beneficial in coming up with individualized treatment for OCD, and supports the use of EEG recordings during our tasks, as they have the goal of developing these markers to assist in individualizing patient treatments (Dohrmann et al. 2016). Another study confirmed the potential benefits of measuring brain activity with EEG in identifying treatment responders of SRIs in OCD, showing a correlation between Y-BOCS the score reduction and OFC/ACC activity at baseline (Krause et al. 2016). The analysis showed significantly reduced activity in the beta 1, 2, and 3 bands, as well as the alpha 2 band compared to non-responders at baseline, confirming results of previous studies (Krause et al. 2016). A positive correlation between frequency alpha 1 and 2, beta 1 and 3, delta, and theta of the OFC, as well as the bands delta, alpha 1 and 2, and beta 3 of the ACC with a reduction of OCD symptoms was found in the same study, possibly suggesting a transition to a "normal" brain pattern, although this one study is not enough to make that a definitive statement (Krause et al. 2016). There are still a limited amount of studies using EEG in general, and even fewer to using it to find a control signal in OCD patients, warranting more research using EEG to record brain activity, especially during OCD provocation. Our goal is to advance this promising work by testing EEG responses during symptom provocation, which has yet to be done extensively. EEG could thus be a "control signal" for brain-circuit-based treatments, including DBS, or noninvasive stimulation.

Non-Invasive Brain Stimulation:

New non-invasive treatment methods like repetitive Transcranial Magnetic Stimulation (TMS) have provided a promising alternative therapy for non-treatment resistant OCD (Modirrousta et al. 2015). Researchers have found that 1 Hz deep rTMS over the dorsomedial prefrontal cortex (dmPFC) can at least be partially effective in reducing aspects of error monitoring that are commonly impaired in OCD, like conscious error report and post error slowing, while also improving OCD symptoms (Modirrousta et al. 2015; Dunlop et al. 2016). Responders to this type of treatment often showed higher dmPFC-ventral striatal connectivity at baseline, and the degree of reduction in YBOCS symptom severity is usually directly correlated to the reduction of connectivity in these regions (Dunlop et al. 2016).

Surgical Treatment:

Ablative treatment like cingulotomy and anterior capsulotomy are reserved for the most severe and refractory cases (Jenike et al. 1991; Dougherty et al. 2002; Jung et al. 2006). Anywhere from 25%-56% of patients show some degree of response to the therapy, depending on the study, with even higher rates of response in patients receiving a bilateral anterior cingulotomy (Jenike et al. 1991; Dougherty et al. 2002; Jung et al. 2006; Steven A Rasmussen, M.D1., Georg Norén M.D.,Ph.D.2, Benjamin Greenberg, M.D., Ph.D.1, Richard Marsland R.N1., Nicole McLaughlin, Ph.D.1, Paul Malloy, Ph.D.1, Stephen Salloway, M.D.1, David Strong, Ph.D.,3 Jane Eisen, M.D.1, Michael Jenike, M.D.3, Scott L. Rauch, M.D.3 Lee Baer, Ph.D.3, & Christer Lindquist, M.D.4, n.d.). Studies have not seen signs of significant adverse

cognitive side-effects or personality changes after surgery in both the short and long term (Jung et al. 2006; Mindus, Edman, and Andreewitch 1999). Adverse events are rare, though may include problems with apathy, executive functioning, and disinhibition, and the worst noted was an asymptomatic radiation-induced cyst (Ruck et al. 2008; Lopes et al. 2014; Steven A Rasmussen, M.D1., Georg Norén M.D.,Ph.D.2, Benjamin Greenberg, M.D., Ph.D.1, Richard Marsland R.N1., Nicole McLaughlin, Ph.D.1, Paul Malloy, Ph.D.1, Stephen Salloway, M.D.1, David Strong, Ph.D.,3 Jane Eisen, M.D.1, Michael Jenike, M.D.3, Scott L. Rauch, M.D.3 Lee Baer, Ph.D.3, & Christer Lindquist, M.D.4, n.d.). After MRI analysis of patients post-surgery, researchers have noticed that the risk of adverse side effects may go down if the medial and posterior extension is reduced, and reducing the lateral lesion extension increases OCD symptom reduction (Ruck et al. 2008).

The ablative surgery can be performed with either laser interstitial thermotherapy (LiTT) or gamma knife radiation (GK) (Hoppe et al. 2017; Jung et al. 2006; Mindus, Edman, and Andreewitch 1999). While neurosurgery in general has a complication rate of 25%, this type of surgery sees complications of less than 5% in patients with epilepsy (Hoppe et al. 2017). While no studies have been published on this surgical method in OCD patients, in epileptic patients who have received this surgery, LiTT has been as effective as GK, and while patients often experience fewer long-term side effects after LiTT, it is a more invasive surgery with more short-term risks like hemorrhage or hematoma, making the overall differences between the two surgeries negligible (Hoppe et al. 2017).

Ablative procedures and exactly how they work to reduce OCD symptomatology is still not fully understood, especially since many circuits connecting the thalamus, basal ganglia,

medial prefrontal cortex, and OFC have been implicated in the pathophysiology and treatment response of OCD (Benjamin D. Greenberg, Rauch, and Haber 2009). Symptom reduction has been seen in surgeries targeting different structures of the brain, possibly due to the different subtypes of OCD and their partially separable neural correlates (Benjamin D. Greenberg, Rauch, and Haber 2009). Ablation or stimulation of VC/VS, or using procedures like limbic leucotomy, subcaudate tractotomy, anterior capsulotomy, and anterior cingulotomy can improve both depression and OCD severity (B. D. Greenberg et al. 2003). There seems to be a potentially greater response in the VC/VS region in patients with fear-based OCD symptoms over patients with incompleteness-based OCD (Benjamin D. Greenberg, Rauch, and Haber 2009).

Deep Brain Stimulation Treatment:

Both ablative surgeries and brain stimulation methods for OCD evolved from therapeutic use in other psychiatric disorders, epilepsy, and/or other movement disorders (W. K. Goodman and Insel 2009). Deep brain stimulation (DBS) especially has been extensively used in motor disorders, using the lessons learned from those experiences in treating more complicated neurological-based disorders like OCD (Gradinaru et al. 2009). DBS targets similar areas of the brain as ablative surgeries, but has the added benefit of being reversible and adjustable (W. K. Goodman and Insel 2009). In 2010, the FDA approved a Humanitarian Device Exemption (HDE) for DBS in intractable OCD because of the device's proven efficacy, safety, and its possible benefit for up to 4,000 people a year in the US that would meet criteria for implantation (W. K. Goodman and Insel 2009). Since then it has shown a 40%-70% response rate when used in the anterior limb of the internal capsule (ALIC), VC/VS, and nucleus accumbens (NAc) (W.

K. Goodman and Insel 2009; Abelson et al. 2005; Nuttin et al. 1999; Denys 2008). As clinicians get more experience in the use of DBS in treating OCD, results are showing that clinical benefits are improved when targeting more posterior locations at the junction of the anterior capsule, anterior commissure, and the bed nucleus of the stria terminalis (de Koning et al. 2011; Benjamin D. Greenberg, Rauch, and Haber 2009).

Recent DBS studies suggest that DBS may do more than just disrupt neural activity and act as a "functional ablation" as was previously believed, and may have effects on neuronal function that include axonal activation (W. K. Goodman and Insel 2009; Abelson et al. 2005). The possibility that DBS could work even better than lesion procedures, as well as the option to reverse the procedure are enough reasons to pursue an adaptive closed-loop form of DBS. In a DBS study targeting the NAc results showed the normalization (increase) of NAc activity, reducing the connection between the NAc and prefrontal cortex (Figee et al. 2013). Researchers also saw a reduction in the frontal low-frequency oscillations while performing symptom provocation in OCD patients, suggesting the DBS works to reduce maladaptive connections and actions in the targeted regions (Figee et al. 2013). DBS has also been found to assist in CBT through the facilitation of fear extinction by reducing fear expression and strengthening extinction memory (Rodriguez-Romaguera, Do Monte, and Quirk 2012). This result was maximized in DBS of the dorsomedial VS specifically, showing increased plasticity marker expression in areas known to learn and express extinction like the the prelimbic and infralimbic prefrontal cortices, intercalated cells, the amygdala central nucleus (lateral division), and the orbitofrontal cortex (Rodriguez-Romaguera, Do Monte, and Quirk 2012).

DBS helps about 60% of patients suffering from intractable OCD, but there is still a lot of room for improvement (Pino Alonso et al. 2015). While clinicians are continuously refining the positioning of DBS electrodes to improve clinical results, that may not be enough to make a significant difference. The limitations of the existing open-loop DBS technology act as a barrier to larger progress. DBS devices deliver fixed stimulation which can only be changed by visiting a physician, despite the constantly changing states and needs of patients, which sometimes results in stimulation-specific adverse events like hypomania (Wayne K. Goodman and Alterman 2012).

What is needed to develop a closed-loop system:

In order to develop a closed-loop system capable of adapting to patients' changing states, we will need to build classifiers for state separation to accurately notice worsening OCD symptoms and react accordingly while avoiding hypomania. This will be done by combining EEG recordings of spontaneously occurring cortical activity triggered by OCD symptom provocation with annotated concurrent expressive behavior (Automated Facial Affect Recognition (AFAR)). This new computational technology will allow behaviors like facial expressions, vocal expression, and movement velocity to be quantified and compared to brain recordings to identify behavioral indicators of distress related to OC-distress (Jeffrey M. Girard and Cohn 2015).

Locating the biomarkers of change during OCD symptom provocation will be imperative in effectively developing a closed-loop DBS system. Biomarkers of disease are defined as ‘‘a characteristic that is objectively measured and evaluated as an indicator of normal biological

processes, pathogenic processes or pharmacological responses to a therapeutic intervention'' (Strimbu and Tavel 2010). Finding these biomarkers can help to discover the biological basis of diseases like OCD, specific phobias, and anxiety disorders to develop individually-tailored treatments (Bandelow et al. 2016).

Methodology for this type of research:

This type of research has basis in the initiative started by the National Institute of Mental Health (NIMH) called the Research Domain Criteria (RDoC) strategy. This approach to psychiatric research is focused on incorporating data on pathophysiology in ways that will help to identify novel targets for treatment development, find subgroups for treatment selection, and make a better match between research findings and making decisions in clinical treatment (MacNamara and Phan 2016; Insel et al. 2010; Miller et al. 2016). The main focus in the use of RDoC is on neural circuitry, with analysis moving either upwards from circuitry function measurements to clinically relevant variation, or downwards to the genetic and molecular factors influencing that function (MacNamara and Phan 2016; Miller et al. 2016). The goal is to supplement what we know of a clinical diagnosis like OCD with data from structural and functional imaging, genomic sequencing, and lab-based tests on symptomatology to develop a forecast of the disease and the best course of treatment (MacNamara and Phan 2016; Miller et al. 2016). Analogous to what is being done in areas like infectious diseases, cancer, and heart disease, the hope is that identifying syndromes based on their pathophysiology will help to improve outcomes (Insel et al. 2010). Creating a successful closed-loop DBS system will mean we have accurately located reliable biomarkers for obsessive-compulsive distress, which can

only be done through multiple levels of analysis. In this study, we will be combining EEG recordings during provocation, clinical information, and facial analysis to develop these biomarkers.

Another relevant approach in developing biosignatures of obsessive-compulsive behaviors is the Ecological Momentary Assessment (EMA) approach, which should help to track the behaviors in the clinic and native environment (Shiffman, Stone, and Hufford 2008). This method emphasizes ecologically valid observations as close to the subject's natural environment as possible, in this case by using OC-triggering items based on what they encounter and cause them distress on a regular basis (Shiffman, Stone, and Hufford 2008). This approach should be more effective in collecting biomarkers that are generalizable to the real world, a necessary part in developing an effective adaptive DBS system.

Developing the Methods:

Previous Provocation Studies:

Developing a method of provocation to find biomarkers of change in OCD requires a multilayered approach, as discussed above. The goal of our study is to elicit a response similar to the provocation experienced by patients in the real world as they come into contact with their specific OC-stressors. Finding a way to do this requires a review of past provocation studies and what they found to be most effective. Most of these studies focus on comparing the reactions between OCD-specific stimuli, generally aversive stimuli, and neutral stimuli. Our study will include both OCD-specific and neutral stimuli, but we are aiming to replicate an interaction that could take place on a daily basis in normal environments.

Simon et al performed one of the first studies in putting together individually-tailored pictures and videos for OCD symptom provocation. They created a standardized set of pictures that could be used across various subgroups that was effective in eliciting a response. They found a difference between OCD patients and controls in only the OCD triggers (Simon et al. 2010). Anxiety ratings for the OCD themes, of which there were seven, were highly correlated with the patient's specific symptoms, with the reaction to less relevant OCD stimuli being comparable to the generally aversive control stimuli (Simon et al. 2012). This group managed to come up with a picture set which included images that applied to each subgroup which has been used in almost every OCD provocation study since.

Across all provocation studies in OCD patients, researchers generally found increased activation in the lateral frontal, medial orbitofrontal, anterior cingulate, anterior temporal, and insular cortex, as well as the amygdala, and caudate during OC-trigger exposure (Breiter et al. 1996; Schienle et al. 2005; Roh et al. 2017). OCD patients also typically exhibited increased insular activity in response to non-OCD related aversive stimuli, possibly as a result of their heightened susceptibility to negative somatic stress (Schienle et al. 2005; Breiter et al. 1996). This was true in provocation studies using pictures of OCD triggers from patients' personal environments, standardized picture sets, and individually tailored photo blocks, across all symptom dimensions, from washing and checking obsessions to sexual, religious, aggressive, and hoarding obsessions.

Mataix-Cols et al looked deeper into differences between the brain activity during symptom provocation in different OCD subtypes. In washers, they noticed increased activity in right caudate nucleus and bilateral ventromedial prefrontal regions (Mataix-Cols et al. 2004). In

checkers, they saw greater activation in dorsal cortical areas, putamen/globus pallidus, and the thalamus (Mataix-Cols et al. 2004). Hoarders showed more activity in left precentral gyrus and right orbitofrontal cortex (Mataix-Cols et al. 2004). All of these studies saw very specific positive correlations between questionnaire scores, neural response, and subjective anxiety, providing evidence that different OCD symptoms or subgroups are controlled by distinct but overlapping brain pathways which are all contained in the frontostriatothalamic circuits, an area known to play a large role in emotional and cognitive processing (Mataix-Cols et al. 2004; Simon et al. 2012; Breiter et al. 1996; Schienle et al. 2005).

A study by Roh et al confirmed previous studies which noticed hyperactive error monitoring in OCD, in this case by measuring error-related negativity (ERN), which was much higher in patients than in controls in both OCD symptom-specific and neutral conditions (Roh et al. 2017). Not only are the error-signals overactive in general settings, but the researchers found that they can be enhanced even further through individually-tailored symptom provocation. This was also seen through increased amygdala activation during both OCD symptom specific and nonspecific provocation, which requires more frontolimbic processing to decrease ERN and anxiety levels (Roh et al. 2017; Simon et al. 2010). This led them to suggest focusing patients' treatment on affective regulation when faced with these triggering items or scenarios, and shows a tendency towards generalized emotional hyperresponsivity related to increased amygdala involvement, linking it to other anxiety disorders (Roh et al. 2017; Simon et al. 2010). The patients in this study consisted of a mostly checking and contamination fear-based population based on their individual anxiety rankings.

By the end of the literature review, we came to the conclusion that it was going to be necessary to focus on contamination-based OCD patients if we were going to most effectively imitate their real-world interactions. While it is possible to show pictures of OCD-relevant stimuli pertaining to hoarding, counting, and religious obsessions, it is much more difficult to use real life stimuli that may be encountered on a daily basis related to these specific subtypes. However, because of the increased amygdala activation and heightened emotional sensitivity of OCD patients, we thought that there was a close enough connection to anxiety disorders to include one that may provide more insight into the biomarkers of change during both OCD and general anxiety-induced provocation. The nature of Specific Phobia (SP) made it a perfect disorder to include in this study.

Patients suffering from SP anxiety disorders exhibit irrational fears towards a variety of specific stimuli (Antonio Del Casale et al. 2012). There are five subtypes: blood-injection-injury (needle/dental), animal, natural environment, situational, and other (Antonio Del Casale et al. 2012). SP has already been shown to be associated with a similar pathophysiology to OCD. The biomarker therefore should be the same for OCD provocation as SP exposure as it's triggering a similar anxiety-based response. SP patients are also easier to find in the general population, with lifetime prevalence estimates of 10% (Antonio Del Casale et al. 2012).

In provocation studies with SP patients, activation of fear circuitry structures encompassing the insula, anterior cingulate cortex and thalamus are typically seen. A study by Leuken et al also noted activation of the prefrontal and orbitofrontal cortex (PFC/OFC) in dental phobics (DP) but not snake phobics (Lueken et al. 2011). This is comparable to the results from a study by Simon et al in which OFC activation was only seen with exposure to OCD-relevant

stimuli when directly compared to symptom-unrelated aversive stimuli (Simon et al. 2010). Like OC-symptoms, SP disorders can be separated by subtype, with DP being controlled by orbitofrontal areas, while reactions in snake phobics are mainly guided by limbic and paralimbic structures (Lueken et al. 2011).

Literature reviews and provocation studies have come to the general agreement that SP patients show increased activity in the insula, anterior cingulate cortex, amygdala, and prefrontal and orbitofrontal cortex, with impairments in emotional modulation often noted after exposure to phobic stimuli (Linares et al. 2012; A. Del Casale et al. 2011).

Methods- Developing the Tasks:

Developing the exact methods of provocation for this study required substantial collaborative efforts between engineering and clinical research groups. Symptom provocation tasks are very difficult in general, especially because of the risks associated with knowingly triggering patients and the increased possibility of causing adverse reactions. The original idea was to provoke OCD patients with ecologically relevant stimuli in order to obtain symptomatic neural data that would reflect real-life provocation. Questions regarding the amount of uncertainty and deception that could and should be implemented, how intensely to provoke patients, and what the most effective method to accurately locate biomarkers without interfering with the EEG signals were all discussed at length.

Provocation Props:

One of the first decisions made was to use actual props instead of images when provoking patients. After a review of the literature, this seems to be the first study of its kind in using real-life stimuli in a provocation study for OCD patients that aims to measure the reaction relative to the object's distance. While most previous studies simply measured brain activation in response to a triggering image, we decided that we wanted to measure how the brain's response changes not only after exposure, but as the possibility of coming in contact with the stimulus grows and wanes. This would not be as effective or ecologically valid as if we simply used a picture. One of the first questions that arose was what objects are we going to present to the patients? We knew that we wanted to use individually-tailored triggering objects, but there were several aspects of choosing those objects that we needed to sift through. We decided that we would need to elicit a fear pathway with something that would be a direct correlate of the person's symptoms. This led us to the decision that we needed to restrict subtypes to contamination in order to get the type of response we want. We decided that contamination patients would be easiest because it is the easiest subtype to most accurately mirror real world triggers, unlike religious or sexual obsessive patients whose triggers may not be as easily replicated in this type of study. Some general items we came up with included bloody band-aids, used tissues, and vials of blood, although the exact props will change with each subject depending on their individual stressors. The next step was deciding the best way to present the objects, and how to move them closer to and farther away from the patients.

Provocation Timing:

There were many options in deciding exactly which approach would elicit the best responses from patients, regarding both subjective anxiety and neurological activity. We thought that possibly randomizing the timing of an object moving closer to and farther away from them would be a fairly good way to mimic real-life interaction with stimuli. However, doing this in a way that would be not only replicable from patient to patient, but that would also be easily compared to the data collected in EEG and AFAR recordings became a problem. We could time out the movements with a stopwatch and move the stimuli by hand, but that would not be 100% accurate between tests, and it would be difficult to align those timings with the physiological signals. This would also probably require marks on the table that could give the patients some hint as to where the objects might land and could potentially interfere with our measurements.

In order to allow for accurate and replicable timing of object movement that would be easily compared to the other recordings, we decided to use a conveyor belt that would move objects closer to and farther away from patients in several steps that would make the quantitative analysis of affective state relative to the object's positioning much easier. Once this was decided many other questions arose- how many steps should there be? How long will the belt be? How long should the objects stop at each step? How much information should we provide patients on when and where the objects will move, and how should we convey that information to them?

We first decided that object presentation would be key. We knew it would be necessary to begin recording right before presenting the object to the patient, because that original reveal will be the first moment of exposure and therefore should be the first signal of change in affective state. Although we plan to come up with the provoking object with the patients' help

beforehand, we want to cover the object until the initial reveal, because the thought of the object in their head should not show the same brain patterns as the actual object right in front of them. The idea of covering the belt from the patients' view while moving the object came up in discussion, however it was decided that once the object was revealed it should remain in their view since in real life patients aren't surprised every time they come into contact or move closer to a trigger, making this method more consistent with a day-to-day exposure.

The choice of belt size was relatively easy, based on limitations from the sizes of available rooms to work in, as well as the understanding that an excessively long belt probably wouldn't add any helpful data, we decided that a 6-8 foot treadmill would be ideal. The original version of the task consisted of a 2-meter long belt with the contaminated object starting off on one end under a box. When the task begins we would uncover the box and then it would be randomized movements towards or away from the person. A yellow light would signal that the object is about to move, though in what direction nobody is certain, and a green light would signal that the object will remain still for the time being.

Soon after this plan was conceived, we decided that instead of a box, we should use a screen to hide the object from the subject, and the placement of the screen was debated- do we keep it close to leave some mystery as to how far away the object will be once revealed, or do we keep it at the other end of the belt to assure the subject that the initial reveal will not be up close, therefore reducing initial anxiety? We decided that patients would be subjected to enough anxiety during the task, and that by letting them know what objects they are going to be presented with beforehand and also allowing them to know a general idea of what exactly would

happen once they are exposed to the objects (including how far away the initial reveal would be) we could reduce any unnecessary stress for the patients.

In addition, we decided that it would also be important to add subjective anxiety ratings to compare the patient's subjective feelings in the moment with their measured physiological activity. A subjective unit of distress scale (SUDS) rating would be done on day one while choosing provoking objects in order to choose individual triggers that would cause a similar level of distress across each person, and to be sure that the stress was enough without being completely overwhelming. The way in which to measure subjective anxiety was not immediately clear. Because of the sensitivity of EEG recordings, there is the issue of interfering with the signals because of muscle artifact movements. This ruled out the possibility of having subjects say their anxiety level out loud or write it down, as this would almost definitely cause excess eye or muscle movements that would disrupt the recordings.

Our first solution was to place a box with five buttons under the dominant hand of each participant, allowing them to rank their anxiety on a scale from one to five with minimal excess movement. This, however, did not seem like a large enough scale to rank the level of distress that we were expecting. Eventually we landed on the idea of a dial that could be turned in 360 degrees, allowing patients to rank their anxiety on a scale from 0-100 (in increments of 5) but only using their fingers, keeping muscle movement to a minimum and expanding the rating scale. We were able to reduce excess eye movement by placing an LED screen directly behind the belt which shows the anxiety levels in the same view of the triggering object. Once we decided on this setup, we were able to come up with some initial outlines for how we thought the entire setup would look.

Version 1:

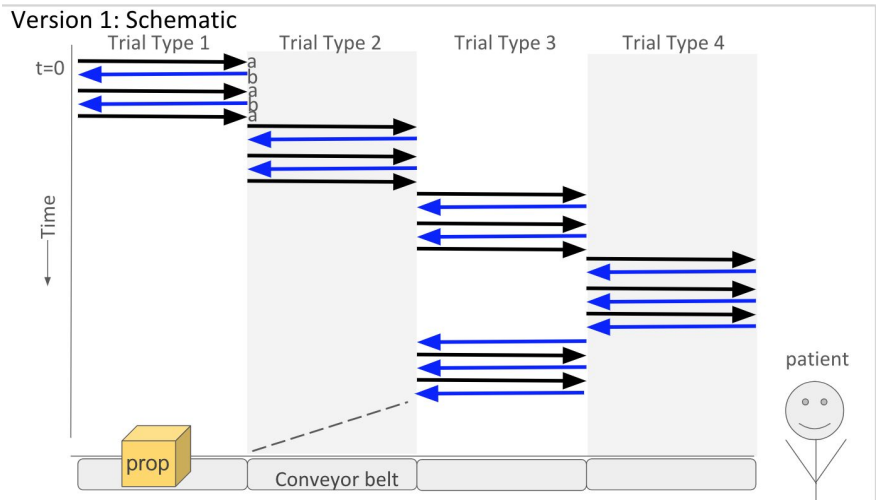


Figure 1. Schematic of provocation task, version #1

The first version of the provocation task, as depicted in Figure 1, consisted of four trials. Each trial consisted of the object moving toward or away from the patient, then pausing. There were eight trial types (1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b) which are defined by their proximity to the patient (4=closest, 1=furthest), and the direction the object is moving (toward=a, away=b). We defined epoch as either motion epoch, which would be a three second movement towards or away from the patient, or hold epoch, which would be no movement for fifteen seconds. During each hold epoch, patients would rank their subjective anxiety before the prop moved again. We would also ask them to rank their distress before and after the initial object reveal.

In this version, the prop would begin at the opposite end of the belt and take steps in a pattern of 1a, 1b, 1a, 2a, 2b, 2a, etc. to progressively move the object closer to the patient while taking steps back in between. After the object gets as close as possible, we would then progressively move it back down to the farthest end of the table in the same pattern, but this time backwards (4b, 4a, 4b, 3b, 3a, 3b, etc.). The idea was to allow the subject's anxiety to

progressively build as the prop moves closer and closer, and hopefully we would see those progressive changes not only in their subjective anxiety ratings, but also in their facial affect and neurological activity.

Version 2:

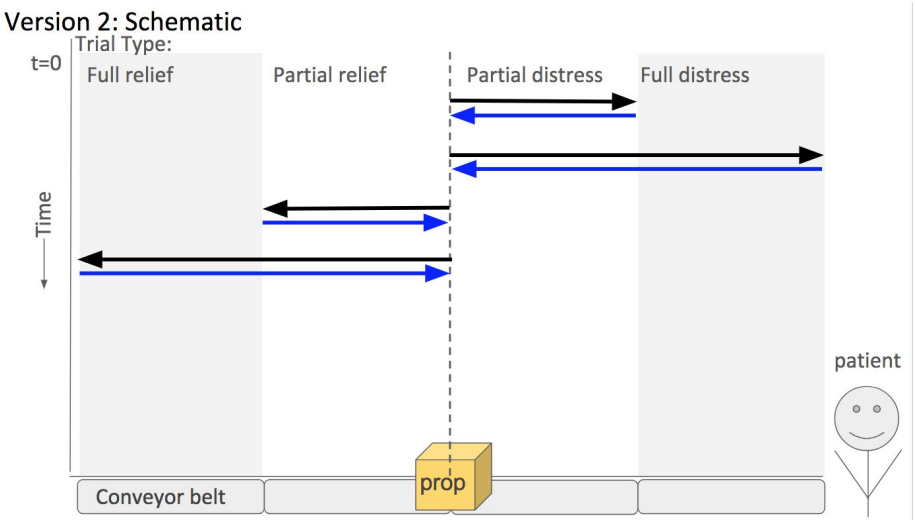


Figure 2. Schematic of provocation task, version #2

The second version of the provocation task, as depicted in Figure 2, also consisted of four trials. There are again 4 trial types, this time defined as full relief, partial relief, partial distress, and full distress, based on how far the object is relative to the patient. In this version the object would start in the middle of the belt instead of the opposite end. It would then move in a pattern of partial relief, back to the middle, partial distress, back to the middle, full relief, back to the middle, and finally full distress, and back to the middle. Each movement epoch would last 3-6 seconds depending on the distance of the trial, with hold epochs in between each that would last 15 seconds each. In this version patients would rank their subjective anxiety during the 15 second hold epoch as well.

The main issue the group had with version #2 was the possibility that habituation might occur after the original partially distressing approach, and any more distance wouldn't bother them at all. The benefits of this design would be a more seemingly random pattern of movement for the patient, making it more unpredictable. The idea of habituation also came up as an issue with the design of version #1, as we worried about the possibility of obtaining a good reaction after the object reaches its closest point to the patient, making the whole second half of the trial potentially pointless.

We decided that version #1 would be better for the collection of relevant data. While randomizing the location of the prop by using the middle of the belt as the beginning location, it might be difficult for patients to handle if the movements are too random because they will likely anticipate the more distressing scenario, which could add contamination because of the "what if" anxiety dominating the distress caused by the actual movement of the object. Version #1 would allow for a larger sample size of trials, even if we finished the task with the object at its closest proximity to the patient rather than continuing to move it back across the belt. We decided that instead of using one object moving all the way down and all the way back the belt, we could use two different objects moving down the belt. The backwards measurements probably would not be as useful since the stress would be at its highest when the object is closest to the patient, and doing two trials using different triggering objects would give us more data to analyze.

The idea of changing the trial types from four movements of equal distances to an exponential method in which each trial length was half the distance of the previous trial was also considered. It is unknown whether or not this type of task would elicit a linear or exponential decay sort of reaction, and is hard to find out without preliminary tests. We decided that the task

would take too long with the amount of steps this would require, and the difference in data would not be large enough to warrant the extra time and stress that would be needed from the patients.

Subjective anxiety ratings were also changed from the original versions. The experienced clinicians in the group said from their own experience they believed that the patients' anxiety levels would habituate in large part 30 seconds after the prop stopped moving. We are interested in recording not only the initial anxiety caused by the object's movement, but also any possible habituation that might occur after prolonged exposure. In order to gather both anxiety measurements, we decided that each hold epoch would consist of three separate 20-second intervals. The first interval would give the subject time to rate their initial anxiety. The second interval would allow time for habituation to occur, and the third would give them time to rank their anxiety after habituation. This should allow enough time for patients to submit their ratings without feeling pressured by the time constraints, and give enough exposure to permit habituation to take place.

Version #3 (Final Provocation Configuration):

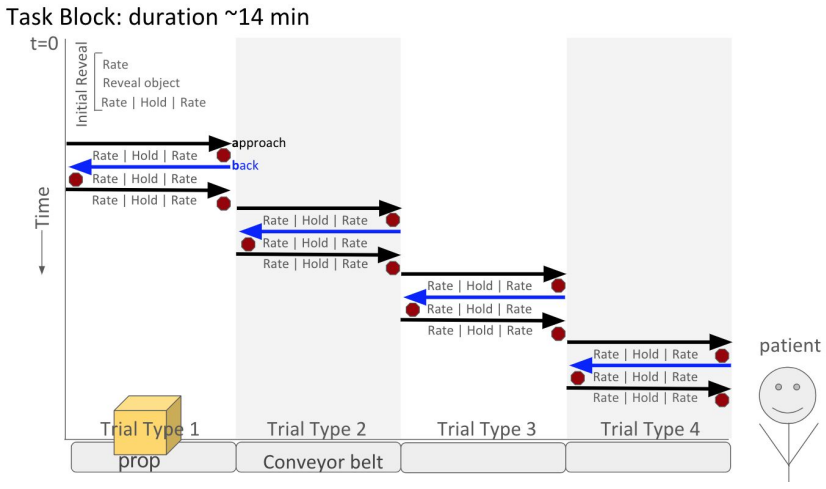


Figure 3. Schematic of provocation task, version #3

Figure 4 shows the final version of the task, which uses a linear progression of movements so that each trial is the same, making them more easily compared to one another. Each trial (1-4) will consist of an a,b,a movement and should take 13 minutes total (~5 seconds per movement epoch, 60 seconds per hold epoch). This will happen twice, each time with a different pre-chosen, individually-tailored triggering object. The subject will rate their distress once before the object is revealed, and twice after, mirroring the three 20-second intervals that will occur during hold epochs. The LED screen with the patient's anxiety rating will flash when it's time to rate their anxiety, and the ratings will be done using a dial from 0-100 in steps of 5. We will ask participants to restrict their head movement and keep their field of view focused on the object and LED screen. They will press down on the dial to submit their anxiety ratings, all the while EEG and facial video recordings will be collected. We also decided that heart rate measurements are easy enough to gather and would be good physiological data to include alongside everything else, so ECG electrodes will be attached to the patient's chest as well during the task.

Use of Materials to Measure Changes During Provocation:

Normal provocation tasks are often intricate, and ours was further complicated by the necessity to take EEG measurements. From the start we knew that we were going to use the Open-Ephys system for our EEG recordings. This system was developed by Black et al at Brown University, to be used as a cheaper and open-sourced system of taking EEG recordings for studies like this, since commercially available EEG systems are expensive and difficult to alter the specifications for the needs of the user. This system, with its open-sourced tools have helped

to develop a new EEG platform that not only drives down research costs, but also promotes collaboration and innovation. This system is ideal for developing closed-loop paradigms, which is the ultimate end goal of this project.

Electroencephalography (EEG) has been around since the 1920s, and essential in studying human neural activity, diagnosing clinical condition, studying cognitive processes, and use in studying transcranial electric stimulation (Black et al. 2017). EEGs work by placing electrodes on the scalp which monitor changes in electric potential caused by the synchronous activation of 10-20 cm^2 of cortical tissue (Black et al. 2017). The electrodes can detect frequencies as high as 500 Hz (fast ripples) or as low as below 1 Hz (slow wave oscillations) (Black et al. 2017). The past decade has seen open-source data sharing which has helped to start the production of easily accessible EEG systems.

There has been extensive research done using EEG in human patients, and has been used for the clarification of covariance, coherence, and classification of motor, emotional, and alert states. We are going to be interested in alpha, theta, and gamma powers, as those are regularly noted in emotional changes (Balconi and Lucchiari 2006; Aftanas et al. 2004). The frontal asymmetry of alpha (8-12 Hz) power is correlated with varied valence states and discrete emotions (happiness, sadness, fear), as well as approach/withdrawal (Balconi and Lucchiari 2006; Davidson 1992; Harmon-Jones, Gable, and Peterson 2010). Gamma powers have been connected with happiness and sadness through event-related synchronization (ERS) and desynchronization (ERD), and ERS in theta power changes significantly during emotional state transitions (Balconi and Lucchiari 2006; Aftanas et al. 2004). Studies using EEG have confirmed hyperactivity at subcortical circuitry in OCD patients seen in neuroimaging studies (Desarkar et

al. 2007). Spectral power in the LFP has been shown to be a disease-relevant indicator in many disease states, including Parkinson's and dystonia (Schnitzler and Gross 2005; Uhlhaas and Singer 2006; Priori et al. 2013). Therapeutic outcomes in DBS are correlated with LFP signals, and when they are recorded from the VS in OCD patients, could potentially show a biomarker for developing an adjustable DBS system. It is challenging to locate biomarkers for psychiatric disorders that are valid for diagnosis and objectively monitoring outcomes of treatment. However, OCD's phenotype is very distinctive with plenty of evidence suggesting dysregulation in the CSTC loop, which should make any potential biomarkers easier to locate (Milad and Rauch 2012).

This particular EEG system consists of an electrode cap, a data acquisition system, digital amplifiers, and a computer (Black et al. 2017). The amplifiers amplify the small signals gathered from the electrodes which are registered by the acquisition board and tagged with a timestamp, all of which is shown on the computer (Black et al. 2017). In our study, the acquisition board will also be connected to the anxiety rating dial/screen, the electrocardiography (ECG) (heart rate measurement), and the conveyor belt. This will allow us to analyze the various data alongside each other with timestamps so we know precisely how it all matches up to what was happening during the task. We will also be collecting electromyography (EMG) recordings along with the EEG readings to help with data quality and analysis.

We will be using the standard 10-20 electrode cap layout for data collection at the beginning, although we may change electrode placement to focus more around the CSTC loops in the frontal region of the brain as that is the main area of interest. We will decide on that after

some development testing, however until then we will be using the layout shown in Figure 4 (Black et al. 2017).

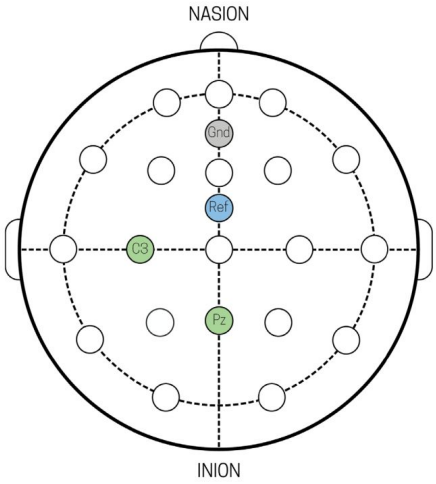


Figure 4. Schematic of standard 10–20 electrode cap layout. Recording electrodes Pz and C3 (light green) used for analysis, reference electrode (light blue), and ground electrode (light grey). From Black et al, 2017.

The system is further improved through the use of tripolar electrodes, which have been proven by Besio et al to be more effective in collecting detailed electrode data than conventional disk electrodes. The tripolar system works better because of their ability to automatically attenuate muscle artifacts which improves the quality of the signal (Besio et al. 2014). These electrodes have been shown to be better at detecting high frequency oscillations on the scalp surface than conventional disk electrodes, which may help to more effectively locate increased brain activity during symptom provocation (Besio et al. 2014).

These electrodes help to reduce noise to get optimal signals, but that was not the only potential source of noise interfering with the EEG signals. Environmental noise is always an issue with EEG, caused by anything from improper grounding to AC devices (Black et al. 2017). Power lines are often the source of noise, and can be reduced by using a common-reference, which has a significantly lower impedance than each electrode, producing a large noise signal

(Black et al. 2017). When compared to the ground signal, this should remove any existing noise. Any impedance mismatch across the electrodes can also introduce noise, making it necessary to take impedance measurements during EEG application (Black et al. 2017).

In initial development testing without the conveyor belt, we were able to record clean EEG signals in the testing room without much issue. After assembling the conveyor belt, however, we ran into problems with noise caused by the belt, interfering with our ability to collect optimal signals. The problem was that we saw electrical noise in the EEG during the motion epochs while the conveyor was running. We attempted to reduce the noise by moving the belt from a metal table, where the noise was coupling through the metal frame, to a wooden table where noise coupling is not an issue. However, we have continued to experience some noise while the belt is moving.

The main issue seems to be noise caused by sudden flow changes in the wires, and the current system uses alternating pulses of power through two separate wires which generates a lot of noise in the EEG signal. We are now in the process of trying an opto-isolation approach, although it doesn't seem like that will stop the problem because there is still noise being generated through the cables. Our hope is that by switching over to a DC motor, which will send a constant flow instead of alternating pulses, and adding ground shielding everywhere possible, we will be able to get rid of any extra noise, but we are still in the process of coming up with a final solution.

Along with EEG and subjective anxiety, we will use AFAR to measure changes in valence states. The AFAR system is a computer-vision based approach, which objectively measures at 30 to 60 frames per second the timing, intensity, and occurrence, of facial action

units, head pose, and gaze (Jeni, Cohn, and Kanade 2015; J. M. Girard et al. 2015; Chu, Torre, and Cohn 2013). This measurement system requires that participants be videotaped. Action units are visually based actions that, when analyzed by this system in combination or individually have the ability to describe nearly every possible facial expression (EKMAN and P 2002). AFAR has been proven to show similar validity when compared to manual measurements of facial action units, as well as other factors like depression severity, holistic expressions, and psychological distress (J. M. Girard et al. 2015; Cohn and Sayette 2010; Scherer et al. 2015, 2013). Action units associated with positive (e.g., joy) and negative (e.g., fear, anxiety) emotion have been identified through past research (Ekman and Rosenberg 2005; Zhang et al. 2016). Those action units were then used to create scales for positive and negative valence, which are used to measure subjects' emotions (Messinger et al. 2009; Baker, Haltigan, and Messinger 2010; Prkachin and Solomon 2008). Head orientation and gaze have also been found to be strongly related to emotion and valence, so they are included in positive and negative valence scales as well (Baron-Cohen et al. 1997; Ekman, Friesen, and Tomkins 1971; Keltner 1995; Armstrong et al. 2010).

In the end, the entire setup will look like the depiction in Figure 5.

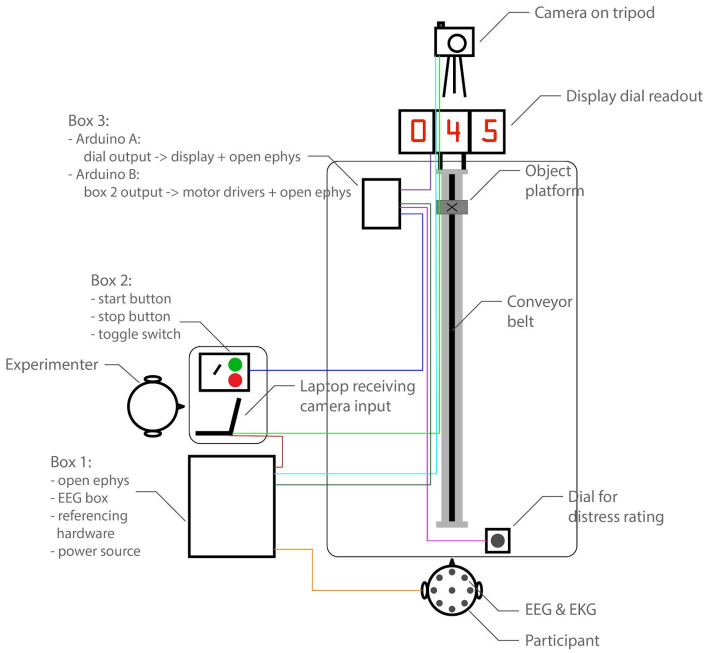


Figure 5. Final task setup

Addition of Specific Phobia Anxiety Patients:

At this point we began discussions of piloting the task in general at disorders that are amenable to exposure because the pathways should be similar, specifically patients with specific phobia (SP) anxiety. Patients who suffer from specific phobia anxiety disorders have irrational fears which are associated with avoidance of specific stimuli, making it very easy to choose a triggering object for a provocation task. General Anxiety Disorder (GAD) would show much more of a generalized fear that would be harder to trigger than specific phobias, making it necessary to narrow the category down to just SP. The pathways between SP and OCD should be similar and the facial recognition would be interesting to compare between the two, along with EEG markers. The higher percentage of people with specific phobias in the general population, along with the similar harm avoidance-based circuitry, makes this an ideal group to compare to OCD patients in a pilot study. Based on previous provocation studies in SP patients and the logistics of triggering them with real objects, for the development studies using these patients we

have decided to use pictures to trigger them instead of real life stimuli. The pictures will still be individually-tailored and be decided upon beforehand with the clinician. The pictures used for SP provocation will be from a sample of triggering photos we have collected from the internet that relate to various subtypes of specific phobias (snakes, spiders, clowns, needles, etc.)

Timeline of Study:

The development of this study has taken much longer than the team had originally planned for. While we originally planned on bringing in patients before the end of November 2017, we are now looking at a realistic start date sometime in May 2018. This was mostly caused by unforeseen delays in technical aspects of the project related to EEG setup, development of the anxiety rating dial, and complications with the conveyor belt. While testing with actual patients has not yet begun, we have been able to run some development tests with various pieces of the setup to make sure that we are able to gather clean recordings and troubleshoot any potential problems we may come across before we bring in patients. We considered starting the provocation study with SP patients without the use of the conveyor belt, however we did not want to complete part of the study without the full setup and switch over part of the way through, so we decided to take the extra time to wait for the belt to be finished. We did this in order to minimize the potential differences between data due to the different configurations of the task.

Results- Final Protocol:

Participants and Risks:

Subject Population:

The subject population will consist of 60 people: 20 men and women, diagnosed with OCD; 20 men and women, diagnosed with specific phobia anxiety disorder; and 20 men and women control subjects.

Eligibility:

Each patient whose clinical status conforms to the inclusion/exclusion criteria and who is willing to participate in the study as demonstrated by signing the informed consent will be enrolled in the study. After the patient signs the required documents, he/she will begin participating in one or more of the tasks listed above.

Inclusion Criteria

- Men and women (non-pregnant) between ages 18 and 65 years;
- The patient meets criteria for OCD;
- The patient has a minimum score of 16 on the Y-BOCS;
- Or, instead of the two criteria above, the patient has significant anxiety related to a specific phobia (snakes, spiders, needles, etc.)

Exclusion Criteria

- The patient has a lifetime diagnosis of psychotic disorders such as schizophrenia;
- Alcohol or substance abuse/dependence within 6 months, excluding nicotine;
- The patient is deemed at high risk of suicidal behavior or impulsivity.
- The patient is pregnant or plans to become pregnant in the next 24 months.

Material Inducements:

Participants will receive a total of $100 for participation in the study. For participants who do not complete the study, they will be compensated with a payment of $25 after the first

day of participation. They will receive the additional $75 after the second day. Participants will have the option to receive payment by gift cards to various retailers (Walmart, Stop & Shop, Amazon, etc).

Recruitment and Consent Procedures

Participants will be recruited through ads placed within the OCD clinic at Butler Hospital (including a clinic newsletter), as well as ads throughout the community. They will also be recruited from a database of OCD patients who have agreed to be contacted for research studies. An early verbal screening open-ended question over the phone for "potentially distressing items" could be completed during recruitment to inform this process.

In the consent form and discussion with an investigator, subjects will be advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without negative consequence, their right to terminate participation at any moment without negative consequence, and the name and telephone number of the PI. Written informed consent for the screening procedures is obtained on the first visit. The study and the related risks have been reviewed and approved by the Butler Hospital IRB.

Final Protocol:

Patients who have a diagnosis of OCD or specific phobia anxiety disorder will participate in a clinical interview and cognitive tasks, during which they will be exposed to their individual OC stressors or will be asked to make decisions related to information value and quantity while measuring neural activity and filming facial reactions. This will help us to look for biomarkers of that change. This study offers a unique opportunity to develop biomarkers for key domains of

OCD, and other neuropsychiatric disorders, that are grounded in brain neurocircuitry at the individual-patient level.

Subjects will participate in a clinical interview (Day 1), and then cognitive tasks with EEG (Day 2). Day 1 will be 4 hours or less, and Day 2 will be 2.5 hours or less. The two days will take place within one week of each other to make sure that all clinical measures remain the same. We will collect neural data (through EEG) from patients when their symptoms are provoked, so we can look for biomarkers of that change. The patients will be monitored through EEG and facial recognition. After initial video and EEG setup subjects will complete the Provocation task.

Day 1:

Demographics Questionnaire. Assesses psychiatric and medical treatment history. Cognitive-Behavioral Treatment History: Assesses CBT history.

SCID-5: Structured Clinical Interview for the DSM 5 (SCID): (First et al. 1997) The SCID will be used to determine comorbid diagnoses at baseline.

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; (W. K. Goodman et al. 1989)): The YBOCS is a 10-item inventory that assesses severity of OCD symptoms

Y-BOCS Symptom Checklist: The YBOCS symptom checklist assesses OCD symptom subtypes.

Obsessive-Compulsive Inventory (OCI) (Foa et al. 1998): A scale developed to help determine the severity of OCD.

Trait Core Dimensions Questionnaire (TCDQ): The TCDQ measures prevalence of harm avoidance or incompleteness traits related to OCD.

Beck Anxiety Inventory (BAI; (Beck et al. 1988)). The BAI is a 21-question self-report inventory that is used for measuring the severity of anxiety. The questions used in this measure ask about common symptoms of anxiety that the participant has had during the past week.

Beck Depression Inventory (BDI; (Beck et al. 1961)) The BDI is a 21-question self-report inventory designed to measure depression severity.

Severity Measure for Specific Phobia- Adult: This measure assessed the severity of specific phobic symptoms.

The end of the clinical interview will consist of researchers and participants deciding on one or two triggering objects based on the subject's specific OCD-related triggers. Most of these patients will suffer from contamination OCD and the triggering objects will reflect that specific subtype. We will take a SUDS measurement regarding the subject's anxiety towards the object to make sure that it will elicit a manageable response.

Day 2 Overview:

Provocation of OC symptoms (PROVOC) will be used to evoke manageable levels of OCD related distress (Steketee et al. 1996). Three tasks will be developed collaboratively between the participant and experimenter. This will involve the participant being exposed to triggers that they consider to be impossible to confront without ritualizing. The goal is for the participants to confront the triggers without ritualizing starting with easier distances, and will continue to allow the objects to approach until they feel their distress is intolerable, or ideally until the task is finished. The first two tasks will involve researchers and subjects deciding upon a few different

triggering items (bloody napkin, used tissue, etc) that will be moved closer and closer to the subject on a conveyor belt as they wear the EEG measuring system, a cap on their head with sensors on the scalp to measure brain activity through the skin on their head. The sensors will be attached to scalps with a paste that will require washing out after the tasks are completed. Each of the tasks will be broken up into 4 steps, which will provoke increasing levels of distress. Each step will last the same amount of time, with the potential of 12 steps with 60 seconds between each step, during which the patient will measure their subjective anxiety twice, and the patient will always have the option of stopping if the task becomes too distressing. There will be a similar process (which will last the same amount of time) involving getting closer to a "neutral" object that should not cause any distress to be used as a control. We will pilot the provocation protocol with SP patients, and start addressing problems that come up (e.g. EEG movement artifacts). Sessions will be videotaped with AFAR system concurrent to recording of LFPs from VS and scalp EEG. The camera will record their facial, physical, and vocal reactions to the tasks from across the table. We will continue to record until the end of the session unless they request to stop early. These recordings will be analyzed by a computer system designed to measure the behaviors exhibited during OCD/SP symptom provocation. Day 2, including EEG setup and task participation, should take 2-3 hours.

Day 2 Specifics:

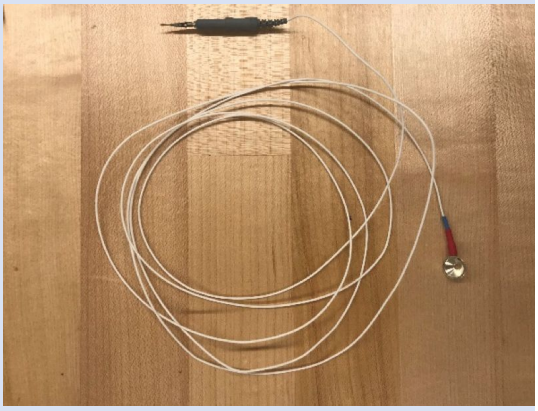
The tasks will take place at Butler Hospital, in the Annex W334. The room should be set up with the conveyor belt along the top of the desk, the EEG system on the table to the left of the patient, with the patient seated at the end of the belt. A dial to measure their subjective anxiety

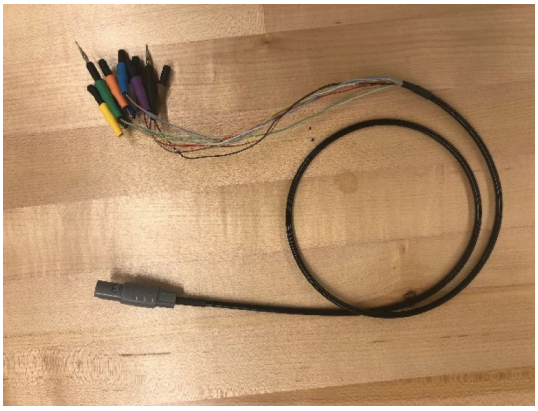
will be on the table in front of them on the side of their dominant hand, with a connected screen showing the SUDS score at the other end of the belt. The distress ratings will be saved in the open-ephys system along with all the other measurements. The person running the tasks should be to the left of the patient with a laptop connected to the whole system.

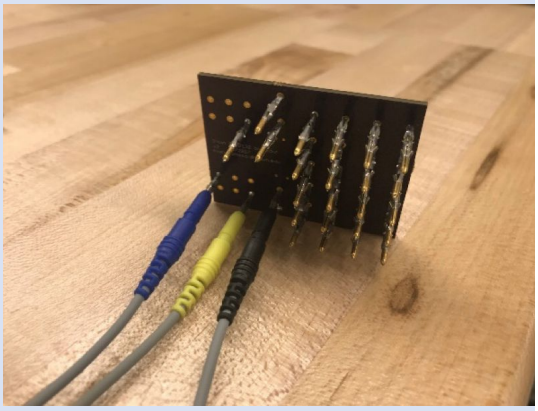
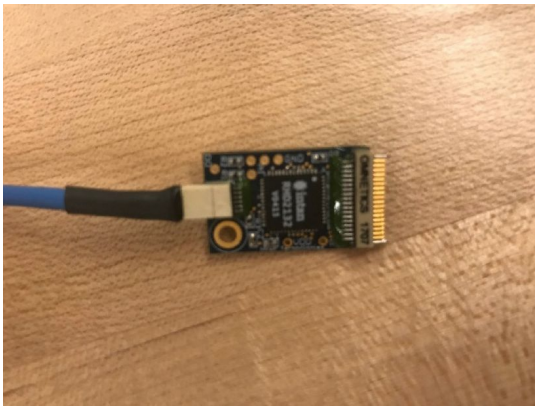
Day 1 we will have chosen an item or two that triggers the subject's OCD/SP symptoms, but not so severely that it causes them extreme anxiety. We will also choose a neutral item that will not elicit any response. Next, we will begin the EEG, video, and computer setup.

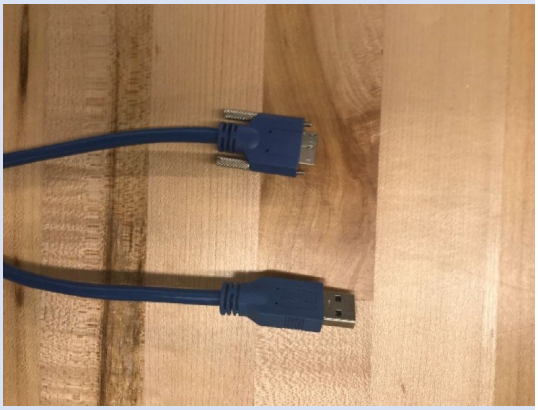
Table 1: EEG System Details

Equipment	Purpose	Photo
tEEG amplifier (CREmedical)	Amplifies tEEG electrode signals	
20 Tripolar electrodes	Scalp electrodes that plug into tEEG amplifier	

2 Grass electrodes	Scalp electrode used for ground or reference	
Nu-prep gel	Cleans scalp before tripolar electrodes are placed	
ten20 paste	Gel for attaching tripolar electrodes and grass electrodes to scalp	

4 tEEG output cables	Sends EEG and signals out of the tEEG amplifier to the breakout board	
3 ECG electrode leads	Chest electrode leads that that plug into INTAN ADC	
Sticky electrode pads	Stick ECG electrodes to chest	

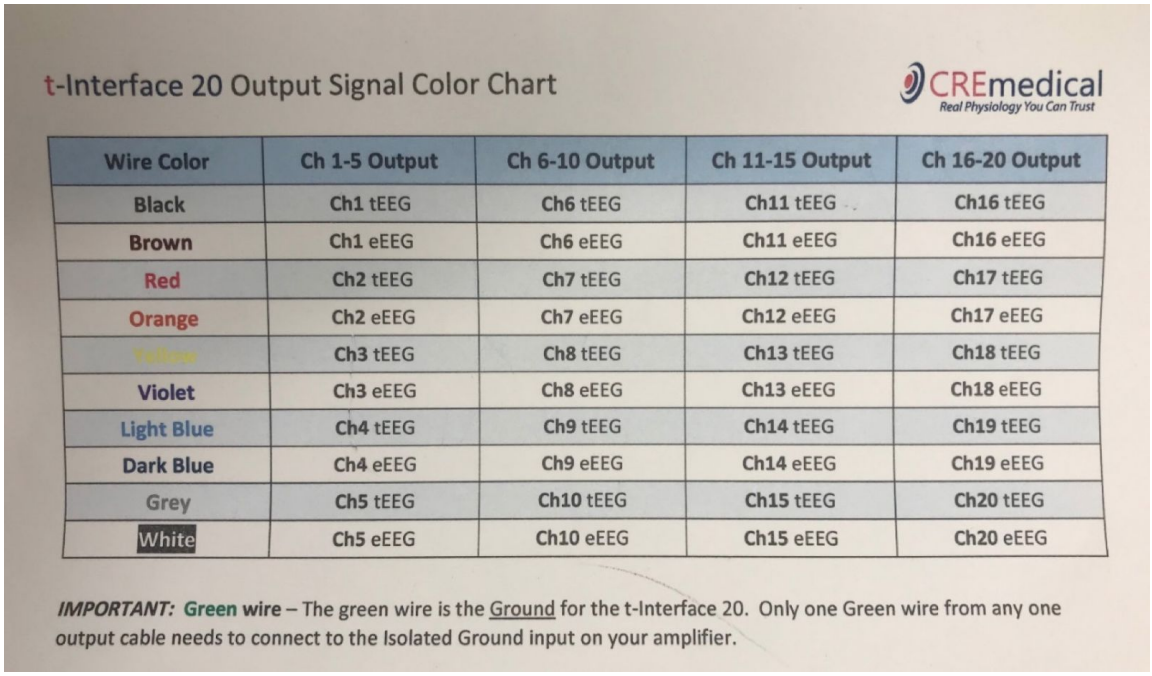
Breakout board	Takes tEEG outputs and ECG outputs and connects to INTAN ADC	
INTAN ADC (Analog to Digital Converter)	Digitizes the electrophysiological signals and transmits them over the SPI cable	
SPI (Serial Peripheral Interface) cable	Transmits signals from the INTAN ADC to the open ephys acquisition board	

Open ephys acquisition board	Acquires both the electrophysiological signals and other analog inputs like button presses, and sends the data to the computer to be saved	
USB3 cable	Connects acquisition board to the computer	
5 V battery	Powers open ephys acquisition board	

USB to barrel jack connector	Attaches 5 V battery to open ephys	

Equipment setup instructions

The first step is to plug all 4 tEEG output cables into the back of the tEEG amplifier. Next, plug the opposite ends of the tEEG output cables into the breakout board. Only colors corresponding to tEEG should be used (see the chart below: black, red, yellow, light blue, grey, green for ground).



t-Interface 20 Output Signal Color Chart

CREmedical
Real Physiology You Can Trust

Wire Color	Ch 1-5 Output	Ch 6-10 Output	Ch 11-15 Output	Ch 16-20 Output
Black	Ch1 tEEG	Ch6 tEEG	Ch11 tEEG	Ch16 tEEG
Brown	Ch1 eEEG	Ch6 eEEG	Ch11 eEEG	Ch16 eEEG
Red	Ch2 tEEG	Ch7 tEEG	Ch12 tEEG	Ch17 tEEG
Orange	Ch2 eEEG	Ch7 eEEG	Ch12 eEEG	Ch17 eEEG
Yellow	Ch3 tEEG	Ch8 tEEG	Ch13 tEEG	Ch18 tEEG
Violet	Ch3 eEEG	Ch8 eEEG	Ch13 eEEG	Ch18 eEEG
Light Blue	Ch4 tEEG	Ch9 tEEG	Ch14 tEEG	Ch19 tEEG
Dark Blue	Ch4 eEEG	Ch9 eEEG	Ch14 eEEG	Ch19 eEEG
Grey	Ch5 tEEG	Ch10 tEEG	Ch15 tEEG	Ch20 tEEG
White	Ch5 eEEG	Ch10 eEEG	Ch15 eEEG	Ch20 eEEG

IMPORTANT: **Green wire** – The green wire is the Ground for the t-Interface 20. Only one Green wire from any one output cable needs to connect to the Isolated Ground input on your amplifier.

Figure 6: EEG cable color labels.

Plug the ends of the ECG leads into the opposite side of the breakout board, and then snap the sticky electrode pads onto the heads of the 3 ECG leads. Plug the INTAN ADC into the breakout board. The dark blue side should be up – you shouldn't be able to see any text. Hold the INTAN board by the edges, and wiggle it a tiny bit from side to side as you push it in and pull it out. It should be flush with the white piece on the breakout board that says omnetics. Plug the SPI cable into the INTAN ADC, and plug the other end of the SPI cable into slot A of the open ephys acquisition board.

Next, Plug the USB end of the barrel jack to USB connector into the 5 V battery. The barrel jack end of the barrel jack to USB connector goes into the barrel jack port on the open ephys acquisition board that is next to the USB3 port. Press the button on the battery to check the charge level. Plug the USB3 cable into the corresponding port on the open ephys acquisition board, and the other end of the cable into the USB port on your computer.

EEG Setup:

All experimenters will have practiced this setup on volunteers before doing this on test subjects. The EEG setup requires completing the following steps. First, plug all electrodes into the CRE amplifier and make sure the cap is centered on the patient's head. Mark all the locations by twisting the grease pencil in the holes of the cap. Plug the USB into the battery, turn on the battery and EEG amplifier. Next, place the ground on Cz, reference on the collarbone, and put a piece of tape over it to keep it in place. Use the NuPrep gel to clean the marked areas with a cotton swab before putting Ten20 paste directly on the electrode – ensuring that there is about ~1mm of paste between the scalp and electrode. If you tap and the hair bounces up, there is

probably an insufficient amount of paste. It is important to note that all electrodes are labeled at both ends, so the researchers just need to match the electrodes with the corresponding spot on the cap.

Make sure all cables are going behind the participant and are clipped to the back of their shirt, and have the subject place the ECG sticky pads to their chest (see Figure 8 for exact locations). Some troubleshooting suggestions include using an impedance sensor to find noisy channels, making sure there's enough paste on the electrodes, and making sure there is minimal hair in between the scalp and electrodes.

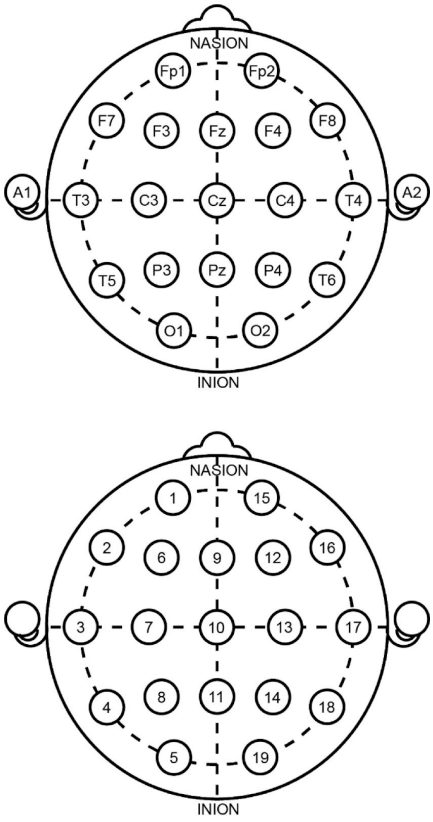


Figure 7: Top: Standard 10-20 setup labels
Bottom: Our numbered electrode placement labels

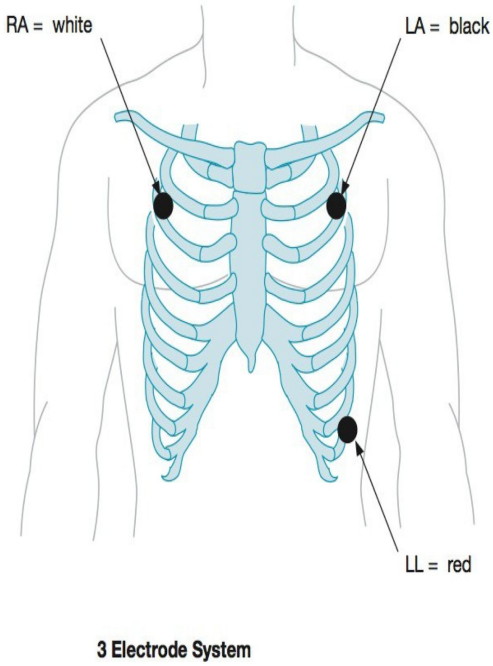


Figure 8: ECG Electrode placement by lead color.

Open ephys software setup:

- Make sure file -> reload on startup is checked.

- Make sure A32 is showing under rhythm FPGA – this means everything is plugged in and on.
- The circle button starts the recording.
- The triangle button stops data acquisition.
- Clicking triangle button in top right hand corner shows you where data was saved after you do a recording.

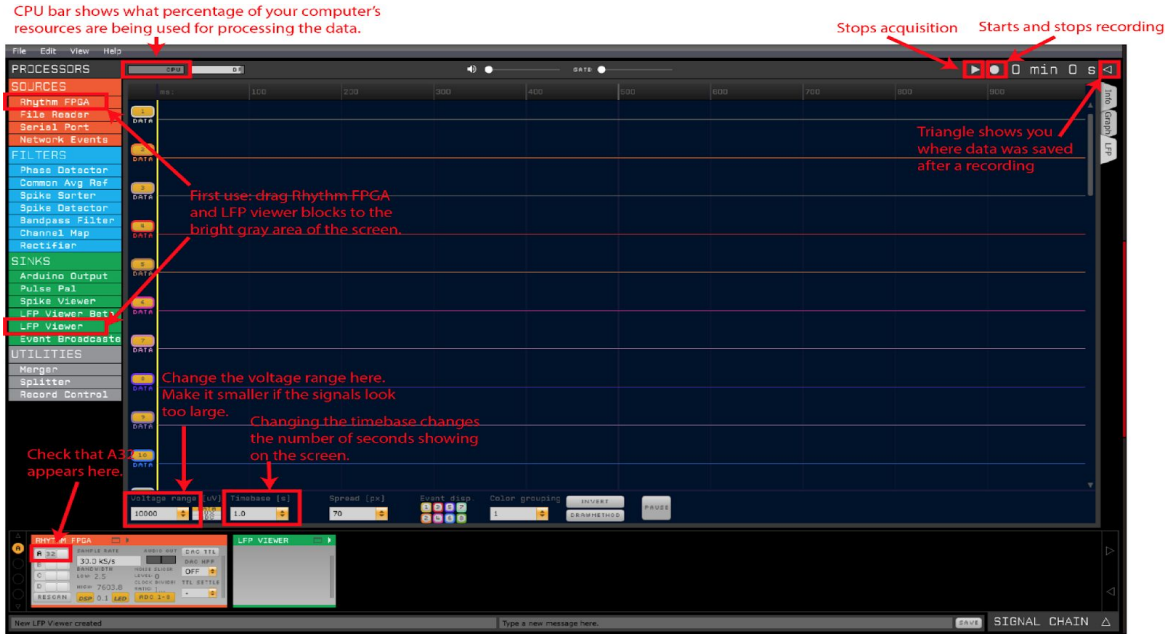


Figure 9: Open-Ephys Screen

Experimenter Task Instructions:

Turn on the video camera and make sure it is recording. Next we will read the following instructions aloud to the participant to explain the task:

"We will now ask you to place your dominant hand on top of this dial. When we ask you to rank your anxiety you should turn the dial to match your level of anxiety on a scale from one to ten. The dial will change the number on this screen at the end of the conveyor belt, so just turn the dial until you reach the appropriate number and press down to submit the score. As you can

see, you are seated at the end of a conveyor belt with a screen covering part of it. The triggering object is somewhere on the belt behind the screen. We will very slowly over many minutes move the object randomly closer to you on the belt. At every point that the object stops we will allow you twenty seconds to rank the initial anxiety that you feel as soon as the object is finished moving. We will then pause for twenty seconds to allow you to habituate to the object. Next, you will have twenty seconds to rank your anxiety after this habituation period. You will know when to enter your ranking when you see the screen at the end of the belt start flashing. We will ask you to do your best not to ritualize during the exposure to the triggering item. The measurements will be most accurate if you keep your eyes only on the object and the screen showing your anxiety levels at all times, so please do your best to stay focused throughout the task. Do not look at the dial when ranking your anxiety, just keep your eyes on the screen. If at any point the task becomes too stressful for you to complete, let the researchers know and we will remove the object. This process will be performed three times, twice with triggering items and once with a neutral object. Now, please rank your level of distress before we remove the screen."

We will allow the patient to rank their anxiety before the screen is removed and then say:

"Please try to stay seated still and refrain from extra movements or speaking if possible because it could potentially interfere with the EEG signals. Again, please do your best to keep your eyes on the object at all times to keep our recordings as accurate as possible."

Begin the task. While the participant is seated facing the belt with EEG and video being recorded, make sure they are watching as we raise the screen and reveal the triggering object. Ask them to rank their anxiety on a scale from 0-100 using the dial. Start the belt and after each movement ask the participant to once again rank their anxiety.

If at any point the participant asks to stop, turn off the belt and remove the object from their sight. We will complete this twice with triggering stimuli, and once again with neutral objects/pictures. Once all three tasks are completed, read aloud:

"Now that you have completed the tasks we will help you to remove the electrodes from your scalp. They are attached with a paste that may require some washing out later in order to fully remove it from your hair."

We will have to make sure that all subjects are no longer in a triggered state before they leave, which may involve a rest period in the lobby area to allow them to settle down before heading home. Patients will be compensated and then sent home once they feel they are ready.

Images of the Provocation Task Setup (Figures 10-20):

Figure 10: Tripolar Electrodes, labeled and the clip used to attach the wires to the back of the participant's shirt

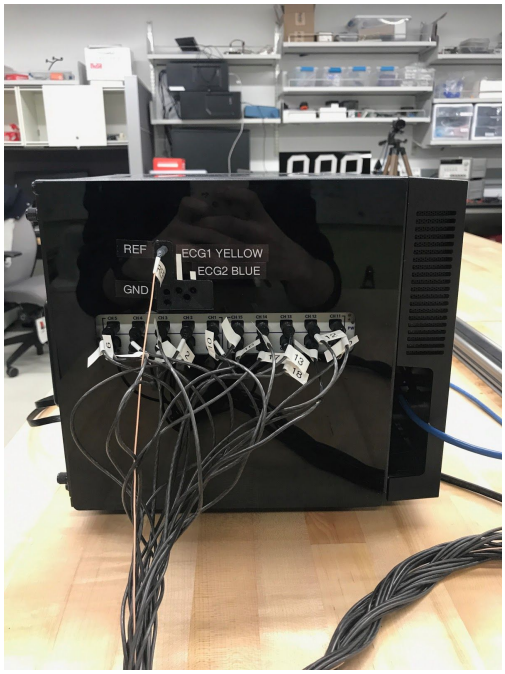


Figure 11: Labeled EEG cables and reference cable plugged into the acquisition board

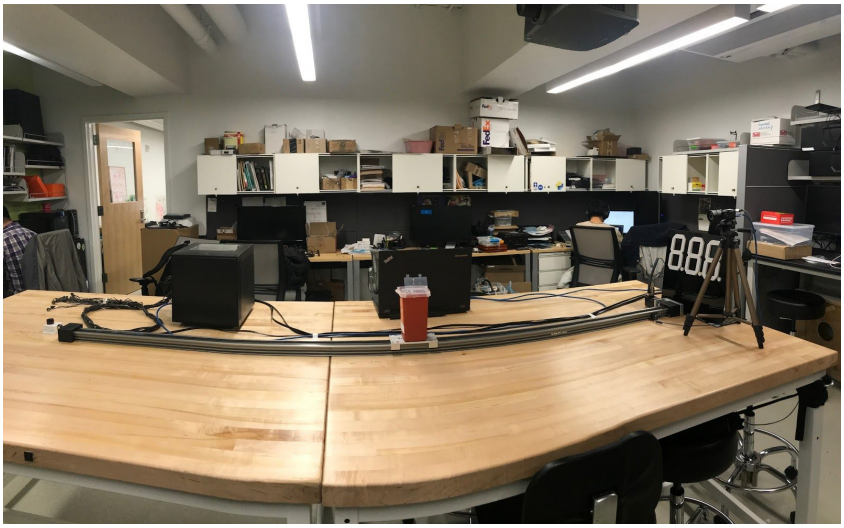


Figure 12: Full EEG, conveyor belt, laptop, video camera, dial, and rating screen setup

Figure 13: Participant's view of conveyor belt/screen/dial

Figure 14: Experimenter's view of the task setup

Figure 15: Subject with full electrode and ECG setup during developmental testing of the tasks.

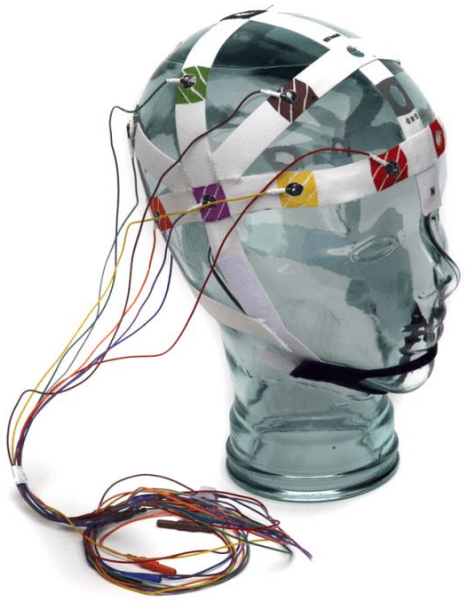


Figure 16: 10/20 BraiNet Placement Cap (https://bio-medical.com/brainet-placement-caps.html)

Figure 17: Sample specific snake phobia picture used for symptom provocation. (http://smakterrarium.pl/czy-jestes-gotowy-aby-miec-agresywnego-weza/)

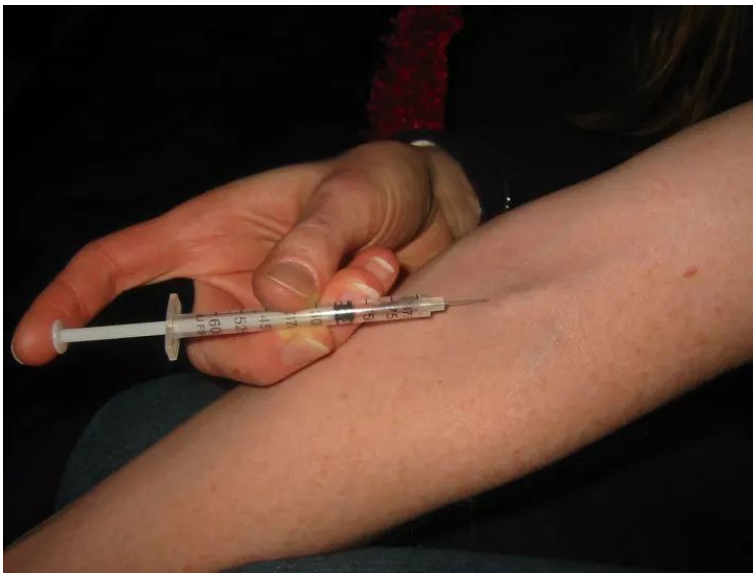


Figure 18: Sample specific needle phobia used for symptom provocation. (https://www.taringa.net/posts/info/18044292/Fotos-que-haran-revelar-tus-fobias.html)

Figure 19: Sample specific spider phobia used for symptom provocation. (https://www.independent.co.uk/news/uk/home-news/banana-drama-terrified-family-flee-london-home-after-finding-dozens-of-world-s-most-venomous-spiders-8920937.html)

Figure 20: Picture stand being used for SP provocation.

Other Experiment Considerations:

Data Analysis:

The EEG system is equipped with innovative data acquisition and data analysis software that allows sophisticated signal processing and data analysis capabilities. The system includes a

3D scalp digitizer that maps the scalp in the stereotactic space for EEG source localization. Other capabilities of the system include eye-tracking and acquisition of physiological data (SpO2, pulse and skin conductance). For the provocation task, 5 scores are calculated including percentage of steps completed, subjective units of distress (SUDS) across steps, avoidance, ritual engagement, and composite provocation score, which will be associated with changes in biosignature from brain recordings (EEG). The EEG measurements will be compared to the AFAR analysis in order to compare the visual and neurological changes caused by OC stressors. These results will also be used to test how well the AFAR estimates of affective state correlate to patient self-reports of their mood during these tasks.

Discussion- Anticipated Results:

EEG:

With the proposed research design we aim to capture biomarkers relevant to OCD and its DBS therapy. Through the use of a gradual approach provocation model, we expect to see a change in brain activity as the object approaches, that should be matched by a linear growth in subjective anxiety, heart rate, and negative change in facial affect with respect to distance. We expect to see changes in the frequency bands of interest (theta, alpha, and gamma) in the CSTC loop in the EEG readings, as these are the areas that are most frequently associated with changes in valence state. We expect that theta bands should rate positively with distress, possibly with stronger intensity over the right frontal-lateral region.

Subjective Anxiety:

During the experiment, we expect that that patients will show a gradual change in anxiety and arousal that corresponds positively with the distance of the triggering object, but not with neutral stimuli. This should result in increased anxiety as measure by the SUDS score and HR during each approach epoch, and a decrease in anxiety with each away epoch. We also expect that patients will show a decrease in subjective anxiety during each habituation period, based on previous experience showing some level of habituation occurring within 30 seconds of presentation. We may see that the patient's own imagination will impact their anxiety by expecting the object to move as close as possible each time it moves, therefore causing heightened brain activity and subjective anxiety levels regardless of the object's position.

There is the possibility that we will see an exponential effect change based on distance. There is also the possibility that some patients will become aroused once the object is revealed and remain at the same level throughout the task, however because no study has been done using this provocation technique there is no way to know until we begin testing patients.

Specific Phobia Anxiety:

SP patients should show similar brain patterns and anxiety levels as OCD patients, however there is the possibility that they will be somewhat different. We probably will not experience as strong of a response by the SP patients due to the use of pictures instead of actual objects, but it should be enough to trigger a measurable change in valence state. We expect that the pilot study using these patients will also help us to troubleshoot any potential problems that

we may come across that we did not already anticipate or come across in developmental testing with asymptomatic volunteers.

One piece that we are specifically considering adjusting is the timing of the hold epochs. Three tasks lasting about thirteen minutes each could be a lot for patients, so reducing the rating periods from twenty seconds to ten seconds could add up to be a significant reduction in overall time required from the patients. There is the concern that some people will be slower in recording their anxiety, especially under distress, and that this reduced rating period could be too short and potentially cause unnecessary extra stress. The pilot testing in SP patients will allow us to learn the best timing to use when it comes time to begin testing OCD patients.

Task and Overall Experimental Considerations:

Another goal of this study is to replicate it at Baylor Hospital in order to retrieve more data, as well as to eventually perform these provocation tasks in OCD patients implanted with DBS devices in order to measure the difference in brain activity during provocation with and without stimulation. There is some concern that there will not be a clear applicability in provoking patients with non-contamination symptoms using this type of method. However, the goal of this provocation study is to measure how linear the change in brain activity actually is depending on the patient's symptoms. By using this standardized provocation approach method we will be able to calibrate the results across patients, which we would be unable to do without a systematic movement.

Having all pieces of the task (belt movement, EEG recordings, AFAR visuals, SUDS rating) time locked together is central to obtaining good data. This way, even if the signals are

not as strong as we expect or we do not see the anticipated linear growth, we will still be able to average out the trials across patients to get a good idea of what is actually happening relative to the object's positioning on the belt. We will also be able to look at individuals' reactions to see if these reactions are core feature or symptom-subtype specific. While we have a general idea of what we are looking for, we still do not know exactly, so the more ability we have to connect the exact movements of the object to the patient's reactions at that point the better we will be able to recognize any potential biomarkers. Upon obtaining this information, we will have the ability to adjust the provocation methods to provoke an intense degree of OC symptoms to get the best possible signals and locate the biomarkers we are looking for.

Implication for Adaptive DBS:

One of the most important pieces of this study will be measuring the changes in affect. Unlike movement disorders, which show immediately apparent physical changes upon the use of stimulation, OCD patients do not show immediate changes in displays of symptomatology. This makes it difficult for clinicians in deciding on the best level of stimulation to use for each patient, and usually entails semi-daily visits during the optimization period. This can be difficult or impossible for patients who live far away from centers with trained psychiatrists who are qualified to work with DBS in OCD patients, which is a reason that some people choose surgical treatment instead of DBS.

One way that physicians have been able to notice some obvious change, however, is an immediate difference in mood once stimulation begins. While it does not occur in every patient, this is important because it shows that there is a connection between affect and reduction of

symptoms, so psychiatrists have the ability to make changes based on the mood effects. By taking subjective anxiety and AFAR measurements into consideration alongside EEG, we will have an improved ability to connect these specific changes in affect with changes in brain activity, helping clinicians to administer the best stimulation levels per individual, and is crucial in the development of an adaptive system that can make these changes on its own. This is especially important for patients living far from their treating psychiatrists who currently have to endure negative side effects of stimulation for longer because of the inability to immediately adjust the system based on their current brain activity.

While this is a novel approach in locating biomarkers of OCD and treating patients based on those markers, there is still some uncertainty as to whether or not it will be successful in locating the specific biomarkers of change during OC symptom provocation. This study will be important in laying the groundwork for the overall effort of developing an adaptive DBS system, especially in finding initial connections between affect and brain activity change during symptom provocation. The discoveries made here will allow researchers to look more closely at specific brain regions of interest and their impact on the clinical outcomes associated with DBS treatment of OCD.

Works Cited

Abelson, J. L., G. C. Curtis, O. Sagher, R. C. Albucher, M. Harrigan, S. F. Taylor, B. Martis, and B. Giordani. 2005. "Deep Brain Stimulation for Refractory Obsessive-Compulsive Disorder." *Biological Psychiatry* 57 (5): 510–16.

Adam, Yuki, Gunther Meinlschmidt, Andrew T. Gloster, and Roselind Lieb. 2012. "Obsessive-Compulsive Disorder in the Community: 12-Month Prevalence, Comorbidity and Impairment." *Social Psychiatry and Psychiatric Epidemiology* 47 (3): 339–49.

Aftanas, L. I., N. V. Reva, A. A. Varlamov, S. V. Pavlov, and V. P. Makhnev. 2004. "Analysis of Evoked EEG Synchronization and Desynchronization in Conditions of Emotional Activation in Humans: Temporal and Topographic Characteristics." *Neuroscience and Behavioral Physiology* 34 (8): 859–67.

Alonso, Pino, Daniel Cuadras, Loes Gabriëls, Damiaan Denys, Wayne Goodman, Ben D. Greenberg, Fiacro Jimenez-Ponce, et al. 2015. "Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Meta-Analysis of Treatment Outcome and Predictors of Response." *PloS One* 10 (7): e0133591.

Alonso, P., J. M. Menchon, J. Pifarre, D. Mataix-Cols, L. Torres, P. Salgado, and J. Vallejo. 2001. "Long-Term Follow-up and Predictors of Clinical Outcome in Obsessive-Compulsive Patients Treated with Serotonin Reuptake Inhibitors and Behavioral Therapy." *The Journal of Clinical Psychiatry* 62 (7): 535–40.

Armstrong, Thomas, Bunmi O. Olatunji, Shivali Sarawgi, and Casey Simmons. 2010. "Orienting and Maintenance of Gaze in Contamination Fear: Biases for Disgust and Fear Cues." *Behaviour Research and Therapy* 48 (5): 402–8.

Baker, J., J. D. Haltigan, and D. S. Messinger. 2010. "Non-Expert Ratings of Infant and Parent Emotion: Concordance with Expert Coding and Relevance to Early Autism Risk." *International Journal of Behavioral Development* 34 (1): 88–95.

Balconi, Michela, and Claudio Lucchiari. 2006. "EEG Correlates (event-Related Desynchronization) of Emotional Face Elaboration: A Temporal Analysis." *Neuroscience Letters* 392 (1-2): 118–23.

Ball, S. G., L. Baer, and M. W. Otto. 1996. "Symptom Subtypes of Obsessive-Compulsive Disorder in Behavioral Treatment Studies: A Quantitative Review." *Behaviour Research and Therapy* 34 (1): 47–51.

Bandelow, Borwin, David Baldwin, Marianna Abelli, Carlo Altamura, Bernardo Dell'Osso, Katharina Domschke, Naomi A. Fineberg, et al. 2016. "Biological Markers for Anxiety Disorders, OCD and PTSD--a Consensus Statement. Part I: Neuroimaging and Genetics." *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry* 17 (5). Taylor & Francis: 321–65.

Baron-Cohen, Simon, Sally Wheelwright, Jolliffe, and Therese. 1997. "Is There a' Language of the Eyes'? Evidence from Normal Adults, and Adults with Autism or Asperger Syndrome." *Visual Cognition* 4 (3). Taylor & Francis: 311–31.

Beck, A. T., N. Epstein, G. Brown, and R. A. Steer. 1988. "An Inventory for Measuring Clinical Anxiety: Psychometric Properties." *Journal of Consulting and Clinical Psychology* 56 (6): 893–97.

Beck, A. T., C. H. Ward, M. Mendelson, J. Mock, and J. Erbaugh. 1961. "An Inventory for

Measuring Depression." *Archives of General Psychiatry* 4: 561–71.
Besio, Walter G., Iris E. Martínez-Juárez, Oleksandr Makeyev, John N. Gaitanis, Andrew S. Blum, Robert S. Fisher, and Andrei V. Medvedev. 2014. "High-Frequency Oscillations Recorded on the Scalp of Patients With Epilepsy Using Tripolar Concentric Ring Electrodes." *IEEE Journal of Translational Engineering in Health and Medicine* 2 (June): 2000111.
Black, Christopher, Jakob Voigts, Uday Agrawal, Max Ladow, Juan Santoyo, Christopher Moore, and Stephanie Jones. 2017. "Open Ephys Electroencephalography (Open Ephys+ EEG): A Modular, Low-Cost, Open-Source Solution to Human Neural Recording." *Journal of Neural Engineering* 14 (3). IOP Publishing: 035002.
Bloch, M. H., A. Landeros-Weisenberger, B. Kelmendi, V. Coric, M. B. Bracken, and J. F. Leckman. 2006. "A Systematic Review: Antipsychotic Augmentation with Treatment Refractory Obsessive-Compulsive Disorder." *Molecular Psychiatry* 11 (7): 622–32.
Breiter, H. C., S. L. Rauch, K. K. Kwong, J. R. Baker, R. M. Weisskoff, D. N. Kennedy, A. D. Kendrick, et al. 1996. "Functional Magnetic Resonance Imaging of Symptom Provocation in Obsessive-Compulsive Disorder." *Archives of General Psychiatry* 53 (7): 595–606.
Chu, W. S., F. D. L. Torre, and J. F. Cohn. 2013. "Selective Transfer Machine for Personalized Facial Action Unit Detection." In *2013 IEEE Conference on Computer Vision and Pattern Recognition*, 3515–22.
Cohn, Jeffrey F., and Michael A. Sayette. 2010. "Spontaneous Facial Expression in a Small Group Can Be Automatically Measured: An Initial Demonstration." *Behavior Research Methods* 42 (4): 1079–86.
Davidson, R. J. 1992. "Anterior Cerebral Asymmetry and the Nature of Emotion." *Brain and Cognition* 20 (1): 125–51.
Deacon, B. J., and J. S. Abramowitz. 2004. "Cognitive and Behavioral Treatments for Anxiety Disorders: A Review of Meta-Analytic Findings." *Journal of Clinical Psychology* 60 (4): 429–41.
Del Casale, A., G. D. Kotzalidis, C. Rapinesi, D. Serata, E. Ambrosi, A. Simonetti, M. Pompili, S. Ferracuti, R. Tatarelli, and P. Girardi. 2011. "Functional Neuroimaging in Obsessive-Compulsive Disorder." *Neuropsychobiology* 64 (2): 61–85.
Del Casale, Antonio, Stefano Ferracuti, Chiara Rapinesi, Daniele Serata, Massimo Piccirilli, Valeria Savoja, Georgios D. Kotzalidis, et al. 2012. "Functional Neuroimaging in Specific Phobia." *Psychiatry Research* 202 (3): 181–97.
Denys, D. 2008. "[Deep Brain Stimulation in Psychiatric Disorders]." *Nederlands Tijdschrift Voor Geneeskunde* 152 (43): 2330–35.
Desarkar, Pushpal, Vinod Kumar Sinha, Karuppiah Jagadheesan, and Shamshul Haque Nizamie. 2007. "Subcortical Functioning in Obsessive-Compulsive Disorder: An Exploratory EEG Coherence Study." *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry* 8 (3): 196–200.
Dickel, D. E., J. Veenstra-VanderWeele, N. J. Cox, X. Wu, D. J. Fischer, M. Van Etten-Lee, J. A. Himle, B. L. Leventhal, E. H. Cook Jr., and G. L. Hanna. 2006. "Association Testing of the Positional and Functional Candidate Gene SLC1A1/EAAC1 in Early-Onset Obsessive-Compulsive Disorder." *Archives of General Psychiatry* 63 (7): 778–85.
Dohrmann, A. -. L., I. Jahn, K. Stengler, and S. Olbrich. 2016. "EP 108. EEG-Based Arousal Markers for Individualized Treatment in Obsessive Compulsive Disorder." *Clinical*

Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology 127 (9). Elsevier: e287.

Dougherty, D. D., L. Baer, G. R. Cosgrove, E. H. Cassem, B. H. Price, A. A. Nierenberg, M. A. Jenike, and S. L. Rauch. 2002. "Prospective Long-Term Follow-up of 44 Patients Who Received Cingulotomy for Treatment-Refractory Obsessive-Compulsive Disorder." *The American Journal of Psychiatry* 159 (2): 269–75.

Dunlop, Katharine, Blake Woodside, Marion Olmsted, Patricia Colton, Peter Giacobbe, and Jonathan Downar. 2016. "Reductions in Cortico-Striatal Hyperconnectivity Accompany Successful Treatment of Obsessive-Compulsive Disorder with Dorsomedial Prefrontal rTMS." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 41 (5): 1395–1403.

Ecker, W., and S. Gonner. 2008. "Incompleteness and Harm Avoidance in OCD Symptom Dimensions." *Behaviour Research and Therapy* 46 (8): 895–904.

Eisen, J. L., W. K. Goodman, M. B. Keller, M. G. Warshaw, L. M. DeMarco, D. D. Luce, and S. A. Rasmussen. 1999. "Patterns of Remission and Relapse in Obsessive-Compulsive Disorder: A 2-Year Prospective Study." *The Journal of Clinical Psychiatry* 60 (5): 346–51; quiz 352.

EKMAN, and P. 2002. "Facial Action Coding System (FACS)." *A Human Face*. https://ci.nii.ac.jp/naid/10025007347/.

Ekman, Paul, Wallace V. Friesen, and Silvan S. Tomkins. 1971. "Facial Affect Scoring Technique: A First Validity Study." *Semiotica* 3 (1). https://doi.org/10.1515/semi.1971.3.1.37.

Ekman, Paul, and Erika L. Rosenberg. 2005. *What the Face Reveals: Basic and Applied Studies of Spontaneous Expression Using the Facial Action Coding System (FACS)*. Oxford University Press.

Feinstein, S. B., B. A. Fallon, E. Petkova, and M. R. Liebowitz. 2003. "Item-by-Item Factor Analysis of the Yale-Brown Obsessive Compulsive Scale Symptom Checklist." *The Journal of Neuropsychiatry and Clinical Neurosciences* 15 (2): 187–93.

Figee, M., J. Luigjes, R. Smolders, C. E. Valencia-Alfonso, G. van Wingen, B. de Kwaasteniet, M. Mantione, et al. 2013. "Deep Brain Stimulation Restores Frontostriatal Network Activity in Obsessive-Compulsive Disorder." *Nature Neuroscience* 16 (4): 386–87.

First, M. B., M. Gibbon, R. L. Spitzer, J. B. Williams, and L. S. Benjamin. 1997. "Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)." *American Pscyiatric Press*.

Foa, Edna B., Michael J. Kozak, Paul M. Salkovskis, Meredith E. Coles, and Nader Amir. 1998. "The Validation of a New Obsessive--Compulsive Disorder Scale: The Obsessive--Compulsive Inventory." *Psychological Assessment* 10 (3). American Psychological Association: 206.

Girard, Jeffrey M., and Jeffrey F. Cohn. 2015. "Automated Audiovisual Depression Analysis." *Current Opinion in Psychology* 4 (August): 75–79.

Girard, J. M., J. F. Cohn, L. A. Jeni, S. Lucey, and F. De la Torre. 2015. "How Much Training Data for Facial Action Unit Detection?" In *2015 11th IEEE International Conference and Workshops on Automatic Face and Gesture Recognition (FG)*, 1:1–8.

Goodman, Wayne K., and Ron L. Alterman. 2012. "Deep Brain Stimulation for Intractable Psychiatric Disorders." *Annual Review of Medicine* 63: 511–24.

Goodman, W. K., K. D. Foote, B. D. Greenberg, N. Ricciuti, R. Bauer, H. Ward, N. A. Shapira, et al. 2010. "Deep Brain Stimulation for Intractable Obsessive Compulsive Disorder: Pilot Study Using a Blinded, Staggered-Onset Design." *Biological Psychiatry* 67 (6): 535–42.
Goodman, W. K., and T. R. Insel. 2009. "Deep Brain Stimulation in Psychiatry: Concentrating on the Road Ahead." *Biological Psychiatry* 65 (4): 263–66.
Goodman, W. K., L. H. Price, S. A. Rasmussen, C. Mazure, R. L. Fleischmann, C. L. Hill, G. R. Heninger, and D. S. Charney. 1989. "The Yale-Brown Obsessive Compulsive Scale. I. Development, Use, and Reliability." *Archives of General Psychiatry* 46 (11): 1006–11.
Gradinaru, Viviana, Murtaza Mogri, Kimberly R. Thompson, Jaimie M. Henderson, and Karl Deisseroth. 2009. "Optical Deconstruction of Parkinsonian Neural Circuitry." *Science* 324 (5925): 354–59.
Greenberg, B. D., L. A. Gabriels, D. A. Malone Jr., A. R. Rezai, G. M. Friehs, M. S. Okun, N. A. Shapira, et al. 2010. "Deep Brain Stimulation of the Ventral Internal Capsule/ventral Striatum for Obsessive-Compulsive Disorder: Worldwide Experience." *Molecular Psychiatry* 15 (1): 64–79.
Greenberg, B. D., L. H. Price, S. L. Rauch, M. A. Jenike, D. Malone, G. Friehs, G. Noren, L. L. Carpenter, and S. A. Rasmussen. 2003. "Neurosurgery for Intractable Obsessive-Compulsive Disorder and Depression: Critical Issues." *Neurosurgery Clinics of North America* 14 (2): 199–212.
Greenberg, Benjamin D., Scott L. Rauch, and Suzanne N. Haber. 2009. "Invasive Circuitry-Based Neurotherapeutics: Stereotactic Ablation and Deep Brain Stimulation for OCD." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 35 (1): 317–36.
Haber, Suzanne N., and Sarah R. Heilbronner. 2013. "Translational Research in OCD: Circuitry and Mechanisms." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 38 (1): 252–53.
Harmon-Jones, Eddie, Philip A. Gable, and Carly K. Peterson. 2010. "The Role of Asymmetric Frontal Cortical Activity in Emotion-Related Phenomena: A Review and Update." *Biological Psychology* 84 (3): 451–62.
Harrison, B. J., J. Pujol, N. Cardoner, J. Deus, P. Alonso, M. Lopez-Sola, O. Contreras-Rodriguez, et al. 2013. "Brain Corticostriatal Systems and the Major Clinical Symptom Dimensions of Obsessive-Compulsive Disorder." *Biological Psychiatry* 73 (4): 321–28.
Harrison, B. J., C. Soriano-Mas, J. Pujol, H. Ortiz, M. Lopez-Sola, R. Hernandez-Ribas, J. Deus, et al. 2009. "Altered Corticostriatal Functional Connectivity in Obsessive-Compulsive Disorder." *Archives of General Psychiatry* 66 (11): 1189–1200.
Heuvel, Odile A. van den, Ysbrand D. van der Werf, Kim M. W. Verhoef, Stella de Wit, Henk W. Berendse, Erik Ch Wolters, Dick J. Veltman, and Henk J. Groenewegen. 2010. "Frontal-Striatal Abnormalities Underlying Behaviours in the Compulsive-Impulsive Spectrum." *Journal of the Neurological Sciences* 289 (1-2): 55–59.
Hoppe, Christian, Juri-Alexander Witt, Christoph Helmstaedter, Thomas Gasser, Hartmut Vatter, and Christian E. Elger. 2017. "Laser Interstitial Thermotherapy (LiTT) in Epilepsy Surgery." *Seizure: The Journal of the British Epilepsy Association* 48 (May): 45–52.
Insel, T., B. Cuthbert, M. Garvey, R. Heinssen, D. S. Pine, K. Quinn, C. Sanislow, and P. Wang. 2010. "Research Domain Criteria (RDoC): Toward a New Classification Framework for

Research on Mental Disorders." *The American Journal of Psychiatry* 167 (7): 748–51.
Jenike, M. A., L. Baer, T. Ballantine, R. L. Martuza, S. Tynes, I. Giriunas, M. L. Buttolph, and N. H. Cassem. 1991. "Cingulotomy for Refractory Obsessive-Compulsive Disorder. A Long-Term Follow-up of 33 Patients." *Archives of General Psychiatry* 48 (6): 548–55.
Jeni, L. A., J. F. Cohn, and T. Kanade. 2015. "Dense 3D Face Alignment from 2D Videos in Real-Time." In *2015 11th IEEE International Conference and Workshops on Automatic Face and Gesture Recognition (FG)*, 1:1–8.
Jung, H. H., C. H. Kim, J. H. Chang, Y. G. Park, S. S. Chung, and J. W. Chang. 2006. "Bilateral Anterior Cingulotomy for Refractory Obsessive-Compulsive Disorder: Long-Term Follow-up Results." *Stereotactic and Functional Neurosurgery* 84 (4): 184–89.
Keltner, Dacher. 1995. "Signs of Appeasement: Evidence for the Distinct Displays of Embarrassment, Amusement, and Shame." *Journal of Personality and Social Psychology* 68 (3). American Psychological Association: 441.
Koning, Pelle P. de, Martijn Figee, Pepijn van den Munckhof, P. Richard Schuurman, and Damiaan Denys. 2011. "Current Status of Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Clinical Review of Different Targets." *Current Psychiatry Reports* 13 (4): 274–82.
Koran, Lorrin M., Gregory L. Hanna, Eric Hollander, Gerald Nestadt, Helen Blair Simpson, and American Psychiatric Association. 2007. "Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder." *The American Journal of Psychiatry* 164 (7 Suppl): 5–53.
Krause, D., M. Folkerts, S. Karch, and D. Keeser. 2016. "Prediction of Treatment Outcome in Patients with Obsessive-Compulsive Disorder with Low-Resolution Brain Electromagnetic Tomography: A Prospective EEG …." *Frontiers in*. frontiersin.org. https://www.frontiersin.org/articles/10.3389/fpsyg.2015.01993/full.
Kwon, Jun Soo, Joon Hwan Jang, Jung-Seok Choi, and Do-Hyung Kang. 2009. "Neuroimaging in Obsessive–compulsive Disorder." *Expert Review of Neurotherapeutics* 9 (2). Taylor & Francis: 255–69.
Linares, Ila M. P., Clarissa Trzesniak, Marcos Hortes N. Chagas, Jaime E. C. Hallak, Antonio E. Nardi, and José Alexandre S. Crippa. 2012. "Neuroimaging in Specific Phobia Disorder: A Systematic Review of the Literature." *Revista Brasileira de Psiquiatria* 34 (1): 101–11.
Lopes, A. C., B. D. Greenberg, M. M. Canteras, M. C. Batistuzzo, M. Q. Hoexter, A. F. Gentil, Cab Pereira, et al. 2014. "Gamma Ventral Capsulotomy for Obsessive-Compulsive Disorder A Randomized Clinical Trial." *JAMA Psychiatry* 71 (9): 1066–76.
Lueken, Ulrike, Johann Daniel Kruschwitz, Markus Muehlhan, Jens Siegert, Jürgen Hoyer, and Hans-Ulrich Wittchen. 2011. "How Specific Is Specific Phobia? Different Neural Response Patterns in Two Subtypes of Specific Phobia." *NeuroImage* 56 (1): 363–72.
MacNamara, Annmarie, and K. Luan Phan. 2016. "Psychobiological Operationalization of RDoC Constructs: Methodological and Conceptual Opportunities and Challenges." *Psychophysiology* 53 (3): 406–9.
Mancebo, Maria C., Jane L. Eisen, Nicholas J. Sibrava, Ingrid R. Dyck, and Steven A. Rasmussen. 2011. "Patient Utilization of Cognitive-Behavioral Therapy for OCD." *Behavior Therapy* 42 (3): 399–412.
Mataix-Cols, D., S. Wooderson, N. Lawrence, M. J. Brammer, A. Speckens, and M. L. Phillips. 2004. "Distinct Neural Correlates of Washing, Checking, and Hoarding Symptom

Dimensions in Obsessive-Compulsive Disorder." *Archives of General Psychiatry* 61 (6): 564–76.
McDougle, C. J., W. K. Goodman, J. F. Leckman, N. C. Lee, G. R. Heninger, and L. H. Price. 1994. "Haloperidol Addition in Fluvoxamine-Refractory Obsessive-Compulsive Disorder. A Double-Blind, Placebo-Controlled Study in Patients with and without Tics." *Archives of General Psychiatry* 51 (4): 302–8.
McLaughlin, N. C., D. Strong, A. Abrantes, S. Garnaat, A. Cerny, C. O'Connell, R. Fadok, et al. 2015. "Extinction Retention and Fear Renewal in a Lifetime Obsessive-Compulsive Disorder Sample." *Behavioural Brain Research* 280: 72–77.
Meier, Sandra M., Manuel Mattheisen, Ole Mors, Diana E. Schendel, Preben B. Mortensen, and Kerstin J. Plessen. 2016. "Mortality Among Persons With Obsessive-Compulsive Disorder in Denmark." *JAMA Psychiatry* 73 (3): 268–74.
Messinger, Daniel S., Mohammad H. Mahoor, Sy-Miin Chow, and Jeffrey F. Cohn. 2009. "Automated Measurement of Facial Expression in Infant-Mother Interaction: A Pilot Study." *Infancy: The Official Journal of the International Society on Infant Studies* 14 (3): 285–305.
Milad, M. R., S. C. Furtak, J. L. Greenberg, A. Keshaviah, J. J. Im, M. J. Falkenstein, M. Jenike, S. L. Rauch, and S. Wilhelm. 2013. "Deficits in Conditioned Fear Extinction in Obsessive-Compulsive Disorder and Neurobiological Changes in the Fear Circuit." *JAMA Psychiatry* 70 (6): 608–18; quiz 554.
Milad, M. R., and S. L. Rauch. 2012. "Obsessive-Compulsive Disorder: Beyond Segregated Cortico-Striatal Pathways." *Trends in Cognitive Sciences* 16 (1): 43–51.
Miller, Gregory A., Brigitte S. Rockstroh, Holly K. Hamilton, and Cindy M. Yee. 2016. "Psychophysiology as a Core Strategy in RDoC." *Psychophysiology* 53 (3): 410–14.
Mindus, P., G. Edman, and S. Andreewitch. 1999. "A Prospective, Long-Term Study of Personality Traits in Patients with Intractable Obsessional Illness Treated by Capsulotomy." *Acta Psychiatrica Scandinavica* 99 (1): 40–50.
Modirrousta, Mandana, Benjamin P. Meek, Jitender Sareen, and Murray W. Enns. 2015. "Impaired Trial-by-Trial Adjustment of Cognitive Control in Obsessive Compulsive Disorder Improves after Deep Repetitive Transcranial Magnetic Stimulation." *BMC Neuroscience* 16 (October): 63.
"NIMH » Obsessive-Compulsive Disorder." n.d. Accessed April 10, 2018. https://www.nimh.nih.gov/health/topics/obsessive-compulsive-disorder-ocd/index.shtml.
"NIMH » Obsessive-Compulsive Disorder (OCD)." n.d. Accessed April 10, 2018. https://www.nimh.nih.gov/health/statistics/obsessive-compulsive-disorder-ocd.shtml.
Norberg, M. M., J. E. Calamari, and R. J. Cohen. 2008. "Quality of Life in Obsessive‐compulsive Disorder: An Evaluation of Impairment and a Preliminary Analysis of the Ameliorating Effects of Treatment." *Depression*. Wiley Online Library. http://onlinelibrary.wiley.com/doi/10.1002/da.20298/full.
Nuttin, B., P. Cosyns, H. Demeulemeester, J. Gybels, and B. Meyerson. 1999. "Electrical Stimulation in Anterior Limbs of Internal Capsules in Patients with Obsessive-Compulsive Disorder." *The Lancet* 354 (9189): 1526.
Öst, Lars-Göran, Audun Havnen, Bjarne Hansen, and Gerd Kvale. 2015. "Cognitive Behavioral Treatments of Obsessive–compulsive Disorder. A Systematic Review and Meta-Analysis of Studies Published 1993–2014." *Clinical Psychology Review* 40 (August): 156–69.

Pauls, David L., Amitai Abramovitch, Scott L. Rauch, and Daniel A. Geller. 2014. "Obsessive-Compulsive Disorder: An Integrative Genetic and Neurobiological Perspective." *Nature Reviews. Neuroscience* 15 (6): 410–24.

Pigott, T. A., and S. M. Seay. 1999. "A Review of the Efficacy of Selective Serotonin Reuptake Inhibitors in Obsessive-Compulsive Disorder." *The Journal of Clinical Psychiatry* 60 (2): 101–6.

Pinto, A., B. D. Greenberg, M. A. Grados, O. J. Bienvenu 3rd, J. F. Samuels, D. L. Murphy, G. Hasler, et al. 2008. "Further Development of YBOCS Dimensions in the OCD Collaborative Genetics Study: Symptoms vs. Categories." *Psychiatry Research* 160 (1): 83–93.

Pittenger, Christopher, and Michael H. Bloch. 2014. "Pharmacological Treatment of Obsessive-Compulsive Disorder." *The Psychiatric Clinics of North America* 37 (3): 375–91.

Priori, Alberto, Guglielmo Foffani, Lorenzo Rossi, and Sara Marceglia. 2013. "Adaptive Deep Brain Stimulation (aDBS) Controlled by Local Field Potential Oscillations." *Experimental Neurology* 245 (July): 77–86.

Prkachin, Kenneth M., and Patricia E. Solomon. 2008. "The Structure, Reliability and Validity of Pain Expression: Evidence from Patients with Shoulder Pain." *Pain* 139 (2): 267–74.

Rasmussen, S. A., and J. L. Eisen. 1992. "The Epidemiology and Clinical Features of Obsessive Compulsive Disorder." *The Psychiatric Clinics of North America* 15 (4): 743–58.

Rodriguez-Romaguera, Jose, Fabricio H. M. Do Monte, and Gregory J. Quirk. 2012. "Deep Brain Stimulation of the Ventral Striatum Enhances Extinction of Conditioned Fear." *Proceedings of the National Academy of Sciences of the United States of America* 109 (22): 8764–69.

Roh, D., J-G Chang, S. W. Yoo, J. Shin, and C-H Kim. 2017. "Modulation of Error Monitoring in Obsessive–compulsive Disorder by Individually Tailored Symptom Provocation." *Psychological Medicine* 47 (12). Cambridge University Press: 2071–80.

Romanelli, Robert J., Frances M. Wu, Ryan Gamba, Ramin Mojtabai, and Jodi B. Segal. 2014. "Behavioral Therapy and Serotonin Reuptake Inhibitor Pharmacotherapy in the Treatment of Obsessive--Compulsive Disorder: A Systematic Review and Meta-Analysis of Head-to-Head Randomized Controlled Trials." *Depression and Anxiety* 31 (8). Wiley Online Library: 641–52.

Ruck, C., A. Karlsson, J. D. Steele, G. Edman, B. A. Meyerson, K. Ericson, H. Nyman, M. Asberg, and P. Svanborg. 2008. "Capsulotomy for Obsessive-Compulsive Disorder: Long-Term Follow-up of 25 Patients." *Archives of General Psychiatry* 65 (8): 914–21.

Ruscio, A. M., D. J. Stein, W. T. Chiu, and R. C. Kessler. 2010. "The Epidemiology of Obsessive-Compulsive Disorder in the National Comorbidity Survey Replication." *Molecular Psychiatry* 15 (1): 53–63.

Salkovskis, Paul M., J. McGuire, and web. 2003. "Cognitive-Behavioural Theory of OCD." In *Obsessive-Compulsive Disorder: Theory, Research and Treatment.Vol. 65.*, edited by R. G. Menzies and P. De Silva, 20. Wiley Series in Clinical Psychology. Chichester: Wiley.

Saxena, S., and S. L. Rauch. 2000. "Functional Neuroimaging and the Neuroanatomy of Obsessive-Compulsive Disorder." *The Psychiatric Clinics of North America* 23 (3): 563–86.

Scherer, S., L. P. Morency, J. Gratch, and J. Pestian. 2015. "Reduced Vowel Space Is a Robust Indicator of Psychological Distress: A Cross-Corpus Analysis." In *2015 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 4789–93.

Scherer, S., G. Stratou, M. Mahmoud, J. Boberg, J. Gratch, A. Rizzo, and L. P. Morency. 2013. "Automatic Behavior Descriptors for Psychological Disorder Analysis." In *2013 10th IEEE International Conference and Workshops on Automatic Face and Gesture Recognition (FG)*, 1–8.

Schienle, Anne, Axel Schäfer, Rudolf Stark, Bertram Walter, and Dieter Vaitl. 2005. "Neural Responses of OCD Patients towards Disorder-Relevant, Generally Disgust-Inducing and Fear-Inducing Pictures." *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology* 57 (1): 69–77.

Schnitzler, Alfons, and Joachim Gross. 2005. "Normal and Pathological Oscillatory Communication in the Brain." *Nature Reviews. Neuroscience* 6 (4): 285–96.

Shiffman, Saul, Arthur A. Stone, and Michael R. Hufford. 2008. "Ecological Momentary Assessment." *Annual Review of Clinical Psychology* 4: 1–32.

Simon, Daniela, Christian Kaufmann, Kathrin Müsch, Eva Kischkel, and Norbert Kathmann. 2010. "Fronto-Striato-Limbic Hyperactivation in Obsessive-Compulsive Disorder during Individually Tailored Symptom Provocation." *Psychophysiology* 34 (February): 317.

Simon, Daniela, Eva Kischkel, Rüdiger Spielberg, and Norbert Kathmann. 2012. "A Pilot Study on the Validity of Using Pictures and Videos for Individualized Symptom Provocation in Obsessive–compulsive Disorder." *Psychiatry Research* 198 (1). Elsevier: 81–88.

Sookman, Debbie, Jonathan S. Abramowitz, John E. Calamari, Sabine Wilhelm, and Dean McKay. 2005. "Subtypes of Obsessive-Compulsive Disorder: Implications for Specialized Cognitive Behavior Therapy." *Behavior Therapy* 36 (4). Elsevier: 393–400.

Steketee, G., D. L. Chambless, G. Q. Tran, H. Worden, and M. M. Gillis. 1996. "Behavioral Avoidance Test for Obsessive Compulsive Disorder." *Behaviour Research and Therapy* 34 (1): 73–83.

Steven A Rasmussen, M.D1., Georg Norén M.D.,Ph.D.2, Benjamin Greenberg, M.D., Ph.D.1, Richard Marsland R.N1., Nicole McLaughlin, Ph.D.1, Paul Malloy, Ph.D.1, Stephen Salloway, M.D.1, David Strong, Ph.D.,3 Jane Eisen, M.D.1, Michael Jenike, M.D.3, Scott L. Rauch, M.D.3 Lee Baer, Ph.D.3, & Christer Lindquist, M.D.4. n.d. "Gamma Ventral Capsulotomy in Intractable Obsessive-Compulsive Disorder." *Biological Psychiatry, in Press*.

Strimbu, Kyle, and Jorge A. Tavel. 2010. "What Are Biomarkers?" *Current Opinion in HIV and AIDS* 5 (6): 463–66.

Uhlhaas, Peter J., and Wolf Singer. 2006. "Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology." *Neuron* 52 (1): 155–68.

Veale D, Roberts A. 2014. "Obsessive-Compulsive Disorder." *BMJ* , no. 348: g2183.

Zhang, Z., J. M. Girard, Y. Wu, X. Zhang, P. Liu, U. Ciftci, S. Canavan, et al. 2016. "Multimodal Spontaneous Emotion Corpus for Human Behavior Analysis." In *2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, 3438–46.