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## Inherited Obsession: The Role of Genetics and Serotonin in the Etiology of Obsessive-Compulsive Disorder

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**Inherited Obsession:**  
**The Role of Genetics and Serotonin in the Etiology of Obsessive-Compulsive Disorder**

**Senior Project submitted to**  
**The Division of Social Studies**  
**of Bard College**  
**by**  
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**Abstract**

We still do not understand why some individuals are more likely to develop OCD than others. Research has implicated the serotonin system specifically the serotonin transporter and the 5-HT<sub>2A</sub> receptor as potential neurochemical underpinnings of OCD. Innovations in genetics have allowed research to hone in on the specific genes which code for the neurochemical dysfunction implicated in OCD. In this literature review, I gathered data in the form of research which addresses the neurochemical and genetic underpinnings of OCD in order to gain a better understanding of the etiology of the disorder. The findings presented represent my analysis of current research in the field in the hopes of drawing conclusions about the etiology of OCD. My conclusions implicate the specific genes which code for the serotonin transporter and the 5-HT<sub>2A</sub> receptor as the potential neurochemical and genetic underpinnings of OCD.

## Chapter One

### Introduction

Obsessive-compulsive disorder (OCD), a psychological disorder characterized by intrusive thoughts and out-of-control repetitive behaviors, is the fourth most common mental disorder, and yet to many the disorder remains a mystery. Individuals who develop the disorder are often unaware of its existence before they seek treatment and are diagnosed. These people suffer silently from invasive thoughts which cripple their ability to function normally, and yet most ironically of all, most are aware that their thought patterns and behaviors are irrational but still cannot control them.

James Bailey is an example of a case of OCD. In his memoir, *Man, Interrupted*, Bailey recounts his time at a treatment facility in Berkeley, California where he underwent exposure therapy for his OCD. Bailey's obsessions revolved around drugs and drug users and the fear that they might contaminate him with mind-altering substances. Whenever Bailey came into contact with drugs or drug users, he was compelled to extricate himself from the situation to wash his hands in order to get rid of the contamination. Bailey understood that his obsessions and their corresponding compulsions were a product of his own mind, yet he still could not prevent himself from complying with their demands. Bailey's case may seem peculiar, but for individuals with OCD, the thoughts and behaviors he exhibits are all too familiar (Bailey, 2006).

James Bailey is one example out of many documented cases of OCD. Why did Bailey and individuals like him develop this disorder when the rest of us did not? Could his genetics be responsible for the onset of his OCD? Maybe an imbalance of the chemicals in his brain known as neurotransmitters is to blame? These are two of the leading biological explanations in the field of research into the etiology of OCD and as such are the areas of research I will address in this

paper. Thus, the research question guiding my current paper is what are the neurochemical and genetic explanations for the etiology of OCD?

### **What is OCD?**

OCD is an anxiety disorder characterized by obsessions or compulsions, with patients often exhibiting symptoms of both. The obsessions and compulsions are often connected in some way that makes sense to the patient but not necessarily to others. For example, a patient could have an obsession about harming his mother and the only way to reduce the anxiety brought on by this obsession is to compulsively count the cracks in the sidewalk (“step on a crack, break your mother’s back”).

In order to be diagnosed with OCD, patients must endorse criteria related to obsessions and compulsions. Obsessions are defined as “recurrent and persistent thoughts, impulses, or images” that are experienced as distressing “at some time during the disturbance” (American Psychiatric Association, 2000, p.462). These thoughts, images, or impulses cannot be “excessive worries about real-life problems” (American Psychiatric Association, 2000, p.462). The patient must attempt to cancel out the thoughts, impulses, or images “with some other thought or action” (American Psychiatric Association, 2000, p.462). Finally the patient must recognize “that the obsessional thoughts, impulses, or images are a product of his or her own mind” (American Psychiatric Association, 2000, p.462).

Compulsions are defined by “repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly” (American Psychiatric Association, 2000, p.462). In addition “the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are

designed to neutralize or prevent or are clearly excessive” (American Psychiatric Association, 2000, p.462).

Obsessions or compulsions are the primary criterion for OCD; however, a patient must also endorse four more criteria to warrant a diagnosis. (1) The patient must recognize “at some point during the course of the disorder” that their behaviors or mental acts are “excessive or unreasonable” (American Psychiatric Association, 2000, p.462). (2) The patient’s obsessions or compulsions must “cause marked distress, (be) time consuming (e.g., take more than 1 hour a day), or significantly interfere with the person’s normal routine, occupational (or academic) functioning, or usual social activities or relationships” (American Psychiatric Association, 2000, p.463). (3) The obsessions or compulsions cannot be better explained by another axis I disorder, and “the disturbance (cannot be) due to the direct physiological effects of a substance or a general medical condition” (American Psychiatric Association, 2000, p.463). Finally, (4) the diagnostician must specify if the patient has poor insight into their condition meaning that the patient “does not recognize that the obsessions and compulsions are excessive or unreasonable” (APA, 2000, p.463).

### **Psychosocial predictors**

The onset of OCD is usually gradual and patients do not typically have an explanation for the development of their symptoms. However, there is at least one demonstrated psychosocial predictor of OCD: a traumatic life event. Several studies (de Silva & Marks, 1999; Gershuny et al., 2003; Pitman, 1993) have revealed an etiologic link between the presence of a traumatic life event and the onset of OCD. Pitman (1993) found this link in the onset of OCD among combat veterans who had been exposed to trauma. De Silva & Marks (1999) identified this connection through a series of case studies of patients who had experienced trauma and developed OCD.



Gershuny and colleagues (2003) looked at the relationship between trauma and OCD through a series of four cases of individuals who met criteria for comorbid OCD and PTSD and examined connections between symptoms of OCD and PTSD. Cromer and colleagues' (Cromer, Schmidt, & Murphy, 2007) study investigates the effect of traumatic life events on the severity and symptoms of a group of individuals diagnosed with OCD.

### **Environmental predictors**

In addition to the presence of a traumatic life event, environmental factors may play a role in predicting the onset of OCD. Classical conditioning is the psychological principle most often cited in the development of OCD. In the case of OCD, classical conditioning posits that when a particular stimulus is paired with anxiety or fear, an obsession is born. Foa & Kozak (1986) propose that emotions such as fear can be viewed as information structures in the memory of an individual. When an information structure is developed which ties fear to a particular obsessive stimulus, the individual develops OCD. For example, in the case of James Bailey, an early LSD experience became associated with anxiety in his memory and as such he developed an information structure in which drugs are associated with fear. It was an environmental factor, a drug experience, which became associated with anxiety and in turn produced chronic OCD.

### **Brain structure**

A characteristic pattern of activation in the brain structures of patients may predict the onset of OCD. Rauch, Jenike, Alpert, Baer and colleagues (1994) demonstrated that activation in the orbitofrontal cortex, caudate nucleus, and anterior cingulate cortex is associated with worry in the brains of OCD patients. Rauch and colleagues (1994) found this activation by provoking symptoms in patients with OCD using a stimulus of their own choice such as a contaminated object. Once patient's symptoms had been provoked, their patterns of brain activation were

measured using positron emission tomography (PET). Oxygen-15 labeled carbon dioxide, a radioactive pharmaceutical, was used to trace patterns of brain activation. Patients whose symptoms had been provoked showed enhanced activation in the bilateral orbitofrontal cortex (OFC), left anterior cingulate cortex, and right caudate nucleus compared to the same group of patients before symptom provocation. This finding indicates that these brain structures are involved in the process of worry in patients with OCD. There is more to the biology behind OCD than brain structure alone. Neurotransmitters and genetics both play a role in the development of the disorder.

### **What is a neurotransmitter?**

A dysregulation in the neurotransmitters serotonin and dopamine is one of the demonstrated etiologic underpinnings of OCD. What is a neurotransmitter, how are they assessed, and why are they important in the genesis of OCD? Neurotransmitters are the chemical messengers of the nervous system. There are many different types of neurotransmitters, each of which perform a different set of functions and are present in varying quantities in different parts of the brain. In order for a substance to be classified as a neurotransmitter it must endorse two criteria: (1) “The proper nerve trunk or set of nerve axons can be selectively stimulated” to release the substance and (2) the “release of the transmitter can be detected in the amounts released by single nerve endings after one action potential” (Cooper et al., 2003, p.31). The neurotransmitters dopamine and serotonin (5-HT) are the two neurotransmitters implicated in the development of OCD. (da Rocha et al., 2008, Flaisher-Grinberg et al., 2008, Kontis et al., 2008)

Dopamine was originally thought to be a precursor to norepinephrine until it “was recognized as a transmitter in its own right” (Hökfelt, Johansson, & Goldstein, 1984, p.1328). Dopaminergic neurons are located primarily in the “mid and rostral parts of the brain--that is, in

the mesencephalon (mid brain), hypothalamus (hormones), and olfactory bulb (smell), with scattered cells in some other brain regions” (Hökfelt, Johansson, & Goldstein, 1984, p.1328).

The mesencephalon contains the substantia nigra, a brain region associated with the development of Parkinson’s disease. The substantia nigra produces dopaminergic neurons which are transmitted to the striatum. Parkinson’s patients do not produce as many dopaminergic neurons in the substantia nigra which leads to less dopamine in the striatum, the major input to the basal ganglia which is the brain region responsible for movement. This demonstrates the importance of dopamine for voluntary movements. (Cooper et al., 2003, p.225)

Serotonin (5-HT) is one of the best understood neurotransmitters. Serotonin “nerve terminal networks” have been discovered in “virtually all parts of the brain” (Hökfelt, Johansson, & Goldstein, 1984, p.1328). Assessment of serotonin was challenging until “Steinbusch et al. used antibodies to 5HT conjugated with bovine serum albumin to visualize the 5HT systems in an easy and reproducible way” (Hökfelt, Johansson, & Goldstein, 1984, p.1328). This technique allows for serotonin in the brain to be easily tracked and identified. Because of the “widespread projections and highly regulated pacemaker pattern of activity that is characteristic of serotonin neurons, a broad homeostatic function has been suggested for serotonergic systems” (Cooper et al., 2003, p.291) In other words, serotonin is responsible for so many sensory and motor functions that it is difficult to characterize its role in simple terms. Dysregulation of serotonin can lead to a wide variety of disorders. The development of OCD is the one disorder this paper is focused on.

### **What is a genetic marker?**

All genetic variation in the population is the result of mutation. Mutations occur randomly in individuals at some point along a particular chromosome. Mutations are then

inherited through generations which lead to the expression of a particular phenotype, in this case the development of OCD. In order to locate a particular mutation on a chromosome such as a mutation which causes OCD, genetic markers are used. Genetic markers are particular points along a chromosome which can be assayed for (identified using biological testing). When gametes (sex cells) undergo meiosis (cell division) during sexual reproduction, chromosomal crossover occurs where sections of one chromosome are split and linked up with sections of another chromosome. Genetic linkage describes the proclivity for two genetic markers which are physically close together along a chromosome to be inherited together. In other words the chance of those two genetic markers getting separated during the crossover which occurs during meiosis is very slim. Linkage can be used as a way of locating a particular mutation along a chromosome. If the mutation is consistently inherited along with two genetic markers which are linked (physically close together), one can deduce that the mutation must occur at some point between those two markers, otherwise the mutation would have been separated from those markers during meiosis. It is important to note that mutations occur randomly and may develop at any point on a chromosome. Genetic linkage describes the method for locating a particular mutation, such as one which may manifest as OCD. (Strachan & Read, 1999).

### **Scope of Project**

Attempting to empirically demonstrate the exact genetic and neurochemical mechanisms which cause the development of OCD is a tall order and one that is truly out of my grasp. The empirical research required to answer this question would require resources far beyond what I have at my disposal. What I do have at my disposal is the cutting edge research into this question from scholars at the forefront of their field. Therefore, in order to address my topic, I will review

current literature on the genetic and neurochemical etiology of OCD from empirical journals and books in the hopes of drawing biologically based conclusions about the underpinnings of OCD.

Some of the research into the etiology of OCD is well established. The environmental and psychosocial predictors of OCD, as well as several of the brain structures involved, have been studied extensively. However, the neurochemical and genetic underpinnings of OCD are not as well understood, and a burgeoning degree of research into the etiology of OCD over the past decade concerns these topics. Research concerning the role of the neurotransmitters serotonin and dopamine in the etiology of OCD comprises a large percentage of my project because patients with OCD display irregular levels of these neurotransmitters. Research concerning genetic markers for OCD also makes up a large percentage of my project because these markers potentially hold the key to predicting the onset of the disorder. These two areas of research converge in several studies concerning the serotonin transporter (5-HTT) gene which may play a pivotal role in the etiology of OCD. The areas of research above consist of the scope of the studies included in my project.

Much of the recent research into OCD is about comorbidity, course, and treatment of the disorder. Studies concerning these topics were not included in my project because my research question concerns the etiology of OCD and the neurotransmitters and genes associated with the disorder. Comorbidity studies confound my research topic because any etiologic factors identified could be attributed to the comorbid disorder. Studies concerning the course of OCD and treatment were excluded from my project because I am concerned with how and why the disorder develops which is a different question from how best to treat an active case of OCD.

My research question is ultimately what dictates the scope of my project. My question is: what are the neurochemical and genetic underpinnings of obsessive-compulsive disorder? This

question is broad enough to include a variety of theories on the etiology of OCD and it is simultaneously specific enough to limit the scope of my project to be achievable within the relatively short amount of time I have to complete it.

## **Chapter Two**

### **Neurochemical Underpinnings of OCD**

Neurochemicals are the chemical messengers of the brain. Whenever any brain activity occurs, it is the result of a chemical message. There are many different types of neurotransmitters; however, the two that I will be focusing on for the sake of this review are serotonin and dopamine because these are the two neurotransmitters whose dysfunction is implicated in OCD. Neurotransmitter dysfunction is currently believed to be the leading biological explanation for the development of OCD.

#### **Serotonin**

##### **Selective Serotonin Reuptake Inhibitors (SSRIs)**

There is a substantial body of evidence suggesting serotonin has a role in the etiology of OCD. Some of the strongest evidence for serotonin's role comes from studies investigating the mechanisms behind selective serotonin reuptake inhibitors (SSRIs), the primary pharmacological treatment for OCD. Several studies have investigated the mechanisms and role of SSRIs in the etiology of OCD (El Mansari & Blier, 2006; Mavorgiorgou et al., 2010).

El Mansari & Blier (2006) investigated the state of research on OCD medication. Their article reviewed the chemical action of SSRIs as well as the mechanisms underlying those actions. In their review, the authors first elucidate the effects of SSRIs on 5-HT neurotransmission. Upon first starting SSRI or MAOI treatment, patients experience a reduction of the firing activity of serotonin neurons. This initial reduction is followed by a recovery process in which, after the first two weeks, patients experience symptom relief simultaneous with an increase in synaptic 5-HT. SSRIs desensitize 5-HT autoreceptors (presynaptic receptors) and trick the neuron into thinking that less serotonin is being transmitted in each action potential than

is actually the case. The neurons then compensate by firing more 5-HT in each action potential. The authors also point out that SSRI treatment takes longer to take effect in OCD patients than in depressive patients. They suggest that this is because it takes SSRIs eight weeks to desensitize 5-HT autoreceptors in the OFC, a brain region associated with OCD, compared with only four weeks for the medication to desensitize 5-HT autoreceptors in the frontal cortex and hypothalamus. They also suggest that higher doses may be required to obtain this same desensitization effect in OCD patients. The authors go on to show that the desensitization of 5-HT autoreceptors in the OFC actually causes a desensitization of the postsynaptic 5-HT<sub>1A</sub> receptor but not the 5-HT<sub>2A</sub> or 5-HT<sub>2C</sub> receptors. Based on this finding the authors suggest that activation of the 5-HT<sub>2</sub> receptors is partially responsible for the symptom reduction produced by the effect of the greater 5-HT release in the OFC of OCD patients. This makes sense in light of findings that hallucinogens which act as 5-HT<sub>2</sub> receptor agonists provide symptom relief in OCD patients. These findings suggest that the beneficial action of SSRIs is at least partially mediated by the activation of postsynaptic 5-HT<sub>2</sub> receptors.

A recent study by Mavorgiorgou and colleagues (2010) hypothesized that OCD patients were typified by a strong loudness dependence of auditory evoked potentials (LDAEP) of the primary, not secondary, auditory cortex, which would indicate low serotonergic function. LDAEP is an established method of measuring serotonergic function. LDAEP is inversely correlated with serotonergic function meaning the higher the LDAEP, the lower the serotonergic function. The authors measured LDAEP in patients with OCD before and after a ten week treatment with sertraline, better known as Zoloft, an SSRI, and compared them with a group of healthy controls. The authors found that the LDAEP of the primary auditory cortex of OCD patients without medication was significantly higher than healthy controls. Furthermore, the



LDAEP of primary auditory cortex was significantly lower in OCD patients after treatment with sertraline, as were their OCD symptoms compared with baseline. These results support the notion that OCD is characterized by serotonergic dysfunction, which SSRIs may correct.

Taken together, El Mansari & Blier (2006) and Mavorgiorgou and colleagues (2010) put forth a strong case that the mechanisms underlying the therapeutic success of SSRIs are linked to the mechanisms which underlie OCD. El Mansari & Blier's (2006) discussion of the desensitization of 5-HT autoreceptors elucidates the pharmacological action of SSRIs. Together with the findings in the next section which discuss the beneficial effects of 5-HT<sub>2A</sub> psychedelic drugs, a strong case is suggested that activation of 5-HT<sub>2</sub> receptors is associated with therapeutic effects on OCD. Mavorgiorgou and colleagues' (2010) study used LDAEP as a measure of serotonergic function to provide empirical evidence that OCD is characterized by serotonergic dysfunction and that SSRIs improvement of serotonergic function may represent the mechanism underlying their therapeutic effect upon OCD patients.

### **5-HT<sub>2A</sub> Psychedelic Drugs**

Additional evidence for serotonin's role in the etiology of OCD comes from studies investigating the administration of psychedelic drugs to patients with OCD (Zghoul & Blier, 2003; Moreno et al., 2006).

Zghoul & Blier (2003) suggest that LSD has an enhancing action on the responsiveness of neurons in the OFC to 5-HT. It has been well established that the availability of 5-HT to neurons in the OFC is a mediating factor in the severity of OCD. The authors administered 5-HT and LSD to patients with OCD via microiontophoresis, a process used to measure neuronal responsiveness to an ejected substance. Microiontophoresis uses a micro pipette with multiple barrels, one for the LSD, one for 5-HT, and one for a saline solution. In the experimental

condition, the LSD was ejected first, then the 5-HT, the saline solution followed. The neurons reaction to the saline solution provides a measurement of responsiveness produced by the 5-HT. The authors then followed up with a control condition in which only 5-HT and saline solution were included. If the neurons were more responsive after the LSD condition compared with the control condition, then the LSD increased those neurons responsiveness to 5-HT. The authors conducted this procedure first on the OFC, then on the hippocampus, a brain structure associated with depression. They found that the LSD made neurons significantly less responsive in the hippocampus but it did make them more responsive in the OFC. This finding indicates that LSD has an enhancing action on 5-HT in the OFC, a brain region associated with OCD. This study was one of the first to provide neurological evidence for hallucinogenic drugs' beneficial effects on OCD symptoms.

Several years later, Moreno and colleagues (2006) investigated the safety, tolerability, and efficacy of psilocybin on nine patients diagnosed with OCD. While Zghoul & Blier (2003) were searching for a neurological basis for hallucinogens' beneficial effects on OCD, Moreno and colleagues (2006) examined the actual effectiveness and safety of using these drugs in a clinical setting. Psilocybin is the psychoactive drug found in the most commonly used hallucinogenic mushrooms. The authors were interested in experimenting with psilocybin as a treatment for OCD after hearing of several anecdotal reports in the literature of reduction of OCD symptom severity while individuals were under the influence of these drugs. It has already been well established that these drugs exert their effects through agonizing 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>3A</sub> receptors and that increasing synaptic 5-HT may be the pathway through which SSRI treatments exert their effects. Following from these two findings, the authors hypothesized that treatment with psilocybin would decrease symptoms in a sample of patients with OCD. The

author's results indicate that all nine patients tolerated the procedure well and experienced a statistically significant decrease in their OCD symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS). These findings indicate that the serotonergic action of psilocybin affected the severity of patients' OCD symptoms providing further proof for serotonin's role in OCD.

These two studies provide empirical evidence that hallucinogenic drugs, which act as 5-HT<sub>2A</sub> receptor agonists, exert anti-OCD effects on those afflicted with the disorder. Zghoul and Blier (2003) found that LSD has an enhancing effect on the action of serotonin in the OFC, a brain region implicated in OCD. This finding indicates that the anti-OCD effect produced by LSD is mediated through its serotonergic effects on the OFC. This suggests that OCD is caused by an inherent dysfunction in serotonin. Moreno and colleagues (2006) found that psilocybin was tolerated well by a sample of patients with OCD and produced a statistically significant reduction in their OCD symptoms as measured by YBOCS. This finding suggests that 5-HT<sub>2A</sub> agonists may prove to be a novel target for drug treatments for OCD. Psilocybin exerted its anti-OCD effects as soon as the drug took effect and the decrease in symptoms outlasted the effects of the drug. These findings propose that hallucinogenic drugs may be a better treatment than SSRIs which can take up to eight weeks to take effect and often require increases in dose to achieve similar anti-OCD effects. While it seems impractical to administer hallucinogens to OCD patients regularly for treatment, these findings suggest that the 5-HT<sub>2A</sub> receptor which these drugs agonize may be a potential target for new OCD medication.

### **Serotonin Transporter (5-HTT)**

Recent studies have implicated a dysfunction in the serotonin transporter (5-HTT) as a hypothetical etiologic underpinning of OCD (Stengler-Wenzke et al., 2004; Hasselbalch et al., 2007; Zitterl et al., 2007; Shanahan et al., 2009; Matsumoto et al., 2010). Stengler-Wenzke and colleagues (2004) conducted one of the earlier studies to investigate the role of 5-HTT in the etiology of OCD using new imaging technology. They propose that patients with OCD will display a reduction in 5-HTT availability in the midbrain, brainstem, and thalamus. In order to answer this question, the authors used a magnetic resonance imaging (MRI) technique called single-photon emission computed tomography (SPECT), a technique using gamma rays, and statistical analysis. SPECT imaging uses radioligands, substances used in research which bind to neurotransmitter receptors and imitate the neurotransmitter. Their results indicate a statistically significant reduction in ten OCD patient's 5-HTT availability in the midbrain and upper brainstem compared with a group of healthy controls. This result suggests a decreased number of serotonergic neurons in the brains of OCD patients compared with healthy controls. This would explain why administration of SSRIs is an established clinical treatment for OCD. The authors suggest that this reduced availability of serotonin is most likely genetically predisposed in patients with OCD.

Three years later, Hasselbalch and colleagues (2007) took this question a step further and suggested that patients with OCD have a reduced binding potential (BP) for 5-HTT in the midbrain. The authors used SPECT imaging and statistical analysis and found that OCD patients had a reduced 5-HTT BP in the midbrain-pons compared to healthy controls. They did not find a correlation between this reduced 5-HTT BP and similar reductions in clinical variables which they attribute to the small sample size. This study adds further evidence to the 5-HTT

dysfunction hypothesis of OCD by implicating reduced binding potential in the midbrain-pons as a possible underpinning of OCD.

In the same year, Zitterl and colleagues (2007) sought to investigate serotonergic function in the thalamus/hypothalamus of compulsive checkers. The authors used SPECT imaging and statistical analysis to measure the availability of 5-HTT in the thalamus/hypothalamus region. The authors conducted their study with a sample of 24 patients diagnosed with OCD and found statistically significant reduced 5-HTT availability in the thalamus/hypothalamus region of the compulsive checkers when compared with a sample of 24 healthy controls. This study adds further support to the 5-HTT dysfunction hypothesis of OCD by implicating reduced 5-HTT availability in the thalamus/hypothalamus as a potential underpinning of the disorder.

Two years later, Shanahan and colleagues (2009) used prepulse inhibition (PPI) as a measure of compulsive behavior in mice to conduct their study on the reduction of 5-HTT availability in OCD. PPI is a measure of the diminishing of the startle response when a barely detectable prepulse precedes the stimulus by 30-500ms. The idea is that PPI provides a measure of an individual's ability to filter out excess stimulation. Individuals with some psychological disorders such as schizophrenia and OCD have lower PPI than healthy controls. In their study, the authors used PPI as a measure for compulsive behavior in rodents and treated mice with 5-HT<sub>1B</sub> agonists, which mimic compulsive behavior. The authors theorized that by reducing 5-HTT function in mice, either by breeding mice with deficient 5-HTT genes or extended administration of SSRIs, the PPI deficit caused by administration of 5-HT<sub>1B</sub> agonists would diminish. Thus, the authors created a model for compulsive behavior in mice and then attempted to treat that compulsive behavior with either SSRIs or genetics. The author's results supported their hypothesis. 5-HT<sub>1B</sub> agonists increased compulsive behavior and created a PPI deficit in mice,

and the authors were able to correct this deficit by breeding mice with reduced 5-HTT gene expression or chronic administration of SSRIs. This study lends further support to the 5-HTT hypothesis of OCD etiology through a different model (PPI). These authors also investigated a possible genetic predisposition for OCD through breeding 5-HTT deficient mice to measure their compulsive behavior compared to controls.

One year later, Matusumoto and colleagues (2010) conducted an additional study on the BP of 5-HTT. Their study focused on the insular cortex (disgust emotion) of patients and used a radioligand with a higher binding potential for serotonin receptors than previous studies. The authors found the expected reduced BP in the insular cortex of OCD patients compared with healthy controls. They did not find lower BP in brain regions rich in 5-HTT such as the midbrain, thalamus, and striatum; all areas which other research has implicated. The authors attribute these discrepancies to their relatively small sample size and use of a different radioligand from other studies. Further research will have to be conducted to account for these inconsistencies and further examine 5-HTT availability in all of these brain regions.

All of the above studies, apart from Shanahan and colleagues (2009) used SPECT imaging and statistical analysis to measure 5-HTT dysfunction in different brain regions. Stengler-Wenzke and colleagues' (2004) study suggests that decreased 5-HTT availability in the midbrain, brainstem, and thalamus is associated with OCD. Hasselbalch and colleagues' (2007) study posits decreased BP for 5-HTT in the midbrain-pons is associated with OCD. Zitterl and colleagues' (2007) study proposes that decreased 5-HTT availability in the thalamus/hypothalamus region is associated with OCD. Matsumoto and colleagues' (2010) study suggests decreased BP for 5-HTT in the insular cortex is associated with OCD. Shanahan and colleagues (2009) was the only one of these studies to use a different measure of 5-HTT

function. They used PPI and a 5-HT<sub>1B</sub> receptor agonist to measure and model OCD and an SSRI to treat the model OCD. Their study also suggests that 5-HTT dysfunction is linked with OCD. Taken together, all of these studies make a strong case for decreased 5-HTT in various brain regions as a potential neuroanatomical model of OCD. Some studies did not find decreased 5-HTT in the other brain regions which other studies implicated. This is most likely due to sample size and statistical error. Nevertheless a more thorough investigation of 5-HTT across all of the brain regions implicated in the development of OCD is necessary before conclusions can be drawn about 5-HTT availability as an etiologic factor in OCD.

### **Dopamine**

There is a large body of evidence suggesting a role for serotonin in the etiology of OCD. However, a few studies have also suggested a role for dopamine in the etiology of OCD (Kim et al., 2007; Olver et al., 2009). Kim and colleagues (2007) suggest that serotonergic drugs such as SSRIs may alter dopamine function in the striatum of patients with OCD and that this change could be associated with OCD symptoms. In order to investigate this question, the authors used SPECT to measure the density of the dopamine transporter (DAT) in the basal ganglia of patients with OCD before and after treatment with an SSRI. Their results indicate a significant decrease in DAT binding in the right basal ganglia (RBG) of patients after treatment with an SRI. In addition a relationship was observed between the decrease in DAT binding in the RBG and a decrease in compulsive symptoms of patients. These results suggest that a dysregulation in the functioning of dopamine in the basal ganglia may be responsible for OCD symptoms, and that medication which can correct this dysfunction may be responsible for improvement in OCD symptoms.

Olver and colleagues (2009) investigated the role of dopamine acting on the D1 receptor in the striatum (input to basal ganglia) of patients with OCD. The authors proposed that dopamine in the striatum of patients with OCD may have a role in regulating OCD symptoms. They used positron emission tomography (PET) scans to measure the binding potential (BP) of a D1 antagonist in the striatum of patients with OCD and healthy controls. Their results indicate a decrease in BP of the D1 antagonist in both sides of the caudate nucleus and the putamen (the two sectors in the striatum). A decrease in dopamine binding potential in the striatum makes sense considering that a dysfunction in the cortico-striatal-thalamic pathways of the brain is one of the established neuroanatomical models for OCD.

Taken together, Kim and colleagues (2007) and Olver and colleagues (2009) suggest that greater binding potential of the dopamine transporter in the striatum of OCD patients may result in more severe OCD symptoms. This problem can be corrected through treatment with SSRIs which increase the amount of serotonin in the synapse, which in turn decreases binding of dopamine. This finding seems to suggest that the origin of the dopaminergic dysfunction in OCD actually lies in an imbalance of the serotonin system.

### **Neurochemical Summary**

The studies reviewed in this section propose several different pathways through which neurochemical dysfunction may lead to the development of OCD. Evidence from studies investigating the therapeutic effects of SSRIs suggest that because SSRIs desensitize many serotonin receptors yet not the 5-HT<sub>2</sub> receptors, activation of this receptor type may be responsible for these medication's beneficial effects in treating OCD. Evidence from studies investigating the effects of 5-HT<sub>2A</sub> hallucinogens provide further support that activation of these serotonin receptors may be responsible for the therapeutic effect of SSRIs and that novel OCD



drugs might specifically target these receptors. Studies examining the role of 5-HTT in the etiology of OCD provide evidence that 5-HTT dysfunction in several brain regions implicated in OCD may be responsible for the development of the disorder and that patients with OCD may be genetically predisposed to 5-HTT dysfunction. Finally, studies investigating the role of dopamine in OCD found that greater binding potential for DAT in the striatum of patients may result in greater symptom severity. However, these studies suggest that because this dysfunction can be corrected with SSRIs by increasing the amount of serotonin in the synapse, the source of this dysfunction probably lies in the serotonin system.

### **Neurochemical Critique**

The studies reviewed in this section provide a wealth of evidence that neurochemical dysfunction, especially in the serotonin system, may be responsible for the etiology of OCD. However, these studies are not definitive and leave plenty of room for improvement. Because drugs used to treat OCD such as SSRIs were discovered prior to the identification of the biological basis for the disorder, researchers have assumed that the mechanisms underlying these drugs must be related to the dysfunction inherent in the disorder. However, SSRIs work by drastically increasing serotonin in the synapse, leaving the exact mechanism through which this effect works to alleviate OCD unknown.

Evidence from the beneficial effects of 5-HT<sub>2A</sub> hallucinogenic drugs on OCD suggest that activation of these serotonin receptors may be the mechanism through which SSRIs are relieving OCD symptoms. While the two studies cited investigating these drugs do provide evidence that hallucinogens do relieve OCD symptoms through increasing neuronal responsiveness to serotonin and that the experience is well tolerated and effective on human probands, they leave open the question of how exactly this knowledge can be applied. It seems to

me that by finding or designing a drug which selectively activates 5-HT<sub>2</sub> receptors without causing the disruptive cognitive effects of hallucinogenic drugs, one might be closer to a more effective treatment for OCD.

The studies investigating the role of 5-HTT in the etiology of OCD provide evidence that 5-HTT dysfunction in brain regions implicated in OCD may be partially responsible for the development of the disorder. These studies, apart from Shanahan and colleagues (2009) all used SPECT imaging and statistical analysis to determine whether patients with OCD had significantly reduced binding potential for 5-HTT in several different brain regions. While their findings do suggest that reduced 5-HTT BP is an etiologic factor in the disorder, their results conflict with each other and none of the studies carries enough statistical power to determine with confidence whether these dysfunctions are a root cause of OCD. Future research is needed to determine the exact nature of this 5-HTT dysfunction, including the genes responsible for the dysfunction, in order for this research to have a practical application in managing the disorder.

The studies reviewed concerning dopamine provide support that over activity of dopamine is associated with compulsive symptoms of OCD. While these findings are compelling and point to a neurochemical basis for these behaviors, they ultimately suggest that because treatment with SSRIs corrects this surplus of dopamine, the etiologic basis of this imbalance lies in serotonergic dysfunction. This suggests that the increased BP for DAT is a symptom rather than a cause of OCD. While this research is intriguing it suggests that future research on the etiology of OCD should concern itself with serotonin, not dopamine.

## **Chapter Three**

### **Genetic Underpinnings of OCD**

Genes refer to specific loci on chromosomes which code for aspects of the biology of an organism. Humans inherit their genetic makeup from their parents and pass on their genes through Mendelian inheritance, a process of recombination which passes on some genes from the mother and others from the father. While neurochemistry and genetics are both searching for biological explanations of OCD, there is a fundamental difference between the two.

Neurochemical underpinnings refer to the dysfunction within the brain of an individual which is responsible for OCD. Genetic underpinnings refer to the abnormal genes which an individual inherited from their parents which are responsible for the neurochemical dysfunction thought to underlie OCD.

#### **Family and Twin Studies**

Several studies have demonstrated familial inheritance of OCD (Clifford et al., 1984; Pauls & Alsobrook, 1999; Hasler et al., 2007; van Groothest et al., 2007; Wilcox et al., 2008; Katerberg et al., 2010). Clifford and colleagues (1984) conducted one of the earliest twin studies comparing samples of Monozygotic (MZ) and dizygotic (DZ) twins to investigate the heritability of obsessional traits and symptoms. They found that just under half of the differences in two scales of obsessional symptoms and traits could be attributed to familial inheritance indicating a potential genetic contribution to the development of OCD. It would be many years before studies were published which replicated and built on the findings of Clifford and colleagues (1984).

Sixteen years after Clifford and colleagues (1984), Pauls and Alsobrook (1999) concluded that because no twin studies had been published to replicate the findings of Clifford and colleagues (1984), the degree of genetic control over OCD was still uncertain. The authors

posited that family and twin studies into the etiology of OCD can only advance the field's knowledge to a certain extent. They suggested that the future of research into the inheritance of OCD lies in studies of genetic linkage which can help locate the exact genes which cause the development of the disorder. Future twin studies investigating the etiology of OCD would focus not only on the heritability of OCD but of specific OCD symptom dimensions.

Several years later, Hasler and colleagues (2007) found that certain clusters of OCD symptoms are particularly heritable. These authors used the YBOCS symptom dimensions and found that hoarding obsessions and compulsions, as well as aggressive, sexual, religious, and somatic obsessions and checking compulsions were the most familial symptom categories. These results indicate that certain subtypes of OCD are more likely to run in families than other subtypes.

Van Grootheest and colleagues (2007) investigated the stability, as well as the genetic and environmental influences of obsessive-compulsive (OC) behavior in children. These authors found that OC behavior was moderately stable in children between the ages of seven and twelve and that the stability of OC behavior was influenced by genetics, as well as by shared and non-shared environmental factors. The stability of OC phenotypes in children were rated by both the mother and father separately in order to determine which behaviors parents agreed upon and which they differed on. The findings of this study suggest that genetic and environmental factors combine to predict the development of OC symptoms in children.

Wilcox and colleagues (2008) found that certain aspects of parental behavior contributed to the development of OCD in children. Maternal and paternal care, overprotection, and control were the three factors tested in the study. The authors found that maternal and paternal overprotection were associated with the development of OCD in offspring, whereas paternal care

was found to be a protective factor. Upon further analysis it was found that these results only proved true when neither parent were diagnosed with OCD themselves. Paternal care as a protective factor proved to be the only result which remained true after further analyses were performed.

Katerberg and colleagues (2010) used the largest sample size yet for an OCD symptom dimension study and found that OCD and its individual symptom dimensions are heritable. Their results also suggest that the particular genes which are believed to put individuals at risk for OCD in general are different from the genes which make individuals susceptible to separate symptom dimensions. These results further support the notion that there is a genetic component to both OCD and to the various ways the disorder can manifest in different individuals.

All of these studies provide familial evidence for the inheritance of OCD. However, as Pauls and Alsobrook (1999) pointed out, the limitations of all of these studies is the lack of evidence pointing to the specific gene or genes responsible for the disorder. Clifford and colleagues (1984) were the first to point out that OCD runs in families and twins. Van Grootheest and colleagues (2007) and Wilcox and colleagues (2008) both identified environmental influence as a key factor in determining heritability of OCD in families and twins. Hasler and colleagues' (2007) study suggests that certain clusters of OCD symptoms are inherited together. Katerberg and colleagues (2010) brought all of this research together and found that OCD as well as certain OCD symptom dimensions are inheritable and the particular genes responsible for OCD in general are different from those regulating the expression of certain symptom dimensions. Twin studies can be useful in identifying the heritability of a particular disorder; however, they do not bring the field much closer to locating the genes responsible for the disorder.

## White Matter Studies

Several studies have suggested that white matter abnormalities in the brain structures of individuals with OCD may be involved in the etiology or pathogenesis of the disorder (Garber et al., 1989; Jenike et al., 1996; Szeszko et al., 2005; Stewart et al., 2007; Nakamae et al., 2008; Atmaca et al., 2010). White matter is a term which describes axons (shafts of neurons) which are covered in myelin sheath (fatty tissue which speeds transmission of signals). This is as opposed to grey matter which contains the cell bodies of neurons.

Garber and colleagues (1989) were the first researchers to identify white matter abnormalities as predictors of OCD. The authors took MRI scans of 32 OCD patients and 14 healthy controls and found frontal lobe white matter differences in the scans of OCD patients compared with control group. In addition, these differences were correlated with severity of OCD symptoms.

It would be seven years before Jenike and colleagues (1996) would build on the results of Garber and colleagues (1989). These authors conducted an MRI study comparing the brains of 10 women diagnosed with OCD with 10 healthy age-matched controls. They found significantly less white matter in the postero-inferior pericallosal, retrocallosal, and cerebellar regions of the brains of women diagnosed with OCD. The callosal brain regions surround the corpus callosum, the bundle of neurons which binds the two halves of the brain together, while the cerebellum (latin for little brain) is a region located in the lower rear of the brain responsible for balance and motor control. Less white matter means less myelin which means slower transmission of neural signals in the affected brain regions. Several studies have since replicated the findings of Garber and colleagues (1989) and Jenike and colleagues (1996) but it would be nine years before new technology would allow research on white matter to progress further.

Szeszko and colleagues (2005) used an MRI technique called diffusion tensor imaging (DTI) to measure the diffusion of water in brain tissue in order to produce neural tract images. This technique allows the researchers to determine the degree of anisotropy, or directionality of diffusion across myelinated axons. The output of this investigation is a value called a fractional anisotropy (FA) which varies from zero to one. A value of zero indicates that the diffusion is isotropic, meaning diffusion is unrestricted in all directions. A value of one indicates that diffusion is only occurring along a single axis and is restricted in all other directions. The authors found significantly lower FA in three white matter areas of the anterior cingulate gyrus, one of the brain regions associated with OCD. In addition, the authors also found lower FA in other areas of the brain and did not find higher FA in any white matter areas of the brains of OCD patients compared with healthy controls.

Stewart and colleagues (2007) conducted a family-based gene association study to determine whether the gene which codes for Oligodendrocyte lineage transcription factor 2 (OLIG2) could be responsible for the transmission of OCD. OLIG2 helps regulate the development of oligodendrocyte cells which produce white matter. Abnormalities in white matter have been associated with OCD. Therefore, polymorphisms in the OLIG2 gene could be the etiological link which leads to the development of abnormalities in white matter which are associated with the presence of OCD. The authors found the suspected polymorphisms in the OLIG2 gene only in the patient samples that had OCD without comorbid Tourette's disorder. This finding indicates that the development of white matter abnormalities may be specifically linked to the "pure" OCD phenotype without comorbidity.

Nakamae and colleagues (2008) used DTI to measure FA and apparent diffusion coefficient (ADC) of fifteen patients with OCD compared with fifteen healthy controls. ADC

represents another method of measuring the degree of diffusion throughout neural tracts in DTI. The authors found higher FA in the white matter of the bilateral semioval center extending to the subinsular cortex as well as higher ADC in the white matter of the left medial frontal cortex. These brain areas are commonly associated with the emotion of disgust suggesting that disgust may play an important role in the pathogenesis of OCD.

Atmaca and colleagues (2010) used genotyping and MRI techniques to determine whether a polymorphism of the myelin oligodendrocyte glycoprotein is associated with volume of white matter in patients with OCD. The authors found larger white matter volumes in patients with OCD compared with healthy controls and found that the aforementioned polymorphic genotype was associated with a diagnosis of OCD. These findings provide evidence that a polymorphism of the myelin oligodendrocyte glycoprotein might be associated with higher volumes of white matter in the brains of patients diagnosed with OCD.

All of these studies provide evidence that white matter abnormalities exist in the brains of OCD patients. Garber and colleagues (1989) were the first to discover differences in white matter in the brains of OCD patients compared with healthy controls. Szeszko and colleagues (2005) and Nakamae and colleagues (2008) used new MRI technique DTI to measure directionality and nature of white matter differences in specific regions of the brain which further developed the white matter findings in OCD patients. Stewart and colleagues (2007) conducted a study to find the genetic basis for these white matter differences and found it in the OLIG2 gene. Atmaca and colleagues (2010) combined the two halves of this research by conducting a study which used genotyping for the oligodendrocyte gene to identify the genetic polymorphism responsible for the white matter abnormalities as well as MRI techniques to identify the abnormalities themselves.



## Genetic Markers

Several studies have taken advantage of recent innovations in genetics which have allowed researchers to hone in on specific genes which may be implicated in the transmission of OCD. (Shugart et al., 2006; Wang et al., 2009; Voyiaziakis et al., 2011) Shugart and colleagues (2006) conducted the first large scale study to search for specific genetic loci which may put individuals at risk for developing OCD. Their study was part of the OCD Collaborative Genetics study (OCGS), conducted at six sites including 219 families affected with OCD. The authors used scans for genetic linkage across each chromosome to find specific points along any chromosome which were consistently inherited in families of patients with OCD. The authors found regions on chromosomes 1, 3, 6, 7, and 15 which showed evidence of linkage with particularly strong support of linkage on chromosome 3. The region on chromosome 3 implicated in the study, 3q27-28, is of particular interest because it includes the location of three candidate genes, 5HTR3C, 3D, and 3E, all of which are serotonin receptor-like genes. A dysregulation of serotonin is one of the proposed mechanisms for the pathogenesis of OCD in the brain which makes this finding particularly salient. While Shugart and colleagues (2006) found some evidence suggesting genetic heritability of OCD, they did not find significance for linkage on any of the chromosomes. The authors suggest that future studies could use more advanced statistical techniques and larger sample sizes in order to narrow down the search for candidate genes in OCD.

Wang and colleagues (2009) used blood sampling and statistical analyses to determine whether there was an association between expression of the catecholamine-o-methyl-transferase (COMT) gene and OCD. They found an abnormally low expression of the COMT gene in the blood of OCD patients compared with healthy controls. This makes sense in light of the finding

that COMT is important in regulating the amount of dopamine and other catecholamines in the prefrontal cortex. Dysregulation of these neurochemicals in the prefrontal cortex is associated with OCD.

Voyiaziakis and colleagues (2011) used the OCGS sample to investigate whether SLC6A4, the 5-HTT gene, was genetically associated with the development of OCD. These authors genotyped 1241 DNA samples from the OCGS and applied several statistical methods to determine whether variation in the SLC6A4 gene was associated with a statistically significant increased risk of developing OCD. While they did find some evidence of genetic association between the SLC6A4 gene and a propensity to develop OCD, their results were not statistically significant. However, when the authors stratified their sample by sex, they did find significant results for genetic association between a particular variant of the SLC6A4 gene and OCD in females. These results suggest that a genetic predisposition for developing OCD may be gender specific.

In their article, Pauls & Alsobrook (1999) suggested that genetic association studies were the final piece necessary to complete the etiologic puzzle of OCD. Since their article came out, several candidate gene studies have been published, yet no conclusions have been reached. Shugart and colleagues (2006) found evidence of linkage on several chromosomes but produced no statistically significant results due to the large scope of their study and the lack of statistical power in their results. Wang and colleagues (2009) targeted a single candidate gene and found statistically significant results. Voyiaziakis and colleagues (2011) conducted a similarly targeted genetic association study on the gene which codes for 5-HTT. They did not find statistically significant results overall, but did when the results were stratified by gender. Taken together these three studies suggest that future research must take a more targeted approach in searching

for OCD candidate genes, and that genetic association may be affected by other factors such as gender.

### **Genetic Summary**

The studies reviewed in this section provide evidence for a genetic predisposition to develop OCD in addition to linking the genes implicated in the etiology of OCD with the neurochemical dysfunction they are responsible for. Early studies investigated the inheritance of OCD by looking at cases where the disorder ran in families and twins. Another relevant line of research investigated white matter abnormalities in the brains of patients with OCD and searched for the genes responsible for these abnormalities. Finally, recent studies have taken advantage of new developments in genotyping technology to narrow down the search for potential candidate genes for OCD to a select few. These recent studies, which scanned the genome for specific genetic loci implicated in the etiology of OCD, provide hope for future research that the exact genes responsible for the disorder will be located and could hopefully be corrected for.

### **Genetic Critique**

The studies reviewed in this section present evidence that genetics has come a long way in the past couple decades. Early research concerning inheritance of OCD focused on family and twin studies which provided evidence through statistical analysis that OCD was very likely inheritable. While these studies were useful, they could only move the field further to a certain extent. By nature of their design, they lacked the ability to definitively pinpoint the genes responsible for this inheritance and thus were studies describing a problem with no solution as to how to fix it.

The early studies reviewed concerning white matter abnormalities were able to detect differences in white matter in the brains of OCD patients compared with healthy controls. Later

studies were able to determine a more exact nature and direction of these differences. More recent studies concerning white matter examined the gene responsible for regulating white matter (OLIG2) and found that OCD patients were predisposed to be polymorphic for the OLIG2 gene. The final and most recent white matter study reviewed conducted genotyping and MRI scans in order to determine that OCD patients not only were polymorphic for the OLIG2 gene but that they also exhibited the reduced white matter volume. Each successive study cited in this section built on the research of the last and improved it in a qualitative way. As MRI technology improved, researchers were able to more specifically describe the nature and direction of the white matter abnormalities. Innovation in genetic linkage allowed researchers to locate the gene responsible for regulating white matter, suggesting a possible candidate gene in the etiology of OCD. As technology improves even more, new studies will surely crop up elucidating the role these white matter abnormalities play in patients with OCD.

Recent genetic association studies reviewed have attempted to find the specific genetic loci responsible for the development of OCD. Shugart and colleagues (2006) conducted the first genomewide scan for linkage but because of the broad scope and low statistical power of their study, they failed to find any significant evidence of linkage. Wang and colleagues (2009) conducted a study targeting the COMT gene and did find statistically significant results linking this gene to OCD. Voyiaziakis and colleagues (2011) used the same sample as Shugart and colleagues (2006) to conduct a study targeting the SLC6A4 gene which codes for 5-HTT. They did not find statistically significant results overall but did find significant evidence of genetic linkage when the results were stratified by gender. These three studies represent the first attempts to pinpoint the gene or genes responsible for the etiology of OCD. While these studies were too broad to provide hard evidence of linkage, they identify several genetic loci which warrant

further investigation in the search for candidate genes for OCD. Future genetic association studies need to take a more targeted approach, taking into consideration the pitfalls of the current research such as small sample sizes and limited statistical analyses. While they did not find the definitive answers that Pauls and Alsobrook (1999) anticipated from genetic association studies, they do suggest that future research in genetics will be able to discern the gene or genes implicated in the development of the disorder.

## Chapter Four

### The Convergence of Genetic and Neurochemical Underpinnings of OCD

#### 5-HTT Gene and Polymorphisms

Much of the research I have reviewed so far has investigated the etiology of OCD from either a genetic or a neurochemical standpoint. Several recent studies have explored both of these routes simultaneously by examining the relationship between serotonergic candidate genes and 5-HT dysfunction in the etiology of OCD (Denys et al., 2006; Lin, 2007; Grados et al., 2007; da Rocha et al., 2008; Liu et al., 2010). Denys and colleagues (2006) conducted a study to genotype a group of OCD patients and healthy controls to look for polymorphisms in the chromosome promoter regions which code for 5-HTT, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub>. The authors chose these three promoter regions due to the demonstrated influence of the serotonergic system on the development of OCD. The authors did not find the strong correlations they expected; however, they did find an association between a higher frequency of the S-allele, associated with low expression of 5-HTT, in the 5-HTT promoter region in female OCD patients compared to female controls. They also found evidence that a variation on the 5-HT<sub>2A</sub> promoter region was associated with a positive family history of early onset OCD. These results, particularly the 5-HTT genotype result, further support the notion put forth by Voyiaziakis and colleagues (2011) that OCD may be genetically heritable, particularly among females. In addition it appears that there is more evidence that early onset OCD has a genetic component than later onset OCD.

Lin (2007) conducted a meta-analysis investigating the relationship between the 5-HTT gene polymorphism (5-HTTLPR) and OCD. He reviewed thirteen studies researching the association between genotypic frequencies and OCD. In his meta-analysis, Lin found that the SS genotype was associated with OCD but the LS genotype had an inverse association with OCD

suggesting a genetic protective effect. This makes sense in light of the finding that the S allele is associated with lower expression of 5-HTT whereas the L allele is associated with higher expression of 5-HTT. Overall, Lin found a significant correlation between the 5-HTTLPR and the OCD phenotype; however, specific variants of the 5-HTTLPR need to be studied in order to determine the exact nature of this correlation.

Grados and colleagues (2007) built on previous studies investigating the 5-HTTLPR as a potential candidate gene for OCD. The authors of this study used genotyping to determine the allelic frequency and genotype of a sample of OCD probands. They did not find the expected significant correlation between the SS genotype or the S allele frequency and OCD. They did find that the SS genotype was associated with anxiety and OCD to a small degree but not significantly. The authors of this study suggest that a far greater sample of OCD patients is required to have the statistical power necessary to determine whether 5-HTTLPR is correlated with OCD.

Da Rocha and colleagues (2008) suggest that the characteristic decision making impairment in patients with OCD could be explained through 5-HTTLPR's dysfunctional effect on serotonin reuptake in the OFC, frontal lobe region associated with executive function. In order to answer this question, the authors administered a group of OCD patients a series of cognitive decision making tasks, the most prominent being the Iowa gambling task (IGT). They genotyped each patient using polymerase chain reaction to magnify the 5-HTT promoter region. The authors found a significant association between 5-HTTLPR and decision making processes such that individuals in the higher expression group had fewer symptoms of anxiety and performed significantly better than the low expressing group on the IGT. In choosing the cognitive tasks as a measure of dysfunction, the authors hope to inspire the use of phenotypic

variables which are more concrete as opposed to clinical definitions of a disorder. The findings of this study combine the findings that the OFC is a brain region prominently implicated in OCD and that 5-HTTLPR is a genetic polymorphism commonly implicated in OCD. The authors took this connection one step further by examining the relationship that 5-HTTLPR had on the cognitive processes mediated by the OFC, leading to a potential new cognitive way of measuring OCD.

Liu and colleagues (2010) authored an article currently in press which examines the association of several potential candidate genes, including 5-HT<sub>2A</sub> gene and the COMT gene, to OCD in the genetically homogenous Chinese population. They genotyped a sample of 103 parent-child trios diagnosed with OCD and found a significant association between late-onset OCD and the 5-HT<sub>2A</sub> gene polymorphism as well as a significant association between early-onset OCD and the 5-HT<sub>1B</sub> gene polymorphism. The most significant finding of the study was linkage disequilibrium with OCD in the 5-HT<sub>2A</sub> polymorphism. This finding suggests that the presence of the 5-HT<sub>2A</sub> polymorphism is significantly associated with late onset OCD.

All of these recent studies suggest a connection between genetics and serotonergic dysfunction as the key to understanding the development of OCD. These studies built on previous research investigating heritability of OCD as well as studies examining serotonergic dysfunction as a potential cause of the disorder. The logical next step in research was to look into specific serotonergic candidate genes for OCD. Denys and colleagues' (2006) study examined three candidate genes, 5-HTT, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub>, all regions which previous research had implicated in the pathology of the disorder. These authors found associations between low expression of 5-HTT as well as 5-HT<sub>2A</sub> and OCD. The results of da Rocha and colleagues (2008) and Lin (2007) support the idea that the 5-HTTLPR is associated with OCD and the results of



Liu and colleagues (2010) support the notion that the 5-HT<sub>2A</sub> is associated with OCD. I find it interesting that the Denys and colleagues (2006) finding that the 5-HTT polymorphism is associated with OCD in females is further supported by Voyiaziakis and colleagues' (2010) finding. In addition, the results of two of these studies conflict in that Denys and colleagues (2006) found that the 5-HT<sub>2A</sub> polymorphism was associated with early onset OCD whereas Liu and colleagues (2010) found that the 5-HT<sub>2A</sub> polymorphism was associated with late onset OCD. I do not think that these conflicting findings indicate that both are on the wrong track; instead I propose that the fact that these authors are finding associations between these candidate genes and OCD indicate that some relationship does exist and further research must be conducted to elucidate the nature of this relationship.

## Chapter Five

### Integrated Summary and Critique

In writing this review, my goal was to address the question of what the neurochemical and genetic underpinnings of OCD are. In order to answer this question I reviewed literature on the neurochemicals commonly implicated in OCD as well as literature on the genetic underpinnings of the disorder. In searching for these topics, I came across literature which examined both of these topics simultaneously by investigating the particular genetic loci which may code for the neurochemical dysfunction implicated in OCD.

The bulk of the neurochemical research on OCD suggests that dysfunction in the serotonergic system is to blame for the development of the disorder. Some studies suggest a role for dopamine in the etiology of OCD (Kim et al., 2007; Olver et al., 2009). However, these studies indicate that the dysfunction in dopamine present in the striatum of patients with OCD is modulated by the amount of serotonin present, suggesting that the source of this neurochemical dysfunction lies in the serotonergic system.

As is the case for most psychiatric medication, SSRIs were discovered to effectively reduce OCD symptoms before researchers had determined what caused the disorder in the first place or why SSRIs worked. Research into the pharmacological action of SSRIs indicated that they exerted their anti-OCD effects by increasing the amount of serotonin in the synapse leading researchers to investigate serotonergic dysfunction as a potential underpinning of OCD. However, SSRIs essentially bomb the brain with serotonin which means that there are many different mechanisms through which an increase in serotonin leads to a reduction in OCD symptoms. El Mansari & Blier (2006) report that in order to increase the amount of serotonin in the synapse, SSRIs actually desensitize the 5-HT<sub>1A</sub> receptor but not the 5-HT<sub>2A</sub> or 5-HT<sub>2C</sub>

receptors indicating that the anti-OCD effects of SSRIs could be a result of activation of the postsynaptic 5-HT<sub>2</sub> receptors, receptors which are also implicated in the effects of hallucinogenic drugs such as LSD and psilocybin.

Further evidence of serotonin's role in the etiology of OCD comes from studies investigating the effects of 5-HT<sub>2</sub> agonist hallucinogenic drugs on OCD. Zghoul and Blier (2003) found that LSD had an enhancing effect on OFC neurons' responsiveness to serotonin in rodents. This finding links the research of Rauch and colleagues (1994) who name the OFC as part of the OCD worry circuit with previous SSRI research implicating a dysfunction of serotonin as a potential underpinning of OCD. LSD reduces OCD symptoms through enhancing OFC neurons' responsiveness to serotonin. The drug's role as a 5-HT<sub>2</sub> agonist suggests that this receptor is implicated in the development of the disorder. Moreno and colleagues (2006) found that the administration of psilocybin had a statistically significant reduction in patient's OCD symptoms and that patients tolerated the procedure well. Taken together, the results of these studies suggest that the anti-OCD effects exerted by these hallucinogenic drugs implicate the 5-HT<sub>2</sub> receptors specifically and that novel OCD medication might target these receptors to produce more beneficial effects with a faster onset.

There is a substantial body of evidence provided by recent research which implicates 5-HTT dysfunction in the etiology of OCD. Technological advances in MRI technology have allowed researchers in several studies to investigate the nature and direction of 5-HTT dysfunction as measured by SPECT (Stengler-Wenzke et al., 2004; Hasselbalch et al., 2007; Zitterl et al., 2007; Matsumoto et al., 2010). All of these studies found that 5-HTT dysfunction in various brain regions were associated with OCD. The findings were not completely consistent between studies. However, the fact that all of these studies found significance in some brain

region indicates a potential connection between 5-HTT dysfunction and OCD. Future research must be conducted to determine the exact nature and directionality of this relationship.

Research on the heritability of OCD began with twin and family studies, most notably Clifford and colleagues (1984). While Clifford and colleagues (1984) were the first to identify this familial trend, their study paved the way for research investigating environmental factors (Van Grootheest et al., 2007; Wilcox et al., 2008). Recent research on the inheritance of OCD has also suggested that certain clusters of symptoms may be more heritable than the disorder itself (Hasler et al., 2007). Finally, Katerberg and colleagues (2010) found that OCD in general, as well as certain symptom dimensions of the disorder are heritable, and that the genes responsible for the heredity of the disorder as a whole are different from those genes responsible for certain clusters of obsessive-compulsive symptoms. Taken together, these studies provide a strong case that OCD runs in families and that the exact nature of this inheritance may be more complex than originally conceived. Further research on heredity is necessary however, as Pauls & Alsobrook (1999) pointed out, this research will most likely come in the form of genetic association studies to search for the specific genes responsible for the disorder.

Abnormalities in the white matter (myelinated axons) of the brains of patients with OCD have been discovered by several researchers. Garber and colleagues (1989) were the first to identify differences in the white matter in the MRI scans of OCD patients compared with healthy controls. Jenike and colleagues (1996) furthered research on this topic by identifying the postero-inferior pericallosal, retrocallosal, and cerebellar regions of the brains of OCD patients as being deficient in white matter compared with brains of healthy controls. Szeszko and colleagues (2005) and Nakamae and colleagues (2008) used an MRI technique called DTI to better measure the nature and direction of these abnormalities and found poor diffusion in brain

regions associated with OCD. Stewart and colleagues (2007) investigated the OLIG2 gene, which codes for oligodendrocyte which is responsible for producing white matter. They found the suspected polymorphism in the OLIG2 gene in a sample of patients with OCD, suggesting that this gene may be responsible for the development of these white matter abnormalities which may lead to the development of the disorder. Finally, Atmaca and colleagues (2010) conducted a study which consisted of genotyping a sample of OCD patients to determine whether they had the OLIG2 polymorphism and using MRI techniques to identify the white matter abnormalities themselves. Taken together these studies provide a body of evidence suggesting that patients with OCD exhibit characteristic deficiencies in white matter and that the gene which codes for the protein which is responsible for these deficiencies may prove to be a potential candidate gene for the disorder.

New technology has allowed researchers to search with greater precision for specific genes which may be implicated in OCD. Shugart and colleagues' (2006) study consists of a genomewide search for specific genes which are linked to OCD. While they did find some evidence of genetic linkage on several chromosomes their results were not significant, most likely due to the lack of statistical power. The authors of this study nevertheless paved the way for researchers to further hone in on candidate genes for OCD. Wang and colleagues (2009) investigated the COMT to determine whether a polymorphism in this gene could be linked to the development of OCD. These authors did find a significant association between COMT and OCD. This finding is especially salient considering that COMT is responsible for regulating the amount of dopamine in the prefrontal cortex, a region associated with OCD. Voyiaziakis and colleagues (2011) took up where Shugart and colleagues' (2006) study left off by targeting one specific candidate gene, SLC6A4, the gene which codes for 5-HTT. While they did not find a significant

association in the overall sample, they did find a significant association when the results were stratified by gender. Female OCD patients were significantly more likely to have the polymorphic variant of the SLC6A4 gene than were healthy controls. This finding provides evidence for a gender division in the heritability of the disorder. The results of these three studies suggest that the search for potential candidate genes in the development of OCD will lead to answers in the etiology of the disorder. While these three studies do not draw definitive conclusions, they do provide hope in the search for an understanding of the genetics of OCD.

Research into the etiology of OCD primarily concerns itself with genetic or neurochemical underpinnings. However, perhaps the most promising studies into the development of the disorder investigate the point where these two areas intersect. Recent studies examining the convergence of neurochemical and genetic underpinnings in the form of the polymorphic serotonergic candidate genes provide a clear picture of the future of this research. Denys and colleagues (2006) studied the promoter regions for 5-HTT, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub> to search for an association between abnormal expression of these genes and OCD. These authors found an association between low expression of the 5-HTT and 5-HT<sub>2A</sub> genes and OCD. These results are further supported by the findings of Lin (2007) and da Rocha (2008) who found an association between the 5-HTTLPR and OCD. In addition, Liu and colleagues' (2010) results support the Denys and colleagues (2006) finding that the polymorphic 5-HT<sub>2A</sub> promoter region is associated with OCD. Grados and colleagues (2007) were the only one of these studies which did not find a significant association between serotonergic candidate genes and OCD. Nevertheless, they did find a slight correlation between the polymorphic 5-HTT promoter region and anxiety and OCD generally. Taken together, the results of these studies make a strong case suggesting polymorphisms in serotonergic candidate genes could potentially cause OCD. Future research

focusing on this convergence of genetics and neurochemicals which are responsible for OCD is necessary to fully elucidate the mechanisms behind this dysfunction. However, these studies provide promising results which aid our understanding of potential underpinnings of OCD.

Of all the studies I have reviewed in this project, the serotonergic candidate gene studies offer the strongest evidence that this line of research may ultimately lead to answers regarding the etiology of OCD. These studies represent a convergence of neuroscience and genetics which seek to identify particular regions along chromosomes which are polymorphic in patients with OCD. Patients who exhibit these polymorphic regions have an abnormally low expression of 5-HTT and 5-HT<sub>2A</sub>. This low expression of serotonin is associated with OCD symptoms as evidenced by the beneficial effects of 5-HT<sub>2</sub> agonist hallucinogenic drugs on patients with OCD. Judging by the limitations in the findings of several studies, the genetic predisposition for 5-HT polymorphic genes seems to be affected by factors such as gender: Denys and colleagues (2006) and Voyiaziakis and colleagues (2011) found that a 5-HTT polymorphism thought to be responsible for the development of OCD was significant only in female patients. Age of onset represents another factor affecting genetic predisposition for polymorphic genes: Denys and colleagues (2006) and Liu and colleagues' (2010) findings conflict about whether a 5-HT<sub>2A</sub> polymorphism was associated with either early or late onset OCD. While the exact manner in which these polymorphisms are linked with the etiology of OCD is uncertain, there is a substantial body of evidence that suggests that these polymorphic regions may turn out to be the genetic coding for the etiology of OCD.

These studies represent the closest that the fields of neuroscience and genetics have come to explaining the development of OCD. There are no definitive answers yet as to why this disorder develops. The results of these studies collectively suggest that OCD is a genetically

inheritable disorder and that the neurochemical dysfunction which is inherited is related to the serotonin system, more specifically the serotonin transporter and the 5-HT<sub>2</sub> receptors. While most of the studies I have reviewed focus on finding a biological basis for the disorder, some of these studies attempt to answer the question of whether more effective medication might be developed to help alleviate symptoms. El mansari and Blier (2006) investigated the pharmacological action of SSRIs, the current medication of choice for OCD, and found results which suggest that SSRIs may actually exert their effects by increased serotonin binding at the 5-HT<sub>2A</sub> receptor, the same receptor activated by hallucinogenic drugs such as LSD and psilocybin which are known to rapidly reduce OCD symptoms. Denys and colleagues (2006) and Liu and colleagues' (2010) finding that a polymorphic variant of the gene which codes for the 5-HT<sub>2A</sub> receptor was associated with OCD further supports this notion that the 5-HT<sub>2A</sub> receptor is implicated in the behavioral symptoms of the disorder. Together these studies suggest that novel medication, which specifically targets the 5-HT<sub>2A</sub> receptor, may prove to be the future of faster acting, more effective treatment for OCD.

### **Limitations**

In attempting to answer the question what are the neurochemical and genetic underpinnings of OCD, I chose to conduct a literature review. While I was able to draw some conclusions about the neurochemicals and genes potential implicated in the development of OCD, my review lacked the weight of an empirical study and the statistical power of a meta-analysis. I chose to describe the state of current research on OCD in order to gain a better understanding of this topic myself, and to hopefully draw some conclusions about where the future of this line of research lies. By researching both the serotonergic imbalance associated with OCD, and the candidate genes currently thought to code for the disorder, I was able to



articulate not only which genes are implicated in OCD, but also why they lead to the development of the disorder through neurochemical changes. While I may not have come up with any definitive answers to this question, I have identified the state of the research on this topic and predicted where the future of this investigation may lead.

### **Future Research**

Future research into the biology of OCD is necessary in order to find solutions to issues brought up in the studies in this review. The future of neurochemical research into the etiology of OCD needs to be able to identify the exact serotonergic imbalance which SSRIs correct. Because of the beneficial effects of 5-HT<sub>2A</sub> hallucinogens on OCD patient's symptoms, I suggest that the 5-HT<sub>2</sub> receptor system is that mechanism. I think that these receptors need to be investigated further in order to understand why hallucinogens exert this therapeutic effect. Ideally, the beneficial effects of hallucinogens could be harnessed for their therapeutic value without the added cognitive confusion caused by these drugs. Additionally, the serotonergic imbalance seems to be caused at least in part by a dysfunction of the serotonin transporter. Future research needs to identify ways in which this imbalance can be corrected in a more efficient manner than OCD medication currently on the market. Ultimately, future research into this topic should yield results in the form of newer, more effective medication for patients with OCD.

Most of the limitations in the reviewed genetic studies are a result of researchers casting too small or too large of a net. Some candidate gene studies tested for only one specific polymorphism whereas other studies conducted a genomewide search for abnormalities, and lacked the power to say definitively whether any one specific polymorphic region was significantly associated with OCD. While these broad searches for genetic linkage are useful for identifying several regions which exhibit some association with obsessive behavior, future

research must take the results of these genomewide scans and conduct more focused studies with greater statistical power in order to determine whether the polymorphic regions identified by the broader studies are indeed significantly associated with the etiology of OCD. Once future research has identified the gene or genes responsible for the development of the disorder, medical professionals will be able to predict with great accuracy whether an individual is at risk for OCD. This knowledge could dramatically shift the way society views the disorder, from stigmatization to acceptance as a medical illness with a biological basis.

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