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The Neuroanatomical Functions of Tourette Syndrome and a Treatment Analysis

Kacie L. Curd
Claremont McKenna College

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THE NEUROANATOMICAL FUNCTIONS OF TOURETTE SYNDROME AND A TREATMENT ANALYSIS

SUBMITTED TO

PROFESSOR CATHERINE L. REED

AND

DEAN GREGORY HESS

BY

KACIE L. CURD

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The Neuroanatomical Functions of Tourette Syndrome and a Treatment Analysis

Kacie L. Curd

Claremont McKenna College

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Abstract

The etiology of Tourette syndrome has been elusive for researchers ever since its discovery, making treatment especially difficult. After proving the disorder was organic in the second half of the 20th century, researchers have been creating theories of the underlying neural basis for Tourette's symptomatology. These theories include abnormalities in brain structure, dysregulation of the dopamine system, dysregulation of the serotonin system and overall neurotransmitter system interactions. The etiology is likely a complex combination of all of these. Treatments for this disorder include pharmacological, behavioral and surgical. I believe the best approach for treatment is behavioral first, followed by pharmacological if behavioral does not work, and then surgical as a last resort if the previous two do not show results.

THE NEUROANATOMICAL FUNCTIONS OF TOURETTE SYNDROME AND A TREATMENT ANALYSIS

The words Tourette syndrome[1] have an immediate effect on most people, conjuring images of people running around screaming profanities and making awkward and obscene motions. However, these individuals are considered to be severe Tourette's[1] patients and make up only a small portion of the Tourette's population. Many people who have the disorder exhibit minor symptoms that others rarely notice and are considered mild Tourette's patients. The national branch of the Tourette Syndrome Association in the United States estimates that as many as 200,000 people in the Unites States are known to have the disorder, but there are many more cases that go undiagnosed ("Facts About," n.d.). Males are 4 times more likely to have the disorder than females and some studies have suggested that 5 out of every 100 boys are afflicted (Kushner, 1999). These individuals are mothers, fathers, daughters and sons. They are teachers, scientists, musicians and pro athletes. They are Christians, Jews, Buddhists and Atheists. Currently, there is debate regarding the etiology of Tourette's. Generally, Tourette's is said to be a hereditary disorder, meaning it has to be inherited from a parent. Genetic studies have indicated that the gene for Tourette's is dominant, so the child has a 50% chance of getting it if a parent has it ("Facts About," n.d.). On the other side though, there has been some evidence that suggest Tourette's can be caused by pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, or PANDAS. In this case, the symptoms would be caused by a body's post-infectious autoimmune response to strep (Harris & Singer, 2006). Whatever the cause, Tourette's has affected people from

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[1] Generally in the literature, Tourette syndrome is spelled with a capital "T" and a lower case "s," and Tourette's is spelled with an apostrophe "s"

every race and ethnicity ("What is," n.d.). Yet, many people wonder whether Tourette's funny noises and random movements really are involuntary? Could an organic source really be behind it all?

In a word, yes. Generally, signs of Tourette syndrome show up between ages 5 to 9. In order to be diagnosed with Tourette's, both motor and vocal tics must be present. Often misspelled as "ticks," the medical term for the movements or sounds people make is "tics". Tics can be anything from high-pitched squeals to violently punching the air, however, most tic behavior is far less severe. In some individuals, tics can be so subtle that many would not even notice unless they knew what to look for. Motor tics generally include "head and neck jerking, eye blinking, tongue protrusions, shoulder shrugs, and various torso and limb movements," while vocal tics can involve "barks, grunts, yelps, and coughs" (Kushner, 1999, p. 3). Not only can ticcing be a source of embarrassment and teasing, but it can also be painful and debilitating; "for instance, aside from the muscle strain caused by severe head-jerking, tics can make reading an arduous, if not impossible task" (Kushner, 1999, p. 3).

Tics are involuntary. This means that the person experiencing a tic cannot control the movements or sounds they are making. Tics are preceded by a feeling of discomfort and an uncontrollable urge to tic, which is relieved as soon as the person completes the tic. Many patients with mild Tourette's, however, perceive the tic as voluntary and will often try to suppress the urge. While they can be successful in this temporarily, the tic will almost always eventually come out. In fact, the suppression of tics only increases the tension and discomfort a person feels and the only way to relieve this feeling is with an increased outburst of tics ("Definitions and Classification," 1993).

While the symptoms of the disease are outlined in the Diagnostic and Statistical Manual of Mental Disorders IV, Tourette syndrome can still be difficult to identify. Not only is the etiology unknown, there is no blood test that can be administered to determine a diagnosis, only observations of a patient's symptoms. This can be much more complicated than it sounds, though, because Tourette's has many co-morbid diseases that can come in any combination, or not at all. Obsessive Compulsive Disorder, Attention Deficit Hyper Disorder, and Bipolar Disorder are a few of the many other afflictions a person with Tourette's can have. Other problems such as severe sleep problems and depression are also quite common in patients ("What is," n.d.). Because a diagnosis is so challenging, many cases of Tourette's are either missed or misdiagnosed. Another reason for this is that many physicians, other than neurologists, would not automatically think of Tourette's, but instead may check for things like allergies or muscular disorders.

Along with a difficult diagnosis, Tourette syndrome is still a bit of a mystery in terms of why and how the disorder functions. Some of the neural bases are known, and will be further discussed in this paper, but there are still many holes that need to be filled. This, obviously, makes medication and treatment for the disorder very difficult. There are no medications specifically designed for Tourette's; instead, physicians prescribe drugs generally used for other disorders such as ADHD or schizophrenia. Non-drug treatments include things like relaxation and habit retraining. There are pros and cons to each treatment option. I will address the current treatment choices as well as explore new and different ones that may be more beneficial.

History of Tourette Syndrome

The most famous and most referenced historical case is that of the Marquise de Dampierre. The Marquise was a noblewoman in 19th century France who was notorious for her obscene public outbursts. In 1825, the chief physician at l'Institution Royale des Sourds-meuts, Gaspard Itard, described her case in *Archives Générales de Médecine* as such:

> In the midst of a conversation that interests her extremely, all of a sudden, without being able to prevent it, she interrupts what she is saying or what she is listening to with bizarre shouts and with words that are even more extraordinary and which make a deplorable contrast with her intellect and her distinguished manners. These words are for the most part gross swear words and obscene epithets and, something that is no less embarrassing for her than for the listeners, an extremely crude expression of a judgment or of an unfavorable opinion of someone in the group. The more she was revolted by a word's 'grossness,' the more she is tormented by the fear that she will utter them, and this preoccupation is precisely what puts them at the tip of her tongue where she can no longer control it (Itard, 1825 cited in Kushner, 1999, p. 11).

For almost 100 years, the Marquise's symptomatology has been used as a perfect example of Tourette's, but in the early 1800's, it ignited speculation from physicians and philosophers alike throughout Europe. After Itard's article was published, physicians and philosophers from all different concentrations began citing the Marquise's case as evidence of their own pet theories for the etiology of a subset of these symptoms. Yet, none of them had ever actually examined the Marquise themselves. Itard, for his part,

believed that an “underdeveloped will” was the cause of all women’s tics. At the time, he had in his care seven men and two women all troubled with the same tic symptoms. However, he believed the men’s tics were brought on by some organic cause, while the women merely had weak wills. He believed the Marquise was unhappy in her domestic life, leading to a weak will and thus all her strange behaviors. For the two women he treated, in addition to the other cures of the time such as leeches and chicken soup, Itard focused on treatments in morality. He felt that their uncontrollable tics were the result of the women not devoting themselves to their roles of women and mothers. He treated the two women with these moral treatments and stated that after a short time, they were completely cured. The Marquise, however, was not given over to his care. Itard was upset, asserting that he could have completely cured her had she been put through the same treatment as the other two women (Kushner, 1999).

Sixty years after Itard’s article about the Marquise was published, another top physician in France, Jean-Martin Charcot, examined her. One of Charcot’s pupils of the time was a man named Georges Gilles de la Tourette who was a neurologist and had some past experience with ticcing patients, as well as a general interest in the phenomena. At Charcot’s instruction, Gilles de la Tourette examined ticcing patients in Charcot’s clinic and organized their cases for publication. In 1885, Gilles de la Tourette published his two-part study, titled “Study of a Nervous Affliction,” in which he established a prognosis based on twelve patients. Charcot immediately renamed the tic disorder “Tourette syndrome” in honor of Gilles de la Tourette, as it is known today. Gilles de la Tourette selected the case of the Marquise de Dampierre as his first example in the “Study of a Nervous Affliction” and classified the disorder as “maladie des tics” (tic

maladies), even though he had never before met or examined her. He described the "maladie des tics" as a chronic disease beginning in childhood in which children progress from motor tics to vocal tics and finally to cursing. He stated that it was "both progressive and hereditary; it might wax and wane, but ultimately resisted all interventions" (Kushner, 1999, p. 23). The only patient that accurately fit this description, though, was the Marquise. All his other clinical cases deviated in some way from his description, whether it was an absence of vocal abnormalities or tics almost entirely disappearing a year or two after he examined them. Thus, Charcot and Gilles de la Tourettes' assertions were greatly challenged, and many instead saw Tourette syndrome not as its own disorder, but merely on a continuum with other movement disorders (Kushner, 1999).

Some colleagues of Charcot and Gilles de la Tourette classified the patients' ticcing behavior as a form of hysteria, but numerous others thought it was a form of chorea (a neurological disorder that causes involuntary, jerky movements), which were thought to be the consequence of contracting rheumatic fever. A neurologist named Georges Guinon erected particularly convincing evidence against Gilles de la Tourette's theory that "maladie des tics" was its own disorder. Guinon argued that, due to their "common etiology in hereditary degeneration… compulsive behaviors, [that] had been ignored by Gilles de la Tourette… [as well as the fact that] severe cases [of hysterics] also exhibited the most florid symptoms of convulsive tic disorder," the symptoms were on a continuum and fit in with the diagnosis of hysteria (Kushner, 1999, p. 28). While Charcot and Gilles de la Tourette argued that hysterical patient's cursing outbursts could be easily cured through treatments like hypnosis while patients with "maladie des tics"

could not, Guinon argued that patients who displayed tics like echolalia (repeating what another person has just said) were acting like hypnotized hysteric patients. He also found evidence refuting Charcot's theory that "maladie des tics" and hysteria were completely separate disorders but could still exist simultaneously in a patient (Kushner, 1999).

Those in Charcot's circle thought the tics were a consequence of psychopathology. They believed that the patient's bizarre behaviors were a consequence of psychological degeneration that left the patients with underdeveloped higher cerebral functions. They became so dogmatic in their belief in psychopathology that they completely ignored data that could have raised other interesting explanations and explain away contradictory evidence instead of considering it. The researchers came across many cases that suggested that the tics might be caused by a previous bacterial infection of the patient, but that would have required rethinking their hypothesis, and they were unwilling to do that (Kushner, 1999).

Charcot and Guinon, as well as many of Charcot's colleagues, disputed the matter until Charcot's death in 1893. By this time, the symptomatology defining Tourette syndrome was blurring further. Practitioners were in great need of some uniform, comprehensive diagnosis guidelines, and in 1902 (translated into English in 1907) Henry Meige and E. Feindel did just that in their study *Tics and their Treatment*. This became the bible for motor and vocal tic disorders for the next 50 years. Meige and Feindel rejected Gilles de la Tourette's boundaries for the disorder and instead endorsed a psychopathological cause that meshed well with both degenerative inheritance as well as Sigmund Freud's early childhood repressive sexual conflicts. Like others before them had with the Marquise de Dampierre, Meige and Feindel came up with their etiology before

examining patients. They found a person who fit their criteria for patients with compulsive tics and used him as the prime example in their study. This patient, simply called "O.," wrote a very eloquent memoir called *The Confessions of a Victim to Tic.* Meige and Feindel edited and annotated the memoir as the opening for their study, and destroyed O.'s extremely articulate and insightful information on his own disorder. Using their previously created etiology, Meige and Feindel went through the memoir and noted places where they felt O. had a weak will or degeneration by regressive infantile behavior or other behavior that fit with their assumptions. *Tics and their Treatment* formed the basic assumptions held by both American and European practitioners about tics until the 1960's (Kushner, 1999).

During the time from the early 1900's to the 1960's, there were still many physicians with conflicting views. In 1921 a Hungarian psychoanalyst named Sandor Ferenczi analyzed tics in a purely psychoanalytic view. His views were updated by another psychoanalyst named Margret Mahler in the 1940's for a new generation of psychiatrists. Mahler allowed for an organic role, but still maintained that organic causes were merely a starting point and that tics would not present if there were no psychic conflicts to accompany them. Mahler said that tics were the last defense of the mind against psychosis and went so far as to say that some patients with tics became psychotic at the age of puberty. Yet, there were still many critics that cited physiological, organic causes for tics. For example, a worldwide epidemic of encephalitis (i.e., swelling of the brain) in the 1920's led to many cases of tics being observed as a sequel to the infection. Also, many cases were found that removal of infected areas such as the tonsils or sinuses presented with relief of tics for the patients. However, during World War II, most of the

psychoanalysts views were moved from central Europe to the United States, Canada and Britain, leaving the organic proponents very isolated for that time. Thus, after the war was over, the psychoanalysts in the United States and Canada saw the organist's views as highly suspicious because of the possible Nazi influence it could have had during of the war. Psychosexual conflict was upheld as the reason for tics even in the 1960's when drugs like Haloperidol, which is an antipsychotic that inhibits dopamine transmissions in the movement areas of the brain, or drugs used as antidepressants today, effectively suppressed tics (Kushner, 1999).

Though the psychoanalysts did not give it much notice, the organic view was finally emerging with more evidence in the late 1950's. Many neurologists were finding damage in the basal ganglia structures, found mostly in autopsies, that was prevalent in many people with tic disorders. They also found that the number of cells in the striate cortex of patients with tics were intact but much smaller than normal cells. This was opposed to the normal size of cells but greatly reduced number of them found in patients with chorea. This effectively separated the tic disorder as its own disease rather than on a continuum of chorea. Very slowly, North American practitioners began changing their views to organic positions due to medical interventions showing tic improvement, which included brain surgery (lobotomies) and the use of various medications (Kushner, 1999).

In 1975, an American mother of a 9 year-old boy suffering from tics came across an article on Tourette syndrome in *Today's Health*, a medical magazine. Her son had been suffering from both motor and vocal tics and had been going to a psychiatrist three times a week, which was straining the family's expenses. The mother demanded why she had not been told about Tourette's and the psychiatrist claimed that he had thought her

son might suffer from the disorder, but he was convinced her son's tics had to do with an underlying emotional disturbance instead. Seeing that the Tourette Syndrome Association was close to where she lived, the mother quickly took her son there, had him diagnosed with Tourette's by Dr. Arthur K. Shapiro, and put on Haloperidol. Her son's tics soon disappeared and her story was run in the magazine *Good Housekeeping* in 1976. Soon after, stories just like her son's showed up in periodicals such as *The Wall Street Journal*, *The New York Times* and *The New York Daily News*, which could all be traced back to the mother's article in *Good Housekeeping*. Dr. Shapiro and his wife, Elaine S. Shapiro, were instrumental in providing evidence that Tourette syndrome is an organic disorder and claimed that psychiatric treatments were more harmful than helpful. Their publications of successful results in treating Tourette's with Haloperidol (though doses that were too high produced movement effects like those seen in Parkinson's disease) was covered extensively by the media and led to the formation of the Tourette Syndrome Association (TSA). In 1980, TSA published vast materials aimed at educating doctors, patients, families, teachers, and other professionals on the disorder. The TSA also funded many studies of Tourette's with the donations it received and was extremely influential in advocacy in many areas, including educational legislation and support for continued production of certain drugs. The TSA was crucial in expanding public awareness of Tourette syndrome and its organic causes, and continues to do so today (Kushner, 1999).

In summary, even though a full understanding of Tourette syndrome and what causes it is still relatively unknown, it is clear that physicians and neurologists have come a long way from explaining its etiology as a lack of morality and willpower. The TSA is still important for public education, advocacy and support, and there are now multiple

chapters of the TSA throughout the United States. Although there are still some that would argue that Tourette's is psychogenic, resulting from a psychological cause instead of a physiological one, they are very few in number. There are also no longer any serious studies or treatments in North America that claim symptoms of Tourette's are present due to psychological problems.

Neuroanatomy of Movement

Tourette syndrome is primarily a movement disorder, and the first area of interest in the neuroanatomy is the basal nuclei. Recently, the names "basal ganglia" and "basal nuclei" have been used interchangeably. The basal ganglia is a group of structures in the medial midbrain that regulate most of the body's coordinated motion. A more in depth look shows that there are five nuclei that make up this structure. These structures are the caudate, putamen (these two are referred to as the striatum), globus pallidus, subthalamic nucleus and substantia nigra.

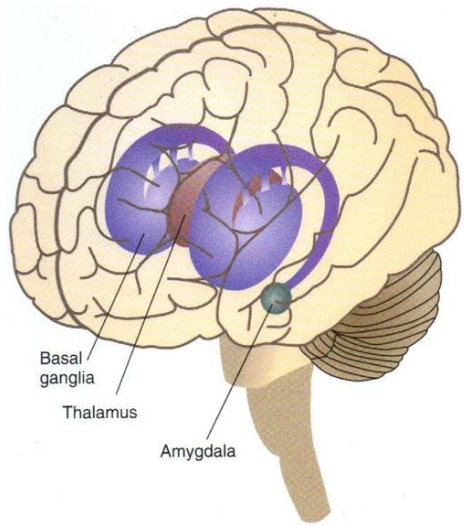

Figure 1. The Basal Ganglia ("Basic Brain," n.d.)

These structures work together, along with the thalamus, in a complicated network to produce movement. The striatum receives inputs from the cerebral cortex, including the sensory, motor and association cortices, as well as indirect thalamus projections. The basal ganglia's output is inhibitory with high base line firing rates in the globus pallidus and substantia nigra neurons. When the motor plan is forming, the basal ganglia inhibits the target neurons, and as the plan becomes clearer, the inhibitory signal decreases in select neurons

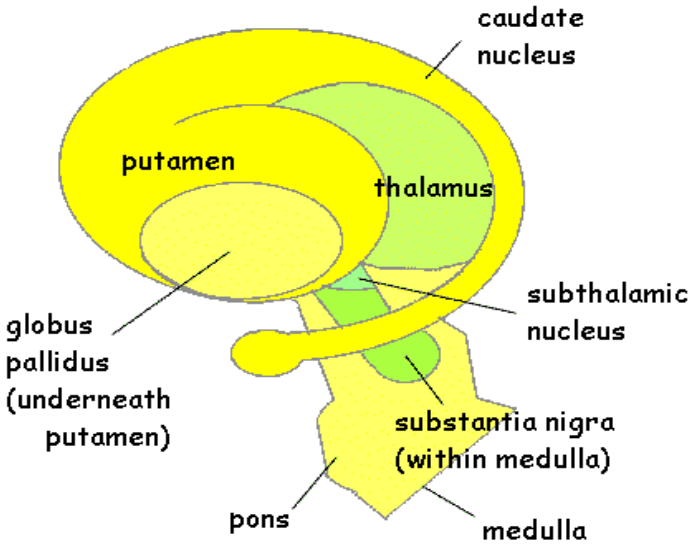

Figure 2. Basal Ganglia Structures (Boree, 2011)

until it is gone. Once the inhibitory signal is fully removed, movement occurs (Gazzaniga, Ivry & Mangun, 1998).

The internal basal ganglia processing, however, is more complicated. There are two pathways for processing from the striatum to the internal segment of the globus pallidus and the pars reticula of the substantia nigra, or output nuclei. These pathways consist of the direct pathway and the indirect pathway. As the name suggests, the direct pathway projects inhibitory signals from the striatum straight to the output nuclei. The inhibition of these output nuclei through the direct pathway creates excitation of the thalamus and cortical motor areas. The indirect pathway also connects the striatum with the output nuclei, but only via processing in the external globus pallidus and the subthalamic nucleus. Activation in the striatum through the indirect pathway creates increased activation of the output nuclei and thus increased inhibition of the cortical motor areas. The other important pathway in basal ganglia processing is from the pars compacts of the substantia nigra to the striatum. The pars compacta of the substantia nigra interacts with the neurotransmitter dopamine through two different dopamine receptors. In the first type of dopamine receptor, D_1, the substantia nigra

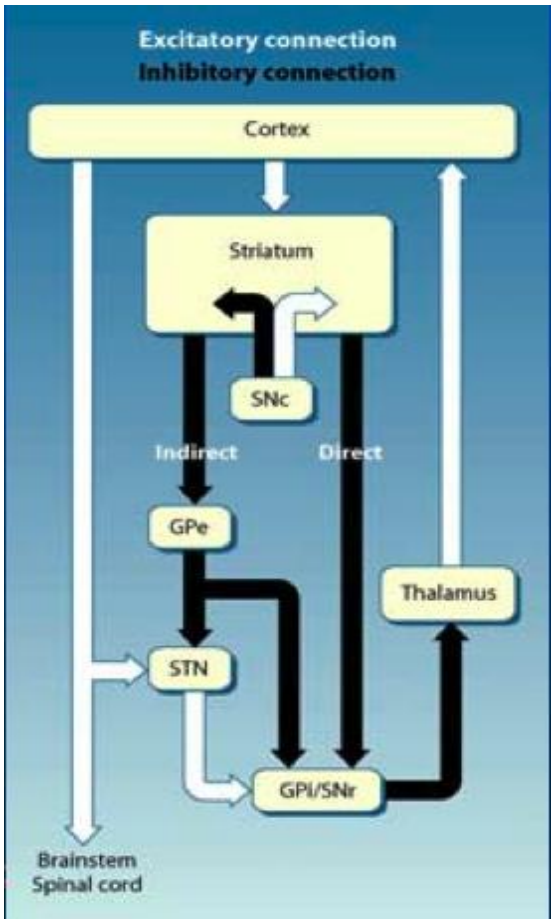

Figure 3. Basal Ganglia Wiring (Adapted from Wichmann and DeLong, Gazzaniga et al., 1998)

excites the direct pathway from the striatum, whereas in the second type of dopamine receptor, D_2, the substantia nigra inhibits the indirect pathway from the striatum (Gazzaniga et al., 1998).

The effects of disruptions in the basal ganglia can most clearly be seen in patients with Huntington's disease and Parkinson's disease. In Huntington's patients, the inhibitory signals from the striatum to the external globus pallidus is reduced, resulting in increased inhibitory signals to the output neurons and thus increased excitation in the cortical motor areas. This causes increased random, involuntary movement in patients and less coordinated movement. Parkinson's disease, on the other hand, is caused by decreased inhibitory signals in the direct pathway, resulting in increased inhibition from the internal globus pallidus to the thalamus and thus reduced excitation in the cortical motor areas. This causes reduced voluntary movement in patients and periods where they become "frozen" and unable to move, as well as resting tremors that vanish once the patient makes a voluntary movement (Gazzaniga et al., 1998).

The basal ganglia are the most important structures for movement, but there are other parts of the brain that are necessary for the process. The somatosensory cortex and motor cortex are regions that are also involved in movement. The somatosensory cortex is a narrow strip of cortex located posterior, or behind, the central sulcus and the motor cortex is narrow strip of cortex located anterior, or before, the central sulcus. Both the motor cortex and the somatosensory

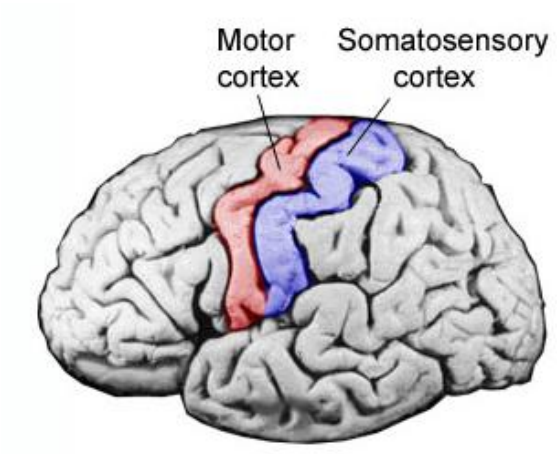

Figure 4. Motor and Somatosensory Cortices (Stenerson, 2001)

cortex have what is called a homunculus, which means “little man.” The homunculus is basically a map of the body in each of the cortices with each body part corresponding to a specific part of the narrow strips. The body parts, though, do not all get the same weight. So, for example, the lips and fingers have much larger spaces on the homunculus than do the calves or the elbows. That is why people feel things more acutely with their fingers than with their elbows. The motor cortex is involved in preliminary motor processing and planning and is also important for movement control, like in direction. The somatosensory cortex is also important in motor processing and planning, but it is more involved in transforming sensory information into appropriate movements (Gazzaniga et al., 1998).

The cerebellum is also involved in movement and regulates balance and posture. The cerebellum is a large structure located at the bottom of the brain, near the brain stem. The cerebellum receives widespread sensory information from areas including auditory, visual, vestibular, somatosensory and association areas in the cortex. It is extremely important in learning timing relationships between stimuli. This is so that the body can make the right movement responses and not be too early or too late in accordance with the stimuli. It is critical in distinguishing short time intervals, planning chronological aspects of movement and judging the velocity of objects in the environment. It is also important for movement fine-tuning (Gazzaniga et al., 1998).

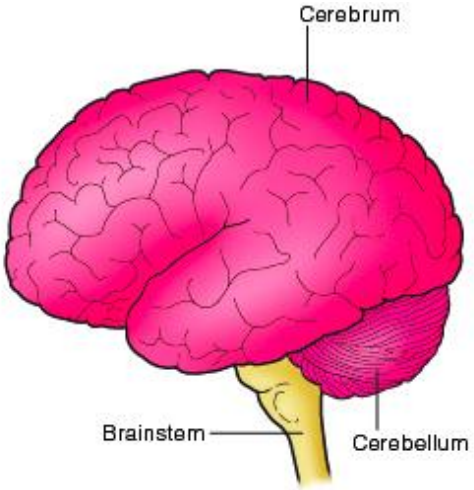

Figure 5. The Cerebellum (“What is a Stroke?,” 2011)

The thalamus and the hypothalamus combine to make the diencephalon. The thalamus is a medial structure in the brain that is like a relay station for sensory and motor information to the cerebral cortex. Signals come in and go out to their destinations constantly. For movement, outputs from the basal ganglia, specifically the globus pallidus, come into the thalamus and are then sent out to the motor and premotor cortex and the prefrontal cortex. Thus, the motor outputs do not come directly from the basal ganglia, but must go through a motor loop. This process is thought to help monitor motor and nonmotor behavior. The hypothalamus is located right under the thalamus and controls the functions for homeostasis. It is important in the automatic nervous system and endocrine system, and is also important in emotional processing (Gazzaniga et al., 1998).

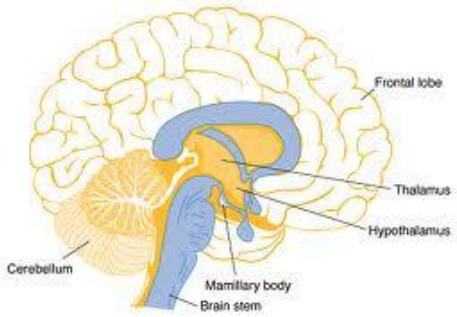

Figure 6. The Thalamus
("Thalamus – What is the Thalamus?," n.d.)

The insula, or insular cortex, is another region that has been suggested to be important in recent Tourette's research. The insula is a part of the brain located directly beneath the Sylvian fissure. It has been associated with attention (Gazzaniga et al., 1998) and especially active with adverse emotions like disgust. The insula is very important in experiencing emotions as well as memory of procedures. It is involved

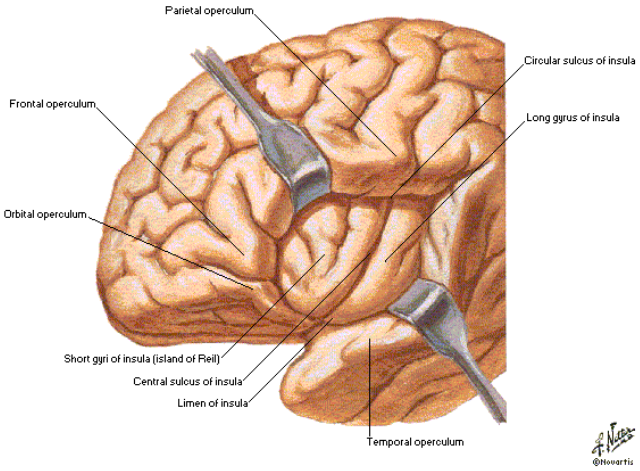

Figure 7. The Insula
("Cerebellum - Insula," n.d.)

in bodily sensations like feeling pain and is even activated when seeing others in pain. As for movement, the insula is necessary for motor control like eye movement, swallowing and speech (Moss, 2009).

The amygdala is a medial brain structure that is part of the limbic network (discussed further below). This is the part of the brain that is generally associated with emotion. It is important in the providing the emotional aspect to memories. It is also important for feelings of anxiety (Gazzaniga et al., 1998). Also, it has been found that the amygdala is extremely important in distinguishing threats and fear. When the amygdala is lesioned, people have trouble distinguishing threats and therefore will not be afraid of things they should be afraid of, which can lead to them getting hurt or into trouble (Canteras, Mota-Ortiz & Motta, 2011).

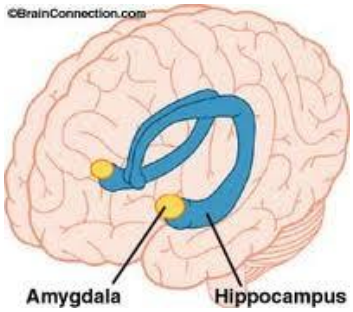

Figure 8. The Amygdala ("The Amygdala," n.d.)

The brain has three general networks for movement. These are the sensori-motor network, the limbic network and the association network. The sensori-motor network is composed of the somatosensory and motor cortices, the cerebellum, and basal ganglia. The limbic network is an interconnected network and is composed of the amygdala, hypothalamus, thalamus, cingulate gyrus and the basal ganglia. The limbic network is also involved in memory, learning and emotional processing. The association network is composed of the other structures that are important for movement but not necessarily directly involved in movement, such as the visual cortex, auditory cortex and prefrontal cortex, in connection with the basal ganglia (Gazzaniga et al., 1998).

Neuroanatomical Functions of Tourette Syndrome

The etiology, or underlying neural bases, of Tourette syndrome symptoms is not yet fully known, but researchers have proposed some plausible theories. Theories of how Tourette syndrome arises include atypicalities in the dopamine system, serotonin system, overall neurotransmitter system interactions, and chromosomal expressions. Each of these theories will be discussed in turn.

Generally, people think the symptoms present in reaction to a problem with the neurotransmitter dopamine. Some investigators believe that movement abnormalities associated with Tourette's is not a problem with the dopamine itself, but rather an abnormality in the connections within the striatum (Harris & Singer, 2006). The more widely held belief, though, is there is a dysfunction in the processing or production of the neurotransmitter dopamine.

Dopamine is produced in the substantia nigra by specific dopamine producing neurons that project to particular regions of the brain (for an overview of basic neuron physiology, see Appendix). It is essential for stimulus response movements and voluntary movements, as well as the brain's learning about and feeling rewards. Dopamine has two main patterns of release from the neuron, either tonic or phasic. Tonic dopamine is a very small amount that is kept inside the cell in order to maintain dopamine balance as well as regulate the postsynaptic receptors (dopamine receptors that are across the synaptic cleft). Phasic dopamine, on the other hand, is held in larger quantities in the cell and is the dopamine that actually crosses into the postsynaptic cleft to bind with the postsynaptic receptors. In some cases, it can escape from the cleft, which is what happens with drugs

like amphetamines because they block the postsynaptic receptors (Harris & Singer, 2006).

One theory regarding an underlying cause of Tourette syndrome symptoms identifies a problem with the tonic and phasic dopamine balances. Researchers hypothesize there is too little tonic dopamine so the postsynaptic receptors no longer have a proficient regulator and, as a consequence, are up-regulated. This means that the postsynaptic receptors cannot tell how much dopamine to release, so they end up releasing too much phasic dopamine. One possible reason for the decrease in tonic dopamine is that the dopamine transporter system is hyperactive causing lower amounts of dopamine that stay in the neurons instead of being pushed out, more dopamine in the axonal terminal branches, higher incidents of stimulus-dependent dopamine release, and over-sensitivity in the presynaptic dopamine receptors (the receptors before the synaptic cleft) (Harris & Singer, 2006).

Another possible theory for the symptoms associated with Tourette syndrome focuses on phasic dopamine. In Tourette's, the overly receptive phasic dopamine system is a modification of the cortical inputs that bring the information from sensory and receptor neurons to the brain. Whether the problem lies with phasic or tonic dopamine, the evidence of these dopamine abnormalities have been well documented and are supported by: a) the fact that stimulant medications increase tics because of increased releases of phasic dopamine, b) environmental causes like stress, anxiety and medications increase tics because these events and others like them increase bursts of phasic dopamine, and c) low doses of compounds that activate dopamine receptors without the

presence of dopamine show tic reduction because of decreased presynaptic release of phasic dopamine (Harris & Singer, 2006).

Graybiel and Canales (2001) performed a study on rats to observe these different types of dopaminergic transmissions. Stimulant drugs, such as cocaine and amphetamines, can be used to artificially create involuntary repetitive behaviors in both humans and animals, thus allowing rats to act as animal models for studying Tourette syndrome. Cocaine works by blocking dopamine reuptake, as well as two other neurotransmitters serotonin and norepinephrine, so there is an excess of dopamine that can possibly escape the synapses. Amphetamines, on the other hand, work by releasing an excess of dopamine. In animals, movement can be produced with a low level dose of the drugs, but higher dosages of the drugs produce involuntary repetitive behaviors, which are referred to as *stereotypies* in animal literature. The dose of the drug and the stereotypies are proportionally related, so as the dose increases, the stereotypies increase, and vice versa. Although these movements are artificially induced, they can provide valuable clues for involuntary repetitive behavior because the drugs also cause discriminable changes in gene expression in the basal ganglia and the cerebral cortex (Graybiel & Canales, 2001). By using different levels of the drugs to create different levels of stereotypies and then seeing how this changes the animal's gene expressions, Graybiel and Canales distinguished among possible neural correlates for involuntary repetitive behaviors: cocaine produced locomotor activity and head up movements in the rats, whereas amphetamines produced strong locomotion and head down movements (Graybiel & Canales, 2001).

Graybiel and Canales focused on the striatum in the basal ganglia because this area is responsively dependent on dopamine and serotonin receptors. The striatum has two separate compartments, the matrix compartment, which is larger and generates the direct and indirect dopamine pathways, and the striosomes, which are imbedded in the matrix and project directly to the substantia nigra. Thus, the matrix compartment is more involved in motor output and movement control, whereas the striosomes are more important in the reward signals that result from movement (discussed further below). In this study, Graybiel and Canales found amphetamines produced more pronounced stimulation in the striosomes, as well as higher levels of stereotypies. In contrast, cocaine produced relatively uniform stimulation in both the matrix and the striosomes. This result suggested dopamine was particularly important for repetitive movements. Another stimulant drug, apomorphine was given to the rats, and this resulted in greater oral stereotypies and striosomal stimulations, supporting the earlier finding that the dopamine system was involved in repetitive movements (Graybiel & Canales, 2001).

More specifically, the fact that different stimulants produced such different brain activations as well as different stereotypies suggests different movements and their frequencies may be controlled by different neural activations in the basal ganglia. Moreover, a relative increase in the striosomes may be the factor that shifts the balance and creates the involuntary repetitive behaviors (Graybiel & Canales, 2001).

Focusing on Tourette syndrome, Graybiel and Canales proposed that their findings provide new insights into the underlying neural bases of the symptoms. A surprising feature of Tourette syndrome is patients are simultaneously aware of their movements and that they cannot control the movements. This suggests normal cognitive

function with only a dysregulation in the motor system. Thus, according to Graybiel and Canales, excess movements arise from a problem in the balance between the limbic and motor loops in the basal ganglia, creating anxiety cycles and movement repetitions. The basal ganglia are involved in learning habits and sequential behaviors. The repeated movements and behaviors of Tourette's are generally set off by certain contexts or cues. The basal ganglia have been hypothesized to formulate behaviors into "chunks" that appear when exposed to a particular situation. For example, when a person gets ready for bed, they may wash their face, brush their teeth, floss their teeth, rinse with mouth wash, and put in their retainer. These five separate behaviors are made into a "chunk" of behaviors a person performs when they are exposed to the situation of getting ready for bed. This chunking is thought to play a part in Tourette syndrome. So, a person with Tourette's might have three separate tics that present when they read: short, rhythmic exhales, winking, or tensing their left bicep. The basal ganglia, though, formulates these three behaviors into a "chunk" because they all appear when the person is reading. Thus, the three once separate behaviors are now a "chunk" and performed together as a set when this person is exposed to the situation of reading (Graybiel & Canales, 2001).

Although Graybiel and Canales' results implicate the dopaminergic system in Tourette's, their results do not exclude the involvement of other areas of the brain. Another area that could be important in Tourette's is the attentional system in the brain. A patient's focus on a tic may be just as much about attention fixation as it is about the movement. The relationship between attention and movement may hold answers as to how habits and tics develop in people. Graybiel and Canales' findings, however, are only at the point of correlations and further studies are needed to explore the conclusions and

their possible effects for humans and repetitive movement disorders (Graybiel & Canales, 2001).

The Graybiel and Canales' study focused on movement-related aspects of the dopamine system, but other studies have examined the effects of dopamine as reinforcement, rather than motor learning. The release of phasic dopamine has been shown as a reward related signal, by encoding reward predicted errors, or obtained versus predicted results. The theory is the dopamine release strengthens the synaptic connections between the basal ganglia and the frontal cortex that are involved in selecting actions that produce more reward than the brain expected. Thus, the actions are more easily produced in the future in similar situations. Palminteri et al. (2011) demonstrated the fact that phasic dopamine levels affect reinforcement learning in people with Tourette syndrome.

The participants in the study consisted of typical controls (TC's), unmedicated Tourette syndrome patients (TS's) and medicated Tourette syndrome patients (MTS's). Because of the proposed mechanism of phasic dopamine in Tourette's, the researchers predicted that TS's would show stronger reinforcement on motor skill learning than the TC participants (Palminteri et al., 2011). They also predicted that MTS's, who were medicated with neuroleptics (a medication that inhibits dopamine receptors), would be the same as or worse in reinforcement on motor skill learning than the TC subjects. Participants were given a motor learning task on a computer followed by two forced choice tasks and were either given 1 cent Euro or 10 Euros. In the motor learning task, the participants pressed three out of five predetermined keys in a specific sequence; if they did it correctly, they were rewarded either 1 cent Euro or 10 Euros. Note, the sequences were predetermined randomly with the amount they were worth for each

subject, so not time dependent, but once the sequences were assigned a worth, the sequence's reward amount was kept constant for each subject's subsequent two tasks. If participants performed the task correctly, they were awarded the amount the task was worth, but if they did not, they received no money. After the first motor learning task, the participants were given the same 10 key press sequences, but were forced to choose whether that specific combination was worth 1 cent Euro or 10 Euros, as determined from the first round (Palminteri et al., 2011).

Paminteri et al. found that reinforcements improved motor skill learning as the time between key presses decreased with monetary rewards in both the TC group and the TS group. Improvements were not seen in the MTS group, suggesting that dopaminergic transmission is essential in motor skill learning. This is because the difference between the other two groups and MTS's was the MTS's were taking neuroleptics, which block dopamine receptors. Since the MTS's were the only participants who didn't see time improvements, a logical conclusion would be that dopamine transmission is essential in motor skill learning (Palminteri et al., 2011).

Moreover, Palminteri et al. dissociated reinforcement from motor learning by manipulating the different reward amounts: one negligible (1 cent Euro) and the other large (10 Euros). Thus, when the reward was negligible, only motor learning should occur but not reinforcement, because 1 cent Euro is not very motivating. Yet, when the reward was large, reinforcement should occur, because 10 Euros is very motivating (and 1,000 times greater than 1 cent Euro). Palminteri et al. defined the reinforcement effect as the cumulative difference between the 1 cent Euro and 10 Euro conditions for each participant, taking the 1 cent Euro time minus the 10 Euro time. So, the higher the

reinforcement effect, the more reinforcement learning occurred, as opposed to just pure motor learning (Palminteri et al., 2011).

The TC group, as stated above, showed time improvement for the key press sequences, exhibiting motor learning. They also showed a reinforcement effect, showing that the monetary rewards were good at predicting motivation for learning the key press sequences, but the reinforcement effect was small. (Palminteri et al., 2011).

The TS group also showed time improvement for the key press sequences, and thus, motor learning. When the negligible reward of 1 cent Euro was given, the TS participants showed impaired motor skill performance compared to the TC's. Motor learning still occurred, but it was slower than the TC participant's. However, the reinforcement effect found in the TS participants was significantly higher than the TC participants. This suggests reinforcements are extremely important for motor skill learning for TS patients (Palminteri et al., 2011).

The MTS group did not show significant time improvement in the key press sequences, suggesting impaired motor learning. MTS participants were also impaired in the reinforcement task compared to TC's and showed no reinforcement effect at all. When the negligible reward was given, the MTS showed no effect on motor learning, better or worse. These results imply that reinforcements were not important for the MTS participants (Palminteri et al., 2011).

Because the only difference between the TS participants and the MTS participants were the neuroleptics (dopamine inhibitors) that the MTS's were taking, the results suggest reinforcement learning is specifically mediated by dopamine transmissions, and that pure motor learning is not. This was shown by the fact that TS participants learned

the key presses so much more quickly when a high reward was given, but the MTS patients did not because they were taking medications that inhibited their dopamine transmissions. Also, since the TS participants learned motor skills so much quicker when high reinforcements were given, the implications are that people with Tourette syndrome should be taught motor skill tasks using positive reinforcement. TS participants did not respond well to motor learning when a negligible reward was given, but they responded to the task much better when the reinforcement was important. Positive reinforcements clearly have a strong effect on Tourette's patient's motor learning (Palminteri et al., 2011).

Dopamine is a very important neurotransmitter in the brain both for allowing and inhibiting motion. Whether the problem in Tourette syndrome lies in the striatum or in the processing and production of dopamine is not clear, but the argument for a dysfunction having something to do with dopamine is strong. Additional research is needed to discover more clues to the underlying problems creating the symptoms in Tourette's. However, dopamine is not the only neurotransmitter in the brain that influences Tourette's symptoms.

Serotonin is a compound that delays gratification. This explains why researchers implicate atypical serotonergic systems as an underlying neural basis for Obsessive Compulsive Disorder (OCD). People with OCD perform the same motions repeatedly because the gratification of the motion is delayed and they stop the motion once they finally feel that gratification and are able to stop. OCD is often a co-morbid condition with Tourette's, so researchers became interested in how the neural bases of Tourette's might relate to those of OCD. Although it is clear the serotonin and dopamine systems

interact in the brain, it is still unclear exactly how this occurs. Some mechanisms that have been proposed to explain their relationship include: 1) presynaptic serotonin receptors that regulate serotonin as well as other neurotransmitters, 2) serotonin action at the site of the dopamine receptors and 3) serotonin might cause dopamine to be released without a stimulating ligand. There has been evidence that the levels of a serotonin metabolite are lower in the basal ganglia and cerebrospinal fluid of people with Tourette's. Also, there has been evidence suggesting that serotonin crossing from one neuron to the next in the midbrain and the thalamus is important in the symptoms of Tourette's (Harris & Singer, 2006).

Recently, Worbe et al. (2012) explored how various systems within the brain might interact on a global brain level. Specifically, they investigated the "global integrative state and organization of functional connections of sensori-motor, associative and limbic cortico-basal ganglia networks, which are likely involved in tics and behavioural [sic] expressions of… Tourette syndrome." (Worbe et al., 2012). This global integrative state and organization of functional connections refers to the interactions between the neuroanatomical networks the researchers were looking at. The researchers examined 64 adult Tourette's patients and 27 controls using a 3T magnetic resonance imaging (MRI) scanner. The participants with Tourette's had a lack of what the researchers termed "hubs," or nodes in the brain that have the highest number of connections and thus are crucial for information transfers between networks. The hubs found in control subjects were located in the sensorimotor network: bilateral supplementary motor area, bilateral posterior insula, left ventral premotor cortex, left cerebellum, and right primary motor cortex; associative network: bilateral posterior

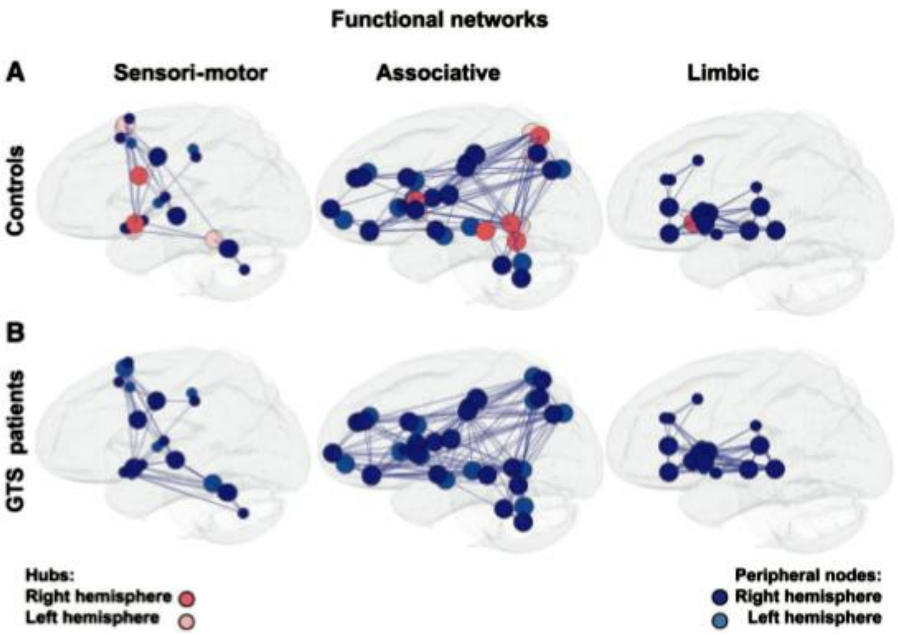

Figure 9. Functional Networks of the Controls (A) and GTS Patients (B) (Worbe, et al., 2012)

temporal cortex, bilateral superior parietal cortex, right medial temporal cortex, right anterior dorsal putamen, and left thalamus (prefrontal, dorsolateral and anterior ventral); and limbic network: bilateral anterior cingulate cortex, and the left hippocampus. No hubs were found in any of the networks for the Tourette's subjects (Worbe et al., 2012).

Worbe et al. also found that the participants with Tourette's not only had stronger functional connections than the controls, but the connections were significantly shorter as well in all three cortico-basal ganglia networks. The stronger and shorter functional connections allowed for faster information transfer in the nodes and indicated higher functional interactions between brain areas. In the associative network, the Tourette's patients presented with better local information transfer between nodes, and in the limbic and associative networks, the Tourette's patients had more numerous functional connections than the controls. Worbe et al. concluded that the differences found in the basal ganglia networks of Tourette's subjects, namely more numerous and stronger functional connections between the basal ganglia and cortex, could indicate a defect in

brain maturation responsible for the symptoms of Tourette syndrome (Worbe et al., 2012).

A possible explanation of this defect could be the brain's pruning process in childhood. Giedd's longitudinal study of MRI scans of healthy children's brains (1999,2000), explained that during the time between ages 6 and 12, the neurons in children's brains undergo changes, getting bushier and making many new connections between neurons. This creates many new pathways for nerve signals to travel throughout the brain. Then, around the age of 12, the brain undergoes a pruning process in which it decreases not the number of neurons, but the number of connections in between the neurons. This leads to fewer, but much faster, longer, and more efficient neural connections (Wallis, 2004). A study by Supekar, Musen and Menon (2012) supports this in their findings that children's brains contain "…a higher number of connections, a lower path length and a higher efficiency of local information transfer between cortical and sub- cortical regions," whereas "…young adults showed stronger cortico-cortical connections mostly between associative and limbic areas" (Worbe et al., 2012, p. 8).

From the above research on the neural bases of Tourette syndrome, I developed my own thoughts about how these various circuits are effected in people with Tourette syndrome. First, regarding the work by Worbe et al., I thought this type of methodology could provide evidence that people's brains with Tourette syndrome do not undergo this process of decreasing neural connections since their brain connections so closely resemble those of children before pruning. The hubs that the controls had in Worbe et al.'s study could also be formed during the pruning phase. Worbe et al. proposed that these hubs were pivotal nodes that connected the different basal ganglia networks for

quick information transfers (Worbe et al., 2012). It is possible the hubs are created by decreasing all the excess localized connections, thus forming the faster, longer, more efficient pathways in between networks. This would also explain why the brains of Tourette's patients don't have nodes, because they never went through that connection-decreasing phase. Scientists believe one of the driving forces for the pruning is genetic, further supporting this theory, since Tourette syndrome is a genetic disorder (Wallis, 2004). It also makes sense that if there was a problem in brain maturation, children would start exhibiting tics around the age of pre-puberty.

In order to test this theory, I would propose a longitudinal study of several families known to have Tourette syndrome in their family histories (preferably with a parent currently diagnosed with the disorder). Since it is not yet possible to determine if a person has Tourette's until they start exhibiting symptoms, the experiment would have to start with children younger than age 5. So, from the age of 3, each child from the family would come and get an MRI scan of their brains twice a year until they were 18. Since it is common to find families in which one sibling has the disorder and another doesn't, it is likely that the scans will show the brain developments of normal children as well as children with Tourette's. In this way, researchers will be able to see the differences in the maturations of normal brains as opposed to those with Tourette syndrome.

Finally, in addition to atypicalities in neurotransmitters and neural circuits in Tourette's, there have been a number of studies to determine the genetic expression of Tourette syndrome. Nonetheless, the evidence on the exact chromosomes is ambiguous because studies do not agree on the chromosomes involved. One study in 2007 found significant evidence for chromosome 2p involvement, and less so chromosomes 3p, 3q,

5p, 6p and 14q (The Tourette Syndrome Association International Consortium for Genetics, 2007), but another study claimed evidence for chromosomes 4q and 8p (TSAICG, 1999). A French Canadian study found significant involvement in chromosomes 11q, 19p and 5p (Barr et al., 1999), while an earlier study also found evidence suggesting chromosome 17q was significant (Paschou et al., 2004). Yet another study claimed evidence for significance in chromosome 13q (Abelson et al., 2005). Clearly, understanding of the genome expression of Tourette syndrome is still in its early phases, and much more research needs to be done to narrow down the chromosomes involved.

The etiology of Tourette syndrome has a long way to go, but we are continually getting closer to uncovering the neuroanatomical functions that create the symptoms in the disorder. Through carefully selected studies, we can begin to build on our current knowledge, and hopefully, the truth is not far from being uncovered. Theories for an abnormality in brain structure, dysregulation of the dopamine system, dysregulation of the serotonin system and overall neurotransmitter system interactions all have validity. It is likely that the true etiology is some complex integration of all of these.

Treatment Options

The history of treatments for Tourette syndrome follows the medical diagnosis history in its focus shifting from a mental health disorder to a neural system atypicality. As seen in the history section, it took a long time for people to accept that Tourette's has an organic cause. The first useful medical treatment for Tourette syndrome was the use of antipsychotic drugs, or neuroleptics, around the 1970's. The term "antipsychotic" is misleading, though, because these drugs are really just dopamine antagonists and are used for more than just psychosis patients. Antipsychotics were originally used to treat people with schizophrenia, a psychotic disorder, thus earning the name antipsychotics. However, these drugs are used today on many other conditions as well that are not considered psychoses, such as autism, bipolar disorder, personality disorders, dementia, depression, anxiety, and Tourette syndrome (Spector, 2011). The reason they are used frequently with Tourette's patients is because they are thought to be highly effective in blocking dopamine receptors, thus helping the proposed imbalance of dopaminergic transmissions (Huys et al., 2012).

The first antipsychotic that was cleared by the FDA for use in patients with Tourette's was Haloperidol. This drug was used because it is extremely effective in blocking dopamine receptors, thus helping reduce excess movement in Tourette's. However, the maximum dosage is only 10 mg because it is so effective in blocking dopamine that it can cause Parkinson-like symptoms, or extrapyramidal reactions. Other side effects of Haloperidol include drowsiness, restlessness, and sexual dysfunction. After Haloperidol was shown to be effective, other antipsychotics such as Pimozide and Fluphenazine were prescribed to patients, but Haloperidol is still the most widely used

neuroleptic today (Huys et al., 2012). There is wide debate as to whether Haloperidol or Pimozide is more effective in treatment. Many studies have been conducted on this question and evidence for both sides persists. While antipsychotics have proved beneficial for patients in the right doses, their side effects can prove debilitating with the Parkinson-like symptoms (Kushner, 1999), and others including weight gain, diabetes and heart disease (Spector, 2011).

Because the extrapyramidal reactions were so prevalent and difficult for schizophrenic patients to deal with, researchers successfully developed new antipsychotic drugs that did not include these extra movement side effects. They called these new drugs atypical antipsychotics, or second-generation antipsychotics. The original antipsychotics were thought to completely block only one kind of dopamine but have no effect on the other kinds, whereas the atypical antipsychotics blocked multiple kinds of dopamine less completely. Mostly, they inhibit the kind of dopamine D_2 ("Schizophrenia Typical & Atypical," 2009). Although, they still include the side effects like weight gain and heart problems, doctors started prescribing them for use on patients with Tourette syndrome. Some of the atypical antipsychotics that have been used include Benzamide, Tiapride, Clozapine and Respiridone. Of these medications, Respiridone seems to be the most widely used. Yet, all of these medications still have some serious side effects, including weight gain, drowsiness, depressive symptoms, restlessness and sleep problems (Huys et al., 2012).

Another type of drug that can be used for symptom control of Tourette syndrome is Tetrabenazine. Tetrabenazine is not an antipsychotic or an atypical antipsychotic, but it also blocks dopamine receptors while reducing the storage of pre-synaptic monoamines,

such as dopamine and serotonin. One of its biggest selling points is it helps reduce tics but is less associated with weight gain than other medications. Some studies have demonstrated a reduction of tics, functional improvement, and long-term benefits after taking the drug for two years. The side effects generally associated with Tetrabenazine are nausea, depression, drowsiness, insomnia, and sometimes Parkinson-like symptoms (Eddy & Rickards, 2011).

Clonidine is a drug that does not inhibit dopamine receptors, but instead blocks noradrenalinee receptors, which is another neurotransmitter. There have been multiple studies with this drug in the treatment of Tourette's. Some studies claim it is less effective than neuroleptics, while others say it is just as effective in treating tics. For those patients that Clonidine shows improvement in tics, there are also possible positive benefits for compulsive, impulsive and hyperactive behaviors. The side effects of Clonidine are generally less severe than those associated with neuroleptics, including headaches, dizziness, constipation, drowsiness, sedation and an abnormally slow heart beat. A similar noradrenalinee inhibitor, Guanfacine, has been suggested as a possible alternative to Clonidine because it may have less sedation side effects and better cognitive performance while still reducing tics (Eddy & Rickards, 2011).

GABA modulating medications, which control a neurotransmitter called gamma-aminobutyric acid (GABA), are another possible pharmacological option for Tourette syndrome. GABA is a major neurotransmitter that has inhibitory effects in the brain, blocking information transmissions from one neuron to another. Benzodiazepines, which are drugs like Valium or Librium, have been shown to possibly help in tic treatments. However, the evidence is not very conclusive in its effectiveness, and benzodiazepines

have an addiction potential as well as side effects like drowsiness, irritability and paradoxical aggressions (Eddy & Rickards, 2011). Other GABA modulating medications include Topiramate and Leventiracetam and are generally used as anticonvulsants in epileptic treatments. These drugs have been used recently in controlling tic symptoms as well. There is conflicting evidence as to whether or not it is effective in reducing tics, but even in the studies where it has been found to help, the reductions are only small to moderate (Eddy & Rickards, 2011).

Nicotine has been suggested as a possible treatment for alleviating tics. However, the evidence is not backed up very well. Even if it were, it would require patients to either smoke or use nicotine patches (Eddy & Rickards, 2011). Hayslett and Tizabi (2005) found nicotine may have tic reducing benefits because it is a type of serotonin receptor antagonist (Hayslett & Tizabi, 2005). Mihailescu & Drucker-Colín (2000) theorized that the benefits in Tourette's from nicotine were because of desensitization of nicotine receptors in the striatum responsible for nicotine release. So, in low doses, chronic intake of nicotine would inhibit nicotinitic receptors by desensitizing them (Mihailescu & Drucker-Colín, 2000). In the case of nicotine, although it has been shown to provide some benefits in tic reduction, I do not believe the side effects are worth the health risk to the patients. Even if nicotine was taken in through a patch, addiction is still a disabling side effect.

THC is another form of treatment that has shown some promising benefits in reducing tics. THC, of course, is a cannabinoid coming from the cannabis plant, which produces marijuana. THC stands for tetrahydrocannabinol and is the chemical responsible for the high people feel when they ingest or inhale large doses. In small doses

though, THC has been shown to alleviate nausea and pain, increase appetite, and reduce some of the aversive effects of chemotherapy for cancer patients. There are also synthetic forms of THC found in the medication Marinol, but those who have used marijuana claim Marinol is not as effective as the real THC ("What is THC?," n.d.). Many Tourette's patients who, when interviewed, admitted to having used marijuana, said they felt it reduced their tics as well as the uncontrolled urges to tic and their obsessive compulsive symptoms. In some studies, researchers found that THC, in small doses (up to 10mg) showed reduction of not only tics, but also tic frequency, tic severity, the uncontrolled urges to tic, and obsessive compulsive symptoms. The side effects, though, included impairments of short-term memory, coordination, attention and time and space perception. There is also the risk of addiction and withdrawal symptoms that can include restlessness, depression, anxiety, insomnia and tremor. THC can also worsen psychotic symptoms and can increase phobic anxieties. Of course, these studies have limitations. For example, these studies may have reported inflated effects because those participants who dropped out could have left due to lack of response to the drug. More studies are needed to confirm these results (Eddy and Rickards, 2011).

One strange, slightly counterintuitive treatment of Tourette syndrome is the use of dopamine agonists. The reason this is counter-intuitive is dopamine agonists are the opposite of dopamine antagonists, so these drugs actually stimulate the production of dopamine in the brain ("Definition of Agonist," 2012). Because one of the main hypotheses for Tourette's symptoms comes from too much phasic dopamine being released, a dopamine agonist doesn't make intuitive sense as a treatment option. However, both Apomorphine and Busipirone have proven to be viable medications for

tics and there is evidence that Ropinirole reduces both the frequency and severity of tics in both motor and vocal tics. Another dopamine agonist, Pergolide, has been used as an effective medication for Parkinson's disease. In much lower doses, Pergolide was shown to significantly decrease tic severity in Tourette syndrome and if the patients had a co-morbidity of restless legs syndrome, Pergolide also reduced those symptoms (Eddy & Rickards, 2011).

There is one type of drug not seen much in the literature, but that I think should be used more as a treatment and that is a beta blocker. Beta blockers are a common medication choice for anxiety and stress, and Tourette syndrome is a very stressful disorder according to most people who have it. This is not hard to understand because Tourette's patients are constantly under the bombardment of uncontrollable urges to move or make sounds. Not only is it stressful to attempt to control these tics, but the tics come every day and rarely give the patient a long reprieve. Peterson showed that anxiety and stress were both constantly and closely involved in the maintenance and intensifying of tics, thus providing evidence for an intimate relationship between tics and stress-related reactivity (Peterson, 1996). Yet, despite the observed relationship, not much research has been conducted on stress and anxiety and how that could affect the secretion of hormones involved with stress.

During normal times of stress, the body reacts to a potential stressor and secretes various hormones such as adrenaline and cortisol. These hormones increase heart rate, raise glucose levels in the blood stream, and alter the immune, digestive and reproductive systems. When the perceived threat passes, the heart rate lowers and the other systems go back to their regular functions. However, in chronic stress, the body is constantly in this

state of “fight or flight” responses and the body’s levels of adrenaline and cortisol are constantly raised as is the heart beat. This can also cause problems such as depression, obesity, memory impairment, and sleep problems (Mayo Clinic Staff, n.d.).

I believe that most people with Tourette’s have chronic stress disorder due to their tics. I think it is more pronounced in children because tics are often worse in childhood. Cortisol has a daily rhythm in the body where the level is highest in the morning, decreases throughout the day and is lowest at night. One study found children with Tourette syndrome showed a lower level of evening cortisol than children without the disorder (Corbett, Mendoza, Baym, Bunge & Levine, 2008). This trend of a lower evening cortisol has been shown in conditions of chronic stress (Nickel et al., 2007), and thus may be evidence that children with Tourette syndrome suffer from chronic daily stress.

Corbett et al. (2008) also showed a correlation between stress-related neurobiological functions and the neuropathology of Tourette syndrome. Their results showed a heightened reactivity to stressors in Tourette’s patients rather than an error in regulation of the stress hormones, though, providing further evidence for chronic stress and not a problem with the regulation system of the hormones (Corebtt et al., 2008).

Beta blockers, also called beta-adrenergic blocking agents, are commonly used as a treatment for heart conditions, including hypertension, heart failure and obstructive cardiomyopathy. They have also been used to treat migraine headaches, essential tremors and anxiety (Frishman & Saunders, 2011). Tics are exacerbated by anxiety and stress, so the fact that they’re used as a treatment for anxiety is one reason they should be given more often to Tourette syndrome patients to see if they help reduce tics. Beta blockers

obstruct the effects of the adrenaline hormone by blocking the adrenaline receptors on nerves. By doing this, they lower a person's heart rate and blood pressure (Mayo Clinic Staff, n.d.). A study by Oei, Tollenhaar, Elzinga and Spinhoven (2009) looked at the effect of the beta blocker Propranolol on working memory. In their research, they found that propranolol significantly lowers heart rate and blood pressure compared to a placebo, but also that it significantly increases cortisol levels compared to a placebo (Oei et al., 2009). This may look counterproductive, but some other evidence suggests otherwise. Corbett et al. found that higher levels of cortisol in patients with Tourette syndrome correlated with fewer tics. Although this may seem strange, it actually fits because when a patient performs their tics, it reduces the tension and discomfort they feel in the uncontrollable urge to tic (Corbett et al., 2008). So, their stress level, and consequently their cortisol level, would be lowered once the tic is out. If the patient does not tic, it would make sense that their cortisol levels would be heightened. The problem with this is the finding is a correlation, not a causation. More research would have to be done to see if a high cortisol level was merely related to fewer tics or if the high cortisol level caused the reduction in tics. It would also have to be shown that artificially raising the cortisol levels still resulted in fewer tics and that it wasn't just a phenomena that happened with natural cortisol levels. If the relationship was causational, this would provide even more evidence for Tourette syndrome patients taking beta blockers than just to help curb anxiety and lower adrenaline. Another thing to keep in mind is the study with Propranolol was performed on healthy men, so the cortisol effect on someone with Tourette syndrome may be different and further research is needed to test this.

Of course, there are other treatments that are not pharmacological. One of these alternatives is behavioral. There are several types of behavioral treatments, some more researched than others. One option is a treatment called Contingency Management. In this treatment, it is thought tics can be modified by consequences. Consequences can be either positive (reinforcements) or negative (punishments). The premise is the patient should receive positive reinforcement like praise and rewards for the reduction of tics, and punishments such as loss of privileges or electric shocks for recurrence of tics (Singer, 2010). I do not believe this would be a productive, nor a healthy treatment. Since people with Tourette syndrome have no control over their premonitory urges to tic, it would be unfair to punish them for performing their tics. Not only that, but punishing them for ticcing sends the message that they are bad because they have Tourette syndrome, something they definitely did not choose. Because the symptoms are organic and not just a problem of misbehaving, I do not believe this treatment should ever be used on a person with Tourette's.

Another behavioral treatment that has been used frequently in helping people get over phobias is called Relaxation Training. In this technique, people are taught ways to relax such as breathing exercises, muscle relaxation and maintaining postures. This training was suggested as a method because stress and anxiety can exacerbate tics, so if the patient could learn to calm themselves down and relax, their tics might abate (Singer, 2010). Bergin, Waranch, Brown, Carson and Singer (1998) found evidence that Tourette's children who went through Relaxation Training were better able to relax compared to others who had minimal therapy (such as quiet time), but the differences were not significant. Also, no difference was found in either group after three months,

showing that the effects were short-lived (Bergin et al.,1998). This is probably not the best behavioral treatment option for Tourette's patients due to its minimal and extremely temporary results. However, although it is advisable to use this treatment alone, I would recommend patients to use it in conjunction with other treatments, whether behavioral or pharmacological, because it does provide reduction in anxiety and stress.

The most prominent, and in my opinion, the most beneficial behavioral treatment, is Habit Reversal Training. In this technique, patients with Tourette syndrome are taught to become aware of their tics and the premonitory urges as well as things that trigger their tics, such as certain environments or situations. Then, the patients are instructed to perform a voluntary competing response that does not allow them to perform the tic in order to prevent or interrupt the tics (Singer, 2010). The competing response should be something that can be upheld for a few minutes (so the urge to tic can pass), involve muscles that will not allow the tic to happen, and be socially inconspicuous. One such behavior might be slow, rhythmic breathing in place of a vocal tic. Another example might be a boy who has an explosive arm jerking tic to instead apply the competing response of moving his arm much slower and make it look like he is smoothing out his hair. Once a person gains more control over the specific tic, the competing response becomes more forceful and hopefully greater tic control is attained (Piacentini & Chang, 2005). Evidence for this method of treatment is encouraging. Wilhelm, Deckersbach and Coffey (2003) showed evidence that Habit Retraining Therapy was more effective than supportive psychotherapy for Tourette syndrome patients. They also showed that the Habit Retraining Therapy was still effective after ten months (Wilhelm et al., 2003). Another study comparing Habit Retraining Therapy and supportive therapy and education

also found Habit Reversal Training was the more effective treatment for Tourette syndrome showing lasting improvement in tic severity (Piacentini et al., 2010). In comparing Habit Retraining Therapy to just awareness training, one study showed support for Habit Retraining in significant tic reduction as well as maintained tic reduction three months after the treatment (Piacentini, Chang, Barrios & McCracken 2002).

There have been some critics for behavior therapy as a treatment option for Tourette syndrome, though. Some have argued behavioral training may worsen psychiatric and psychosocial outcomes as well as create family strain. Woods et al. (2010) addressed this theory in their behavioral therapy study. They found behavioral therapy actually does not cause improvement or worsening of psychiatric and psychosocial outcomes. In addition, six months after completing the behavioral training, the researchers found the patients experienced decreases in anxiety, disruptive behavior and family strain and saw improvements in their social functioning (Woods et al., 2010).

The last option for treatment of tics is surgical. Ablative procedures, in which the surgeon removes whole chunks of unwanted tissue, is obviously not the method of choice because of the extremely adverse side effects, not to mention its generally unsatisfactory results (Savica, Stead, Mack, Lee & Klassen, 2012). Therefore, the type of surgery that is performed is called Deep Brain Stimulation (DBS). DBS is a surgical procedure where an electrode is placed in a specific, targeted spot in the brain, and then, when the electrode is activated, the neural activity in the implantation area actually decreases (Eddy & Rickards, 2011). Surgery is more often an option used for those patients with a higher severity of tics whom are not finding improvements with any other treatments. In fact, the

current criteria for ideal Tourette's DBS candidates include: at least 25 years of age, possession of severe tics that have not been helped by other medical or behavioral treatments, no history of medical, neurological or psychiatric conditions, be prepared for no outcome or an adverse outcome from the procedure, and have a total tic score of 35 or above on the Yale Global Tic Severity Scale (YGTSS) (scores range from 0 to 100) for at least twelve months (Mink et al., 2006). These are the optimal conditions for candidates considering DBS, but are not necessarily required. For example, DBS can be performed on a person a few years younger than 25 years old, say at age 18, if they are exhibiting intense self-injurious tics that are disruptive in many facets of their life, including developmentally, socially and educationally (Savica et al., 2012).

DBS is a treatment that is in its infancy and has not been used very often. DBS is often used when treating other conditions, such as Parkinson's disease. Parkinson's disease has had much success with the procedure because there is currently a good animal model of the disease and the underlying circuitry involved. Tourette syndrome, on the other hand, has no good animal model and the underlying circuitry and physiology are not well known, so this makes it very difficult deciding where the electrodes should be placed (Mink et al., 2006). Since the basal ganglia is hypothesized to be involved in the disorder, researchers have suggested electrodes be placed in these structures and their associated networks.

One area that has shown some promising evidence for DBS is the centromedian and parafascicular nuclei (bilaterally, meaning in both the left and right hemispheres of the brain), which are both located in the thalamus. Case studies of this implantation site have reported improvements in tics on the YGTSS scale from 45% (Shields, Cheng,

Flaherty, Gale & Eskandar, 2008) to 90% (Visser-Vandewalle et al., 2003) and a recent study of three patients reported an average of 70% improvement (Savica et al., 2012). Another area that has been used is the globus pallidus. One case study of a patient with severe Tourette syndrome found a decrease of 73% in his mean tic frequency per minute after the operation (Diedrich, Kalteis, Stamenkovic, Pieri & Alesch, 2005). The anterior limb of the interior capsule (a brain area separating the caudate nucleus and thalamus from an area called the lentiform nucleus) has also been studied as an implantation site. One case study reported significantly reduced tic severity and tic frequency after electrode implantation in this area (Flaherty et al., 2005).

This treatment, as stated before, is still extremely new. Much more research needs to be done to test current targets and new targets, seeing which targets are optimal. Side effects from the procedure should also be thoroughly tested. In Savica et al.'s study (2012), patients reported abnormal tingling sensations and light-headedness after the operation, but these symptoms went away after a few weeks. Other studies have reported drowsiness and sexual behavior alterations (Visser-Vandewalle et al., 2003), a decrease in energy (Servello, Porta, Sassi, Brambilla & Robertson, 2008), and psychosis and random tic recurrence (Maciunas et al., 2007). More studies should be done to see if there are other adverse side effects, and complications are always a dangerous possibility when surgery is involved. The effect of the surgery on patient's co-morbid conditions should also be studied and taken into account when weighing the pros and cons for this new treatment. Also, this procedure is definitely not recommended for everyone, rather only a select few adults with Tourette syndrome who have severe tics and have tried pharmaceutical and behavioral treatments, but have not been able to reduce their tics.

Conclusion

After reviewing the treatment options, I believe Habit Retraining Therapy should be the first attempted treatment for Tourette's patients. Not only is it a noninvasive treatment, it also does not require a person to take medications. Medications could have adverse side effects and parents of Tourette's children often worry about what the long term effects will be from the medications they are prescribed. No harmful side effects have been found to be associated with this type of behavioral therapy and there are no known adverse long term effects from the therapy. I think any treatment that has shown evidence for improvement for tic reduction that is also natural should be the first method suggested. Relaxation Training in conjunction with any therapy method would also be advisable. There is no risk if it does not work and it can be implemented with any other form of treatment. Because Tourette's is so stressful, I think a natural form of stress relief would be helpful to patients.

If Habit Retraining Therapy does not work, then I believe their physician should try medication. Because everyone reacts differently to the medications available and different medications work better than others for different people, I would leave it up to the patient and the doctor to decide what the best agent is for them.

Only after every other alternative has been tried should surgery become an option. If the person has tried all the other treatments, simply cannot function in society, and their quality of life is extremely compromised, then they should consider surgery. It has been shown to be an effective treatment option, I just would not advise anyone to undergo such an invasive procedure without exhausting all the other alternatives open to them.

In conclusion, the etiology and treatment of Tourette syndrome is extremely important to me because I have a family history of the condition. The better the treatment is in treating the disorder, the better those afflicted with it will be able to function. Not only will it add to their happiness, but it will add to their overall life experience. Although a cure for Tourette syndrome would be the best outcome, the second best outcome would be an effective and lasting treatment option.

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Appendix

Physiology of the Neuron

The smallest building blocks of neuroanatomy are neurons. The brain is composed of billions of neurons with most estimates somewhere around the 100 billion mark (Williams & Herrup, 1988). Neurons are made up of three main parts: the dendrite, the cell body and the axon. The dendrite is the first part of the neuron and it is where the information from the previous neuron enters the cell. This information travels to the cell body and then the cell body sends the information through the axon, which is covered with a fatty substance called myelin. The information is sent as an electric signal called an action potential. It is then sent out of one of the terminal branches of the axon into the space between neurons called the synapse. From there, it enters the next neuron through the dendrite, and the cycle repeats, spreading information through the brain. A pictorial diagram of this is below:

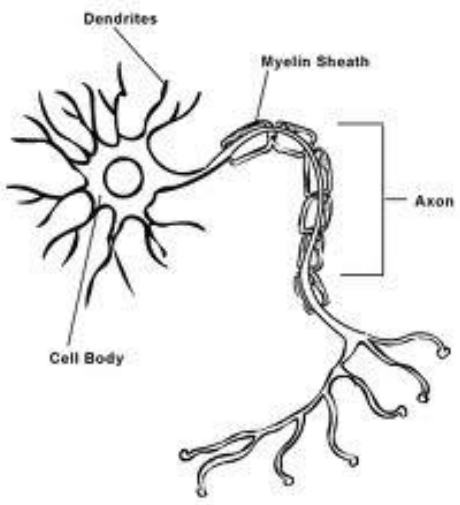

Figure 10. Neuron
("Brain Power," 2008)