What Might Be Causing OCD Symptoms?

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In the August 23, 2007 issue of Nature magazine, Jeffrey Welch, Jing Lu, Guoping Feng and colleagues in the Department of Neurobiology at Duke University's School of Medicine reported that a scaffolding protein called Sapap3 is involved in synaptic communication (see Figure1) within basal ganglia. They reported that disabling the scaffolding protein leads to OCD-like behavior, but replacing the broken scaffolding protein with a normal protein restores normal behavior.[1,2]

Figure 1 Brain Synapse.

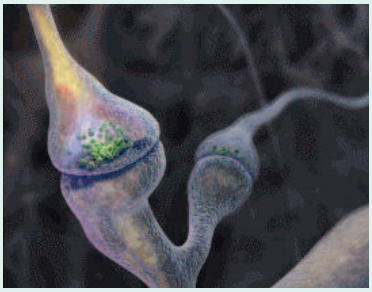

Figure 1 is from "Engineering Visualization Challenge," Science, September 23, 2005.

A synapse is one of the basic units of brain communication. In the Welch, Lu and Feng study mentioned above, the synaptic function, as well as OCD-like behavior, was rendered on and off at will in mice.

What does this mean to OCD Newsletter readers? To explain, I will briefly describe essential principles of brain organization and functions relevant to the paper discussed above. When it comes to the brain, the parts of the brain that regulate vital signs such as rhythmic breathing and heartbeat developed first. Then a bigger and more complicated emotional brain evolved above the brain stem. The parts that regulate reasoning and abstract thinking were the latest addition to our brain. Most of the primitive animals possess either no or only a rudimentary reasoning brain.

Before the brain evolution that made human beings human, there were two primary brain cores. One of these two is called the olfactory

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(smell) core, and the other is called the hippocampal core. The orbital frontal cortex (OFC)[3] (see Figure 2) has evolved from the olfactory core, and the hippocampus emerged from the hippocampal core. The former is used to recognize an object, and the latter is used to recognize a place (and to process memory). These two functions are essential for animals to survive in their environment because they have to know where (place) to go to find prey (object).

OCD researchers study the OFC because research has shown that something has gone awry in this part of the brain in OCD patients (see Figures 2 and 3).

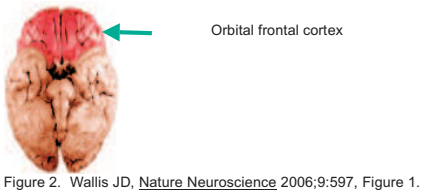

Figure 2. Wallis JD, Nature Neuroscience 2006;9:597, Figure 1.

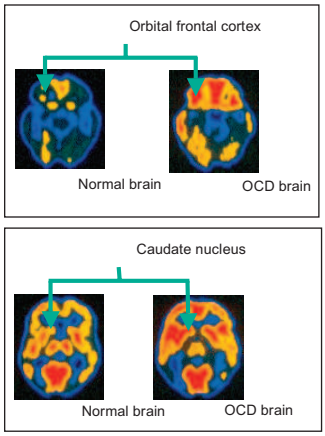

Figure 3. Baxter LR, Jr. and colleagues, Archives of General Psychiatry 1987; 44:216, Figure 6 (adapted).

The findings reported in the Baxter, et al article have been replicated by a number of other investigators in the ensuing years. Both the orbital frontal cortex and caudate nucleus are overly active in OCD patients.

The OFC carries out several essential functions in our daily lives:

(1) Cells in the OFC process incoming information from the environment and also from within the body. These cells determine the relative value of a given object based on one's real or abstract need at a given time. For example, if one is hungry, food (object) carries more value than when one is satiated (alliesthesia); a $100 bill carries more value than a $1 bill.

(2) Cells in the OFC compute and predict an upcoming reward based on available information and participate in forming a goal-directed behavior to secure the reward.

(3) Cells in the OFC detect and recognize if there was an error in predicting a reward. For example, if the actual reward was much smaller than had been anticipated, cells in the OFC recognize this and allow an alternative strategy on the next trial (reversal learning). If cells in this part of the OFC are damaged, the person tends to engage in risky behavior repeatedly, yet fails to recognize the error (perseveration).

(4) In general, reward learning information is registered in the inner part of the OFC; and financial loss, punishment or aversive information are registered in the outer part of the OFC (go to www.impulsecontroldisorders.org and click on the "Reinforcement Learning" and see the study by O'Doherty). In the case of OCD, abnormal metabolic activity is usually registered on the outer portion of the OFC (see Figure 3).

Although this is an oversimplification, broadly speaking, an incentive-imbedded behavior is more closely linked to the inner part of the OFC and inner part of the prefrontal cortex (impulsivity), but OCD symptoms are more closely linked to the outer part of the OFC. We would like to alert readers here that when it comes to seeking the causes of OCD, compulsive behavior is not a core feature of OCD. Although there are OCD patients who have only obsessions, we almost never see patients who have only compulsions. People engage in compulsive rituals to overcome their underlying obsessions and anxiety.

The fact that a portion of the OFC becomes activated in OCD does not necessarily mean that this portion is linked to the cause of OCD. The reason or reasons why a portion of the OFC becomes activated in OCD are not well understood. We, however, do know that that part of the brain is not working correctly in OCD. There are other parts of the brain that are also involved in OCD, but space does not allow us to discuss them.

In most cases, OCD patients suffer from intrusive obsessions that they cannot control. These obsessions do not intrude into patients' minds spontaneously, except in a small number of subjects.[4] Obsessions are often triggered by a stimulus or stimuli. Thus, many patients tell us that nighttime is their best time because they are in their quiet bedroom and no longer bombarded with obsession-triggering stimuli in the environment.

This finding, in part, suggests that a gating or filtering mechanism (thought or action release) has run amok in OCD. The part of the brain that screens out irrelevant or irrational information, including rewarding or punishing ones, is not working well in OCD.

For example, a person who might be watching a movie called "Rent," sees homosexuals on the screen; and from then on, the person might be bombarded by recurrent intrusive homosexual thoughts. An ordinary person would have screened this out easily. The same thing can be said about another person watching an AIDS program on TV.

Another problem with OCD patients is that they do not seem to know the "task-end point." In the 80's, in writing a BASIC language computer software program, one had to enter "end" over and over after each task. A computer, no matter how primitive it is, follows certain basic principles like the human brain. OCD patients, somehow, cannot do this. When a normal person shuts a door or turns a light switch off, the person puts an "end" to it. It's over, it's done; but OCD patients can't. They do not seem to know how to put an "end" to a task. They go over and over it for fear that the house might burn down, etc.

In some sense, OCD is like Parkinson's disease. In Parkinson's disease, patients have difficulty initiating movement (procrastination for OCD), shifting movement (feeling stuck for OCD), and terminating movement (see the paragraph above). Both are basal ganglia diseases: one affects the movement domain, the other affects the mental domain.

Evolution has refined our brain so well that there is an elaborate infrastructure within the brain that helps us learn rewarding events. For example, animals have to learn to recognize fearful situations; otherwise, they may be harmed or killed. OCD patients seem to have serious problem with this task. Their fear-learning strategy seems to have gone astray. Environmental cues that are harmless to most people often cause severe fear to some OCD patients.

Although external stimuli might be important in OCD, this principle does not apply to all OCD-like disorders. For example, in case of Tourette's Syndrome, tics, skin picking or trichotillomania (hair pulling disorder), tension or urges often build up within the sufferer, especially under stress. Then the person is compelled to act even if there is no known external stimulus.

A significant proportion of the symptoms described above are processed within the basal ganglia (striatum is a part of it), and this will be briefly discussed (see Figures 4 and 5 below). Converging evidence suggests that the basal ganglion is one of the critical brain

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regions, if not the most critical region, involved in OCD.[5] Welch, Lu, Feng and colleagues homed in on this part of the brain.

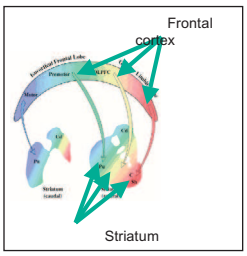


Figure 4 from Heimer L and Van Hoesen GW. Neuroscience and Behavioral Reviews 2006;30:129, Figure 3 (adapted).

In Figure 4. Light blue color = primarily mediates movement; yellow = mediates thinking like obsessions; red = mediates emotion. In the Welch, Lu and Feng experiment, Sapap3 proteins were expressed (or deprived) in all three areas. The OFC (orbital frontal cortex) is imbedded in the red color.

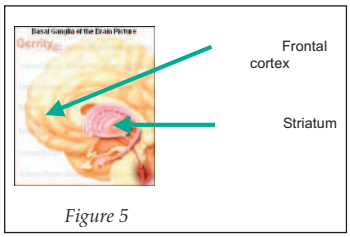


Figure 5

In Figures 4 and 5 above, communication between the frontal cortex and striatum is, primarily, mediated by glutamate synapses (see Figure 1). Feng and colleagues zeroed in on glutamate signal transduction (transmission). The Sapap3 proteins the authors exploited in the striatum are an important component of glutamate synaptic functions. In the absence of Sapap3, glutamate mediated communication gets disrupted. The authors made Sapap3 proteins appear or disappear at will in the striatum. When Sapap3 proteins disappeared from the striatum, mice showed OCD-like abnormal grooming behavior, but when Sapap3 proteins reappeared the grooming behavior stopped.

Previously, Greer and Capecchi reported that 100% of Hoxb8 mutant mice showed bald spots and open wounds from hair pulling and self mutilation. Examination of mice revealed trapped body hair between the gums and teeth suggesting that mutant mice removed their own hair.[6,7] In another study, one third of the Hoxb8 mutant mice have shown lesions in the skin and deeper tissue of neck and lower back.[8]

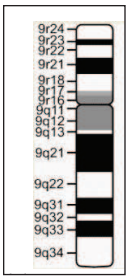
In the current *Nature* report, appearance of hair loss mimics more closely clinical trichotillomania (hair pulling disorder) or skin picking than in the report by Greer and Capecchi. However, since mice do not speak, it is difficult to tell if they were also having obsessions.

This is the first study of its kind in which the authors have tested a number of leads that are linked to the putative OCD pathology, namely:

(1) It involved the striatal-frontal circuit.

(2) Glutamate mediated communication between striatum and frontal cortex was disrupted.

(3) It zeroed in on the glutamate (signal carrier) instead of the serotonin (signal modulator) mechanism. Recent genetic studies have pointed out a glutamate transporter gene abnormality (9p24) in OCD cases.[9-12] At www.schizophreniaforum.org, it is said "9p24 is the only genomic region whose linkage to OCD has been replicated." This gene (9p24) is located on the top of the short arm of the human chromosome 9 (see the 9p24 or SLC1A1 in the web address provided here: http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?taxid=9606&CHR=9&maps=genes-r,pheno,morbid,genec&R1=on&query=SLC1A1&VERBOSE=ON&ZOOM=3, or see Figure 6 below.

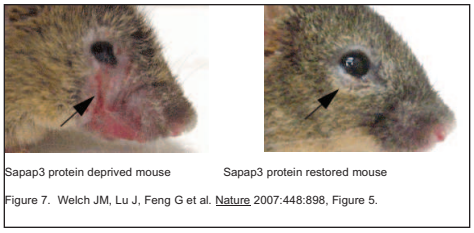


(The genes above are mistakenly marked 9r; they should be 9p)

Figure 6. The 9th human chromosome. 9p24 can be seen on the top of the short arm of the chromosome.

This said, we would hasten to alert readers that variants of the 9p24 gene do not equate to OCD. There are many OCD patients whose conditions do not show linkage to this gene. This genetic association was found only in some of those whose illness started early in life. This gene produces a protein that carries glutamate within the neuronal synapse (see Figure 1). In the brain, a high speed glutamate carrying molecule is essential because once glutamate is released into the synapse, it has to be removed very fast. The structure and function of this glutamate carrying molecule has been characterized.[13] How then does the SLC1A1 (also called EAAC1, excitatory amino acid carrier 1 or glutamate carrier, a 524 amino acid protein) compare to the Sapap3 that Welch, Lu and Feng studied? EAAC1 is a glutamate carrier and appears to be linked to the presynaptic receptors,[13] whereas Sapap3 seems to be linked to the modulation of the protein networks associated with postsynaptic glutamate receptors.[14]

(4) The signs that appeared were very similar to what we see in real trichotillomania or skin picking patients (see Figure 7).



Sapap3 protein deprived mouse Sapap3 protein restored mouse

Figure 7. Welch JM, Lu J, Feng G et al. Nature 2007:448:898, Figure 5.

It is intriguing to see that mice developed OCD-like behavior at 4-6 months. Circuits within the striatum develop slowly from the bottom to the top. A specific maturational stage and the onset of OCD or OCD spectrum disorders might be coupled.

What does the future hold?

For the first time, in the history of psychiatry, we now have basic science. Psychiatry has always been an orphan in medicine. Every other specialty has had basic science all along, but we never had it. Since the emergence of neuroscience, psychiatry has been the primary benefactor. There is breathtaking progress being made in many fronts in neuroscience, and OCD is one of the few areas that neuroscientists have paid close attention to. We now have a scientist who has developed a novel technique to study compulsive behavior such as addictive disorders or obsessive compulsive disorder (Alla Y. Karpova, www.hhmi.org). Others have developed a breakthrough research model to study neural circuits (go to www.PubMed.gov and enter 17485485 or 17643087 in the search area). OCD is a neural circuit disease; and, as such, the new study methods are bound to help our field in the coming years. Guoping Feng and his colleagues have developed creative research methods that have yielded exciting early leads in solving the mysteries of OCD. For any reader who might be overly eager, there is still a long road ahead. Dr. Feng and his group plan to test other molecules in the striatum and continue to search for the root causes of OCD and OC spectrum disorders. For the OCD patients and their families who have been suffering so much for so long, is this a light at the end of the tunnel?

Anyone who is interested in getting the references mentioned in this article can call the Foundation at 203-401-2074.

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