The Olfactory–Limbic System and Multiple Chemical Sensitivity
by
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Introduction

In the previous report – “Neural Sensitization and Multiple Chemical Sensitivity” – it was concluded that there were several biochemical mechanisms possibly involved in the development of neural sensitization, in those with MCS, which warranted further research. They were:

- The Olfactory-Limbic System
- The Trigeminal Nerve
- Excitotoxicity
- Excitation of the Mesolimbic Dopamine Pathway.
- Stimulation of Opioidergic Neurons by Opioid Activating Foods
- Hormonal Imbalances
- Decreased Acetylcholinesterase (AChE) Activity.

In this report we will examine in more detail the olfactory-limbic system.

The olfactory – limbic system is a highly complex system. Though a simple version of how this system works would be to say – odors enter the nose stimulating its receptors which then create a nerve impulse. The nerve impulse then travels to the brain where the perception of odor is created along with associated memories and emotions. This version, though nice and simple, will not suffice in attempting to understand the olfactory-limbic system’s relationship with MCS. Therefore, we must take a much closer look.

The Olfactory System

Olfaction refers to the sense of smell or the detection of airborne molecules/chemicals called odorants. The process of olfaction takes place via several neurological pathways and anatomical structures within the brain collectively referred to as the olfactory system. The olfactory system consists of the - olfactory epithelium, olfactory bulb, olfactory tract and olfactory cortex. Ironically, though the olfactory system is deemed the oldest sensory system in the human body, it is also the least understood.

“The sense of smell is mediated by the olfactory system, a system that is characterized by exquisite sensitivity and discriminatory power.” (Buck – Nobel Lecture 2004)
What is known about the olfactory system is that humans and other mammals can detect what seems to be an infinite number of odorants present in the external environment.

“It is estimated that humans can sense as many as 10,000 to 100,000 chemicals as having a distinct odor. “ (Buck – Nobel Lecture 2004)

All of these odorants are small, volatile molecules - meaning they’re gaseous. The process starts when odorants are detected by olfactory sensory neurons, which are located in the olfactory epithelium lining the nasal cavity. In other words it all starts... in the nose.

Olfactory Sensory Neurons and Receptors

Located on the roof of the nasal cavity, above and behind the nostrils, is a region termed the olfactory mucosa. The olfactory mucosa is made up of the olfactory epithelium and mucus secreting glands. Mucus, which comes from the duct cells of Bowman’s glands, gives protection to this region and allows odorants to dissolve so they may be more easily detected.

The olfactory epithelium is a thin sheet of cells (covered in mucus) and is made up of three primary cell types: (1) olfactory sensory neurons/cells or olfactory receptor neurons/cells – discussed in more detail below, (2) sustentacular cells – are support cells much like glia cells in the brain (3) basal cells – the olfactory sensory neurons are short lived, with an average life span of 30 to 60 days. It is the job of the basal cells to continually replace the olfactory sensory neurons in a process called neurogenesis.

Olfactory sensory neurons are elongated cells. The dendrite end of each olfactory sensory neuron extends down into the mucus layer of the olfactory epithelium and into the nasal cavity. Here the olfactory sensory neuron gives rise to a number of long, slender extensions called olfactory cilia (about
10 - 20 per neuron. Olfactory cilia are the contact points for odorants and the *olfactory receptor* which is entwined in the cell membrane of the olfactory cilia.

“Selective removal of the cilia results in the loss of olfactory responses. The cilia are also the site of olfactory signal transduction.” (Buck – 1991)
Each olfactory receptor consists of a distinctive structural protein chain that transverses the cell membrane seven times. When an odorant molecule or ligand attaches to an olfactory receptor, the shape of the receptor protein is altered, leading to what is called a G-protein activation. G-proteins (guanosine nucleotide binding proteins) act as molecular switches in the cell and once activated it sends into motion a cascade of biochemical events resulting in an electrical signal or nerve impulse being triggered. In essence, the olfactory receptor with its G-protein is a transducer – converting odorants (molecules) into an electrical signal. The generated nerve impulse then travels along the extremely thin unmyelinated axon that group together into small bundles or olfactory fila, which collectively constitute the olfactory nerve or cranial nerve I. These nerves continue up through the cribriform plate and synapse in the olfactory bulb.

![Image: G protein activation](image)

The olfactory epithelium contains millions of olfactory sensory neurons (estimates as high as 10 million) and each olfactory sensory neuron expresses only one type of olfactory receptor. Each receptor type is extremely specialized to a particular odor and a small number of related molecules.

For each type of olfactory receptor there is a corresponding gene which produced the receptor. Humans have about 1000 olfactory receptor gene sequences – “smell genes”. Of which 63% are considered to be non-active or ‘pseudogenes’. While about 363 olfactory receptor gene sequences are active and produce the individual olfactory receptor types. Also, olfactory receptor genes are highly distributed across the genome being found on 21 different chromosomes.

“Odorant receptor genes constitute the largest gene family in the vertebrate genome.”

(Menini - 2004)
What makes this even more interesting is that the visual system needs only three genes to detect the color spectrum. The auditory system just requires a specialized physical structure – the cochlea, which is constructed via genes used for multiple other roles in development.

“In the eye we can discriminate several hundred different hues and we do so with receptor molecules that recognize different wave lengths of light, but we only have three such receptor molecules. In the olfactory system there are at least a thousand, we have a very large number of receptor molecules that interact with the different odors in the periphery in our nose.” (Axel – Nobel Documentary 2004)

The ability of humans to discern the difference of 10,000 to 100,000 different odorants is an amazing feat. This is accomplished by the large number of individual olfactory receptor genes, along with the fact that olfactory receptors are used in a combinational manner to detect odorants. Different odorants are detected by different combinations of receptors creating an immense number of potential receptor combinations.

“...different odorants have different “receptor codes”. (Buck – Nobel Lecture 2004)

In summary there are two important points to remember about olfactory receptors:

1. Each olfactory receptor can recognize multiple odorants.
2. Different odorants are recognized by different combinations of olfactory receptors.

The Olfactory Bulb

There are two olfactory bulbs, corresponding to the two nasal cavities, with each bulb measuring in at about the size of a pea. Despite their small size they may be compared to a super high tech communications center in terms of the tasks they perform. Millions of units of data enter the olfactory bulb every second from the nerve impulses generated by the olfactory sensory neurons and their receptors. This massive amount of information is then re-organized and projected (sent) to specific areas in the brain for interpretation.

“The olfactory bulb is the primary center in the olfactory system and serves as a relay station for all olfactory impulses between the olfactory mucosa and the higher olfactory centers.” (Nieuwenhuys – 2008)

In the olfactory bulb the reception, re-organization and re-transmission of odorant impulses are handled by a handful of specialized cells – mitral cells, tufted cells, periglomerular cells, granular cells and complex structures called glomeruli. Interactions between these cells take place via a symphony of neurotransmitters and neuropeptides.
"The olfactory bulb is enormously rich in neuroactive substances, rivaling any other brain region." (Shepherd - 2004)

Glomeruli are round bundles of axon-dendritic processes (relay stations). They are also the most distinct features of the olfactory bulb and number in the thousands.

"In the young adult humans, approximately 8,000 glomeruli have been counted.” (Nieuwenhuys – 2008)

Each glomerulus receives axon input from several thousand olfactory sensory neurons, but not just any olfactory sensory neuron. Input is received only from those olfactory sensory neurons which contain the same type of identical olfactory receptor and receptor G-protein. Or to put another way, olfactory sensory neurons with their own particular olfactory receptor type (1 of 363) are randomly distributed in the nasal mucosa but converge on the same glomerulus.

Image: Summary of actions taking place in olfactory epithelium and bulb
Once in the glomerulus the olfactory sensory neurons branch out and synapse with mitral and tufted cells. The synaptic interaction between these cells is an excitatory process and uses glutamate as the primary neurotransmitter to act on the NMDA receptors of the mitral and tufted cell dendrites. The neural outputs from mitral and tufted cells are then projected to higher olfactory centers in the brain.

**Interneuron Modulation... Who Knew?**

At this point, what is most interesting about the olfactory – limbic system is that odorant nerve impulses exiting from the mitral and tufted cells have been heavily modulated (adjust frequency & amplitude). This is done via a number of interneurons whose nerve impulses originate in the higher olfactory centers in the brain. These nerve impulses are project along centrifugal fibers back to, and give feedback to interneurons within the olfactory bulb. The primary function of interneurons is to modulate, usually by inhibiting, the odorant nerve impulses before they are projected to the brain.

Interneurons are found in two areas of the olfactory bulb. First, a type of interneuron called periglomerular cells, are found surrounding the glomeruli. The axons of the periglomerular cells enter the glomeruli and synapse with both the mitral and tufted cells. It has been reported that some of the periglomerular cells use the neurotransmitter dopamine in their synaptic junctions (dopaminergic), which in this context acts as an inhibitory neurotransmitter. While other periglomerular cells use the inhibitory neurotransmitter GABA (GABAergic).

“Dopamine has been shown to inhibit synaptic transmission from the olfactory nerves.” (Shepherd -2004)

“Thus, the periglomerular cells exert an inhibitory influence on the mitral and tufted cells... evidence indicates that most of these elements are GABAergic, that many are dopaminergic and that GABA and dopamine co-localize within some of them.” (Nieuwenhuys – 2008)
Deeper in the olfactory bulb, the second area of interneurons is found. Here interneurons called \textit{granular cells}, in a similar fashion, also synapse with both mitral and tufted cells. However, this is done outside the glomerulus further along the axons of the mitral and tufted cells. Granular cells also use the inhibitory neurotransmitter GABA (GABAergic) to modulate the odorant impulse.

“Nocturnal studies point to GABA as the neurotransmitter released by the synapses of the granule spine onto the mitral/tufted cell dendrites... Because the granule-to-mitral/tufted synapse is the sole output of the granule cell, the inhibition it delivers is very powerful and is the main means for mediating control of output from the olfactory bulb.” (Shepherd – 2004)

“Most of the granule cells contain GABA, which inhibits mitral and tufted cells.” (Shipley – 1996)

Interneuron modulation, combined with the observation that cellular models of memory are evident in the activity of olfactory bulb neurons, suggest that the olfactory bulb is more than just a relay station and a passive conduit for odorant information.

“There is ample evidence that the olfactory bulb physiology is modulated by prior exposure and experience with odorants and evidence for feedback superimposed on the olfactory bulb. It is possible that the olfactory bulb acts as a filter of some sort that matches expected patterns of activity associated with food, mates or predators.” (Brewer – 2006)

“The inner layers of the olfactory bulb, therefore, seem to integrate sensory stimuli with centrifugal impulses and thus perform higher level data processing to aid in olfactory perception and control of olfactory guided behavior.” (Benignus – 1982)

**Olfactory Adaptation... Hmmmm...**

What arises from the inhibition of the odorant nerve impulse, via interneuron modulation, is the mechanism of \textit{olfactory adaptation} or sometimes referred to as \textit{olfactory fatigue}. Olfactory adaptation simply means there is a decrease in the sensitivity to a pre-existing odor within the olfactory bulb. Or in layman’s terms – you simply grow accustomed to a particular odor/smell.

“It is known that olfactory adaptation is not due simply to the exhaustion of receptor cells. The receptor cells keep firing... So the olfactory structure responsible must then be at the bulb or higher in the olfactory pathway... Physiological experiments show that the bulbar mitral cells firing decreases with long exposure to a single odor, suggesting the bulb’s involvement in olfactory adaptation.” (Li – 1990)
There are numerous examples of olfactory adaptation, for an example when you enter a restaurant you immediately perceive the aromas of the foods being cooked, but soon afterwards you become unaware of them. Two classic examples of olfactory adaptation, which pertain to MCS, occur with the use of perfumes/colognes and from cigarette smokers.

A woman may put on perfume early in the morning before heading out for the day. But by noon time this woman will barely be able to smell it anymore... though if someone new were to enter her space they most likely would have no problem “picking-up” her perfume. Unfortunately, thanks to olfactory adaptation and thinking that the perfume has worn off, the woman may re-apply more perfume to herself. This creates a situation where some people in her environment may now be overwhelmed by the second application of perfume to the point that the heavy odor may cause headaches, breathing problems, change of mood, etc.

The situation with cigarette smokers is very similar. Most smokers are completely unaware that the smell of the cigarette they just finished outside is “all over them”. And not just the cigarette they finished five minutes ago, but the one they finished an hour ago. Because most smokers partake in the habit of smoking cigarettes throughout the day and every day, their olfactory systems have adapted to the odor of cigarette smoke long ago. Unfortunately, most people in a smoker’s surroundings haven’t... yuk!

It is unclear as to the actual purpose of olfactory adaptation, though there may be more than one purpose. One of those purposes may serve as a means of protection. Take our restaurant example and consider the cooks who work in the kitchen full of dense odors. If their sensitivity to the ambient odors did not decrease, their situation would become extremely uncomfortable and even intolerable. Also, in the same scenario, if the olfactory sensory receptors were kept constantly busy with all these dense odors, they may then be unable to detect any real dangers, like a gas leak.

“Since the major olfactory problem of an animal in a rich olfactory environment is to identify odor objects, it would be desirable if the olfactory system could detect individual odors in a mixture. Olfactory adaptation may be a strategy used to detect individual odor components. It should not be understood as an olfactory fatigue, but as an active mechanism used by the olfactory system to screen out pre-existing odors, which have already been detected, while staying sensitive to new odors mixed with the pre-existing odors. For example, after a human adapts to vanillin, a mixture of vanillin and coumarin smells only of coumarin. Without adaptation, the new odors may be masked or counteracted by the pre-existing odors and not detected as the appropriate odor object.” (Li -1990)
The Olfactory Cortex

After interneuron modulation the axons of the mitral and tufted cells bunch together to form the olfactory tract and project their axons to several higher olfactory centers in the brain (though, the projection sites of the mitral cells differ from those of the tufted cells). These higher olfactory centers or nuclei structures are collectively referred to as the olfactory cortex or the primary olfactory cortex.

The olfactory cortex is an area located on the base of the frontal lobe and medial aspect (towards the middle of the brain) of the temporal lobe. Another interesting note – the olfactory cortex is the one area of the cerebral cortex that receives direct sensory input, unlike other sensory input that is first projected to the thalamus and then relayed to various cortical areas (other grey matter/cortex areas). Besides the fact that these structures jointly form the olfactory cortex, they are highly interconnected via an elaborate and dense associational fiber system.

Image: Structures of the olfactory cortex and their axon projections
In addition some odorant nerve impulses, from the primary olfactory cortex, are further projected to deeper nuclei structures within the brain. These structures are referred to collectively as the secondary olfactory regions or secondary olfactory cortex.

“Auditory and visual sensory information reach the orbitofrontal cortex after having undergone significant processing. The olfactory system is exclusive in that it has more direct contact to the external environment via olfactory receptor cells, input is relayed directly to the cortex and is not initially relayed to the thalamus. Lastly, cortical olfactory areas are phylogenetically older than other sensory cortical areas. This implies both an anatomical and functional proximity to the limbic system that is much closer than other sensory modalities.” (Brewer – 2006)

In the order of occurrence along the olfactory tract the primary olfactory cortex structures and their projected secondary olfactory regions are:

1. **Anterior olfactory nucleus** - poorly developed and understood.

   “… contributes fibers to the medial forebrain bundle which terminates in the hypothalamus as well as sending centrifugal fibers to the granule cells of the olfactory bulb.” (Benignus – 1982)
2. **Olfactory tubercle** – receives heavy projections from tufted cells in the olfactory bulb and is the last projection reached by the tufted cells. Cholinergic neurons from the olfactory tubercule send projections into the thalamus that then project to the **orbitofrontal cortex** (deeper area within the prefrontal cortex). This pathway may regulate cortical excitability and influence processing of odor information.

“... (the olfactory tubercle) is poorly developed... is an ambiguous and somewhat enigmatic structure... shows an intense staining for acetylcholinesterase, apparently related to intrinsic cholinergic neurons.” (Nieuwenhuys – 2008)

3. **Piriform cortex** – also termed the pyriform or prepiriform cortex, is the largest structure in the olfactory cortex and is the primary target structure for mitral cell projections. The neurons in the piriform cortex can be classified as either **pyramidal cells** or **non-pyramidal cells** (inhibitory cells using GABA). The piriform cortex transmits information to the frontal cortex and the thalamus (and in turn to the orbitofrontal cortex). Lesion studies of the piriform cortex demonstrate that it is also important in initial signal processing leading to conscious odor perception.

“The piriform cortex receives the largest conglomeration of direct inputs from the olfactory bulbs, which is why it has traditionally been considered the primary olfactory cortex, and the fact that the primary olfactory cortex contains a series of other structures has often been ignored.” (Brewer – 2006)

“Perpyriform cortical fibers are traceable to the amygdala, the hypothalamus and possibly the hippocampus. Amygdala cells fibers send axons to the hypothalamus, the prepyriform cortex and the hippocampus.” (Benignus – 1982)

4. **Amygdala - Periamygdaloid cortex** – olfactory bulb projections terminate densely on the periamygdaloid cortex that inhabits the medial surface of the amygdala and the lateral entorhinal cortex. **Anterior cortical nucleus of the amygdala** or **cortical amygdaloid nuclei** – borders with the piriform cortex.

“...also project to medial and anterior parts of the hypothalamus”. (Shipley - 1996)

5. **Entorhinal cortex** – borders with the piriform cortex and is poorly understood. The entorhinal cortex projects its neurons to the hippocampus.

It is thought that the purpose of the olfactory cortex, with its nuclei structures, is similar to that of the olfactory bulb. Similarly, the olfactory cortex receives odorant impulses from the mitral and tufted cells of the olfactory bulb and...

“It then organizes these odorant impulses into a more sophisticated manner and may even further modulate them” (Buck – Nobel Interview 2004).
Finally, as mentioned above, some of these new improved odorant impulses are projected to the secondary olfactory regions or deeper limbic structures. And some are projected to the higher olfactory centers within the prefrontal cortex, either directly from the olfactory cortex or indirectly via the thalamus. The prefrontal cortex with its deeper orbitofrontal cortex is part of the frontal lobe that is highly developed in humans and is involved in cognitive, emotional behavior functioning. It has also been reported that the prefrontal cortex receives direct neural projections not only from the olfactory cortex but also from the olfactory bulb itself.

Image: A more detailed view of the olfactory system and its neural pathways projected into the primary olfactory cortex

(ac – anterior commissure; am – amygdaloid complex; aon – anterior olfactory nucleus; aps – anterior perforated substance; entcx – entorhinal cortex; front – frontal lobe; hf – hippocampal formation; lai, lam, lapm – all areas of the insular; ncam – cortical nucleus of amygdala; olb – olfactory bulb; olped – olfactory peduncle; orbcx – orbital cortex; ot – olfactory tubercle; pamcx – periamygdaloid cortex; prpcx – prepiriform cortex; temp – temporal lobe)
The Limbic System

The limbic system (which is covered in more detail in an earlier report – “Hypothalamus and The Human Nervous System) is intimately involved in olfaction. For starters the olfactory bulb is a limbic structure. Second, the olfactory bulb projects odorant nerve impulses to structures in the primary olfactory cortex. Several of these structures - the anterior cortical nucleus, the periamygdaloid cortex and the nucleus of the lateral olfactory tract - are considered to be part of the amygdale, a limbic structure. And finally, structures of the primary olfactory cortex project their axons directly to the thalamus, hypothalamus and hippocampus, all limbic structures.

“The primary olfactory cortex projects to several other parts of the forebrain, including the amygdale, the hippocampus, the hypothalamus, the dorsal thalamus and the neocortex. The fibers that pass to the hippocampus and the amygdale arise principally from the periamygdaloid cortex and from the adjacent entorhinal cortex... the fibers that connect the primary olfactory cortex with the hypothalamus join the medial forebrain bundle and terminate predominantly in the lateral hypothalamic area.” (Nieuwenhuys – 2008)

Therefore, in olfaction the link between the outside world, with its infinite number of odorant molecules, and the olfactory bulb is direct and immediate. The extended link, to the primary olfactory cortex and to the deeper limbic structures, is only a synapse or two away. Unlike the other senses where limbic projections must go through a series of cortical relays.

The limbic system, like the olfactory cortex, is not a structure but a series of nerve pathways between a complex set of structures. A reminder of what the limbic structures and their function are:

- **Thalamus** – a large dual lobed mass of gray matter (neurons) found deep in the brain just above the brain stem. It acts as an integration unit that performs complex functions relaying all sensory signals (except for olfaction) to and from the spinal cord and the cerebrum.

- **Hypothalamus** – is attached to the underside of the thalamus and controls many functions in the body by acting as an interface between the limbic, endocrine and autonomic nervous systems.

“The hypothalamus is basically the major control center of the brain. It’s very primitive, it’s there in humans and animals, it’s highly conserved in its structure and in the genes that are expressed there and in the neural circuits and most if not all instinctive behaviors and emotional responses are controlled by the hypothalamus... and because odors can cause stress, fear, pheromones and maybe some odors can control sexual behavior, we can use the olfactory system to try to gain information about those circuits.” (Buck – Nobel Interview 2004)
“Olfactory cortex projects to the hypothalamus. The hypothalamus is thought to use olfactory information to affect feeding, reproductive activity, and autonomic reflexes triggered by olfactory signals - “the smell of fear.” (Voron – 2006)

- **Hippocampus** – plays a significant role in the formation of long-term memories and is very susceptible to damage from disease, anoxia (loss of oxygen) and environmental toxins. The major outputs of the hippocampus are to the cortex and to the hypothalamus.

- **Amygdala** – serves in attaching emotional significance to perceived stimuli and therefore is considered the emotional center of the brain. It is strongly associated with the emotions of fear and anxiety. As a whole the amygdala is highly interconnected with the hippocampus and the hypothalamus and because of these connections the amygdala is also involved in the processing, storing and retrieving of memories.

  “Highly aversive odorants activate the left orbitofrontal cortex and the amygdala... Thus, the greater activation by unpleasant odors reflects the strength of the emotional response rather than sensory intensity. This is consistent with the hypothesis that the amygdala mediates both negative and positive emotions.” (Brewer – 2006)

  “Studies showed that emotionally pleasant or unpleasant odors, but not pictures or sounds induced bilateral activation in the amygdala suggesting a superior potency of olfactory over visual and auditory stimuli to activate the amygdala.” (Brewer – 2006)

- **Olfactory System** – In this report we describe the olfactory system (above) as a separate system from the limbic system. When in fact many consider the olfactory system to be an integral part of the limbic system.

Therefore, it is the limbic system that integrates odorant nerve impulses or olfactory information with other neural, endocrine and immune functions.

  “Smell is recognized by cells that project to different areas in the cortex and some of those areas are new brain – cognitive brain and others are old brain – emotive brain. And one might think that the odors that activate emotive brain might elicit emotions and innate behavioral responses and neuro-endocrine responses without the consciences awareness of those signals.” (Axel –Nobel Interview 2004)
Centrifugal Fibers

Earlier it was discussed that centrifugal fibers are nerve axons that project back to the olfactory bulb in order to modulate incoming odorant nerve impulses. Centrifugal fibers originate from a variety of higher centers in the brain. Therefore, it is these higher centers that are responsible for regulating neural excitability in the olfactory bulb and the mechanism of olfactory adaptation.

Centrifugal fibers fall into two categories according to their point of origin. The first category is from the areas that receive odorant nerve impulses from the olfactory bulb and the olfactory cortex – in essence making a feedback loop. The other category is from non-olfactory cortex areas – which are mainly nuclei that release neuromodulators, such as noradrenaline, serotonin, and acetylcholine. The fibers from these nuclei project not only to the olfactory bulb, but also to other areas in the brain.

“One feature of the olfactory system that distinguishes it from other sensory systems is a tremendously rich supply of centrifugal fibers. These centrifugal projections may play a substantial role in the modulation of behavior.” (Brewer – 2006)

“The mammalian olfactory bulb receives a substantial number of projection fibers from other regions of the brain, and the abundance of centrifugal fibers indicates that the olfactory bulb is under extensive control by the rest of the brain.” (Matsuntani – 2008)

Image: Showing centrifugal fibers (feedback axons) in relationship to olfactory bulb
Neuromodulatory Centrifugal Fibers:

- **Noradrenaline fibers** - the olfactory bulb receives noradrenaline inputs from the *locus coeruleus*. The locus coeruleus is a nucleus in the brain stem involved with physiological responses to stress and panic. Noradrenaline has been shown to block the inhibitory effect of granule cells, which may lead to the enhancement of excitatory responses evoked by odorant nerve impulses.

  “Subsequent studies on rat olfactory bulb slices have shown that noradrenaline increases mitral cell responses to weak olfactory nerve input via $\alpha_1$-receptors, and that noradrenaline directly excites mitral cells... thereby enabling detection of relatively weak odors.” (Matsuntani – 2008)

- **Serotonin fibers** - the olfactory bulb contains abundant fiber projections from the *raphe nuclei*. The raphe nuclei are a cluster of nuclei also found in the brain stem whose primary function is to release serotonin to the rest of the brain.

  It is thought that the appearance of serotonin in the olfactory bulb acts as a kind of “survival molecule” for incoming olfactory nerve fibers. The loss of this support eliminates the odorant nerve impulse and the ability to detect odors (loss of smell).

- **Acetylcholine fibers** - the major source of acetylcholine fibers is the *basal forebrain*. The basal forebrain is a collection of nuclei structures that lie near the bottom of the front of the brain. The main purpose of the basal forebrain nuclei is to produce and distribute acetylcholine through the brain.

  “Also contradicting a simple relay function are the dense centrifugal projections into the bulb, including the large cholinergic input from projection neurons in the nucleus of the horizontal limb of the diagonal band of Broca (basal forebrain).” (Pressler – 2007)

  It is unclear as to the main role of acetylcholine fibers in the olfactory bulb. But it has been suggested that basal forebrain cholinergic neurons are involved in the regulation of cell survival. And in turn are associated with olfactory dysfunction and neurodegenerative disorders, including Alzheimer’s disease.

One common role among the different centrifugal neuromodulatory fibers is that of **neural plasticity** in the olfactory bulb, as well as in other regions of the brain. Neural plasticity is the ability of the brain to change and reorganize its neural networks in order to adapt to new conditions.
**Olfactory Cortex Centrifugal Fibers:**

In addition to the neuromodulatory centrifugal fibers, a large number of centrifugal fibers have been found to originate in the nuclei structures of the olfactory cortex. The origins of these fibers, is pretty much identical to the structures that received the original odorant nerve impulse. They include the:

- Anterior olfactory nucleus
- Olfactory tubercle
- Piriform cortex
- Periamygdaloid
- Anterior cortical nucleus of the amygdala or cortical amygdaloid nucleus
- Nucleus of the lateral olfactory tract of the amygdala
- Entorhinal Cortex

*“Extrinsic centrifugal fiber projections to olfactory bulb arise from nearly all of the primary olfactory cortical structures targeted by the outputs of mitral/tufted cells, including the anterior olfactory nucleus, and piriform, periamygdaloid and lateral entorhinal cortex.”* (Laaris – 2007)

The centrifugal projections from the olfactory cortex are often referred to as “feedback” projections - neurons in the olfactory cortex receive inputs from the olfactory bulb, and in turn, return their axons back to the bulb. These feedback or reciprocal centrifugal fibers synapse with the periglomerular and granular cells of the olfactory bulb and release inhibitory neurotransmitters.

*“Excitation of the centrifugal fibers has been shown to exert a profound depressive influence on the electrical activity of the bulb... depressive influences were evoked by exciting the basal rhinencephalic area, made up of the prepyriform cortex, cortical amygdaloid nucleus and olfactory tubercle.”* (Kerr – 1955)

*“These feedback projections from olfactory cortex to the olfactory bulb are believed to primarily excite the GABAergic granule cells in olfactory bulb, which in turn inhibit firing of mitral cells via dendrodendritic synapses between granule and mitral cell dendrites.”* (Shipley - 1996)

It is important to note that the centrifugal fibers, originating from the various nuclei of the olfactory cortex, are heavily influenced by other brain regions. Those brain regions are none other than the same areas that the primary olfactory cortex projected the original odorant nerve impulse too – the secondary olfactory areas. This further extends the feedback loop to include the prefrontal cortex and the deeper limbic structures - amygdala, thalamus, hypothalamus and hippocampus.
“Because the olfactory cortex receives inputs from limbic and neocortical areas in addition to inputs from the bulb, the centrifugal inputs from the cortex can modulate odor processing in the bulb in response to non-olfactory as well as olfactory cues.” (Matsuntani - 2008)

Conclusion... The MCS Connection

After researching and writing this report it seems clear, to this author, that there is a direct relationship between the centrifugal fibers, olfactory adaptation and MCS. More specifically, it is the biochemical mechanisms behind olfactory adaptation that appears to be dysfunctional, thereby causing hypersensitivity to odorants.

It is important to note that this conclusion is a theory (my) and potentially explains some of the symptomatology of MCS. It is also a major piece to the MCS puzzle and confirms the author’s original hypothesis (earlier reports) that – it’s the hypothalamus! Actually, after researching and writing this report I need to make a slight adjustment - it’s the amygdala and hypothalamus!

Somehow, neurological damage has taken place within the amygdala and hypothalamus. Presently, it is not known what type of damage has occurred, how severe the damage is or even the root cause of the damage. Possible candidates for the cause are your usual suspects – viruses, bacteria, fungi, pollutants, toxins, heavy metals, etc. Damage occurs when one or more of these exogenous agents gains access to these nuclei structures. This may occur due to the lack of a blood brain barrier in specific areas of the brain where the hypothalamus and amygdala are located.

Once damaged, the amygdala and hypothalamus function poorly at their main task of processing sensory stimuli. And as we just learned the main source of sensory stimuli, with its 363 gene sequences, millions of sensory neurons, thousands of processing/relay stations and with direct access to higher cortical regions and the limbic system is none other, than our sadly taken for granted, sense of smell – olfaction.

Instantly, the amygdala and hypothalamus receive odorant nerve impulses from the olfactory bulb. It is now their job to process this information and via centrifugal fibers, send a feedback nerve impulse back to the olfactory bulb. There granule and periglomerular cells receive the feedback nerve impulse and release inhibitory neurotransmitters – GABA and Dopamine - which modulate and inhibit the original excitatory odorant nerve impulse.

If any of the nuclei structures in the higher olfactory centers, like the amygdala and hypothalamus, are damaged this will result in a poorly functioning feedback mechanism. A poorly functioning feedback mechanism will result in highly excitatory odorant nerve impulses, with no modulation (inhibition), being projected directly to the prefrontal cortex, olfactory cortex and limbic structures. Neurons in these
regions and nuclei structures will then become over stimulated. If this scenario continues the neurons and their neural pathways will become highly sensitized and easily stimulated. The result – neural sensitization, and soon neurons in the affected areas will begin to dysfunction causing symptoms related to the function of the particular nuclei structure affected.

Finally, as discussed in the report – “Neural Sensitization & MCS”, the acute hypersensitivity to odorants may be perceived as some type of a biochemical mechanism that is amplifying the original odorant nerve impulse. This is understandable however, what we have now just learned is that the actual mechanism involved is in fact just the opposite of amplification.

Meaning, the original odorant nerve impulse is already highly amplified due to the incredibly high number of olfactory sensory neurons and their specialized odorant receptor genes. What is needed and what normally happens is that the highly amplified original odorant nerve impulse is then modulated by means of a feedback mechanism and inhibitory neurotransmitters. The result – olfactory adaptation with people milling about adapting to the various environments they are a part of.

Bottom line, people with MCS do not adapt!

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