DOI: 10.7860/JCDR/2012/3408.2382

Review Article

Physiology Section

Olfactory Memory Impairment in Neurodegenerative Diseases

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ABSTRACT

Olfactory disorders are noted in a majority of neurodegenerative diseases, but they are often misjudged and are rarely rated in the clinical setting. Severe changes in the olfactory tests are observed in Parkinson's disease. Olfactory deficits are an early feature in Alzheimer's disease and they worsen with the disease progression. Alterations in the olfactory function are also noted after severe head injuries, temporal lobe epilepsy, multiple sclerosis, and migraine. The purpose of the present review was to discuss the available scientific knowledge on the olfactory memory and to relate its impairment with neurodegenerative diseases.

Key Words: Olfaction, Memory, Neurodegenerative diseases

INTRODUCTION

The memory is encoded with the help of inputs which are received from the various special senses, of these, the roles of the auditory and the visual stimuli in the memory formation has been the area of interest for a majority of neuroscientists. The least studied special sense which has a major role in the memory is the olfactory sense. The olfactory system is a relatively simple system and it has long been implicated as having unique ties to the memorial processes [1]. Olfactory disorders are noted in a majority of neurodegenerative diseases but they are often misjudged and are rarely rated in the clinical setting. In spite of being present in neurological diseases, they are rarely reported by patients and they should be looked for with the olfactory tests. Severe changes in the olfactory tests are observed in Parkinson's disease. Olfactory deficits are an early feature in Alzheimer's disease and they worsen with the disease progression [2]. Alterations in the olfactory function are also noted after severe head injuries, temporal lobe epilepsy, multiple sclerosis, and migraine. The purpose of the present review was to discuss the available scientific knowledge on the olfactory memory, to relate its impairment with neurodegenerative diseases and to hence identify the individuals who were prone to develop a cognitive impairment in future.

WHAT IS MEMORY?

Memory is the ability to store and to subsequently retrieve past experiences and it is central to many cognitive functions. It is an intriguing topic that has garnered a widespread interest in the field of medical research. Memory is an interesting but ill understood subject. The depths of this fascinating process have yet to be explored. Memory makes us unique and our personality ceases to exist once our memory is lost. The experience of memory loss is one of the most devastating events that affect many people around the world. The prevention or the treatment of memory loss would be possible only if the mechanisms which underlie the formation and the storage of memory are understood. Immediate, recent and past memories are the three important categories of memory. Memory is further divided into implicit memory and explicit memory.

Short-term memory is the cognitive system which is responsible for the temporary maintenance and the manipulation of information [3]. Synaptic potentiation is one of the mechanisms which underlie the phenomenon of short term memory. Long-term memory is accompanied by actual structural changes rather than only chemical changes. The olfactory system presents unique opportunities for examining the neurobiology of the simple memory.

OLFACTORY MEMORY

The olfactory memory has been referred to as unique and it is considered to be different from other types of memory systems [4]. Olfaction is the sensory modality that is physically closest to the limbic system. The olfactory memory is highly advantageous for the multipronged investigation of the memory that lasts for a significant duration of a lifetime. Although the study on the olfactory memory began at the end of the last century, most of the memory models have ignored this nonverbal, non visual stimulus. Exactly how smells are perceived, stored in the memory, and are then recalled many years later, has not yet been fully understood. Much of what we know about olfaction has been learned from animal studies that may or may not be applicable to the olfaction in humans. White and Treisman [5] posited that the olfactory memory occurs because individuals assign verbal meanings to the olfactory stimuli. They also claimed that just as the olfactory sense was a crucial sense for other animals, "there is no prior reason why humans alone should lack an olfactory memory". The olfactory memory is believed to have only the long term memory component as opposed to the other sensory modalities, which have both long and short term components [6] but this view was in vast contrast to most of the current cognitive views on the memory organization [3]. The research which has been done on the olfactory memory is limited as compared to the studies on visual and auditory memories. The evidence from the research which was conducted by Engen and colleagues [4,6] claimed the absence of a short term memory in olfaction. However, the more recent research has suggested the presence of a short term component as well [5]. The patients with temporal lobe lesions showed impairment of the olfactory memory, as was noted by the studies which were conducted by using the

technique of functional neuroimaging [7].

The evidence on the presence of the olfactory short-term memory system could be inferred from experimental results which had demonstrated that the smaller number of odours was remembered better than the greater number of odours. Schab's [8] research on the olfactory memory proved that the olfactory system was slow in processing information; hence, the immediate memory performance was less as compared to the ability to recollect the odour memory after 2 or 3 weeks. Hence, by suggesting that olfaction has a long-term memory with a rather larger capacity, but based on the neuropsychological differences, the presence of the short and long-term memories in olfaction is disputable. Many groups of neuropsychological patients were tested for their olfactory abilities, but most were found to be either impaired in both the olfactory detection and the quality discrimination [9,10] or to be impaired only in the quality discrimination [11]. Thus, the disassociation is primarily between the detection and discrimination and hence the evidence on the existence of the 2 streams of memory is rather slim.

A long-term olfactory memory formation requires the coincident release of glutamate and Nor Epinephrine (NE). A long held view of the synaptic plasticity has been that the short-term synapse modification occurs through the phosphorylation of proteins and that the long-term synapse modification requires gene expression, which in turn is regulated by the gene expression cascade. This cascade is induced by the cAMP responsive element binding protein (CREB) and it is inhibited by repressors. These repressors are degraded by the ubiquitin proteosome pathway. Ubiquitin marks the proteins which have to be degraded i.e. the repressors, by forming covalent linkages. These linkages are then identified by the proteolytic complex, the proteosome [11-14]. This pathway is activated by Protein Kinase C (PKC). Hence, long term facilitation is induced by the regulation of the proteolysis CREB repressor by PKC [15].

THE PHYSIOLOGY OF OLFACTION

Odourant substances bind to specific receptor proteins which are present in the olfactory mucous membrane. Each olfactory receptor protein has one type of molecule that it responds to, which is known as the one-olfactory-one-neuron rule, and approximately one thousand kinds of which have been identified [16]. The axons of the olfactory neurons pierce the cribriform plate and end in the olfactory bulb [17,18]. The olfactory receptor cells make glutaminergic synapses on the second order neurons in the olfactory bulb, which are known as the mitral cells. The olfactory bulb itself determines how odours come to be encoded through its temporal structure and firing rate, which in turn influences the likelihood of an odourant being remembered. The mitral cells and the tufted cells of the olfactory bulb help in the modification of the stimulus which is perceived and from the olfactory bulb; the information is relayed onto the olfactory cortex. The olfactory cortex includes regions of the temporal lobes which include the pyriform cortex, the entorhinal cortex, the periamygdaloid cortex and the anterior cortical nucleus of amygdala . The mitral cells are glutaminergic and they target the pyramidal cells within the piriform cortex, which is a major subdivision of the olfactory cortex, which has *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors which include metabotropic glutamate receptors [19]. The metabotrophic receptors are G protein coupled receptors which decrease the cAMP levels. The presynaptic terminals of mitral cell axons also express metabotropic glutamate receptors [20]. The pyramidal cells of the pyriform cortex project to the amygdala, which in turn has projections to the hypothalamus and the brain stem.

The highest level processing of the olfactory information takes place in the olfactory cortex which lies in close association with the amygdala and the hippocampus. The information which is gained by the olfactory system not only is relayed to the olfactory cortex, but it is extended to the limbic system and the cortex. The limbic system is the primitive part of the brain that control emotions, memory and behaviour. In comparison, the cortex is the outer part of the brain that has to do with conscious thought. Because the olfactory information goes to both the primitive and the complex parts of the brain, it effects our actions in more ways than we think. The olfactory memory forms an important part of our day to day activities. From the olfactory cortex, the information is relayed to the amygdala and the hippocampus. The amygdala is involved with the emotional memory while the hippocampus is related to the short term and the working memory. Other relay stations for odour are the hypothalamus, the thalamus, the pituitary glands, the raphe nucleus and the locus ceruleus. These areas determine the kind of odour sensation and the feelings and the memories which are associated with it. Neuro-modulators exist in the olfactory system, which regulate the storage of information in a way that maintains the significance of the olfactory experiences [21]. Both the implicit and the explicit memories depend highly on the concentrations of the neurotransmitters like norepinephrine and acetyl choline, as was noted from research studies which were conducted in rats [22,23]. Olfaction and memory are so infused that they allow us to make connections with experiences that we have had in the past. Due to their connections with the limbic system, each scent which is recognized by the receptors will basically be stored as memories.

IMPLICIT ODOUR MEMORY

This does not involve the awareness or the conscious recollection of the initial exposure to the stimulus. Its retention does not involve processing in the hippocampus.

The techniques which are used to study the implicit olfactory memory are considered to be applicable to both humans and animals. The evidence of the formation of the implicit memory is found in the tests of habituation, sensitization, perceptual learning and classical conditioning [24]. In olfaction, there exists a strong tendency for habituation [25]. By evaluating the memory performance of the tasks which involve one of these 'subsets' of implicit memory, the effect of the previous odour stimulus experience which does not involve the conscious recollection can be measured [26].

Habituation is the decreased responsiveness to a particular stimulus that is no longer perceived as novel. In the olfactory memory, habituation is the result of the adaptation of the receptor neurons and the mitral cells. The pyriform cortical neurons also play an important role in the adaptation. The neurotransmitters, norepinephrine and acetyl choline are also involved in the adaptations, though the exact mechanism by which it is being brought about is not yet clear [21].

McNamara et al proposed that the odourant exposure elicits two physiological responses which are relevant to the habituation [27]. A short-time scale odour habituation is mediated within the anterior piriform cortex and a longer timescale odour habituation is mediated at the level of the olfactory bulb. Thus, they demonstrated two neural mechanisms which underlie the simple olfactory learning. The infusion of MK-801, which is an NMDA receptor antagonist,

into the olfactory bulbs, prevented the odour habituation only at longer timescales. LY341495, a class II/III metabotropic glutamate receptor antagonist, blocked the habituation only when the induction time-scale was short. The involvement of the NMDA receptors in the olfactory bulb plasticity has been established in studies which were done on both the bulbar cellular activities [28,29].

Explicit memory: The phenomenon of explicit memory is exclusive to humans. It refers to the memories that are remembered with a conscious awareness of doing so. Being related to olfaction, explicit memory refers to attributing an associative meaning to the odours. The explicit memory of odours includes the information which can be used to process and to compare the other encountered odours. The two most commonly used tests for the explicit memory are odour identification and odour recognition.

ODOUR RECOGNITION

This is the most common means which is used to measure the odour memory. In this test, the participants are asked as to whether they recognize a particular odour or not. The participants of the test are exposed to a particular olfactory related stimulus and after a delay period, they are asked to decide whether a probe was the same as that which they had once previously encountered. The memory accuracy is assessed by the amount of the correct recognition decisions that are made [25,26].

ODOUR IDENTIFICATION

In odour identification, the specific labelling of the presented olfactory stimulus is required. In humans, the odour identification process is quite weak as compared to the odour recognition, due to a weak link between the odours and the language. The difficulty in identifying and giving a label to the olfactory stimulus is known as verbal semantic processing, and this becomes increasingly worse with age [25,26].

NEURODEGENERATIVE DISEASES

As the research on neurodegenerative diseases is progressing, many similarities which relate these diseases on a sub-cellular level have been identified [27,28]. Numerous studies have quoted that olfactory impairments have been associated with dementia and neurodegenerative diseases, but the exact nature of how the olfactory disorders are related to the neurodegenerative diseases, has not yet been established.

Neurological diseases like Alzheimer's Disease(AD) and Parkinson's Disease (PD) are associated with non-inflammatory neuronal cell loss and they are accompanied in the early stages with olfactory disturbances. This important fact has garnered a widespread interest among the neuroscientists. Some other neurodegenerative diseases such as Progressive Supranuclear Palsy (PSP) are not similarly associated with the smell dysfunction, thus suggesting that the olfactory testing may be of value in their differential diagnosis. In neurodegenerative diseases like Alzheimer's and Parkinson's disease, there is a significant and an early impairment of the olfactory functions [27,28]. A meta-analysis which was conducted by Mesholam [29] further asserted the presence of abnormalities in the three major domains which were related to olfaction i.e., odour identification, odour recognitions and the threshold for odour detection. These showed similarities in both AD and PD and the impairments are noted even before the onset of the other clinical symptoms. The understanding of the relationship between dementia and olfactory memory loss at the molecular level is critical and it may facilitate the identification of the individuals who are more prone to dementia. An early detection of these slowly progressive diseases offers the promise of a presymptomatic diagnosis and, hence, the instillation of disease modifying medications early in disease and during the presymptomatic period.

MEMORY LOSS IN ALZHEIMER'S DISEASE

Memory loss is the key feature of a majority of neurodegenerative diseases and these patients show a particular vulnerability for the odour memory. Alzheimer's Disease (AD) has been identified as a proteopathy which is caused by the accumulation of abnormally folded A beta and tau proteins in the brain, resulting in the loss of neurons and synapses in the cerebral cortex, and in the certain subcortical regions [30]. In the early phase of Alzheimer's disease, there is a loss of the short-term memory and as the disease progresses, there is long-term memory loss. The cholinergic system plays an important role in the memory, and anticholinergic agents such as atropine and scopolamine interfere with the memory. The cortex of the patients with Alzheimer's disease is known to be deficient of cholinergic receptors and the enzyme, choline acetyl transferase. In Alzheimer's disease, the Amyloid Precursor Proteins (APP), by some unknown mechanism, are divided into smaller fragments by enzymes through proteolysis [31].

The basic pathological evidence of Alzheimer's disease is the presence of amyloid beta in the brain, but the molecular mechanism by which this affects the memory remains unclear. Turner [32] and Hooper [33] have highlighted that amyloid-beta effectively blocks a cascade of enzymatic reactions that activate a protein which is critical for the memory formation, which is called Creb (Cyclic adenosine monophosphate response element binding). They also found that an increase in the amyloid beta level was linked to the deficiency of an enzyme, uch–L1, which was involved in the ubiquitin proteosome system. Hence, it was noted that by focusing on this enzyme, the memory loss could be prevented. The neuropathological changes in Alzheimer's disease begin in the entorrhinal and trans entorrrhinal areas which are the regions which are important in processing the olfactory memories [34-36].

Why there is loss of olfactory memory in Alzheimer's disease, is not yet known but it is a known fact that anosmia and Alzheimer's go hand in hand. In the studies which were conducted by Solomon, [37] and Nordin et al., [38] it was noted that the AD victims were not aware of the onset of anosmia or the severity of damage and that therefore they did not recognize their loss of olfactory sensitivity. A smell sensitivity which is about 10% less than that of the normal population can be taken as a criteria that could indicate the onset of AD. Anosmia can be used as a probable indicator of the diagnosis of AD, but anosmia itself cannot be a definite factor.

PARKINSON'S DISEASE

The olfaction related deficits in Parkinson's disease were noted as early as 1975. This study was further reinforced by Doty et al., [39]. The aetiology of Parkinson's disease, whether it is genetic or environmental or the genetic susceptibility to an environmental agent, is still a matter of debate. A large study which involved male twin pairs was undertaken by Tanner [40], to assess the role of genetic factors in Parkinson's Disease (PD). The genetic factors are strong in those with a young age of onset, while in those with late onset disease, the genetic factors appear less important, hence emphasizing the role of the olfactory neurotoxin as a possible pathogenic mechanism.

The olfactory vector hypothesis suggests that the causative agent for Idiopathic Parkinson's Disease (IPD) enters the brain via the nasal route, but the reason for the olfactory dysfunction may be more subtle. It has been proposed that the initial causative event in IPD may start in the rhinencephalon (olfactory brain), prior to the damage in the basal ganglia. Daniel et al., [41] demonstrated in his study that the loss of the olfactory nucleus was associated with the duration of PD. The pathological evidence i.e., the presence of Lewy bodies confirms the presence of the cellular damage which is characteristic of PD in the olfactory bulb and the hippocampus [42]. The genetic theory regarding PD is the presence of point mutations in the gene which codes for α-synuclein. It was noted that in rats, the area of major expression of alpha synuclein was in the primary olfactory areas, while the nigrostriatal regions had a second place. The areas with a major expression of synuclein in the human brain have not yet been characterized, but considering their homology with rats, the roles of the olfactory pathways have been emphasized [43].

HUNTINGTON'S DISEASE

In Huntington's disease, there is loss of the medium spiny neurons and the presence of astrogliosis. The areas which are affected are the striatum and the regions of the frontal and the temporal lobes. The mutant, huntingtin is an aggregate-prone protein. Normally. these proteins are retrograde, they being transported to the cell body where they are destroyed. It is a possibility that these mutant protein aggregates damage the retrograde transport of the important cargoes such as the Brain-Derived Neurotrophic Factor (BDNF), by damaging the molecular motors as well as the microtubules.

The patients with Huntington's disease exhibited significant deficits in the odour identification, but the odour recognition memory was not affected [44,45]. The early olfactory impairment in Huntington's disease may be due to the accumulation of the huntingtin protein, as was noted by the studies which were done in animal models [46].

The devastating effects of neurodegenerative diseases on individuals could be controlled by the preclinical detection of these diseases. In the present review, the role of the olfactory dysfunction in the preclinical detection of neurodegenerative diseases has been highlighted. Further characterization and a deeper understanding of the olfactory deficits in neurodegenerative diseases will augment our acumen for the preclinical detection and for the elucidation of the pathogenic mechanisms to guide the development of new therapeutic modalities.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Jan 25, 2012**
Date of Peer Review: **Jun 06, 2012**
Date of Acceptance: **Jul 24, 2012**
Date of Publishing: **Oct 10, 2012**