Decline in olfactory capability as an early indicator of Alzheimer's Disease

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Abstract

Most adults experience some degree of memory impairment as a normal side effect of aging. However, in 75% of patients, Alzheimer's disease is the cause of these impairments. The two hallmark characteristics of Alzheimer's disease are the presence of neurofibrillary tangles and amyloid-beta plaques. These prevent normal functioning of the regions of the brain in which they are present. Symptoms of Alzheimer's disease can range from difficulty remembering recently learned information and subtle differences in abstract thinking in the early stages, to a dramatic reduction in language capabilities and inability to remember important details regarding one's own life history in the advanced stages of the disease. Interestingly, many patients also exhibit an inhibited sense of smell and may have difficulty correctly detecting and identifying odors. Research has shown that patients suffering from Mild Cognitive Impairment (MCI) and the earliest stages of Alzheimer's disease show significant decreases in both odor detection threshold and ability to correctly identify odors when compared to matched, healthy controls; this points strongly to the use of smell inventory tests, such as the commonly-administered University of Pennsylvania Smell Inventory Test (UPSIT-40), as diagnostic tools to aid physicians in making a diagnosis and beginning treatment for the disease earlier.
**Introduction**

Most adults experience some degree of memory impairment as a normal side effect of aging. However, in 75% of patients, Alzheimer's disease is the cause of these impairments (Eschweiler et al. 2010). Symptoms can range from difficulty remembering recently learned information and subtle differences in abstract thinking in the early stages, to a dramatic reduction in language capabilities and inability to remember important details regarding one's own life history in the advanced stages of the disease. This is alarming because of the severe impact that Alzheimer's disease has on patients and their families, who typically become caregivers on whom the patient is completely dependent. Perhaps the most devastating aspect of the disease is the way in which the patient's dementia becomes progressively worse; while many patients are still able to function at time of diagnosis, they are often rendered incapable of most activities of daily living as the disease runs its course. The fact that it is so widespread (as many as one in twelve individuals over the age of 65 is diagnosed with Alzheimer's disease) calls for research to examine the specific characteristics of the disease, as well as ways to better screen at-risk persons in an effort to detect the disease in its earliest stages. This will presumably lead to better prognosis for the more than 5 million Alzheimer's disease patients that live in the U.S. alone.

The two hallmark characteristics of Alzheimer's disease from an anatomical standpoint are the presence of neurofibrillary tangles and amyloid-beta plaques. These create lesions which cause synapse loss in key brain areas, which eventually lead to neuron death. These lesions can be observed through use of low microscope and, thus far, a diagnosis of Alzheimer's disease can only be confirmed by a
In an animal model study conducted by Wirths & Bayer (2010), Alzheimer's model mice typically showed significant neuron loss associated with the accumulation of amyloid-beta plaques in the neurons themselves (as opposed to extracellular accumulations of these plaques). Interestingly, one of the first brain areas to be affected is the parahippocampal cortex; this manifests itself as olfactory dysfunction which can be detected much earlier than a diagnosis of Alzheimer's can be made (Erschweiler et al. 2010).

Another theory suggests that neurotransmitters, especially acetylcholine and, to a lesser extent, glutamate, may play a significant role in the degeneration of CNS areas seen in Alzheimer's disease patients. The cholinergic hypothesis suggests that degeneration of the basal forebrain results in a deficit of the neurotransmitter acetylcholine (Martorana, et al. 2010). The premise of this theory is that the role of acetylcholine in cognitive processes is such that an increase in acetylcholine levels in the brain should lead to increased cognitive function in patients suffering from Alzheimer's disease symptoms. This has been attempted through the use of acetylcholinesterase inhibitors, but has been met with little success. Though the authors note that these drugs are not terribly cost-effective, they suggest that this is not the cause of the low clinical value of these drugs. Instead, the authors suggest that although acetylcholinesterase inhibitors show a certain level of effectiveness, they are unlikely to be of significant clinical value because they do not address the way in which multiple transmitters are involved in the cognitive deficits and therefore only address one probable cause of the symptoms they seek to alleviate. The article concludes with a discussion of treatment options that address the interplay between these neurotransmitters have yet to be explored and will likely produce better results than targeting just one
neurotransmitter as the source of cognitive decline.

Steinbach et al (2010) state that neurofibrillary tangles always appear first in the hippocampus, amygdala, and other limbic/paralimbic structures; only after accumulating in high amounts in these structures can they begin to be found in other areas such as the prefrontal and parieto-temporal cortices. By the time the neurofibrillary tangles have become this prevalent, patients typically display the characteristic debilitating symptoms of the later stages of Alzheimer's. Given that the areas first affected by these neurofibrillary tangles are linked to olfaction as well as memory, this follows with other evidence that highlights olfactory dysfunction as one of the earliest signs that indicate the probability of an Alzheimer's disease diagnosis.

Anosmia, or complete loss of one's ability to smell, and hyposmia, impairment of one's olfactory capabilities, can have a profound impact on quality of life (Gaines, 2010). In addition to occluding perception of familiar smells that are tied to emotional memories, loss of olfaction is also often linked to loss of or reduction in gustation, though no causal relationship has yet been established (Stinton, et al. 2010). Loss of the ability to smell is often not regarded as seriously as the loss of other sense such as hearing or vision, but many patients who experience anosmia or hyposmia also report depressive symptoms related to their inability to smell. In addition, one's sense of smell is important for perceiving environmental cues that indicate danger, such as gas leaks or spoiled food. For the purposes of this review, olfactory dysfunction as a symptom of Alzheimer's disease is of primary concern; assuming that it is not caused by damage to the olfactory epithelium or brain trauma affecting structures which process olfactory information, olfactory dysfunction can be an important early
indicator of the presence of Alzheimer's disease.

Olfactory dysfunction is typically measured using one of several tests. The most common and well-documented of these is the University of Pennsylvania Smell Inventory Test or UPSIT-40, which consists of 40 different odors which are presented in a scratch-and-sniff format, each followed by four choices of answers. The UPSIT-40 test takes only 10-15 minutes to administer and is inexpensive and completely non-invasive. Because of this, it is generally the most widely-used measure of olfactory function; scores range from 0-40 (a score of 40 indicating that all odors were correctly identified). The typical, healthy young adult generally scores around 37 (+/- 1.7). Through use of the UPSIT-40 as a diagnostic tool, it may be possible to achieve earlier detection of Alzheimer's Disease in many patients, presumably resulting in delayed progression of the disease. Research has indicated that the UPSIT-40 or other comparable smell inventory test administered in conjunction with other measures such as latency of olfactory event-related potentials, or the amount of time between when a smell becomes present and when a person becomes aware of it, can result in a remarkable rate of correctly classifying patients with Alzheimer's disease of nearly 100%. This is incredibly important for furthering the goal of early detection of Alzheimer's disease through use of olfactory measures.

I. Olfactory Dysfunction

Bitter et al (2010) found a correlation between patients with anosmia, or loss of the sense of smell, and a decrease in volume of several brain areas, including the parahippocampal gyrus. This follows with the findings of the previously mentioned study by Erschweiler et al. (2010) and indicates that one of the areas affected in the earliest stages of Alzheimer's is also responsible in part for a
patient's ability to detect odors. This is significant because it provides the basis for establishment of a link between Alzheimer's and olfactory capability; this opens the door for further research to determine the extent of this correlation and if this information can be used to influence clinical practices and result in earlier diagnosis of the disorder.

Anosmia can be caused by damage to peripheral structures, such as the olfactory epithelium, as well as by degeneration of CNS structures responsible for processing of incoming olfactory signals (Wang et al. 2010). Researchers were able to observe differences in brain activity during olfaction between 12 Alzheimer's patients and 13 healthy subjects through the use of fMRI; the most notable of these was decreased activity in the primary olfactory cortex and hippocampus. Though only confirmed Alzheimer's patients were used in this particular study, it provides the basis for use of fMRI as a diagnostic tool in potential cases of Alzheimer's disease.

This follows with research that highlights the parahippocampal gyrus' role in normal olfaction in healthy populations of both young and old adults (Wang, et al. 2005). By using fMRI data to examine which brain areas become active during olfaction, researchers observed activation of known olfactory areas, including the piriform cortex and certain parts of the limbic system, in healthy young and old adults. Differences between the populations were consistent with scores on a test of olfactory ability (the commonly-administered UPSIT-40), which indicates that in a healthy older individual experiencing normal aging, all primary structures involved in olfaction still function in proportion to the amount of expected decline in olfactory ability. Given this information, it would be expected that in an individual with early or presymptomatic Alzheimer's disease, one or more of those same neural
structures would show decreased activity during olfaction, even if the individual's sense of smell was relatively the same as it would be if they were healthy.

In addition to the parahippocampal gyri, another area which shows volume loss in conjunction with Alzheimer's disease symptoms is the left hippocampus (Murphy et al. 2003). Given our understanding of the role of the hippocampus in long-term memory, it makes sense that it is one of the first areas to show structural abnormalities due to Alzheimer's disease. Through the use of structural MRI data, the authors observed a strong correlation ($r=0.85$) between performance on the UPSIT-40 and volume of limbic structures in the left hemisphere in 13 Alzheimer's disease patients compared to 22 healthy, matched controls. In this study, the most pronounced changes were observed in the hippocampus but also the parahippocampal gyrus and amygdala as well. This supports findings from previous research in addition to providing further evidence that the structural changes in neuroanatomy that have long been observed in patients with Alzheimer's disease have an impact on olfactory function as well.

The UPSIT-40 test is primarily used to measure a patient's odor identification ability. To measure the degree to which a patient's odor detection threshold has been affected by the disease, the Sniffin' Sticks test is typically used, though this test does contain subtests for discrimination and identification. The test is administered using a pen-shaped canister that contains a specific odor. The concentration of the odor can be adjusted to measure detection threshold, which is the primary advantage this test has over the UPIST-40, in which adjustment of the strength of individual odors is difficult. To test a patient's odor detection threshold, multiple pens containing the same odor at
increasing concentrations are presented until the patient reports that they detect an odor. Despite the
sniffin' sticks high test-retest reliability, the results are often less applicable as those from the UPSIT-40
(Haehner, et al. 2009). The authors of this study introduced an extended version of the sniffin sticks
test; the higher number of odorants used (32 compared to 12 in the standard test) was intended to
replicate the reliability and applicability that the UPSIT-40 test, which is more accurate in part because
of the wider range of odorants tested. The authors conclude that the sniffin' sticks test, especially the
extended version, can be used to track the progression of an individual patient's olfactory ability over
time. This has applicability for populations of Alzheimer's disease patients because it can theoretically
be used to track the progression of the disease as it correlates to decline in ability to smell, providing a
clearer understanding of the differences between the stages of the disease.

II. Structural abnormalities as they relate to olfaction

It is interesting to note that hyposmia progressively worsens through the first stages of
Alzheimer's disease, but there is virtually no difference in detection threshold or identification ability
between patients in stages three and four (Serby et al. 1991). The authors note in their discussion that
the loss of ability to correctly identify odors progressively worsens as the disease worsens, supporting
previously discussed evidence from Murphy (2003) that indicates a correlation between loss of volume
of select structures of the limbic system and performance on measure of olfaction. Early research by
Talmo et al (1989) suggested that changes to the structure and viability of neurons in the olfactory
epithelium occurring in Alzheimer's disease patients were indicative of and possibly correlated with
olfactory impairment seen in these patients. In addition, Serby et al state that diminished detection
threshold is generally a phenomenon that occurs later in the progression of Alzheimer's and therefore is not as viable as a potential diagnostic tool. Perhaps most importantly, the authors posit that the peripheral structures involved in olfaction are relatively resilient compared to the CNS structures associated with olfaction and as such, changes to peripheral structures less likely to be the cause of deficits in olfactory capability. Research by Trojanowski et al (1991) also confirms this assertion; while abnormalities in the olfactory epithelium were found in 100% of Alzheimer's disease patients involved in the study, 75% of healthy age-matched controls also showed similar degrees of degeneration and/or abnormalities. This indicates that normal aging produces the same changes to the peripheral structures involved in olfaction as Alzheimer's disease does, further strengthening the argument that the CNS is the site of the most important causes of olfactory dysfunction in patients with Alzheimer's disease.

Additional research confirms that the earliest site of structural abnormalities linked to Alzheimer's disease are limbic olfactory regions, especially the amygdala (Mann et al. 1988), and as shown in more recent research, the anterior olfactory nucleus, piriform cortex, and entorhinal cortex (Li et al. 2010). This article focused primarily on the piriform cortex, whose primary function is processing olfactory signals; this is also the site of the previously discussed parahippocampal gyrus. When compared to ten matched controls, the ten Alzheimer's subjects involved in the study were found to have significantly lower scores on the UPSIT-40 test but not on tests of detection threshold; this is consistent with other research. Interestingly, the Alzheimer's subjects in this study had difficulty assigning qualitative labels to odors; for instance, it was observed that they were equally as likely to describe 'minty' stimuli as being 'floral' as they were to describe the stimuli correctly. This indicates
that, in addition to difficulty identifying individual odors, Alzheimer's disease patients may also show a decreased ability to group similar odors based on qualitative assessments.

Research has indicated that even in patients who do not display Alzheimer's disease symptoms or mild cognitive impairment, widely regarded as a precursor to Alzheimer's disease, olfactory scores are related to both the development of the disease as well as the presence of the hallmark Alzheimer's disease pathology after a post-mortem brain autopsy (Wilson et al. 2009). This is significant because it indicates that decline in olfactory function begins well before any other measurable signs that an individual might be in the developing stages of Alzheimer's disease; patients who incorrectly identified four odors on a brief smell identification test (BSIT) were 50% more likely to develop mild cognitive impairment ($p = 0.028$). Furthermore, those patients showed more rapid decline in episodic memory ($p = 0.001$) and upon post-mortem brain autopsy, showed significantly increased amounts of Alzheimer's disease pathology such as neurofibrillary tangles and abundance of amyloid-beta plaques ($p = 0.028$). This provides clear support for use inexpensive tests of olfactory function in clinical settings to screen for possible Alzheimer's disease and to begin intervention sooner, possibly resulting in longer delay of appearance of symptoms for patients suffering from the disease.

**III. Relationship between olfactory dysfunction and decline in cognitive function**

In a review by Christopher Hawkes (2006), the importance of olfaction as a diagnostic tool in presymptomatic Alzheimer's patients or those in the very early stages of the disease is examined. In particular, the author notes that the smell pathways in the brain are impacted by the disease but that the olfactory bulb is usually the first site of structural abnormalities. In addition, Hawkes makes an
important note that olfactory dysfunction in patients with Parkinson's disease and Alzheimer's disease patients is similar across all categories (threshold detection, odor identification, and odor recall specifically); it is essentially impossible to distinguish between the two conditions based on the state of a person's sense of smell. The author also discusses research that indicates that the actual mechanism by which the odor stimuli are perceived is relatively unaffected, but that the signals that reach the CNS are incorrectly interpreted. Despite the mechanism that causes the olfactory dysfunction, it is stated that hyposmia is simply easier to measure than cognitive decline characteristic of the early stages of Alzheimer's disease, leading to the assumption that this is why it makes for a useful tool in detecting the earliest stages of the disorder. In addition, tests of olfactory function that have high clinical applicability are generally inexpensive and non-invasive, making them a favorable alternative to more costly and time-consuming diagnostic tools.

One of the most interesting links between olfactory dysfunction and dementia is examined in a study by Devanand et al (2000). The focus of this particular study was whether or not patients were aware of their olfactory deficits. The participants were 90 individuals with a mean age of 66.7 who experienced mild cognitive impairments and 45 individuals with a mean age of 64 who qualified as healthy control subjects. Participants were given an array of tests of their cognitive abilities as well as the UPSIT-40. Of these subjects, 77 returned for a follow-up examination after 10-20 months; out of 47 participants with low olfaction scores, 19 were diagnosed with Alzheimer's disease at the time of their follow-up examination. In contrast, none of the 30 subjects with normal-range olfaction scores developed Alzheimer's disease. Of the 19 patients who received Alzheimer's diagnoses, 16 reported that
they had no difficulty smelling, despite their low olfaction scores. This study highlights the prevalence of olfactory dysfunction in patients with cognitive impairments and, in conjunction with a subjective lack of awareness of these deficits, provides the basis for using this as a criteria for early diagnosis of probable Alzheimer's disease. As mentioned previously, early detection of Alzheimer's disease may help patients and clinicians work together on strategies to slow the development of symptoms. The authors conclude by stating that further research, including studies which examine the effects over longer follow-up periods as well as in larger sample sizes, is necessary in order to fully understand the implications of their results.

Another aspect of the interaction between dementia and olfactory dysfunction is examining whether or not poor scores on tests of olfaction are a product of memory loss or if they are are actually indicative of a diminished sense of smell. In a 1998 study by Nordin and Murphy, the authors assert that the most pronounced deficits in olfaction are caused by decline in “odor memory,” particularly episodic odor memory and semantic memory associated with applying the correct name (label) to the odor perceived. The latter in particular has the potential to affect scores on odor identification tests; patients with otherwise unimpaired abilities to qualitatively discriminate between odors might score poorly on the test if their ability to remember the correct name for a particular odor is impaired, for example. The authors also found there to be a difference in ability to recall odors in both short-term and long-term recall tests between healthy elderly adults and those with Alzheimer's. Interestingly, the authors also observed a difference in results when the subjects were presented with picture-based identifiers for the odors, rather than words. This supports the idea that patients may simply have trouble
with semantic memory and thus have a harder time remembering the name or label for an odor, but can correctly identify the source of the odor when presented with picture cues. The authors are careful to point out, however, that olfactory abilities are affected by normal aging, though not as severely as in Alzheimer's disease patients, and that care should be taken when examining olfactory dysfunction as a possible symptom/early indicator of dementia. This follows with the findings of previous research by Morgan et al (1995), which indicated that using pictures instead of verbal identifiers increased the likelihood that a patient would correctly identify a particular smell, despite the fact that Alzheimer's subjects performed worse than matched controls on both the verbal and picture-based assessment.

Research also indicates that the link between semantic memory and odor detection is actually stronger than originally thought (Razani et al. 2010). In assessing subjects abilities to identify and conceptualize stimuli based on written labels, subjects with Alzheimer's disease were far less likely to use abstract cues and instead relied heavily on perceptual differences between odors. This resulted not only in a decreased ability to correctly identify odors based on name, but subjects also showed a decreased ability to correctly associate similar odors, indicating that their ability to conceptualize relatively abstract concepts such as odors was impaired in contrast to their ability to perform the same tasks with relatively concrete stimuli such as colors. Chan et al (1998) have suggested that perhaps this is indicative that stimulus-specific semantic memory pathways may be affected differently in individuals suffering from Alzheimer's disease.

The effect of Alzheimer's on gustation has been demonstrated in an animal model, supporting the idea that certain pathways pertaining to the chemical senses might be impaired differently than for
other senses (Devi & Ohno, 2010). Specifically, researchers observed an impaired ability to acquire conditioned taste aversions in Alzheimer's model mice; this suggests that they have deficits involving coding the memory of an aversive stimulus. The authors did observe, however, that the absence of an enzyme that cleaves amyloid-beta precursor proteins (called BACE1) results in recovery of the implicit memory deficits exhibited by the Alzheimer's disease model mice. The most important aspect of the study, however, is that it provides a clear example of how implicit memory is affected in an animal model; previously, testing on animal models focused primarily on explicit memory, limiting the degree to which findings in animal studies were related to humans. Further research to determine the specific effects of amyloid-beta plaque deposition on olfactory dysfunction indicates that in an animal model, amyloid-beta plaques develop in mice earlier than neurofibrillary tangles (Wesson et al. 2010).

A later article by Murphy (1999) suggests that the threshold at which a patient detects a particular odor becomes higher as their dementia progresses; this follows with previous findings that indicate that olfactory dysfunction may not be quite as pronounced in patients in the early stages of the disease. In particular, Murphy discusses the differences in odor sensitivity and odor identification as a means of gauging the progression of dementia in elderly patients. The threshold at which odors are detected is certainly affected in the early stages of dementia, but typically not as dramatically as a patient's scores on tests of odor identification, which is also consistent with the findings of Doty et al (1987). Murphy states that the best approach is to consider a patient's sensitivity to odors in conjunction with their ability to properly identify odors when attempting to identify probable Alzheimer's disease.

Studies have shown that noninvasive cognitive treatments can assist in prevention and treatment
of Alzheimer's disease; when combined with pharmacological therapy, the results are better than either
treatment alone (Buschert et al. 2010). There is a strong indication that inability to correctly identify as
few as three odors on a standard smell identification test may increase the likelihood of a diagnosis of
Alzheimer's disease by four times (Eschweiler et al. 2010), indicating that even in the event that a
patient is lucky enough to not develop Alzheimer's symptoms, cognitive intervention is still a good idea
as it is noninvasive and would have no foreseeable negative consequences for healthy patients.

Discussion

The consistency of the findings of research on the subject of olfactory dysfunction as a
precursor to the development of cognitive symptoms of Alzheimer's disease is staggering; when taken
into consideration that this research has increased greatly in amount and depth in the past decade, it
becomes obvious that there is building evidence for the likelihood that measures of olfaction will play a
role in clinical diagnoses of Alzheimer's disease in the future. Unfortunately, it is difficult to say at this
time that there is clear and indisputable evidence that tests of olfaction alone can indicate the presence
of Alzheimer's disease.

In summary, the literature reviewed indicates a strong likelihood that elderly individuals who
experience olfactory dysfunction will develop, at the very least, mild cognitive impairment. In addition,
many of the studies also observed a strong correlation between brain areas that typically undergo
structural changes in Alzheimer's and olfaction; this indicates that as these structures degenerate or lose
volume during the course of Alzheimer's disease, there is nearly always an effect on olfaction. This
manifests itself at first as an impaired ability to correctly identify odors, possibly as a function of a
degeneration of the semantic memory pathways involved in olfaction. In the later stages of Alzheimer's
disease, it is not uncommon to observe an increased detection threshold; this is less useful as a
diagnostic tool, however, because the main cognitive symptoms of Alzheimer's disease are typically
measurable before this characteristic manifests itself.
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