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Smell and Taste Dysfunction as Early Markers for Neurodegenerative and Neuropsychiatric Diseases

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Abstract

During the last few decades a significant literature has evolved, suggesting that sensory dysfunction, particularly smell and taste dysfunction, can be early markers for neurodegenerative diseases such as Parkinson's and Alzheimer's and neuropsychiatric diseases including ADHD and Schizophrenia, all diseases that involve dopaminergic pathology. Smell loss and taste dysfunction appear in clinical versus non-clinical groups, and in longitudinal studies these symptoms have been noted years earlier than motor signs in the first degree relatives of individuals who already have the diseases. This paper is a review of the recent literature on empirical studies and reviews that have documented the results of sensory screenings of several groups with neurodegenerative and neuropsychiatric diseases and those first-degree relatives at risk for those diseases. Although early biomarkers could be useful in identifying those needing preventive intervention, the treatment literature is very limited.

Keywords: Smell and taste dysfunction; Neurodegenerative and neuropsychiatric diseases

Introduction

Smell is one of the oldest senses in evolution, plays a key role in development, relationships, pleasure, health, safety and survival [1]. Smell is associated with memories, moods and emotions, food preferences, pheromones, mating and parent-infant bonding. Although humans are less dependent on smell for survival than other mammals, smell is critical for detecting polluted air and water, smoke and leaking gas, and spoiled foods [2]. Despite these important functions, smell has been one of the neglected senses.

Although the sense of smell functions as early as the fetal stage,decreased olfactory function occurs with aging, with over half of those between the ages of 65 and 80 and over three quarters of those over the age of 80 experiencing this problem [3]. In a sample with olfactory disorder, 68% of the patients presented with hyposmia and 32% with anosmia [4]. Olfaction has been notably worse in men in most studies [2,5] ,although there are some exceptions[6]. In the latter study, lower olfaction scores were also related to lower educational status.

An inability to identify smells or tastes predates the clinical symptoms of several neurodegenerative and neuropsychiatric diseases, highlighting their importance as markers for early interventions. Neurodegenerative diseases that have been associated with inferior smell identification include Parkinson's [7-12], Alzheimer's [9, 13,14] and a myotrophic lateral sclerosis [8] and the neuropsychiatric/smell disorder conditions include ADHD [15,16], anxiety disorders [17], Autism Spectrum Disorder [18-20], depression [21], eating disorders [22] and schizophrenia [23-26].

Most of the empirical studies have compared clinical and non-clinical groups on smell tests, although more recently, some longitudinal studies have documented sensory dysfunction in at-risk, first degree relatives who later show the cardinal motor signs [8,27]. The University of Pennsylvania Smell Identification Test (UPSIT) is the most frequently used test [8], although several other shorter and less expensive versions have been developed including the Sniffin Sticker Test (SST) [9], the Brief Smell Identification Test (B-SIT) [28], the Odor Stick Identification Test (OSIT) [8], the San Diego Odor Identification Test (SDOIT) [28] and most recently the peanut butter smell test [14]. These tests, for example the Sniffin' Sticks test has been significantly correlated with a visual analogue scale in at least one study [29].

Because of cross-cultural differences in smell identification, researchers from other countries have developed alternative versions that feature smells that are prevalent in their cultures including Brazil [30], Japan [31] and South Korea (who call theirs the cross-cultural smell test) [32]. Although most of the smell tests were designed for adults, a child's version exists called the Sensory Identification Score [15], and infants with developmental delays are also being tested for sensory integration problems [33]. Others have evaluated the relationships between smell identification, taste threshold, dopamine transporter scan (DaTSCAN) and motor function and their diagnostic accuracy in early Parkinson's disease and have suggested that a basic smell test is as sensitive as the DaTSCAN in the diagnosis of Parkinson's [34],and, still others claim that they have not been as sensitive as the self-report measures [8].

Tests for taste have also been developed including sweetness, creaminess and pleasantness [35]. In that study, pleasantness identification was the most reliable of the three tests for taste. Liquid taste solutions for sweet, sour, salty and bitter have also been developed and have acceptable reliability [36]. Less conclusive data have been documented for taste dysfunction, although smell and taste disorders might be expected to be comorbid as those senses are often interactive, and many patients who have lost their sense of smell complain that their sense of taste is also blunted [9]. Some have noted that a damaged olfactory system reduces taste perception including sweet, sour, bitter and salty via the facial, glossopharyngeal and vagus nerves [37]. Comorbid smell and taste dysfunction has been reported for eating disorders, both bulimia nervosa and anorexia nervosa [22]. These were determined using the "Sniffin Sticks" method and the "Taste Strip" kit. Taste has been tested less often, probably because its assessment has been more difficult and aversive for research participants [35].

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The etiology and development of these sensory dysfunctions are not known, but the dopamine, norepinephrine, serotonin, acetylcholine and orbitofrontal cortex systems have been implicated in several of the neurodegenerative and neuropsychiatric conditions associated with smell dysfunction [8,38]. These include, for examples, Parkinson's and ADHD. Although sensory tests have been developed for infants and young children who are noted to have hypo or hypersensitivity as well as sensory integration problems [33], longitudinal studies have not been conducted to determine whether the negative effects that these problems have on child development persist into adulthood

Olfactory dysfunction appears to precede the motor and cognitive symptoms of several conditions, making it an earlier marker forpreventive interventions, althoughvery few effective interventions have been identified. Reportedly the medications that are effective for motor symptoms are not effective for sensory dysfunction [8]. Some corticosteroid and anti-inflammatory medications have been effective. For example, estradiolhas been effective but has only been tested in the rat [39]. And, methylprednisolone has been an effective medication in at least two studies [9]. Reputedly, olfactory training has also been effective [9].

Olfactory functions and development

The sense of smell is the oldest in evolution and functions as early as the fetal stage [1]. Some have noted fetal perception of aromas based on increased fetal activity and neonatal perception by changes in respiration, heart rate and facial expressions [40-42]. The newborn has shown positive reactions to amniotic fluid and breast milk odors [43,44] and negative responses to acetic acid odors [45]. In a study we conducted, 2-month-old infants cried less, had lower cortisol levels and spent more time in deep sleep after a bath in lavender oil than one without lavender [46]. In another study from our lab EEG recordings of 3-week-old infants showed a shift to greater left frontal EEG activation (which is a positive shift) following exposure to lavender aroma [47].

Adults show a similar relaxation response to lavender (as compared to rosemary) as measured by their EEG patterns and decreased heart rate and they also performed math computations in less time and with greater accuracy [48]. In still another study in our laboratory, adults who were exposed to lavender fragrance showed decreased heart rate, increased theta power and greater left frontal EEG activation, variables that are typically associated with relaxation [49]. Thus smell perception happens very early in life and smell preferences of young infants mimic those of older adults. These studies have been limited to lavender and rosemary aromas, and while lavender seems to have calming effects and rosemary arousing effects, the underlying mechanisms for these differential responses are not clear, and other odorants need to be tested for their effects on heart rate and EEG patterns.

Olfactory functions, anatomy and demographic factors

The sense of smell plays a critical role in the quality of life from infancy to old age [1], serving many functions in safety, e.g. detecting hazardous smells, in health, e.g. in food preferences and getting adequate nutrition, in emotions, e.g. memories of pleasurable experiences, feelings of pleasure, in behavior, e.g. sensing pheromones, in mother-infant attachment, and in longevity.Odorants that enter the nose are absorbed by the nasal mucosa and once absorbed stimulate olfactory receptors in the epithelium located over the cribriform plate [50]. Smell is then transmited via the olfactory bulb to the olfactory cerebral cortex and the orbitofrontal cortex. The orbitofrontal cortex receives both olfactory and taste stimuli.

Olfactory functions and dysfunctions are affected by several demographic factors.Demographic factors that affect the sense of smell include at leastgender, education and aging. Women have been noted to have a better sense of smell [8], although studies in other cultures have yielded mixed results. In a study on healthy Turkish adults the Sniffin Sticks scores were lower than in other countries and they decreased with age, and adults with less education had lower scores, but the scores were not related to gender or smoking [6]. In contrast, in a cross-sectional population-based survey in Spain in which four microencapsulated odorants (rose, banana, musk and gas) were distributed, the olfaction scores for men werelower, smell recognition declined after the sixth decade and scores were also lower for less educated adults [5]. The data on declining function with age appear to be consistent. In a recent review by [3],decreased olfactory function appeared in over half the population ages 65 to 80 years and in 75% of those over the age of 80. They further suggested that a disproportionate number of the elderly have died in accidental gas poisonings.

Incidence of olfactory dysfunction

In the cross-sectional population-based survey already mentioned, olfaction was normal for detection in 81% of the sample, for recognition/memory in 56% of the individuals and for identification in 51% of the sample [5]. Dysfunction was defined as hyposmia or anosmia if the adults recognized or identified one to three odors in the case of hyposmia or none of the odors as in anosmia. Most of the dysfunction was hyposmia (19%). This happened for recognition (44%) and identification (48%). Surprisingly,smoking and exposure to noxious substances were positively related to smell recognition in that study.

The incidences of hyposmia and anosmia were notably higher in a sample of patients seeking treatment for smell disorders in a study conducted in Portugal [4]. In this study, 68% of the patients had hyposmia and 32% had anosmia. The primary diagnoses were idiopathic (32%).

Psychophysical tests for olfactory dysfunction

Smell functions are most frequently assessed by psychophysical, self-report measures including odor identification and discrimination tests (central) and odor threshold tests (peripheral) [51]. Most of the studies to date have assessed odor identification using the UPSIT (the University of Pennsylvania Smell Identification Test) or some variation of that test. Most of the results from the different tests are highly correlated, although they feature different odorants and vary in their reliability and sensitivity [8].

The UPSIT is comprised of 4 booklets (10 pages each) with 40 microencapsulated "scratch and sniff" odorant strips that are scratched with a pencil tip and an odor selected from 4 odor descriptors. The UPSIT is strongly correlated with odor threshold tests and is reported to have a sensitivity of 91% and a specificity of 88% which are higher than the sensitivity/specificity measures of other biomarkers including PET and SPECT [8].

The Brief Smell Identification Test (B-SIT) which includes 12 odorants has been compared to the San Diego Odor Identification Test (SDOIT) comprised of 8 odors. In this comparison, both tests were in agreement on identifying impairment in 96% of the participants [28]. The "Sniffin Sticks" (SST) system features pen-like odor dispensers that are held under the nose and each odor is identified from a list of four choices [52]. The dispensers have the advantage of being reusable, and in one study the Sniffin Sticks scores were correlated with the participants' ratings of their sense of smell on a visual analogue scale [29].

Perhaps the simplest and shortest of the odor tests is a container of 14 g of peanut butter [14] that is held at the bottom of a 30 cm ruler and is moved gradually (1 cm at a time) up the ruler while the participant is exhaling and with eyes closed. The score is the distance the jar was from the nose when the peanut butter was detected. This inexpensive test also had good sensitivity and specificity, and the authors reported dysfunction for the left but not the right nostril. However, others have failed to replicate at least their left/right nostril asymmetry findings [53].

A self-report measure is the Screening Questionnaire for Parosmia (inability of the brain to identify an odor's natural smell) [54]. This is a four-item questionnaire with the first and fourth questions having the highest sensitivity and specificity (#1 Food tastes different than it should because of a problem with odors and #4 The biggest problem is not that I do not or only weakly perceive odors, but that they smell different than they should).

The UPSIT has been translated into a dozen languages and modified by replacing unfamiliar with familiar odors, for example, in Portugal [30], Taiwan and Australia. In the Portuguese version, the popcorn odor was replaced by rubber because more participants thought the popcorn odor smelled more like rubber. And, in Japan, the Japanese Odor Stick Identification Test includes odors like the bromine of China ink, curry, rose, cypress, menthol, sweaty socks and condensed milk [31], and a Cross-Cultural Smell Identification Test has been used in Korea [32].

A cross-cultural difference is one of the problems with cross-study comparisons. Others are that the tests assess different types of odorants and different odorant intensities. These problems are further compounded by the different alternative responses, both number and types of alternative responses. Nonetheless, the sensitivity, specificity and test-retest reliabilities are relatively high for most studies.

Olfactory tests have also been developed for children and infants. In one study children were presented with the essences of apple, banana, lemon and orange and asked to smell the essence from a bottle for 3 seconds and choose the smell from a list of 4 descriptors [15]. No age or gender differences were noted. Sensory Rating Scales have also been developed for parents' ratings on the senses of their infants and toddlers that include the degree of responsively to all the senses, i.e. to taste, smell and touch stimuli along with hearing and vision [33]. A laboratory paradigm called The Sensory Challenge Protocol has also been developed for use with children with Autism Spectrum Disorder [55]. In that protocol all senses except taste are assessed by presenting timed stimuli like a fire engine siren and wintergreen oil.

Psychophysiological and electrophysiological measures have also been used such as changes in heart rate, blood pressure and respiration, odor event-related potentials (OERP) and the electro-olfactogram (EGM)[56]. These have not been widely used because of their variability and the invasiveness of the measures (e.g. electrodes in the nose for the electro-olfactogram). In one study, several of these measures were used in addition to a dopamine transporter scan (DaTSCAN) [34]. In this study the sensitivity of the UPSIT (86%) was not significantly different from the DaTSCAN (92%) and these measures were moderately correlated. However, The OERP was not correlated with the DaTSCAN and the EGM was not correlated with any of the other measures, highlighting again the clinical utility of the UPSIT for assessing odor identification.

Taste testing

The sense of taste is less often tested even though it is closely interconnected with the sense of smell. The less frequent assessment of taste function may relate to the lesser frequency of taste dysfunction. Some 95% of perceived taste disorders are reputedly caused by olfactory rather than gustatory loss [57]. The gustatory system (facial,glossopharyngeal and vagus nerves) is closely related to the olfactory system [9]. Often the same individuals who lose their sense of smell also complain that they have lost their sense of taste. One set of contradictory findings including data from both regional and whole mouth tests of 581 patients at a smell and taste center suggests that olfactory dysfunction did not affect taste perception when the effects of sex, age and etiology were controlled [37].

The taste buds (approximately 10,000 of them) are located in the mucosa of the epiglottis, the palate, the pharynx and the tongue with each taste bud having a receptor [58]. The sensory nerve fibers from the taste receptors are transmitted to the gustatory nucleus of the medulla oblongata by the facial, glossopharyngeal and vagal cranial nerves and from there to the thalamus and to the gustatory cortex [58]. Some have speculated that the involvement of multiple nerves in taste may explain the lower incidence of taste versus olfactory dysfunction [50]. Taste has typically been categorized as sweet, sour, bitter, salty and umami (savory) and the disorders ageusia (complete loss), dysgeusia (distorted perception) and hypogeusia (reduced ability to taste) can involve one or more of these 5 basic tastes [50].

A common test for taste perception includes ratings of 20 mixtures of 5 dairy drinks on sweetness, creaminess and pleasantness [59]. The participants are asked to take a sip of the mixture and swirl it around in their mouth and then make the ratings and spit out the mixture. In a recent study these ratings were tested for their test-retest reliability, and only the pleasantness ratings were reliable [35]. The authors suggested that simply rating pleasantness would make the test 83% shorter and result in less burden and unpleasantness for the participants as well as unconfined the test that was affected by negative states experienced by the participants.

Liquid taste solutions for sweet, sour, salty and bitter tastes have also been developed [36]. In this study, taste discrimination was superior in women but declined with age. Whole mouth and Taste Strip Tests have also been used [60].

Questionnaires are perhaps the simplest. In one study a 4 item questionnaire was used including ratings on 1)saltiness in chips, pretzels or salted nuts; 2)sourness in vinegar, pickles or lemons; 3) sweetness in soda, cookies or ice cream and 4)bitterness in coffee, beer or tonic water [57]. These authors claimed that patients who had no difficulty detecting these tastes rarely had taste dysfunction based on other tests. Perhaps with these less aversive taste tests more research will be conducted on taste dysfunction and its relationship to smell dysfunction.

Drug-induced taste disorder was the most common diagnosis among patients attending a taste clinic in Japan. Other disorders that have been associated with taste dysfunction include Parkinson's disease, multiple sclerosis, chronic kidney disease and cancer, studies that are reviewed in a later section on dysfunction.

Sensory Dysfunction in Neurodegenerative Diseases

Sensory dysfunction has been noted in neurodegenerative diseases including Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (Table 1). The commonality across these diseases is dopaminergic pathology and possibly damage to cholinergic, serotonergic and noradrenergic systems [8]. As some have noted,olfactory

Neurodegenerative diseases	Parkinson's –odor detection threshold, recognition and identification, taste, comorbid smell and color, smell and pain
	Alzheimer's-odor detection threshold, recognition and identification
	Amyotrophic lateral sclerosis-smell
Neuropsychiatric diseases	Autism spectrum disorder-odor identification
	Attention deficit/hyperactivity disorder-odor detection and identification
	Obsessive compulsive disorder-odor identification
	Posttraumatic stress disorder-odor identification
	Depression-odor detection threshold
	Schizophrenia-odor detection threshold, recognition and identification
Other diseases	Irritable bowel syndrome- smell and taste
	Diabetes type 2-smell
	Kidney disease-taste
	Multiple sclerosis-smell and taste
	Child survivors of cancer-taste

Table 1: Summary of smell and taste dysfunctions in different diseases.

dysfunction and less frequently gustatory dysfunction are early markers of neurodegenerative disease that precede the motor and cognitive disturbances by several years. Early diagnoses could lead to interventions including, for example, anti-inflammatory medications and olfactory training.

Parkinson's:Reputedly 95% of those with Parkinson's (PD) show dysfunctional smell (75% having hyposmia or anosmia) which apparently precedes the motor symptoms by approximately 4-6 years [9]. The smell dysfunction is more prevalent than tremors (approximately 75% more prevalent) and other signs [61]. Surprisingly, most of the individuals with PD are unaware of their smell dysfunction until they are tested [8]. Longitudinal studies have documented smell dysfunction in a significant number of asymptomatic first degree relatives of those with PD [62].

In a review of the literature on smell dysfunction in several diseases [8] made several "generalizations" about smell dysfunction in PD including: 1)the dysfunction is bilateral and is a better diagnostic marker than motor tests [63]; 2) as already mentioned, women with PD perform better on the tests than men [64]; 3)usually there is not a total loss of smell, i.e. the loss is usually hyposmia; 4)the poor performance on smell tests is not related to specific odorants; 5)the average score across many diseases including PD and early stage Alzheimer's is 20 on the UPSIT; 6)medications that are effective for the motoric dysfunction in PD are not effective for the olfactory dysfunction(e. g. dopamine agonists); 7)the olfactory dysfunction in PD is stable and is not stage-dependent or related to severity of the disease;8) the olfactory deficit precedes the motor signs often by several years, serving as a pre-motor marker [65]; and 9) some asymptomatic relatives have olfactory dysfunction that predicts later PD.

Some exceptions to the generalizations made by Dotty [8] have appeared in the literature. For example, in a recent study using the 16 Sniffin' sticks with 148 PD patients and 148 healthy controls, disease severity was associated with low odor identification scores [7]. In addition, although [8] suggested that poor performance on smell tests is not related to specific odorants, [7] reported that their Parkinson's patients had the most difficulty identifying the coffee, peppermint and anise odorants.

In a study on taste in Parkinson's, 61 patients were compared to controls on Whole Mouth and Taste Strip Tests [60]. Although the Parkinson's patients' Taste Strip Test scores were lower, their Whole Mouth Test scores did not differ from those of the control group. The authors suggested that these contradictory results may relate to taste dysfunction not being detectable at supra-threshold concentrations of daily life foods. In contrast, in another study on Parkinson's patients only the women patients' Taste Strip Test scores were inferior to controls [66]. The authors attributed this finding to the women's Mini-Mental State Examination score being lower. This potentially confounding variable may explain some of the mixed findings in the literature, although this exam on mental function typically has not been included in research protocols on taste and smell.

Comorbid sensory dysfunction has also been noted in PD patients including color and smells discrimination and pain and smell disturbances. In a study on color and smell discrimination in PD patients the UPSIT and the Farnsworth-Munsell Color Discrimination Tests were given [67]. Both color and smell discrimination were impaired in the PD patients, and color and smell scores were significantly correlated in the PD group.To assess pain and olfactory disturbance in PD patients, somatosensory evoked potentials (SEPs) were recorded and the Odor Stick Identification Test for Japanese (OSIT-J) was used [68]. Pain processing was impaired in the PD group and their OSIT-J scores were correlated with their SEP amplitude.

Several other non-motor symptoms have been reportedly associated with smell dysfunction in PD including sleep disturbances, gastric and bowel dysfunction, cardiovascular conditions, mood and cognition problems, depression and anxiety [34]. These authors reported that 26% of theparticipants in their Parkinson At-Risk Syndrome study who had four or more nonmotor complaints were hyposmic compared to only 12% who had three or fewer symptoms [34]. However, as [10] has suggested, these non-motor symptoms are common in the general population, except idiopathic REM sleep behavior disorder which is predictive of PD. These researchers suggest the use of more specific markers, i.e. serial dopamine transporter imaging even though the sensitivity of the scan is reportedly similar to the sensitivity of the UPSIT which is much cheaper [34]. Nonetheless, identification deficits have effectively differentiated idiopathic from non-idiopathic Parkinsonism in at least one study [69].

Alzheimer's: Olfactory dysfunction is reputedly as serious in patients with Alzheimer's (AD) as it is in those with PD [9]. A meta-analysis studyrevealed that early AD could not be distinguished from early PD by odor tests [70]. However, unlike the mixed literature on the relationship between olfactory dysfunction and severity of PD, olfactory dysfunction and severity of AD were correlated. A more recent meta-analysis suggested that while both AD and PD patients were more impaired on odor identification and recognition tasks than odor detection thresholds, the PD patients did not perform as well as AD patients on detection thresholds [11]. A study on first–degree relatives at risk for Alzheimer's disease also reported olfactory dysfunction as an early biomarker [27].

The recent study using peanut butter odor detection suggested that AD patients had left nostril detection problems but not right nostril problems which is consistent with their having more degeneration of their left than right hemisphere (olfactory detection being ipsilateral) [14]. However, as already mentioned, another group failed to replicate this asymmetry using the same test [3].

In AD patients the olfactory dysfunction symptoms apparently emerge before cognitive deficits [71]. In a study using the Sniffin'Sticks odor identification test, AD patients also had significantly higher levels

of apathy relative to non-AD participants, but odor identification deficits were correlated with apathy levels, not depression, across the AD and non-AD samples [13].

Amyotrophic lateral sclerosis

In a study on amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's disease ALS patients' UPSIT scores were significantly lower than they were for a control group [72].

Sensory dysfunction in neuropsychiatric diseases

Sensory dysfunction is also an early marker for neuropsychiatric diseases including autism spectrum disorder, attention deficit/hyperactivity disorder, eating disorders, depression, obsessive compulsive disorder, posttraumatic stress disorder and schizophrenia, with the lion's share of the published research being on attention deficit/hyperactivity disorder and schizophrenia. And, as in neurodegenerative diseases, smell testing has been the most prevalent assessment of early biomarkers.

Autism spectrum disorder (ASD): Children and adolescents with autism spectrum disorder have shown poor performance on smell tests [73]. Although they are noted to have hypersensitive responses to visual and auditory stimuli, they have diminished olfactory function. In a study comparing individuals with ASD and Asperger syndrome, olfactory identification (higher-order olfactory processing) was impaired in the individuals with ASD relative to the participants with Asperger's [19]. However, their odor detection thresholds and discrimination abilities (lower-order processing) were not affected. In a recent review, two unpublished data sets on olfactory dysfunction in children with autism were consistent with the published data [16]. Potential confounding effects are related to the cognitive dysfunction, attention problems and sleep disorders of these children [74]. These data on children with ASD are, nonetheless,similar to findings on detection thresholds in adults with ASD [20].

Attention deficit/hyperactivity disorder (ADHD): In a review of olfactory function in children and adolescents with psychiatric disorders, the authors noted that those disorders that involved smell dysfunction also had pathology related to dopamine metabolism and orbito frontal cortex functioning including ASD, ADHD, obsessive compulsive disorder (OCD) and schizophrenia [16]. They also suggested that the child and adolescent smell dysfunction literature is much more limited than the adult literature and mentioned the heterogeneity of findings that they ascribed to methodological limitations including confounding variables like intelligence and infections and the use of different tests and odors. Their attention deficits alone could contribute to their smell dysfunction along with their sleep disorders.

Studies on children and adolescents with ADHD suggest alterations in olfactory processing (identification and detection threshold) [75,76] that are consistent with findings on ADHD adults [77,78]. In a more recent study odor detection was assessed with phenyl ethyl alcohol and odor identification with the essences of apple, banana, lemon and orange [15]. Both the Sensory Threshold Score and the Sensory Identification Score were lower for the group of children with ADHD than a group of non-ADHD children who were matched on age, gender and Mean School Scores. Further, the dysfunctions in detection and identification wereunrelated to age, gender and School Scores.

In contrast, thereare studies showing increased olfactory sensitivity in ADHD. For example, in one study odor sensitivity (lower thresholds) was noted in those ADHD individuals who were not on medications [76].This enhanced function was normalized under stimulant medication. Just as individuals with ADHD may be hyperactive without stimulant medication, they may be hypersensitive without medication. Other sensory modalities might be examined in this population to determine whether this hypersensitivity crosses senses.

Anxiety disorders: A recent review suggests that anxiety disorders have rarely been assessed for olfactory dysfunction.However, those with obsessive compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) appear to have identification deficits [17].

Depression: Depressed individuals have been characterized as having normal olfactory function except for detection threshold [79,17]. In a study on depressed individuals, smell threshold, discrimination and identification as well as chemosensory event related potentialsand functional magnetic resonance imagingwas assessed[21]. At the beginning of psychotherapy the female inpatients with depression had reduced smell discrimination, prolonged latencies on the event related potentials and reduced activation in olfactory structures including the thalamus, insula and left middle orbitofrontal cortex. By the end of the psychotherapy period the depressed women did not differ from the healthy age-matched women.It is not clear how psychotherapy could alter smell discrimination and the associated event related potentials and activation of olfactory structures. The preserved performance on identification tasks by individuals with depression has made it a suitable tool for differential diagnosis of other pathologies like Alzheimer's disease [80]. As in Parkinson's and Alzheimer's, depressed individuals have sleep disorders and are often on medications that can confound the assessments of sensory function[81].

Schizophrenia: Deficits in the odor identification domain have been reported consistently across many studies on individuals with schizophrenia [79,82]. In the [82] meta-analytic study, substantial olfactory deficits were noted across all domains (identification, detection threshold sensitivity, discrimination and memory) in patients with schizophrenia.And no differential deficits were noted across those domains. Further, they noted no significant gender, medication or smoking effects. These authors suggested that their meta-analytic review "supports the hypothesis of primary dysfunction in the olfactory system that is regulated by brain regions where structural and functional abnormalities have also been reported in neuroimaging studies" [82].

In contrast, in a recent study, patients with schizophrenia did not differ from psychiatric outpatients on olfactory function, although those with schizotypy rated smells as less pleasant than healthy control participants [23]. The authors concluded that olfactory identification problems may be characteristic of several severe mental illnesses. On the other hand, at least two research groups have identified relationships between olfactory dysfunction and negative symptoms of schizophrenia (blunted affect, apathy and anhedonia). One group used the UPSIT and assessed positive and negative symptoms using the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) [24]. They reported a correlation of SANS with UPSIT performance, but particularly with blunted affect, apathy and anhedonia. The positive symptom scores (hallucinations, delusions) were not correlated with smell identification. In a more complex study, similar findings were noted [25]. In this paradigm, the severity of negative symptoms in individuals with schizophrenia was associated with reduced olfactory event-related potentials and poorer odor detection, identification and thresholds. Sex differences were noted in a third study that explored the relationship between olfaction and cognition in patients with schizophrenia [26]. In this study better smell identification was associated with better cognition on several measures, but especially in female patients.

Other diseases: Smell and/or taste dysfunctions have also been noted in other diseases including irritable bowel disease, diabetes type 2, kidney disease, multiple sclerosis and child survivors of cancer. Diabetes type 2 patients as compared with a group with Diabetes type 1 showed impaired smell function but no taste dysfunction in at least one study [83]. Patients with irritable bowel disease (Crohn's disease and ulcerative colitis), on the other hand, have been noted to have both smell and taste dysfunction [84]. In that study 58% of the patients were hyposmic (less olfactory function) and 31% were hypogeusic (less gustatory function).

Gustatory function and olfactory function have also been assessed in patients with multiple sclerosis by the Taste-Powder Test and the Threshold, Discrimination and Identification Sniffin' Sticks [85]. There was a significant loss in gustatory function in 22% of the patients and a significant loss in olfactory function in 40% of the patients. The complex cognitive tasks on the olfactory test may confound these results as might the disability status of the patients as well as the depression and fatigue that they often experience.

Children with various medical conditions have also been given taste and smell tests. For example, children with advanced chronic kidney disease have scored lower on taste tests than clinical and healthy control children [86]. Their smell test scores did not differ from the control children, although their smell scores were correlated with their BMIs which were an expressed concern of the authors inasmuch as these children often have loss of appetite and delayed growth.

Child survivors of cancer who were assessed more than five years after the end of chemotherapy scored lower on a taste identification test (25 sample taste test) but not on a smell test (16 common odorants) [87]. Taste dysfunction was noted in 28% of the children while smell dysfunction was only noted in 4% of the children. Food preferences were also assessed on a 94-item list. Although the children preferred less healthy foods such as flavored drinks, takeaway and snack foods, taste dysfunction and food preferences were not related. It is not clear whether these apparent side effects of cancer therapy on taste dysfunction also affect the actual diet of these children.

Potential Underlying Mechanisms

Underlying mechanism studies havebeen conducted, most frequently in animal models, although with the increasing use of fMRI and neuro transmitter metabolite testing, central nervous systems have been implicated including the orbito frontal cortex and several neurotransmitter systems, mainly the nor adrenergic, serotonergic and dopaminergic systems [8]. Although several of the neurodegenerative diseases, e.g. Parkinson's and Alzheimer's and the neuropsychiatric conditions, e.g. ADHD and schizophrenia, involved opaminergic pathology, the research on that pathology is lacking, probably because of the complex interactions between the dopaminergic and other neurotransmitter systems(i.e.serotonergic and noradrenergic systems) and the greater expense of the research (urine metabolites still being the only non-invasive assays of these).

Other mechanisms have been explored including damaged olfactory epithelium, aberrant proteins in the olfactory bulb and altered transmission through the primary and secondary olfactory centers and intersensory region of the brain [3]. Examples of these are neuropathology studies on the olfactory bulb [88], including studies on Lewy bodies in the olfactory bulb [89,90] and studies showing limited gray matter volume in the right piriform cortex and the right amygdala [91].

Environmental agents such as herbicides, pesticides, solvents and viruses have also been implicated. Data on the effects of these agents come from large sample studies. For example, in a study on 5000 patients at The Taste and Smell Clinic in Washington, D.C. 27% of the patients had influenza-related smell loss and 15% of smell loss patients had allergic rhinitis [92]. And, in a study on 132 patients from the first Smell and Taste Clinic in Thailand, as many as 67% of the smell disorder patients had sinonasal disease followed by head injury (12%), idiopathic cause (11%), and upper respiratory tract infection (7%) [93]. Sinonasal disease has been implicated in 52-72% of olfactory disorders [54] and head trauma is a frequent cause of olfactory loss [50].

Medications can also affect the dopamine system, interfering with the ability to detect olfactory dysfunction. For example, a rat study showed that antipsychotics (haloperidol) increased dopamine (D2) receptors in schizophrenia which were most noticeable in the olfactory tubercle [94]. Methylphenidate (an amphetamine-like drug commonly used by those with ADHD) has been noted to increase dopamine transporter inhibition in mice [95]. This effect could explain the mixed findings on olfactory dysfunction in children with ADHD. A further example is the use ofL-dopa therapy which increases dopamine metabolism in the mouse model of Parkinson's disease [96].

Potential Interventions

As already noted in[8] list of generalizations regarding the sensory dysfunction in individuals with Parkinson's, the medications that have been effective with the motor dysfunction of PD have no effect on the loss of sense of smell, specifically L-DOPA, the dopamine agonists and the anticholinergic drugs [8,97]. Odor discrimination deficits have been noted in mice who are lacking the dopamine transporter [98]. However, giving a dopamine agonist to rats has enhanced their odor detection performance [99], although these effects were weak,and there is no evidence that these findings would generalize to humans. Some have noted positive effects of estradiol on induced smell dysfunction in rats [39]. Others have reported that anti-inflammatory medicationssuch as methylprednisolone are effective [9].

The psychosocial stress that reduces serotonin also influences odor detection [100]. Massage therapy (and similar treatments like acupuncture and progressive muscle relaxation) have been noted to increase serotonin and dopamine, two systems that have been implicated in olfactory impairment [101]. Massage therapy has also been effective in reducing sleep disturbances in Parkinson's along with enhancing their activities of daily living as well as increasing the production of serotonin and dopamine [102], although we did not assess the patients' motor or olfactory function. The positive effects of massage therapy have been especially noted following moderate pressure massage and attributed to the stimulation of pressure receptors and enhanced vagal activity [103].

Repetitive trans cranial magnetic stimulation has also been assessed for its effects on smell and taste dysfunction [104]. In this study both taste and smell acuity were improved in 88 percent of the patients, although repeated sessions were necessary to achieve these effects. Acupuncture has been assessed for its effects on olfactory function [105]. In this placebo-controlled, randomized trial, acupuncture (laser needle) enhanced olfactory sensitivity (lowered olfactory detection thresholds) in healthy subjects even though half the subjects were skeptical about the treatment. Although the authors called this a double-blinded study, it's not clear how an acupuncture study could be single-blinded let alone double-blinded. Nonetheless, the stimulation of pressure receptors by acupuncture, as in massage therapy, might be expected to have positive effects on sensory functioning.

Limitations of The Literature and Future Directions

Odor identification deficits have been documented in many studies on neurodegenerative (mostly Parkinson's and Alzheimer's) and neuropsychiatric diseases (mostly ADHD and schizophrenia) since the development of the UPSIT. The UPSIT as well as several other abbreviated, less expensive and more culturally appropriate forms of the olfactory test have had high sensitivity and specificity ratings and they have been highly correlated. They are easy to administer and inexpensive (especially the latest peanut butter identification test) even though they are difficult to compare and to meta-analyze because of the different odorants used, the different cognitive demands made by the tests and the cross-cultural differences noted.

Comorbid sensory dysfunction is also probable given the interacting nervous systems.Research that assessesmultiple senses may further enhance the identification of early markers of these diseases, e.g. smell and taste, smell and pain.Studies on comorbid sensory dysfunction have been limited. For example, taste research, as already mentioned, has been limited possibly because it is more expensive to assess and, except for ratings of pleasantness, can be more aversive for participants. And, the assessment of pain is more difficult for human subjects forethical reasons, except for some limited assessments, for example, thresholds of different pressure points with a dolorimeter. Nonetheless, the study of other dysfunctional senses may more accurately identify and differentiate the risk, for example, for Parkinson's versus Alzheimer's. Making differential diagnoses is increasingly a problem as these sensory dysfunctions are associated with increasing numbers of neurodegenerative and neuropsychiatric conditions.

The treatment literature has been primarily limited to animal models, and the human treatment research has not been blinded, let alone double-blinded. Treatments have not been compared and effective treatment studies have not been replicated. The treatment literature is far less developed than the literature on the use of olfactory identification tests as early biomarkers of neurodegenerative and neuropsychiatric diseases. The purpose of identifying early biomarkers is to be able to identify those at risk for the development of the diseases and to then provide preventive interventions. Having documented olfactory dysfunction might naturally lead to olfactory training [106], but these training needs to be replicated and compared with other treatments using randomized trials and at least blind assignment to groups.

Anti-inflammatory medications may be promising inasmuch as they have been effective in the animal model. Having shown that dopamine and serotonin deficits are associated with olfactory dysfunction may lead to the use of agonists, although at least in two studies [8,97],agonists have not been effective for the olfactory dysfunction as they had been for motor impairment.

A further consideration is the target intervention groups and whether they should have multiple risk factors including being the first-degree relatives of those who have the disease and having tested positive for anosmia or at least hyposmia. Identifying early biomarkers for neurodegenerative and neuropsychiatric diseases may be a moot process ifthere are no effective preventive interventions. Although olfactory testing has identified several neurodegenerative and neuropsychiatric diseases, the intervention literature is lacking, and it is not clear whether different preventive interventions may need to be tailored to different diseases.

Potential future directions are suggested by the current limitations of the literature. More replications are needed, using the same olfactory assessments and including the same odorants. More research is needed on central olfactory problems like discrimination and memory and peripheral problems like sensory threshold.Research on multiple senses is needed to more accurately differentiate the at-risk disease that close relatives may ultimately experience. Cost-effective tests like the UPSIT need to be developed for the other senses so that comorbidities can be identified. Having multiple reliable early sense biomarkers may help with differential diagnoses and with designing protocols for preventive interventions. Studies are needed on the relationships between the senses biomarkers like olfactory dysfunction and the motor signs of the different diseases, e.g. the bradykinesia, tremors, rigidity and postural instability of Parkinson's. Little is known about the relationships between the early sensory and motor biomarkers. Additional research is needed on the interactions between the neurotransmitter systems. In the interim, at least those who are at risk by virtue of being first- degree relatives can be tested with these cost-effective reliablesensory tests.

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