

Olfaction in Neurodegenerative Disease

A Meta-analysis of Olfactory Functioning in Alzheimer's and Parkinson's Diseases

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Background: Olfactory deficits in Alzheimer's disease (AD) and idiopathic Parkinson's disease (PD) have been well established.

Objective: To clarify and review the literature by evaluating the evidence for olfactory deficits in 3 olfactory domains, including odor identification, recognition, and detection threshold.

Data Sources: A literature search of English-language studies of olfaction in AD, PD, and healthy controls was conducted via online databases (PsycInfo and MEDLINE) and reference lists from review articles.

Study Selection: To meet selection criteria for meta-analysis, each study required a control group and complete and usable data. This review yielded 26 publications of olfactory identification, recognition, and/or detection threshold. Because of the inclusion of more than 1 relevant study of olfaction in several of these publications (eg, both identification and threshold assessed), 43

studies were ultimately appropriate for meta-analysis.

Data Extraction: Effect sizes were calculated for each study by expressing differences between patient and control group means in SD units (Cohen's *d*).

Data Synthesis: Extremely large effect sizes were shown across all tasks in both AD and PD groups. Both between-group analyses using the Mann-Whitney *U* test and within-group analyses using Friedman 2-way analysis of variance did not reveal any significant differences (all $P > .30$).

Conclusions: As expected, severe deficits were found for both patients with AD and PD in each of the 3 olfactory domains relative to controls. However, no discriminating olfactory deficits were seen between patient groups or among the 3 measured olfactory domains, suggesting a similar disturbance in olfactory function between patients with AD and PD.

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SINCE THE pioneering studies of olfactory dysfunction in Alzheimer's disease (AD)¹ and Parkinson's disease (PD),² interest in the olfactory deficits of patients with neurodegenerative diseases has soared. This increased attention has in part been spurred by an increasing recognition of the scientific and clinical significance of olfactory dysfunction. Issues such as preclinical diagnosis, safety and quality of life concerns (eg, reduced detection of toxic odorants), inadequate nutritional intake, a diminished ability to experience the pleasures associated with the social and cultural contexts of eating, the possible contribution of olfactory brain pathways to the pathogenesis of neurodegenerative illness, the potential link between presymptomatic olfactory disturbance and genetic markers, and similarities between neuroanatomic substrates and pathologi-

cal mechanisms serve to highlight the importance of research related to the role of olfaction in neurodegenerative disease.

Deficits in olfactory function have now been described in a number of neurodegenerative disorders, including AD,^{3,4} idiopathic PD,^{5,6} Huntington's chorea,^{7,8} alcoholic Korsakoff's syndrome,^{9,10} Pick's disease,¹ the parkinsonian dementia complex of Guam,¹¹ and amyotrophic lateral sclerosis.¹² Of these disorders, olfactory deficits in patients with AD and PD have received the most attention.

Despite the emphasis on olfactory dysfunction in AD and PD, only a few studies have examined the specificity of these deficits. It can be argued that the olfactory dysfunction may simply reflect general alteration of central nervous system functioning. However, this seems unlikely given that differential findings have been described for a number of neurodegenerative disorders (eg, progres-

METHODS

SELECTION OF STUDIES

An extensive literature review of English-language studies of olfactory function in patients with AD, patients with PD, and healthy controls published before November 1996 was conducted via online databases (PsycInfo and MEDLINE) and reference lists from review articles. This literature search yielded 26 publications that were deemed suitable for meta-analysis. Because of the inclusion of more than 1 relevant study of olfactory function in several of these publications (eg, both identification and threshold assessed), 43 studies were ultimately found to be appropriate for meta-analytic review. Studies that lacked control groups, presented incomplete or unusable data, or used samples that were judged to overlap with other, as well as larger studies by the same group, were excluded. **Tables 1** through **3** present individual study characteristics and unbiased effect size estimates for AD and PD groups for tests of olfactory identification, recognition, and threshold, respectively.

METHODOLOGICAL VARIABLES

As seen in Tables 1 through 3, the type of olfactory tests used within a given domain of olfactory function varied widely. For example, in the 14 studies examining odor threshold, there was great heterogeneity with regard to the odorant types used; such odorants included phenylethyl alcohol, n-butyl alcohol, amyl acetate, geraniol, cinnamon oil, isovaleric acid, γ -undecalactone, and skatol. Given this variability, we sought to define olfactory function more broadly by incorporating all method types within a given domain.

Eighteen of the 43 studies (10 AD, 8 PD) were categorized under the domain of olfactory identification. All these studies incorporated an experimental procedure that required the subject to identify an odor after being

exposed to it. Most identification studies used the University of Pennsylvania Smell Identification Test.¹⁸ This standardized olfactory test uses 40 microencapsulated, scratch and sniff odorants and requires the subject to choose among 4 written alternatives for each odorant. Other identification studies required naming an odor spontaneously or choosing an odor from a list of alternatives.

Eleven studies (8 AD, 3 PD) met the criteria for the domain of olfactory recognition memory. Inclusion in this domain required an assessment technique in which the subject is asked to distinguish between a choice of odorants and the one that was presented to him or her before. These methods included match to sample and forced choice types of tests.

Fourteen studies (8 AD, 6 PD) fit the criteria for the domain of olfactory threshold. Studies that were categorized under this domain included instruments that determined the lowest concentration at which a subject was able to detect a particular odorant. Most studies incorporated a single ascending series into the experimental procedure, although a few used a staircase procedure.

STATISTICAL ANALYSIS

Analyses were conducted according to procedures suggested by Rosenthal.¹⁷ The dependent measure was effect size for tests of olfactory identification, recognition, and detection threshold expressed in Cohen's *d*.^{17,19} The *d* score is simply the difference between patient and control group means, within each study or comparison, expressed in SD units. Where the means and SDs were not reported, *t*, *r*, *F*, or χ^2 statistics were converted to *d* using formulas provided by Glass.²⁰ By expressing effect size in SD units, we were able to make a direct comparison of outcomes across studies. Thus, each study or independent comparison was treated as a subject in a statistical analysis. To examine the generalizability of these results to other studies from the same populations and to take between-study variability into account, the unbiased Cohen's *d* was used.¹⁷

sive supranuclear palsy and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism are accompanied by little olfactory dysfunction).¹³ Furthermore, it appears that the severity of olfactory identification deficit in AD, but not in PD,^{14,15} may be related to progression of the illness,¹⁶ although the difficulties in testing patients with moderate or severe dementia make psychophysical findings somewhat enigmatic.¹³

Several investigators have gone so far to suggest, based on differential task deficits in AD, that central nervous system mechanisms for olfaction are damaged, but more peripheral processes are not.¹⁴ However, other studies have not documented such a dissociation.^{3,4} Furthermore, the type of olfactory tests used, sample size, and age and gender distributions have varied so widely that direct comparison of study outcomes has been problematic. More important, there is no strong evidence for the inference that deficits on an odor identification test reflect central damage and differ from detection task peripheral damage.

While the magnitude of deficits differs among a number of neurodegenerative disorders, no study has ex-

plored the severity of olfactory dysfunction with regard to the psychophysical tests used and olfactory domains assessed (ie, identification, recognition, or threshold). Among neurodegenerative diseases, AD and PD have typically been regarded as prototypical examples of cortical and subcortical dementias, respectively, although empirical support for this classification has been equivocal. Given these purported differences in neuroanatomic loci, it may be expected that the olfactory impairment documented in AD and PD would vary between the olfactory domains examined. However, if these differential findings were not demonstrated, such impairment may reflect a common dysfunction in olfactory brain regions between the 2 illnesses.

To more definitively address this issue, we reviewed the English-language literature on olfactory function in AD and PD and used meta-analytic procedures incorporating effect size of each study as the unit of analysis to examine the influences of AD and PD on 3 nominally distinct olfactory domains. Effect size is defined as the magnitude of the mean difference between patient and control groups on a given measure, ex-

Table 1. Olfactory Identification Study Characteristics and Unbiased Effect Size Estimates for AD and PD Groups*

Source, y	Type of Test	No. of Subjects (by Diagnosis)	Gender	Mean (\pm SD) Age, y	Effect Size (Unbiased Estimator)
Doty et al, ³ 1987	UPSIT, 40 types	25 AD	11 M, 14 F	69.17 (8.43)	0.976
		25 Control	Matched	Matched	†
Kesslak et al, ⁵⁸ 1991	UPSIT, 40 types	8 AD	5 M, 3 F	72.3 (8.4)	5.29
		7 Control	4 M, 3 F	68.5 (7.1)	‡
Kesslak et al, ⁵⁹ 1988	UPSIT, 40 types	18 AD	8 M, 10 F	64.16 (1.65)	7.84
		18 Control	8 M, 10 F	63.44 (1.83)	‡
Kesslak et al, ⁵⁹ 1988	UPSIT, 40 types	14 PD	10 M, 4 F	65.42 (3.2)	12.15
		18 Control	8 M, 10 F	63.44 (1.83)	‡
Knupfer and Spiegel, ¹⁴ 1986	Identification, 10 pairs	18 AD	6 M, 12 F	81.6 (5.8)	1.16
		19 Control	7 M, 12 F	72.2 (3.2)	†
Koss et al, ⁶⁰ 1988	UPSIT, 36 types	10 AD	10 M	61.7 (8.7)	1.23
		10 Control	10 M	66.3 (7.8)	†
Morgan et al, ⁶¹ 1995	UPSIT, 40 types	18 AD	15 M, 3 F	73.5 (9.5)	1.80
		18 Control	15 M, 3 F	76.4 (6.0)	‡
	Identification, 8 types	18 AD	15 M, 3 F	73.5 (9.5)	2.17
		18 Control	15 M, 3 F	76.4 (6.0)	‡
Rezek, ⁶² 1987	Identification, 5 types	18 AD	...	70.0 (4.8)	8.55
		26 Control	...	70.4 (3.7)	‡
Serby et al, ⁶³ 1991	UPSIT, 40 types	55 AD	...	69.3 (9.1)	2.22
		57 Control	...	70.1 (5.3)	‡
Warner et al, ⁶⁴ 1986	UPSIT, 40 types	17 AD	12 M, 5 F	66.7	1.32
		17 Control	12 M, 5 F	67.9	‡
Barz et al ⁶⁵ (in press)	Identification, 8 types	31 PD	13 M, 18 F	67.5	1.75
		23 Control	12 M, 11 F	63.3	‡
Busenbark et al, ⁶⁶ 1992	UPSIT, 40 types	16 PD	5 M, 11 F	52.1 (8.3)	1.86
		16 Control	4 M, 12 F	51.5 (8.5)	‡
Doty et al, ⁶⁷ 1992	UPSIT, 20 types	20 PD	15 M, 5 F	61.8 (9.76)	1.46
		20 Control	15 M, 5 F	65.4 (9.66)	‡
Doty et al, ⁵ 1992	UPSIT, 40 types	13 PD	9 M, 4 F	39.08 (4.75)	1.27
		10 Control	4 M, 6 F	38.2 (7.33)	†
Ward et al, ⁶ 1983	Identification, 4 types	46 PD	5.36
		19 Control	‡
Wenning et al, ⁶⁸ 1995	UPSIT, 40 types	118 PD	116 M, 2 F	59.4 (11.6)	2.38
		123 Control	82 M, 41 F	46.4 (17.3)	‡
Zucco et al, ⁶⁹ 1991	Identification, 10 types	8 PD	5 M, 3 F	61.5 (9.3)	1.17
		16 Control	7 M, 9 F	80.0 (10.2)	‡

*AD indicates Alzheimer's disease; PD, Parkinson's disease; UPSIT, University of Pennsylvania Smell Identification Test¹⁸; and ellipses, not applicable.

†Key for type of statistic used to calculate effect size: † value from P level.

‡Mean (SD).

pressed in SD units.¹⁷ Such procedures are superior to the traditional method of tallying statistically significant and nonsignificant results used in most narrative reviews because the latter method disproportionately penalizes highly reliable studies with null findings. In our study, the primary effect size examined is the difference between patients with AD and PD on measures of olfactory identification, recognition, and detection threshold.

RESULTS

Analysis of the distribution of effect sizes for both groups across different olfactory tasks revealed that the distributions of scores deviated significantly from normal. As a result, nonparametric analysis was subsequently used to evaluate group and test differences. In general, effect sizes across tasks in both the AD and PD groups would be considered enormous in that they were well above the criteria of a large effect ($\geq .80$) as described by Cohen's¹⁹ metric.

Figure 1 shows the mean d values for patients with AD and PD on olfactory identification measures. Both AD and PD groups showed similar levels of impairment on measures of olfactory identification (mean d 's, 3.26 and 3.42, respectively; Mann-Whitney U , 37.0, $P=.79$).

Figure 2 shows the mean d values for patients with AD and PD on measures of olfactory recognition. Again, the 2 groups did not differ significantly with regard to recognition scores (mean d 's, 4.21 and 2.81, respectively; Mann-Whitney U , 17.0, $P=.30$).

Figure 3 plots the mean d values for odor detection threshold for both AD and PD groups. Once again, the 2 groups did not differ in effect size on these measures (mean d 's, 2.61 and 3.15, respectively; Mann-Whitney U , 19.0, $P=.51$).

Within-group analyses using Friedman 2-way analysis of variance comparing measures of olfactory identification, recognition, and threshold did not reveal any differential task difficulty within either AD or PD groups (all $P>.60$).

Table 2. Olfactory Recognition Study Characteristics and Unbiased Effect Size Estimates for AD and PD Groups*

Source, y	Type of Test	No. of Subjects (by Diagnosis)	Gender	Mean (\pm SD) Age, y	Effect Size (Unbiased Estimator)
Buchsbaum et al, ⁷⁰ 1991	Recognition, match to sample (30 types)	6 AD	4 M, 2 F	71.2	3.33
Corwin et al, ⁷¹ 1985	Recognition, 10-pair forced choice	6 Control	3 M, 3 F	67.8 (5.2)	†
		11 AD	3.18
	Recognition, 10-pair forced choice	20 Control	†
		5 PD	2.68
Kesslak et al, ⁵⁸ 1991	Recognition, match to sample	20 Control	†
		8 AD	5 M, 3 F	72.3 (8.4)	7.82
Kesslak et al, ⁵⁹ 1988	Recognition, match to sample (15 types)	7 Control	4 M, 3 F	68.5 (7.1)	†
		15 AD	7 M, 8 F	...	6.99
	Recognition, match to sample (15 types)	18 Control	8 M, 10 F	63.44 (1.83)	†
		4 PD	3 M, 1 F	...	5.11
Knupfer and Spiegel, ¹⁴ 1986	Recognition, 10 pairs	18 Control	8 M, 10 F	63.44 (1.83)	†
		18 AD	6 M, 12 F	81.6 (5.8)	1.16
Koss, ⁷² 1986	Recognition, 10-pair forced choice	19 Control	7 M, 12 F	72.2 (3.2)	†
		15 AD	8 M, 7 F	65.33 (7.03)	2.18
Moberg et al, ⁷ 1987	Recognition, 30 types	6 Control	2 M, 4 F	66.5 (7.66)	†
		42 AD	...	72.45 (7.83)	3.38
Rezek, ⁶² 1987	Recognition, match to sample (5 types)	42 Control	...	71.38 (5.79)	†
		18 AD	...	70.0 (4.8)	5.62
Zucco et al, ⁶⁹ 1991	Recognition, match to sample (10 types)	26 Control	...	70.4 (3.7)	†
		8 PD	5 M, 3 F	61.5 (9.3)	0.650
		16 Control	7 M, 9 F	80.0 (10.2)	†

*AD indicates Alzheimer disease; PD, Parkinson disease; and ellipses, not applicable.

† Mean (SD).

‡ Value from P level.

Table 3. Olfactory Threshold Study Characteristics and Unbiased Effect Size Estimates for AD and PD Groups*

Source, y	Type of Test	No. of Subjects (by Diagnosis)	Gender	Mean (\pm SD) Age, y	Effect Size (Unbiased Estimator)
Doty et al, ³ 1987	Detection threshold, PEA: s	15 AD	1.31
		15 Control	†
Feldman et al, ⁷³ 1991	Threshold, butanol: a	21 AD	...	72.6 (4.7)	0.699
		21 Control	...	74.6 (5.5)	†
Knupfer and Spiegel, ¹⁴ 1986	Detection threshold, 3 types odorants: a	18 AD	6 M, 12 F	81.6 (5.8)	1.16
		19 Control	7 M, 12 F	72.2 (3.2)	†
Morgan et al, ⁶¹ 1995	Detection threshold, butanol: a	18 AD	15 M, 3 F	73.5 (9.5)	0.998
		18 Control	15 M, 3 F	76.4 (6.0)	†
Murphy et al, ⁷⁴ 1990	Threshold, butanol: a	21 AD	10 M, 11 F	72.8 (5.4)	6.23
		21 Control	10 M, 11 F	72.3 (5.4)	†
Nordin et al, ⁷⁵ 1995	Threshold, butanol: a	80 AD	42 M, 38 F	74.0 (6.7)	7.48
		80 Control	27 M, 53 F	73.1 (7.0)	†
Rezek, ⁶² 1987	Threshold, amyl alcohol and cinnamon oil: a	18 AD	...	70.0 (4.8)	2.45
		26 Control	...	70.4 (3.7)	†
Serby et al, ⁶³ 1991	Threshold, geraniol: a	46 AD	...	68.6 (7.6)	0.544
		40 Control	...	70.2 (4.9)	†
Doty et al, ⁵ 1992	Detection threshold, PEA: s	13 PD	9 M, 4 F	39.08 (4.75)	1.55
		10 Control	4 M, 6 F	38.2 (7.33)	†
Quinn et al, ⁵⁰ 1987	Threshold, amyl acetate: d	78 PD	50 M, 28 F	61.5	0.761
		40 Control	27 M, 13 F	Matched	†
Murofushi et al, ⁷⁶ 1991	Detection threshold, 5 types, T&T olfactometry: a	18 PD	11 M, 7 F	59.6	1.42
		10 Control	5 M, 5 F	56.7	†
	Recognition threshold, 5 types, T&T olfactometry: a	18 PD	11 M, 7 F	59.6	1.06
		10 Control	5 M, 5 F	56.7	†
Ward et al, ⁶ 1983	Detection threshold, phenylethyl methylcarbinol: ?	28 PD	5.68
		30 Control	†
	Detection threshold, amyl acetate: ?	49 PD	8.43
		39 Control	†

*AD indicates Alzheimer's disease; PD, Parkinson's disease; ellipses, not applicable; PEA, phenylethyl alcohol; s, staircase; a, ascending order of presentation; d, descending order of presentation; and question mark, order of presentation not specified in study.

† Value (from P level).

‡ Mean (SD).

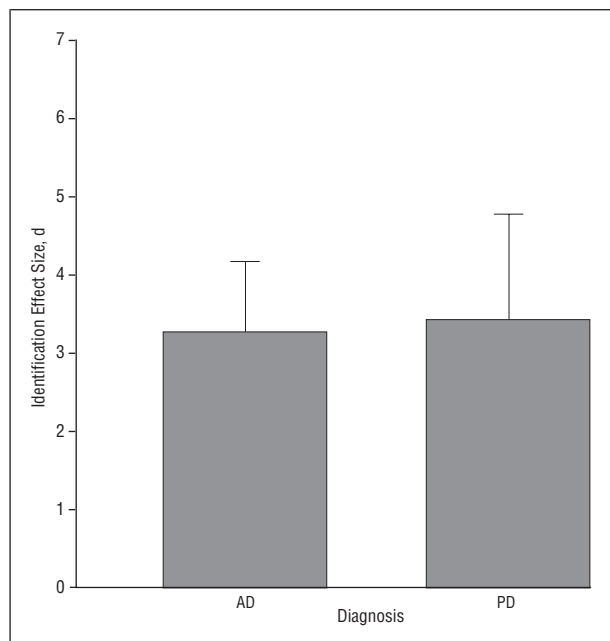


Figure 1. Effect sizes (Cohen's *d*) on olfactory identification measures for Alzheimer's disease (AD) and Parkinson's disease (PD) groups (mean ± SE).

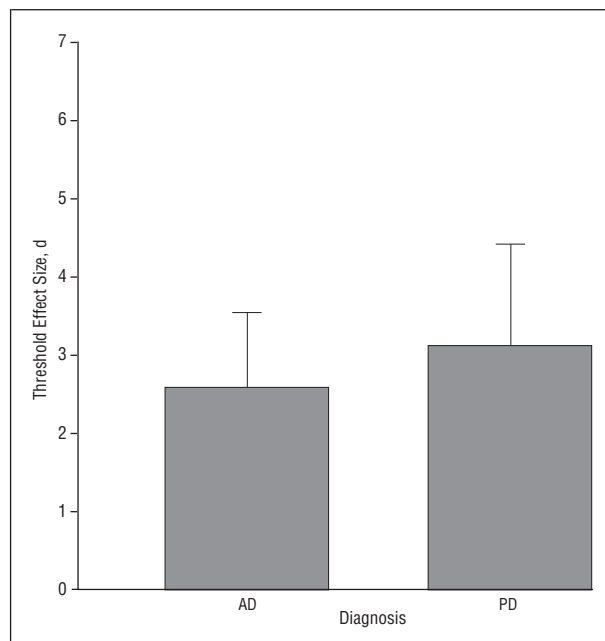


Figure 3. Effect sizes (Cohen's *d*) on olfactory threshold measures for Alzheimer's disease (AD) and Parkinson's disease (PD) groups (mean ± SE).

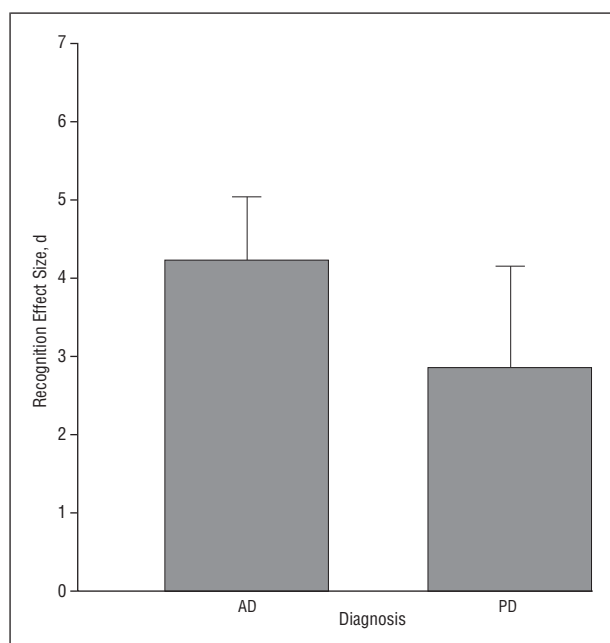


Figure 2. Effect sizes (Cohen's *d*) on olfactory recognition measures for Alzheimer's disease (AD) and Parkinson's disease (PD) groups (mean ± SE).

COMMENT

A quantitative analysis of 43 studies of olfactory identification, recognition memory, and threshold in AD and PD revealed extremely large effects across all domains. Cohen¹⁹ considers an effect size to be large when the value is $\geq .80$, suggesting a severe degree of generalized olfactory deficit in patients with AD and PD relative to controls. While there was a trend toward somewhat better performance on threshold measures in comparison with recognition and identification tasks, the current meta-

analytic review suggests that all tests of olfactory function show relatively uniform impairment in AD and PD and that no measure discriminates between these groups. This finding is consistent with studies by Doty and colleagues^{3,21} that examined olfactory identification and detection threshold in AD and PD groups and found no discriminating differences on these measures.

It may be possible that measures of 3 seemingly different olfactory processes (identification, recognition, or threshold) actually tap one larger olfactory domain, in that a similar construct is being measured in each case. For example, Doty et al,²² in a principal components analysis of various tests of olfactory function, found that in healthy controls most tests load on a single olfactory factor. Additionally, if impaired olfaction is the result of a pathological epithelium, then deficits on tests of odor memory and identification may simply reflect a peripheral defect. While some studies have drawn a central vs peripheral distinction on the basis of threshold and nonthreshold tests in patients who have undergone temporal lobectomy for intractable seizures,^{23,24} others examining patients with temporal lobe lesions did not find results that would be congruent with such a distinction.²⁵ First, discrepancies may be due to differences in the measures and procedures used, although there is evidence that participants with epilepsy in the studies demonstrated olfactory deficits before surgical intervention.^{26,27} Second, olfactory detection thresholds correlate highly with odor identification scores in controls and patients,^{22,28} and both load on the same component in principal component work in PD.²⁸ Third, the reliability of threshold determination, while acceptable, is lower than that for other measures and this could partly explain some of the variability in findings. Last, although increased thresholds could imply that sensory capacity is affected, it is clear that many patients with AD have residual function and that their deficits are rarely those of complete anosmia.²⁹

The present findings may provide direction for several avenues of scientific query and empirical exploration. For example, the lack of differential olfactory deficits in AD and PD may be reflective of the presence of pathological features in olfactory brain regions during the earliest stages of the disease process, so that by the time a definitive diagnosis of either disorder is made, distinguishing olfactory deficits may be obscured. These results may also implicate a similar dysfunction in olfactory brain regions existent in both illnesses. Several researchers have already documented a variety of neuropathological features common to both AD and PD, including reduced levels of choline acetyltransferase in a number of brain regions such as the olfactory tubercle^{30,31}; decreased metabolism of some classes of nasal tissue xenobiotics³²⁻³⁵; dopamine system insufficiencies in several neuroanatomic structures, including the olfactory tubercle³⁶⁻³⁸; and marked pathological features within mesolimbic brain areas such as the olfactory tubercle and nucleus accumbens.^{13,39} Examination of patients at risk for AD and PD will be helpful in further explaining these deficits. For example, a possible genetic contribution to the olfactory dysfunction of AD has been suggested by recent findings of decreased olfactory function in patients with questionable AD,⁴⁰ as well as in family members of patients with AD.⁴¹ In contrast, investigation of the genetic contributions to the olfactory deficit seen in Huntington's disease has indicated the absence of olfactory dysfunction in at-risk family members⁴² and asymptomatic gene carriers,⁴³ suggesting that presymptomatic olfactory dysfunction is not present in all dementing illnesses. Further investigation into specific genetic markers of AD or PD may extend these findings. For example, it has been found that individuals with the *ApoE4* gene are at a higher risk for developing AD than those in the general population.⁴⁴⁻⁴⁸ Investigating the link between olfactory dysfunction and the presence of this gene may also yield valuable information concerning preclinical diagnosis.

While the current review suggests that olfactory measures may lack specificity, the utilization of olfactory tests as early diagnostic tools may prove to be one of the most useful clinical applications of the study of olfactory dysfunction in these disorders. For example, Nordin and Murphy⁴⁰ found impaired odor recognition memory in patients with questionable AD, demonstrating olfactory deficits early in the disease process before the classic signs and symptoms are obvious enough to be noticed by significant others. Similar decrements in olfactory functioning have also been documented in patients with early PD independent from the presence or progression of the cardinal motoric signs of PD and the use of antiparkinsonian medications.^{5,6,16,49,50} Furthermore, varying levels of olfactory dysfunction have been found in different subtypes of PD, depending on which one of the classic signs of PD is most pronounced in the individual.⁵¹ Recently, using the University of Pennsylvania Smell Identification Test,¹² Doty and colleagues¹⁸ developed criteria for assessing olfactory impairment in patients with PD that best discriminate them from healthy controls.

The clinician's recognition and assessment of the significantly disrupted olfactory processes in patients with AD and PD are also important when considering the im-

pact that such deficits may have on daily functioning. Disturbed olfaction may increase an individual's susceptibility to environmental safety hazards (eg, reduced detection of potentially toxic substances such as natural gas and spoiled food), interfere with a person's ability to adequately monitor proper nutritional intake, and lead to an impoverished quality of life in general (eg, a decrement in one's enjoyment of the social and cultural aspects of eating and one's appreciation of the diversity of flavors and tastes inherent in food).^{52,53}

As noted, measurements of olfactory abilities from different laboratories are not often directly comparable because of significant variation both in method of psychophysical assessment and in the types of stimuli used. Effect size, a standardized index based on mean group differences and SDs within each study, can be used to integrate qualitatively different findings from different laboratories. While meta-analytic procedures are generally considered to be superior to traditional narrative reviews in the ability to quantify effect sizes, assess heterogeneity, and identify moderator variables, there are limitations that warrant consideration. First, meta-analytic procedures are most powerful when the calculations are based on a large number of studies. While this review represented an exhaustive review of the English-language literature, our analysis was based on only 26 publications (43 studies). Second, a number of authors have argued that the results of meta-analytic procedures are questionable when dependent variables and measures are heterogeneous. However, the aim of this review was to examine olfactory functions broadly defined. Glass²⁰ has argued that mixing "apples and oranges" is valid when one wishes "to study fruit." As such, the current review examined the unitary sensory modality of olfactory function through the examination of 3 of its domains (ie, identification, recognition memory, or threshold). Last, not all studies included data for mean age and gender of subjects. Given the known impact of these variables on olfactory function,⁵⁴⁻⁵⁷ such information may prove extremely helpful in further elucidating the nature of olfactory deficits in neurodegenerative disease. Further studies are needed to address these issues more thoroughly.

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