Lewy Bodies and Olfactory Dysfunction in Old Age

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Abstract

As part of a clinical-pathologic project, older people completed a standard odor identification test at study entry. During a mean of 3.5 years of observation, 201 people died and underwent brain autopsy and neuropathologic examination (6 with a history of Parkinson's disease were excluded). Lewy bodies were identified with antibodies to alpha-synuclein and classified as nigral, limbic, or neocortical based on their distribution in 6 brain regions. Plaques and tangles in 5 regions were summarized with a previously established composite measure, and neuron loss in the substantia nigra was rated on 6-point scale. Odor identification scores ranged from 0 to 12 correct (mean = 8.0, standard deviation = 2.6). On neuropathologic examination, 26 persons had Lewy bodies (13 neocortical, 9 limbic, and 4 nigral). In an analysis adjusted for age, sex, education, and time from olfactory testing to death, limbic (estimate = −2.47, standard error [SE] = 0.73, $P < 0.001$) and neocortical (estimate = −4.36, SE = 0.63, $P < 0.001$) Lewy body subgroups were associated with impaired olfaction. Results were comparable in analyses that controlled for dementia or parkinsonism during the study or postmortem measures of plaques and tangles or nigral cell loss. A final set of analyses suggested that impaired olfactory performance may aid detection of underlying Lewy body disease. The findings indicate that Lewy body disease impairs late life olfactory function even in otherwise asymptomatic individuals.

Key words: Alzheimer's disease, Lewy body disease, odor identification, substantia nigra

Introduction

Both cross-sectional (Doty et al. 1984; Russell et al. 1993; Ship et al. 1996; Larsson et al. 2000) and longitudinal (Ship et al. 1996; Calhoun-Haney and Murphy 2005) data indicate substantial loss in olfactory functioning in old age. The factors underlying this age-related decline are uncertain, but it is likely that some of the dysfunction is due to age-related degenerative processes occurring in the brain. For example, Alzheimer's disease (AD) neuropathologic changes in the brains of people who die without dementia (Wilson, Arnold, et al. 2007) or mild cognitive impairment (Wilson et al. 2009) have been associated with impaired olfaction proximate to death. Lewy bodies, another common postmortem sign of neurodegenerative disease, may also be contributing to late life olfactory dysfunction. Thus, impaired olfactory function

is a prominent feature of 2 common Lewy body disorders, Parkinson's disease (Ansari and Johnson 1975; Doty et al. 1988, 1992; Tissingh et al. 2001) and dementia with Lewy bodies (McShane et al. 2001; Olichney et al. 2005; Williams et al. 2009), and central olfactory areas (i.e., olfactory bulb) appear to be among the first brain regions affected in both disorders (Braak et al. 2003; Beach et al. 2009). Furthermore, Lewy bodies are commonly observed on postmortem examination of the brains of older persons who died without Parkinson's disease or dementia (Jellinger 2004; Saito et al. 2004), possibly representing a preclinical stage of a Lewy body disorder (DelleDonne et al. 2008; Frigerio et al. 2009). However, there is little information about the effect of Lewy bodies on olfactory functioning in people without

other clinical evidence of a Lewy body disorder (Ross et al. 2006).

The present study examines the relation of Lewy bodies to olfactory impairment using data from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study. Older persons without Parkinson's disease completed a standard test of odor identification, died during a 3–4 year follow-up period, and underwent a brain autopsy and uniform neuropathological examination to identify Lewy bodies and other pathologic changes. In analyses, we tested the hypothesis that Lewy bodies are associated with impaired olfaction and examined the feasibility of using olfactory data to identify those with the neuropathologic hallmark of Lewy body disorders.

Materials and methods

Participants

All subjects were from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study that involves annual clinical evaluations and brain donation at death (Bennett, Schneider, Buchman, et al. 2005). Older persons were recruited from a variety of retirement facilities in the Chicago area. After a presentation about the project, interested persons met with study personnel who discussed the study in further detail and obtained informed consent. The study was approved by the Institutional Review Board of Rush University Medical Center.

Annual clinical evaluations began in 1997 and are continuing. Eligibility for the present analyses required completion of the Brief Smell Identification Test (see below) as evidenced by responses to at least 10 of the 12 items, a brain autopsy with neuropathological examination, and no history of Parkinson's disease. Of 1232 persons with olfactory data, 368 died. Brain autopsy was obtained in 290 (78.8%), the results of which were pending in 83, leaving 207 still eligible. We excluded a further 6 persons who had a history of Parkinson's disease, resulting in a final group of 201 individuals. They had a mean age of 84.8 years (standard deviation [SD] = 6.2) at the time of olfactory testing and died a mean of 3.5 years later (SD = 1.8). They had completed a mean of 14.7 years of schooling (SD = 2.8); 63.7% were women and 95.0% were white and non-Hispanic.

Odor identification

The Brief Smell Identification Test (Doty et al. 1989, 1996) was administered as part of the baseline clinical evaluation. It assesses the ability to recognize 12 familiar odors (e.g., black pepper, cinnamon). On each item, a microcapsule containing the target odor was scratched with a pencil and placed under the nose of the participant who then matched the smell to one of 4 choices. The score for the test was the number of correct choices plus 0.25 assigned for each missing response to a maximum of 2, as previously described (Wilson et al. 2006; Wilson, Schneider, et al. 2007). The olfactory score was treated as missing if more than 2 item responses were missing. Previous research has suggested that performance on this test has adequate short-term temporal stability (Doty et al. 1989), and a Cronbach's coefficient alpha of 0.72 in this data set suggests adequate internal consistency.

Clinical classification

The annual clinical evaluation included a medical history, complete neurological examination, and detailed cognitive performance testing. On the basis of these data, an experienced clinician diagnosed dementia and AD using the criteria outlined by the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann et al. 1984). Dementia required a history of cognitive decline and impairment in at least 2 domains of cognitive function, one of which had to be memory to meet criteria for AD. All clinical data collection and clinical classification were done without knowledge of previously collected data. Further information on this clinical classification system (Bennett, Schneider, Buchman, et al. 2005; Bennett, Schneider, Aggarwal, et al. 2006) and supporting neuropathological (Bennett, Schneider, Bienias, et al. 2005; Bennett, Schneider, Arvanitakis, et al. 2006) and clinical (Wilson, Krueger, et al., 2010; Boyle et al. 2006) data are published elsewhere.

As part of each annual clinical evaluation, a modified version (Bennett et al. 1997) of the motor portion of the Unified Parkinson's Disease Rating Scale (Fahn and Elton 1987) was administered. Ratings of bradykinesia (4 items), gait and postural reflex impairment (6 items), rigidity (5 items), and tremor (2 items) were combined to yield a composite measure of parkinsonism. This measure has been shown to have adequate interrater reliability and short-term temporal stability (Bennett et al. 1997), predict subsequent risk of dementia (Wilson et al. 2003) and death (Wilson et al. 2002), and be related to neuronal loss in the substantia nigra (Schneider et al. 2006).

Neuropathological assessment

Death occurred a mean of 3.5 years (SD = 1.8; range: 0.2–8.1) after olfactory testing. The brain was removed in a standard fashion (Bennett, Schneider, Buchman, et al. 2005; Bennett, Schneider, Bienias, et al. 2005) a median of 5.8 h (interquartile range = 4.4) after death. It was cut into 1-cm-thick coronal slabs that were fixed in 4% paraformaldehyde for 72 h and then stored in a graded glycerol solution. All neuropathologic data were collected by persons blinded to all clinical data.

Lewy bodies were identified with antibodies to alpha-synuclein (Zymed, LB509; 1:100) using the avidin–biotin method and including a positive control in each immunohistochemical run as reported in more detail elsewhere

(Schneider et al. 2007). Tissue from 6 brain regions was studied: substantia nigra, entorhinal cortex, anterior cingulate cortex, midfrontal cortex, superior or middle temporal cortex, and inferior parietal cortex. Subjects with Lewy bodies were subdivided into 3 mutually exclusive categories, as previously described (Schneider et al. 2007 ; Wilson et al. 2010; Wilson, Leurgans, et al., forthcoming): Lewy bodies confined to substantia nigra (nigral type); Lewy bodies in entorhinal cortex or anterior cingulate cortex but not neocortex (limbic type); Lewy bodies in midfrontal, superior or middle temporal, or inferior parietal regions (neocortical type). In most cases, Lewy bodies progressed in stages, such that most cases with limbic Lewy bodies also had nigral Lewy bodies and most cases with neocortical Lewy bodies also had nigral and limbic Lewy bodies. In analyses, those without Lewy bodies were treated as a reference group and contrasted with each Lewy body subgroup. Neuronal loss in substantia nigra was rated from 0 (none) to 5 (severe) based on a 6-μm nigral hemisection as described in an earlier report (Schneider et al. 2006).

AD pathology was quantified in 5 brain regions: hippocampus, entorhinal cortex, midfrontal cortex, superior or middle temporal cortex, and inferior parietal cortex. Paraffin-embedded tissue was sectioned at 6 μm and stained with modified Bielschowsky silver. A neuropathologist or technician separately counted neuritic plaques, diffuse plaques, and neurofibrillary tangles in each brain region. Raw counts in each region were divided by the standard derivation of all counts in that region which yielded a standard score. Standard scores across regions and lesion types were averaged to yield a composite measure of AD pathology. Further information on the derivation of this measure is available in a previous publication (Bennett et al. 2003).

Data analysis

The relation of Lewy bodies to olfactory performance was assessed in a series of linear regression models with olfactory test score as the outcome. All models included terms for age at death, sex, education, and time from olfactory testing to death. An initial model added an indicator for the presence of any Lewy bodies. In a second analysis, each of 3 Lewy body subgroups was contrasted with a no Lewy body reference group. This latter model was repeated with an indicator for dementia at the time of olfactory testing, with an indicator for dementia at any point in the study, with an indicator for parkinsonism at the time of olfactory testing, and with an indicator for parkinsonism at the last evaluation before death. We also conducted analyses with a term for AD pathology with and without indicators for Lewy body subgroup and with a term for nigral neuronal loss with and without terms for Lewy body subgroup.

To assess the utility of olfactory data in identification of underlying Lewy body disease, we constructed a series of logistic regression models with postmortem Lewy bodies as the outcome. A receiver operating characteristic curve was derived from each model fit, and area under the receiver operating characteristic curve, a measure of predictive accuracy, was determined using the trapezoidal rule. The trapezoidal area was estimated for models with and without olfactory data, and a Wald test was used to determine if the estimated areas statistically differed. We repeated these analyses, first with a term added for dementia at the time of olfactory testing and then again with a term for dementia at any point during the study.

Results

Performance on the Brief Smell Identification test ranged from 0 to 12 correct (mean = 8.0, SD = 2.6). Scores were inversely related to age at death (estimate = –0.10, standard error [SE] = 0.03, $P < 0.001$) but unrelated to sex (estimate = –0.033, SE = 0.32, $P = 0.31$) and education (estimate = –0.09, SE = 0.06, $P = 0.11$).

Odor identification and Lewy bodies

On neuropathological examination, Lewy bodies were identified in 26 individuals (12.9%) and classified as nigral predominant (i.e., restricted to substantia nigra) in 4, limbic type (i.e., in both nigral and limbic regions) in 9, and diffuse neocortical type (i.e., in nigral, limbic, and neocortical regions) in 13. Those with Lewy bodies did not demographically differ from unaffected persons, but they had lower olfactory test scores, higher likelihood of developing dementia, more parkinsonian motor dysfunction, and higher levels of AD pathology and nigral cell loss (Table 1).

We examined the relation of Lewy bodies to olfactory performance in a series of linear regression models that controlled for age at death, sex, education, and time from olfactory testing to death. In an initial analysis, the presence of any Lewy bodies was associated with a loss of about 3 points on the olfactory test (estimate = –3.03, SE = 0.47, $P < 0.001$) and accounted for 15.4% of the variance on the test.

To determine whether the association of Lewy bodies with olfaction depended on their distribution, we repeated the analysis with separate indicators for the 3 Lewy body subgroups. As shown in model A of Table 2, there was no olfactory impairment in the nigral predominant Lewy body subgroup but substantial olfactory dysfunction in the other 2 Lewy body subgroups. Lewy bodies accounted for 19.1% of the variance in olfactory performance in this model. Figure 1 shows the model-based estimates of the mean olfactory score and 95% confidence interval for each Lewy body subgroup in comparison to unaffected persons. The figure suggests decreased olfactory function with increased severity of Lewy body disease, with no impairment in the nigral subgroup, moderate impairment in the limbic subgroup, and profound impairment in the neocortical subgroup.

Cognitive impairment is associated with both Lewy bodies (Wilson et al. 2010) and olfactory identification (Wilson et al. 2006). Therefore, we repeated the previous analysis with a term to control for the presence of dementia at the time of olfactory testing ($n = 28$). Both limbic and neocortical Lewy bodies continued to be robustly related to olfactory performance (Table 2, model B). As shown in model C of Table 2, results were similar when we repeated the analysis with a term to control for dementia at any time during the study ($n = 67$).

To determine whether preclinical Parkinson's disease was affecting results, we repeated the core analysis with a term added for parkinsonian motor dysfunction at the time of olfactory testing, as assessed with a modified version of the Unified Parkinson's Disease Rating Scale. The association of Lewy body subgroups with olfactory score was not substantially changed in this analysis or in a subsequent model that controlled for parkinsonian score most proximate to death (data not shown).

Odor identification and AD pathology

To see if AD pathology affected the association of Lewy bodies with olfactory functioning, we conducted further analyses using a composite measure of diffuse plaques, neuritic plaques, and neurofibrillary tangles. Pathologic scores ranged from 0 to 3.2 (mean = 0.62, SD = 0.61). In an initial model, higher level of AD pathology was associated with lower olfactory score and accounted for 8.4% of the variability in performance (estimate = -1.25, SE = 0.27, $P < 0.001$). When terms for Lewy body subgroups were added to the model, the effect of Lewy bodies was undiminished and AD pathology accounted for an additional 4.1% of performance variability (Table 2, model D).

Odor identification and nigral neuronal loss

We conducted additional analyses to determine whether another neuropathologic hallmark of Parkinson's disease, neuronal loss in the substantia nigra, affected olfaction or its association with Lewy bodies. The neuropathologist's ratings of nigral cell loss ranged from 0 (none) to 5 (severe), had an approximately normal distribution (mean = 2.33, SD = 0.94, skewness = 0.41), and were higher in those with Lewy bodies (Spearman rho = 0.31, $P < 0.001$). In a regression analysis, higher level of nigral cell loss was associated with lower olfactory score (estimate = 0.71, SE = 0.19, $P < 0.001$). However, the effect was reduced by more than half and no longer significant when terms for Lewy bodies were added to the analysis (Table 2, model E).

Detection of underlying Lewy body disease

Logistic regression analyses were used to assess the value of olfactory test performance in identifying individuals with underlying Lewy body disease (Table 3). Each model provided an estimate of the area under the receiver operating

Table 1 Descriptive information on persons with versus without Lewy bodies on neuropathological examination[a]

Characteristic	No Lewy bodies ($n = 175$)	Lewy bodies ($n = 26$)	P value
Age at death, years	88.0 (6.4)	89.8 (4.3)	0.07
Education, years	14.7 (2.7)	15.2 (3.5)	0.49
Women, %	64.6	57.7	0.50
Odor test score	8.5 (2.2)	5.1 (3.0)	<0.001
Dementia at test, %	12.6	23.1	0.22
Dementia ever, %	29.7	57.7	0.005
Parkinsonism score at test	13.0 (8.8)	18.1 (10.3)	0.004
Last parkinsonism score	15.7 (10.6)	23.5 (12.4)	0.001
AD pathology score	0.58 (0.59)	0.91 (0.70)	0.036
Nigral cell loss score	2.19 (0.79)	3.27 (1.28)	<0.001

[a]Data are presented as mean (SD) unless otherwise indicated

Table 2 Relation of postmortem pathological measures to odor identification[a]

Model Term	Model A			Model B			Model C			Model D			Model E		
	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P
Nigral LBs	−0.17	1.08	0.879	−0.48	1.00	0.633	0.35	0.98	0.720	−0.39	1.05	0.711	0.25	1.12	0.821
Limbic LBs	−2.47	0.73	<0.001	−2.28	0.68	<0.001	−2.03	0.66	0.003	−2.07	0.72	0.004	−2.42	0.73	0.001
Neocortical LBs	−4.36	0.63	<0.001	−3.99	0.58	<0.001	−3.85	0.57	<0.001	−3.99	0.62	<0.001	−3.92	0.69	<0.001
Dementia at baseline				−2.42	0.41	<0.001									
Dementia ever							−2.15	0.31	<0.001						
AD pathology										−0.91	0.25	<0.001			
Nigral cell loss													−0.29	0.19	0.131

[a]Estimated from separate linear regression models adjusted for age at death, sex, education, and time from olfactory testing to death. LB indicates Lewy bodies and AD indicates Alzheimer's disease.

characteristic curve, an overall index of how well affected individuals were identified. The first analysis included a core set of 4 covariates (i.e., age at death, sex, education, and time from olfactory testing to death). As shown in Table 3 (model A), the area under the receiver operating curve for this model was 0.62. When the analysis was repeated with a term added for odor identification score, the area under the curve was 0.82. Figure 2, which is based on these analyses, shows a substantial increase in predictive accuracy in the model with olfactory data (red line) compared with the reference model without olfactory data (blue line) and chance (dashed line). Results were comparable when the analyses were repeated controlling for dementia at the time of olfactory testing (Table 3, model B). The relation of olfactory score to postmortem Lewy bodies was similar when the analysis adjusted for dementia at any point during the study except that the increase in predictive accuracy was not quite significant because of improved prediction in the reference model (Table 3, model C).
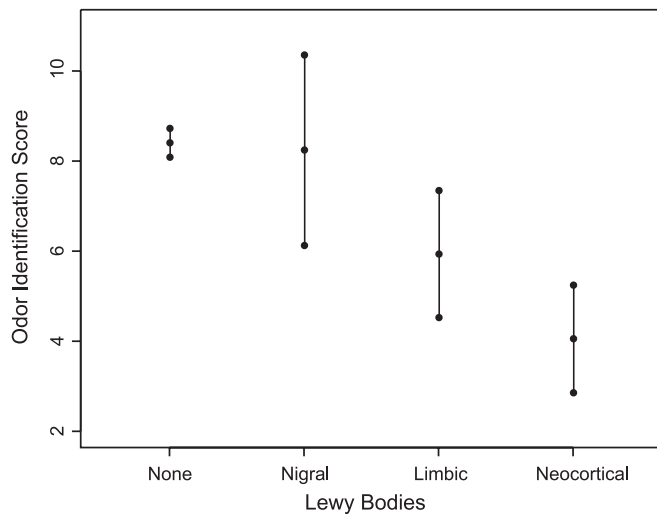

Figure 1 Odor identification in Lewy body subgroups. Estimated mean and 95% confidence intervals on odor identification test in Lewy body subgroups, adjusted for age at death, sex, education, and time from olfactory testing to death.

Discussion

We assessed the ability to identify familiar odors in older persons participating in a longitudinal clinical-pathologic study. During a mean of 3.5 years of follow-up, more than 200 persons died and underwent brain autopsy. We found that a substantial proportion of age-related olfactory dysfunction was associated with the presence Lewy bodies in the brain.

Although impaired olfaction is a recognized manifestation of Lewy body disorders, the contribution of Lewy bodies to olfactory function in people without these disorders is not well understood. One previous study found that impairment on the Brief Smell Identification Test, the same measure used in the present study, was associated with postmortem evidence of Lewy body disease in older persons without Parkinson's disease or dementia (Ross et al. 2006). The results of the present study are consistent with this finding. In addition, results were not affected by controlling for subclinical parkinsonian motor dysfunction or nigral cell loss, a pathologic hallmark of Parkinson's disease (Hughes et al. 1992) that has been associated with parkinsonian motor dysfunction (Schneider et al. 2006). This suggests that olfactory impairment has a different neuropathologic basis than parkinsonian motor signs.

Because Lewy bodies affect some brain regions more than others, disease staging systems have been proposed based on the distribution and density of lesions. In the present study, we used a modified version of a system proposed for dementia with Lewy bodies (McKeith et al. 1996) to classify cases as nigral, limbic, or neocortical. The results suggest a relationship between Lewy body disease severity and olfactory function. That is, there was no olfactory impairment when Lewy bodies were confined to the midbrain, mild impairment was evident in the limbic or transitional stage, and marked impairment was seen in the neocortical or diffuse stage. The lack of olfactory impairment at the nigral stage should be interpreted cautiously, however. Only 4 individuals were in this subgroup thereby limiting statistical power. In addition, the olfactory bulb, thought to be affected before the midbrain (Braak et al. 2003; Beach et al. 2009), was not assessed. Thus, further research will be needed to clarify the impact of very mild Lewy body disease on olfactory function.

Table 3 Relation of odor identification score to postmortem evidence of Lewy bodies[a]

Model	Covariates	Without odor test			With odor test					
		Area under curve	SE	P	Area under curve	SE	P	Area difference	SE	P
A	Core	0.62	0.06	<0.046	0.82	0.05	<0.001	0.20	0.06	0.002
B	Core, dementia at test	0.64	0.06	<0.020	0.82	0.05	<0.001	0.18	0.06	0.002
C	Core, dementia ever	0.69	0.05	<0.001	0.81	0.06	<0.001	0.11	0.06	0.065

[a]Estimated from separate logistic regression models. All analyses adjusted for age at death, sex, education, and time from olfactory testing to death (core covariates).
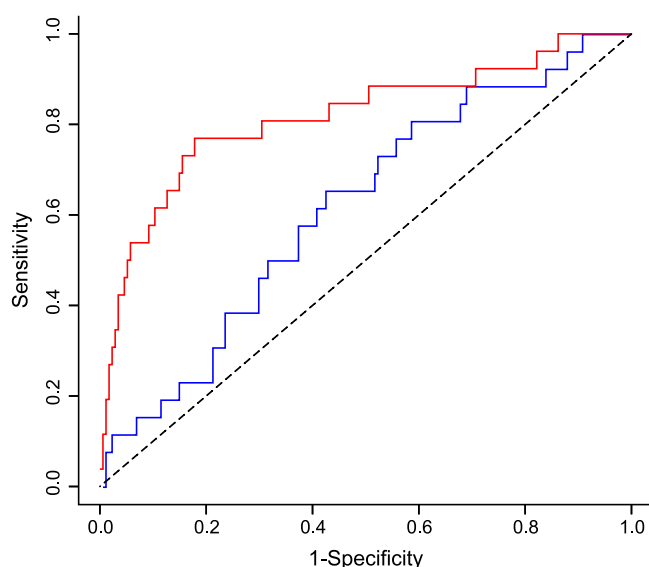
Figure 2 Use of olfactory data to detect Lewy body disease. Estimated area under the receiver operating characteristic curve for models with (red line) and without (blue line) odor identification score, adjusted for age at death, sex, education, and time from olfactory testing to death.

Because the clinical manifestations of Lewy body disorders develop gradually over a period of years, it is likely that some asymptomatic individuals with Lewy body pathology would have developed dementia or Parkinson's disease had they lived longer. With this assumption, the present results suggest that olfactory testing may be useful in identifying individuals with Lewy body disorders, as has been previously suggested for Parkinson's disease (Ponsen et al. 2004; Ross et al. 2008). It is uncertain, however, whether olfactory testing would be useful in discriminating between different Lewy body disorders or between the effects of Lewy bodies and those of AD. This suggests that olfactory testing may enhance early detection of neurodegenerative disease primarily when used in conjunction with other biologic and behavioral markers (Devanand et al. 2008).

Confidence in these findings is strengthened by several factors. Olfaction was assessed with a standard test. A large number of individuals was studied, enhancing statistical power. The high brain autopsy rate makes it unlikely that selective attrition biased estimates of the association of Lewy bodies with olfactory functioning.

The study also has important limitations. We assessed a single component of olfactory function with a brief test administered a mean of several years before death. Furthermore, we did not examine key parts of the central olfactory system often affected by Lewy bodies, including the olfactory bulb and tract, piriform cortex, and amygdala. It is likely, therefore, that the current results underestimate the strength of the association of Lewy bodies with olfactory dysfunction.

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