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The Lateralized Smell Test for Detecting Alzheimer's Disease: Failure to Replicate

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Abstract

Objectives—A widely publicized study by Stamps, Bartoshuk and Heilman (2013) reported that a simple measure of left:right naris differences in the ability to detect the odor of peanut butter is a sensitive marker of Alzheimer's disease (AD). AD patients were said to have abnormal smell function on the left side of the nose and normal function on right side of the nose. In light of its implications for medical practice and the world-wide publicity that it engendered, we sought to replicate and expand this work.

Methods—Two studies were performed. In the first, 15 AD patients were tested according to the procedures described by Stamps et al. in which the nostril contralateral to the tested side was occluded by the patient using lateral pressure from the index finger. Since this can potentially distort the contralateral naris, we repeated the testing using tape for naris occlusion. In the second, 20 AD patients were administered 20 odors of the University of Pennsylvania Smell Identification

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Contributions: Richard L. Doty conceived of the study and provided the data of Study 2. He was primarily responsible for writing the paper and performing the statistical analyses. Fidias E. Leon-Sarmiento played a major role in organizing the testing of the patients in Study 1 and in writing sections of the manuscript. Britney Vazquez was responsible for identifying and organizing the data of Study 2 from earlier data sets, as well as reading and commenting on the final manuscript. Inna Chung played a significant role in aiding in the statistical analyses of both Study 1 and Study 2 and in writing sections of the paper. Edgardo A Bayona, Daniel S. Leon-Ariza, and Juan Cuadros recruited the patients employed in Study 1 and played the primary role in their testing.

Competing interests: RLD is President and major shareholder of Sensonics International, a manufacturer and distributor of tests of taste and smell, including the UPSIT used in Study 2 of this paper. The other authors report no competing interests.

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Test (UPSIT) to each side of the nose, with the contralateral naris being closed with tape. In both studies, the order of the side of testing was systematically counterbalanced.

Results—No evidence of a left:right asymmetry on any test measure was observed.

Conclusion—Although hyposmia is well-established in AD, no meaningful asymmetry in smell perception is apparent. If olfactory function on the right side of the nose was normal as claimed, then AD patients should exhibit normal function when tested bilaterally, a phenomenon not seen in dozens of AD-related olfactory studies.

Keywords

Alzheimer's disease; olfaction; psychophysics; laterality; UPSIT; neurodegeneration

1. Introduction

It has been known for decades that Alzheimer's disease (AD) is associated with decreased ability to smell, regardless of whether measures of odor detection, recognition, identification, discrimination, or memory are performed.¹ Recently, Stamps, Bartoshuk and Heilman² reported that patients with AD exhibited a marked disparity between the left and right sides of the nose in detecting the odor of peanut butter. Eighteen patients with probable AD, 24 patients with amnesic mild cognitive impairment, 26 patients with other forms of dementia, and 26 healthy controls were tested.* During testing, each subject was asked to close their eyes and mouth, breathe normally, and to occlude one naris by applying lateral pressure with the ipsilateral index finger. During each exhalation, a one-ounce exposed container of 14 g of peanut butter was moved in 1 cm steps towards the open naris from a distance of 30 cm until the subject reported perceiving the odor. This was repeated on the other side of the nose 90 sec later. Each subject was allowed to choose the nose side that was first tested. The distance from the naris at which the subject reported smelling the odor was measured. A demonstration of the procedure is available at www.youtube.com/watch?v=z1mcAAgrCnw.

For the AD group, the mean distance for detecting the odor on the left side of the nose was 5.1 cm, whereas that for the right side was 17.4 cm. In all 18 patients, the distance was reported to be shorter for the left than the right side of the nose. The left side distances were found to differ significantly from the distances obtained from the left and right sides of the other tested groups. The distances on the right side of the nose were essentially the same as those in the other groups, including the normal controls. However, since bilateral testing is a general indication of the better functioning side of the nose,³⁻⁵ this observation is incongruent with the large number of studies of AD patients that report bilateral olfactory dysfunction on numerous olfactory measures,^{1;6} including olfactory thresholds.⁷⁻⁹ Their findings also differ from earlier studies examining laterality in PD. Thus, Murphy et al.,⁸ in a study of 21 AD patients, found no differences in n-butanol thresholds between the left and right sides of the nose ($p > 0.82$). Similarly, the sole study that specifically examined

*In the supplementary data listed for their paper, the AD sample size is 17, not 18, and the other dementia sample size is 24, not 26 (<http://dx.doi.org/10.1016/j.jns.2013.06.033>).

left:right naris differences in odor identification and memory in AD patients found no evidence for a lateralized difference.¹⁰

The goal of the present research was to replicate and expand the study described by Stamps et al. In the first of two studies, we repeated the Stamps et al. procedure exactly on a group of AD patients to determine whether their findings could be replicated. In addition to occluding, as was done by Stamps et al., each naris by having the patient apply lateral pressure from the index finger (a procedure that can potentially distort the contralateral nasal aperture), we also tested the patients when the naris was closed with a piece of air-tight tape fitted over the ala nasi and nasal sill. The second study, which was performed in a different group of AD patients, determined whether left:right differences were evident in a forced-choice test of odor identification. Under the assumption made by Stamps et al. that lateralized olfactory differences in odor perception may reflect differing degrees of pathology within the olfactory cortex, one could argue that odor identification might be a more sensitive and reliable probe of such dysfunction than odor detection.

2. Study 1

2.1 Methods

2.1.1 Subjects—Fifteen patients with probable AD, 4 men and 11 women, served as subjects [mean (SD) age = 68.3 (4.4); years of education = 16.4 (4.1)]. All met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD¹¹ and had Mini-Mental State Examination (MMSE) scores < 24 [mean (SD) = 13.1 (2.7)].¹² Most were residents in a regional Pura Vida Foundation care giving center in Bogota, Colombia, a center that specializes in memory disorders. The medical history of each participant was obtained from a knowledgeable family member, the caregiver, or, in some cases, the patient. Each patient received comprehensive general and clinical neurological examinations by board certified neurologists that led to the diagnosis of AD. Comorbid dementia or other neurological disorders evidenced by neuroimaging or medical history were excluded. Laboratory studies excluded causes of dementia other than AD. With the exception of one patient, all patients were right handed. The study protocol was reviewed and approved by the ethics committee of the Medicinencias Research Group and by the Pura Vida Foundation, and the study was conducted according to the principles of the Declaration of Helsinki. Subjects were not paid for participation.

2.1.2 Procedure—The same general paradigm and test procedure described by Stamps et al. was followed. Thus, the olfactory stimulus was 14 g of peanut butter located in a one-ounce container whose cap was removed during testing. Similarly, a 30 cm ruler was used to measure the distance from the open nostril to the stimulus upon its detection. The same instructions – to report when an odor was first detected – were employed. As noted above, the initial testing was performed when each subject held his or her contralateral nostril shut by exerting lateral pressure on the side of the nose with the index finger. As in the original protocol, the subject's eyes and mouth were closed during testing, and a 90-sec delay interval was interspersed between the testing of the two sides of the nose. As in Stamps et al., the subjects were allowed to determine which of the two sides of the nose was tested

first. The testing was repeated with the same constraints except that the contralateral naris was occluded by Microfoam™ tape (3M Corporation, Minneapolis). Each patient was tested individually in a large quiet room with adequate ventilation.

2.1.3 Results—The mean, median, standard deviation, interquartile range, and range of the test scores are presented in Figure 1. The p values in the figure represent those from paired t -tests. An analysis of covariance (ANCOVA) with occlusion procedure (finger, tape) and test side (L, R) as within subject factors and the covariates of age and MMSE score found no evidence for greater left-side sensitivity [$F(1,12) = 1.71, p = 0.22, \eta_p^2 = 0.11$], with a non-significant trend in the direction *opposite* to that reported by Stamps et al. No other factors or interactions were significant, although, in accord with evidence that olfaction and cognition may be inversely related in AD,⁸ the MMSE covariate trended in this direction [$F(1,12) = 3.46, p = 0.09, \eta_p^2 = 0.22$]. When separate ANOVAs were computed for the finger and tape closure data for the dependent measure of left minus right side distance and the factor of first side tested, no significant influence of first side tested was observed [Finger occlusion: $F(1,13) = 0.05, p = 0.82; \eta_p^2 = 0.004$; Tape occlusion: $F(1,13) = 3.21, p = 0.10, \eta_p^2 = .20$].

Pearson correlations computed between the MMSE scores and the lateralized differences, i.e., left minus right distances, showed no trends [finger occlusion $r = 0.02$ ($p = 0.96$); tape occlusion $r = -0.17$ ($p = 0.55$)]. A comparison of the finger occlusion difference data of the three most demented patients (MMSE scores of 9, 10 & 10) to those of the three least demented patients (MMSE scores of 17, 17 & 18) revealed no evidence of differences between these subjects (respective left-right difference scores = -1, -1, +2 and -1, 0, 0). The same was the case for the equivalent comparisons for the tape occlusion difference data (respective left-right difference scores = +2, -1, -1 and -3, +1, 0). The relatively small left-right differences suggested that the distance measures were reliable. This was confirmed by Pearson correlations computed between the left and right nose side data under the finger and tape occlusion conditions (respective $r_s = 0.84$ and $0.92, p_s < 0.001$).

Correlations computed between MMSE scores and the distance measures for each side of the nose separately were similar for the left and right sides of the nose [r_s for the left & right finger occlusion conditions = 0.41 (one-tailed $p = 0.06$) and 0.44 ($p = 0.05$), respectively; r_s for the left and right tape occlusion conditions = 0.41 ($p = 0.06$) and 0.47 ($p = 0.04$), respectively].

3. Study 2

3.1 Methods

3.1.1 Subjects—Twenty patients who met the same criteria for probable AD as described in Study 1 served as subjects [6 men and 14 women, mean (SD) age = 73.80 (9.07); mean (SD) MMSE = 18.75 (4.08)]. Most were patients of board certified neurologists at Jefferson Medical Center and at the Hospital of the University of Pennsylvania. The study protocol was reviewed by the human subject committees of both institutions and informed consent was obtained from all participants and co-signed by a family member or a designated care giver. The study was conducted according to the principles of the Declaration of Helsinki.

Subjects were paid \$200 for their participation as part of a more extended longitudinal study that included other tests.

3.1.2 Procedures—Half (i.e., 20) of the 40 University of Pennsylvania Smell Identification Test (UPSIT) odorants were administered to each side of the nose.¹³ The UPSIT is a well-established, reliable, and standardized olfactory test that correlates with olfactory threshold tests in both normal subjects¹⁴⁻¹⁷ and in patients with a number of neurological diseases,^{18;19} including AD.⁹ The stimuli were presented by a trained test administrator who released the stimuli under each subject's nose, read aloud the response alternatives, and recorded the responses. As in the second component of Study 1, the naris contralateral to the tested side was comfortably but tightly sealed with a piece of Microfoam™ tape fitted to the perimeter of the naris. The testing order of the nares and the presentation order of the UPSIT odors (two 10-odor booklets per side) were counterbalanced across subjects.

3.1.3 Results—As evident in Figure 2, there was no meaningful difference in the odor identification test scores of the left and right sides of the nose. An analysis of covariance with the within subjects factor of nose side, the between subjects factor of sex, and covariates of age and MMSE found no evidence of differential performance on the left and right sides of the nose [$F(1,16) = 1.60, p = 0.22, \eta_p^2 = 0.04$]. None of the other measures or their interactions was significant ($ps > 0.33$). As in Study 1, there was no evidence for an association between MMSE scores and left:right odor identification test score differences ($r = -0.05, p = 0.84$). Although, as in Study 1, positive correlations were observed between the MMSE and both the left and right olfactory test measures, they were very weak and non-significant (respective rs for the left & right nose sides = 0.05 ($p = 0.42$) and 0.10 ($p = 0.34$)).

4. Discussion

The present study provides no support for the concept that patients with AD exhibit a meaningful left vs. right nose side difference in their ability to detect peanut butter odor or to identify smells. Our findings are in accord with earlier studies that found no significant AD-related nasal lateralization in odor detection, identification, or memory.^{8;20} Importantly, they throw into question the recent and highly publicized report that a simple test of lateralized odor detection can be employed in the diagnosis of AD.² The claim by Stamps et al. that all 18 of their patients exhibited more dysfunction on the left than on the right side of the nose, and that, on average, normal smell function was present on the right side of the nose, does not comport with what is known from other studies of smell dysfunction of AD. As noted in the introduction, bilateral testing is a general indication of the better functioning side of the nose.³⁻⁵ Hence, if AD patients have normal function on the right side, as claimed, then bilateral tests would be expected to demonstrate no overall AD-related olfactory dysfunction, which is clearly not the case in the dozens of studies that have evaluated olfaction in AD.^{21;22}

One might argue that differences in the degree of dementia, as measured by MMSE scores, might explain the disparity between our work and that of Stamps et al. The mean MMSE in Stamps et al. was 19.2 (SD = 4.8), whereas that of our first study was 13.1 (SD = 2.7) and

our second study was 18.8 (SD = 4.1). Such an argument is weak for several reasons. First, if an association between the degree of dementia and lateralization of test scores was present, a meaningful correlation in Study 1 between MMSE scores and left minus right peanut butter distance scores would have been expected. This was not the case. Furthermore, no such associations were observed in regards to the left minus right UPSIT scores of Study 2, whose subjects had MMSE scores essentially equivalent to those of Stamps et al. Second, based on their reported standard deviation of 4.8, a number of the Stamps et al. subjects presumably had test scores less than 19.2, yet according to the authors, all 18 of their subjects exhibited the lateralization phenomenon. Third, the average MMSE scores of the studies by Murphy et al. (20.0) and Bahar-Fuchs et al.¹⁰ (23.3) -- studies which found no left:right difference in tests of odor detection, identification, and memory -- were similar or slightly above the MMSE score of the Stamps et al. study. This throws into question the notion that such lateralization would be evident only in less demented individuals. Finally, the difference measures obtained in Study 1 were reliable across nares as well as across two test procedures (finger and tape naris closures), implying that the subjects were not too demented to accurately report their perceptions.

To explain their findings, Stamps et al. bring up the concept of lateralization of AD-related neuropathology and its potential influences on the ability to smell. While there is support for the idea that left hemisphere pathology in mild cognitive impairment (MCI) is predictive of the development of future AD,²³ considerable variability is present and left lateralized findings are not universal. One study, for example, found that individuals with MCI have unilateral atrophy in the right medial temporal lobe.²⁴ Similarly, evidence for left-side lateralized pathology in AD is contradictory, with bilateral pathology generally overshadowing directional asymmetry.^{25;26} One study found right side hypometabolism in early onset AD cases.²⁷ A number of workers have pointed out that most asymmetries in pathology in AD are not systematically biased in any specific direction.²⁸⁻³¹ For example, Derflinger et al., in a study of 35 AD brains, found asymmetries in gray-matter atrophy that were not directionally lateralized.²⁸ These authors point out, as have others,³² that left-side lateralization can result in some cases from the selection of subjects on the basis of neuropsychological test measures that are heavily weighted towards left hemisphere processes such as verbal learning.

In conclusion, the present study throws into question the findings of Stamps et al. that AD is associated with lateralized asymmetry of olfactory dysfunction. While the possibility exists that such asymmetry might occur in a few well-selected cases, our research clearly indicates that such a phenomenon is not a general one and cannot be relied upon in diagnosing AD.

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Highlights

- Clear demonstration of lack of asymmetry in olfaction with AD.
- Reaffirmation of early smell loss in AD.
- Clarified disparities in disparate findings of olfactory laterality in AD.

Figure 1.

Distance from the nose at which the peanut butter odor was perceived in the AD patients of Study 1. Left represents results when the naris contralateral to testing was closed by the patient's lateral pressure with the index finger, whereas right represents results when naris occlusion was done with tape. Horizontal lines in blue boxes represent medians. Edges of boxes reflect the interquartile range. The blue vertical lines represent ranges. The green stars are means and the green lines reflect ± 1 SD. The p values are from paired t-tests that compare the means of the left and right sides of the nose. Copyright © 2014 RL Doty.

Figure 2.

Scores on two booklets of the University of Pennsylvania Smell Identification Test (UPSIT) administered to each side of the nose ($n = 20$ odors) in the AD patients of Study 2. The naris contralateral to testing was closed with tape. Horizontal lines in blue boxes represent medians. Edges of boxes reflect the interquartile range. The blue vertical lines represent ranges. The green stars are means and the green lines reflect ± 1 SD. The p values are from paired t-tests that compare the means of the left and right sides of the nose. Copyright © 2014 RL Doty.