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Neuroimaging Biomarkers and Impaired Olfaction in Cognitively Normal Individuals

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Abstract

Objective—There is a need for inexpensive non-invasive tests to identify older healthy persons at risk for Alzheimer's disease (AD) for enrollment in AD prevention trials. Our objective was to examine whether abnormalities in neuroimaging measures of amyloid and neurodegeneration are correlated with odor identification (OI) in the population-based Mayo Clinic Study of Aging (MCSA).

Methods—Cognitively normal (CN) participants had olfactory function assessed using the Brief Smell Identification Test (B-SIT), underwent magnetic resonance imaging (MRI; n=829) to assess a composite Alzheimer's disease (AD) signature cortical thickness and hippocampal volume (HVa), and, ^{11}C-Pittsburgh compound B (^{11}C-PiB; n=306) and ^{18}fluorodeoxyglucose (^{18}F-FDG; n=305) positron emission tomography (PET) scanning to assess amyloid accumulation and brain hypometabolism, respectively. The association of neuroimaging biomarkers with OI was examined using multinomial logistic regression and simple linear regression models adjusted for potential confounders.

Results—Among 829 CN participants (mean age 79.2 years; 51.5% men), 248 (29.9%) were normosmic and 78 (9.4%) had anosmia (B-SIT score <6). Abnormal AD signature cortical

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AUTHOR CONTRIBUTIONS

ROR, MV and RCP contributed to study concept and design; MV, ROR, TJC, WKK, MMMi, MMMa, DSK, YEG, CRJ, VJL and RCP contributed to data acquisition, analysis and interpretation; MV, ROR and TJC contributed to drafting the manuscript and preparing the figures. All authors critically revised the manuscript for important intellectual content.

POTENTIAL CONFLICTS OF INTEREST

Nothing to report.

thickness and reduced HVa were associated with decreased OI as a continuous measure (slope=−.43; (95%CI −.77, −.09); p=.01 and slope=−.72; (95%CI −1.15, −.28); <.01, respectively). Reduced HVa, decreased AD signature cortical thickness and increased amyloid accumulation were significantly associated with increased odds of anosmia.

Interpretation—Our findings suggest that OI may be a non-invasive, inexpensive marker for risk stratification, for identifying participants at the preclinical stage of AD who may be at risk for cognitive impairment, and eligible for inclusion in AD prevention clinical trials. These cross-sectional findings remain to be validated prospectively.

INTRODUCTION

The prevalence and severity of impaired olfaction increases with age.[1] It affects more than half of the population aged 65–80 years old, and 62–80% of persons older than 80 years.[1] Impaired olfaction negatively affects quality of life, enjoyment of food, physical and mental well-being or safety, and mortality.[2, 3] The association with increased mortality in older individuals may be mediated by cognitive impairment.[2, 4]

Factors that may contribute to olfactory loss in aging include damage to olfactory epithelium, nasal engorgement, sensory loss of receptor cells to odorants, decrease in mucosal metabolizing enzymes, and neurochemical changes in the brain.[1, 3] However, olfactory impairment in aging or neurodegenerative disease may result from the expression of aberrant proteins in the olfactory system that cause structural or functional abnormalities in the olfactory system (e.g., olfactory epithelium, olfactory bulb, central olfactory cortex, or olfactory circuitry).[1]

Olfactory impairment has been associated with cognitive decline,[5] mild cognitive impairment (MCI),[6] Alzheimer ’s disease (AD) dementia,[7–11] vascular dementia,[12] Parkinson’s disease,[13] dementia with Lewy bodies,[14] as well as, the progression from MCI to AD dementia.[6, 8] In cognitively normal elderly individuals, worse odor identification (OI) has also been associated with markers of brain pathology, such as increased cortical amyloid and thinner entorhinal cortex,[15] and with neurofibrillary pathology in the entorhinal cortex and hippocampus in autopsy studies.[16] Thus, changes in olfactory function in cognitively normal persons, could represent “pre-clinical” neurodegenerative disease.[3]

There is a need for inexpensive non-invasive tests to identify older healthy persons potentially at risk for AD for enrollment in AD prevention trials. One of the earliest brain regions affected by AD is the olfactory system,[17, 18] suggesting that olfactory impairment may be an early sign of AD brain pathology, an intermediate marker in the causal pathway from brain biomarker pathology to cognitive impairment. Amyloid-β (Aβ) accumulation has been described in areas of the olfactory network in AD and amnestic MCI participants but also in elderly persons with normal neuropsychological test scores.[19] A recent meta-analysis suggested that odor identification and recognition could be the most interesting candidate for inclusion in a group of biomarkers to detect subclinical AD,[20] especially when combined with clinical/neuropsychological[21] assessment and imaging biomarkers.[22]

We hypothesized that *in vivo* neuroimaging biomarkers of AD pathology are associated with olfactory impairment among older cognitively normal (CN) individuals. The objective of the present study, therefore, was to examine the cross-sectional associations between neuroimaging measures of amyloid accumulation and neurodegeneration and a simple measure of OI in a large population-based cohort of cognitively normal older persons.

METHODS

Study population

Details of the MCSA design and methodology have been previously reported.[23, 24] Residents in Olmsted County, MN aged 70–89 years on October 1, 2004 (prevalence –index date), were enumerated using the Rochester Epidemiology Project (REP)[25] resources and an age and sex-stratified random sample of eligible subjects (without dementia, not terminally ill or in hospice) was invited to participate. Ongoing recruitment was performed beginning from 2008 through 2011, using the same protocols as in 2004. Participants were comprehensively evaluated for a diagnosis of MCI[16] or dementia[26] and normal cognition as previously described.[23, 24] Overall, this analysis includes 829 cognitively normal participants (822 participants were white), who were recruited between 2004 and 2010, completed an in-person evaluation, the Brief Smell Identification Test (B-SIT),[27] and underwent magnetic resonance imaging (MRI). Of these individuals, 351 had ^{11}C-PiB PET scans and 350 had ^{18}F-FDG PET scans available during the same MCSA follow-up visit as the B-SIT. Participants with a diagnosis of Parkinson's Disease (PD) were excluded. During follow-up, two participants developed PD, 138 developed MCI and 13 developed dementia.

Standard Protocol Approvals, Registrations, and Patient Consent

The study was approved by the Institutional Review Boards of the Mayo Clinic and the Olmsted Medical Center. Written informed consent was obtained prior to participation in the study.

Assessment of Olfactory Function

Olfactory impairment was assessed using the B-SIT[27] version A that consists of six food-related and six nonfood-related smells (cherry, clove, strawberry, menthol, pineapple, lemon, leather, lilac, smoke, soap, natural gas, and rose). Participants had to scratch, sniff and select one of 4 possible choices. The B-SIT score was calculated as the sum of the correct responses for persons with ≤2 missing responses; for persons with 1 (n=10) or 2 (n=4) missing responses a score of 0.25 was assigned for each missing response.[7, 10] Osmia categories were defined by B-SIT score as: anosmia (score <6), hyposmia (or microsmia) (men 6–10, women 6–10.25), and normosmia (men 10.25–12; women 10.5–12)[9].

Acquisition of MRI measures

MRI studies were performed at 3 tesla (Signa; GE Healthcare, Waukesha, WI) with an 8-channel phased-array head coil acquiring both a 3-dimensional magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence and a fluid-attenuated inversion recovery (FLAIR) sequence.[28] Hippocampal volume (HVa) was measured using the FreeSurfer software (version 5.3), and adjusted for total intracranial volume (n=821).[29]

Cortical thickness was measured using FreeSurfer (v 5.3) and an AD-signature cortical thickness measure[30] was computed by averaging the cortical thickness for entorhinal, inferior temporal, middle temporal, and fusiform cortices (n=826).

^{18}F-FDG PET and ^{11}C-PiB PET Acquisition

PET images were acquired using a PET/CT scanner operating in 3-dimensional mode.[31] A detailed ^{18}F-FDG PET and ^{11}C-PiB PET acquisition process is published.[31–33] An amyloid PET standardized uptake value ratio (SUVR) was formed from the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest (ROIs) normalized to the whole cerebellum (n=306).[31] An AD signature[34] ^{18}F-FDG PET SUVR (non-sharpened, non-partial volume corrected) was calculated based on glucose metabolic rates from an AD signature meta-ROI and consisted of the average bilateral angular gyri, posterior cingulate, and inferior temporal cortical ROIs from both hemispheres normalized to pons and vermis uptake (n=305).[35–37]

Neuroimaging biomarkers cut points

The cut-points for biomarker abnormality were defined such that 90% of a group of 75 clinically diagnosed AD dementia subjects from the Mayo Clinic Alzheimer Disease Research Center and MCSA were categorized as abnormal. Abnormal HVa was defined as < −2.40 cm^3 (adjusted for total intracranial volume); abnormal FDG PET was defined as SUVR <1.32; abnormal AD signature cortical thickness was defined as <2.74 mm; abnormal amyloid PET was defined as SUVR >1.40 and was validated by autopsy correlation with Thal amyloid phase.[30, 34, 38, 39]

Covariates

Information on age, sex, years of educational, body mass index (weight in kilograms divided by height in meters squared), smoking habits, self-reported alcohol problems and gait-speed (m/s), was collected at the baseline evaluation; history of type 2 diabetes, hypertension and stroke was obtained from medical record abstraction; apolipoprotein E (APOE) genotyping was performed at baseline.

Statistical Analysis

Cross-sectional associations of abnormal ^{11}C-PiB PET, abnormal AD signature ^{18}F-FDG PET [hypometabolism], abnormal AD signature cortical thickness and abnormal HVa with the osmia categories were examined using multinomial logistic regression models (odds ratios [ORs], 95% confidence intervals [CIs]) having normosmia as the comparison group. Examination of the residuals of regressions of the continuous B-SIT score on abnormal neuroimaging biomarkers, adjusting for age, sex and education, suggested linear associations. We also used multivariable linear regression models to examine the association (slope, 95% CIs) of abnormal biomarkers with continuous B-SIT as the dependent (outcome) variable.

Separate models were fit with each neuroimaging biomarker as the independent (exposure) variable and the B-SIT score (categorical and continuous) as the dependent (outcome) variable. All models were adjusted for age (at B-SIT), sex and education (basic model); TIV

was included in models with amygdala volume. We assessed the interaction between abnormal ^{11}C-PiB PET and each of the other three neuroimaging biomarkers (i.e., abnormal AD signature cortical thickness, abnormal HVa and abnormal ^{18}F-FDG PET) and separate analyses were performed in individuals with and without abnormal ^{11}C-PiB PET as there was a statistically significant interaction between abnormal ^{11}C-PiB PET and abnormal ^{18}F-FDG PET.

The association of biomarker groups defined by the combination of abnormality for amyloid (A+/A−) and neurodegeneration (N+/N−) (i.e., A−N−, A+N−, A−N+, and A+N+)[34] with the B-SIT score and osmia categories were examined with adjustment for age, sex and education. Presence of neurodegeneration was defined as either HVa ≤−2·40 cm^3 or FDG ≤1.32 SUVR.[34]

Multinomial logistic regression models were also fit to additionally adjust (in separate models) for APOE ε4 carrier status (ε4 carrier vs noncarrier), Unified Parkinson Disease Rating Scale,[40] the Boston Naming Test[41] and history of head trauma (i.e, the participants were asked “Have you ever experienced any head injuries that led you to see a doctor, stay in the hospital, lose your memory, or become unconscious”). Final model simultaneously adjusted for APOE e4 allele, type 2 diabetes, hypertension, stroke, self-reported alcohol problem and ever smoking; the estimates were essentially unchanged therefore only estimates from the previous more parsimonious models are reported.

In multivariable linear regression models, the associations (slopes [beta estimates], 95% CIs) of MRI and PET ROI measurements in areas of the primary olfactory cortex (e.g. amygdala, entorhinal cortex), the secondary olfactory regions (e.g., e.g., hippocampus, hypothalamus, thalamus, insula, orbitofrontal cortex), and areas where odorant-induced activation has been recorded in previous fMRI and PET studies, including precentral gyrus, superior and inferior temporal gyrus, cingulate gyrus, occipital lobe, parietal lobe,[42, 43] and inferior frontal gyrus[44] with continuous B-SIT score were examined. No mathematical correction[45] was applied for multiple comparisons to avoid increasing type II error, as the investigation broadly examined the associations of smell and neuroimaging measures of amyloid and neurodegeneration so as to generate hypothesis for future prospective studies.

Associations were considered significant at a p value < 0.05, and were performed using SAS statistical software version 9.3 (SAS Institute, Cary, North Carolina) and Stata/SE statistical software version 14.2 (StataCorp LP, College Station, Texas).

RESULTS

Characteristics of participants

Table 1 presents characteristics of 829 participants by osmia categories. Of the 829 participants, (mean age 79.2 years; 51.5% men), 248 (29.9%) were normosmic, 78 (9.4%) had anosmia and 503 (60.7%) had hyposmia; anosmia was significantly more frequent in men. Thirty percent (n=249) of the participants had abnormal cortical thickness and 15.5 % (n=128) had abnormal HVa. Among participants with available PET scans, 38.9 % had abnormal ^{11}C-PiB PET (n=119) and 29.5 % had abnormal ^{18}F-FDG PET (n=90), while

16.9% (n=51) were positive for both β-amyloidosis and neurodegeneration biomarkers (A+N+). The frequencies of abnormal ^{11}C-PiB PET, abnormal AD cortical thickness and abnormal hippocampal volume increased with increasing impairment in OI. Compared to MCSA participants with B-SIT assessment who did not participate in imaging studies (n=595), participants with imaging (n=829) performed better on cognitive tests (i.e., had higher global composite scores) and had a lower frequency of hypertension (data not shown).

Association of olfactory function and imaging biomarkers

Individuals with abnormal ^{11}C-PiB PET, abnormal AD signature cortical thickness and abnormal HVa had significantly increased odds of having anosmia (vs. normosmia) (OR: 2.74, 95% CI: 1.12–6.66; OR=2.20, 95%CI (1.25, 3.86); and OR=2.45, 95%CI (1.21, 4.94), respectively, adjusting for age, sex and education) (Table 2). These estimates remained relatively stable with adjustments for APOE ε4 allele, Unified Parkinson Disease Rating Scale,[40] the Boston Naming Test[41] and history of head trauma in separate models (Table 2). Biomarkers were not significantly associated with hyposmia.

In analyses examining the association of imaging biomarkers with B-SIT as a continuous outcome variable, abnormal AD signature cortical thickness and abnormal HVa were significantly associated with lower B-SIT score (slope (95%CI)=−.43 (−.76, −.09), p=.01; slope (95%CI)=−.72 (−1.15, −.28), p<.01, respectively), adjusting for age, sex and education (Table 3).

There were statistically significant interactions between abnormal ^{11}C-PiB PET and abnormal ^{18}F-FDG PET (i.e., p=0.017 for interaction for the anosmia (vs. normosmia) comparison and p=0.061 for the hyposmia (vs. normosmia) comparison in the multinomial logistic regression models and p = 0.004 when B-SIT was used as a continuous outcome in the linear regression model), thus we performed separate analyses in those with and without abnormal ^{11}C-PiB PET (Table 4). Of interest the point estimates for associations in the abnormal PiB stratum remained elevated; however, the wide-confidence intervals suggested lower precision and possibly overestimated point estimates due to the small numbers. The association of abnormal HVa with the continuous B-SIT score was significant only in those with abnormal ^{11}C-PiB. There were no statistically significant associations in persons without abnormal PiB. In analyses for imaging biomarker groups defined by the combination of abnormality for amyloid (A+/A−) and neurodegeneration (N+/N−), individuals with A+/N+ imaging biomarker combination (when compared to those with the A−/N− combination) had a 3.84 fold increased odds of having anosmia (OR, 3.84; 95%CI: 1.14, 12.97; p = .03) (Table 5). Having the A+/N+ (vs. A−/N−) imaging biomarker combination was also significantly associated with lower B-SIT score (slope (95%CI) = −.99 (−1.71, −.27).

Figures 1 and 2 present the associations (linear regression slopes and 95%CIs) of MRI and ^{18}F-FDG PET ROI measurements with continuous B-SIT score. Associations were stronger (and statistically significant) between MRI (Fig 1) and ^{18}F-FDG PET (Fig 2) ROIs representing areas of the primary olfactory cortex and secondary olfactory regions and B-

SIT. None of the associations between ^{11}C-PiB ROIs and B-SIT reached statistical significance.

DISCUSSION

The present study examined associations of amyloid deposition, markers of neurodegeneration, and neurodegeneration conditioned on amyloid status with OI. In this sample of cognitively normal elders, increased amyloid deposition, abnormal AD signature cortical thickness and abnormal HVa were significantly associated with anosmia Abnormal AD signature cortical thickness and abnormal HVa were significantly associated with decreasing B-SIT score. The association of the B-SIT score with HVa could be driven by abnormal ^{11}C-PiB PET.

The present study examined associations of OI with neurodegeneration conditioned on amyloid status. The association of biomarkers of neurodegeneration (i.e., reduced HVa and hypometabolism) with B-SIT remained statistically significant and was stronger in individuals with abnormal PiB. In addition, the A+N+ biomarker category was strongly associated with severe OI impairment (anosmia). These cross-sectional findings have potential clinical significance if validated prospectively since previous reports suggest that CN individuals with reduced HVa are at risk for MCI[46] and those with A+/N+ pathology have higher rates of future medial temporal neurodegeneration.[47]

These results are partly in agreement with a previous study[15] that reported that in PiB positive clinically normal participants, a thinner entorhinal cortex was associated with worse olfactory function. However, previous studies are few and inconclusive. Antemortem OI (using B-SIT) was demonstrated[16] to be negatively associated with post-mortem AD brain pathology (amyloid load and tangle density) but authors reported that when both measures of AD pathology were in the same analysis model, the association with tangles persisted but the association with amyloid was 70% attenuated.[16] Similar conclusions were reached in studies conducted in mouse models.[17] In addition, elevated soluble Aβ has been associated with detrimental effects on neural circuits and altered connectivity of olfactory neurons in mice (overexpressing human APPsw (Swedish mutation)) before the onset of plaques.[48] Investigators[17] have demonstrated a moderate inverse linear association between OI and PiB binding (global or regional) when pooling together individuals with AD, amnestic MCI or CN individuals, but the association was not verified within each of these groups.

In the present study, abnormal ^{11}C-PiB PET scan was strongly associated with .anosmia.. Although we cannot assess a temporal relationship between amyloid deposition and OI impairment and amyloid deposition, this finding might suggest that a threshold of AD pathology burden in CN individuals might be necessary for severe OI to be present. We did not measure tau, thus we cannot determine whether overall the burden of AD pathology (i.e., both amyloid and tau deposits) was increased but given the study population median age (78.4 years), we could speculate that nearly all participants had some level of neurofibrillary tangle pathology.[29, 49]

Aging is characterized also by a decrease in cortical thickness,[3] and hippocampal volume. We considered atrophy on MRI as a measure of neurodegeneration,[29] however hippocampal atrophy is not specific for AD. It could represent other age-related processes leading to neurodegeneration, including tauopathy.[29] Investigators[18] have found that worse OI was associated with smaller hippocampal volume in a group of MCI and AD patients but not in healthy individuals; however the authors acknowledged the need for larger studies.[18] In additional previous reports, OI scores cross-sectionally correlated with hippocampal volume in a study of non-demented elders,[50] OI deterioration prospectively correlated with decreased hippocampal volume (and cognitive function deterioration) among MCI patients[21] and was associated with greater AD pathology (based on a composite measure including neuritic plaques, diffuse plaques, and neurofibrillary tangles) in an autopsy study of individuals without cognitive impairment.[51]

The present study examined the association of abnormal (decreased) cortical thickness specifically in AD signature cortical regions OI,[30] which we expect would most likely differentiate those individuals at risk for clinical AD. Having abnormal AD signature cortical thickness (vs. not having abnormal AD signature cortical thickness) was most strongly associated with severe OI impairment (anosmia vs. normosmia). We observed significant positive associations between AD signature cortical thickness (as a continuous measure), entorhinal, temporal pole and parahippocampal cortical thicknesses, key regions associated with olfaction and with cortical atrophy in AD dementia, and B-SIT score. In patients with early AD, OI scores were associated with normalized FDG uptake with peaks in the right inferior frontal gyrus, the right fusiform gyrus, precuneus and superior parietal lobe.[44] In the present study, FDG ROIs of the olfactory pathway and AD pathology including amygdala, hippocampus, entorhinal, or olfactory ROIs showed significant positive associations with B-SIT score. However, abnormal AD ^{18}F-FDG-PET ratio was associated with B-SIT only in those with abnormal ^{11}C-PiB PET. Potential explanations could include that the abnormal AD ^{18}F-FDG-PET ratio does not include key areas of the olfactory pathway (i.e., it includes average bilateral angular gyri, posterior cingulate, and inferior temporal) or that OI may precede brain hypometabolism in those areas early in the AD process, especially when the Aβ burden is not significant (i.e. in individuals without abnormal PiB PET).

AD pathology develops several decades[52] prior to AD symptomatology. Current cross-sectional findings if validated in prospective studies are clinically relevant as the olfactory system demonstrates measurable impairment in the early pre-clinical stages of the disease when the AD pathological markers are also present.[17] Because of the nature of the logistic models, when analysis direction is reversed, the results are quite similar, suggesting that in a clinical setting OI could be used to as a marker for neuroimaging abnormality.

The association of imaging biomarker abnormalities with OI suggests that OI may be a non-invasive, inexpensive marker for risk stratification, for identifying participants at the preclinical stage of AD who may be at risk for cognitive impairment, and eligible for inclusion in AD prevention clinical trials. Although, olfactory assessment cannot currently be used as a stand-alone diagnostic test,[17] a combination of olfactory assessment with other AD biomarkers (e.g., imaging biomarkers) could strengthen the AD diagnostic sensitivity

and specificity.[17, 53] However, our findings are preliminary and remain to be validated prospectively.

Limitations of the study should be considered when interpreting the results. The cross-sectional study design precludes our ability to assess causality. Participants in imaging studies performed slightly better cognitively and had a slightly lower frequency of hypertension than individuals without imaging studies, suggesting a potential bias of our estimates toward the null. Analysis stratified by PiB status (normal/abnormal) suggested lower precision and could have overestimated the point estimates. Lastly, the population of Olmsted County, MN, 70 years and older, is predominantly white of European ancestry; thus assessment of these associations in more heterogeneous populations would be of interest.

Despite the potential limitations, the study has several important strengths. The population-based design diminishes potential selection bias. Cognitive status was comprehensively assessed using published criteria, without consideration of any previous diagnoses, thereby reducing the potential bias in ascertainment of CN status. In addition, reliable measures of brain pathology were ascertained by multimodal, state-of-the-art, imaging and the study had a relatively large sample size.

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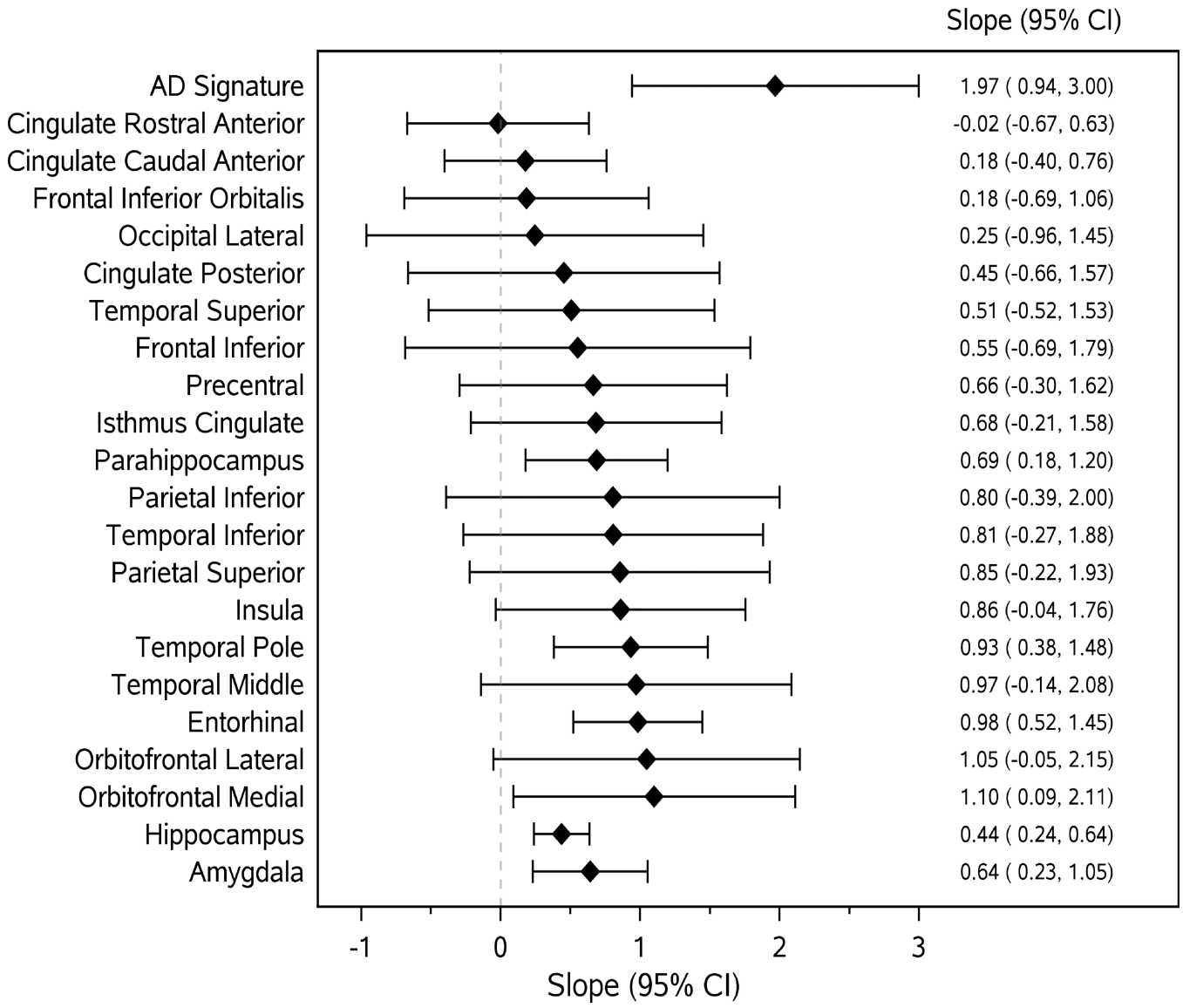

Figure 1.

Forest plots for associations (slopes, 95%CI) of continuous cortical thickness and volume measures (i.e., amygdala and hippocampus) with continuous B-SIT as the outcome variable. The diamonds represent slopes (estimated change in B-SIT per unit increase in cortical thickness (in mm) and volume measures (in cm^3)) from general linear models adjusted for age, sex, education. The solid horizontal lines represent the 95% confidence intervals.
AD signature = an AD-signature cortical thickness measure was computed by averaging the cortical thickness for entorhinal, inferior temporal, middle temporal, and fusiform cortices.

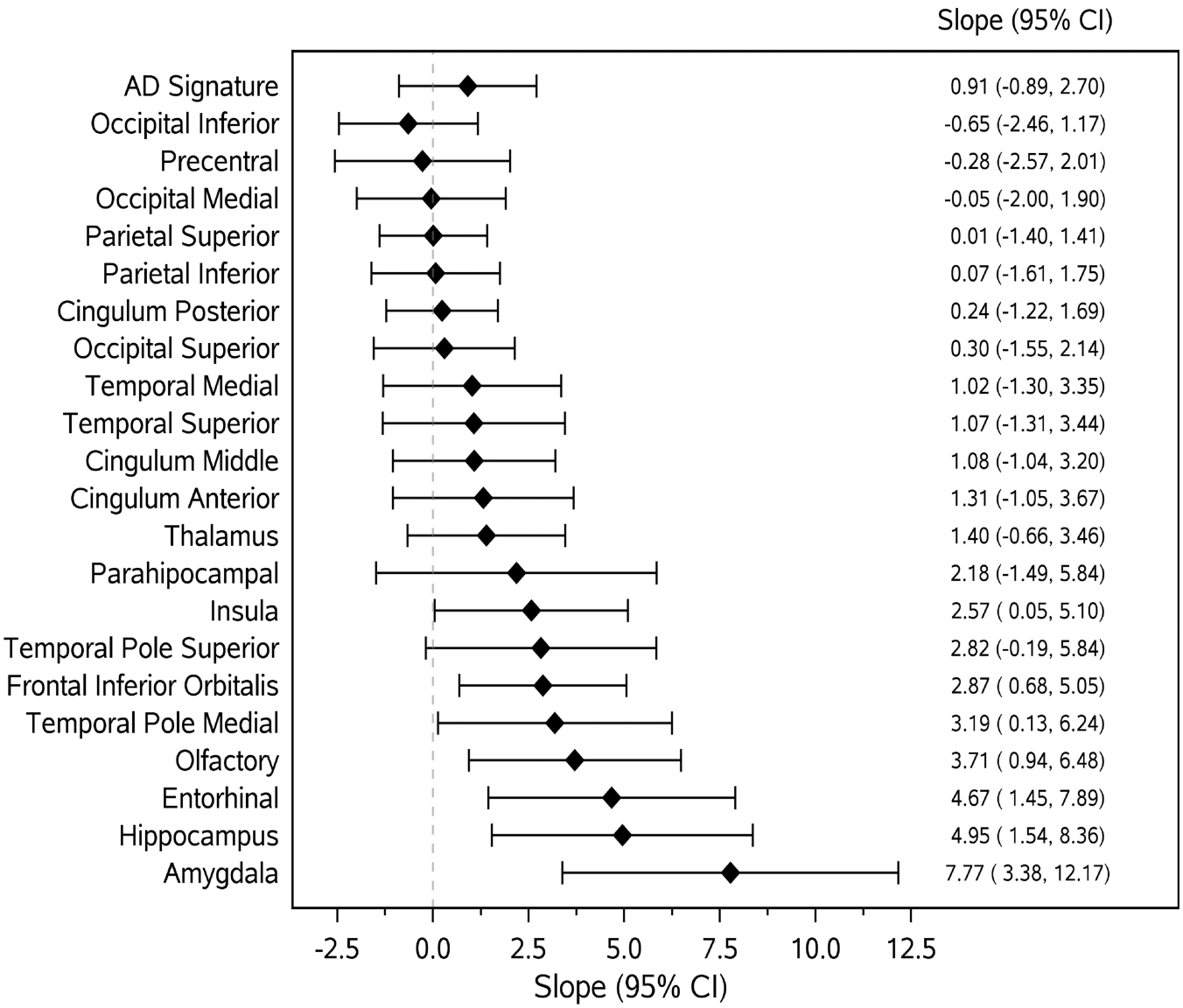

Figure 2.

Forest plots of associations (slopes, 95%CI) of continuous ^{18}-F-FDG PET biomarkers with continuous B-SIT as the outcome variable. The diamonds represent slopes (estimated change in B-SIT per unit increase in FDG PET standardized uptake value ratio) from general linear models, adjusted for age, sex, education. The solid horizontal lines represent the 95% confidence intervals.

AD signature = an AD signature ^{18}F-FDG PET SUVR was calculated based on glucose metabolic rates from an AD signature meta-ROI and consisted of the average bilateral angular gyri, posterior cingulate, and inferior temporal cortical ROIs from both hemispheres normalized to pons and vermis uptake.

Table 1

Characteristics of Participants - the Mayo Clinic Study of Aging.

Characteristics	Normosmia[a] (N=248)	Hyposmia (N=503)	Anosmia (N=78)	p[b]
Age (years) at time of B-SIT, mean (SD)	77.7 (4.7)	79.7 (5.2)	81.3 (5.4)	<0.001
Female	145 (58.5)	227 (45.1)	30 (38.5)	<0.001
Education (years), mean (SD)	14.6 (2.7)	14.2 (2.9)	14.9 (2.8)	0.037
Ever Smoker (at time of B-SIT)	113 (45.6)	238 (47.3)	42 (53.8)	0.441
APOE ε24/ε34/ε44	61 (24.6)	134 (26.6)	15 (19.2)	0.357
Depressive symptoms BDI (>=13) (at time of B-SIT)	8 (3.2)	32 (6.4)	4 (5.1)	0.196
History of diabetes mellitus II (definite/probable)	33 (13.3)	104 (20.7)	9 (11.5)	0.015
History of stroke	7 (2.8)	18 (3.6)	6 (7.7)	0.135
History of hypertension	178 (71.8)	387 (76.9)	60 (76.9)	0.287
History of self-reported alcohol problems	7 (2.8)	20 (4.0)	2 (2.6)	0.645
Continuous B-SIT score, mean (SD)	11.4 (0.5)	8.7 (1.3)	3.9 (1.2)	<0.001
Abnormal ^{11}C-PiB PET[c]	33 (32.4)	69 (39.2)	17 (60.7)	0.024
Abnormal ^{18}F-FDG PET[d]	26 (25.5)	54 (30.9)	10 (35.7)	0.481
Abnormal AD Sig. CT[e]	54 (21.8)	159 (31.8)	36 (46.2)	<0.001
Abnormal HVa[f]	21 (8.5)	85 (17.2)	22 (28.2)	<0.001
Imaging Biomarker Group[g]				0.016
A−/N−	47 (46.1)	68 (39.5)	8 (28.6)	
A+/N−	24 (23.5)	37 (21.5)	6 (21.4)	
A−/N+	22 (21.6)	36 (20.9)	3 (10.7)	
A+/N+	9 (8.8)	31 (18.0)	11 (39.3)	

N (%) unless otherwise noted.

[a] Osmia categories were defined as follows based on the B-SIT score: anosmia (score <6), hyposmia (men 6–10, women 6–10.25), normosmia (men 10.25–12; women 10.5–12).

[b] Chi-squared test for categorical variables or Wilcoxon rank sum test for continuous variables.

[c] Abnormal ^{11}C-PiB PET (elevated amyloid) was defined as standardized uptake value ratio (SUVR)>1.40; 306 participants had ^{11}C-PiB PET.

[d] Abnormal ^{18}F-FDG PET (hypometabolism) was defined as SUVR <1.32; 305 participants had ^{18}F-FDG PET.

[e] Abnormal (reduced) AD Sig. CT was defined as <2.74 mm.

[f] Abnormal (reduced) hippocampal volume was defined as <−2.40 cm^3 (adjusted for total intracranial volume).

[g] Imaging biomarker groups defined by the combination of abnormality for amyloid (A+/A−) and neurodegeneration (N+/N−).

B-SIT = Brief Smell Identification Test; APOE = apolipoprotein E; BDI = Beck depression inventory; ^{11}C-PiB PET = Pittsburgh compound B positron emission tomography; ^{18}F-FDG = ^{18}fluorodeoxyglucose; AD Sig. CT = Alzheimer's Disease signature cortical thickness; HVa = hippocampal volume adjusted for total intracranial volume.

Table 2

Association between Neuroimaging Biomarkers and Impaired Odor Identification in Cognitively Normal Individuals - the Mayo Clinic Study of Aging.

	Impaired Olfaction					
	Anosmia vs. normosmia[a]			Hyposmia vs. normosmia[a]		
Imaging Biomarkers	**No. Abn /All**	**OR (95%CI)[b]**	**p**	**No. Abn /All**	**OR (95%CI)**	**p**
Basic model[c]						
Abnormal ^{11}C-PiB PET[d]	28/130	2.74 (1.12, 6.66)	.03	176/278	1.25 (.74, 2.12)	.40
Abnormal ^{18}F-FDG PET[e]	28/130	.99 (.38, 2.55)	.98	175/277	1.06 (.59, 1.91)	.84
Abnormal AD Sig. CT[f]	78/326	2.20 (1.25, 3.86)	<.01	500/748	1.34 (.92, 1.94)	.13
Abnormal HVa[g]	78/326	2.45 (1.21, 4.94)	.01	495/743	1.61 (.95, 2.72)	.08
Basic model adjusted also for APOE ε4 carrier status						
Abnormal ^{11}C-PiB PET	28/130	2.78 (1.11, 7.01)	.03	176/278	1.23 (.72, 2.12)	.45
Abnormal ^{18}F-FDG PET	28/130	.97 (.38, 2.50)	.95	175/277	1.05 (.58, 1.89)	.86
Abnormal AD Sig. CT	78/326	2.21 (1.25, 3.89)	<.01	500/748	1.33 (0.91, 1.93)	.14
Abnormal HVa	78/326	2.47 (1.22, 5.00)	.01	495/743	1.60 (.94, 2.71)	.08
Basic model adjusted also for the Boston Naming Test[h]						
Abnormal ^{11}C-PiB PET	26/126	2.70 (1.08, 6.78)	.03	173/273	1.24 (.73, 2.11)	.42
Abnormal ^{18}F-FDG PET	26/126	.98 (.37, 2.62)	.97	172/272	1.09 (.60, 1.97)	.78
Abnormal AD Sig. CT	75/319	2.05 (1.15, 3.66)	.01	485/729	1.29 (.88, 1.88)	.19
Abnormal HVa	75/319	2.30 (1.12, 4.69)	.02	480/724	1.56 (.92, 2.65)	.10
Basic model adjusted also for UPDRS						
Abnormal ^{11}C-PiB PET	28/130	2.80 (1.14, 6.86)	.02	176/278	1.25 (.74, 2.12)	.40
Abnormal ^{18}F-FDG PET	28/130	.96 (.37, 2.49)	.94	175/277	1.05 (.59, 1.89)	.86
Abnormal AD Sig. CT	78/326	2.15 (1.22, 3.79)	<.01	500/748	1.32 (.91, 1.92)	.14
Abnormal HVa	78/326	2.43 (1.20, 4.90)	.01	495/743	1.60 (.94, 2.71)	.08
Basic model adjusted also for history of head trauma[i]						
Abnormal ^{11}C-PiB PET	27/102	2.65 (1.04, 6.72)	.04	144/219	1.12 (.63, 2.02)	.70
Abnormal ^{18}F-FDG PET	27/102	.98 (.37, 2.59)	.97	143/218	.97 (.51, 1.85)	.93

	Impaired Olfaction					
	Anosmia vs. normosmia[a]			Hyposmia vs. normosmia[a]		
Imaging Biomarkers	**No. Abn /All**	**OR (95%CI)[b]**	**p**	**No. Abn /All**	**OR (95%CI)**	**p**
Abnormal AD Sig. CT	75/285	2.22 (1.24, 3.98)	<.01	454/664	1.31 (.88, 1.95)	.18
Abnormal HVa	75/285	2.20 (1.08, 4.49)	.03	451/661	1.45 (.85, 2.47)	.18

[a] Osmia categories were defined based on the Brief Smell Identification Test (B-SIT) score as follows: anosmia (score <6), hyposmia (men 6–10, women 6–10.25), normosmia (men 10.25–12; women 10.5–12).

[b] OR (95% CI) retained from multinomial logistic regression. Separate models were run for each neuroimaging biomarker, represented by one row in the table, having osmia as the outcome variable.

[c] Basic model is adjusted for age, education, sex.

[d] Abnormal ^{11}C-PiB PET (elevated amyloid) was defined as standardized uptake value ratio (SUVR)>1.40.

[e] Abnormal ^{18}F-FDG PET (hypometabolism) was defined as SUVR <1.32.

[f] Abnormal (reduced) AD Sig. CT was defined as <2.74 mm.

[g] Abnormal (reduced) hippocampal volume was defined as <−2.40 cm^3 (adjusted for total intracranial volume).

[h] Kaplan EGH, Weintraub S. The Boston Naming Test, 2nd ed. Boston, MA: Lea & Fabiger, 1978.

[i] History of head trauma: “Have you ever experienced any head injuries that led you to see a doctor, stay in the hospital, lose your memory, or become unconscious”.

No. Abn. - the number of persons with abnormal B-SIT; All - participants with and without abnormal biomarker in the specific analysis strata; OR – odds ratio; CI – confidence interval. ^{11}C-PiB PET - Pittsburgh compound B positron emission tomography; ^{18}F-FDG PET - ^{18}fluorodeoxyglucose PET; AD Sig. CT - Alzheimer’s Disease signature cortical thickness; HVa: hippocampal volume adjusted for total intracranial volume; UPDRS - Unified Parkinson’s Disease Rating Scale.

Table 3

Association between Neuroimaging Biomarkers and B-SIT Score in Cognitively Normal Individuals - the Mayo Clinic Study of Aging.

	Continuous B-SIT	
Imaging Biomarkers	**slope (95%CI)[a]**	**p**
Basic model		
Abnormal ^{11}C-PiB PET[b]	−.41 (−.91, .08)	.10
Abnormal ^{18}F-FDG PET[c]	−.12 (−.67, .42)	.66
Abnormal AD Sig. CT[d]	−.43 (−.76, −.09)	.01
Abnormal HVa[e]	−.72 (−1.15, −.28)	<.01
Basic model adjusted also for APOE ε4 carrier status		
Abnormal ^{11}C-PiB PET	−.36 (−.87, .15)	.16
Abnormal ^{18}F-FDG PET	−.09 (−.64, .46)	.75
Abnormal AD Sig. CT	−.42 (−.76, −.08)	.01
Abnormal HVa	−.71 (−1.15, −.28)	<.01
Basic model adjusted also for the Boston Naming Test[f]		
Abnormal ^{11}C-PiB PET	−.38 (−.87, .11)	.13
Abnormal ^{18}F-FDG PET	−.15 (−.70, .40)	.60
Abnormal AD Sig. CT	−.37 (−.71, −.02)	.04
Abnormal HVa	−.71 (−1.14, −.27)	<.01
Basic model adjusted also for UPDRS		
Abnormal ^{11}C-PiB PET	−.42 (−.91, .07)	.09
Abnormal ^{18}F-FDG PET	−.09 (−.64, .45)	.74
Abnormal AD Sig. CT	−.40 (−.74, −.06)	.02
Abnormal HVa	−.70 (−1.14, −.26)	<.01
Basic model adjusted also for history of head trauma[g]		
Abnormal ^{11}C-PiB PET	−.37 (−.93, .19)	.20
Abnormal ^{18}F-FDG PET	−.02 (−.64, .60)	.95
Abnormal AD Sig. CT	−.39 (−.75, −.03)	.03
Abnormal HVa	−.67 (−1.13, −.22)	<.01

[a] Slopes (95%CI) retained from multivariable linear regression models. Separate models were run for each neuroimaging biomarker, represented by one row in the table, having continuous B-SIT as the dependent (outcome) variable. Basic model is adjusted for age (at B-SIT testing), education, sex.

[b] Abnormal ^{11}C-PiB PET (elevated amyloid) was defined as standardized uptake value ratio (SUVR)>1.40.

[c] Abnormal ^{18}F-FDG PET (hypometabolism) was defined as SUVR<1.32.

[d] Abnormal (reduced) AD Sig. CT was defined as <2.74 mm.

[e] Abnormal (reduced) hippocampal volume was defined as <−2.40 cm^3 (adjusted for total intracranial volume).

[f] Kaplan EGH, Weintraub S. The Boston Naming Test, 2nd ed. Boston, MA: Lea & Fabiger, 1978.

[g]History of head trauma: “Have you ever experienced any head injuries that led you to see a doctor, stay in the hospital, lose your memory, or become unconscious”.

B-SIT = Brief Smell Identification Test; CI = confidence interval. ^{11}C-PiB PET = Pittsburgh compound B positron emission tomography; ^{18}F-FDG = ^{18}fluorodeoxyglucose; AD Sig. CT = Alzheimer’s Disease signature cortical thickness; HVa = hippocampal volume adjusted for total intracranial volume; UPDRS = Unified Parkinson’s Disease Rating Scale.

Table 4

Association between Imaging Biomarkers and Impaired Odor Identification in Cognitively Normal Individuals by PiB PET status - the Mayo Clinic Study of Aging.

	Impaired Olfaction						Continuous B-SIT	
	Anosmia vs. normosmia[a]			Hyposmia vs. normosmia[a]				
Imaging Biomarkers	**Abn /All**	**OR (95%CI)[b]**	**p**	**Abn /All**	**OR (95%CI)**	**p**	**slope (95%CI)**	**p**
^{11}C-PiB SUVR>1.40[c,d]								
^{18}F-FDG SUVr<1.32[c]	17/50	3.10 (0.84, 11.52)	.09	68/101	2.20 (0.81, 5.99)	.12	−.96 (−1.84, −.08)	.03
AD Sig. CT <2.74 mm	17/50	2.22 (0.59, 8.39)	.24	69/102	1.31 (0.49, 3.50)	.59	−.72 (−1.63, .19)	.13
HVa <−2.40 cm^3	17/50	7.15 (1.36, 37.58)	.02	69/102	1.76 (0.44, 7.05)	.43	−1.74 (−2.79, −.69)	<.01
^{11}C-PiB SUVR≤1.40								
^{18}F-FDG SUVr<1.32	11/80	0.12 (0.01, 1.14)	.07	107/176	0.64 (0.30, 1.36)	.25	.65 (−.05, 1.34)	.07
AD Sig. CT <2.74 mm	11/80	2.53 (0.59, 10.82)	.21	104/173	1.15 (0.50, 2.64)	.74	−.46 (−1.20, .28)	.23
HVa <−2.40 cm^3	11/80	1.41 (0.22, 9.18)	.72	104/173	1.53 (0.50, 4.69)	.46	−.29 (−1.24, .66)	.55

[a] Osmia categories were defined as follows: anosmia (score <6), hyposmia (men 6–10, women 6–10.25), normosmia (men 10.25–12; women 10.5–12); B-SIT score was calculated as the sum of the correct responses for persons with ≤2 missing responses.

[b] Odds ratios (95% CI) and slopes (95%CI) were retained from multinomial logistic regression and simple linear regression models, respectively, adjusted for age (at B-SIT testing), education, sex. Separate models were run for each neuroimaging biomarker (i.e., each model is represented by one line in the table, having Osmia or continuous B-SIT as the outcome variable) in participants with ^{11}C-PiB SUVR>1.40 and in participants with ^{11}C-PiB SUVR≤1.40.

[c] Abnormal PiB defined as ^{11}C-PiB SUVr>1.40.

[d] p=0.017 for the interaction term between abnormal PiB (SUVR) >1.40) and abnormal FDG (SUVr <1.32) in the anosmia vs. normosmia comparison and p=0.061 for the hyposmia vs. normosmia comparison (in the multinomial logistic regression model) and p = 0.004 when B-SIT was used as a continuous outcome (linear regression model). Interaction terms between abnormal PiB and abnormal AD cortical thickness (<2.74 mm) or abnormal hippocampal volume (<−2.40 cm^3) did not reach statistical significance.

B-SIT = Brief Smell Identification Test; OR = odds ratio; CI = confidence interval; ^{11}C-PiB PET = Pittsburgh compound B positron emission tomography; SUVR = standardized uptake value ratio; ^{18}F-FDG = ^{18}fluorodeoxyglucose. AD Sig. CT = Alzheimer's Disease signature cortical thickness; HVa = hippocampal volume adjusted for total intracranial volume;

Table 5

Association between Neuroimaging Biomarkers and impaired odor identification (outcome variable) in cognitively normal individuals - the Mayo Clinic Study of Aging.

	Impaired Olfaction						Continuous B-SIT	
	Anosmia vs. normosmia[a]			Hyposmia vs. normosmia[a]				
Imaging Biomarkers	**Abn /All**	**OR (95%CI)[b]**	**p**	**Abn /All**	**OR (95%CI)**	**p**	**slope (95%CI)[c]**	**p**
A+/N− vs. A−/N−[d]	14/85	1.13 (.33, 3.81)	.85	105/176	.97 (.51,1.85)	.92	.14 (−.49, .77)	.66
A−/N+ vs. A−/N−	11/80	.40 (.09, 1.78)	.23	104/173	.87 (.43, 1.73)	.68	.26 (−.41, .94)	.44
A+/N+ vs. A−/N−	19/75	3.84 (1.14, 12.97)	.03	99/155	1.91 (.80, 4.54)	.14	−.99 (−1.71, −.27)	<.01

[a] Osmia categories were defined as follows: anosmia (score <6), hyposmia (men 6–10, women 6–10.25), normosmia (men 10.25–12; women 10.5–12); B-SIT score was calculated as the sum of the correct responses for persons with ≤2 missing responses.

[b] Odds ratio (95% confidence interval) reported for anosmia vs. normosmia and hyposmia vs. normosmia were retained from a single multinomial logistic regression model, having osmia as the dependent variable and adjusted for age (at B-SIT testing), education, sex.

[c] Slopes (95% CI) retained from a single multivariable linear regression model, adjusted for age (at B-SIT testing), education, sex.

[d] Imaging biomarker groups defined by the combination of abnormality for amyloid (A+/A−) and neurodegeneration (N+/N−); A+, is defined as ^{11}C-PIB standardized uptake value ratio (SUVR)>1.40 and A− if otherwise; and N+ is defined as either HVa <−2·40 cm^3 or FDG <1.32 SUVR and N− if otherwise.

B-SIT = Brief Smell Identification Test; Abn. - the number of persons with abnormal B-SIT; All - participants with and without abnormal biomarkers in the specific analysis strata; OR – odds ratio; CI – confidence interval.