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RESEARCH ARTICLE

Language deficits across PET-based Braak stages of tau accumulation in Alzheimer's disease

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Abstract

INTRODUCTION: Language complaints in cognitively unimpaired (CU) individuals may reflect Alzheimer's Disease (AD) pathology and future objective impairments.

METHODS: 211 participants (138 CU, 45 with mild cognitive impairment (MCI), and 28 with dementia) from the TRIAD cohort underwent ^{18}F-MK-6240 tau-PET and ^{18}F-AZD-4694 amyloid-PET. Word-finding complaints, confrontation naming, semantic fluency, phonemic fluency and word-knowledge were evaluated.

RESULTS: Complaints about forgetting the names of objects appeared in early tau stages (Braak 1–2), followed by naming difficulties (Braak 3–4), and widespread language impairments in later stages (Braak 5–6). Across the biologically-defined AD continuum, lower language performance was associated with tau accumulation predominantly in left-temporal language regions. In CU, only subjective word-finding complaints related to tau, indicating language concerns could reflect underlying pathology before measurable cognitive decline.

DISCUSSION: Language measures support early detection and staging of AD pathophysiology and contribute to better align cognitive assessment with biological definitions of the disease.

KEYWORDS
Alzheimer, biomarkers, cognitive decline, fluency, language, lexicosemantic, naming, preclinical, subjective word-finding complaints, tau-PET

Highlights

- Subjective word-finding difficulties emerge in early tau spread stages (Braak 1–2).
- Objective naming deficits emerge in the middle tau spread stages (Braak 3–4).
- Verbal fluency and word knowledge decline in late tau spread stages (Braak 5–6).
- Language impairments traced to tau accumulation mostly in left-temporal areas.
- Word-finding complaints reflect tau pathology before objective cognitive decline.

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1 | BACKGROUND

The clinical screening and preliminary diagnosis of Alzheimer's disease (AD) have historically been guided by its hallmark syndromic features, namely a progressive decline in cognition and daily functioning that may involve episodic memory, language, executive or visuospatial skills, as well as changes in usual behavior or personality traits.[1] Over the years, this clinical framework has come to encompass the stages of cognitive unimpairment (CU), subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and dementia.

Recent advances in in vivo imaging have, however, permitted the formulation and use of a separate, biological definition of AD.[2] Under this new framework, a definitive diagnosis is no longer contingent upon AD's symptomatology, and is instead evidenced by the accumulation of amyloid beta (Aβ) and tau protein fragments within the brain.[2]

Tau has been a central focus of biological staging frameworks, because its characteristic progression from the transentorhinal cortex (Braak 1–2) to the limbic structures (Braak 3–4) and eventually the neocortex (Braak 5–6),[3,4] appears to closely parallel AD's elicited symptoms.[2] Consistent with this idea, a study utilizing positron emission tomography (PET) has shown that tau which accumulated in Braak 1–3 regions was correlated to dysfunctions of delayed recall, whereas tau in Braak 3–5 regions was more closely related to recognition memory.[5]

By anchoring cognitive performance to specific brain regions, such studies help align cognitive assessments to this new biomarker-based approach, reducing the conceptual gap that currently separates clinical and biological stagings.[6] Continuing this effort beyond episodic memory, into other AD cognitive domains, such as language, is therefore warranted, as language provides a sensitive diagnostic window into AD[7] and its decline place substantial strain on communications and quality of interactions with caregivers.[8]

Language impairments in AD have traditionally been studied through clinical staging (CU → SCI → MCI → dementia) and grey matter (GM) atrophy. Naming impairments have been linked to GM atrophy within the left anterior temporal lobe[9,10] and the left inferior prefrontal gyrus[11] and have been observed from the MCI stage of AD. Verbal fluency impairments have also been observed as early as the MCI stage[12,13] and have been linked to GM atrophy within the left inferior temporal gyrus, left insular cortex, bilateral hippocampus and parahippocampal gyrus; with the addition of the anterior and posterior cingulate cortices, as well as bilateral caudate and cerebellar crus II regions,[14] which more closely related to semantic fluency. In the dementia stage, semantic impairments on word knowledge tasks have also been reported.[15] When moving earlier along the continuum, subjective word-finding complaints were found to be amongst the most commonly reported in CU older adults,[16] with such complaints being linked to atrophy in the left fusiform gyrus and to elevated levels of Aβ.[16,17] Whilst these findings inform the current study, the timing and brain regions where tau accumulation and language impairments might coincide remains to be clarified.

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed using traditional sources. Aligning cognitive abilities to the core biomarker-based definition of Alzheimer's Disease (AD), would improve preliminary screening, prognosis, management and understanding of the disease. Subjective language complaints amongst cognitively unimpaired (CU) older adults and objective language impairments observed across the typical amnestic AD continuum suggests language is of high relevance.
2. **Interpretation**: Our findings establish the likely staging of language impairments across the biologically-defined AD continuum. Subjective word-finding complaints are highlighted as a non-negligible measure that is linked to tau accumulation in early Braak regions in CU and improves the prediction of early Aβ and tau pathology.
3. **Future directions**: We recommend the use of subjective word-finding complaints, alongside genetic risk to significantly enhance the prediction of underlying AD pathophysiology. The most commonly used language tests in clinical practice remain significantly limited. More sensitive measures exist and should be developed.

This study therefore aimed to investigate (a) how individuals at different stages of the AD biological progression differed in terms of their language abilities; (b) which of the brain regions where tau accumulates could be linked to language impairments across the whole AD continuum, as well as when looking in CU individuals specifically; and (c) how language measures might improve the screening of early amyloid and tau pathologies, when considered alongside established features such as age, sex, education, APOE genotype and the Montreal Cognitive Assessment (MoCA). We hypothesized that (1) in the earliest stages of AD pathology, individuals would exhibit elevated word-finding complaints, followed with impaired confrontation naming and semantic fluency in the middle stages, and impaired phonemic fluency and verbal comprehension in the later stages; (2.1) across the whole AD-continuum, language impairment would primarily reflect tau accumulation in the left temporal lobe, along with other previously highlighted regions; and (2.2) in CU specifically, word-finding complaints would reflect left fusiform tau accumulation.

2 | METHODS

The data used in the preparation of this article were obtained from the Translational Biomarkers of Aging and Dementia (TRIAD[18]; https://triad.tnl-mcgill.com/cohort-description/) cohort and, to a much lesser extent, the Head-to-head Evaluation of tau tracers in Alzheimer's Disease (HEAD[19]; https://head-study.info/head-cohort) cohort.

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2.1 | Participants

We included 211 participants classified into biomarker groups (Aβ−Tau− [N = 100], Aβ+Tau− [N = 25], Aβ+Tau1–2 [N = 35], Aβ+Tau3–4 [N = 24], Aβ+Tau5–6 [N = 27]). Eligible participants had available amyloid status, an ^{18}F-MK-6240 tau-PET scan, at least one measured language function, and were either cognitively unimpaired (CU; Aβ+ or Aβ−), diagnosed with MCI (Aβ+ only) or diagnosed with typical/amnestic dementia due to AD (Aβ+ only). Within our final sample, the mean difference in acquisition dates between amyloid-PET, tau-PET, and MRI scans was 28 ± 27 days. In over 90% of cases, the second and third scans were acquired within 3 months of the first scan, and the maximum interval from the first to the last scan was 6 months. The age range for inclusion was defined based on Aβ+ participants who met all criteria (59–88 years), and this same range was applied to Aβ− CU participants. Although our analyses relied on the biomarker-based staging described above, the clinical diagnostic distribution of our sample was as follows: 138 CU (100 Aβ−, 38 Aβ+) older adults, 45 Aβ+ individuals with MCI, and 28 Aβ+ individuals with dementia due to AD. Clinical diagnosis was performed prior to the collection of biomarker data and was established through consensus reached by a multidisciplinary team composed of neuropsychologists, physicians and nurses. Participants were classified as CU if they showed no objective cognitive or functional impairment. Participants classified with MCI exhibited subjective and objective cognitive impairments, but no functional impairment. Participants classified with Dementia due to AD exhibited more significant cognitive impairments in at least two of the recognized AD continuum domains which in this case interfered with independence and activities of daily living.

Cohorts exclusion criteria included (a) inability to speak either French or English; (b) sensory impairment hampering neuropsychological evaluation; (c) recent major surgery or traumatic brain injury; (d) magnetic resonance imaging (MRI) or PET contraindications; (e) neurological, psychiatric or systemic conditions not adequately controlled through a stable medication regimen; (f) likely co-pathology of vascular disease based on Hachinski Ischemic score and medical history; (g) ongoing substance abuse; and (h) unavailability of reliable informant, such as a family member or close friend.[20,21] Detailed, step-by-step participant selection procedures, the number of exclusions, and all study-specific inclusion criteria are provided in the supplementary materials.

2.2 | Procedure

2.2.1 | Cognitive assessments

Everyday cognition questionnaire

Subjective cognitive complaints regarding one's word-finding abilities were assessed using two specific items from the self-reported Everyday Cognition questionnaire (ECog).[22] Based on a previous study, we selected ECog Language 1: "forgetting the names of objects" and ECog Language 3: "Finding the right words to use in a conversation".[16] Participants rated these items on a scale from one to four, reflecting perceived changes in their abilities relative to 10 years prior: they (1) now performed better or had not changed; (2) occasionally performed worse, but not all of the time; (3) consistently performed a little worse; or (4) consistently performed much worse. Throughout the manuscript, references to "word-finding complaints" pertain to both ECog language items 1 and 3.

Boston naming test

Objective confrontation naming was assessed using the Boston Naming Test (BNT),[23] which requires participants to name black-and-white line drawing of objects, animals, and other items. The present cohorts only administered odd numbered items on the standard 60 item BNT, which gives a maximum score of 30.

Delis-Kaplan executive function system

Phonemic and semantic verbal fluency were assessed using the Delis-Kaplan Executive Function System.[24] In the letter (phonemic) fluency condition, participants are given 60 seconds to generate as many words as they can, beginning with a designated letter ("P, F, L" for French and "F, A, S" for English). In the category (semantic) fluency condition, participants are given 60 seconds to generate as many words as they can, belonging to a designated semantic category ("animals" and "boys' names"). We used the total number of correctly produced words across the three trials as our measure of phonemic fluency, and the total across the two trials as our measure of semantic fluency.

Wechsler abbreviated scale of intelligence-II: vocabulary subtest

Word knowledge was assessed using the Wechsler Abbreviated Scale of Intelligence's second edition (WASI-II).[25] Participants were asked to define various words, receiving a score based on the accuracy of their definition (either 0, 1 or 2), following the criteria outlined in the test manual, with some answers prompting queries from the examiner for additional details. Three consecutive failures lead to the discontinuation of the test. We used the sum score of all items as our measure of word knowledge.

2.2.2 | Neuroimaging

Structural magnetic resonance imaging acquisition and processing

To obtain anatomical images of the brain, structural MRI was conducted using a 3T Siemens MAGNETOM scanner equipped with a standard head coil. A Magnetization Prepared Rapid Gradient Echo sequence was employed (repetition time of 2300 milliseconds, echo time of 2.96 ms, 9° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1 × 1 mm^2 in-plane resolution of 1 mm slab thickness,[26] see cited paper's supplementary materials) to obtain brain wide 1 mm isotropic voxels with T1-weighted contrast which were then corrected for field distortions and non-uniformity, followed by parcellation into substructures (using FreeSurfer; https://surfer.nmr.mgh.harvard.edu/),[27] with regions of interest defined according to the Desikan-Killiany-Tourville (DKT) atlas,[28] and segmentation

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into probabilistic types of tissue maps (using Statistical Parametric Mapping 12 segmentation tool; https://fil.ion.ucl.ac.uk/spm/),[29] using a Montréal Neurological Institute (MNI) Translational Neuroimaging Laboratory (TNL) in-house pipeline. GM probability maps were then non-linearly transformed to the Alzheimer's Disease Neuroimaging Initiative (ADNI) reference space (using Advanced Normalization Tools; ANTs; https://stnava.github.io/ANTs/).[30] Resulting images were then finally smoothed using an 8 mm full-width half-maximum Gaussian kernel, followed by visual inspection to ensure proper alignment to the ADNI template (see cited paper's supplementary materials).[26]

Amyloid-PET and Tau-PET acquisition and processing

To locate and measure AD-related pathological protein aggregation in the brain, PET scans were conducted using a brain-dedicated Siemens High Resolution Research Tomograph.

^{18}F-MK-6240 radioligand was used to image tau neurofibrillary tangles aggregation, with acquisition proceeding 90 to 110 minutes following intravenous bolus injection. Scans were reconstructed using an ordered-subsets expectation maximization (OSEM)[31] algorithm on a four-dimensional volume with four frames (4 × 300 seconds).[32,33]

^{18}F-AZD-4694 radioligand was used to image amyloid-β plaques aggregation, with acquisition proceeding 40 to 70 minutes following intravenous bolus injection. OSEM was once again used, this time on a four-dimensional volume with three frames (3 × 600 seconds).[34,35]

For attenuation correction, PET acquisition was followed by a 6-min transmission scan conducted with a rotating ^{137}Cs point source. Images were additionally corrected for motion, dead time, radioactive decay as well as random and scattered coincidences and were also meninges and skull stripped.[36] PET registration to corresponding T1-weighted MRI images was finalized, once again using a MNI TNL in-house pipeline, by linear registration of PET images to native T1 space (using ANTs)[30] and non-linear transformation to ADNI reference space (using the transform obtained from the MRI processing step). The resulting PET images were likewise smoothed using the same 8 mm full-width half-maximum Gaussian kernel.

To quantify radioligand binding, standardized uptake value ratios (SUVR)[36] were computed using the (a) inferior cerebellar GM as a reference region in the case of tau-PET ^{18}F-MK-6240;[33] and (b) whole cerebellar GM in the case of amyloid-PET ^{18}F-AZD-4694.[35]

Amyloid positivity and PET-Braak staging

Individuals were categorized based on previously established pathological thresholds of protein accumulation.

Amyloid-β pathology was classified using a dichotomous threshold (negative [−]/positive [+]), with individuals considered "amyloid-β positive" (Aβ+) when ^{18}F-AZD-4694 SUVR composite average across the precuneus, prefrontal, orbitofrontal, parietal, temporal, and cingulate cortices exceeded 1.55.[35]

Tau pathology was classified using a tau-based Braak staging system for AD.[3,4] This system is based on Braak's proposed framework, which describes typical AD-related tau aggregation in its hierarchical movement throughout the brain following disease progression, with each stage characterized by specific and accumulating regional abnormalities. In TRIAD, this was defined as beginning in the transentorhinal cortex (Braak stage 1); and progressing thereafter onto the entorhinal cortex and hippocampus (Braak stage 2); the amygdala and parahippocampal, fusiform, and lingual gyri (Braak stage 3); the insular cortex, lateral temporal lobe, posterior cingulate cortex, and inferior parietal lobule (Braak stage 4); the orbitofrontal cortex, superior temporal and inferior frontal gyri, cuneus, anterior cingulate cortex, supramarginal gyrus, lateral occipital cortex, precuneus, superior parietal lobule, superior frontal gyrus, and rostromedial frontal cortex (Braak stage 5); ultimately extending to the paracentral lobule, postcentral and precentral gyri and pericalcarine cortex (Braak stage 6)[33,37] and beyond. An absence of such abnormalities was categorized as "Braak 0". Upon reaching any Braak stage and to be considered representative of the "typical progression" of tau accumulation, one must have surpassed abnormality thresholds in previous Braak stages. Abnormality thresholds were defined as 2.5 standard deviations above mean SUVR of CU individuals younger than 26 years old.[20,33]

With regards to this study, participants were categorized based on their Aβ status, with segregated Aβ− and Aβ+ individuals of Braak stage 0, and, like previously mentioned, similar to other works before us, rejected Aβ− individuals of Braak 1 through 6.[38,39] Similarly again, to increase the sample size of each Braak-amyloid subgroup, we used a simplified Braak stage grouping, resulting in the following final subgroups: Braak 0 Aβ− (N = 100), Braak 0 Aβ+ (N = 25), Braak 1–2 Aβ+ (N = 35), Braak 3–4 Aβ+ (N = 24) and finally, Braak 5–6 Aβ+ (N = 27).

2.3 | Statistical analyses

2.3.1 | Behavioral analyses

To describe the sample, Fisher's exact test was used to assess between-subgroup pairwise categorical differences, applying Bonferroni correction to adjust for multiple comparisons. One-way analyses of variance (ANOVA) and Tukey post-hoc tests were used for all other (continuous) variables.

To test subgroup differences in terms of language performance (aim a), we modeled a number of multiple linear regressions that predicted a given language score based on Braak subgroups, extracting an ANOVA table (with Tukey post-hoc) to test for the factor as a whole, and controlling for (a) sex; (b) age; (c) education; (d) primary language spoken (French or English as first language); (e) handedness (left or right); and (f) ordinally-computed risk related to APOE genotype. Epsilon Square was used as a measure of effect size (ε^2).[40] This can also be understood as a series of analyses of covariance (ANCOVA).

To find the variables which most informed screening of early AD pathology (aim c) we conducted a forward stepwise discriminant analysis on Braak 0 Aβ−, Braak 0 Aβ+ and Braak 1–2 Aβ+ subgroups using the "folda" R package[41] with Pillai's trace set as test for forward selection and alpha setting of 0.05. In preparation for the stepwise selection, we first ran a direct discriminant analysis on the whole sample (see supplementary table 1 and Figure 1) to visualize the data and to highlight potentially unforeseen subgroup differences. Our model included

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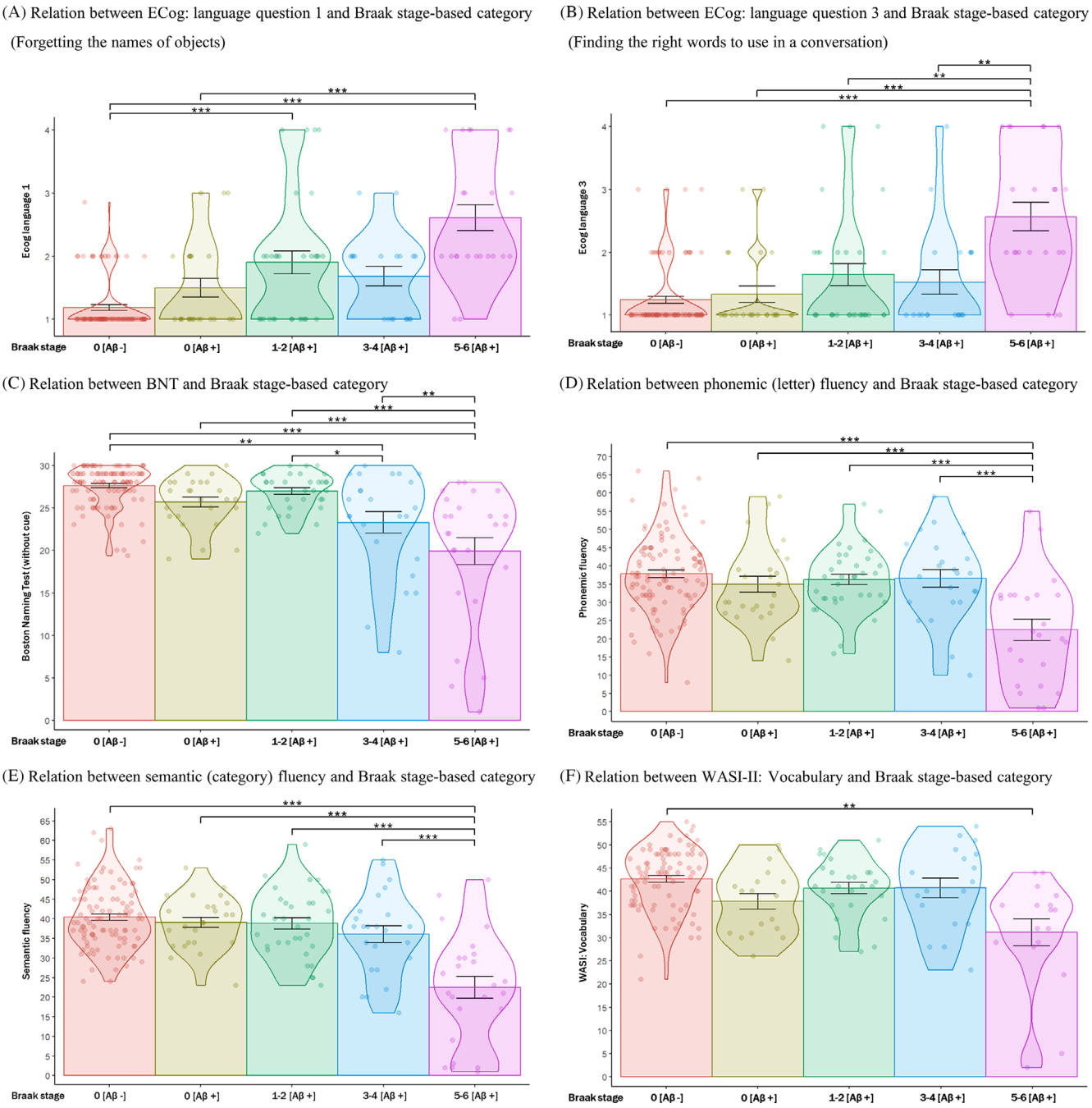

FIGURE 1 Language deficits across the biologically-defined AD continuum. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

(a) age; (b) sex; (c) education; (d) primary language spoken; (e) handedness; (f) ordinally-computed risk related to APOE genotype; (g) Ecog language question 1: Forgetting the names of objects; (h) Ecog language question 3: Finding the right words to use in a conversation; (i) BNT; (j) phonemic fluency; (k) semantic fluency; and (l) WASI-II: Vocabulary. In the stepwise model, we additionally included the MoCA, which served as a baseline of comparison for usefulness in screening. The stepwise model includes variables in order of the variance they explain, once a variable is included, only non-explained variance can be contributed towards, ensuring variables selected are minimally redundant for screening purposes.

All behavioral statistical analyses were performed using R Statistical Software (version 4.4.1 for Windows operating system.[42]

2.3.2 | Neuroimaging analyses

To evaluate the associations between language variables and in vivo aggregation of tau proteins in the brain (aim b), voxel-wise regression analyses were conducted using the "RMINC" R package (version 1.5.2.3)[43]. This was done twice, once with the whole sample and once again with CU individuals alone. Our linear models predicted voxel-

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wise tau-PET SUVR using a given language score and controlling for (a) age; (b) sex; (c) education; (d) primary language spoken; (e) handedness; (f) APOE genotype; (g) amyloid-PET ^{18}F-AZD-4694 full cerebellum GM SUVR composite and (h) MMSE (when looking at the whole sample, to additionally control for severity of overall cognitive symptomatology). We corrected for multiple comparisons using a random field theory[44] cluster threshold of $p < 0.001$. To better interpret regions of tau aggregation, we checked for overlap between the significant T-statistical parametric maps and lateralized DKT atlas reference substructures.

All neuroimaging analyses were performed using R Statistical Software (version 3.6.1 for Ubuntu, a Linux-based operating system).[42]

3 | RESULTS

The demographic and clinical characteristics of our sample are presented in Table 1. Groups differed with regards to age (F [4, 206] = 2.39, $p = 0.05$, $\varepsilon^2 = 0.03$) and APOE genotype (based on the presence of at least one ε4 allele; χ^2 [4] = 48.81, $p < 0.001$). Groups also differed with regards to global CDR (F [4, 197] = 54.15, $p < 0.001$, $\varepsilon^2 = 0.51$), MMSE (F [4, 197] = 30.82, $p < 0.001$, $\varepsilon^2 = 0.37$) and MoCA (F [4, 197] = 61.06, $p < 0.001$, $\varepsilon^2 = 0.54$) as well as amyloid-PET load (based on ^{18}F-AZD-4694 full cerebellum GM SUVR composite; F [4, 206] = 124.77, $p < 0.001$, $\varepsilon^2 = 0.70$), all of which followed expected AD continuum progression.

3.1 | Language impairment across Tau-PET-based braak stages of AD

As presented in Table 1 and Figure 1, when controlling for sex, age, education, primary language spoken (English or French), handedness and ordinally-computed risk related to APOE genotype; groups differed significantly in the level at which they reported forgetting the names of objects (ECog language 1; F [4, 149] = 15.95, $p < 0.001$, $\varepsilon^2 = 0.28$) and being able to find the right words to use in a conversation (ECog language 3; F [4, 150] = 13.25, $p < 0.001$, $\varepsilon^2 = 0.24$), as well relative to their performance on the BNT (F [4, 168] = 21.63, $p < 0.001$, $\varepsilon^2 = 0.32$), phonemic fluency (F [4, 170] = 9.17, $p < 0.001$, $\varepsilon^2 = 0.16$), semantic fluency (F [4, 169] = 18.18, $p < 0.001$, $\varepsilon^2 = 0.28$) and WASI-II: vocabulary (F [4, 135] = 8.21, $p < 0.001$, $\varepsilon^2 = 0.32$) tests.

More precisely, compared with biomarker-negative individuals (Braak 0 Aβ–), individuals at Braak 1–2 Aβ+ exhibited significantly elevated ECog language 1; whilst those at Braak 3–4 Aβ+ exhibited impaired performance on the BNT; and those at Braak 5–6 Aβ+ exhibited elevated ECog language 1 and 3 alongside impaired performance on the BNT, phonemic fluency, semantic fluency and WASI-II:Vocabulary tests. Compared with amyloid-positive individuals showing no pathological tau accumulation (Braak 0 Aβ+), those at Braak 5–6 Aβ+ exhibited relatively preserved performance on the WASI-II:Vocabulary test and otherwise exhibited elevated ECog language 1 and 3 alongside impaired performance on the BNT and phonemic fluency and semantic fluency tests. Compared with individuals at Braak 1–2 Aβ+, those at Braak 3–4 Aβ+ exhibited impaired performance on the BNT and those at Braak 5–6 Aβ+ exhibited elevated ECog language 3, alongside impaired performance on the BNT and phonemic fluency and semantic fluency tests. Finally, compared with individuals at Braak 3–4 Aβ+, those at Braak 5–6 Aβ+ exhibited elevated ECog 3 alongside impaired performance on the BNT and phonemic fluency and semantic fluency tests.

3.2 | Language impairment association to tau aggregation within the brain

Significant associations between language scores and tau-PET, when looking across the whole AD continuum, are presented in Figure 2. Corresponding models' statistics and overlap with DKT atlas reference substructures are presented in Figure 3. When controlling for sex, age, education, primary language spoken (English or French), handedness, ordinally-computed risk related to APOE genotype, amyloid-PET ^{18}F-AZD-4694 full cerebellum GM SUVR composite and MMSE, ECog language 1 was associated with left-hemisphere tau accumulation in the parahippocampal gyrus (Braak 3) and insular cortex (Braak 4). ECog language 3 was associated with left-hemisphere tau accumulation in the entorhinal cortex and hippocampus (Braak 2), in the fusiform and parahippocampal gyri (Braak 3), in the inferior temporal gyrus and insular cortex (Braak 4) and in the superior temporal cortex and the right-hemisphere rostral anterior cingulate region (Braak 5). BNT was associated with left-hemisphere tau accumulation in the superior temporal cortex (Braak 5). Phonemic fluency was associated with tau accumulation in the right-hemisphere posterior cingulate cortex (Braak 4) and with widespread Braak 5 regions in both hemispheres, most notable of which are the left caudal middle frontal, right pars orbitalis, bilateral pars triangulis, left rostral middle frontal and right supramarginal regions. Semantic fluency was associated with tau accumulation in the left isthmus cingulate and bilateral posterior cingulate gyri (Braak 4), and most notably regarding Braak 5 regions, in the left-hemisphere caudal anterior cingulate, caudal middle frontal, pars triangulis, precuneus, rostral middle frontal and superior frontal regions. WASI-II: Vocabulary showed no association with tau accumulation after controlling for severity of cognitive symptoms using the MMSE.

Results specifically looking at the sample of CU individuals are similarly presented in Figure 4 and Figure 5. Association between language scores and tau accumulation was significant this time almost exclusively in subjective word-finding complaints, namely ECog Language 1 and ECog Language 3. Significant associations were in this case exclusive to the left-hemisphere and overlap was concentrated primarily in Braak 3′s fusiform and Braak 4′s inferior temporal substructures. However, relationship to tau also extended to the entorhinal (Braak 2), parahippocampal and lingual (Braak 3), middle temporal (Braak 4) as well as to the lateral occipital and superior temporal (Braak 5) substructures. The BNT was also significantly associated with tau accumulation, however, in this case the total number of significant voxels was so small (672) that no region of overlap with the DKT atlas could be found.

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TABLE 1 Demographic, clinical and language characteristics across subgroups.

	Braak 0 Aβ−	Braak 0 Aβ+	Braak 1–2 Aβ+	Braak 3–4 Aβ+	Braak 5–6 Aβ+	*p* value
N, [subgroups distribution]	100	25	35 [9/26]	24 [6/18]	27 [10/17]	= 211
Sex, M/F	41/59	10/15	12/23	8/16	11/16	***p* = 0.92**
Age, years	70.60 ± 5.40 [60–85]	72.67 ± 5.03 [65–83]	73.44 ± 5.79 [61–84]	72.54 ± 5.28 [64–81]	69.89 ± 7.32 [59–88]	***p* = 0.05**
Education, years	15.73 ± 3.71 [7–25]	13.84 ± 3.01 [7–20]	15.57 ± 4.06 [11–28]	16.54 ± 3.97 [9–27]	14.69 (26) ± 3.58 [8–22]	***p* = 0.08**
Primary language						
French / English	84/16	20/3 (23)	31/3 (34)	18/3 (21)	17/10	***p* = 0.08**
Handedness						
Left / Right-handed	12/88	2/23	2/32(34)	2/21(23)	1/26	***p* = 0.76**
APOE genotype	c,d,e	d,e	a	a,b	a,b	***p* < 0.001**
ε2 ε3	14	5	0	0	0	= 19
ε3 ε3	57	15	16	3	6	= 97
ε3 ε4	19	4	13	12	11	= 59
ε4 ε4	1	0	5	5	5	= 16
NA	9	1	1	4	5	= 20
Diagnostic category						
CU	100	19	15	3	1	= 138
MCI due to AD	0	5	18	13	9	= 45
Dementia due to AD	0	1	2	8	17	= 28
Global cognition / Severity						
CDR	0.00 (98)[c,d,e] ± 0.00	0.15 (23)[d,e] ± 0.28	0.31 (34)[a,e] ± 0.28	0.48 (22)[a,b,e] ± 0.24	0.90 (25)[a,b,c,d] ± 0.68	***p* < 0.001**
MMSE	29.16[d,e] ± 0.99	28.74 (23)[e] ± 1.57	28.64 (33)[e] ± 1.85	27.09 (22)[a,e] ± 2.43	23.25 (24)[a,b,c,d] ± 5.76	***p* < 0.001**
MoCA	27.90[c,d,e] ± 1.77	27.36[d,e] ± 1.96	26.21 (33)[a,d,e] ± 2.93	22.96 (23)[a,b,c,e] ± 3.71	17.43 (21)[a,b,c,d] ± 6.19	***p* < 0.001**
Amyloid-PET						
^{18}F-AZD-4694 full cerebellum GM SUVR composite	1.27[b,c,d,e] ± 0.10	1.94[a,d,e] ± 0.34	2.14[a,e] ± 0.39	2.38[a,b] ± 0.50	2.55[a,b,c] ± 0.56	***p* < 0.001**
Language measures						
ECog 1: Forgetting the names of objects	1.19 (85)[c,e] ± 0.42	1.50 (24)[e] ± 0.72	1.90 (31)[a,e] ± 1.01	1.68 (19) ± 0.67	2.61 (23)[a,b,c] ± 0.99	***p* < 0.001**
ECog 3: Finding the right words to use in a conversation	1.24 (86)[e] ± 0.53	1.33 (24)[e] ± 0.64	1.65 (31)[e] ± 0.98	1.53 (19)[e] ± 0.84	2.57 (23)[a,b,c,d] ± 1.08	***p* < 0.001**
Boston naming test	27.60[d,e] ± 2.39	25.68[e] ± 2.93	26.97 (32)[d,e] ± 2.18	23.29[a,c,e] ± 6.13	19.92 (25)[a,b,c,d] ± 7.91	***p* < 0.001**
Phonemic fluency (letter)	37.79[e] ± 10.36	34.92[e] ± 10.89	36.26[e] ± 8.72	36.57 (23)[e] ± 11.50	22.46 (24)[a,b,c,d] ± 14.48	***p* < 0.001**
Semantic fluency (category)	40.44[e] ± 8.07	39.08[e] ± 6.66	38.82 (33)[e] ± 8.50	36.08[e] ± 10.52	22.52 (25)[a,b,c,d] ± 13.84	***p* < 0.001**
WASI-II: Vocabulary	42.69 (87)[e] ± 6.70	37.83 (28) ± 7.19	40.69 (26) ± 6.23	40.72 (18) ± 9.00	31.18 (17)[a] ± 11.93	***p* < 0.001**

Notes: Groups means +/− standard deviation or categorial distribution (using *N*). Number in parentheses indicate numbers of participants with the score when less than total. Row total N is calculated and provided in the *p value* column (not bolded and aligned right) when space allowed.

Abbreviations: AD, Alzheimer's Disease; CDR, Clinical Dementia Rating Scale; CU, cognitively unimpaired; ECog, Everyday Cognition Questionnaire; F, female; GM, grey matter; M, male; MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montréal Cognitive Assessment; SUVR, standardized uptake value ratios; WASI-II, Wechsler Abbreviated Scale of Intelligence.

[a]differed significantly from Braak 0 Aβ−.

[b]differed significantly from Braak 0 Aβ+.

[c]differed significantly from Braak 1–2 Aβ+.

[d]differed significantly from Braak 3–4 Aβ+.

[e]differed significantly from Braak 5–6 Aβ+.

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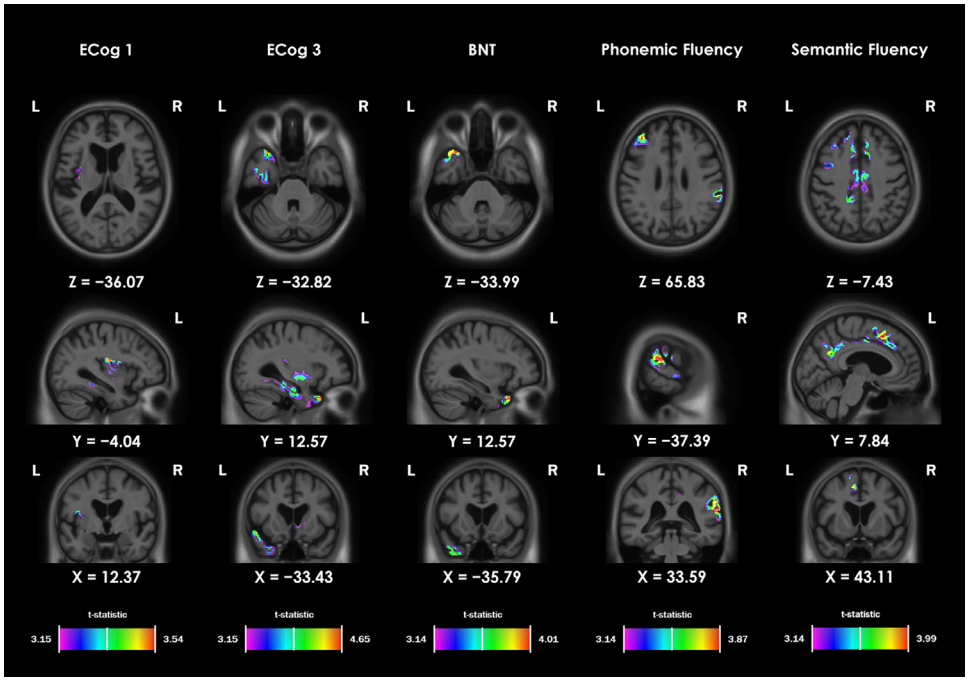

FIGURE 2 Whole sample — Location of significant associations between language scores and tau-PET. Voxel-wise tau-PET SUVR using a given language score and controlling for (a) age; (b) sex; (c) education; (d) primary language spoken; (e) handedness; (f) APOE genotype; (g) amyloid-PET ^{18}F-AZD-4694 full cerebellum GM SUVR composite and (h) MMSE, and corrected for multiple comparisons using a random field theory cluster threshold of $p < 0.001$. Color gradient indicates the strength of the association between language measures and tau accumulation.

3.3 | Prediction of early AD amyloid and tau biological stage

The variables selected by the stepwise method are presented in Table 2. They are ranked according to their contribution to the classification of participants into groups of amyloid and early tau pathology (Braak 0 Aβ−, Braak 0 Aβ+, Braak 1–2 Aβ+). The most contributive variable was ECog language 1, followed by ordinally-computed risk related to APOE genotype and BNT. They were the only three variables significantly contributing to the classification of participants. Analysis of a model without alpha threshold indicated that MoCA followed BNT, but did not meet the threshold for variable selection. This was followed by sex; ECog language 3; education; semantic fluency; age; WASI-II: Vocabulary; handedness; primary language and phonemic fluency.

4 | DISCUSSION

The present study aimed to investigate the language abilities of individuals found at different stages of tau accumulation according to a PET-based Braak staging framework. Our observations highlighted a progression of language impairments which paralleled tau's progressive accumulation within the brain. The earliest stages of tau accumulation (Braak 1–2) were characterized by elevated complaints about forgetting the names of objects, followed by objective impairments in confrontation naming in the middle stages (Braak 3–4) and further widespread impairments of semantic fluency, phonemic fluency and word knowledge processes accompanied by elevated complaints about finding the right words to use in a conversation in the final stages (Braak 5–6). Across the whole continuum, lower language performance was associated with tau accumulation predominantly in left-temporal language regions. Importantly, in theCU, associations to tau were nearly exclusive to subjective word-finding complaints and centered around the left fusiform and inferior temporal gyri. Subjective complaints about forgetting the names of objects were additionally the strongest contributors to the screening of early AD pathology (Aβ−T−vs. Aβ+T−vs. Aβ+T1-2), outperforming other variables such as age, sex, education, MoCA, and APOE genotyping. Overall, our findings permit the staging of language symptoms across the core biological definition of AD and point to subjective word-finding complaints as a promising avenue for the development of cost-effective screening tools for AD pathology.

This work recontextualizes the emergence of various types of language impairments across the AD continuum. Consistent with studies indicating subjective memory complaints could be sensitive to earlier impairment than objective measurements,[45,46] we found that complaints about forgetting the names of objects were sensitive to earlier AD pathology than objective language measurements. This finding aligns with previous work which showed that even in CU older adults, subjective word-finding complaints were associated with amyloid found in the cerebrospinal fluid.[16] Now that those results extend to a different cohort and to tau pathology, future investigations should attempt to determine whether subjective complaints capture truly unique aspects of early language decline, or whether our findings

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		ECog language 1		ECog language 3		Boston Naming		Phonemic Fluency		Semantic Fluency		WASI-II: Vocabulary		Maximal possible DKT Atlas Overlap in number of voxels	
	Degrees of freedom	159 – 14 – 1 = 144		159 – 14 – 1 = 144		176 – 14 – 1 = 161		178 – 14 – 1 = 163		177 – 14 – 1 = 162		146 – 13 – 1 = 132			
	Model mean *r*	0.16		0.16		0.18		0.17		0.18		0.18			
	Model *t* values range	-2.77	3.54	-3.16	4.65	-3.43	4.01	-2.70	3.87	-3.03	3.99	-2.60	3.35		
	t significant threshold after RFT correction	3.15		3.15		3.14		3.14		3.14		3.15			
	Brain hemisphere	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Braak 2	entorhinal	0%	0%	17%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 181	986
	hippocampus	1%	0%	20%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 915	2 050
Braak 3	amygdala	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 578	1 585
	fusiform	3%	0%	35%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 075	6 041
	lingual	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	0%	3 960	4 089
	parahippocampal	25%	0%	42%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 292	1 213
Braak 4	inferior parietal	0%	0%	0%	0%	0%	0%	0%	2%	0%	0%	0%	0%	7 608	9 594
	inferior temporal	0%	0%	32%	0%	1%	0%	0%	0%	0%	0%	0%	0%	9 568	10 355
	insula	16%	0%	37%	0%	0%	0%	0%	0%	0%	0%	0%	0%	5 264	5 248
	isthmus cingulate	0%	0%	0%	0%	0%	0%	0%	0%	14%	0%	0%	0%	1 422	1 307
	middle temporal	0%	0%	4%	0%	4%	0%	0%	0%	0%	0%	0%	0%	10 148	11 528
	posterior cingulate	0%	0%	0%	0%	0%	0%	0%	18%	36%	35%	0%	0%	1 817	1 989
	transverse temporal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	472	360
Braak 5	caudal anterior cingulate	0%	0%	0%	0%	0%	0%	0%	0%	24%	4%	0%	0%	1 641	1 383
	caudal middle frontal	0%	0%	0%	0%	0%	0%	35%	11%	15%	0%	0%	0%	4 824	4 252
	cuneus	0%	0%	0%	0%	0%	0%	0%	0%	1%	1%	0%	0%	2 539	2 644
	lateral occipital	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	8 638	8 611
	lateral orbitofrontal	0%	0%	0%	0%	0%	0%	0%	11%	0%	6%	0%	0%	3 938	4 007
	medial orbitofrontal	0%	0%	0%	0%	0%	0%	0%	17%	0%	6%	0%	0%	2 272	2 637
	pars opercularis	0%	0%	2%	0%	0%	0%	23%	14%	5%	0%	0%	0%	2 357	3 140
	pars orbitalis	0%	0%	0%	0%	0%	0%	0%	60%	0%	0%	0%	0%	730	605
	pars triangularis	0%	0%	0%	0%	0%	0%	33%	34%	12%	0%	0%	0%	2 828	2 723
	precuneus	0%	0%	0%	0%	0%	0%	0%	0%	27%	6%	0%	0%	6 680	6 715
	rostral anterior cingulate	0%	0%	0%	20%	0%	0%	0%	0%	0%	0%	0%	0%	3 142	1 710
	rostral middle frontal	0%	0%	0%	0%	0%	0%	33%	4%	13%	0%	0%	0%	8 243	8 210
	superior frontal	0%	0%	0%	0%	0%	0%	4%	13%	18%	8%	0%	0%	14 850	17 709
	superior parietal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 315	5 636
	supramarginal	0%	0%	0%	0%	0%	0%	0%	30%	0%	0%	0%	0%	6 265	5 221
	superior temporal	0%	0%	27%	0%	13%	0%	0%	15%	0%	0%	0%	0%	8 883	8 137
Braak 6	paracentral	0%	0%	0%	0%	0%	0%	5%	0%	2%	6%	0%	0%	2 564	2 248
	pericalcarine	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 044	1 416
	postcentral	2%	0%	3%	0%	0%	0%	0%	9%	0%	0%	0%	0%	5 135	4 389
	precentral	2%	0%	7%	0%	0%	0%	6%	0%	1%	0%	0%	0%	6 885	6 156
	Hemispheric load	1%	0%	9%	1%	1%	0%	5%	6%	5%	2%	0%	0%	152 073	153 894
	Significant voxels overlapping DKT atlas	1%		5%		1%		5%		4%		0%		305 967	
	Total significant voxels in the regression model	2493 (0%)		3%		2647 (0%)		4%		3%		0%		639 106	

FIGURE 3 Whole sample — Regions of significant associations between language scores and tau-PET after controlling for severity of impairment using the MMSE. Overlap in terms of voxel number between (a) DKT atlas voxels; and (b) Masks of significant association between language scores and tau-PET, in all individuals across the tau continuum, controlling for age + sex + education + APOE genotype + primary language + handedness + mean full cerebellar grey ^{18}F-AZD-4694 standardized uptake value ratio i.e, Aβ-PET load + MMSE; after T-statistical parametric maps were corrected for multiple comparisons using a random field theory cluster threshold of $p < 0.001$. Maximal possible DKT Atlas (totalling 305 967 voxels when excluding off-target basal ganglia) was based on DKT atlas reference substructures voxel count. Maximal total significant voxels (639 106 voxels) was based on mask file upon which the regression is drawn, that is a mask of grey matter within the whole cortex and Basal ganglia (Basal ganglia are excluded from this table due to known off-target binding). Cells are colored in accordance with the percentage of significant voxels in a specific region, higher percentages cells have their background colored in a darker shade of green as they tend towards 100%, starting from full white at 0%, this process is automated and additionally depends on value range of related cells. Red borders indicate regions of T-statistical peaks. DKT: Desikan–Killiany–Tourville, RFT: random field theory.

instead reflect the limitations of current objective language measures. These limitations are most evident in traditional tests such as the BNT, which was found to be impaired from the middle stages of tau progression (Braak 3–4). The relative sensitivity of the BNT comes in spite of previous studies not finding it to be the most ideal or sensitive measure of AD-related lexicosemantic deficits.[9,47] More sensitive measures, such as those involving the naming of unique exemplars, for example, through the recall of famous people, historical events, places or buildings,[9,16] could therefore be even better suited at detecting early AD pathology or at tracking between-stage progression. Our results nonetheless align with prior studies indicating naming impairments would emerge within the MCI stage. They are also consistent with the higher proportion of MCI individuals found within our Braak 3–4 subgroup. Next, and in contrast with previous studies in clinical stages of AD,[12,13] neither phonemic nor semantic fluencies were found to be impaired from the middle stages of tau progression (Braak 3–4). Instead, most of the overall loss in verbal fluency was only observed within the last stages (Braak 5–6). A possible explanation for this discrepancy lies in the fact that verbal fluency involves many cognitive processes including language, executive control, and processing

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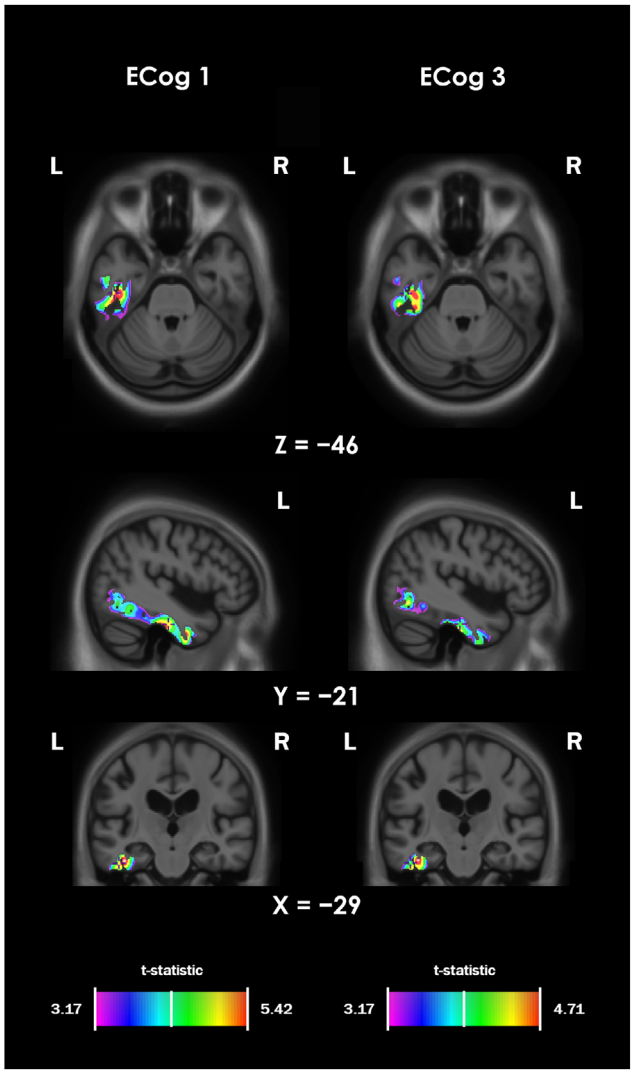

FIGURE 4 CU sample – Location of significant associations between language scores and tau-PET. Voxel-wise tau-PET SUVR using a given language score and controlling for (a) age; (b) sex; (c) education; (d) primary language spoken; (e) handedness; (f) APOE genotype; and (g) amyloid-PET ^{18}F-AZD-4694 full cerebellum GM SUVR composite, and corrected for multiple comparisons using a random field theory cluster threshold of $p < 0.001$. Color gradient indicates the strength of the association between language measures and tau accumulation.

speed.[9] This multidomain nature could make fluency highly sensitive when impairment is defined on the basis of symptomatology alone. However, when considered within the context of biological progression, early disease processes may be successfully compensated for.[48,49] Our imaging findings support this interpretation as verbal fluency was associated mainly with later-stage widespread frontal and parietal tau accumulation. This may explain the steeper decline in fluency compared with naming observed in the final stages of tau progression (Braak 5–6). Next, and consistent with previous findings, word knowledge was preserved until the final stages of tau progression (Braak 5–6).[15] Although semantic decline is often considered an early marker of AD,[50] its detectability likely depends on the difficulty and nature of the task. Vocabulary performance draws on deeply consolidated lexicosemantic representations and benefits from education and lifelong language exposure, both of which likely contribute to substantial cognitive reserve. This may help individuals maintain normal performance on the tasks through extensive use of circumlocutions. Future studies should therefore consider semantic tasks that probe finer-grained conceptual features or less frequent items to determine whether semantic impairment can be detected at earlier biological stages.

Our work served to localize the brain regions where tau pathology could be linked to language impairments. In the context of previous findings linking language measures to AD-related GM atrophy, we found associations (a) between words-finding complaints and the left fusiform gyrus[16]; (b) between confrontation naming and the left anterior temporal lobe,[9,10] but not with the left inferior prefrontal gyrus[11]; (c) between verbal fluency and the anterior and posterior cingulate cortices, but not with the left inferior temporal gyrus, left insular cortex, hippocampus or parahippocampal gyrus.[14] Despite some differences, relationships that had not been found between the left inferior prefrontal gyrus and confrontation naming were found instead with fluency. Further, relationships that had not been found between verbal fluency and the left inferior temporal gyrus, left insular cortex, hippocampus and parahippocampal gyrus were found instead with ECog language 1 and 3. One potential explanation for those differences could be that language complaints are mapping onto regions which will later come to atrophy and be linked to more objective impairments. Nonetheless and overall, results appear to indeed tap into expected left-weighted language networks,[51,52] that is, in accordance with the specificity of each task. Verbal fluency, a multidomain task, was associated with widespread frontal, cingulate, and parietal regions, indicating greater reliance on the frontoparietal executive network than on language-specific areas. These findings contribute to refining our understanding of the neurobiology of language in AD.

Our work also highlights language-based indicators that may assist in screening some of the earliest biological changes which can be associated with AD pathology. Alongside APOE genotyping, complaints about forgetting the names of objects and confrontation naming were found to significantly contribute to the correct classification of early AD pathology (Braak 0 Aβ– vs. Braak 0 Aβ+ vs. Braak 1–2 Aβ+), being first most and third most contributing respectively. Contrary to previous findings,[53] female sex did not reach the significance threshold for classification and neither did age. Sex, however, ranked as the second-highest nonsignificant variable in our stepwise analysis. Additionally, females were disproportionately represented in our sample's later Braak stages, which suggests a larger sample size could have revealed statistical significance. Age appeared to be similarly impacted, as its nonsignificant involvement could be primarily explained by the restricted age range of our sample (59–88 years). It is noteworthy, although to be interpreted with caution, that a single self-reported item outperformed established demographic risk factors and a global cognitive measure such as the MoCA, as well as approaching the predictive value of APOE despite its well-documented influence on AD risk.[54] This pattern suggests that subjective language difficulties may reflect subtle neurodegenerative changes that remain undetected by

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		ECog language 1		ECog language 3		Boston Naming		Phonemic Fluency		Semantic Fluency		WASI-II: Vocabulary		Maximal possible DKT Atlas Overlap in number of voxels	
	Degrees of freedom	109 – 9 – 1 = 99		110 –9– 1 = 100		125 – 9 – 1 = 115		126 – 9 – 1 = 116		125 – 9 – 1 = 115		107 – 9– 1 = 97			
	Model mean *r*	0.11		0.11		0.11		0.11		0.11		0.12			
	Model *t* values range	-2.58	5.42	-2.76	4.71	-4.11	2.57	-2.30	3.44	-1.85	3.95	-2.52	2.22		
	t significant threshold after RFT correction	3.17		3.17		3.16		3.16		3.16		3.18			
	Brain hemisphere	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Braak 2	entorhinal	5%	0%	7%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 181	986
	hippocampus	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 915	2 050
Braak 3	amygdala	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 578	1 585
	fusiform	71%	0%	38%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 075	6 041
	lingual	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	3 960	4 089
	parahippocampal	14%	0%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 292	1 213
Braak 4	inferior parietal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	7 608	9 594
	inferior temporal	63%	0%	53%	0%	0%	0%	0%	0%	0%	0%	0%	0%	9 568	10 355
	insula	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	5 264	5 248
	isthmus cingulate	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 422	1 307
	middle temporal	8%	0%	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%	10 148	11 528
	posterior cingulate	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 817	1 989
	transverse temporal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	472	360
Braak 5	caudal anterior cingulate	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 641	1 383
	caudal middle frontal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	4 824	4 252
	cuneus	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2 539	2 644
	lateral occipital	3%	0%	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%	8 638	8 611
	lateral orbitofrontal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	3 938	4 007
	medial orbitofrontal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2 272	2 637
	pars opercularis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2 357	3 140
	pars orbitalis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	730	605
	pars triangularis	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2 828	2 723
	precuneus	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 680	6 715
	rostral anterior cingulate	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	3 142	1 710
	rostral middle frontal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	8 243	8 210
	superior frontal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	14 850	17 709
	superior parietal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 315	5 636
	supramarginal	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 265	5 221
	superior temporal	6%	0%	8%	0%	0%	0%	0%	0%	0%	0%	0%	0%	8 883	8 137
Braak 6	paracentral	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2 564	2 248
	pericalcarine	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1 044	1 416
	postcentral	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	5 135	4 389
	precentral	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	6 885	6 156
	Hemispheric load	8%	0%	6%	0%	0%	0%	0%	0%	0%	0%	0%	0%	152 073	153 894
	Significant voxels overlapping DKT atlas	4%		3%		0%		0%		0%		0%		305 967	
	Total significant voxels in the regression model	3%		2%		672 (0%)		0%		0%		0%		639 106	

FIGURE 5 CU sample – Regions of significant associations between language scores and tau-PET. Overlap in terms of voxel number between (a) DKT atlas voxels; and (b) Masks of significant association between language scores and tau-PET, in CU individuals, controlling for age + sex + education + APOE genotype + primary language + handedness + mean full cerebellar grey ^{18}F-AZD-4694 standardized uptake value ratio i.e, Aβ-PET load; after T-statistical parametric maps were corrected for multiple comparisons using a random field theory cluster threshold of $p < 0.001$. Maximal possible DKT atlas (totalling 305 967 voxels when excluding off-target basal ganglia) was based on DKT atlas reference substructures voxel count. Maximal total significant voxels (639 106 voxels) was based on mask file upon which the regression is drawn, that is a mask of grey matter within the whole cortex and Basal ganglia (Basal ganglia are excluded from this table due to known off-target binding). Cells are colored in accordance with the percentage of significant voxels in a specific region, higher percentages cells have their background colored in a darker shade of green as they tend towards 100%, starting from full white at 0%, this process is automated and additionally depends on value range of related cells. Red borders indicate regions of T-statistical peaks. DKT: Desikan–Killiany–Tourville, RFT: random field theory.

TABLE 2 Contribution of predictor variables to classification of early AD pathology.

Classification for:	Braak 0 [Aβ –] Braak 0 [Aβ+] Braak 1–2 [Aβ+]	Singular Pillai	Pillai advancement Threshold
Model		Overall Pillai's trace = 0.32, $p < 0.001$	
Ecog language 1: Forgetting the names of objects*		.16	.07
APOE genotyping*		.09	.07
Boston Naming Test*		.07	.07
MoCA		.04	

*Significant to the prediction model. Alpha threshold for Pillai's advancement was set to $p = 0.05$.

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traditional screening tools, although replication in larger and more diverse cohorts is required to replicate these findings. Importantly, the marginally significant contribution of the BNT, in spite of its previously discussed poor sensitivity,[6,52] suggests once again that more sensitive objective cognitive measures may yet manage to capture the evidence of an ongoing decline.

While the current study fulfills many gaps in the literature, these results also need to be considered within the context of several limitations. First, the cross-sectional design of the study does not confirm that word-finding complaints and objective language impairments evolve with time across the biologically-defined AD continuum, as a longitudinal design would. Second, combining Braak stages may have affected results dependent on group comparisons. Third, the biological AD continuum is not limited to Aβ and tau detected using ^{18}F-MK-6240 and ^{18}F-AZD-4694 radioligands, nor is it restricted to the brain'sGM.[2] Moreover, the exclusion of mixed pathologies and brain areas of off-target binding may have influenced our results and limited their clinical utility. Fourth, whilst most of the limitations of the language measures used within this study have been discussed, other important domains of language have been neglected, such a those involving connected speech features.[55] Further research is therefore essential to expand upon our findings.

Taken together, our results underscore how language measures can be meaningful early indicators of underlying AD pathology, complementing the traditionally amnestic focus that has shaped both clinical practice as well as research. Additionally, results remind us that the sincere belief that one's abilities have been worsening should not be discredited on the sole basis that it involved subjectivity or that these worries are frequent in the population, as they may instead reflect subtle neurobiological changes that remain outside the reach of conventional cognitive screening. These worries instead highlight a need to develop and implement more sensitive language assessments in clinical settings, particularly tools that can detect early semantic and lexical changes.

AUTHOR CONTRIBUTIONS

Anna Marier: Conceptualization (support); data curation (lead); formal analysis (lead); methodology (lead); project administration (lead); software (support); validation (lead); visualization (lead); writing - original draft preparation (lead); writing - review and editing (lead). **Jaime Fernández Arias**: Conceptualization (support); methodology (support); resources (support); software (support); supervision (support); writing - review and editing (support). **Étienne Aumont**: Formal analysis (support); methodology (support); resources (support); software (support); supervision (support); validation (support); writing - review and editing (support). **Brandon J. Hall**: Formal analysis (support); Methodology (support); resources (support); software (support); supervision (support). **Arthur C. Macedo**: Conceptualization (support); methodology (support); project administration (support); resources (support); supervision (support); validation (support); writing - Review and editing (support). **Nesrine Rahmouni**: Conceptualization (support); methodology (support); supervision (support). **Gleb Bezgin**: Formal analysis (support); methodology (support); software (support); resources (support); supervision (support). **Paolo Vitali**: Conceptualization (support). **Pedro Rosa-Neto**: Conceptualization (support); funding acquisition (lead); methodology (lead); resources (lead); supervision (lead); writing - review and editing (support). **Maxime Montembeault**: Conceptualisation (support); project administration (lead); methodology (lead); resources (support); supervision (lead); validation (support); writing - review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

Anna Marier, Jaime Fernández Arias, Étienne Aumont, Brandon J. Hall, Arthur C. Macedo, Nesrine Rahmouni, Gleb Bezgin declare that they have no competing interests relevant to the context of this manuscript.

Paolo Vitali has been affiliated with NovoNordisc, Eisai, Lilly and IntelGenx Corp.

Pedro Rosa-Neto has been affiliated with Roche, Cerveau Radiopharmaceuticals, Lilly, Eisai, Pfizer, Novo Nordisk, and Biogen.

CONSENT STATEMENT

All human participants or their caregivers provided informed written consent to participate in the respective studies.

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