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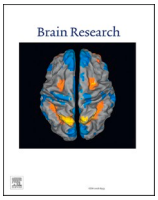

Atypical cortical hierarchy in Aβ-positive older adults and its reflection in spontaneous speech

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ABSTRACT

Abnormal deposition of Aβ amyloid is an early neuropathological marker of Alzheimer's disease (AD), arising long ahead of clinical symptoms. Non-invasive measures of associated early neurofunctional changes, together with easily accessible behavioral readouts of these changes, could be of great clinical benefit. We pursued this aim by investigating large-scale cortical gradients of functional connectivity with functional MRI, which capture the hierarchical integration of cortical functions, together with acoustic-prosodic features from spontaneous speech, in cognitively unimpaired older adults with and without Aβ positivity (total N = 188). We predicted distortions of the cortical hierarchy associated with prosodic changes in the Aβ + group. Results confirmed substantially altered cortical hierarchies and less variability in these in the Aβ + group, together with an increase in quantitative prosodic measures, which correlated with gradient variability as well as digit span test scores. Overall, these findings confirm that long before the clinical stage and objective cognitive impairment, increased risk of cognitive decline as indexed by Aβ accumulation is marked by neurofunctional changes in the cortical hierarchy, which are related to automatically extractable speech patterns and alterations in working memory functions.

1. Introduction

Neuropathological processes underlying Alzheimer's disease (AD), including extracellular Aβ peptide deposition and intracellular neurofibrillary tangles (Mahaman et al., 2022), long predate the onset of cognitive decline at a clinical level (Parnetti et al., 2019). Subtle cognitive changes may accompany this process, which are neither subjectively apparent to individuals themselves, nor objectively detectable through standardized neuropsychological evaluation. While amyloid and tau deposition, as well as neurodegeneration, can be reliably detectable *in vivo* by CSF or neuroimaging, it is not clear yet which non-invasive neurofunctional metrics could pick up these changes and how they might relate to behavioral measures.

A crucial candidate for such behavioral measures is the changes in spontaneous speech, which are objectively detectable non-invasively and ecologically with natural language processing techniques. There is evidence that changes in spontaneous speech or writing may predate the clinical onset of AD several years, if not decades (Iacono et al., 2009; Le et al., 2011), including at the stages of mild cognitive impairment (MCI) (Chapin et al., 2022; Roark et al., 2011; Sherman et al., 2021) and even

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of healthy ageing with subjective cognitive decline (Verfaillie et al., 2019) or with Aβ positivity (Mueller et al., 2021). Automatically extractable speech parameters at the acoustic-prosodic level, which require no transcription, have been shown to have high potential to accurately detect AD (Fraser et al., 2015), MCI (Fraser et al., 2019), and even earlier stages such as people at risk of AD with subjective cognitive decline (SCD) (He et al., 2023). Speech prosody concerns how speakers organize sounds into comprehensible sequences, using language-specific patterns of stress, rhythm, intonation, and tone of voice (Edelson and Diehl, 2013). Changes in speech prosody have shown sensitivity to cognitive decline in the AD continuum (Lofgren and Hinzen, 2022; López-de-Ipiña et al., 2013; Pistono et al., 2016), and specificity for discriminating between different dementia pathologies, such as primary progressive aphasia (Zimmerer et al., 2020), dementia with Lewy bodies (Yamada et al., 2022), and frontotemporal dementia (Pressman et al., 2015).

While evidence of the potential of a speech biomarker for dissecting early disease progression is accumulating, a crucial lacuna across pathologies is direct evidence of a relation between changes in speech and associated neurofunctional changes. Functional connectivity (FC) within and between brain regions or networks can capture such neurofunctional changes (Tosun et al., 2014) and opens a potential path for a neural validation of automatedly extractable behavioral markers of disease progression. Using resting-state functional MRI (rs-fMRI), macroscale brain-functional networks can be shown to exhibit a hierarchical organization, ranging from primary, unimodal and segregated sensorimotor systems, specialized to deal with external stimuli in particular sensory modalities, to transmodal cortices, where information is increasingly *integrated* so as to enable abstract and internally-directed mental functions (memory, thought) (Mesulam, 1998; Taylor et al., 2015; Margulies et al., 2016; Huntenburg et al., 2018). These latter functions are specifically associated with the default mode network (DMN), which lies at the apex of this cortical hierarchy, integrating and orchestrating all other functional networks (Deco et al., 2021). Recent studies have specifically measured the cortical hierarchy using functional connectome gradients, defined as large-scale components of FC obtained with dimension reduction techniques (Huntenburg et al., 2018; Margulies et al., 2016). It turns out that the DMN lies at a maximal cortical 'distance' from sensorimotor cortex regions (at the bottom), while other networks such as the frontoparietal control network (FPN) are interspersed in between. A sufficient such distance between the two poles of the cortical hierarchy is considered to enable or facilitate abstract, higher-order cognitive functions, which depend less on immediate environmental input (Smallwood et al., 2021). This triggers the general expectation that disorders of thought would relate to distortions of the cortical hierarchy, which incipient evidence (specifically in the form of a compression) supports, for multiple mental disorders including AD (Hu et al., 2022), psychosis (Dong et al., 2021), and autism spectrum disorders (Hong et al., 2019).

The purpose of the present study was to identify changes in the cortical hierarchy, as measured with FC gradients, and to link them to automatically extractable speech features. This was motivated by specific reasons for expecting that language changes at the level of spontaneous connected speech should pick up neurofunctional changes in the large-scale hierarchical organization of cognition. In particular, language (and speech, which it incorporates) necessarily *integrates* multiple cognitive functions in its normal use, from memory (e.g. retrieval of semantic concepts under temporal constraints) to social cognition and to complex executive and motor control (Hagoort, 2019; Roger et al., 2022). A distortion in the cross-network organization of these large-scale cognitive systems would therefore be naturally expected to be reflected in speech distortions. In line with this idea, there already is evidence from neurotypical individuals that individual differences in the cortical hierarchy relate to language function (Shao et al., 2022; Wang et al., 2022). In particular, Wang et al. (2022) show that greater cortical distance to primary sensorimotor landmarks predicts higher activations in a story comprehension task during fMRI. However, in any mental disorders where speech biomarkers have been widely discussed, such as the dementias or psychosis, these potential links between the cortical hierarchy and forms of language dysfunction have not been explored to our knowledge. This specifically applies in the context of AD, where Hu et al. (2022) found that the values of the principal gradient spanning between sensorimotor cortices and the posterior DMN decreased notably in patients with AD relative to both MCI and controls, reflecting a diminished segregation between this subnetwork of the DMN and other large-scale networks. Whether and how these changes are related to language changes remains unknown. The present study aims to fill this gap.

Specifically, our aims were to use naturalistic speech samples obtained from telephone interviews, together with cortical gradients in FC as a proxy of the cortical hierarchy, to (i) test for an effect of early amyloid pathology on both speech prosody and cortical gradient changes; (ii) relate these two metrics (speech and cortical gradient changes) to each other; and (iii) to background these relations against those with standard neuropsychological measures. We pursued these aims in a sample of cognitively unimpaired (CU) individuals, half of which were at increased risk of AD in virtue of Aβ-positivity.

2. Materials and methods

2.1. Dataset

188 subjects were sub-selected from the Alfa + study based on data availability in all domains relevant to the present investigation (Fig. 1a). Alfa + is a research cohort of middle-aged CU individuals, most of them with a family history of AD, who undergo clinical interviews, lifestyle and risk factors questionnaires, cognitive testing, CSF biomarkers, and neuroimaging procedures every 3 years with the aim to identify the earliest pathophysiological changes in the preclinical AD continuum (Molinuevo et al., 2016). All subjects came from North-East region of Spain with Spanish and/or Catalan as their native language(s). They were all diagnosed as CU, while approximately half had a higher risk of dementia as indicated by Aβ biomarker positivity. Subjects with CSF Aβ42/40 ratio lower than 0.071 were defined as Aβ pathology positive (A +) in conformity with Milà-Alomà et al. (2020), and else negative (A-).

There were 93 A + subjects and 95 A- subjects. Age and gender were significantly different between groups ($p < .05$), while years in education and language (Spanish vs. Catalan) were not. Table 1 shows the demographic characteristics of all subjects included. Basic sociodemographic data, neuropsychological battery assessment results, magnetic resonance images (MRI), and CSF biomarkers were registered as had been done in the Alfa + study (Molinuevo et al., 2016). In addition, during the COVID pandemic confinement, a team of the Barcelonaβeta Brain Research Center (BBRC) contacted Alfa + participants and asked whether they wanted to participate in a voice characteristics study, to which they were asked orally to give their consent (recorded). If they agreed, they were asked two questions in a recorded telephone interview, one past-directed ('How have you lived these last months of confinement? What activities have you carried out, and how have you felt?'), and one future-directed ('Let's imagine that a vaccine is not found in the next few years. How do you think social relationships would change in the world due to this new post-COVID-19 situation?'). The interviews were recorded over the regular phone line using (mono channel, sample rate at 8000 Hz, 32 bits per sample, bit rate at 16 Kb/s). During the telephone interview, 140 (74.47 %) subjects used Catalan, while 48 (25.53 %) used Spanish. Presence of subjective cognitive decline (SCD) was acknowledged when the subject gave a positive answer to the question: *Do you perceive memory or cognitive difficulties?* (Sánchez-Benavides et al., 2021).

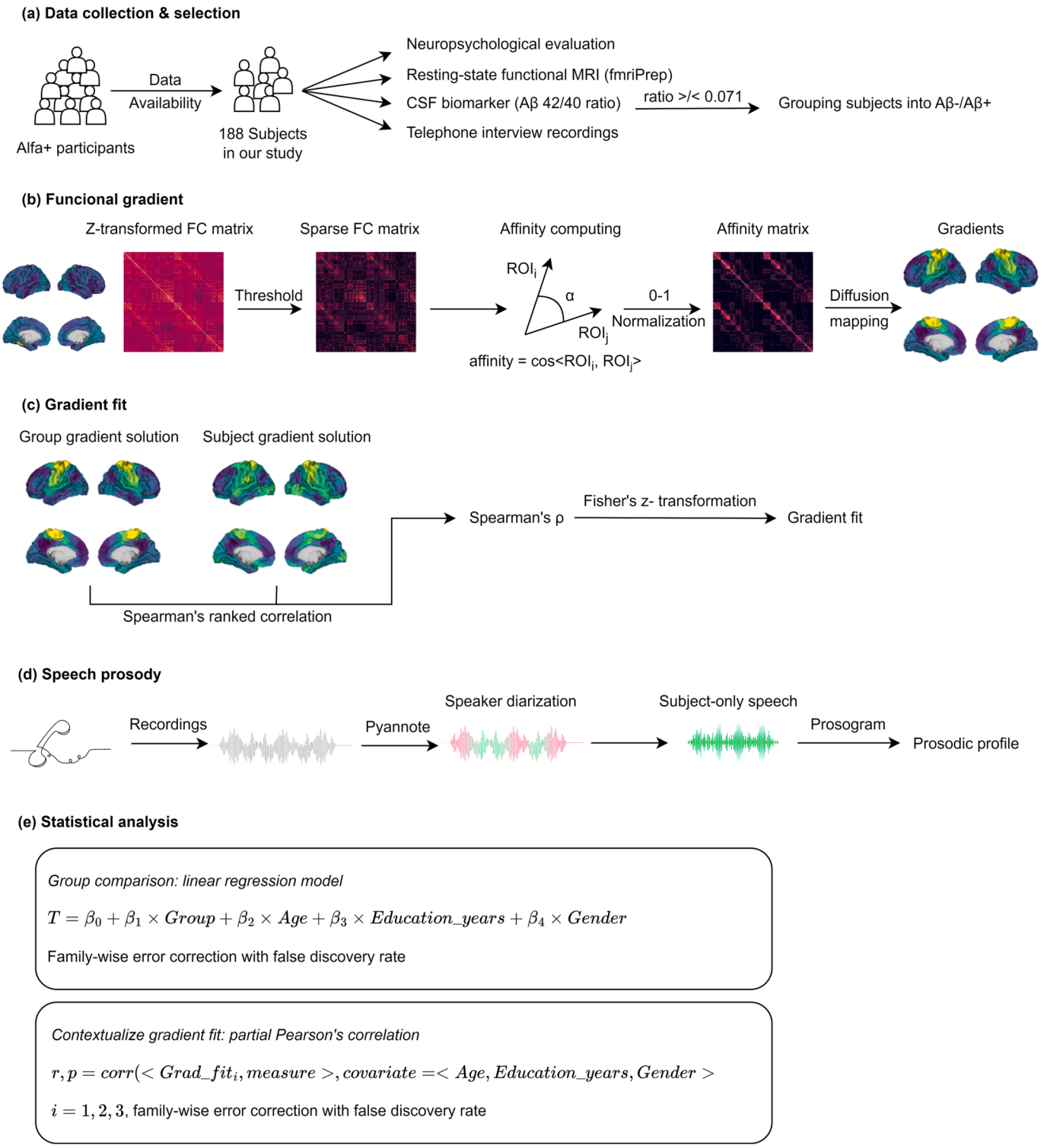

Fig. 1. Experiment schematic for this study.

2.2. Neuropsychological evaluation

Neuropsychological tests included scores from the Mini-Mental State Examination (MMSE), Semantic Fluency (SF), Trail Making Test (TMT), Free and Cued Selective Reminding Test (FCSRT), Memory Binding Test (MBT), Wechsler Adult Intelligence Scale (WAIS)-IV and Wechsler Memory Scale (WMS)-IV tests, and RBANS Line Orientation assessment. Details of the scores used can be found in Supplementary Table 1. Differences in neuropsychological test scores between groups were compared with a linear regression model including age, gender, years of education, and group as exogenous variables and each neuropsychological test result as the endogenous variable. *P*-values from multiple comparisons were corrected using false discovery rate (FDR) and reported as *q* values after correction (Benjamini and Hochberg, 1995). The threshold of statistical significance was set at 0.05 after correction. As the dataset is comprised of two very similar groups, we also set a higher threshold of 0.1 after correction as a marked 'tendency'. The same correction approach and statistical thresholds are applied to other

Table 1
Demographic characteristics of subjects included in the dataset.

Variables	A+	A-	test	*p*	effect size	
	Mean ± SD	Mean ± SD			Indicator	Value
Age[a]	62.16 ± 4.68	60.44 ± 4.78	Mann-Whitney	*0.023*	RBC[e]	−0.084
Sex[b]	64.52 %	49.47 %	χ2 test	*0.037*	Cramer's V	0.152
Educ. years[a]	13.08 ± 3.74	13.59 ± 3.39	Mann-Whitney	0.314	RBC[e]	0.192
Language[c]	75.27 %	73.68 %	χ2 test	0.803	Cramer's V	0.018
SCD[d]	34.41 %	24.21 %	χ2 test	0.124	Cramer's V	0.112

[a] Age and education (Educ.) years are represented by mean ± standard deviation.
[b] Sex is represented by the percentage of female subjects.
[c] The language used in the telephone interview is represented by the percentage of Catalan-speaking subjects.
[d] SCD is represented by the percentage of subjects with presence of Subjective Cognitive Decline.
[e] RBC stands for rank-biserial correlation.

statistical comparisons used in this paper.

2.3. Neuroimaging data acquisition and pre-processing

All participants underwent an MRI protocol in a 3 T Philips Ingenia CX scanner which included a 3D T1-weighted sequence (TE/TR = 4.6 / 9.9 ms, flip angle = 8°; voxel size = 0.75 × 0.75 × 0.75 mm^3) and a 9-minute task-free functional MRI sequence (TE/TR = 35 / 1600 ms, flip angle = 70°; voxel size = 3.0 × 3.0 × 3.1 mm^3). Results included in this manuscript come from preprocessing performed using fMRIPrep 21.0.1 (Esteban et al., 2018b, 2018a) based on Nipype 1.6.1 (Gorgolewski et al., 2011, 2018). The functional images were spatially standardized with MNI152NLin2009cAsym space and all confounds were regressed out based on the output of fMRIrep. Details on the fMRIPrep pre-processing pipeline can be found in the supplementary materials.

2.4. Whole-brain functional connectome gradient analysis

For each subject, after pre-processing, the Schaefer 400-parcels (Schaefer et al., 2018) were applied to extract functional time-series from the 400 regions of interest (ROIs). Then, we computed a 400 × 400 connectivity matrix using correlation matrix from the Ledoit-Wolf covariance estimator (Fig. 1b, i.e. the ConnectivityMeasure function from nilearn package). All connectivity matrices were Fisher-z transformed. For each group, we averaged the connectivity matrices from the subjects within that group to compute a group-level connectivity template. In the group-level connectivity template, for each row, all the negative elements and 90 % smallest elements were zeroed out so that only positive, strong, and less noisy correlations were kept. Next, we obtained an affinity matrix by computing the cosine similarities between the FC of each two ROIs from the sparse FC matrix. These cosine similarity scores were normalized into scores bounded between 0 and 1. Ten gradients were extracted from the affinity matrix for each group using diffusion mapping, to obtain two group-level gradient templates, one for the A + group and another for the A- group. These steps were carried out with the BrainSpace toolbox (Vos de Wael et al., 2020), and the parameters were: number of components = 10, dimension reduction approach = diffusion embedding, kernel = normalized angle, sparsity = 0.9, and random state = 7. The two group-level gradient templates were plotted on the cortical surface. Applying the same toolbox with identical parameters, we built gradient maps at the subject level and aligned these gradient maps to the group-level gradient solution with Procrustes rotation, in order to increase the robustness of subject gradient maps.

While, in line with previous work, the number of gradients was set as 10, only the first three gradients, G1, G2, and G3, were analyzed, due to their more established relationship with cognitive functions (Mckeown et al., 2020), with G1 reflecting the extent of separation between unimodal and transmodal cortex, G2 differentiating the somatosensory and visual cortex, and G3 reflecting the separation between the DMN and executive networks (Shao et al., 2022). The effect of Aβ positivity on these three gradients was investigated with the surface-based linear models (SLM) from the BrainStat toolbox (Larivière et al., 2023). Models included fixed effects of age, gender, years in education, and group (Fig. 1e). P-values from SLM were corrected for multiple comparisons with random field theory and FDR (Benjamini and Hochberg, 1995). In addition to this surface-based comparison, all ROIs were grouped into Yeo's 7 networks: DMN, FPN, limbic network (LN), ventral attention network (VAN), dorsal attention network (DAN), somatomotor network (SMN), and visual network (VN) (Yeo et al., 2011). Gradient scores of ROIs in each network and the whole brain were averaged to generate network-level and brain-level gradient scores. Approximate permutation tests with 10,000 rounds were applied to compare the group differences at the network-level, and brain-level gradient scores. P-values were corrected with FDR.

In addition to the gradient values for the first three gradients, we also measured how similar the subjects' gradient templates were to their corresponding group template (Fig. 1c). Spearman's rank correlation was used to compute the correlation coefficient between the gradient solutions of every subject and the group-level templates of their corresponding groups. These correlation coefficients were transformed with Fisher's z-transformation and are referred to as 'gradient fit' hereafter. Gradient fit indicates the within-group similarity to the gradient templates (Mckeown et al., 2020) and has been previously shown to correlate with behavioral measures (Shao et al., 2022), which motivated the inclusion of such a measure in our analysis pipeline. Similar to neuropsychological comparisons, a linear regression model was used to compare whether the gradient fits significantly differed between the groups, using identical exogenous variables.

2.5. Speech prosodic profiling

As the telephone recordings contained voices from both the interviewers and subjects, they were first processed by the pyannote model for speaker diarization (Fig. 1d, 2 speakers, 300 msec for minimum silence length, 200 msec for minimum voice length, −1.00 for speaker clustering preference) (Bredin et al., 2020; Bredin and Laurent, 2021). Although not perfect, this tool satisfactorily partitioned voices from the two speakers into several segments (diarization error rate of 25.50 % on a Spanish news dataset and 32.37 % on an English telephone recording dataset). After randomly quality-checking 10 processed samples, the partitioned segments were deemed as sound for later analysis. For each subject, we concatenated all voice segments only from themselves into a new recording. Interviewee-only recordings were forwarded to Prosogram, which automatically measures prosodic features for individual syllables and prosodic properties of longer stretches of speech (Mertens, 2004). Prosogram extracted 42 prosodic features, where 33 were selected after removing duplicated variables. Definitions and exclusion criteria for the prosodic features can be found in the Supplementary Table 2. Similar to gradient fit comparison, an identical generalized linear model was applied to test whether prosodic measures significantly differed between groups.

2.6. Relate connectome gradients to neuropsychological and prosodic measures

Third-order partial Pearson's correlation was applied to investigate the correlations between gradient fits with neuropsychological test scores, using age, gender, and years in education as covariates (Fig. 1e). For prosodic features, only those prosodic features that showed a

tendency of differing in the A + group before correction (uncorrected p less than 0.1) entered the partial Pearson's correlation to investigate the correlation between gradient fits with the prosodic features. The correlation coefficients were plotted into heatmaps while the p-values were corrected with FDR.

2.7. Data and code availability

The data that support the findings of this study are selected from the Alfa + study and not publicly available due to their containing information that could compromise the privacy of research participants. The pre-processing application fMRIPrep is publicly available. All analyses were carried out with scripts in Python. Codes for gradient analysis and SLM can be found in the tutorials of BrainSpace and BrainStat toolboxes. Pyannote model is freely available on BAS Web Services for speaker diarization (https://clarin.phonetik.uni-muenchen.de/BASWebServices/interface/SpeakDiar). Prosogram (v301b, https://sites.google.com/site/prosogram/homehttps://sites.google.com/site/prosogram/home) is publicly available. The linear model for group comparison and the FDR correction were carried out with the statsmodels package (0.13.5). We applied the pingouin package (0.5.3) for third-order partial correlation analyses. Other statistical tests were carried out with scipy 1.7.3. Codes can be requested from the corresponding author.

3. Results

3.1. Qualitative comparison of group-level gradient solutions

Fig. 2a displays the first three gradient scores on the cortical surface (fsaverage5 template); the remaining gradients can be found in the supplementary materials (Supplementary Fig. 1 and Supplementary Fig. 2). These first three gradients explained 52 % of the variance as shown by the scree plots (see Supplementary Fig. 3 and Supplementary Fig. 4). Gradients explained similar variance in the A + and A- groups (two-tailed Student's t-test: t = 0.0, p = 1.0). Globally, as shown in the histograms with kernel density estimation (Fig. 2b), the gradient distribution was compressed in the A + group, with a thinner tail but higher peak. This global compression in the A + group was significant as indicated by Kolmogorov–Smirnov test (KS = 0.03, p =.02). The first and the third gradients together are plotted in scatter plots in Fig. 2c, with the color of each dot (=ROI) referring to the specific Yeo's network where it is situated. Changes in distribution in the A + group can be visually observed.

3.2. Significant changes take place in gradients and gradient fit

Vertex-wise comparisons from SLM suggested that there were significant increases in G1 values in the A + group, in the anterior frontal lobe, anterior temporal lobe, and posterior parietal lobe, which strongly overlapped with the DMN (Fig. 3a); and significant decreases in the visual cortex. Network-wise comparisons suggested significant decreases in the A + group in the whole brain, DMN, FPN, and LN, and significant decreases in VN and DAN. For G2 (Fig. 3b), there were significant increases in the somatosensory and motor regions and significant decreases in the frontal, middle and inferior temporal, and parietal lobes, and of the visual cortex. Network-wise comparisons suggested significant decreases in the A + group in the whole brain, DMN, FPN, LN, and VN, and significant increases in VAN and SMN. For G3, fewer significant differences were found, which were weaker and scattered sporadically across the frontal and the parietal lobes (Fig. 3c). In the A + group, network-wise analysis suggested significant decreases in FPN, and significant increases in LN and VN. Despite of these differences in gradient component scores, no significant differences were observed in G1 fit (Fig. 3d) and G2 fit (Fig. 3e). By contrast, G3 fit increased in the A + group (Fig. 3f). This difference was significant before correction (p =.028) and remained a tendency after correction (q = 0.083).

3.3. Differences in neuropsychological scores and prosody

Supplementary Table 3 shows results from the linear regression model for neuropsychological scores, prosodic measures, and gradient fit. For the neuropsychological test scores, the A + group had higher performance in semantic fluency (p =.046) and in total recall of FCSRT (p =.028), but these differences did not survive correction (q = 0.511). As for prosody, before correction, the A + group showed longer total syllable nucleus duration (p =.034), and tendencies for more syllable nuclei (p =.084), more safe syllable nuclei (p =.084), longer speech (p =.081), and longer internucleus duration (p =.097). None of these differences, which are all related to speech timing, survived FDR correction (q > 0.05).

3.4. Relating gradient fit to neuropsychology and prosody

The results of a partial Pearson's correlation analysis are shown in a heatmap in Fig. 4 with coefficients and significant values available in Supplementary Table 4. For neuropsychology, no significant correlations were found with either G1 or G2 fits. For G3 fit, before correction, there was a significant correlation with WAIS-IV digit span subtest scores (r = 0.202, p =.006), which did not survive correction. For prosody, the five measures showing pre-correction significance in the group comparisons showed no significant correlation with G1 or G2 fits either. Four of them, however, significantly positively correlated with G3 fit, both before and after correction: number of nuclei (r = 0.161, q = 0.035), number of safe nuclei (r = 0.161, q = 0.035), speech time (r = 0.172, q = 0.035), and total internucleus duration (r = 0.162, q = 0.035). Only total nucleus duration did not significantly correlate with G3 fit (r = 0.116, q = 0.117).

4. Discussion

In this study, we applied a data-driven approach to investigate changes in speech prosody and functional connectome gradients in a group of CU older adults with Aβ positivity, with a view to explore links behavioral changes in speech prosody to neurofunctional changes. Results showed that gradient changes (including gradient fit) could be observed in numerous brain regions in the Aβ + group. These changes in the large-scale organization of cognitive functions across a cortical hierarchy are not reflected by standard neuropsychological test batteries. The individual gradient fit values, on the other hand, *are* reflected in the prosodic profile of connected speech samples, which we obtained from a short conversational section of a telephone interview. These profile changes are specific, in that they uniquely concern prosodic features characterizing temporal aspects of speech, such as the number of syllabic nuclei produced, the speech time, and total internucleus duration. By contrast, pitch-related features, which do not involve specific aspects of the hierarchical organization of language such as syllables, words, and sentences, were not affected. Our findings thus not only indicate that a large-scale functional reorganization of the brain accompanies Aβ positivity, but that spontaneous speech indexes these changes and forms an objective read-out of them.

Our findings of functional changes in a population at higher risk of AD are partially in line with previous studies of MCI and AD (He et al., 2022; Hu et al., 2022). Consistent with these studies of populations more progressed on the AD continuum, we qualitatively observed a compressed gradient distribution with a higher peak value already in an A + CU group (Fig. 2b). As speech production is an executively demanding task, and the third gradient did indeed relate to working memory as an aspect of executive functioning, we plotted the principle (first) and third gradients together in a scatter plot (Fig. 2c). Qualitative visual impression of the distribution of the values of these two gradients suggests a 'boomerang' shape in the A- group (left subplot of Fig. 2c). In the positive group (right subplot of Fig. 2c), this shape appears distorted, with the DMN and FPN collapsing onto each other, while VN extricates itself

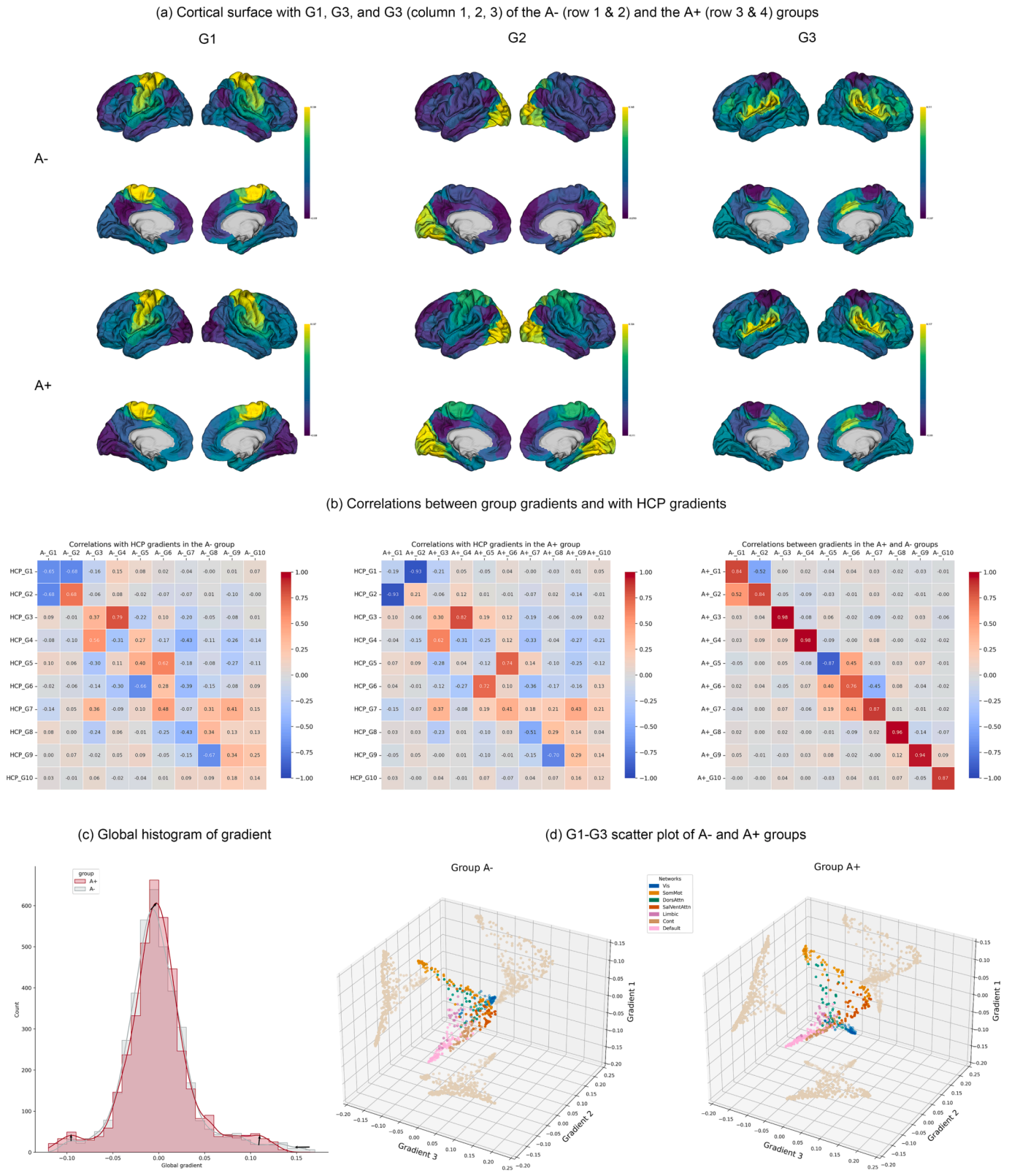

Fig. 2. Qualitatively observing the group-level gradient solutions. (a) Plotting the first three gradients on the cortical surface. (b) Distribution of all 10 gradients. The grey histogram refers to the A- group while the red one refers to the A +. (c) Scatter plots of the first (y-axis) and the third (x-axis) gradient. The color refers to Yeo's 7 networks: blue: visual; orange: somatomotor; green: dorsal attention; red: salience/ventral attention; purple: limbic; brown: frontoparietal control; pink: default mode. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

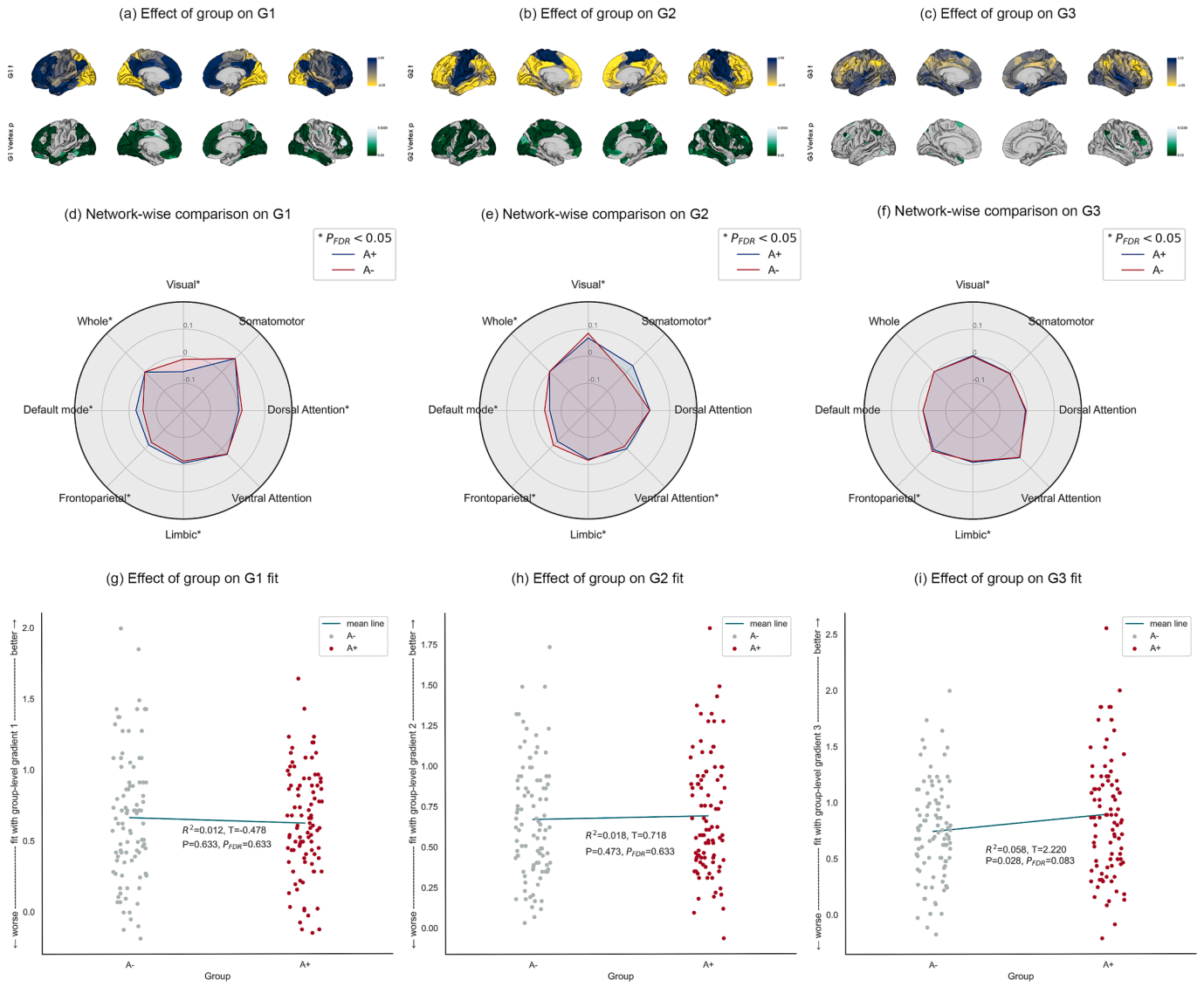

Fig. 3. Investigating the effect of Aβ group. (a-c) Effect of Aβ group on gradient 1, 2, and 3, with t and p values from SLM plotted on the brain surface. For each gradient, t values were plotted on the first row (in blue and yellow, blue for positive values while yellow for negative values). Significant p values (less than 0.05 after FDR correction) were plotted on the second row (in green). The denser the color is, the smaller the p values are. (d-f) Comparing gradient 1, 2, and 3 between groups within the 7 Yeo's networks and the whole brain. (g-i) Effect of Aβ group on G1 fit, G2 fit and G3 shown with strip plots (x axis: group, grey for A- and red for A+; y axis: gradient fit). The R^2, t value, uncorrected p value, and FDR-corrected p value were annotated with the mean line. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

out and disperses into a separate small triangle. Upon quantitative scrutiny, however, it turns out that the directions of changes in specific functional networks differ from changes in MCI and AD observed in the previous work. In particular, the principal gradient increased in the DMN and FPN (transmodal regions), while it decreased in VN and SMN (unimodal regions). On the other hand, He et al. (2022) observed decreases in the transmodal regions and increases in the unimodal regions in their MCI and AD groups. This suggests that neurofunctional changes at preclinical stages are unlikely to be continuous with changes seen at clinical changes. Early neuropathology may imply changes in distinct directions than those seen after a period where the brain cannot maintain neurotypical levels of cognitive functioning as assessed by clinical cognitive tests.

Although changes in prosody features, including both quantitative reductions of production and changes in pitch-related features, have previously been found at the clinical end of AD (Qiao et al., 2020; Vincze et al., 2021), this remains controversial for earlier stages. For temporal aspects of speech production, in particular, the above two studies found *increases* in speech duration in the MCI group (Qiao et al., 2020; Vincze et al., 2021), different from AD. However, decreases in speech duration in MCI have also been observed (Ambrosini et al., 2019; Imre et al., 2022). In the preclinical stage marked by subjective cognitive decline (SCD), a recent study used identical prosodic features as in the present study for a distinct Spanish/Catalan dataset and found speech duration-related features to significantly increase in the preclinical SCD group, but to decrease in MCI and AD groups. Increase of total speech duration, though insignificant, was also found in an another study of a Aβ-positive group (Mueller et al., 2021). Together, these previous studies, as well as the tendencies of increases in speech and nuclei durations observed in the present data, suggest that adults with signals for elevated risk of AD may show compensatory effects resulting in longer speech times. Crucially, subjects in our dataset were unaware of their biomarker status, and the SCD proportions in each group were not significantly different. The compensation in question is therefore not the reflection of

Fig. 4. Heatmap for correlation between gradient fit and behavior measures. The heatmap displays coefficients of the partial Pearson correlation between G1, G2, and G3 fits and the neuropsychological test scores (the first three rows) and the prosodic measures (the last row). White boxes indicate significant correlation after correction, while white underlines indicate significant correlation only before correction.

a conscious effort, but may index a compensatory brain process triggered by an onset of neural degradation. A potential pattern of slight increases in quantitative speech production features in preclinical stages, switching to a mix of increases and decreases in MCI, followed by a consistent decrease, awaits confirmation in future studies. Compensatory effects in the preclinical high-risk group could also explain why changes in the gradient values ran in different directions than previous studies of functional gradients in MCI and AD.

As changes in gradient values are difficult to interpret, the gradient fits were introduced in the present study as a more interpretable variable illustrating a clustering tendency within both groups in relation to their respective templates. In our data, differences in gradient fit were specifically significant for G3, the topography of which previous studies have related to the hierarchical separation between the executive control and DMN networks. The A + individuals showed a better fit suggesting a more cohesive group. This may indicate that they are less variable by virtue of sharing a cognitive characteristic, which predisposes them to cognitive decline. Moreover, the significant correlations between G3 fit and temporal aspects of speech, as well as that between G3 fit and a working memory measure (before correction), together support the possibility that changes in speech duration may specifically relate to executive functioning, which depends on working memory.

An important desideratum for future work is to extend the present study scheme to aspects of linguistic function depending on text-based analysis. While acoustic-prosodic features have a specific virtue for not depending on transcriptions, and have shown high promise in recent machine-learning studies especially at preclinical stages (He et al., 2023), a neurocognitive investigation needs to ask which specific mechanism in the multidimensional organization of language are affected, at which pathological stage. Semantic processing is a case in point, especially because the DMN strongly overlaps with the semantic network and plays an important role in functional gradients (Andrews-Hanna et al., 2014; Binder et al., 2009; Gordon et al., 2020). Additionally, transferring the gradient analysis to subcortical regions like the hippocampus is a promising direction. Incorporating the neuroimaging findings and language analysis may present more extensive and comprehensive understanding on the underlying mechanism of early cognitive decline.

CRediT authorship contribution statement

Rui He: Conceptualization, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jalal Al-Tamimi:** Formal analysis, Methodology, Validation, Writing – review & editing. **Gonzalo Sánchez-Benavides:** Data curation, Validation, Writing – review & editing. **Guillermo Montaña-Valverde:** Software, Validation, Writing – review & editing. **Juan Domingo Gispert:** Data curation, Writing – review & editing. **Oriol Grau-Rivera:** Data curation, Writing – review & editing. **Marc Suárez-Calvet:** Data curation, Writing – review & editing. **Carolina Minguillon:** Data curation, Writing – review & editing. **Karine Fauria:** Data curation, Writing – review & editing. **Arcadi Navarro:** Data curation, Writing – review & editing. **Wolfram Hinzen:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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