Neurophysiological and brain structural markers of cognitive frailty differ from Alzheimer's disease

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Abstract

With increasing life span and prevalence of dementia, it is important to understand the mechanisms of cognitive ageing. Here, we focus on a subgroup of the population we term "cognitively frail", defined by reduced cognitive function in the absence of subjective memory complaints, or a clinical diagnosis of dementia. Cognitive frailty is distinct from cognitive impairment caused by physical frailty. It has been proposed to be a precursor to Alzheimer's disease, but may alternatively represent one end of a non-pathological spectrum of cognitive aging. We test these hypotheses in humans of both sexes, by comparing the structural and neurophysiological properties of a community-based cohort of cognitive frail adults, to people presenting clinically with diagnoses of Alzheimer's disease or mild cognitive impairment, and community-based cognitively typical older adults. Cognitive performance of the cognitively frail was similar to those with mild cognitive impairment. We used a novel cross-modal paired-associates task that presented images followed by sounds, to induce physiological responses of novelty and associative mismatch, recorded by EEG/MEG. Both controls and cognitively frail showed stronger mismatch responses and larger temporal grey matter volume, compared to people with mild cognitive impairment and Alzheimer's disease. Our results suggest that community-based cognitively frail represents a spectrum of normal ageing rather than incipient Alzheimer's disease, despite similar cognitive function. Lower lifelong cognitive reserve, hearing impairment and cardiovascular comorbidities might contribute to the aetiology of the cognitive frailty. Critically, community-based cohorts of older adults with low cognitive performance should not be interpreted as representing undiagnosed Alzheimer's disease.

Significance statement

The current study investigates the neural signatures of cognitive frailty in relation to healthy ageing and Alzheimer's disease. We focus on the cognitive aspect of frailty and show that despite performing similarly to the patients with mild cognitive impairment, a cohort of community-based adults with poor cognitive performance do not show structural atrophy or neurophysiological signatures of Alzheimer's disease. Our results call for caution before assuming that cognitive frailty represents latent Alzheimer's disease. Instead the cognitive underperformance of cognitively frail adults could may a result of cumulative effects of multiple psychosocial risk factors over the lifespan, and medical comorbidities.

Keywords

Cognitive frailty; MEG; Aging; Alzheimer's disease; MRI; Cognitive reserve

Abbreviations

ACE-R: Addenbrooke's Cognitive Examination – Revised; Cam-CAN: Cambridge Centre for Ageing and Neuroscience; DA: Associative deviant; dB: Decibel; DN: Novelty deviant; EEG: Electroencephalogram; ENT: Entorhinal cortex; GMV: Grey matter volume; HIP: Hippocampus; LHG: Left Heschl's gyrus; LIFG: Left inferior frontal gyrus; LSTG: Left superior temporal gyrus; MCI: Mild cognitive impairment; MEG: Magnetoencephalogram; MMSE: Mini Mental State Examination; MNI: Montreal Neurological Institute; MRI: Magnetic Resonance Imaging; PAL: Paired associated learning task; RHG: Right Heschl's gyrus; RIFG: Right inferior frontal gyrus; RSTG: Right superior temporal gyrus; RMS: Root-mean-square; ROI: Region of interest; STD: Standard; TIV: Total intracranial volume.

Author's contributions

JBR, RNH, DN designed the study. LH and RNH designed the paradigm. DN, TE and EK collected the data. RNH preprocessed the structural MRI data. EK pre-processed the MEG data and performed all of the analyses. EK wrote the manuscript, and all authors contributed to the final version.

Introduction

With longer life span and an older population, there is a pressing need to understand the mechanisms that determine cognitive ageing, and its relationship to dementias. The *cognitively frail*, is a population of interest, defined by reduced cognitive function in the absence of subjective memory complaints, or a clinical diagnosis of dementia, mild cognitive impairment (MCI) or other pre-existing neurological explanation. Here cognitive frailty does not refer only to the cognitive impairments of those with comorbid physical frailty (Kelaiditi et al., 2013). Cognitive frailty has been linked to a higher risk of dementia, and is often regarded as a precursor to Alzheimer's disease (Panza et al., 2006; Buchman et al., 2007; Kojima et al., 2016; Shimada et al., 2018). In the absence of physical frailty, cognitive impairment alone is associated with longitudinal decline in functional abilities, activities of daily living (Shimada et al., 2016), increased hospitalisation and all-cause mortality rate (Avila-Funes et al., 2012; Solfrizzi et al., 2012; Ge et al., 2020).

However, there is an alternative hypothesis: poor cognitive performance reflects adverse aspects of normal ageing, without latent Alzheimer's disease or other neurodegenerative process. Psychosocial, educational, medical factors may contribute to cognitive frailty in the absence of latent degenerative or vascular dementia pathologies. For example cognitively under-performing adults are four times more likely to come from disadvantaged socioeconomic backgrounds, and twice as likely to have lower educational qualifications (Rogers et al., 2017). They are more likely to be malnourished (Mulero et al., 2011; Talegawkar et al., 2012; Chye et al., 2018), sedentary lifestyle (Landi et al., 2010; Rogers et al., 2017), have more medical comorbidities such as cardiovascular disease (Patrick et al., 2002; Langlois et al., 2012; Fuhrmann et al., 2019), chronic inflammation (Walston et al., 2002; Weaver et al., 2002; Cappola et al., 2003) and hearing impairment (Valentijn et al., 2005; Panza et al., 2015).

Here we determine whether cognitively frail community dwelling older adults have structural and/or neurophysiological characteristics of normal ageing or early Alzheimer's disease. We quantify brain structure and function using magnetic resonance imaging (MRI) and electro-magnetoencephalography (E/MEG) respectively. In Alzheimer's disease, amyloid plaques and neurofibrillary tangles form early in entorhinal cortex and hippocampi (Hardy and Selkoe, 2002; Braak et al., 2006), leading to disruptions in synaptic and neural function (LaFerla and Oddo, 2005; West and Bhugra, 2015) and atrophy. If the cognitively frail have prodromal or undiagnosed Alzheimer's disease pathology, one would expect similar structural and neurophysiological changes. To assess the neural systems of hippocampal-dependent associative memory, we designed the *cross-modal oddball task*. The trials consisted of repeated pairings of an abstract image with a sound. A mismatch response arose from pairs that included either a novel sound (i.e. *novelty deviant*), or a sound that was not novel, but had been previously associated with a different image (i.e. *associative deviant*). The novelty deviants are akin to typical mismatch negativity responses; proposed to be an index of auditory predictive coding, which is attenuated in Alzheimer's disease (Ruzzoli et al., 2016; Laptinskaya et al., 2018). The associative deviants are a more sensitive test of Alzheimer's disease, since hippocampal dysfunction would impair the ability to establish cross-modal associations (Gottfried and Dolan, 2003; Joassin et al., 2011), and attenuate the response to associative deviants. Indeed, previous studies report impaired performance on the paired-associates learning task (PAL) in MCI and preclinical Alzheimer's disease, which correlates with disease progression (Blackwell et al., 2004; Ahmed et al., 2008). Moreover, in fMRI PAL shows Alzheimer's-related increased hippocampal activity and connectivity between hippocampus and cortical areas, (de Rover et al., 2011; Harrison et al., 2016). We measured novelty and associative deviant responses in lateral

frontotemporal areas, readily detected by E/MEG in auditory oddball paradigms and reduced in dementia (Pekkonen, 2000; Garrido et al., 2009; Phillips et al., 2016).

We proposed that if cognitively frailty represents part of the spectrum of normal ageing, rather than latent Alzheimer's disease, then the neurophysiological responses and structural features of cognitively frail adults would resemble cognitively healthy adults rather than the patients with MCI or Alzheimer's disease.

Materials and Methods

Study design

The Cam-CAN Frail Project is an extension of the large-scale cross-sectional population-based Cambridge Centre for Ageing and Neuroscience study (Cam-CAN (Shafto et al., 2014)), focused on cognitive frailty. It examines the sub-population of community-dwelling adults with cognitive frailty, identified from home screening visits by cognitive screening tests: below 25/30 on the MMSE and/or below 88/100 on the ACER in the absence of a diagnosis or referral for a memory disorder.

The Cam-CAN Frail protocol comprised of three sessions. First, a visit to the participant's home to assess lifestyle, health and cognitive performance on an extensive neuropsychological test battery. The battery included the revised Addenbrooke's Cognitive Examination (ACER), Mini Mental State Examination (MMSE), Wechsler Adult Intelligence Scale logical memory test, Spot the Word test, simple choice reaction time, famous faces test, four-mountains task, virtual object location and orientation, Rey figure recall, and the trail making test. In the second session, participants underwent E/MEG scanning and completed the Cattell and digit symbol tests. During the E/MEG recording, participants completed the cross-modal oddball task. In the final session, participants had a functional and structural magnetic resonance imaging and completed the Hotel task. The study was approved by the East of England – Cambridge Central Research Ethics Committee (10/H0308/50).

Participants

Participants consisted of community-dwelling older healthy controls, and patients diagnosed with either MCI or Alzheimer's disease by secondary healthcare services (Table 1). The cognitively frail individuals were defined by underperformance on cognitive tests, without any subjective memory complaints or clinical diagnosis of dementia, MCI or other significant neurological and psychiatric illness. A control group of cognitively successful healthy older adults was recruited, from the participants who had been assessed at home as part of the Cam-CAN 3000 home assessment (Shafto et al., 2014), but who had not been recruited into the "Cam-CAN 700" or "Cam-CAN 280" re-assessments. These healthy cognitive controls scored >25/30 on MMSE or >88/100 on the ACER during the home interview. The Cam-CAN home visits acquired lifestyle and cardiovascular risk characteristics (alcohol and smoking, hypertension, history of stroke and heart attack).

In addition, patients were recruited from local specialist memory clinics who had MCI or probable Alzheimer's disease diagnosed according to Petersen and McKhann criteria respectively (McKhann et al., 2011; Petersen et al., 2014). Most MCI/AD patients had positive cerebrospinal fluid biomarker status for Alzheimer's disease pathology, or clinical follow up to confirm the diagnosis. Participants were recruited from either sex, and were older than 50 years and were fluent speakers in English, with mental capacity to consent. Participants did not have any

significant psychiatric illness or established neurological condition (other than MCI or Alzheimer's disease in the patient groups).

E/MEG and MRI acquisition

We used E/MEG to quantify neurophysiological dysfunction , as used in studies of healthy successful aging (Vlahou et al., 2014; Tsvetanov et al., 2015; Coquelet et al., 2017; Price et al., 2017), and early signatures of MCI and Alzheimer's disease (Osipova et al., 2005; Stam et al., 2006; de Haan et al., 2012; Maestú et al., 2015; Hughes et al., 2019; Kocagoncu et al., 2020). E/MEG data were acquired using the Elekta Vector View system with 204 planar gradiometers and 102 magnetometers. Simultaneous EEG data were acquired using a 70-channel Easycap. Participants' horizontal and vertical eye movements, and the cardiac activity were recorded using bipolar electro-oculogram and electro-cardiogram electrodes. Five head position indicator coils were placed on the EEG cap, to track the head position every 200 ms. For coregistration of the participant's T1-weighted MRI scan to the MEG sensors, three fiducial points (nasion, left and right pre-auricular) and a minimum of 100 head shape points were digitized using Polhemus digitization.

Participants were seated in a magnetically shielded room (IMEDCO) and positioned under the MEG scanner. Auditory stimuli were delivered binaurally through MEG-compatible ER3A insert earphones (Etymotic Research). The delay in sound delivery due to the length of earphone tubes and sound card was 26 ± 2 ms on average. Visual stimuli were presented on the screen positioned 1.22 m in front of the participant's visual field. Simultaneous E/MEG was recorded continuously at 1000 Hz with a high-pass filter of 0.03 Hz. Before the E/MEG recording, participants performed an automated hearing test in the MEG scanner, to make sure that the earphones were working properly. They presented pure tones at the frequency of 1000 Hz to either ear with varying loudness. Participants were instructed to press the button when they heard the tone. The mean hearing levels of each group is given in **Table 1**, where the normal range is expected to fall within 45-75 dB.

T1-weighted structural images were acquired on a Siemens 3T Magnetom Prisma MRI Scanner using a MPRAGE sequence (repetition time = 2250ms, echo time = 2.99ms; inversion time = 900ms; flip angle = 9 degrees; field of view = 256mm x 240mm x 192mm; voxel size = 1mm isotropic; GRAPPA acceleration factor = 2; acquisition time = 4 minutes 32 seconds). Four participants did not tolerate MRI due to claustrophobia.

Stimuli

The stimuli consisted of abstract images and pure tones. There were four images with distinct patterns. The tones had the following frequencies: 503 Hz, 719 Hz, 1021 Hz and 1451 Hz. Harmonic tones were avoided by choosing frequencies of prime numbers and varying them by at least 3 semi-tones. There were four types of trials. 1) *Standard (STD) trials* were image-tone pairs that participants trained on prior to the task. Standard pairs were the trials presented most frequently. 2) *Associative deviant (DA) trials* presented the same images of the standard pairs but by shuffling the sounds. The DA trials were expected to capture the binding effect arising from a mismatch in association. 3) *Novelty deviant (DN) trials* presented the standard images with rare deviant tones. The frequencies used for the novel deviants were 599 Hz, 857 Hz, 1017 Hz, 1733 Hz. The DN trials were expected to capture the novelty effect, and were essentially the deviants used in conventional mismatch paradigms. The deviant trials were expected to induce a mismatch response with respect to the response to standard trials. 4) *Target trials*: The standard

pairs, where the image was bound by a red circle. Target trials were included to make sure participants were attending to the stimuli. There were in total of 1000 standard trials and associative deviant, novel deviant and target trials were presented 48 times each. Therefore, the associative deviant, novel deviant and the targets were each encountered 4% of the time each, whereas standards 88% of the time.

Paradigm

The cross-modal oddball paradigm depends on both change detection and associative binding. This has two advantages. First, as MEG recording has lower signal to noise ratio in the subcortical areas and deeper sources compared to signal coming from superficial cortices (Goldenholz et al., 2009), the task was specifically designed to capture the indirect response in the superior temporal gyri and inferior frontal gyri, that are dependent on hippocampal associative learning. Secondly, the integrity of the auditory and frontal cortex is preserved until late stages of Alzheimer's disease, allowing us to control for atrophy of the cortical generators of the mismatch response. The task was easy to perform both by all participant groups, require minimal training (reducing potential confounds such as education and cognitive strategies on performance).

Images were presented centrally on a grey screen bounded by a black circle for 800 ms. Then, 300 ms after image onset, the tone was played for 500 ms (**Figure 1A**). The 300 ms lag was introduced to allow participants to form predictions about the upcoming auditory stimuli. In between trials, a black fixation square was presented for a jittered period of 300-500 ms, resulting in a stimulus onset asynchrony between 1000-1200 ms. E-Prime 2 (Psychology Software Tools) was used to present the stimuli and send triggers to the scanner.

In the training phase, participants were presented in total four images and four tones (i.e. standard pairs), 25 times each, and were instructed to try to remember the pairings between the images and the tones. After the training, participants performed a short test where they listened to the four tones twice in a randomised order. After each tone, they were shown four images (i.e. chance level of %25) on the screen and were asked to select the image that was paired with that tone. Irrespective of the participant's performance, training was repeated only once. Following the training participants moved on to the main task. Trials were presented in a different randomised order for each participant across four 5-minute long blocks. Participants were instructed to pay attention to the images and press the button with their right index finger when the image was bound by a red circle.

E/MEG pre-processing and source localization

The raw E/MEG data were pre-processed using MaxFilter 2.2.12 (Elekta Oy). Maxfiltering included detection and interpolation of bad sensors, signal space separation to remove external noise from the data and head movement correction. Cardiac and blink artefacts were detected and removed using an independent component analysis with 800 maximum steps and 64 principal components via the EEGLAB toolbox (Delorme and Makeig, 2004). The independent component time series were correlated with EOG and ECG time series and spatial templates. The components that revealed higher than z=3 in the temporal and z=2 in the spatial dimension were removed and the remaining time series of the independent components were reconstructed. On average 2.38 blink components (*SD* = 0.58) and 1.30 cardiac components (*SD* = 0.49) were removed.

Data were further processed in SPM12 (www.fil.ion.ucl.ac.uk/spm). Data were bandpass filtered between 0-40 Hz using a fifth-order Butterworth filter. The continuous data were epoched

between -100 to 500 ms from the sound onset. OSL's artefact rejection algorithm (github.com/OHBA-analysis/osl-core) was used to remove remaining artefacts (e.g. motor). Bad channels and trials marked by the algorithm were removed. On average 53.04 (4.6 %; *SD* = 35.88) trials and 10.76 channels (2.8 %; *SD* = 5.85) were removed per participant. Trials were averaged within condition, using robust averaging. Low-pass filter was re-applied to correct for the high-frequency noise introduced by robust averaging.

The E/MEG data were source localised using all sensor data: magnetometers, gradiometers and EEG (Henson et al., 2009). The source space was modelled with a medium sized cortical mesh consisting of 8196 vertices via inverse normalization of SPM's canonical meshes. Sensor positions were coregistered to the native T1-weighted MPRAGE scans using the fiducial and head shape points after removing digitisation points around the nose. SPM's canonical template brain was used for participants who did not tolerate the MRI scan. Single shell and Boundary Element models were used for forward modelling of MEG and EEG data respectively. Evoked signal was estimated over the trials using the COH solution in SPM which imposes spatial smoothness on the prior covariance matrix. All inversion accuracies were above 80%, as measured by the proportion of variance explained in the sensor data (*M* = 93.62; *SD* = 3.63).

Although neurophysiological responses in the hippocampus are difficult to detect with E/MEG, owing to its depth, a strong mismatch response can be recorded from temporal cortex, where sensory predictions are assumed to be established from hippocampal-dependent cross-modal associative learning. We therefore focus on the mismatch response in the lateral temporal auditory and frontal cortex, as activated in conventional auditory oddball paradigms (Pekkonen, 2000; Garrido et al., 2009; Hughes and Rowe, 2013; Phillips et al., 2016; Hughes et al., 2018). The source localised data were extracted from 6 areas taken from the Automated Anatomical Labelling atlas: Heschl's gyri, superior temporal gyri and inferior frontal gyri bilaterally (**Figure 2C**). The ROI masks were resliced to 1mm isotropic thickness to allow maximum data extraction. For each participant and condition, the data were extracted from the peak within all the vertices that constitute each ROI. This is to maximise the signal to noise ratio in the data, and to account for individual variability in source activity. We had two contrasts of interest in the analyses: the STD-DN contrast captures the novelty mismatch effect, while the STD-DA contrast captures the associative mismatch effect.

MRI pre-processing and grey matter analysis

The T1 image was rigid-body co-registered to a Montreal Neurological Institute (MNI) template and then corrected for image inhomogeneity and segmented into 6 tissue classes (grey matter, white matter, cerebrospinal fluid, bone, soft tissue, and residual noise) using SPM's unified segmentation algorithm (Ashburner and Friston, 2005). The native space grey and white matter images for all participants were then submitted to diffeomorphic registration (DARTEL) (Ashburner, 2007) to create group template images. The group template was then normalised to the MNI template via an affine transformation and the combined normalisation parameters (native to group template and group template to MNI template) were applied to each individual participant's grey matter image, including modulation in order to preserve local volume. Region of Interest (ROI) from the Harvard-Oxford atlas were then used to extract mean regional GMV from the bilateral hippocampal and entorhinal ROIs for each participant. The GMVs were compared across groups using ANCOVAs where age and total intracranial volume (TIV) were set as covariates.

To calculate local grey matter atrophy at the whole brain level we used voxel-based morphometry (VBM). Grey matter segments were thresholded with an absolute masking level of

0.1, and were smoothed with a Gaussian kernel at 8 mm full width half maximum. Grey matter volumes were compared across groups in pairwise t-contrasts in general linear models accounting for differences in age and total intracranial volume. The cluster level p-values were corrected for multiple comparisons using the family-wise error after a cluster defining threshold of $p < 0.05$.

RMS and statistical analyses

To investigate differences in time series, the root-mean-square of the time series at each ROI and trial were smoothed using a moving average at every 50 time points, to remove jumps. The RMS at each time point was then modelled using general linear models (GLM) accounting for differences in age and hearing levels, and tested for within group task effects by using t-contrasts. The contrasts compared the signal intensity between the DA-STD and DN-STD. The tests comparing the deviant effects were performed firstly within each participant group, to reveal task-specific effects. Secondly, these differences were tested across groups to test for interaction effects between conditions and groups. The observed cluster masses in the GLMs were corrected for multiple comparisons using permutation cluster statistics, by bootstrapping the design matrix using 1000 permutations at $p = 0.05$. The mean of the time series within each contrast were calculated for each participant within the 200-500 ms time window after removing outliers. This time window was selected because task effects were strongest after the N100. The linear relationship between these metrics and predictor variables were further tested through general linear models across the sample including age as a covariate, and after removing outliers. The predictors of interest were years of education, ACER total and memory subscale scores, and hippocampal and entorhinal grey matter volumes.

Results

Sample characteristics

Sample characteristics and scores on neuropsychological tests were compared across the groups using ANOVAs. Age ($F(3,87) = 3.82$; $p = 0.012$) and years of education ($F(3,87) = 11.34$; $p < 0.001$) differed between groups. Tukey's HSD tests showed that the cognitively frail group was older than controls ($p = 0.006$). The duration of formal education was longer in those in the control group than the cognitively frail ($p < 0.001$), and Alzheimer's disease group ($p = 0.032$). The MCI group had had longer education than the cognitively frail ($p < 0.001$) and Alzheimer's disease ($p = 0.001$) groups. Hearing levels were tested for group differences using both ANOVA and ANCOVA (to control for differences in age). There were no significant differences in hearing in the left ear. In the right ear there was a group difference ($F(3,86) = 4.70$; $p = 0.004$): the hearing of the cognitively frail was lower than control ($p = 0.017$) and MCI ($p = 0.005$) groups. When adjusting for the differences in age ($F(3,85) = 3.02$; $p = 0.034$), the hearing levels on the right were still lower in the cognitively frail group compared to the MCI group ($p = 0.019$). Chi-square tests compared the prevalence of lifestyle and cardiovascular risk factors between control and the cognitively frail groups. The prevalence of daily alcohol consumption was lower in the cognitively frail group (19%) compared to controls (43%) ($X^2(1) = 6.11$; $p = 0.006$). The prevalence of hypertension was higher in the cognitively frail group (52%) compared to the controls (35%) ($X^2(1) = 2.74$; $p = 0.048$). There were no significant differences between groups in the prevalence of smoking, history of stroke or heart attack.

Cognitive results

Cognitive scores were tested for group differences after controlling for differences in age (**Table 1**). The MMSE ($F(3,86)$ = 17.64; $p < 0.001$), ACER total score ($F(3,86)$ = 55.41; $p < 0.001$), ACER's subscales in memory ($F(3,86)$ = 37.35; $p < 0.001$), attention ($F(3,86)$ = 9.05; $p < 0.001$), fluency ($F(3,86)$ = 13.87; $p < 0.001$), language ($F(3,86)$ = 7.90; $p < 0.001$) and visuospatial skills ($F(3,86)$ = 11.15; $p < 0.001$) showed strong differences across the groups (**Figure 1A**). Results of the pairwise post-hoc comparisons are given in **Figure 1B**. The cognitively frail group performed similarly to the MCI group across all cognitive tests, except for the fluency subscale, where their scores were significantly lower than the MCI group ($p < 0.001$). All four groups performed above chance level on the training test. The scores were significantly different across groups ($F(3,86)$ = 5.60; p = 0.001). Post-hoc comparisons showed that the controls performed significantly better than the MCI (p = 0.015) and Alzheimer's disease (p = 0.006) groups. There were no significant differences between the training scores of the cognitively frail group and other groups.

Grey matter atrophy

Mean hippocampal GMV, entorhinal GMV, total GMV and total intracranial volume (TIV) were compared across the groups, corrected for age and TIV using ANCOVA. There were no significant differences between groups for TIV or total GMV. However, hippocampal ($F(3,86)$ = 10.35; $p < 0.001$) and entorhinal ($F(3,86)$ = 7.62; $p < 0.001$) GMVs showed a main group effect (**Figure 2A-B**). The hippocampal GMV in the control group was significantly larger compared to the MCI ($p < 0.001$) and Alzheimer's disease groups ($p < 0.001$). Similarly, the entorhinal GMV of the control group was larger compared to the MCI (p = 0.001) and Alzheimer's disease groups (p = 0.003). The hippocampal and entorhinal volumes of the cognitively frail group was similar to the control group.

Atrophy was tested at the voxel level, using VBM (**Table 2**). As expected, the control group had significantly higher GMV in bilateral temporal cortices and hippocampi compared to the MCI and AD. We found a similar pattern comparing cognitively frail group to MCI and Alzheimer's disease group, although cluster extents were smaller (**Figure 2D-E**). In order to confirm that the differences we observe in the neurophysiological responses could be due to local GM atrophy of the lateral frontotemporal areas, we tested the GMV of the lateral frontotemporal areas bilaterally (i.e. IFG, STG, HG), and report that the GMVs of the superficial areas do not differ across groups (**Extended data, Figure 2-1**).

Cross-modal mismatch responses

Figure 3A-D displays the gradiometer topoplots for each condition in 100 ms time windows across the groups. Following N100, topoplots show a strong burst of bilateral activity in frontal and temporal sensors that is sustained until the end of the epoch. Note that compared to the associative deviant and standard, novelty deviant induced a stronger and more widespread activity across the frontotemporal sensors. The gradiometer topoplots are given here for visualisation only; statistical comparisons were made in the a priori source space ROIs.

We tested the time series of each deviant with respect to the standard, within the 6 ROIs (**Table 3, Figure 3E**). We found strongest effects for the novelty deviant in the bilateral IFG early in the epoch, following the onset of the sound. The effects seen in the cognitively frail group mirrored the controls. Further, novelty deviant effects were found across all the ROIs in the control group.

MCI and Alzheimer's disease groups showed no significant novelty effects in the IFG, and weaker clusters limited to STG and HG. Associative deviant effects were found in the IFG across all groups, and in overlapping time windows starting around 200 ms after the sound onset.

We tested for the interaction effects between the deviant responses (i.e. STD-DA, and STD-DN) and group. There was no significant interaction between the control and cognitively frail group or between MCI and Alzheimer's disease groups. However, the control group showed stronger associative and novelty deviant responses compared to both MCI and Alzheimer's disease groups. Similarly, cognitively frail group showed the same interaction effects against the MCI and Alzheimer's disease groups. As a confirmatory analysis, we also repeated these GLMs with log-transformed squared RMS time series to ensure that the normality assumption is met. These results can be found in the Extended data, Table 3-1.

Clinical and structural correlates of the cross-modal mismatch

To assess how the deviant responses relate to clinical severity, education and medial temporal lobe atrophy, the linear relationships between the E/MEG contrast means at 200-500 ms and each predictor variable were tested using general linear models (**Figure 4A**) whilst controlling for differences in age. This revealed strong relationships between the novelty deviant mean in the LHG and RHG with ACER total and ACER-memory subscale scores: the higher the scores on cognitive tests, the more negative (towards normal) the novelty deviant was. A strong negative relationship between the hippocampal and entorhinal volumes and the deviant response was observed for the left hemisphere ROIs, particularly the LHG. This suggests that medial temporal

atrophy is associated with a reduced deviant response even though the MMN response arises from extra-hippocampal auditory cortex. This negative relationship was stronger for the novelty deviant compared to the associative deviant. Education showed moderate positive relationships with the associative deviant in the LSTG and RSTG, whereas it showed a negative relationship with the novelty deviant mean in RIFG.

We calculated the partial correlations amongst predictor variables correcting for differences in age. Education showed positive correlations with ACER total ($r = 0.40$; $p < 0.001$) and ACER memory subscale scores ($r = 0.35$; $p = 0.001$), but did not correlate with hippocampal and entorhinal volumes. ACER total score correlated with both hippocampal ($r = 0.53$; $p < 0.001$) and entorhinal GMV ($r = 0.40$; $p < 0.001$). Similarly, ACER memory subscale score positively correlated with hippocampal ($r = 0.55$; $p < 0.001$) and entorhinal GMV ($r = 0.41$; $p < 0.001$).

Discussion

The principal result of this study is that community-dwelling cognitively frail individuals do not resemble people with MCI or Alzheimer's disease, in terms of their structural or neurophysiological profile, despite similar levels of underperformance on cognitive screening tests. The poor cognitive performance of the cognitively frail participants should not simply be interpreted arising from latent Alzheimer pathology or undiagnosed amnestic MCI. Population screening using standard cognitive tests (e.g. MMSE, or ACER) is therefore unlikely to selectively identify those with latent Alzheimer's disease pathology without additional biomarker evidence of pathology. There are other associations of cognitive impairment, including lower educational level, hearing impairment, and cardiovascular risk factors. Both structural and neurophysiological features of the cognitively frail group were similar to controls. Structural analyses revealed a higher GMV in the latero-medial temporal cortices bilaterally in the control and cognitively frail compared to MCI and Alzheimer's disease groups. Like the controls, the cognitively frail showed

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stronger associative and novelty deviant responses compared to MCI or Alzheimer's disease in relation to hippocampal and entorhinal volumes.

The cross-modal oddball task was designed to induce deviant responses from the superficial frontotemporal cortex, as neurophysiological markers of hippocampal-dependent associative learning. Alzheimer's patients show impairments in both sensory and associative memory, reduced medial temporal lobe activity to novelty (Sperling et al., 2003; Dickerson et al., 2005), and reduced electrophysiological response to oddballs (Engeland et al., 2002; Lee et al., 2013; Ruzzoli et al., 2016). We confirmed that Alzheimer's patients show reduced novelty and associative deviant responses. Neurophysiological profiles of the control and cognitively frail overlapped, and were significantly stronger compared to MCI and Alzheimer's disease groups. Task effects of the novelty deviant responses were observed across all regions of interest for the control and cognitively frail. The group-task interaction effects showing stronger associative and novelty deviant responses for the controls and cognitively frail were located in right Heschl's, bilateral superior temporal and inferior frontal gyri. In other words, the neuropsychologically impaired cognitively frail group does not show the neurophysiological signatures of early Alzheimer's disease. From a theoretical perspective, it is interesting to note that the response associated with associative deviants was weaker than novelty deviants, and did not differ qualitatively in terms of timing or distribution across our ROIs. We had expected the associative deviant response to be more hippocampal-dependent, and hence more impaired with Alzheimer's pathology, but our current analyses suggest it was qualitatively similar to the more typical novelty deviant response.

To explore the differences between the community-based cognitively frail and Alzheimer's disease or MCI, we tested volumetric differences in medial temporal lobe. Structurally, early Alzheimer's disease is characterised by atrophy in the medial temporal lobe as a function of tau burden (Braak et al., 2006; Schwarz et al., 2016). Recent studies of cognitive frailty have suggested frontotemporal and subcortical atrophy (Del Brutto et al., 2017; Gallucci et al., 2018), increased white matter hyperintensities (Avila-Funes et al., 2017; Del Brutto et al., 2017; Sugimoto et al., 2019), and decreased white matter microstructure integrity (Avila-Funes et al., 2017). We did not find structural differences between the control and cognitively frail in medial temporal lobe structures. The community-based groups showed significantly larger hippocampus and entorhinal volumes compared to patients with MCI and Alzheimer's disease, and did not show early structural signatures of Alzheimer's disease. The difference between our study and the previous work may lie in the epidemiological approach to baseline recruitment through the Cam-CAN 3000 cohort, rather than clinical referral pathways.

The neuropsychological profile of the cognitively frail resembled MCI group. They scored lower than the healthy controls on every ACER subscale. Compared to the MCI patients, they were more impaired on fluency, which might indicate an underlying executive deficit. Previous studies have suggested that the neuropsychological profile of cognitive frailty differs from MCI in episodic memory with domains of language, visuospatial skills and executive function relatively spared (Collie and Maruff, 2000). The cognitive impairment profile in frail adults has been described in terms of deficits in executive function and attention. Frail adults tend to not use cues effectively to retrieve stored information (Canevelli et al., 2015; Delrieu et al., 2016); have slower reaction times (O'Halloran et al., 2014; Robertson et al., 2014), show lower meta-cognitive awareness, and error monitoring (Amanzio et al., 2017).

However, many previous studies have focused on cognitive impairment in the context of physical frailty, rather than defining cognitive frailty in terms of poor cognitive function in a non-clinical community-dwelling cohort. The cognitive underperformance of our cognitively frail, might partly be attributed to their shorter education, coupled with a bias in most cognitive tests towards the

better educated (Huppert et al., 2005). That is, highly educated individuals perform better on cognitive tests like MMSE and ACER, unless scores are normalised by education (Crane et al., 2006; Mathuranath et al., 2007; Amaral-Carvalho and Caramelli, 2012).

Our findings support the hypothesis that cognitive frailty represents part of the spectrum of normal neurocognitive function, rather than incipient Alzheimer's disease. This conclusion calls for a re-evaluation of the prior findings that associate cognitive frailty with higher incidence of dementia and faster cognitive decline (Buchman et al., 2007; Kojima et al., 2016; Shimada et al., 2018). These former studies have quantified the dementia incidence including all subtypes of dementia, however this association was highest in non-Alzheimer's dementias, particularly for vascular dementia (Panza et al., 2006; Avila-Funes et al., 2012; Gray et al., 2013; Aguilar-Navarro et al., 2016; Solfrizzi et al., 2017a). Although the link between cognitive frailty and Alzheimer's disease in previous studies is not conclusive, the two entities might share common risk factors such as cardiovascular disease (Panza et al., 2006; Frisoli et al., 2015; Fuhrmann et al., 2019) and hearing impairment (Valentijn et al., 2005; Panza et al., 2015).

In addition to the cardiovascular risk factors (Newman et al., 2001; Patrick et al., 2002; Fuhrmann et al., 2019), the cognitive underperformance of our cognitively frail group could be a result of cumulative effects of multiple psychosocial and medical risk factors. Malnutrition (Mulero et al., 2011; Chye et al., 2018; Rietman et al., 2018), social isolation (Robertson et al., 2013), sedentary lifestyle (Landi et al., 2010), lack of intellectual cognitive activities (Jung et al., 2010), psychiatric illnesses and long term use of antidepressants (Paulson and Lichtenberg, 2013; Gray et al., 2015), chronic inflammation (Weaver et al., 2002; Solfrizzi et al., 2017b) and lower education levels (Rogers et al., 2017) are known risk factors affecting healthy ageing. Here, the cognitively frail group had significantly lower education levels, compared to the controls and MCI. This is a common pattern observed in other frailty studies (Brigola et al., 2019; Margioti et al., 2020). The cognitively frail population have significantly lower occurrence of third-level education (Robertson et al., 2014), and are twice as likely to have no educational qualifications (Rogers et al., 2017). Further, strong association between educational level and frailty was linked to mediating socioeconomic, behavioural, and psychosocial factors such as low income, chronic diseases, obesity, depression, unhealthy lifestyle, and chronic stress (Hoogendijk et al., 2014). This is consistent with the cognitive reserve hypothesis that an individual's prior education and cognitive abilities modify the resilience of brain structure to disease and injury (Stern, 2002). Longer education in early life and continuing diverse cognitive leisure activities in midlife and old age contribute to an individual's cognitive reserve, is related to better cognitive functioning in old age (Singh-Manoux et al., 2011; Borgeest et al., 2018; Lavrencic et al., 2018; Brigola et al., 2019) and having fewer symptoms of cognitive decline and neuropathology (Mortimer et al., 2003; Chapko et al., 2018).

The study has several limitations. Due to the cross-sectional design of the study we are unable to quantify the rates of progression or conversion to dementia from cognitive frailty. Longitudinal cognitive and neuroimaging studies would be useful to confirm the rate of conversion to Alzheimer's disease or other dementia, and potential mediators of conversion. Further, this study did not incorporate Alzheimer's disease biomarkers and instead used clinical criteria and neuropsychological criteria to define the groups. The cognitively frail group was defined using a standard threshold on ACER and MMSE. Future studies investigating the link between cognitive frailty and Alzheimer's disease may test for biomarkers of Alzheimer's such as tau and amyloid-beta measures acquired from blood, cerebrospinal fluid or positron emission tomography. Future studies may also assess the polygenic risk for Alzheimer's disease using common (e.g. APOE) and rare variants associated with the disease, which would help disentangle environmental and psychosocial risk factors from genetic risk factors contributing to cognitive frailty's aetiology.

Further work is needed to clarify genetic and pathology-based features of cognitive frailty in relation to Alzheimer's disease and other dementias.

Our findings provide new evidence that community-dwelling cognitively frail older adults are neurophysiologically and structurally similar to those with more successful cognitive ageing, without the structural or neurophysiological features of MCI or Alzheimer's disease, despite similarly poor cognitive function to MCI. Their underperformance on cognitive tests may be due to lower cognitive reserve and other risk factors across the lifespan.

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Figures and captions

Figure 1. A. The radar chart displays the group means for the neuropsychological tests converted to percentages against the maximum score in each test for ease of comparison across groups. Note that the performance of the cognitively frail group overlaps with the MCI across all tests except for ACER fluency. **B.** Group differences in education levels and neuropsychological tests. The cognitively frail group had lower education levels than the controls. On the neuropsychological tests, the cognitively frail performed similar to the MCI group. **C.** Example stimuli from the cross-modal oddball task. The images were presented together with paired sounds after the 300 ms lag. Participants were asked to press the button whenever they saw a red circle around the image. MCI: Symptomatic mild cognitive impairment after secondary/tertiary memory clinic assessment.
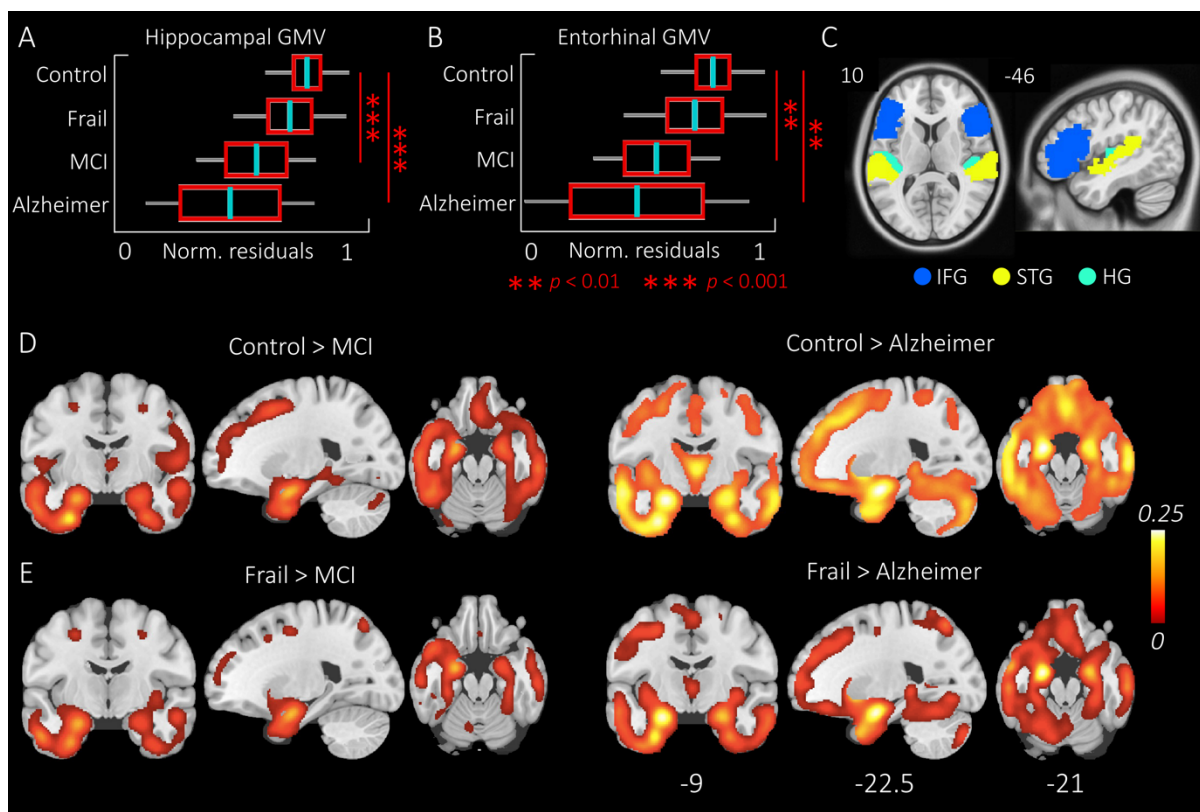
Figure 2. A-B. GMV differences across groups in the hippocampus and entorhinal cortex. The boxplots display the normalised residuals after correcting for differences in age and total intracranial volume (TIV). There were no significant differences in volume between the cognitively frail and the control group. **C.** 6 ROIs used in the RMS analysis. ROIs comprise inferior frontal gyri (IFG), superior temporal gyri (STG) and Heschl's gyri (HG) bilaterally. **D-E.** The contrast images from the VBM analysis. Control and the cognitively frail show similar patterns of grey matter volume compared to the MCI and Alzheimer's disease groups. See the Extended data for the grey matter volume analysis of the lateral frontotemporal ROIs used in the RMS analysis (**Figure 2-1**). MCI: Symptomatic mild cognitive impairment after secondary/tertiary memory clinic assessment.
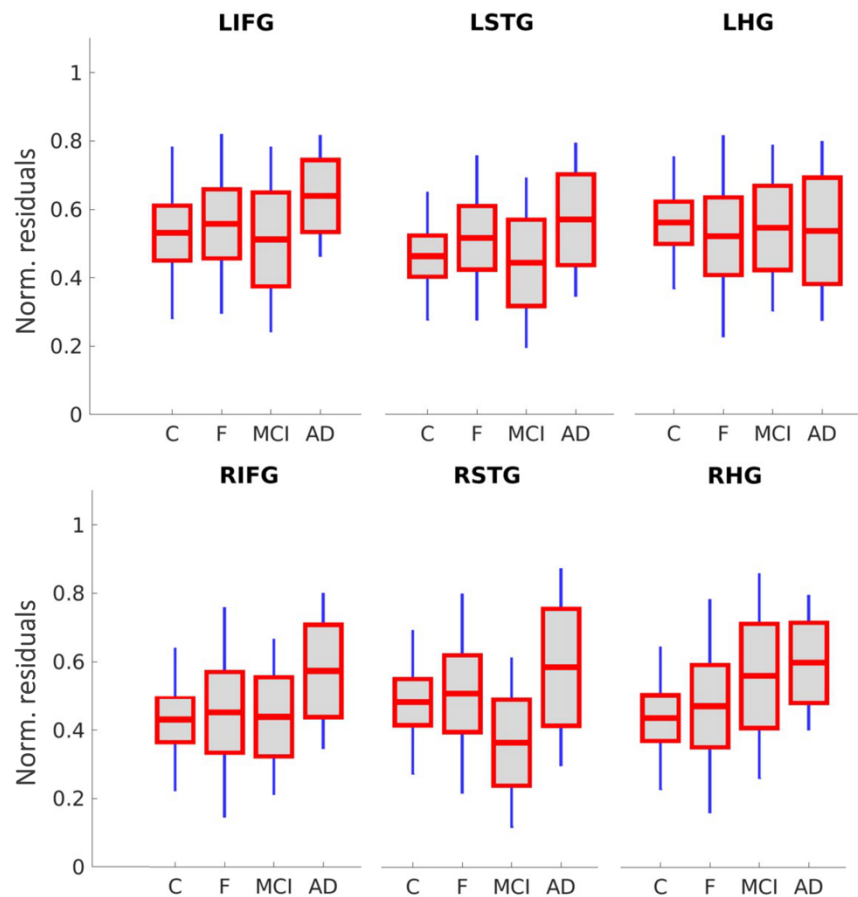
Figure 2-1: Grey matter volume analysis of the lateral frontotemporal network. In Alzheimer's disease. atrophy of the auditory cortex comes at the later isocortical Braak stages (ie V-VI) along with other neocortical areas such as the frontal cortex. Therefore, in the early stages of Alzheimer's disease, the integrity of the auditory cortex is not expected to be compromised, and consequently, diminished deviant responses observed in our clinical population are not expected be attributed to the atrophied auditory cortex. To provide support for this claim, we performed the confirmatory grey matter volume comparisons across the four groups within the lateral frontotemporal ROIs which were used to extract neurophysiological signals from. We performed ANCOVAs to test for group differences whilst accounting for differences in age and TIV. As expected there were no significant effect of the group in any of the six ROIs, confirming that the differences we find in the deviant responses could not be attributed to local GM atrophy. *C: Controls; F: Cognitively frail; MCI: Mild cognitive impairment; AD: Alzheimer's disease.*
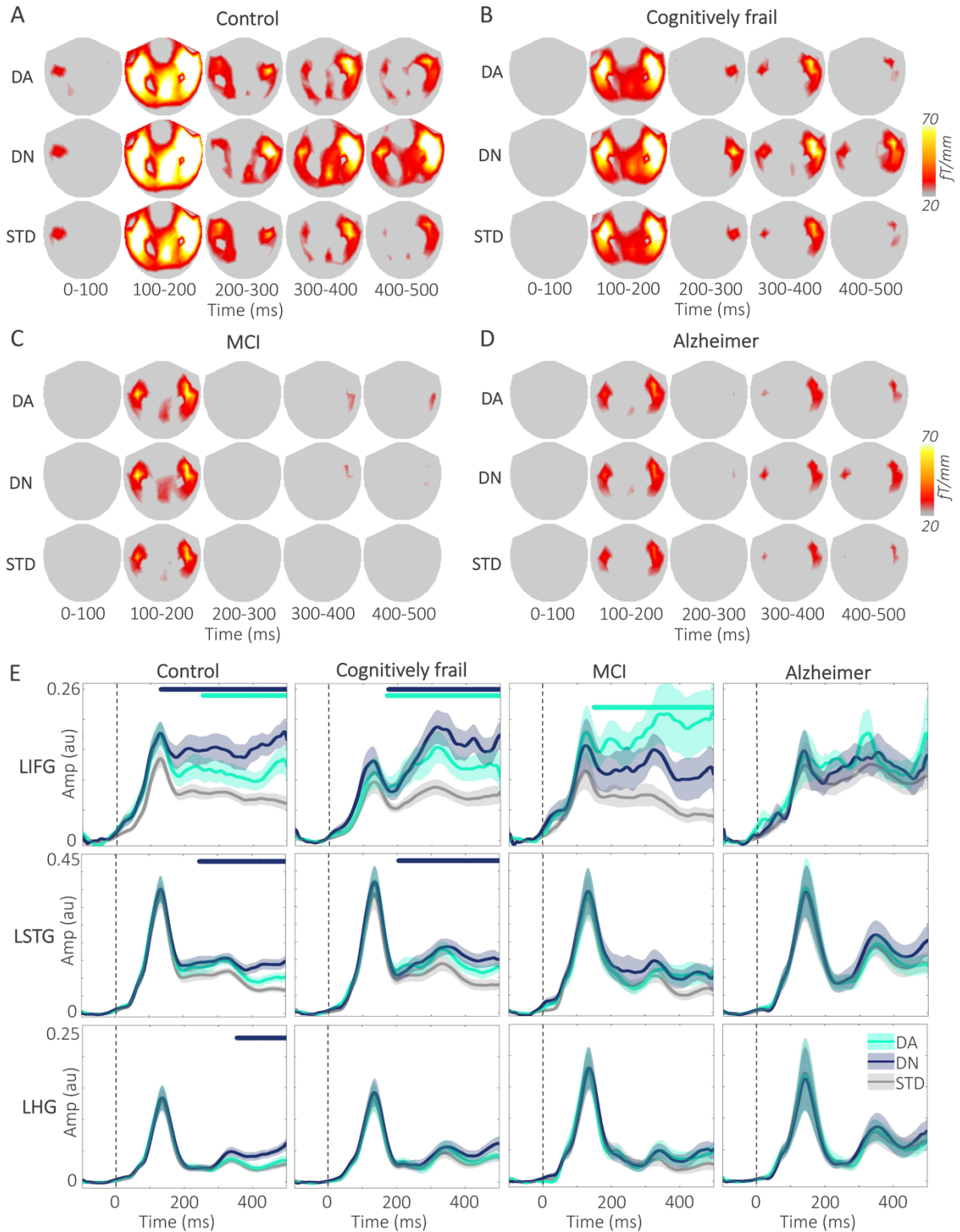
Figure 3. **Associative and novelty deviant responses by group**. **A-D.** Topoplots show the mean gradiometer activity across the scalp for the DA, DN and STD conditions in 100 ms time windows in four groups. Note that the DN amplitude is higher after the N100 peak, compared to both DA and STD conditions in control and cognitively frail groups. The gradiometer activity in the MCI and Alzheimer's disease groups are weaker compared to the control and cognitively frail groups. **E.** Plots display the RMS time series for the left hemisphere ROIs for simplicity. Dashed vertical lines mark the sound onset. Note that the amplitude differences between the deviants and the standard in the frontal regions were larger than the temporal regions, and the deviant effects are stronger in the control and cognitively frail groups; and that there is considerably higher variance in

the MCI group. See the Extended data for the renderings of the source activity (**Figure 3-1**). *Amp: Amplitude; AU: Arbitrary units; DA: Associative deviant; DN: Novelty deviant; fT: Femtotesla; LHG: Left Heschl's gyrus; LIFG: Left inferior frontal gyrus; LSTG: Left superior temporal gyrus; STD: Standard.*
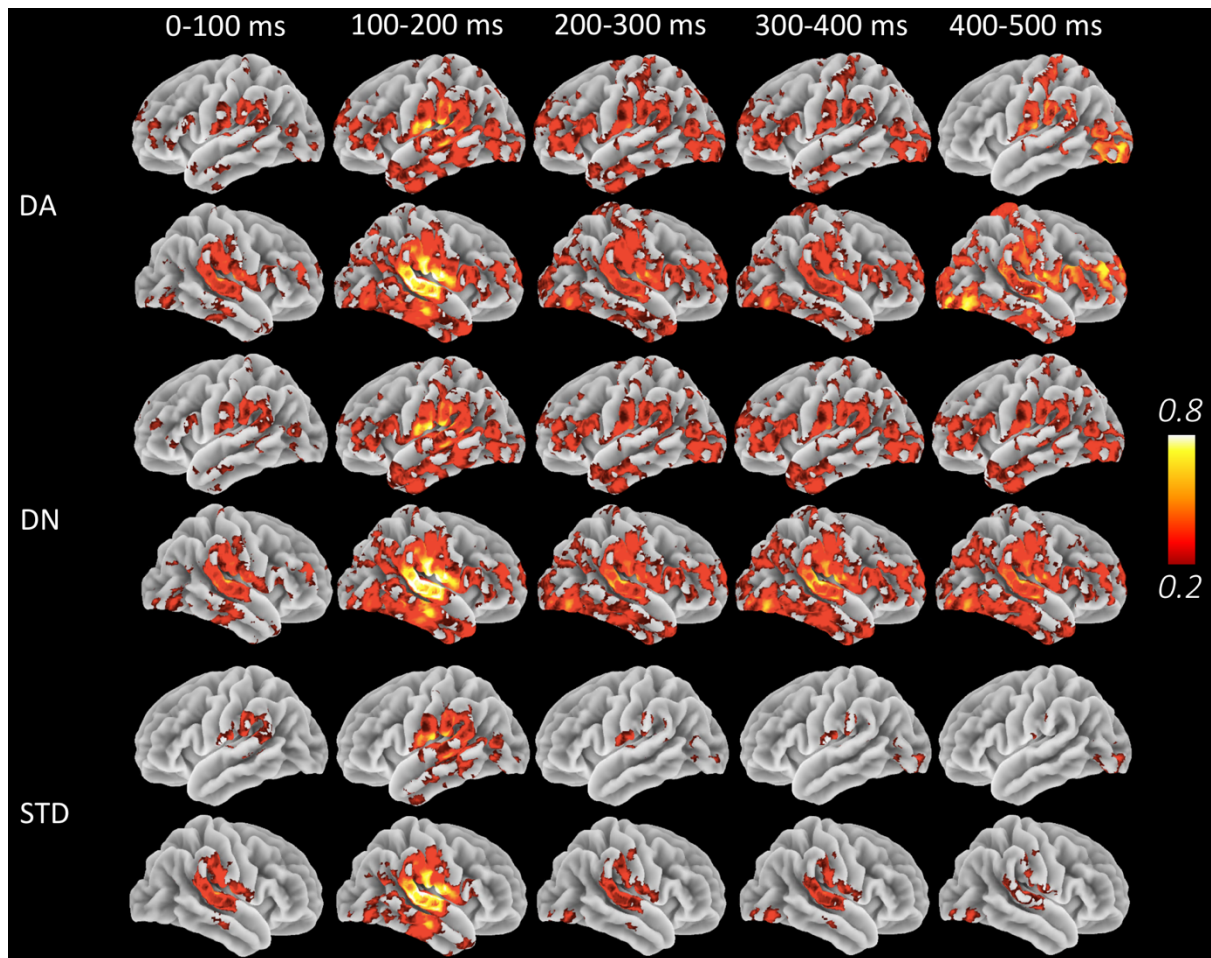
Figure 3-1: Source activity: The renderings display mean source activity in 100 ms moving time windows in the Control group. In line with the topoplots activity and our RMS findings, here we find the activation of a bilateral frontotemporal network peaking at 100 ms. Further compared to the standard condition, deviant conditions show stronger and more widespread activity in the frontotemporal regions 200 ms after the sound onset. *DA: Associative deviant; DN: Novelty deviant: STD: Standard.*
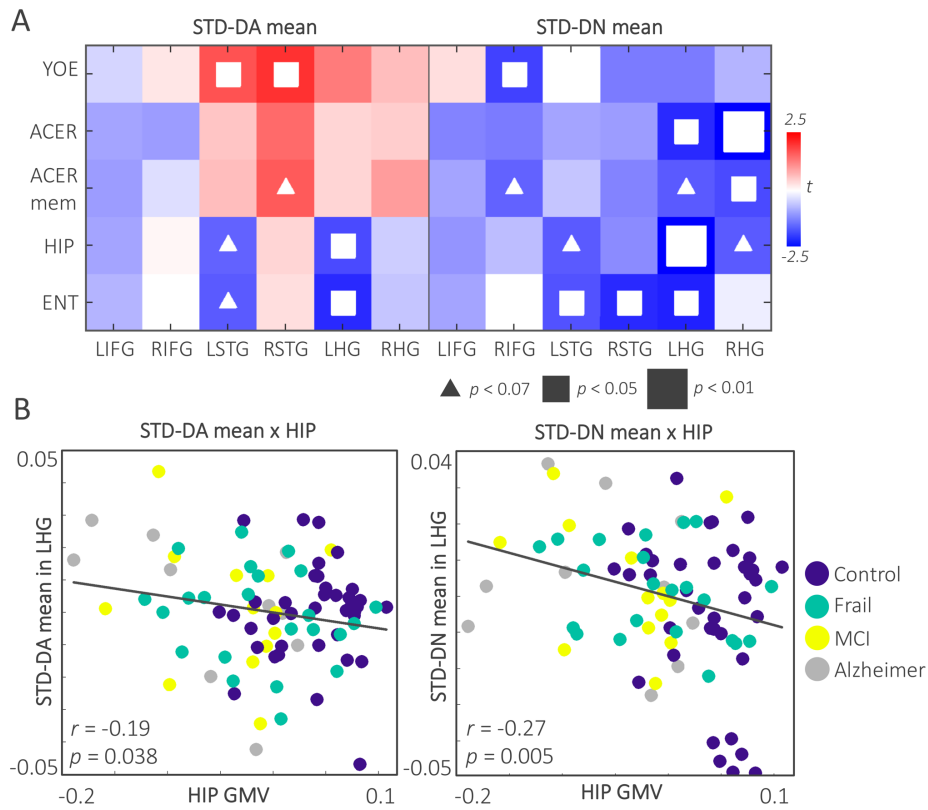
Figure 4. Neurophysiological responses are related to clinical and volumetric differences between individuals. **A.** The t-map displays the general linear model results across predictors and associative and novelty deviant mean responses for each region of interest (ROI). The white squares indicate significant effects. Note that the effects are stronger for the LHG across the ROIs, and for the novelty deviant compared to the associative deviant. **B.** The scatterplots display the negative relationship between the associative and novelty deviant means in the LHG with the hippocampal GMV across the sample. *ACER: Addenbrooke's Cognitive Examination Revised; ACER mem: ACER memory subscale; ENT: Entorhinal grey matter volume; GMV: Grey matter volume; HIP: Hippocampal grey matter volume; LHG: L Heschl's gyrus; LIFG: L inferior frontal gyrus; LSTG: L superior temporal gyrus; RHG: R Heschl's gyrus; RSTG: R superior temporal gyrus; RIFG: R inferior temporal gyrus; YOE: Years of education.*

Tables

Table 1. Demographic and cognitive screening results for the four study populations.

	Controls	Cognitive frail	MCI	Alzheimer
Group size (Female)	38 (17 F)	26 (14 F)	15 (4 F)	11 (6 F)
Age (years)	72.19 ± 8.88	79.98 ± 9.50	75.54 ± 7.60	74.53 ± 11.17
Education (years)	14.97 ± 3.86	11.07 ± 2.88	16.68 ± 4.99	11.55 ± 3.54
Hearing left (dB)	51.92 ± 13.32	44.15 ± 16.06	52.88 ± 14.77	54.80 ± 10.01
Hearing right (dB)	53.55 ± 12.44	43.38 ± 16.35	57.63 ± 9.40	50.00 ± 12.01
MMSE (/30)	28.34 ± 1.47	26.07 ± 2.28	26.37 ± 2.73	23.20 ± 2.78
ACE-R (/100)	93.71 ± 3.04	80.92 ± 6.01	83.68 ± 8.41	68.6 ± 8.11
ACE-R memory (/26)	23.63 ± 1.94	18.38 ± 3.69	16.81 ± 6.09	10.7 ± 3.43
Training test (/100)	65.78 ± 23.55	50.96 ± 20.59	44.16 ± 24.02	37.50 ± 27.95

MCI: Symptomatic mild cognitive impairment after secondary/tertiary memory clinic assessment; ACE-R: Revised Addenbrooke's Cognitive Examination; MMSE: Mini Mental State Examination. See Figure 2B for comparisons between groups.

Table 2. Voxel based morphometry of volume differences between groups. Columns in the table indicate the peak cluster, coordinates of the peak in mm, the extent of the cluster, the cluster mass and corrected p-value for the cluster respectively.

Test	Cluster peak	x, y, z (mm)	Cluster extent	k	p_{FWE}
Control>MCI	R middle temporal	58, -39, 3	R superior temporal, R inferior temporal, R hippocampus, R parahippocampal, R fusiform	26826	< 0.001
	L middle temporal	-52, -54, 12	L fusiform, L inferior, L hippocampus, L parahippocampal	24165	< 0.001
	L middle frontal	-21, 41, 30	L superior frontal	2063	0.004
	L precentral	-40, 6, 36	L inferior frontal	1407	0.020
Control>Alzheimer	R hippocampus	28, -13, -11	L/R parahippocampal, L fusiform, L/R putamen, L caudate, L superior frontal, L hippocampus, L insula, L medial frontal	55790	< 0.001
	L middle temporal	-57, -16, -9	L inferior temporal, L middle temporal	7744	< 0.001
	R middle temporal	64, -12, -20	R inferior temporal	4539	< 0.001
	L postcentral	-50, -18, 34	L inferior parietal	1258	0.028
Cognitively frail>MCI	L inferior temporal	-34, 5, -35	L hippocampus, L parahippocampal, L middle temporal, L fusiform	7546	< 0.001
	R inferior temporal	54, -19, -17	R middle temporal, R hippocampus, R fusiform	2070	0.004
Cognitively frail>Alzheimer	L hippocampus	-22, -13, -14	L parahippocampal, L fusiform, L inferior temporal	3723	< 0.001

k: Cluster mass; p_{FWE}: p-value corrected for family-wise error rate. MCI=symptomatic mild cognitive impairment after secondary/tertiary memory clinic assessment

Table 3. Regional differences in the response to novelty deviants (DN) and associative deviants (DA) compared to standard trials.

Contrast	ROI	Group	k	p_{cor}	Time (ms)
STD-DN	LIFG	Control	-1478.03	< 0.001	31-500
		Frail	-938.79	< 0.001	175-500
	RIFG	Control	-1631.81	< 0.001	1-500
	LSTG	Control	-715.93	0.002	255-500
		Frail	-449.99	0.021	331-500
	RSTG	Control	-1068.44	0.003	172-500
		Frail	-870.95	0.003	197-500
		Alzheimer	-279.53	0.041	391-500
	LHG	Controls	-348.23	0.034	355-500
	RHG	Controls	-464.34	0.021	305-500
		Frail	-253.10	0.046	380-500
		MCI	-261.62	0.041	350-470
STD-DA	LIFG	Control	-480.41	0.023	254-500
		Frail	-680.74	0.014	171-497
		MCI	-974.42	0.004	150-500
	RIFG	Control	-944.45	< 0.001	192-500
		Frail	-561.03	0.013	188-458
		Alzheimer	-929.57	0.003	162-500

*DA: Associative deviant; DN: Novelty deviant; k: Cluster mass; LHG: L Heschl's gyrus; LIFG: L inferior frontal gyrus; LSTG: L superior temporal gyrus; p_{cor}: Corrected p-value; RHG: R Heschl's gyrus; RIFG: R inferior frontal gyrus; ROI: Regions of interest; RSTG: R superior temporal gyrus; STD: Standard. See the Extended data for the log transformed version of this analysis. (**Table 3-1**).*

Table 3-1. Regional differences in the response to novelty deviants (DN) and associative deviants (DA) compared to standard trials. In this version of the analysis, we performed the statistical comparisons on the log transformed squared RMS time series, to ensure the normality assumption of the GLMs is met. The results of the RMS and log transformed RMS time series largely overlap. However in the latter analysis task-group interaction effects do not reach statistical significance. *k: Cluster mass; p_{cor}: Cluster corrected p-value.*

Contrast	ROI	Group	k	p_{cor}	Time
STD-DN	LIFG	Control	-497.43	0.004	167-252
			-595.04	0.002	362-500
		Frail	-774,96	0.002	262-500
	RIFG	Control	-204.22	0.027	23-90
			-134.42	0.051	165-222
			-594.2	0.004	343-500
	LSTG	Control	-433.04	0.006	381-500
		Frail	-177.85	0.045	352-428
			-206.56	0.037	430-500
	RSTG	Control	-275.66	0.022	175-274
			-631.41	0.002	295-500
		Frail	-274.8	0.018	260-380
			-391.41	0.004	382-500
		Alzheimer	-182.9	0.041	438-500
	LHG	Controls	-273.65	0.024	388-500
	RHG	Controls	-336.9	0.01	329-487
		Frail	-138.69	0.043	1-48
STD-DA	LIFG	MCI	-508.9	0.002	214-411
			-155.91	0.047	454-500
	RIFG	Control	-267.28	0.014	211-315
		Frail	-346.16	0.018	305-447
		Alzheimer	-775.37	0.008	177-500