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Causal evidence for the multiple demand network in change detection: auditory mismatch magnetoencephalography across focal neurodegenerative diseases.

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1 **Title:** Causal evidence for the multiple demand network in change detection: auditory mismatch
 2 magnetoencephalography across focal neurodegenerative diseases.

3

4 **Abbreviated title:** Fronto-parietal cortex supports change detection

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Keywords (10)

Multiple demand, Mismatch negativity (MMN), MRI, MEG, Dynamic Causal Modelling (DCM), Dementia, nvPPA, bvFTD, PCA, Alzheimer's disease.

Highlights (4)

- 1) Causal evidence for a top-down role of the multiple demand network in perception.
- 2) A common mechanism for impaired change detection across dementia syndromes.
- 3) Parietal and frontal nodes are necessary to explain mismatch negativity (MMN).

- 58 4) Convergent structure-function mapping, DCM and functional connectivity analyses.

59 **Abstract**

60 The multiple demand system is a network of fronto-parietal brain regions active during the
61 organisation and control of diverse cognitive operations. It has been argued that this activation may be
62 a non-specific signal of task difficulty. However, here we provide convergent evidence for a causal
63 role for the multiple demand network in the ‘simple task’ of automatic auditory change detection,
64 through the impairment of top-down control mechanisms. We employ independent structure-function
65 mapping, dynamic causal modelling, and frequency-resolved functional connectivity analyses of MRI
66 and MEG from 75 mixed-sex human patients across four neurodegenerative syndromes (bvFTD,
67 nvPPA, PCA and AD-MCI) and 48 age-matched controls. We show that atrophy of any multiple
68 demand node is sufficient to impair auditory neurophysiological response to change in frequency,
69 location, intensity, continuity or duration. There was no similar association with atrophy of the
70 cingulo-opercular, salience or language networks, or with global atrophy. Multiple demand regions
71 displayed increased functional but decreased effective connectivity as a function of
72 neurodegeneration, suggesting ineffective compensation. Overall, we show that damage to any of the
73 nodes of the multiple demand network is sufficient to impair top-down control of sensation, providing
74 a common mechanism for impaired change detection across dementia syndromes.

75 **Significance Statement**

76 Previous evidence for fronto-parietal networks controlling perception is largely associative and may
77 be confounded by task difficulty. Here we use a pre-attentive measure of automatic auditory change
78 detection (MMN magnetoencephalography) to show that neurodegeneration in any frontal or parietal
79 multiple demand node impairs primary auditory cortex neurophysiological response to change
80 through top-down mechanisms. This explains why the impaired ability to respond to change is a core
81 feature across dementias, and other conditions driven by brain network dysfunction, such as
82 schizophrenia. It validates theoretical frameworks in which neurodegenerating networks upregulate
83 connectivity as partially effective compensation. The significance extends beyond network science
84 and dementia, in its construct validation of dynamic causal modelling, and human confirmation of
85 frequency-resolved analyses of animal neurodegeneration models.

86 **Introduction**

87 The multiple demand (MD) system is a network of brain regions engaged in flexible organisation and
 88 control of cognitive operations across diverse mental activities (Duncan, 2010; Duncan et al., 2020).
 89 MD robustly comprises domain general regions in middle frontal gyrus, inferior frontal sulcus,
 90 anterior insula and intraparietal sulcus, as well as supplementary motor area and anterior cingulate
 91 cortex (Fedorenko et al., 2013). Within the complex taxonomy of functional brain networks (Uddin et
 92 al., 2019), this lateral and ventral fronto-parietal network has been variously named for its role in
 93 control (Dosenbach et al., 2008; Vincent et al., 2008) and executive function (Seeley et al., 2007;
 94 Niendam et al., 2012), is associated with both fluid intelligence and spatial working memory (Assem
 95 et al., 2020b), and has been implicated in executive abnormalities in logopenic Alzheimer's disease
 96 (Ramanan et al., 2020). MD encompasses nodes that are modulated by alterations in behaviourally
 97 relevant stimuli (Desimone and Duncan, 1995; Corbetta and Shulman, 2002; Macaluso and Driver,
 98 2005), and overlaps with frontal and parietal regions sometimes included in the ventral attention
 99 network (Corbetta et al., 2008; Macaluso, 2010), but is distinct from the cingulo-opercular and
 100 salience networks (Power et al., 2011; Assem et al., 2020a; Dworetsky et al., 2021). MD can be
 101 activated by simple tasks (Crittenden and Duncan, 2014), but increases in activity with task
 102 complexity (Wen et al., 2018) and the difficulty of stimulus discrimination (Woolgar et al., 2011). It is
 103 especially engaged in tasks with high attentional demand (Jung et al., 2021), but it is also visible in
 104 resting state functional connectivity patterns (Smith et al., 2009; Power et al., 2011; Gordon et al.,
 105 2017; Dworetsky et al., 2021). While the activation of this domain-general cognitive core is well
 106 established and precisely delineated (Assem et al., 2020a) some argue that this is a non-specific signal
 107 of task difficulty, rather than playing a direct processing role (Diachek et al., 2020).

108 Here we go beyond this associative evidence, and test whether the MD network plays a causal role in
 109 automatic sensory change detection, when there is no required response, explicit decision, or
 110 attentional demand, through top-down hierarchical influences on auditory brain regions. To do this,
 111 we recorded magnetoencephalography (MEG) during an auditory mismatch (MMN) paradigm from
 112 75 patients across four neurodegenerative syndromes, and 48 age-matched controls. We provide

113 causal evidence by examining the differential effects of chronic network perturbations due to
114 neurodegeneration in separable network nodes (Wolff and Ölveczky, 2018). The graded nature of
115 neurodegenerative disease allows us to do this parametrically, providing information about the
116 function of impaired nodes that would be impossible to observe if they were completely lesioned, for
117 example from stroke. We first demonstrate with structure-function mapping that damage to MD
118 nodes, but not other core cognitive networks, reduces the neurophysiological response to auditory
119 change. We then characterise the nature of the effective connectivity disruption with dynamic causal
120 modelling of the evoked response, which reveals the consequences of damage, and the partially
121 effective compensation from other nodes. Finally, we demonstrate with independent functional
122 connectivity analyses of the induced response that the frequency specificity of compensatory
123 upregulation is in-keeping with animal models and previous human evidence, providing concurrent
124 criterion and construct validity for the dynamic causal modelling. Together, these analyses
125 demonstrate causality by showing that frontal, parietal and auditory regions are functionally and
126 effectively connected during automatic sensory change detection, and that damage to frontal or
127 parietal regions specifically reduces the neurophysiological response to change by altering network
128 dynamics.

Methods

Participants

Seventy-five patients with neurodegenerative syndromes were recruited according to consensus clinical criteria (Table 1). These comprised 23 patients with behavioural variant fronto-temporal dementia (bvFTD) (Rascovsky et al., 2011), 10 patients with non-fluent variant Primary Progressive Aphasia (nfvPPA) (Gorno-Tempini et al., 2011), and 15 patients with Posterior Cortical Atrophy (PCA) (Crutch et al., 2017). Each of these patients with focal degeneration was individually matched to a healthy control of the same age and gender, from the volunteer panel of the MRC Cognition and Brain Sciences Unit, or the population-based Cambridge Centre for Ageing and Neuroscience study (Shafto et al., 2014). A fourth group with early Alzheimer's disease pathology (AD) was recruited to assess the general applicability and specificity of our results in the context of more diffuse pathology. 12 patients with AD (McKhann et al., 2011) and 15 with amnesic mild cognitive impairment (MCI) and a positive amyloid PET scan (Klunk et al., 2004; Dubois et al., 2016) were included. Seven patients with amnesic MCI were recruited but had a negative amyloid PET scans and were not analysed.

All participants underwent neuropsychological assessment with the revised Addenbrooke's cognitive examination (ACE-r) (Mioshi et al., 2006) and the mini mental state examination (MMSE). They had a standardised T1 structural MRI scan at 3T within two months of their MEG session.

	All focal patients	Healthy controls	bvFTD	nfvPPA	PCA	ADMCI
N	48	48	23	10	15	27
Age	63.6 ± 7.99	63.6 ± 8.19	61.8 ± 5.45	71.6 ± 9.11	62.5 ± 8.43	73.4 ± 8.68
Gender	26F 22M	26F 22M	13F 12M	7F 3M	9F 7M	14F 13M
MMSE	23.0 ± 1.8	29.3 ± 0.85	23.2 ± 6.3	27.8 ± 2.3	19.1 ± 5.7	24.4 ± 3.4
ACE-R	66.3 ± 6.2	95.9 ± 3.4	67.0 ± 19.5	84.5 ± 11.5	54.5 ± 23.2	73.2 ± 11.9

Table 1: Participant demographics. bvFTD: behavioural variant fronto-temporal dementia. nfvPPA: non-fluent variant primary progressive aphasia. PCA: posterior cortical atrophy. ADMCI:

Alzheimer's disease mild cognitive impairment with positive amyloid imaging.

Participants gave written informed consent, and ethical approval for the study was given by Suffolk Research Ethics Committee (REC reference 07/H0307/64). Ethical approval for the Cam-CAN study was obtained from the Cambridgeshire 2 Research Ethics Committee (REC reference 10/H0308/50).

Structural MRI voxel based morphometry analysis

Data analysis scripts for this section are available at https://github.com/thomascpe/MMN/blob/master/ICA_denoise/VBM/Master_Script_VBM.m and used a statistical parametric mapping approach in SPM12 r6906 (SPM, Wellcome Trust Centre for Neuroimaging, UCL).

Subjects' individual anatomical T1-weighted MRI images (3D MPRAGE sequence, TR=2300ms, TE=2.86ms, inversion time 900ms, flip angle 9°, field-of-view 192x192x144, 1.25mm slice thickness, collected on a 3T Siemens Tim Trio scanner) were first aligned by coregistration to an average image in MNI space, before segmentation and calculation of total intracranial volume (TIV). After segmentation, a study-specific DARTEL template was created from all study scans using default parameters. The templates were affine aligned to the SPM standard space using 'Normalise to MNI space' and the transformation applied to individual modulated grey-matter segments, with an 8 mm FWHM Gaussian smoothing kernel.

The resulting images were entered into a general linear model with a single regressor for each of the five groups, and age and TIV as covariates of no interest, with an explicit grey-matter mask constructed from the control participants with 80% group agreement at a probability threshold of 5%. This model was estimated in two ways, in order to quantify both atrophy and Bayesian evidence for no atrophy in each group (i.e. to highlight normal as well as abnormal cortex). Firstly, a classical estimation was performed to assess for group difference and thresholded for visualisation as 'hot' colours in Figure 2, both voxelwise multiple-comparison corrected with restricted maximum likelihood (REML) at FWE $p < 0.05$, and uncorrected at $p < 0.001$. Secondly, a Bayesian estimation was performed on the same model, and a Bayesian contrast between each patient group and controls

173 specified. The resulting Bayesian map was subjected to hypothesis testing for the null in SPM12,
 174 resulting in a map of the posterior probability of the null at each voxel (indicating evidence of no
 175 atrophy). This map was thresholded for posterior probabilities for the null above 0.7 and cluster
 176 volumes of greater than 1 cm³, consistent with our previous practice (Cope et al., 2017), for
 177 visualisation in as ‘cool’ colours in the right hand column of Figure 2.

178 **Auditory oddball paradigm**

179 We exposed participants to a stereotyped auditory stimulus train containing ‘oddballs’ that differed
 180 from standard tones in the location, intensity, duration, frequency or continuity domains (Näätänen et
 181 al., 2004), while they watched a silent movie. We used the ‘Optimum-1’ type multi-MMN paradigm
 182 (Näätänen et al., 2004; Hughes et al., 2013) to investigate mismatch negativity responses to multiple
 183 deviant types. In this time-efficient variant of the classic oddball paradigm, standard tones are
 184 alternated with tones that deviate in one of five dimensions, while holding the other four stimulus
 185 properties constant. This paradigm has the advantage compared to traditional MMN paradigms that an
 186 equal number of standard and deviant evoked responses are obtained. Deviant types were presented
 187 pseudo-randomly, such that they never repeated consecutively and each deviant type appears at least
 188 once in a sequence of ten tones. In this way, the occurrence of a deviant tone was entirely predictable,
 189 but the way in which it differed from the standard was entirely unpredictable. Duration deviants
 190 shortened the standard tone from 75ms (including 7ms cosine up and down ramps) to 25ms. Intensity
 191 deviants altered the standard tone +/- 6dB from 60dB HL. Frequency deviants moved the standard
 192 tone, which comprised three harmonics of 500, 1000 and 1500Hz, up or down by 10% to harmonics
 193 with fundamentals of 450 or 550Hz. Laterality deviants presented the standard tone monaurally left or
 194 right, rather than binaurally. Finally, gap deviants had a 25ms silent interval in the middle of a
 195 standard tone.

196 Tones were presented every 500ms in three blocks of 5 minutes while participants watched a silent
 197 movie (BBC Planet Earth Series 1, Episode 9: Shallow Seas). There was no task. Each block began
 198 with fifteen standard tones, which were not included in later analyses. In total, 900 standard and 900
 199 deviant tones (180 of each type) were presented using E-Prime® 2.0 (Psychology Software Tools,

Inc., USA) via plastic tubes and earpieces. Participant hearing level was checked immediately before paradigm delivery using the same equipment and an automated two-down, one-up procedure to ensure that the stimuli were comfortable and audible.

MEG acquisition and preprocessing

MEG recordings were completed at the MRC Cognition and Brain Sciences Unit using the Elekta Neuromag Vectorview System (Elekta Neuromag, Helsinki, Finland). The Vectorview system contained 102 sensor locations, each with one magnetometer and two orthogonal gradiometer superconducting thin-film sensors. Participant head movement was recorded during the MEG recording using five Head-Position Indicator (HPI) coils. Vertical and horizontal eye movements were recorded using two pairs of electrooculogram (EOG) electrodes. We used a 3D digitiser (Fastrak Polhemus) to digitise the HPI coils and >100 scalp points, all in relation to the nasion and bilateral pre-auricular anatomical fiducial points.

Data analysis scripts for all MEG analyses are available at https://github.com/thomascope/MMN/blob/master/ICA_denoise/Integrated_Pipeline.m.

Signal-space separation (Taulu et al., 2005) in Neuromag Maxfilter 2.2 was used to realign raw MEG data, separated from environmental noise and compensated for head movement based on the tracked 3D position of the five HPI coils. Data were downsampled at this stage from 1kHz to 250Hz because of the extremely large size of our cohort and limits on available files server storage. Next, eye movements and blinks were automatically identified and rejected with separate independent component analyses for magnetometers and gradiometers performed in EEGLab (Swartz Center for Computational Neuroscience, University of California San Diego). Components were rejected if they were both significantly temporally correlated with contemporaneous electrooculography data and spatially correlated with separately acquired template data for blinks and eye movements. The data were then pre-processed in SPM12 r6906 with the following steps: trials were defined and the data epoched -100-500ms around the onset of the tone with baseline correction by subtraction of the mean of the -100-0ms period; data were low-pass filtered below 100Hz then notch filtered between 48 and 52 Hz to exclude electrical noise at 50Hz using bidirectional Butterworth filters to obtain zero-phase

distortion; blocks were merged, and trials were subjected to robust averaging (Wager et al., 2005) followed by an repeat lowpass filtering at 100Hz to remove the high frequency noise that is introduced by robust averaging.

Source reconstruction

Two identical source reconstructions were performed in SPM12. One on the time-domain data before averaging for frequency-domain connectivity analyses (Granger Causality, Imaginary Coherence and Phase Locking Value), and another on the trial-averaged data for source-space statistical analyses and dynamic causal modelling.

The forward model (lead field) was estimated from a single shell cortical mesh of each participant's individual anatomical T1-weighted MRI image. The cortical mesh was coregistered to the MEG data using the digitised fiducial and scalp points. We computed the inverse source reconstruction across the whole brain using the sLORETA algorithm (Pascual-Marqui, 2002; Jatoi et al., 2014) and extracted the local field potentials (LFPs) from 5mm radius spheres in literature-defined regions of interest previously identified in MMN connectivity (Garrido et al., 2009a; Dietz et al., 2014): bilateral primary auditory cortex (A1, MNI coordinates: [-42 -22 7], [46 -14 8]), superior temporal gyrus (STG, [-61 -32 8], [59 -25 8]), inferior frontal gyrus (IFG, [46 20 8], [-46 20 8]) and inferior parietal cortex (IPC, [-49 -38 38], [57 -38 42]). We used literature defined co-ordinates to avoid double-dipping our dataset, but all IFG and IPC nodes and no A1 or STG nodes fell within probabilistic maps of the MD network (Dworetsky et al., 2021). The LFP data were then baseline corrected before statistical analysis.

Evoked response analysis

For consistency with the previous literature (Hughes et al., 2013), we quantified MMN amplitude as the average mismatch response in left primary auditory cortex (A1) between 100 and 200ms. A control analysis comparing the amplitude of the M100 response to the standard tone, as defined by the magnitude of the peak deflection between 50 and 150ms, was also performed to demonstrate that reductions in MMN amplitude were not simply due to reduced global signal in the patient populations.

Structure-function relationship

To test the hypothesis that the MD network has a causal role in auditory change detection, structure-function maps were generated, and then compared with published MD functional parcellation maps. A regression general linear model was constructed in SPM to assess the relationship between grey matter volume and MMN amplitude. All participant scans were assessed as a single group against MMN amplitude, with age and TIV as covariates of no interest. To create the illustrative regression plots in Figure 7, filtered grey matter volume data were extracted from the SPM general linear model at voxels of peak effect, and plotted against MMN amplitude. Note that these locations were selected as they were already demonstrated to be significant statistical peaks, so these plots and the associated r-values merely illustrate effect size, without re-estimation of associated p-values.

Overlaps of cluster peak locations with binary maps from Shain et al. (2020) were assessed in MNI space with MRICron. The neuromorphometrics atlas implemented within SPM was used to define anatomical regions of interest.

Voxelwise overlap with probabilistic maps from Woolgar et al. (2018) and Dworetzky et al. (2021) were assessed in SPM (code at https://github.com/thomascpe/MMN/blob/master/ICA_denoise/VBM/visualisation_2020/propvox.m). First, the probabilistic maps were resliced into the same space as the structure-function correlation maps, then thresholded at 5%. These binary images were multiplied in imcalc by binarised structure-function correlation maps thresholded at $p < 0.001$ uncorrected. The proportion of surviving voxels from the thresholded structure-function was then calculated.

The normalised activation ratio map was calculated (code at https://github.com/thomascpe/MMN/blob/master/ICA_denoise/VBM/visualisation_2020/weightedvox.m) from the same resliced probabilistic maps, unthresholded, multiplied in imcalc with t-score structure-function correlation maps thresholded at $p < 0.001$ uncorrected. The total sum of all voxel values in this map was normalised by multiplication with the number of voxels in the grey matter mask used to create the structure-function correlation maps, followed by division by the product of

the total sum of all voxel values in the probabilistic and thresholded structure-function maps. In this way, an activation ratio of between 0 and 1 was created, normalised against map size and range.

$$\text{Normalised activation ratio} = \frac{(\text{voxel } t_score * \text{voxel network_probability}) * \text{mask_size}}{\sum t_score * \sum \text{network_probability}}$$

To ensure that our findings were not non-specific group effects, we assessed the specificity of our results in several ways. In our original model, we checked that the structure-function analysis was not primarily implicating the most atrophic regions, nor was it implicating all the locations found to be atrophic. The ADMCI group, with predominant hippocampal/entorhinal atrophy, and the PCA group, with significant occipital lobe atrophy, are of particular interest here, as we do not propose these regions to contribute to auditory change detection. Next, we ran a series of alternate regression models, each less sensitive but more specific in their assessment of differential neurodegeneration. First, we re-ran the analysis excluding the control participants. Although this reduces the between-subject variance in neurophysiological response, it does not assume that all differences are driven by the same loci. This is important, because the drivers of impaired change detection may be different for example in a patient with left frontal atrophy from nvPPA and a patient with parieto-occipital atrophy from PCA. Indeed, if the MD network is working in an integrated fashion to support auditory change detection, atrophy in any of these areas should be sufficient to alter response. Second, we assessed a linear mixed model, with a factor “group” and two levels (controls, patients), with age and TIV as additional covariates of no interest. This answers the same question in a different way, assuming that the small amount of variance within the control group adds information and not noise. Finally, we assessed this linear mixed model with five “group” levels (controls, bvFTD, nvPPA, PCA, ADMCI). This is the most specific analysis, but also potentially excludes effects of interest in areas of atrophy that are shared between patient groups. This is problematic for areas such as left superior parietal cortex, where no patient group had Bayesian evidence for no atrophy.

Dynamic causal modelling

We used dynamic causal modelling (DCM) of evoked responses to identify the effective connectivity among eight neural sources of the MMN, and to assess the top-down influence of frontal and parietal

305 brain regions on primary and association auditory regions. The models were fitted to the observed
 306 physiological responses, including responses to all tones and their modulation by deviance. We used
 307 biophysically informed canonical microcircuits (*spm_fx_cmc*) at each source to model the extrinsic
 308 connections between sources, and layer-specific intrinsic connections within each source among
 309 populations of pyramidal cells, spiny stellate cells and inhibitory interneurons (Moran et al., 2013).
 310 The canonical microcircuit model enables inferences about the mechanisms that generate the observed
 311 local field potentials and their modulation by experimental stimuli (David et al., 2006; Kiebel et al.,
 312 2006; Kiebel et al., 2008; Muthukumaraswamy et al., 2015; Shaw et al., 2017).

313 We tested alternative hypotheses of the mechanism underlying the MMN through 32 generative
 314 models (Figure 1). The model space was based on a combination of previous studies of the MMN
 315 (Giard et al., 1990; Doeller et al., 2003; Molholm et al., 2005; Garrido et al., 2009b; Dietz et al., 2014;
 316 Phillips et al., 2015). These models described the effective connectivity between temporal, frontal and
 317 parietal sources for the time window of 0-400ms from the onset of each stimulus, encompassing the
 318 MMN interval. Input data were trial-averaged and Hanning windowed, with inversion frequency
 319 bounds of 4Hz-48Hz. All connections between MMN sources were bidirectional and modulated
 320 (Garrido et al., 2007; Phillips et al., 2016).

321 We built the model space from alternative hypothesis of network connections, building on the Garrido
 322 et al. (2009a) winning model (Figure 1A) with driving inputs into bilateral primary auditory cortex
 323 (A1, MNI coordinates: [-42 -22 7], [46 -14 8]), with intrinsic connections within these sources,
 324 bidirectional connections between bilateral A1 and superior temporal gyri (STG, [-61 -32 8], [59 -25
 325 8]), and bidirectional connections between right STG and right inferior frontal gyrus (IFG, [46 20 8]).
 326 The second model (Figure 1B) incorporated left IFG ([-46 20 8]), which has previously demonstrated
 327 greater evidence than model 1 for all deviant types in the optimum-1 MMN paradigm in young
 328 healthy adults (Phillips et al., 2015). Models 3-8 (Figure 1C) build on models 1-2 by adding
 329 bidirectional connections between STG and inferior parietal cortex (IPC, [-49 -38 38], [57 -38 42],
 330 (Dietz et al., 2014) (models 3-4), between IPC and IFG (models 5-6) and between IPC and both IFG
 331 and STG (models 7-8). We repeated models 1-8 with inclusion of top-down temporal expectation

inputs acting on the frontal source (Figure 1D, models 9-16) (Phillips et al., 2015; Chennu et al., 2016; Phillips et al., 2016). Finally, models 17-32 (Figure 1E) repeat models 1-16 with lateral connections between bilateral STGs, IFGs and IPCs (Hughes et al., 2013).

<Figure 1 to go about here>

Model comparison

We used Bayesian model selection to compare the generative models (Penny et al., 2004) and to determine which model best explained the neural responses for each group (Kiebel et al., 2008; Stephan et al., 2009). We used random effects analysis to accommodate group heterogeneity (Stephan et al., 2010) with adjustment of the model fit for model complexity to reduce over-fitting (Kiebel et al., 2008). The free energy estimates of $-\log(\text{model_evidence})$ were used to compare models and estimate the model exceedance probability (that a single model was more likely to have generated the data compared to all other models). We report all models with an exceedance probability of greater than 0.05.

Next, we compared eight model families using random effects Bayesian model averaging (Penny et al., 2010). Each model family contained four models differing in the presence or absence of top-down inputs to the system and cross-hemispheric connections, but with the same pattern of connectivity between STG, IFG and IPC nodes. Specifically, referring to Figure 1, the fully connected family included models 8, 16, 24 and 32, the fully disconnected family models 1, 9, 17 and 25, with the other families being integer increments in between.

Parametric Empirical Bayes (PEB) analysis

We then compared the strength and modulation of DCM connectivity between controls and each patient group for the model with the highest probability using second level parametric empirical Bayes (PEB) analyses (*spm_dcm_peb*) (Friston et al., 2015). This was performed twice; once for the “A-matrix”, or main effect of connectivity strength; and again for the “B-matrix”, the modulation strength or interaction between group and tone identity. These second level models were then

358 subjected to Bayesian model comparison averaging with Bayesian model reduction
359 (*spm_dcm_peb_bmc*). Differences in connection strength are displayed where Bayesian probability
360 >0.95 .

361 **Frequency resolved connectivity analyses**

362 We extracted time series data from all sources, epoched between 0-500ms after each tone. We then
363 subtracted the condition-averaged waveform (i.e. the evoked response) in each source from every
364 trial, resulting in data with zero-mean and approximate stationarity. We then calculated the Fourier
365 spectra in FieldTrip using multitapers with a ± 4 Hz smoothing box and subjected this decomposition
366 to separate frequency-resolved connectivity analyses between every pair of connections in the
367 winning DCM model, with partial imaginary coherence and partial phase-locking value. These
368 measures were chosen as they are robust to source spread, and allow for each extrinsic connection to
369 be individually examined, with the effect of all other sources partialled out. They are also robust to
370 differences in signal to noise ratio between sources and individuals, but to further control for any
371 effect of this the analyses were all repeated with the trial identities shuffled to create a null
372 distribution, 100 times for every connection pair in every individual. Connectivity strength was
373 averaged in the Theta (4-8Hz), Alpha (8-20Hz), Beta (20-30Hz), Low Gamma (30-45Hz) and High
374 Gamma (55-70Hz) bands for between-group statistical comparisons.

Results

Patient groups show differential and graded patterns of atrophy

All patient groups showed atrophy distributions in keeping with expectations from previous literature (Figure 2).

<Figure 2 to go about here>

Patients with bvFTD showed marked atrophy in frontal and temporal lobes, with peaks in right middle temporal gyrus ([55, -15, -15] $t(106)=9.26$, FWE $p < 0.001$), right orbitofrontal gyrus ([38 26 -1] $t(106)=8.93$, FWE $p < 0.001$), left middle temporal gyrus ([-47, -3, -16] $t(106)=8.02$, FWE $p < 0.001$), and left frontal operculum ([-38, 22, 0] $t(106)=7.76$, FWE $p < 0.001$). They showed Bayesian evidence for no atrophy in occipital pole and along superior aspects of the parietal lobe.

As is usual, patients with nvPPA showed relatively little atrophy, with no voxels surviving FWE $p < 0.05$ correction. With cluster-wise correction at an uncorrected $p < 0.001$ cluster defining height, they showed two clusters of atrophy centred on left and right middle frontal gyrus ([-27 -1 48], peak $t(106)=5.55$, cluster extent = 14817, FWE $p < 0.001$; [30 28 37], peak $t(106)=5.33$, cluster extent = 24381, FWE $p < 0.001$). They showed widespread bilateral Bayesian evidence for no atrophy in superior temporal gyri, the motor and sensory cortex, superior parietal cortex and occipital lobe.

By contrast, patients with PCA showed marked atrophy in occipital and parietal lobes bilaterally, with peaks in left and right inferior occipital gyri ([-39 -86 2] $t(106)=10.81$, FWE $p < 0.001$; [43 -83 3] $t(106)=7.92$, FWE $p < 0.001$). They showed Bayesian evidence for no atrophy in both inferior frontal gyri and in the motor and sensory strips.

Patients with ADMCI showed a typical atrophy with prominent medial temporal loss. They displayed atrophy peaks in left parahippocampal gyrus ([-23 -15 -35] $t(106)=8.02$, FWE $p < 0.001$) and right hippocampus ([37 -28 -7] $t(106)=7.55$, FWE $p < 0.001$). They showed Bayesian evidence for no atrophy in superior temporal gyri and inferior frontal gyri

399 When all patients were combined and compared against controls, atrophy peaks were observed in
400 right middle temporal gyrus ([54 -17 -17 $t(106)=10.52$, FWE $p < 0.001$), left supramarginal gyrus ([-
401 47 -48 38] $t(106)=9.60$, FWE $p < 0.001$), right posterior cingulate ([15 -35 44] $t(106)=9.34$, FWE p
402 < 0.001) and right hippocampus ([36 -30 -4] $t(106)=8.40$, FWE $p < 0.001$).

403

404 **All patient groups show reduced MMN amplitude, but preserved responses to standard tones**

405 Source-localised evoked responses for our pre-defined regions of interest are shown in Figure 3 for
 406 each group, for the standard tone and deviant tones combined. A whole-brain SPM contrast confirmed
 407 modulation of all of our regions of interest by the overall contrast between standard and deviant tones:
 408 the strongest mismatch response was around A1 and STG bilaterally (left peak [-42, -18, 20]
 409 $F(1,590)=82.9$, whole brain FWE $p<0.001$, right peak [44 -6 16] $F(1,590)=53.6$, whole brain FWE
 410 $p<0.001$). There were also significant contrasts with small volume correction (8mm spheres) at all of
 411 our literature-based pre-specified co-ordinates of interest: left IFG [-46 20 8] $F(1,590)=12.2$, FWE
 412 $p=0.008$, right IFG [46 20 8] $F(1,590)=19.8$, FWE $p<0.001$, left IPC [-49 -38 38] $F(1,590)=13.2$,
 413 FWE $p=0.006$, and right IPC [57 -38 42] $F(1,590)=12.9$, FWE $p=0.006$. Waveforms for the mismatch
 414 waveform at each of these locations are shown in Figure 4, upper panel.

415 For MMN amplitude in our literature pre-specified left A1 region of interest (Hughes et al., 2013),
 416 repeated measures ANOVA demonstrated a main effect of diagnosis (Figure 4, middle panel;
 417 $F(4,118)=6.57$, Greenhouse-Geisser $p=8.24\times10^{-5}$). Post hoc Tukey-Kramer tests demonstrated that
 418 all groups had lower MMN amplitude than controls ($p=0.036$ - $p=0.0002$). Examining timepoint by
 419 timepoint, patients with bvFTD had lower MMN amplitude than controls between 44-164ms, patients
 420 with PCA between 36-208ms, and patients with AD/MCI between 120-184ms. Patients with nvPPA
 421 did not significantly differ at any timepoint with FDR correction across time, but displayed smaller
 422 MMN responses between 48ms and 180ms at an uncorrected $p<0.05$ threshold. Similar patterns were
 423 observed in right A1 and left STG. There was a diagnosis by deviant-type interaction in MMN
 424 amplitude ($F(16,472)=2.15$, Greenhouse-Geisser $p=0.0095$), but examining the MMN amplitude
 425 (Figure 4, middle panel) and waveform (Figure 4, lower panel) by condition there were no striking
 426 differences in response profile. Specifically, between-group differences in MMN response amplitude
 427 were domain general, being present in all oddball types individually. Additionally, in the whole-brain
 428 SPM analysis, contrasting auditory oddball types across all subjects, there were no significant
 429 differences in activation, even with small volume correction in our IFG and IPC ROIs.

430 Our control analysis confirmed there was no group difference in the amplitude of the M100 response
 431 to the standard tone (Figure 3, upper; $F(4,118)=1.03$, Greenhouse-Geisser $p=0.395$, or the deviant
 432 tone (Figure 3, lower; $F(4,118)=1.38$, Greenhouse-Geisser $p=0.245$), confirming that reductions in
 433 MMN amplitude were not simply due to reduced global signal in the patient populations.

434 An impaired ability to detect and respond to change might be due to either a failure to adapt to
 435 regularities in the environment, reflected in the standard tone, or to an abnormal response to novel
 436 stimuli, reflected in the deviant tone, or both. The MMN is a paired difference response, meaning that
 437 it is not affected by any non-specific influences on the modelled ERP within an individual, leaving
 438 only the response to change. In our data, between-group differences seem to be primarily driven by
 439 the deviant conditions (Figure 3). Across all timepoints, there was no significant pairwise difference
 440 standard tone response between controls and any other group, but there was a significant difference in
 441 deviant tone response between controls and patients with PCA between 84-196ms and 288-412ms,
 442 and patients with ADMCI between 112-180ms. A similar pattern was observed when quantifying
 443 overall standard and deviant response amplitudes in the MMN time-window (Figure 5).

444 Overall, all patient groups had impaired auditory change detection as measured by MMN amplitude in
 445 primary auditory cortex, despite very different loci of neurodegeneration. These impairments were
 446 domain general, and not driven by a global reduction in signal strength, as might be observed if the
 447 changes were simply a marker of atrophy in auditory brain regions.

448 <Figure 3 to go about here>

449 <Figure 4 to go about here>

450 <Figure 5 to go about here>

451

452 **Structure-function relationships selectively implicate the MD network**

453 To assess the neuroanatomical drivers of reduced MMN amplitude in neurodegeneration we
 454 correlated the amplitude of the auditory cortical MMN response against grey matter volume for all
 455 participants (Figure 6 rows 1-2). Correlations were significant, with reduced MMN amplitude related

456 to atrophy in parietal (left supramarginal $t(103)=3.87$, FWE $p=0.013$ at $[-61 -35 43]$, right
 457 supramarginal $t(103)=4.49$, FWE $p=0.002$ at $[60 -30 43]$) and frontal (left triangularis $t(103)=3.39$,
 458 FWE $p=0.026$ at $[-36 43 1]$, right triangularis $t(103)=3.55$, FWE $p=0.016$ at $[44 39 4]$) regions of
 459 interest.

460 Crucially, there were no significant correlations between MMN amplitude and grey matter volume in
 461 primary auditory cortices (left $t(103)=1.39$, FWE $p=1$, right $t(103)=0.89$, FWE $p=1$) or superior
 462 temporal gyri (left $t(103)=0.32$, FWE $p=1$, right $t(103)=1.38$, FWE $p=1$), confirming that impaired
 463 auditory change detection was not simply due to neurodegeneration in auditory brain regions. Nor
 464 were there any significant correlations at any of the overall atrophy peaks across all participants that
 465 fell outside of MD areas (middle temporal gyrus, posterior cingulate and hippocampus), confirming
 466 that the structure-function relationship we report here is not simply picking out the most commonly
 467 atrophic cortical regions in our patients. This lack of non-specific group effects was confirmed by
 468 additional analysis excluding the control participants (Table 2, Figure 6 row 3), and was shown to be
 469 consistent across all groups individually (Table 2, Figure 6 rows 4-5).

470 We tested the specificity of these analyses by comparing the overlap of the structure-function map
 471 from our overall regression model with independent data. The peak correlations of all of clusters fell
 472 within Idan Blank's publicly available MD functional parcellation (Shain et al., 2020), based on 197
 473 participants performing a spatial working memory task. However, binary parcellations run the risk of
 474 confusing functional networks that are spatially overlapping at the group level but segregated at the
 475 single subject level (Fedorenko and Blank, 2020). To address this concern, we compared voxelwise
 476 overlap of our whole brain maps thresholded at $p<0.001$ against probabilistic maps of the MD and
 477 superficially similar language networks derived from functional localisers, thresholded at 5%
 478 between-subject agreement (Woolgar et al., 2018). Our data showed a 67.9% overlap with the MD
 479 contrast and only a 9.2% overlap with the language contrast. Additionally, we repeated this analysis
 480 against published resting state networks derived from the human connectome project (Dworetzky et
 481 al., 2021) (Figure 6). Our structure-function maps showed a 72.9% overlap with their MD (fronto-

482 parietal) network, much more than with the superficially similar cingulo-opercular (26.4%), salience
483 (39%), and language (22.6%) networks.

484 Thresholding in this way may obscure differences in the strength of structure-function relationships
485 and the probability of individual activations with the functional localiser or resting state connectivity
486 network membership. We therefore calculated an activation ratio by combining the maps
487 multiplicatively, normalised against size and range. Against the functional localisers, our structure-
488 function maps showed a normalised activation ratio of 0.54 for the MD contrast, and only 0.17 for the
489 language contrast. Against the resting state networks, our structure-function maps showed a
490 normalised activation ratio of 0.70 for the MD network, and only 0.19 for the cingulo-opercular
491 network, 0.01 for the salience network, and 0.26 for the language network.

492 Finally, as a control analysis to ensure that these results were not a non-specific effect of there being
493 more atrophy in MD than language areas at the group level, we re-calculated these ratios from
494 structural maps alone. Reassuringly, against the functional localiser this resulted in a normalised ratio
495 of 0.19 for the MD network and 0.24 for the language network, and against the resting state networks
496 this resulted in a normalised ratio of 0.18 for the MD network, 0.19 for the cingulo-opercular network,
497 0.17 for the salience network, and 0.22 for the language network. Additionally, we show in (Figure 6
498 row 2). That the specificity of our finding is not the product of an arbitrary statistical thresholding.
499 Reducing the threshold for structure-function relationships resulted in more widespread peaks that
500 filled a larger proportion of the MD map and continued to spare both auditory areas and heavily
501 atrophic areas (middle temporal gyrus, posterior cingulate and hippocampus) outside of MD.

502 Overall, therefore, the loci best explaining impaired change detection are outside of auditory cortex,
503 strongly overlap with the MD system, and are not simply those areas that are most atrophic overall.

504 <Figure 6 to go about here>

505 <Figure 7 to go about here>

Model	Left Parietal [-61 -35 43]	Right Parietal [60 -30 43]	Left Frontal [-36 43 1]	Right Frontal [44 39 4]
-------	-------------------------------	-------------------------------	----------------------------	----------------------------

Combined regression	t(103)=3.87, p<0.001	t(103)=4.49, p<0.001	t(103)=3.37, p<0.001	t(103)=3.55, p<0.001
Combined regression, controls excluded	t(56)=2.20, p=0.016	t(56)=2.85, p=0.003	t(56)=1.43, p=0.078 nearby left frontal peak at [-44 47 -5] t(56)=2.55, p=0.005	t(56)=2.30, p=0.013
Linear mixed model, two groups	t(102)=2.03, p=0.021	t(102)=2.90, p=0.002	t(102)=1.93, p=0.028	t(102)=1.90, p=0.030
Linear mixed model, five groups	t(99)=2.03, p=0.023	t(99)=3.11, p=0.001	t(99)=1.70, p=0.046	t(99)=1.71, p=0.046

Table 2: Table of structure-function relationships for each regression model individually. Across all three confirmatory models and four regions of interest, the voxel of peak significance in the combined regression is significant in eleven of twelve cases. The only exception is the left frontal voxel in the ungrouped regression model with controls excluded, which is only trend significant. However, as shown in the maps (Figure 6, second row), there is an extensive left frontal cluster in this condition, that is slightly more anterolateral than the original analysis, just missing the original peak. The peak of this cluster is also reported.

514 **Frontal and parietal loci both show effective connectivity with auditory regions during MMN**

515 To understand the functional role of frontal (IFG) and parietal (IPC) cortex in generating the MMN
 516 response observed in temporal cortex, we assessed effective connectivity with dynamic causal
 517 modelling (Figure 1). Across all subjects, the exceedance probability (xp) of the fully connected
 518 model 32 was 0.92. No other models had an xp above 0.05. This model was also the single most likely
 519 generative model for controls alone (xp=0.80, with the second placed model omitting direct
 520 connectivity between IPC and IFG, xp=0.16); in ADMCI (xp=0.52, with the second placed model
 521 lacking only cross-hemispheric connections xp=0.14); and in PCA (xp=0.54, with the second placed
 522 model being fully connected again except for direct connectivity between IPC and IFG, xp=0.17). In
 523 bvFTD the single most likely model was fully connected except for absent inter-hemispheric
 524 connections (xp=0.45), with the fully connected model a close second (xp=0.39). In nfVPPA the
 525 models with the highest probabilities were fully connected except for absence of direct connectivity
 526 between IPC and IFG (xp=0.33), cross-hemispheric connections (xp=0.12) or cross-hemispheric and
 527 STG <-> IPC connections (xp=0.13). Overall, therefore, every model with an xp of > 0.05 included
 528 both IFG and IPC bilaterally.

529 We confirmed this finding with a model family comparison using Bayesian model averaging (Penny
 530 et al., 2010) across eight model families, each including four models with the same connectivity
 531 between IFG, IPC and STG. Across all subjects (xp=0.98), and within the control (xp=0.84), bvFTD
 532 (xp=0.94) and ADMCI (xp=0.82) groups individually, there was strong evidence for the family of
 533 models including full bilateral connectivity between IPC, IFG and STG. This model family was also
 534 likely in PCA (xp=0.57) and nfVPPA (xp=0.43), but in these conditions there was additional evidence
 535 (PCA xp=0.36, nfVPPA xp=0.43) for the model family in which IPC and IFG were not connected to
 536 each other (but were still connected to STG). Overall, there was no evidence for widespread
 537 disconnection of fronto-parietal regions from STG in neurodegeneration, demonstrating their
 538 continued involvement in the MMN response even in the face of atrophy.

539

540 **Atrophic frontal and parietal loci have reduced top-down influence, but preserved nodes**
 541 **increase in effective connectivity**

542 To assess group differences in the strength of effective extrinsic connectivity between patients and
 543 controls, both in terms of connection strength and auditory-change related modulation, we compared
 544 the strength of connections in the winning (fully connected) model with Parametric Empirical Bayes
 545 (PEB). Patients differed from controls in the strength of forward and backward effective connectivity,
 546 and their modulation by auditory change (Figure 8). All groups showed a reduction of backward
 547 connectivity from STG to A1 connectivity in at least one hemisphere.

548 <Figure 8 to go about here>

549 Changes in connectivity among association cortex differed according to disease group and the most
 550 widespread connectivity abnormalities were in the more focal neurodegenerative syndromes that
 551 selectively involved frontal or parietal regions. PCA, with predominant occipital-parietal
 552 neurodegeneration, showed reduced task-modulation of connectivity bilaterally from IPC to IFG, and
 553 to right STG; and in contrast, significantly increased top-down modulatory influence of IFG on STG
 554 bilaterally. There was reduced left STG to A1 modulation, and bilaterally increased local (self)
 555 modulation of A1. nvPPA, with left IFG/Insular neurodegeneration, showed reduced modulation of
 556 connections from left IFG to IPC, reduced left IFG to STG connectivity, and a widespread increase in
 557 right-sided and reduction in left-sided influence.

558 Overall, this analysis shows that neurodegeneration reduced top-down effective connectivity from
 559 affected multiple demand nodes and, in the more focal syndromes of nvPPA and PCA, increased
 560 effective connectivity from unaffected multiple demand nodes. This compensation was only partially
 561 effective, as overall top-down influence on A1 fell in all groups.

562

563 **Neurodegeneration increases functional connectivity in a frequency-specific manner**

564 Next, we assessed the frequency specificity of the connectivity changes in the networks, using partial
 565 phase-locking value and partial imaginary coherence. First, we quantified the strength of each

566 connection in each patient group, relative to controls, and compared this to a permutation-based null
567 distribution (Figure 9). Concordant with (Sami et al., 2018), we found that connectivity changes in
568 bvFTD and nfvPPA were restricted to lower frequencies, while in ADMCI and PCA additional
569 connectivity changes were found in higher frequencies. No group showed an overall difference across
570 all nodes in the Beta band, but many individual connections lay outside of the null distribution.
571 Significant differences were all in the direction of stronger average phase-locking value and
572 imaginary in patients than controls.

573 <Figure 9 to go about here>

574 Next, we compared frequency-resolved connectivity between auditory nodes, fronto-parietal (MD)
575 nodes, connections between auditory and MD nodes, or across hemispheres. Results were very similar
576 for phase-locking value (Figure 10) and imaginary coherence (Figure 11). Connectivity abnormalities
577 between auditory and MD regions were marked in the low frequency Theta band in bvFTD and
578 nvPPA, and in the high Gamma band in PCA and ADMCI.

579 <Figure 10 to go about here>

580 <Figure 11 to go about here>

581 These results were not driven by overall differences in power and resultant changes in signal to noise
582 ratio (Aru et al., 2015); in general, patients had the same or lower power compared to controls (Figure
583 12). The exceptions were that patients with PCA had higher Theta power than controls in STG and
584 IPC bilaterally, and patients with nvPPA had higher power than controls in right STG across Alpha
585 and Gamma bands. These were not the frequency bands in which most of the increased auditory-MD
586 functional connectivity was observed; patients with PCA had most significant increases in the Gamma
587 band, while those with nvPPA had most significant increases in the Theta band.

588 <Figure 12 to go about here>

589

590 Discussion

591 Here we provide convergent evidence for a causal role in auditory change detection for bilateral,
 592 ventral frontal and parietal loci within the MD network, by combining structure-function mapping,
 593 dynamic causal modelling, and frequency-resolved functional connectivity analyses across a range of
 594 neurodegenerative diseases. Key outcomes were (i) confirmation that multiple foci of
 595 neurodegeneration impaired auditory change detection (Figure 2, Figure 4); (ii) the impairments were
 596 domain general, over deviation of frequency, location, loudness, duration or timbre (Figure 4); (iii)
 597 crucially, the loci best explaining impaired auditory change detection were outside of auditory cortex,
 598 overlapped selectively with the MD system, and were not simply those areas that are most atrophic
 599 (Figure 6); (iv) whereas there is no evidence for widespread disconnection of fronto-parietal regions,
 600 there is widespread abnormality of effective connectivity within the MD network, and between it and
 601 auditory temporal regions (Figure 8); (v) across all connections, there is stronger average phase
 602 locking and imaginary coherence in patients than controls, consistent with attempted compensation
 603 (Figure 9); (vi) connectivity abnormalities manifest in low-frequency bands in patients with FTLD
 604 pathology, and both low and high frequency bands in patients with Alzheimer's disease pathology
 605 (Figure 9). These changes were most prominent in those connections between auditory (STG) and
 606 MD (IFG and IPC) regions (Figure 10, Figure 11).

607 Environmental change detection requires top-down control from the MD network

608 The detection of sensory regularities is a fundamental neurocognitive process across the lifespan.
 609 However, the ability to detect a change or deviation from such regularities changes with age (De
 610 Kerangal et al., 2021), and in many neurological and psychiatric disorders (Kocagoncu et al., 2020).
 611 This impaired ability to recognise and adapt to unexpected events and environmental changes is
 612 proposed to be a core feature of dementia (Goto et al., 2014; Lee et al., 2016), but its behavioural
 613 assessment is complicated by more general dementia-related impairments, such as problems with
 614 working memory and concentration. Mismatch negativity (MMN) paradigms (Näätänen et al., 2007)
 615 operate independently of attention and are sensitive to the early effects of neurodegenerative diseases
 616 (Pekkonen, 2000; Brønnick et al., 2010; Näätänen et al., 2011; Mowszowski et al., 2012; Jiang et al.,

2017). They can reveal network-level changes in brain connectivity between temporal auditory regions and domain-general loci in frontal lobes (Hughes et al., 2013; Hughes and Rowe, 2013; Phillips et al., 2015; Phillips et al., 2016). These effects are often modelled with a single top-down influence from right frontal cortex, but here we show that this perceptual control (Ptak, 2012) is provided by more widespread dorsal fronto-parietal networks (Kim, 2014), even though the “task” is simple and passive.

Frontal and Parietal nodes are interconnected, and both are required for normal mismatch response

The parietal cortex is modulated by unexpected stimuli (Molholm et al., 2005; Dietz et al., 2014; Kompus et al., 2020), and changes in auditory temporal structure (Andreou et al., 2015). Previous casual evidence for parietal damage leading to an impaired ability to respond to environmental change has largely been provided by the post-stroke neglect and extinction syndromes, which usually results from lesion to non-dominant and dominant inferior parietal cortex respectively. The specificity of this structure-function relationship was difficult to assess, because the complete unilateral destruction of a network node and its underlying white matter results in widespread imbalance in interhemispheric and fronto-parietal connectivity (Corbetta and Shulman, 2011). Similar findings have been reported from electrophysiological assessments of patients with prefrontal stroke (Deouell and Knight, 2005). Our data provide a much more nuanced and sensitive assessment in a large cohort of individuals who do not have ‘lesions’, but rather display differing degrees of relative neurodegeneration across implicated network nodes. This allows us to visualise abnormal connectivity between these nodes and the rest of the network, without the forced widespread reorganisation induced by their absence. Reduced MMN amplitude in all patient groups, despite selective and differential nodal atrophy or sparing, confirms that degeneration of any of the ventral frontal and parietal nodes of the MD network is sufficient to impair change detection in auditory cortex, while degeneration outside of these nodes does not do so. We do not give primacy to prefrontal or parietal nodes, but rather emphasise their interconnected nature, and show that neurodegeneration anywhere in the MD network results in impaired auditory cortical response to change, but neurodegeneration elsewhere does not.

644 **Neurodegeneration increases functional connectivity in the task state, but this is not sufficient to**
 645 **rescue effective connectivity from affected nodes**

646 Our frequency-resolved analyses are concordant with both resting state studies in similar patients
 647 (Poza et al., 2008; Sami et al., 2018) and preclinical studies in animal models (Kurudenkandy et al.,
 648 2014; Koss et al., 2016; Stoiljkovic et al., 2016), providing criterion validity not only for our own
 649 work but also for those simpler models of disease, supporting their use in interventional studies. Our
 650 analyses and theirs all show Alzheimer-type pathology preferentially affecting high frequency bands
 651 and FTLN pathology affecting only low frequency bands. Resting state analyses universally show
 652 reductions in functional connectivity. However this pattern is often reversed when network-level
 653 connectivity is driven by stimulus or task; as here, patients often display increased frequency-resolved
 654 coherence between sources in the same bands (Hughes and Rowe, 2013; Cope et al., 2017), but still
 655 show reduced or delayed causal influence. This is likely to represent a compensatory upregulation as
 656 neuronal hubs increase their firing rate in the face of neurodegeneration (Maestú et al., 2015), but this
 657 mitigation is only partial (Geranmayeh et al., 2014), and breaks down as disease progresses (Jones et
 658 al., 2015; Cope et al., 2018), perhaps because the top-down influences arrive too slowly, or
 659 neurodegeneration results in a loss of signal precision and accuracy. Here we use complementary
 660 model-based DCM of the evoked response, and model-free frequency-resolved analyses of the
 661 induced response to demonstrate this phenomenon in action: coherence increases are most prominent
 662 in the connections between auditory and MD nodes, and yet these same connections have reduced
 663 effective connectivity.

664 **Limitations**

665 The primary limitations of this study are not methodological. We have a far larger group size than
 666 most functional imaging studies in dementia outside of the resting state, including a diverse range of
 667 pathologies and neurodegenerative profiles covering the whole brain, with biomarker evidence of
 668 Alzheimer pathology in our MCI group. We employ three radically different and independent
 669 techniques (structure-function mapping, dynamic causal modelling, and frequency-resolved functional
 670 connectivity analyses) with convergent results, providing reassurance that our findings are not an

671 artefact of a methodological idiosyncrasy. Studies like ours have been criticised for reverse inference
 672 when drawing an association between anatomical localisations and previous functional imaging
 673 findings in healthy individuals, without localising individual MD maps (Blank et al., 2017). Domain-
 674 general regions, like those examined here in frontal and parietal cortex (Fedorenko et al., 2013), by
 675 their nature subserve a wide variety of cognitive tasks. At the individual level, complex maps are
 676 revealed of neuronal subpopulations specialised for particular tasks, intermingled with those with a
 677 more domain-general role (Fedorenko et al., 2012; Fedorenko and Blank, 2020). Given the degree of
 678 smoothing inherent in the atrophy patterns of neurodegenerative disease and methodologically in
 679 MEG source reconstructions, how specific can we be about our core conclusion that the MD network
 680 is the core driver of our findings? A significant advantage we have here over stroke lesion studies is
 681 that our patients have graded and partial pathology that, across the whole cohort, covers widespread
 682 brain networks and implicates multiple loci either simultaneously or differentially. This allowed us to
 683 show strong and specific structure-function relationships that overlapped specifically with MD
 684 regions and not language, cingulo-opercular or salience networks, even though these networks overlap
 685 in some loci, and were all equally atrophic across the overall cohort. We are able to go further than
 686 previous functional connectivity studies in schizophrenia, which have demonstrated a more general
 687 cognitive role for MD and cingulo-opercular networks (Sheffield et al., 2015), because of the
 688 differential neurodegeneration between individuals in our cohort, clustering by diagnosis, with easily
 689 observable group-level differences in our parametric outcome measure (the MMN response). Our data
 690 do, however, contain a degree of smoothness, and therefore cannot speak to any potential
 691 dissociations between the functions of frontal and parietal subregions in change detection, attention
 692 and task switching. In addition, our use of continuous data epoched into a 0-500ms time window for
 693 functional connectivity analyses means that these results may include contributions from re-orienting
 694 processes (Schröger, 2005; Kushnerenko et al., 2013). We therefore use the term MD network
 695 inclusively, but our findings could equally be interpreted as causal evidence for the ventral attention
 696 network if one were to view this as distinct from both the lateral fronto-parietal MD and cingulo-
 697 opercular networks (Corbetta et al., 2008). Our own view would be to support a simplification of the
 698 taxonomy of fronto-parietal brain networks; here we have confirmed that the same MD network nodes

699 are implicated in perceptual control (Dosenbach et al., 2008; Vincent et al., 2008), executive function
700 (Seeley et al., 2007; Niendam et al., 2012) and these roles likely combine to support fluid intelligence
701 and working memory (Assem et al., 2020b).

702 **Conclusion**

703 Overall, we show that MD regions in bilateral ventral frontal and parietal cortex causally mediate
704 auditory change detection across a range of domains, demonstrating that the MD network plays a role
705 in the ‘simple task’ of automatic sensory change detection through the impairment of top-down
706 control mechanisms. Dementia-related reductions in the neurophysiological amplitude of the auditory
707 mismatch response are not a simple reflection of global atrophy, but are rather a specific
708 manifestation of neurodegeneration in these frontal and parietal regions. Neurodegeneration reduced
709 top-down effective connectivity from affected fronto-parietal nodes and increased effective
710 connectivity from unaffected fronto-parietal nodes. This compensation was only partially effective, as
711 overall top-down influence on STG fell with the involvement of any frontal or parietal node set. All
712 degenerative nodes showed increased functional connectivity, again consistent with compensatory
713 upregulation (Maestú et al., 2015). This increase was frequency-specific, and dissociated by
714 underlying neuropathology concordantly with previous resting state analyses (Sami et al., 2018).

715

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Figure Legends

Figure 1. DCM model space. Nodes of interest were literature-specified locations in primary auditory cortex (A1), superior temporal gyrus (STG), inferior frontal gyrus (IFG) and inferior parietal cortex (IPC). Red arrows graphically indicate what has been added to each model compared to the previous, simpler model. **A)** Model 1 is the original winning model from (Garrido et al., 2009a). Subsequent models build from this with our alternative hypotheses based on the subsequent literature, to test our specific hypotheses. **B.** Firstly we included connections between left STG and IFG (model 2). **C.** Secondly, we alternated connections between left or bilateral IPC with STG and/or IFG (models 3-8) **D.** Thirdly, we added top-down IFG inputs to all previous models (models 9-16). **E.** Finally, we repeated all the models with added lateral connections between STGs, IFGs and IPCs (models 17-32).

Figure 2: Distribution of grey matter atrophy in the patient participants. Random field theory t-maps for atrophy assessed with a classical statistical parametric mapping approach is shown in 'hot' colours, REML thresholded at voxelwise FWE $p < 0.05$ (left) and uncorrected $p < 0.001$ (right). On the right hand maps, Bayesian maps for posterior probability of no atrophy (the 'null') are also shown in 'cool' colours, thresholded for illustration at 0.7. bvFTD: behavioural variant fronto-temporal dementia. nfvPPA: non-fluent variant primary progressive aphasia. PCA: posterior cortical atrophy. ADMCI: Alzheimer's disease mild cognitive impairment with positive amyloid imaging.

Figure 3: Source-localised evoked responses for standard the average of all standard and all deviant tones. Means and standard errors across subjects are plotted, along with an illustrative significance bar, showing timepoints at which patient group responses significantly differed from control responses, $p < 0.05$ FDR corrected across timepoints using the Benjamini and Hochberg method. A1: primary auditory cortex, STG: superior temporal gyrus, IFG: inferior frontal gyrus, IPC: inferior parietal cortex. In A1 and STG bilaterally, the response lines for standard (STD) stimuli overly one another for all groups except PCA, which has a slightly more negative trace from 80-200ms. However, in the deviant (DVT) case, the lines separate by group at 100-200ms, albeit not statistically significantly for nfvPPA and bvFTD groups when FDR corrected across time. Quantifications of this difference are shown in Figure 5.

Figure 4: Source-localised evoked responses for mismatch negativity (MMN). Means and standard errors across subjects are plotted, along with an illustrative significance bar, showing timepoints at which patient group responses significantly differed from control responses, $p < 0.05$ FDR corrected across timepoints using the Benjamini and Hochberg method. A1: primary auditory cortex, STG: superior temporal gyrus, IFG: inferior frontal gyrus, IPC: inferior parietal cortex. The middle panel shows MMN amplitude averaged between 100ms and 200ms in left A1 (Hughes et al., 2013). One way ANOVAs in all deviant types showed a main effect of diagnosis. Groups that significantly differed from controls in post-hoc tests are coloured red for each condition. The bottom panel shows the MMN waveform in left A1 for each deviant type individually.

Figure 5: Our literature pre-specified approach was to quantify MMN amplitude in left A1 (Hughes et al., 2013) by averaging amplitude from 100-200ms. To gain insight into whether the differences we demonstrate are primarily driven by adaptation to environmental regularity or response to novel stimuli, we repeated the same procedure with the STD and combined DVT response, as well as for each oddball type individually, and assessed group differences with ANOVA. In left A1 there was no main effect of diagnosis on STD response in the 100-200ms time window ($p = 0.089$). There was a main effect of diagnosis on DVT amplitude ($p = 1.73 \times 10^{-5}$). Post-hoc tests demonstrated that patients with PCA and ADMCI had significantly lower amplitudes than controls, but bvFTD and nfvPPA did not significantly differ from controls. This pattern was broadly the same across deviant types individually, with small changes in pattern resulting in nfvPPA differing from controls in duration deviants and ADMCI not differing in intensity deviants. The data in left STG had slightly better SNR than A1, because of its closer proximity to the scalp. Here there was still no main effect of diagnosis for STD amplitude ($p = 0.245$). For DVT, there was a main effect of diagnosis ($p = 6.28 \times 10^{-7}$), and here we were able to detect a group difference in response amplitude for every group individually vs controls in post-hoc tests. However, it is important to note that left

STG was not our literature specified location of interest for MMN quantification, and is included here only as data illustration, not the basis of any strong claims in the manuscript.

Figure 6: The locations of positive correlation between left A1 MMN amplitude and grey matter volume are shown in ‘hot’ colours for various statistical models. A probabilistic map of the MD (lateral fronto-parietal) network from HCP derived resting state connectivity networks (Dworetsky et al., 2021) is overlaid in ‘cool’ colours. In the first model, all participants are included as a single group, with age and TIV as covariates of no interest, to elucidate the anatomical correlates of auditory MMN amplitude. This model is shown twice, thresholded at $p < 0.001$ for the distributional analyses described in the text, and $p < 0.01$ uncorrected for illustration of more widespread MD involvement below statistical threshold. This regression model’s fits in each of our four ROIs (left and right frontal and parietal nodes) are shown in Figure 7, left panel. Next, in the third row, we show the same model with control participants excluded (i.e. patients only), to ensure non-specific group effects are not the driver of our results. In the fourth and fifth rows we show linear mixed models, with age and TIV as covariates of no interest, and a factor group with either two (controls, patients) or five (controls, bvFTD, nfVPPA, PCA, ADMCI) levels, to exclude Simpson’s paradox. The five-group model’s fits in each of our four ROIs are shown in Figure 7, right panel. All models were topographically similar, and showed overlapping voxels of peak significance in our regions of interest (Table 2).

Figure 7: Regression model datapoints in frontal and parietal hot-spot regions, with individuals colour-coded by group. IFG: inferior frontal gyrus, IPC: inferior parietal cortex. The left column shows the combined model with all participants included as a single group, with age and TIV as covariates of no interest. The global trend line is shown. The right column shows the linear mixed model with age and TIV as covariates of no interest and a factor group with five levels, demonstrating similar structure-function relationships in every group individually.

Figure 8: Differences between patients and controls in effective extrinsic connectivity strength and auditory-change related modulation with Bayesian probabilities > 0.95 . ‘Modulation’ differences represent changes in effective connectivity as a function of the STD-DVT contrast (i.e. the group by condition interaction), while ‘overall’ differences represent changes in effective connectivity across all trial types. Larger coloured arrows represent strengthening in patients compared to controls, while smaller coloured arrows represent weakening. A1: primary auditory cortex, STG: superior temporal gyrus, IFG: inferior frontal gyrus, IPC: inferior parietal cortex.

Figure 9: Frequency resolved connectivity analyses with phase-locking value (plv) and imaginary coherence (icoh). For each frequency band and for each connection, the observed mean plv or icoh in the relevant patient group was subtracted from the same measure in the control group. Negative values indicate stronger plv or icoh in patients than controls. These data were compared to a null distribution of 1,100 values for each frequency band (100 iterations at each of 11 unique connections), generated from the same subtraction for trial-shuffled connectivity, using two-sample Welch’s t-tests. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. The pattern of results was similar for continuous data epoched 0-500ms after tone onset, and discontinuous data focused on the time of the MMN, 0-250ms after tone onset. These findings cannot be accounted for by overall differences in power between groups; in general, patients had the same or higher functional connectivity, and the same or lower power compared to controls (Figure 12).

Figure 10: Partial phase locking value for individual connections, broken down by group and network. Negative values indicate stronger partial phase locking value in patients than controls, and vice-versa. Red boxes highlight consistently increased functional connectivity between multiple demand and auditory regions in low frequencies for patients with bvFTD and nfVPPA, and high frequencies for PCA and ADMCI. Multiple demand to auditory connections were STG-IPC and STG-IFG on each side, cross hemispheric connections were STG-STG, IPC-IPC, and IFG-IFG, within auditory connections were A1-STG in each hemisphere, and multiple demand region connections were IFG-IFG in each hemisphere. A1: primary auditory cortex, STG: superior temporal gyrus, IFG: inferior frontal gyrus, IPC: inferior parietal cortex. These data were

1045 compared to a null distribution of 400 iterations with trial-shuffled connectivity per connection (100 iterations for each of the
1046 four groups). Individual connections were coloured red if they lay completely outside of this null distribution (equivalent to a
1047 permutation p-value of < 0.01 after Bonferroni correction across frequency bands).

1048 Figure 11: Partial imaginary coherence for individual connections, broken down by group and network. Negative values
1049 indicate stronger imaginary coherence in patients than controls, and vice-versa. Multiple demand to auditory connections
1050 were STG-IPC and STG-IFG on each side, cross hemispheric connections were STG-STG, IPC-IPC, and IFG-IFG, within
1051 auditory connections were A1-STG in each hemisphere, and multiple demand region connections were IPG-IFG in each
1052 hemisphere. A1: primary auditory cortex, STG: superior temporal gyrus, IFG: inferior frontal gyrus, IPC: inferior parietal
1053 cortex. These data were compared to a null distribution of 400 iterations with trial-shuffled connectivity per connection (100
1054 iterations for each of the four groups). Individual connections were coloured red if they lay completely outside of this null
1055 distribution (equivalent to a permutation p-value of < 0.01 after Bonferroni correction across frequency bands).

1056 Figure 12: Power spectral density over the whole experiment in each region of interest, colour coded by group. Means and
1057 standard errors across subjects are plotted, along with illustrative significance dots, showing frequency steps at which patient
1058 group power significantly differed from controls, $p < 0.05$ FDR corrected across frequency using the Benjamini and Hochberg
1059 method. Note that the data have been filtered to exclude 50Hz line noise, and the multitaper decomposition uses a ± 4 Hz
1060 smoothing box.

1061

1062 **Table Legends**

1063 Table 1: Participant demographics. bvFTD: behavioural variant fronto-temporal dementia. nvPPA: non-fluent variant
1064 primary progressive aphasia. PCA: posterior cortical atrophy. ADMCI: Alzheimer's disease mild cognitive impairment with
1065 positive amyloid imaging.

1066 Table 2: Table of structure-function relationships for each regression model individually. Across all three confirmatory
1067 models and four regions of interest, the voxel of peak significance in the combined regression is significant in eleven of
1068 twelve cases. The only exception is the left frontal voxel in the ungrouped regression model with controls excluded, which is
1069 only trend significant. However, as shown in the maps (Figure 6, second row), there is an extensive left frontal cluster in this
1070 condition, that is slightly more anterolateral than the original analysis, just missing the original peak. The peak of this
1071 cluster is also reported.

1072

Response to Standard Tone

Response to All Deviant Tones

Overall Mismatch Response

Mismatch Amplitude Left A1

Individual Mismatches Left A1

Partial Phase Locking Value

bvFTD

nfvPPA

PCA

ADMCI

0-500ms

<-Controls stronger Patients stronger->

0-250ms

<-Controls stronger Patients stronger->

Partial Imaginary Coherence

0-500ms

<-Controls stronger Patients stronger->

Partial Imaginary Coherence

Partial Phase Locking Value