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Neural Evidence of Functional Compensation for Fluid Intelligence in Healthy Ageing

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Abstract

Functional compensation is a common notion in the neuroscience of healthy ageing, whereby older adults are proposed to recruit additional brain activity to compensate for reduced cognitive function. However, whether this additional brain activity in older participants actually helps their cognitive performance remains debated. We examined brain activity and cognitive performance in a human lifespan sample (N=223) while they performed a problem-solving task (based on Cattell's test of fluid intelligence) during functional magnetic resonance imaging (fMRI). Whole-brain univariate analysis revealed that activity in bilateral cuneal cortex for hard vs. easy problems increased both with age and with performance, even when adjusting for an estimate of age-related differences in cerebrovascular reactivity. Multivariate Bayesian decoding further demonstrated that age increased the likelihood that activation patterns in this cuneal region provided non-redundant information about the two task conditions, beyond that of the multiple-demand network generally activated in this task. This constitutes some of the strongest evidence yet for functional compensation in healthy ageing, at least in this brain region during visual problem-solving.

eLife assessment

This study provides an **important** advancement of knowledge by showing neural functional compensation in the brains of healthy older adults completing a fluid-intelligence task. Validated whole-brain voxel-wide analyses and multivariate Bayesian approaches provide **compelling** evidence that supports the claims of the authors. The work delivers methods for quantifying reserve and compensation in future studies and will be of interest to researchers in the field of the neuroscience of healthy aging.

Introduction

Preventing cognitive decline in old age is a major public heath priority, which demands a better understanding of the neurophysiological changes that preserve cognitive function despite progressive brain atrophy (Cabeza et al., 2018; Christensen et al., 2009). Neuroimaging has facilitated the idea that the brain can flexibly respond to tissue loss (e.g., due to ageing) by recruiting additional brain activity to support cognitive functions (Cabeza et al., 2018; Grady, 2012). If this additional recruitment in older adults improves their behavioural performance, it is argued that this reorganisation of brain function constitutes a functional compensation mechanism (Cabeza, 2002).

Fluid intelligence (i.e., solving novel abstract problems) is a cognitive function that shows one of the most consistent and largest decreases in older age (Salthouse et al., 2008; Deary, 2012; Ghisletta et al., 2012; Kievit et al., 2014; Bors & Forrin, 1995; Salthouse & Pink, 2008; Schretlen et al., 2000; Clay et al., 2009; Kievit et al., 2018). Functional (Duncan et al., 2000; Gray et al., 2003; Lee et al., 2006; Crittenden et al., 2016; Tschentscher et al., 2017) and structural (Colom et al., 2009; Jauk et al., 2015; Chen et al. 2020; Paul et al., 2016; Zamroziewicz et al., 2018) neuroimaging has shown that fluid intelligence tasks engage the multiple demand network (MDN; Duncan, 2010), which comprises lateral prefrontal, posterior parietal and cingulate regions. MDN activation tends to decrease with age as measured, for example, with fMRI during problem-solving tasks that tax fluid intelligence such as the Cattell task (Samu et al., 2017; Mitchell et al., 2022). So far, these studies have examined age effects in core regions of the MDN but have not explicitly tested for functional compensation in other regions.

To search for brain regions that might support functional compensation, we conducted a whole-brain voxel-wise search for clusters that showed a positive relationship with both age and cognitive performance (i.e., classic univariate criteria for functional compensation; Lövdén et al., 2010; Cabeza et al., 2018). The dependent variable was the difference in fMRI activation for blocks of hard vs. easy odd-one-out problems (**Figure 1A**), as measured in 223 adults between 19 and 87 years of age, from Stage 3 of the Cambridge Centre for Ageing & Neuroscience (Cam-CAN) project (Shafto et al., 2014); performance was measured as the proportion of all problems correct. Second, we applied a Multi-Variate Bayesian approach (MVB; Friston et al., 2008) across all voxels within any candidate regions identified in the whole-brain search, to test whether multivoxel patterns in these regions provided additional information about task difficulty, beyond that in the MDN. We predicted that, if a region were involved in functional compensation, the additional information it contains about the task would increase with age. To pre-empt the results, unlike in our previous applications of MVB (Morcom & Henson, 2018; Knights et al., 2021), we find one region - within the cuneus - that did show evidence of this additional multivariate information, supporting its role in functional compensation.

Results

Behavioural Performance

As expected from prior studies, behavioural performance decreased with age during the fMRI scan on the modified version of the Cattell task (collapsed across hard and easy conditions; see Methods) (standardised coefficient = −5.65, $t(220) = -14$, $p < .001$, $R^2 = 0.48$; **Figure 1B** upper). There was a high correlation between performance measures from the fMRI version and standard version of the Cattell task when the same people performed the standard Cattell task outside the scanner 1-3 years previously ($r = 0.79$, $p < 0.001$; **Figure 1B** lower), suggesting that the version modified for fMRI was capturing the same cognitive ability.

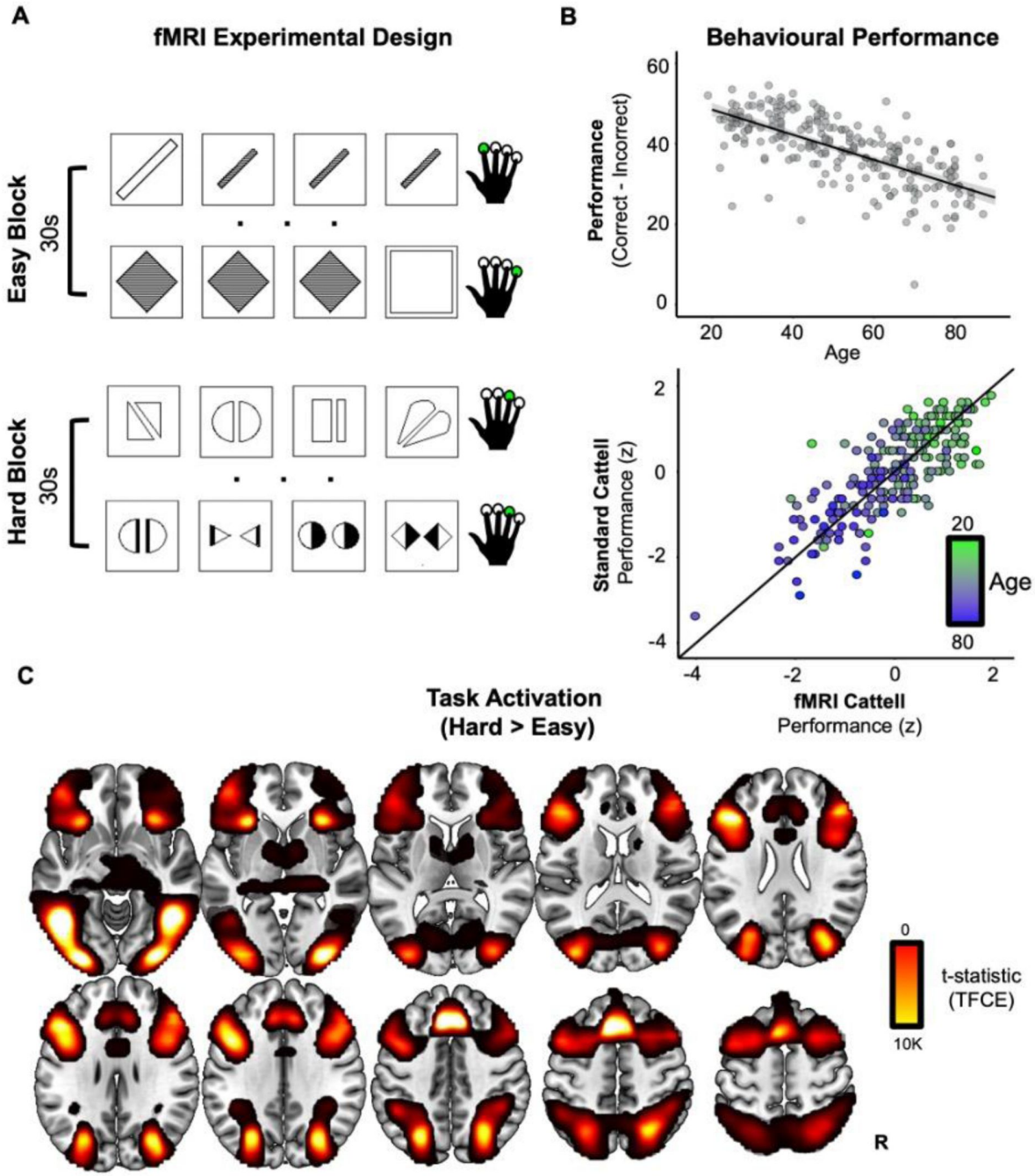

Figure 1.

(A) fMRI version of Cattell task.

On each trial (each row), participants select the odd-one-out from four panels with a single finger button-press (green circles). Condition blocks (30 seconds) alternate between easy vs. hard puzzles. **(B) Behavioural age-related decline.** Performance (correct minus incorrect in fMRI version of Cattell task) significantly declined linearly with age (upper). High reliability was observed between performance measures from the standard Cattell task and the modified version used for fMRI (lower). In the upper panel, the black line represents the fitted-regression estimates with shaded 95% confidence intervals. In the lower panel, the black line represents perfect correlation between the two Cattell versions. **(C) Univariate task effect.** Whole-brain voxel-wise activations for solving the puzzles in the hard, relative to easy, blocks, after threshold-free cluster enhanced (TFCE) correction.

Univariate Response

The [Hard > Easy] contrast showed bilateral activation across regions generally described as comprising the MDN (e.g., Duncan 2010; Smith et al., 2021), including the inferior/middle frontal gyri, intraparietal sulcus, anterior insula and anterior cingulate cortex (**Figure 1C**). Additional activation was observed bilaterally in the inferior/ventral and lateral occipital temporal cortex, likely due to the visual nature of the task.

To search for a potentially compensatory pattern of brain activation, we next overlaid maps that tested for positive effects of age (**Figure 2A** green map) and performance (**Figure 2A** red map) on the [Hard > Easy] contrast. While age and performance are negatively correlated (**Figure 1B**), their effects were estimated simultaneously via multiple regression, and so the activation maps reflect unique effects of each. As reported using related measures and overlapping samples of Cam-CAN participants (Samu et al., 2017; Wu et al., 2021; Mitchell et al., 2022), age-related increases in activity were widespread, including the precuneus, middle frontal gyrus and supplementary motor area. Activity positively related to performance was found in many of the same regions that were more active for hard versus easy problems (i.e., inferior/middle frontal gyrus, anterior cingulate, superior parietal lobule; **Figure 1C**).

Crucially, two areas of the brain showed spatially-overlapping positive effects of age and performance, which is suggestive of an age-related compensatory response (**Figure 2A** yellow intersection). These were in bilateral cuneal cortex (**Figure 2B** magenta) and bilateral frontal cortex (**Figure 2B** brown), the latter incorporating parts of the middle frontal gyri and anterior cingulate. Therefore, based on traditional univariate analyses, these are two candidate regions for age-related functional compensation (Cabeza et al. 2013; 2018).

However, the two candidate compensation regions showed different patterns as a function of age and performance: whereas the frontal region showed additive effects of both variables (**Figure 2C**, upper), the cuneus region showed signs of an interaction ($p = 0.028$; though this would not survive correction for multiple comparisons across the two ROIs), whereby the relationship with performance was strongest in the oldest participants (and there was little sign of a performance relationship in the youngest participants; **Figure 2C**, lower). This is suggestive of compensatory activation only engaged by higher-performing older people in the cuneus specifically.

It has previously been shown that many effects of age on the BOLD signal measured by fMRI relate to vascular effects of ageing, rather than necessarily indicating differences in neural activity (Tsvetanov et al., 2020). We therefore repeated the multiple regressions after scaling the Cattell activation effect by an estimate of the Resting State Fluctuation Amplitude (RSFA) for each ROI from an independent, resting-state scan for each participant. Previous work has shown that RSFA relates to age-related vascular differences (Tsvetanov et al., 2015, 2020), but not neural differences (Tsvetanov et al 2015, Kumar et al 2020). Despite this RSFA adjustment, the pattern of effects remained similar in each ROI (**Table 1**; **Figure 2C**). This suggests that these effects of age (and the relationship with performance) are neural in origin. This check has not been performed in previous fMRI studies of age-related compensation, which could reflect vascular effects of ageing instead.

Multivariate Bayesian Decoding

Next, we examined if these candidate compensation regions showed multivariate evidence of compensation. If their age- and performance-related activation reflects compensation, then multivoxel analyses should show that this “hyperactivation” carries additional information about the task, over and above that already provided by the regions generally activated by the task (i.e., MDN). To test this, we applied Multivariate Bayesian decoding (MVB) of the [Hard > Easy] contrast.

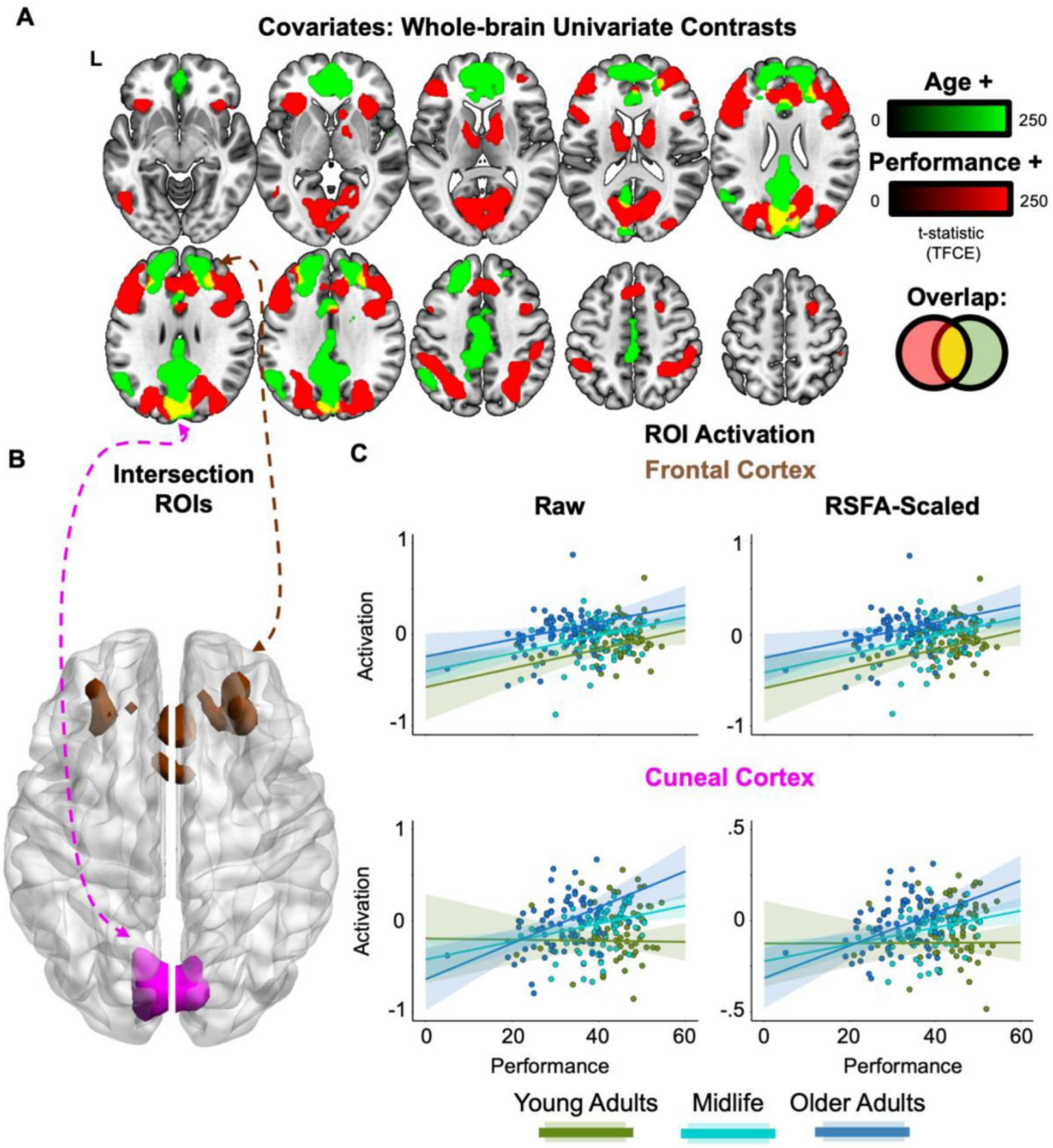

Figure 2.

Univariate analysis. **(A) Whole-brain effects of age and performance.** Age (green) and performance (red) positively predicted unique aspects of increased task activation, with their spatial overlap (yellow) being overlaid on a template MNI brain, using $p < 0.05$ TFCE. **(B) Intersection ROIs.** A bilateral cuneal (magenta) and frontal cortex (brown) ROI were defined from voxels that showed a positive and unique effect of both age and performance (yellow map in **Figure 2A**). **(C) ROI Activation** Activation (raw = left; RSFA-scaled = right) is plotted against behavioural performance based on a tertile split between three age groups.

Region	Coefficient	Estimate	t value	Pr(>|t|)
Cuneal				
	Constant term	-0.06	-2.57	0.011
	Age	0.09	3.57	<.001
	Performance	0.08	3.21	0.002
	Sex	-0.05	-2.59	0.01
	Age x Performance	0.04	2.21	0.028
Cuneal (RSFA)				
	Constant term	-0.03	-2.60	0.010
	Age	0.04	3.24	0.001
	Performance	0.04	3.11	0.002
	Sex	-0.02	-2.52	0.013
	Age x Performance	0.02	1.97	0.049
Frontal				
	Constant term	-0.03	-2.02	0.045
	Age	0.08	4.24	<.001
	Performance	0.08	4.54	<.001
	Sex	<0.001	-0.35	0.728
	Age x Performance	<0.001	-0.15	0.882
Frontal (RSFA)				
	Constant term	-0.02	-1.99	0.048
	Age	0.04	4.12	<.001
	Performance	0.04	4.48	<.001
	Sex	0.00	-0.37	0.709
	Age x Performance	0.00	-0.13	0.898

Table 1.

Standardised coefficients in multiple regression predicting fMRI activation (Hard - Easy) as a function of Age and Performance for the two ROIs identified in

Figure 2. Note that the p-values for the main effects of Age and Performance are biased by the selection of these voxels. RSFA = scaled by Resting-State Fluctuation Amplitudes (see text).

We first implemented MVB with a 'joint model' that contained voxel activation patterns from (1) one of the potential compensation ROIs and (2) the same number of the most significant voxels in the MDN (defined by the orthogonal contrast of [Hard > Easy]; **Figure 1C**; see **Table 2** for voxel numbers). For each joint model (i.e., MDN voxels + cuneal or frontal voxels), we compared the log model evidence for the correct model to ones where the stimulus onsets were shuffled (i.e., to estimate a null distribution of model evidence). Across both joint models (MDN plus cuneal or frontal cortex), we found evidence of above-chance decoding (real vs. shuffled log-evidence difference > 3; see Methods) for all except two participants. These participants (the two points below the y = 3 dashed line in **Figure 3A**, one of whom was the same across models) were removed (Morcom & Henson, 2018; Knights et al., 2021).

Having established that the task condition could be decoded from voxels in the vast majority of participants, the critical test was whether age influenced the likelihood that adding voxel activation patterns from the 'compensatory' ROIs (i.e., joint model) would boost decoding accuracy relative to that for the MDN-only model. A positive age effect on boost likelihood would indicate that, the older someone was, the more likely that activation patterns in the putative "compensation ROI" would provide additional, non-redundant, task-relevant information, consistent with a compensatory role. In line with this compensation account, there was a significant positive effect of age (**Table 2**) on the likelihood that model performance was boosted (i.e., log evidence change > 3) by including voxel activation patterns from the cuneal ROI (**Figure 3B** lower; Odds ratio = 2.21). In other words, the amount of unique task information in the multi-voxel pattern within the cuneal ROI (above that present in the MDN) increased with age. By contrast, this analysis for the model containing the frontal ROI voxel activation patterns showed no effect of age (**Table 2**; **Figure 3B** upper).

Note that, since this age effect in the cuneus was present even though the logistic regression model contained this ROI's univariate response as a covariate of no interest (**Table 2**), the effect of age on boost likelihood is unlikely to be due to differences in the overall signal-to-noise ratio across ages.

Discussion

The existence of age-related functional compensation mechanisms remains a matter of debate in the cognitive neuroscience of healthy ageing. Here, we analysed fMRI data from a problem-solving (fluid intelligence) task and identified two brain regions (in bilateral cuneal and frontal cortex; **Figure 2A**/B) that satisfied traditional univariate criteria for functional compensation. After applying the multivariate criterion that a compensating region should possess additional information about the task, only the cuneal cortex showed an age-related increase in this additional information (**Figure 3B**), beyond that available in the generic task-activated regions (i.e., the MDN; **Figure 1C**). This is the first demonstration of increased multivariate information with age, since previous studies have shown evidence for no such multivariate increase associated with univariate age-related hyper-activation in other ROIs and tasks; leading to previous findings being interpreted in terms of neural inefficiency, rather than compensation (Morcom & Henson, 2018; Knights et al., 2021).

Why would the cuneal cortex demonstrate functional compensation when solving difficult visuospatial problems? Since the cuneus has a well-established role in visual attention (e.g., Corbetta et al., 1998), we hypothesise that the additional recruitment of this brain region facilitates concurrently attending to multiple features of the stimulus array, to correctly select the 'odd-one-out'. The recruitment of this brain region in older adults could drive changes in looking strategy (e.g., Law et al., 1996), where, for example, older adults compensate for their reduced visual short-term memory (Mitchell et al., 2018) - i.e., difficulty sustaining representations of puzzle items - by using more or different saccades. This possibility is consistent with the greater

Model	Coefficient	Estimate	z-statistic	p
Cuneal ROI + Task-network (166 voxels each)				
	Constant term	2.17	8.79	<.001
	Age	0.79	3.23	<.001
	Sex	0.08	0.37	0.714
	Univariate	-0.34	-1.59	0.112
Frontal ROI + Task-network (85 voxels each)				
	Constant term	2.20	9.30	<.001
	Age	0.04	0.19	0.851
	Sex	0.26	1.13	0.257
	Univariate	-0.54	-2.33	0.020

Figure 3.

Multivariate Analysis. **(A) MVB Decoding.** Points represent the difference in log evidence per participant (for the real vs. shuffled model) for the joint model using activation patterns to decode the [Hard > Easy] contrast. **(B) Boost Likelihood Model Comparison.** Across age, a smoothed density estimate represents the likelihood that there was a boost (of log-evidence > 3; green) or no difference (grey) to model evidence per participant when decoding models included activation patterns from either of the compensation ROIs (**Figure 2B**) in addition to the MDN (**Figure 1C**), relative to a model that sampled only from the MDN. A significant positive linear effect of age on boost likelihood was observed for the cuneal (lower) but not frontal ROI (upper).

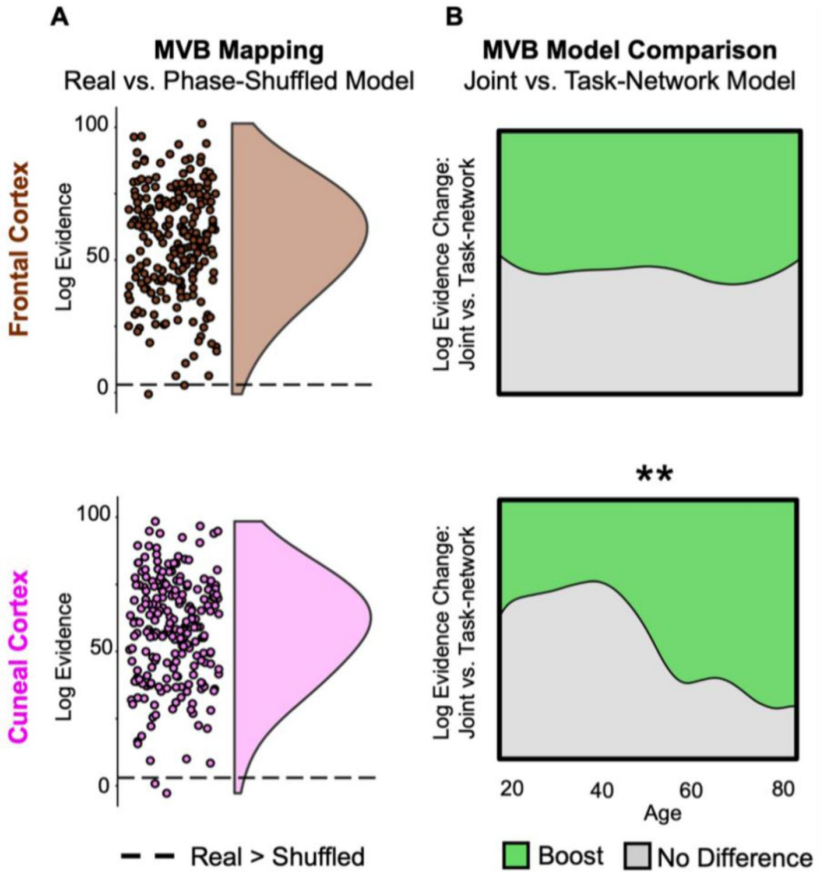

Table 2.

Standardised coefficients in multiple logistic regression predicting MVB Boost likelihood as a function of age (with Sex and Mean Univariate Activation as covariates).

cuneal activation that was observed for older adults who performed better at the task (**Figure 2C**). Future work pairing fMRI behavioural tasks with eye-monitoring could verify this proposed relationship between age, cuneus activation, overt attention and fluid intelligence.

In line with this hypothesised role of the cuneal cortex, there is consistent functional (Yin et al., 2015; Santarnecchi et al., 2017) and structural (Haier et al., 2004; Jauk et al., 2015; Chen et al. 2020) neuroimaging evidence that link this brain region to aspects of fluid intelligence like rule-application. Similarly, responses from sensory areas (like the secondary visual network that overlaps our cuneus ROI; Ji et al., 2019) have been shown to predict fluid intelligence performance (Brumback et al., 2004). In aging, it is well established that sensory and intellectual decline are correlated (see Baltes & Lindenberger, 1997), either because they share a common cause or because performance of fluid intelligence tasks is partially dependent on sensory processing (e.g., Schneider & Pichora-Fuller, 2000). While our data cannot tease apart these hypotheses, it may be that compensatory processes in the cuneal region reflect this shared age-related variance between sensory and higher-order cognitive tasks.

Though activation of the cuneal ROI increased with age, it is worth noting the constant term (reflecting the average across all ages) was negative (**Table 1**), suggesting that most people (other than the older ones) showed greater activation of this region for easy than hard problems. This is more difficult to reconcile with its activation reflecting visual attention or eye movements, since this would suggest greater visual attention/eye movements toward easy than hard problems in the young. One alternative possibility is active suppression of the cuneal region in the hard blocks, to avoid distraction (e.g., minimise attentional capture from neighbouring display panels while processing features in each panel). Thus, the age-related reduction in the Easy-Hard difference (leading to the positive correlation of the Hard-Easy difference with age) could reflect reduced ability to inhibit the cuneus during hard problems, consistent with the established age-related decline in the ability to suppress distracting information in complex stimuli (Tsvetanov et al., 2013, Rey-Mermet et al., 2018, Bouhassoun et al., 2022). However, it is not clear why this alternative account would predict a positive correlation between cuneal activity and task performance, given that greater suppression (in the Hard condition) would be expected to lead to better performance, but more negative activity values for the [Hard - Easy] contrast. Thus, we favour the explanation in terms of functional compensation.

Another possibility is that the age-related increases in fMRI activations (for hard versus easy) in one or both of our ROIs do not reflect greater fMRI signal for hard problems in older than younger people, but rather lower fMRI signal for easy problems in the older. Without a third baseline condition, we cannot distinguish these two possibilities in our data. However, a reduced “baseline” level of fMRI signal (e.g., for easy problems) in older people is consistent with other studies showing an age-related decline in baseline perfusion levels, coupled with preserved capacity of cerebrovascular reactivity to meet metabolic demands of neuronal activity at higher cognitive load (Calautti et al., 2001; Jennings et al., 2005). Though age-related decline in baseline perfusion occurs in the cuneal cortex (Tsvetanov et al., 2021), the brain regions showing modulation of behaviourally-relevant Cattell fMRI activity by perfusion levels did not include the cuneal cortex (Wu et al., 2021). This suggests that the compensatory effects in the cuneus are unlikely to be explained by age-related hypo-perfusion, consistent with the minimal effect here of adjusting for RSFA (**Figure 2C**).

The age- and performance-related activation in our frontal region satisfied the traditional univariate criteria for functional compensation, but our multivariate (MVB) analysis showed that additional multivariate information was absent in this region, which is inconsistent with compensation. This pattern of results suggests that traditional univariate criteria alone are not sufficient for identifying functional compensation. Similar univariate effects have been found in previous studies (though with smaller samples), where lateral and medial frontal areas show increased activation during healthy ageing across a range of tasks, including those related to

executive control or attention (e.g., Grady et al., 2010; for a review, see Spreng et al., 2010; also see Raz et al., 2008, for a neuroanatomical link). Patients with brain damage also demonstrate increased frontal activation during language and semantic processing (Brownsett et al., 2014; Rice et al., 2018) indicating that this mechanism might be a response to brain atrophy generally. Instead, our results suggest that this frontal hyperactivation in older adults reflects "inefficient" processing, in terms of more neural resources being needed to perform the task (i.e., for hard versus easy problems). In fact, neural inefficiency was our favoured interpretation of previous cases when MVB showed no age-related boost, in frontal (Morcom & Henson, 2018) or motor (Knights et al., 2021) regions. From these studies, and all previous fMRI/PET studies that showed age-related hyper-activation, it was not known whether the increased activations reflected greater neural inefficiency, or greater haemodynamic resources needed for the same level of neural activity (i.e., vascular rather than neural inefficiency). Here, we showed for the first time that the age-related increase in both ROIs remained even after adjusting for RSFA (**Table 1**), suggesting that this hyper-activation reflects neural rather than vascular inefficiency.

In Morcom & Henson (2018), we did not explicitly test for a relationship between activation and (memory) performance, and in Knights et al. (2021), we failed to find any relationship between (ipsilateral motor) activation and various (motor) performance measures. In the present study, it may be that the age-related frontal hyper-activation is caused by neural inefficiency, yet the degree of overall activation still relates to (lifespan-stable) problem-solving performance. Converging with the lack of additional multivariate information, this suggests that the frontal region does not show a compensatory response.

In summary, we propose that our results in the cuneus represent the most compelling evidence to date for functional compensation in healthy ageing, with further work needed to determine the precise function of this region in problem-solving tasks like that examined here. Together with the results in prefrontal cortex, the data also suggest that specific compensatory neural responses can coexist with inefficient neural function in older people.

Methods

Participants

A healthy population-derived adult lifespan human sample (N = 223; ages approximately uniformly distributed from 19 - 87 years; females = 112; 50.2%) was collected as part of the Cam-CAN study (Stage 3 cohort; Shafto et al., 2014).

Participants were fluent English speakers in good physical and mental health, based on the Cam-CAN cohort's exclusion criteria which includes poor mini mental state examination, ineligibility for MRI and medical, psychiatric, hearing or visual problems. Throughout analyses, age is defined at the Home Interview (Stage 1; Shafto et al., 2014). The study was approved by the Cambridgeshire 2 (now East of England– Cambridge Central) Research Ethics Committee and participants provided informed written consent.

Materials & Procedure

A modified version of the odd-one-out subtest of the standardised Cattell Culture Fair Intelligence test (Scale 2; Cattell, 1971; Cattell & Cattell, 1973) was developed for use in the scanner (Woolgar et al., 2013; Samu et al., 2017; Wu et al., 2021).

Participants were scanned while performing the problem-solving task where, on each trial, four display panels were presented in a horizontal row (**Figure 1A**) in the centre of a screen that was viewed through a head-coil mounted mirror. Participants were required to make a button press

response to identify the mismatching panel that was unique in some way from the other three (based on either a figural, spatial, complex, or abstract property).

In a block design, participants completed eight 30-second blocks which contained a series of puzzles from one of two difficulty levels (i.e., four hard and four easy blocks completed in an alternating block order; **Figure 1A**). The fixed block time allowed participants to attempt as many trials as possible. Therefore, to balance speed and accuracy, behavioural performance was measured by subtracting the number of incorrect from correct trials and averaging over the hard and easy blocks independently (i.e., ((hard correct - hard incorrect) + (easy correct - easy incorrect))/2; Samu et al., 2017). For assessing reliability and validity, behavioural performance (total number of puzzles correct) was also collected from the same participants during a full version of the Cattell task (Scale 2 Form A) administered outside the scanner at Stage 2 of the Cam-CAN study (Shafto et al., 2014). Both the in- and out-of-scanner measures were z-scored. As with Samu et al (2017), we did not include participants (N = 28; 17 females) who performed poorly on the fMRI task, defined as 10 or more hard incorrect trials, roughly equivalent to >50% errors).

Data Acquisition & Preprocessing

The MRI data were collected using a Siemens 3T TIM TRIO system with a 32 channel head-coil. A T2*-weighted echoplanar imaging (EPI) sequence was used to collect 150 volumes, each containing 32 axial slices (acquired in descending order) with slice thickness of 3.0mm and an interslice gap of 25% for whole brain coverage (TR = 2000ms; TE = 30ms; flip angle = 78°; FOV = 192mm x 192mm; voxel-size 3 x 3 x 3.75mm). Higher resolution (1mm x 1mm x 1mm) T1- and T2-weighted structural images were also acquired (to aid registration across participants).

MR data preprocessing and univariate analysis were performed with SPM12 software (Wellcome Department of Imaging Neuroscience, London, *www.fil.ion.ucl.ac.uk/spm*), release 4537, implemented in the AA 4.0 pipeline (Cusack et al., 2015) described in Taylor et al. (2017). Specifically, structural images were rigid-body registered to an MNI template brain, bias corrected, segmented, and warped to match a grey matter template created from the whole Cam-CAN Stage 2 sample using DARTEL (Ashburner, 2007; Taylor et al., 2017). This template was subsequently affine transformed to standard Montreal Neurological Institute (MNI) space. The functional images were spatially realigned, interpolated in time to correct for the different slice acquisition times, rigid-body coregistered to the structural image, transformed to MNI space using the warps and affine transforms from the structural image, and resliced to 3mm x 3mm x 3mm voxels.

Univariate Analysis

For participant-level modelling, a regressor for each condition was created by convolving boxcar functions of 30 sec duration for each block with SPM's canonical haemodynamic response function. Additional regressors were included in each GLM to capture residual movement-related artifacts, including six representing the x/y/z rigid body translations and rotations (estimated in the realignment stage). Finally, the data were scaled to a grand mean of 100 over all voxels and scans within a session, and the model was fit to the data in each voxel. The autocorrelation of the error was estimated using an AR(1)-plus-white-noise model, together with a set of cosines that functioned to high-pass filter the model and data to 1/128 Hz, that were estimated using restricted maximum likelihood. The estimated error autocorrelation was then used to "prewhiten" the model and data, and ordinary least squares used to estimate the model parameters. The contrast of parameter estimates for the hard and easy conditions, per voxel and participant, was then calculated and combined in a group GLM with independent regressors for age and in-scanner behavioural performance.

ROIs

All ROIs were defined by selecting activated voxels from a group-level GLM (see **Table 2** for number of voxels within ROIs). The two ROIs that were tested as candidate regions for functional compensation (i.e., cuneal cortex and frontal cortex) were defined by contiguous voxels that were significantly positively related to the independent effects of both age and performance (see **Figure 2**). The MDN was defined by the selecting suprathreshold voxels activated by the [Hard vs. Easy] contrast from the Cattell task. For MVB analysis (see below), a subset of the highest activated voxels within the MDN were taken to match the number of voxels with that of the "compensation ROI" being tested (see **Figure 3**; **Table 2**).

For the ROI-based multiple regressions, the activation was averaged across voxels (i.e., mean difference in parameter estimates for Hard – Easy conditions) for each ROI and participant (**Figure 2**, **Table 2**). In the case of RSFA-scaled multiple regression, we used RSFA calculated from independent resting state scans (see Tsvetanov et al., 2015) to scale the task-related BOLD response (by dividing the

Hard – Easy difference in parameter estimates for each voxel by the RSFA value at the same voxel).

Mvb

A series of MVB models were fit to assess the information about task condition that was represented in each ROI or combination of ROIs. Each MVB decoding model is based on the same design matrix of experimental variables used in the univariate GLM, but the mapping is reversed; many physiological data features (fMRI activity in multiple voxels) are used to predict a psychological target variable (Friston et al., 2008). This target (outcome) variable is specified as the contrast [Hard > Easy] with all covariates removed from the predictor variables.

Each MVB model was fit using a parametric empirical Bayes approach, in which empirical priors on the data features (voxelwise activity) are specified in terms of spatial patterns over voxel features and the variances of the pattern weights. As in earlier work (Morcom & Henson, 2018; Knights et al., 2021), we used a sparse spatial prior in which "patterns" are individual voxels. Since these decoding models are normally ill-posed (with more voxels than scans), these spatial priors on the patterns of voxel weights regularize the solution.

The pattern weights specifying the mapping of data features to the target variable are optimized with a greedy search algorithm using a standard variational scheme (Friston et al., 2007). This is achieved by maximizing the free energy, which provides an upper bound on the log of the Bayesian model evidence (the marginal probability of the data given that model). The evidence for different models predicting the same psychological variable can then be compared by computing the difference in log evidences, which is equivalent to the log of the Bayes factor (Friston et al., 2008; Chadwick et al., 2012; Morcom & Friston, 2012).

The outcome measure was the log evidence for each model (Morcom & Henson, 2018; Knights et al., 2021). To test whether activity from an ROI is compensatory, we used an ordinal boost measure (Morcom & Henson, 2018; Knights et al., 2021) to assess the contribution of that ROI for the decoding of task-relevant information (**Figure 3B**). Specifically, Bayesian model comparison assessed whether a model that contains activity patterns from a compensatory ROI and the MDN (i.e., a joint model) boosted the prediction of task-relevant information relative to a model containing the MDN only. The compensatory hypothesis predicts that the likelihood of a boost to model decoding will increase with older age. The dependent measure, for each participant, was a categorical recoding of the relative model evidence to indicate the outcome of the model comparison. The three possible outcomes were: a boost to model evidence for the joint vs. MDN-only model (difference in log evidence > 3), ambiguous evidence for the two models (difference in log evidence between −3 to 3), or a reduction in evidence for the joint vs. MDN-only

model (difference in log evidence < −3). These values were selected because a log difference of three corresponds to a Bayes Factor of 20, which is generally considered strong evidence (Lee & Wagenmakers, 2014). A reduction in model evidence was not observed in the current study.

For this MVB boost analysis, participants were only included if their data allowed reliable decoding by the joint model (Morcom & Henson, 2018; Knights et al., 2021). To determine this, we contrasted the log evidence for the joint model with that from models in which the design matrix (and therefore the target variable) was randomly phase shuffled 20 times. The definition of reliable was based on a mean of 3 or more in the difference of log-evidence between the true and shuffled model (Morcom & Henson, 2018; **Fig. 3A**). Note that decoding is performed after removing the mean across voxels (i.e., MVB results are independent of the results in the univariate analyses presented in **Fig 1C** & **Table 1**).

Experimental Design & Statistical Analysis

Continuous age and behavioural performance variables were standardised and treated as linear predictors in multiple regression throughout the behavioural, univariate (**Table 1**, **Figure 1B**/2A) and MVB boost (**Table 2**) analyses. Sex was included as a covariate. For whole-brain voxelwise analyses, clusters were estimated using threshold-free cluster enhancement (TFCE; Smith & Nichols 2009) with 2000 permutations. Bonferroni correction was applied to a standard alpha = 0.05 based on the two ROIs (cuneal and frontal) that were examined. For Bayes Factors, interpretation criteria norms were drawn from Jarosz & Wiley (2014).

Data Availability

Raw and minimally pre-processed MRI (i.e., from automatic analysis; Taylor et al., 2017) and behavioural data are available by submitting a data request to Cam-CAN (*https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/*). The univariate and multivariate ROI data, and behavioural data, can be downloaded from the Open Science Framework (*https://osf.io/v7kmh*) while the analysis code is available on GitHub (*https://github.com/ethanknights/Knightsetal_fMRI-Cattell-Compensation*).

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Reviewer #1 (Public Review):

Summary:
This work addresses how to quantify functional compensation throughout the aging process and identifies brain regions that engage in compensatory mechanisms during the Cattell task, a measure of fluid cognition. The authors find that regions of the frontal cortex and cuneus showed unique effects of both age and performance. Interestingly, these two regions demonstrated differential activation patterns taking into account both age and performance. Specifically, the researchers found that the relationship between performance and activation in the cuneal ROI was strongest in older adults, however, this was not found in younger adults. These findings suggest that specifically within the cuneus, greater activation is needed by older adults to maintain performance, suggestive of functional compensation.

Strengths:
The conclusions derived from the study are well supported by the data. The authors validated the use of the in-scanner Cattell task by demonstrating high reliability in the same sample with the standard out-of-scanner version. Some strengths of the study include the large sample size and wide age range of participants. The authors use a stringent Bayes factor of 20 to assess the strength of evidence. The authors used a whole-brain approach to define regions of interest (ROIs) based on activation patterns that were jointly related to age and performance. Overall, the methods are technically sound and support the authors' conclusions.

Weaknesses:
While the manuscript is methodologically sound, the following aspects of image acquisition and data analysis need to be clarified to ensure replicability and reproducibility. The authors state that the sample is a "population-derived adult lifespan sample", the lack of demographic information makes it impossible to know if the sample is truly representative. Though this may seem inconsequential, education may impact both cognitive performance and functional activation patterns. Moreover, the authors do not report race/ethnicity in the manuscript. This information is essential to ensure representativeness in the sample. It is imperative that barriers to study participation within minoritized groups are addressed to ensure rigor and reproducibility of findings.

For the whole-brain analysis in which the ROIs were derived, the authors used a threshold-free cluster enhancement (TFCE; Smith & Nichols 2009). The methodological paper cited suggests that individuals' TCFE image should still be corrected for multiple comparisons

using the following: "to correct for multiple comparisons, one [...] has to build up the null distribution (across permutations of the input data) of the maximum (across voxels) TFCE score, and then test the actual TFCE image against that. Once the 95th percentile in the null distribution is found then the TFCE image is simply thresholded at this level to give inference at the $p < 0.05$ (corrected) level." (Smith & Nichols, 2009). Although the authors mention that clusters were estimated using 2000 permutations, there is no mention of the TFCE image itself being thresholded. While this would impact the overall size of the ROIs used in the study, the remaining analyses are methodologically sound.

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Reviewer #2 (Public Review):

This work by Knights et al., makes use of the Cam-CAN dataset to investigate functional compensation during a fluid processing task in older adults, in a fairly large sample of approximately 200 healthy adults ranging from 19 to 87. Using univariate methods, the authors identify two brain regions in which activity increases as a function of both age and performance and conduct further investigations to assess whether the activity of these regions provides information regarding task difficulty. The authors conclude that the cuneal cortex - a region of the brain previously implicated in visual attention - shows evidence of compensation in older adults.

The conclusions of the paper are well supported by the data, and the authors use appropriate statistical analyses. The use of multivariate methods over the last 20 years has demonstrated many effects that would have been missed using more traditional univariate analysis techniques. The data set is also of an appropriate size, and as the authors note, fluid processing is an extremely important domain in the field of cognition in aging, due to its steep decline over aging. However, it might have been nice to see an analysis of a more crystallised intelligence task included too, as a contrast since this is an area that does not demonstrate such a decline (and perhaps continues to improve over aging).

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Reviewer #3 (Public Review):

This neuroimaging study investigated how brain activity related to visual pattern-based reasoning changes over the adult lifespan, addressing the topic of functional compensation in older age. To this end, the authors employed a version of the Cattell task, which probes visual pattern recognition for identifying commonalities and differences within sets of abstract objects in order to infer the odd object among a given set. Using a state-of-the-art univariate analysis approach on fMRI data from a large lifespan sample, the authors identified brain regions in which the activation contrast between hard and easy Cattell task conditions was modulated by both age and performance. Regions identified comprised prefrontal areas and bilateral cuneus. Applying a multivariate decoding approach to activity in these regions, the authors went on to show that only in older adults, the cuneus, but not the prefrontal regions, carried information about the task condition (hard vs. easy) beyond that already provided by activity patterns of voxels that showed a univariate main effect of task difficulty. This was taken as compelling evidence for task-specific compensatory activity in the cuneus in advanced age.

The study is well-motivated and well-written. The authors used appropriate, rigorous methods that allowed them to control for a range of possible confounds or alternative explanations. Laudable aspects include the large sample with a wide and even age distribution, the validation of the in-scanner task performance against previous results

obtained with a more standard version outside the scanner, and the control for vascular age-related differences in hemodynamic activity via a BOLD signal amplitude measure obtained from a separate resting-state fMRI scan. Overall, the conclusions are well-supported by the data.

In the following, I list some points of discussion that I would like to see addressed by the authors in a revision:

1. I don't quite follow the argumentation that compensatory recruitment would need to show via non-redundant information carried by any given non-MDN region (cf. p14). Wouldn't the fact that a non-MDN region carries task-related information be sufficient to infer that it is involved in the task and, if activated increasingly with increasing age, that its stronger recruitment reflects compensation, rather than inefficiency or dedifferentiation? Put differently, wouldn't "more of the same" in an additional region suffice to qualify as compensation, as compared to the "additional information in an additional region" requirement set by the authors? As a consequence, in my honest opinion, showing that decoding task difficulty from non-MDN ROIs works better with higher age would already count as evidence for compensation, rather than asking for age-related increases in decoding boosts obtained from adding such ROIs. It would be interesting to see whether the arguably redundant frontal ROI would satisfy this less demanding criterion. At any rate, it seems useful to show whether the difference in log evidence for the real vs. shuffled models is also related to age.

2. Relatedly, does the observed boost in decoding by adding the cuneal ROI (in older adults) really reflect "additional, non-redundant" information carried by this ROI? Or could it be that this boost is just a statistical phenomenon that is obtained because the cuneus just happens to show a more clear-cut, less noisy difference in hard vs. easy task activation patterns than does the MDN (which itself may suffer from increased neural inefficiency in older age), and thus the cuneaus improves decoding performance without containing additional (novel) pieces of information (but just more reliable ones)? If so, the compensation account could still be maintained by reference to the less demanding rationale for what constitutes compensation laid out above.

3. On page 21, the authors state that "...traditional univariate criteria alone are not sufficient for identifying functional compensation." To me, this conclusion is quite bold as I'd think that this depends on the unvariate criterion used. For instance, it could be argued that compensation should be more clearly indicated by an over additive interaction as observed for the relationship of cuneal activity with age and performance (i.e., the activity increase with better performance becomes stronger with age), rather than by an additive effect of age and performance as observed for the prefrontal ROI (see Fig. 2C). In any case, I'd appreciate it if the authors discussed this issue and the relationship between univariate and multivariate results in more detail (e.g. how many differences in sensitivity between the two approaches have contributed), in particular since the sophisticated multivariate approach used here is not widely established in the field yet.

4. As to the exclusion of poorly performing participants (see p24): If only based on the absolute number of errors, wouldn't you miss those who worked (overly) slowly but made few errors (possibly because of adjusting their speed-accuracy tradeoff)? Wouldn't it be reasonable to define a criterion based on the same performance measure (correct - incorrect) as used in the main behavioural analyses?

5. Did the authors consider testing for negative relationships between performance and brain activity, given that there is some literature arguing that neural efficiency (i.e. less activation) is the hallmark of high intelligence (i.e. high performance levels in the Cattell task)? If that were true, at least for some regions, the set of ROIs putatively carrying task-related information could be expanded beyond that examined here. If no such regions were found, it would provide some evidence bearing on the neural efficiency hypothesis.

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Author Response

The authors appreciate the reviewers' thoughtful and constructive feedback. We are pleased to have the opportunity to address their comments through a revised version to strengthen our work. In particular:

(1) As suggested, we will add references/details in Methods to further help readers to establish the cohort as population-derived and clarify details about the analysis and specificity of results.

(2) We agree that reserve, inefficiency, and compensation are complex issues needing more discussion. We will add definitions and discussion to clarify our approaches, including multivariate/univariate analyses and addressing the specificity of results. We also appreciate the suggestions for future research directions.

A revised version addressing these valuable recommendations will improve our study's contribution towards quantitative methods for understanding reserve and compensation in healthy cognitive ageing.