Supplementary Material

Investigating Compensatory Brain Activity in Older Adults with Subjective Cognitive Decline

Behavioral Analyses

The mean values and standard deviations of the six test scores included in the behavioral composite scores are reported in Supplementary Table 1.

Supplementary Table 1. Description of raw values used for the two behavioral composite scores.

Composite score	Cognitive test	*Mean*	*SD*
Memory	AVLT learning sum	47.86	9.52
	AVLT immediate recall	9.71	3.29
	AVLT delayed recall	9.96	3.90
Spatial Abilities	RCF encoding	34.94	2.17
	RCF immediate recall	20.92	7.08
	RCF delayed recall	21.08	6.36

SD, standard deviation; AVLT, auditory verbal learning test; RCF, Rey–Osterrieth complex figure

In the episodic memory task, there was a significant difference in reaction time and task accuracy between the cued recall and the recognition condition. Reaction times during cued recall were faster and accuracy lower than in recognition blocks. In both spatial abilities control conditions reaction times were significantly faster and more trials had been solved than in the translation/rotation conditions. Additionally, task accuracy was higher in the control versus the translation condition. There was no difference in accuracy in the rotation condition and the control condition (Supplementary Table 2). Furthermore, there was no significant difference between the translation and rotation condition in spatial abilities task accuracy ($t(51) = -0.90$, $p = 0.37$) but a significant difference in reaction time ($t(51) = -3.26$, $p < 0.01$) and number of solved trials ($t(51) = 4.04$, $p < 0.001$). In the translation condition reaction times were significantly faster and more trails were solved.

Supplementary Table 2. Means and standard deviations for the separate blocks for the two fMRI tasks.

Episodic Memory Task

	Cued Recall		Recognition		t-value
	Mean	*SD*	*Mean*	*SD*	
Accuracy	0.62	0.16	0.79	0.20	**- 8.66****
RT (s)	2.12	0.32	2.22	0.35	**2.61***

Spatial Rotation Task

	Translation		Luminance translation		t-value
	Mean	*SD*	*Mean*	*SD*	
Number of Trials	44	7.63	51	10.3	***10.2*****
Accuracy	0.73	0.16	0.78	0.18	***- 3.35****
RT (s)	1.36	0.22	1.14	0.24	***- 10.48*****
	Rotation		Luminance rotation		t-value
	Mean	*SD*	*Mean*	*SD*	
Number of Trials	43	7.69	51	10.6	***12.06*****
Accuracy	0.75	0.17	0.78	0.19	*-1.38*
RT (s)	1.15	0.24	1.42	0.21	***-14.61*****

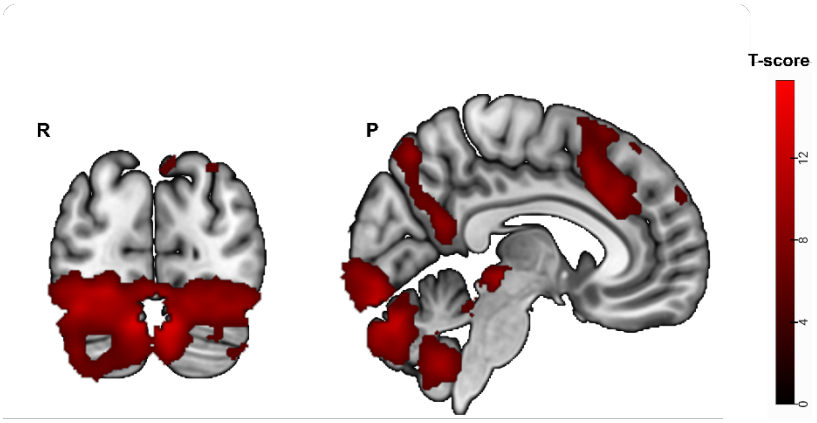
SD, standard deviation; s, seconds; t-value, paired t-test. *p < 0.05, **p < 0.001.

Functional MRI analyses

Age, sex, and study site were included as covariates in all fMRI analyses. Total intracranial volume was added as additional covariate in the whole brain analyses.

Model 1: Episodic memory fMRI task

Supplementary Figure 1 shows a whole brain analysis (cued recall > control contrast, constraint to the GM mask) for the episodic memory fMRI task.



Supplementary Figure 1. Whole brain group-level activity in the episodic memory task (cued recall > control contrast, *pFWE* < 0.05). Clusters with strong activation were located in the occipital lobe, the ventral diencephalon, the middle supplementary motor cortex and the left angular gyrus. R, right; P, posterior.

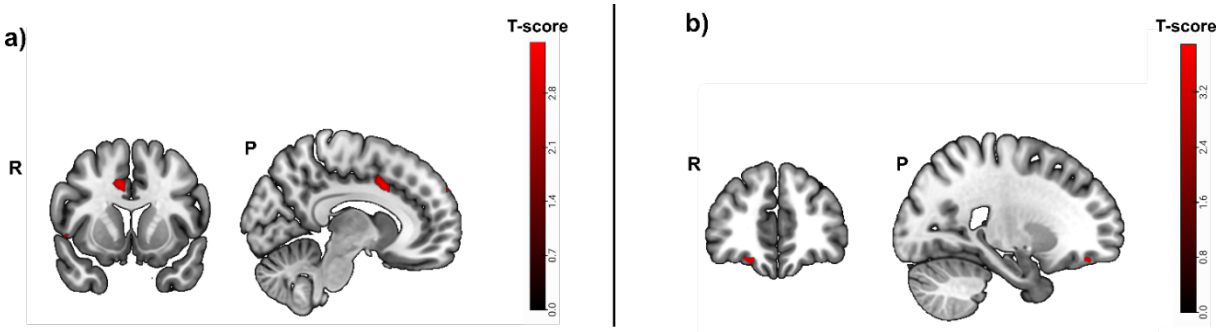
The results showed the strongest activation in an occipital cluster (cluster size: 16598 voxels) including the right (t = 15.90; *pFWE* = 0.000; peak x, y, z coordinates: 32, -86, -12) and the left fusiform gyrus (t = 12.84; *pFWE* = 0.000; peak x, y, z coordinates: -24, -90, -14). Other clusters with strong activation were located in the brain stem/left ventral diencephalon (t = 13.61; *pFWE* = 0.000; x, y, z coordinates: -4, -28, -6 ; cluster size: 253 voxels), left supplementary motor cortex (t = 11.74; *pFWE* = 0.000; peak x, y, z coordinates: -6, 20, 36; cluster size: 7413 voxels), and the left cerebral white matter/left angular gyrus (t = 11.13; *pFWE* = 0.000; peak x, y, z coordinates: -36, -56, 42; cluster size: 1856).

Model 1.2: Compensation related to the memory composite score

The model with inclusive masking described in the manuscript was repeated for activity positively correlated with the episodic memory (memory) composite score instead of fMRI task performance (i.e., accuracy) in the cued recall > control contrast. As binary mask the same image for activity correlated with hippocampal atrophy as in model 1.1 (compensation related to the memory composite score) was used (Supplementary Figure 2a).

A mask for task-related activity positively correlated with hippocampal atrophy ($p_{uncorrected} <$ 0.01) was calculated in a first step in the cued recall > control contrast (Supplementary Figure 2a). The clusters with the strongest activity were detected in the right middle cingulate gyrus (t = 3.50; $p_{uncorrected}$ = 0.001; peak x, y, z coordinates: 8, 12, 36), the right occipital fusiform gyrus (t = 3.47; $p_{uncorrected}$ = 0.001; peak x, y, z coordinates: 18, -98, -20) and the left temporal pole (t = 3.53; $p_{uncorrected}$ = 0.001; peak x, y, z coordinates: -46, 4, -20) . These results were saved as binary mask.

A second contrast was calculated for activity positively correlated with the memory composite score. No significant results remained at $pFWE < 0.05$. Without correction for multiple testing ($p_{uncorrected} < 0.001$) the most significant clusters were located in the right anterior orbital gyrus (t = 3.99; $p_{uncorrected} < 0.001$; peak x, y, z coordinates: 28, 46, -14) and the right middle frontal gyrus (t = 3.54; $p_{uncorrected} < 0.001$; peak x, y, z coordinates: 46, 38, 20) (Fig. 2b).

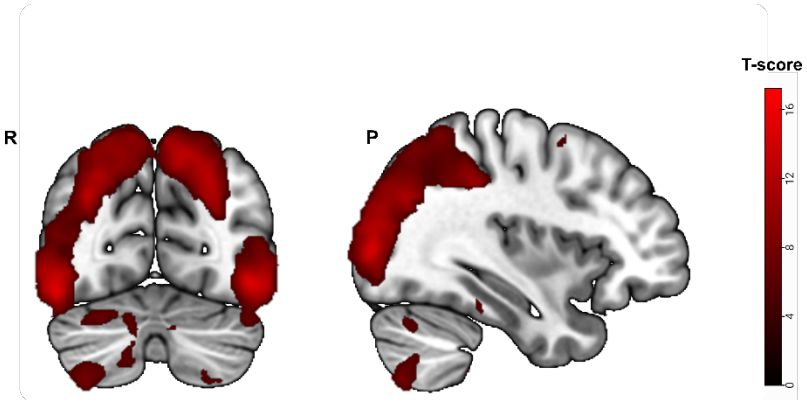


Supplementary Figure 2. a) Greater activity related to increased hippocampal atrophy in the episodic memory task (cued recall > control contrast, $p_{uncorrected} < 0.01$), used as mask. Activity was detected in the right middle cingulate gyrus, the right occipital fusiform gyrus, and the left temporal pole. b) Greater activity related to high memory composite scores (before masking) was located in the right anterior orbital gyrus and the right middle frontal gyrus ($p_{uncorrected} < 0.001$). R, right; P, posterior.

No voxel survived when the binary mask for hippocampal atrophy was applied ($p_{uncorrected} <$ 0.001).

Model 2: Spatial abilities fMRI task

A whole brain analysis (translation+rotation > luminance conditions, constraint to the GM mask) with study site, total intracranial volume age and sex as covariates was calculated and revealed several clusters in the parietal lobe (Supplementary Figure 3).



Supplementary Figure 3. Whole brain group-level activity in the spatial abilities task (translation+rotation > luminance conditions contrast, *pFWE* < 0.05). Clusters with strong activity were located in the right and left inferior occipital gyrus, the right and left superior parietal lobe, the left middle frontal gyrus, the left inferior frontal gyrus, and the right cerebellum. R, right; P, posterior.

The results showed the strongest activation in an occipital cluster (17464 voxels), including the right (t = 16.47; *pFWE* = 0.000; peak x, y, z coordinates: 38, -86, 2) and left (t = 15.43; *pFWE* = 0.000; peak x, y, z coordinates: -44, -70, -10) inferior occipital gyrus as well as the left (t = 14.14; *pFWE* = 0.000; peak x, y, z coordinates: -26, -66, 34) and right (t = 12.82; *pFWE* = 0.000; peak x, y, z coordinates: 30, -62, 36) superior parietal lobe. Other clusters with strong activation were located in the left middle frontal gyrus (t = 9.26; *pFWE* = 0.000; peak x, y, z coordinates: -24,2,48; cluster size: 379 voxels), the left opercular part of the inferior frontal gyrus (t = 8.74; *pFWE* = 0.000; peak x, y, z coordinates: -42, 4, 22; cluster size: 687 voxels) and the right cerebellum exterior (t = 8.50; *pFWE* = 0.000; peak x, y, z coordinates: 28, -66, -30; cluster size: 590 voxels).

Model 2.2: Compensation related to the spatial abilities composite score

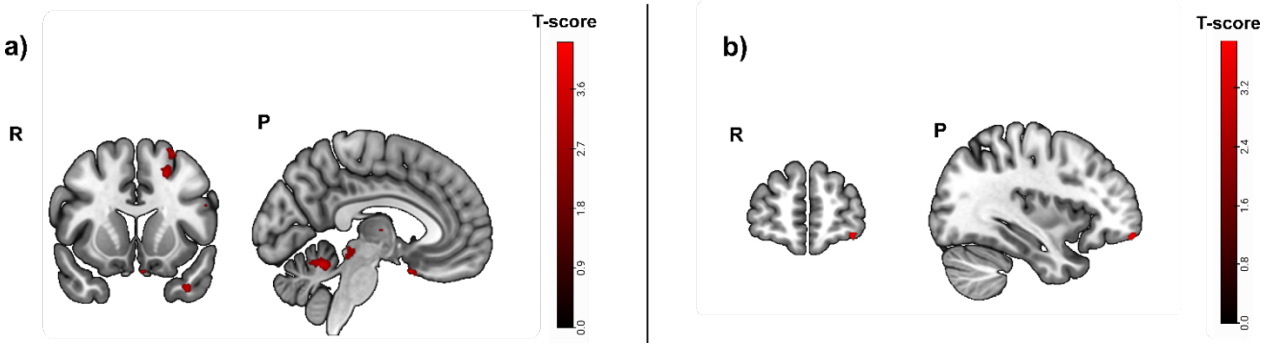
51 participants were included in the fMRI model for spatial abilities including the composite score. Data for one patient was missing because an error occurred during the assessment and the behavioral spatial abilities data obtained outside the scanner were not available.

Therefore, we calculated a new mask for this model.

Activity positively correlated with hippocampal atrophy ($p_{uncorrected}$ < 0.01) was located in the left sucallosal area (t = 4.68; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -4, 10, -24), cerebellar vermal lobules I-V (t = 4.08; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: 0, -54, -16), and the left

cerebral white matter/superior frontal gyrus (t = 3.82; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -20, 12, 46) (Supplementary Figure 4a).

No significant results remained after $pFWE < 0.05$ correction for activity positively correlated with the spatial abilities composite score. With an uncorrected p-value of < 0.001 the strongest activity was found in the left lateral orbital gyrus (t = 4.00; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -34, 56, -14), and the left precuneus (t = 3.28; $p_{uncorrected}$ = 0.001; peak x, y, z coordinates: -14, -60, 8) (Supplementary Figure 4b).



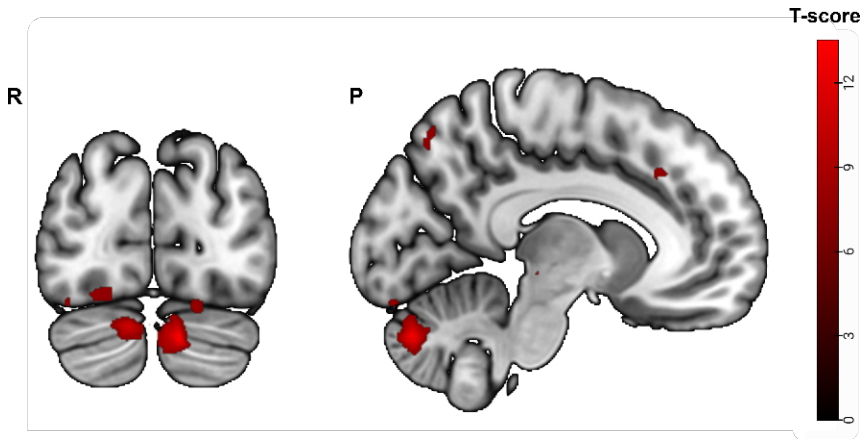
Supplementary Figure 4. a) Greater activity related to increased hippocampal atrophy in the spatial abilities task ([translation + rotation] > luminance conditions contrast, $p_{uncorrected} < 0.01$), used as mask. Activity was detected in the left subcallosal area, the cerebellar vermal lobules I-V, and the left cerebral white matter/superior frontal gyrus. b) Greater activity related to high spatial abilities composite scores (before masking) was located in the left lateral orbital and the left precunes ($p_{uncorrected} < 0.001$). R, right; P, posterior.

There was no significant result after masking ($pFWE < 0.05$ or $p_{uncorrected} < 0.001$).

fMRI Analyses in a Subsample with Positive Blood Biomarkers for Amyloid Positivity

Episodic memory fMRI task

The whole brain analysis (constrained to the grey matter mask) for episodic memory task related activity (cued recall > control contrast, Supplementary Figure 3) showed the strongest activation in the left cerebellum (t = 13.83; $pFWE$ = 0.000; peak x, y, z coordinates: -10, -80 -32; cluster size: 169 voxels). Other clusters with strong activation are located in the left precunes (t = 13.00; $pFWE$ = 0.000; peak x, y, z coordinates: -6, -72, 52; cluster size: 98 voxels) and the right orbital part of the inferior frontal gyrus (t = 12.70; $pFWE$ = 0.000; peak x, y, z coordinates: 40, 22, -8; cluster size: 176 voxels) (Supplementary Figure 5).



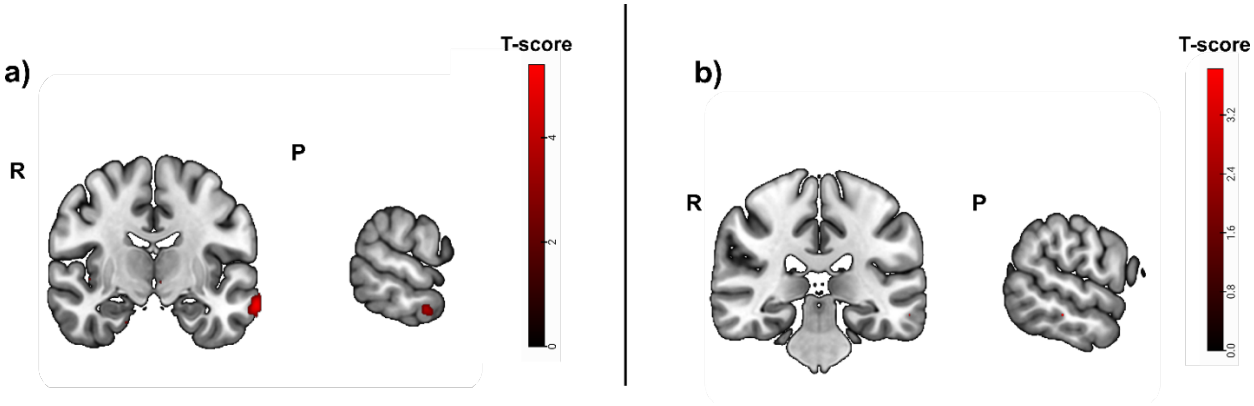
Supplementary Figure 5. Whole brain group-level activity in the episodic memory task (cued recall > control contrast, *pFWE* < 0.05) in a subsample with positive blood biomarkers for amyloid positivity. Significant activity was located in the left cerebellum, the left precunes, and the right orbital part of the inferior frontal gyrus. R, right; P, posterior.

Model 1.4: Compensation related to the memory composite score in a subsample with positive blood biomarkers for amyloid positivity

The model was repeated with the memory composite score instead of the fMRI task performance (model 1.3 in the manuscript).

As mask the same image for hippocampal atrophy as in model 1.3 was used. The clusters with strongest activity were detected in the left middle temporal gyrus (t = 5.50; $p_{uncorrecetd}$ = 0.000; peak x, y, z coordinates: -66, -10, -20), the right angular gyrus (t = 5.41; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: 48, -64, 18) and left cerebral white mater/temporal pole (t = 5.27; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -44, 4, -22) (Supplementary Figure 6a).

The memory composite score was not positively correlated to significant brain activity when corrected for multiple testing (*pFWE* < 0.05). Without correction for multiple testing ($p_{uncorrected}$ < 0.001) the only significant cluster was located in the left middle temporal gyrus (t = 3.83; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -58, -30, -14) (Supplementary Figure 6b).

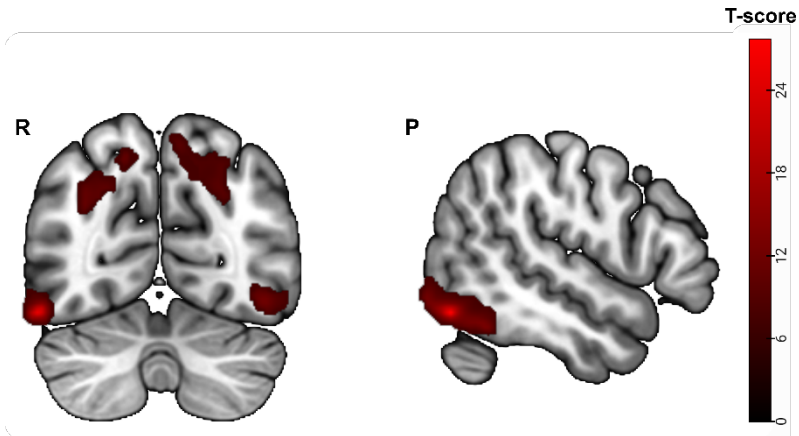


Supplementary Figure 6. a) Greater activity related to increased hippocampal atrophy in the episodic memory task (cued recall > control contrast, $p_{uncorrected} < 0.01$), used as mask in a subsample with positive blood biomarkers for amyloid positivity. Activity was detected in the left middle temporal gyrus, the right angular gyrus and left cerebral white mater/temporal pole. b) Greater activity related to high memory composite scores (before masking) was located in the left middle temporal gyrus ($p_{uncorrected} < 0.001$). R, right; P, posterior.

No significant voxel survived when the binary mask for hippocampal atrophy was applied ($p_{uncorrected} < 0.001$).

Spatial abilities fMRI task

A whole brain analysis (constrained to the grey matter mask) of the spatial abilities task ([translation + rotation] > luminance conditions) was performed (Supplementary Figure 7).



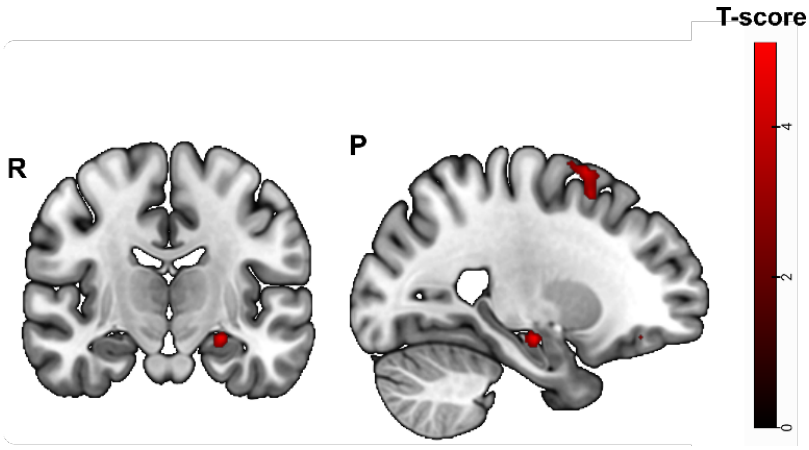
Supplementary Figure 7. Whole brain group-level activity in the spatial abilities task ([translation + rotation] > luminance conditions contrast, *pFWE* < 0.05). Clusters with strong activation Were located in the right inferior temporal gyrus, the right and left inferior occipital gyrus and the right cerebellum exterior. R, right; P, posterior.

The results showed the strongest activation in an occipital cluster, including the right inferior temporal gyrus (t = 30.44; $pFWE$= 0.000; peak x, y, z coordinates: 52, -66, -16; cluster size: 1119 voxels). Other clusters with strong activation were located in the left superior parietal lobe (t = 14.04; $pFWE$ = 0.000; peak x, y, z coordinates: -28, -50, 36; cluster size: 1120 voxels), the left inferior occipital gyrus (t = 12.96; $pFWE$ = 0.000; peak x, y, z coordinates: -42, -70, -10; cluster size: 424 voxels), the right superior parietal lobe (t = 12.23; $pFWE$ = 0.000; peak x, y, z coordinates: 16, -66, 48, cluster size: 400 voxels), and the right cerebellum exterior (t = 11.05; $pFWE$ = 0.000; peak x, y, z coordinates: 12, -72, -34; cluster size: 13 voxels).

Model 2.4: Compensation related to the spatial abilities composite score in a subsample with positive blood biomarkers for amyloid positivity

The activity positively correlated with hippocampal atrophy ($p_{uncorrected} < 0.01$) showed the strongest activity in the left hippocampus (t = 5.25; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -24, -14, -14), the left middle frontal gyrus (t = 4.71; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: -40, 2, 60),) and the right superior occipital gyrus (t = 4.48; $p_{uncorrected}$ = 0.000; peak x, y, z coordinates: 30, -86, 36) (Supplementary Figure 8).

No significant results remained after $pFWE < 0.05$ correction or uncorrected p-value < 0.001 in the contrast positively correlated with the spatial abilities composite score.



Supplementary Figure 8. Greater activity related to increased hippocampal atrophy in the spatial abilities task ([translation + rotation] > luminance conditions contrast, $p_{uncorrected} < 0.01$), used as mask in a subsample with positive blood biomarkers for amyloid positivity. Activity was detected in the left middle frontal gyrus, the left hippocampus, and the left superior frontal gyrus. No significant activity related to high spatial abilities composite scores (before masking) was detected.

As no cluster with significant activity related to high spatial abilities composite scores was detected no inclusive masking was performed.

Further analyses (two-sample t-tests)

We hypothesized that the comparison between two groups would be another way to investigate neuronal compensation (i.e., in group one we expect compensation but not in group two). For one model with this approach we performed a linear regression of hippocampal volume and task performance and used the residuals to split the study sample into two groups (group one: positive residuals, group two: zero or negative residuals) and performed two-sample t-tests. We expect the group with positive residuals to be more likely to show compensatory activity as they scored better than expected regarding their hippocampal volume.

Because these analyses were less conservative than the inclusive masking approach we described in the manuscript, we applied a FWE correction ($p < 0.05$) for multiple testing.

For the episodic memory fMRI task group one with positive residuals consisted of 22 (mean age: 72.27, mean years of education: 15.32, 12 females), group two with negative/zero residuals of 29 (mean age: 69.73, mean years of education: 14.39, 18 females) participants. There were no significant results for this analysis.

For the spatial abilities fMRI task, the group with positive residuals consisted of 26 (mean age: 73.31, mean years of education: 15.65, 13 females), the group with negative residuals of 26 (mean age: 69.89, mean years of education: 14.95, 17 females) participants. There were no significant results for this analysis.

There were also no significant results when data from the in-scan performance of both tasks and the corresponding residuals were used to build the respective subsamples.

Another way to divide the sample is according to the probability of amyloid positivity (sample one: blood-based biomarkers indicate amyloid positivity, sample two: blood-based biomarkers do not indicate amyloid positivity). In in the episodic memory task this led to one sample with 15 participants (mean age: 68.13, mean years of education: 15.40, 7 females) where amyloid positivity is not assumed based on blood-based biomarkers and a sample with 22 participants where blood-based biomarkers indicate amyloid positivity (mean age: 71.95, mean years of education: 15.22, 15 females). There was no significant result ($pFWE < 0.05$).

Also for the spatial abilities, no significant result occurred (probable amyloid positive sample: n = 23, mean age: 72.30, mean years of education: 15.34, 15 females; probable amyloid negative sample: n = 15, mean age: 68.13, mean years of education: 15.40, 8 females).