Increased hippocampal excitability and altered learning dynamics mediate cognitive mapping deficits in human aging

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SUPPLEMENTAL INFORMATION

Priors
$\mu_1 \sim$ HalfNormal $(\log(\bar{y}_1), 0.3)$
$\mu_b \sim$ HalfNormal $(\mu_{b-1}, 0.2)$
$\eta_{b,t} \sim$ HalfNormal (μ_b, θ)
$\theta \sim$ HalfNormal $(0, 1)$
$y_{b,t} \sim$ Lognormal $(\eta_{b,t}, \sigma_b)$
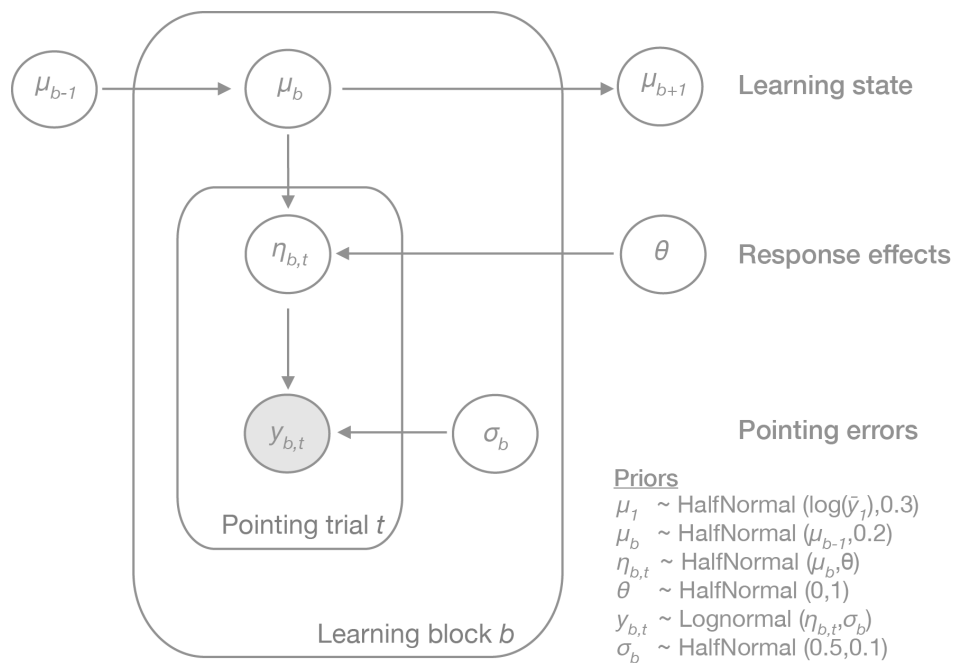$\sigma_b \sim$ HalfNormal $(0.5, 0.1)$

Figure S1, related to Figure 2, Figure 3, and <u>Bayesian Modeling of Performance Data</u> section: Bayesian state-space model to estimate the subject-specific hidden learning state per learning block.

```
data {
  int<lower=0> nblocks;
  int<lower=0> ntrials;
  matrix[nblocks, ntrials] y;           // the data
  int<lower=0, upper=1> fit_model;  // whether to fit data or not
  // vars controlling the priors
  real theta_loc;
  real theta_scale;
  real mulog1_loc;
  real mulog1_scale;
  real mulog_scale;
  real sigma_loc;
  real sigma_scale;
}

parameters {
  real<lower=0> theta; // theta is also *regularizing* the random effects
  vector<lower=0,upper=log(180)>[nblocks] mulog;
  matrix<lower=0>[nblocks, ntrials] eta;
  vector<lower=0>[nblocks] sigma;
}

model {
  theta ~ normal(theta_loc, theta_scale);
  mulog[1] ~ normal(mulog1_loc, mulog1_scale);
  for (b in 2:nblocks) {
    mulog[b] ~ normal(mulog[b - 1], mulog_scale);
  }
  for (b in 1:nblocks) {
    sigma[b] ~ normal(sigma_loc, sigma_scale);
  }
  if (fit_model == 1) {
    for (b in 1:nblocks) {
      for (t in 1:ntrials) {
        if (y[b, t] >= 0) {
          eta[b, t] ~ normal(mulog[b], theta);
          y[b, t] ~ lognormal(eta[b, t], sigma[b]);
        }
        else {
          eta[b, t] ~ normal(log(mean(y[b, :])), 1);
        }
      }
    }
  }
}

generated quantities{
  vector<lower=0>[nblocks] expected_val;
  vector<lower=0>[nblocks] variance_val;
  matrix[nblocks, ntrials] log_lik;          // log likelihood
  for (b in 1:nblocks) {
    expected_val[b] = exp(mulog[b] + ((sigma[b] ^ 2) / 2));
    variance_val[b] = exp((2 * mulog[b]) + (sigma[b] ^ 2)) * (exp(sigma[b] ^ 2) -
1);
    for (t in 1:ntrials) {
      if (y[b, t] >= 0) {
          log_lik[b, t] = lognormal_lpdf(y[b, t] | eta[b, t], sigma[b]);
      }
    }
  }
}
```

Figure S2, related to Figure 2, Figure 3, and <u>Bayesian Modeling of Performance Data </u>section:

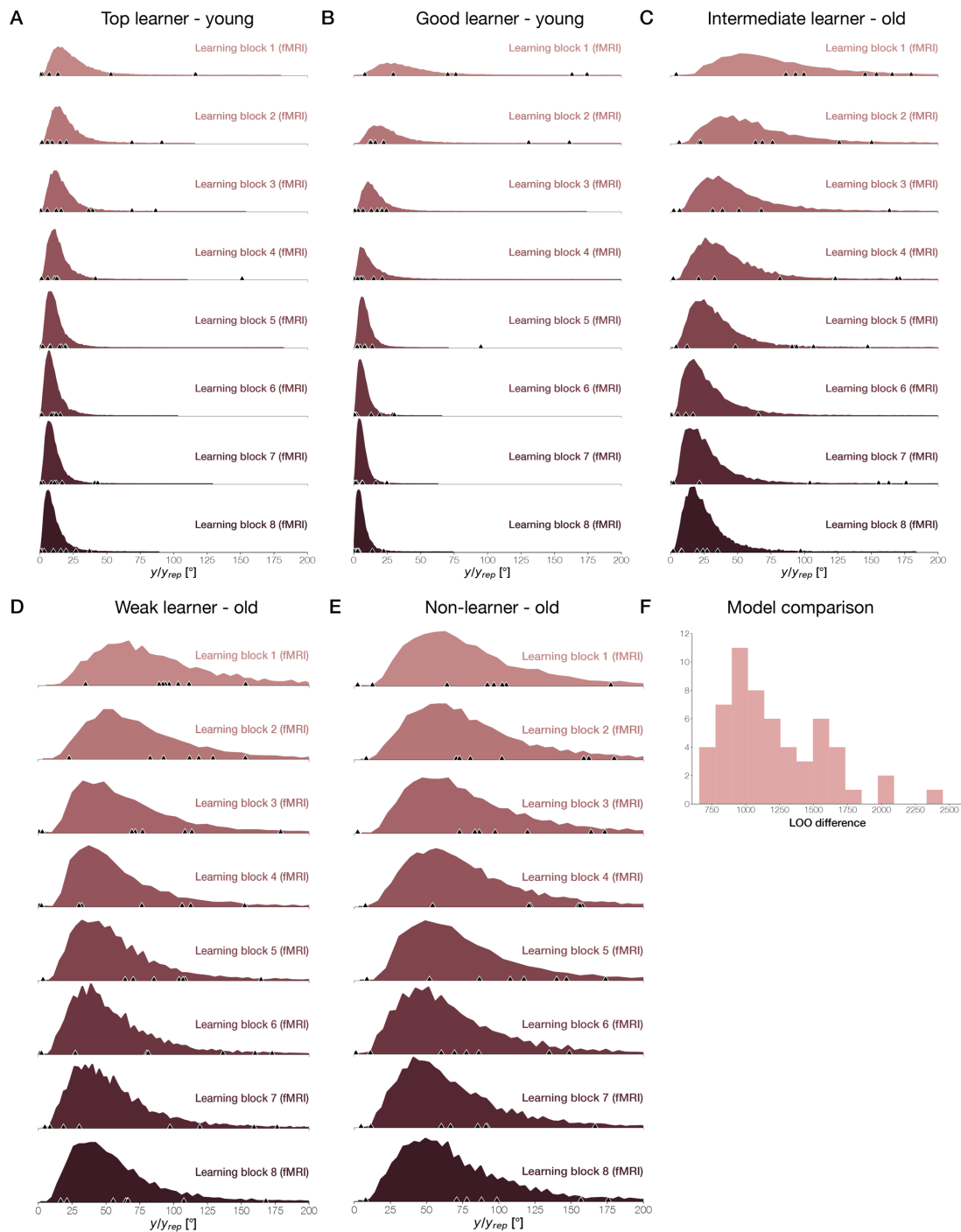Stan code of the Bayesian state-space model.

Figure S3, related to Figure 2, Figure 3, and <u>Bayesian Modeling of Performance Data</u> section:
Results of the posterior predictive checks of the Bayesian state-space model for representative
individuals from each learning sub-group (A: top learner young – E: non-learner old; see <u>Performance
Clustering</u> section; the posterior predictive samples distribution, y_{rep}, plotted together with the
observed data points, y, per learning block) and (F) histogram of the individuals' loo differences for
the comparison of the Bayesian state-space model incorporating the effects of the responses, η, to
an alternative model that estimated the individuals' learning state trial-wise. More positive values
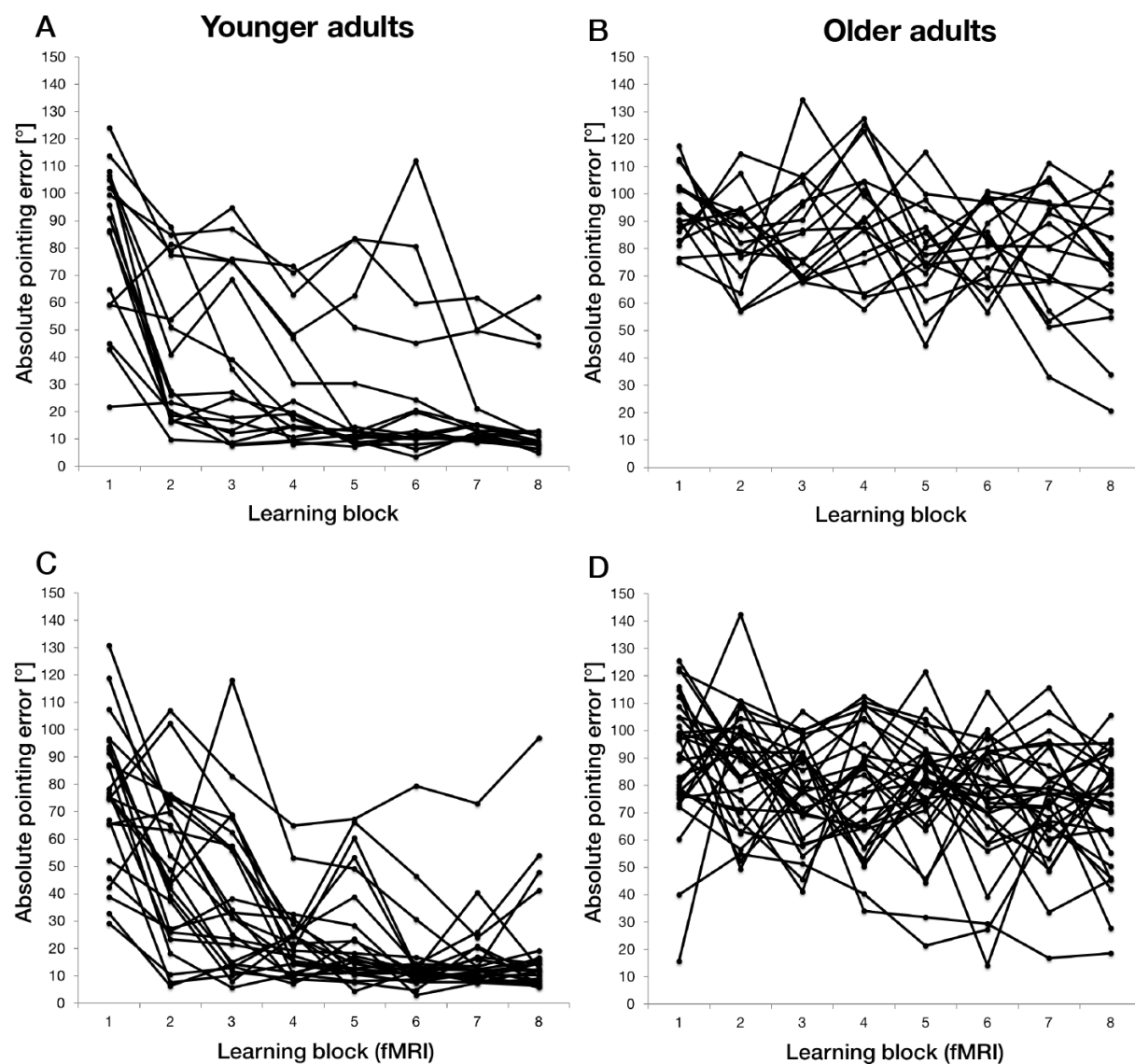indicate a better fit of the first model.

Figure S4, related to Figure 2 and 3: Average absolute pointing errors per learning block for each participant in (A) the younger and (B) the older age group in the behavioral experiment, and for each participant in (C) the younger and (D) the older age group in the fMRI experiment.

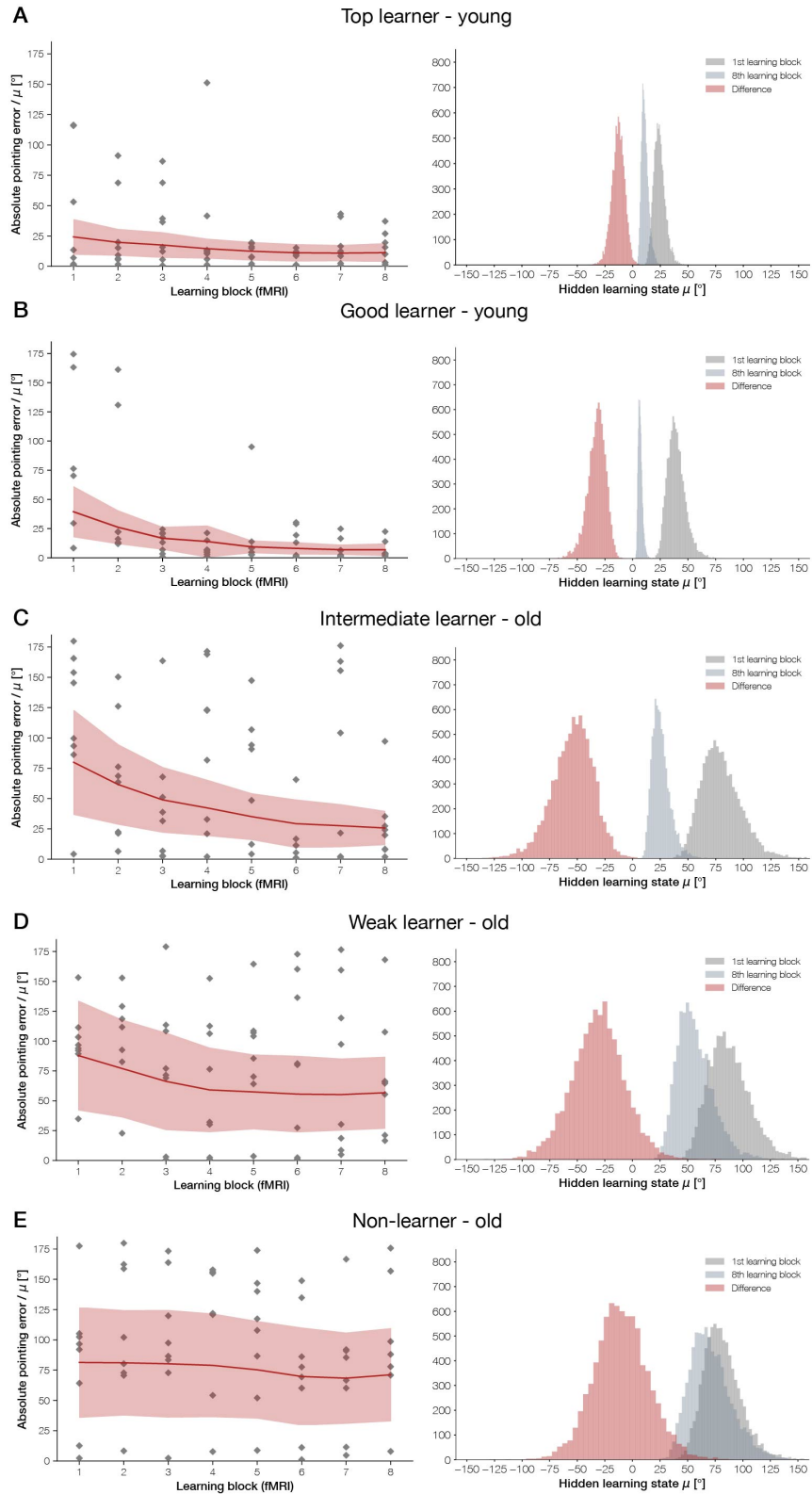**Figure S5, related to Figure 3 and Performance Clustering section:** Definition of learning sub-groups. Difference of the latent state distributions between the last and first learning blocks (right) and their underlying hidden learning states and trial-wise performance data per learning block (left) from representative individuals from each learning sub-group in the fMRI experiment (A: top learner young – E: non-learner old).

Brain region	Cluster size	MNI coordinate			Z-score
		x	y	z	
A) Navigation vs. control across the whole sample					
L Parieto-occipital sulcus	5009	-18	-60	21	Inf
R Retrosplenial cortex		15	-54	21	Inf
L Angular gyrus		-33	-81	34	Inf
R Premotor cortex	2594	33	6	57	Inf
L Premotor cortex		-30	27	1	7.54
Supplementary motor area		0	15	47	7.18
R Cerebellum	204	30	-63	-32	6.58
		39	-69	-29	6.42
L Inferior frontal gyrus	201	-36	51	4	4.91
L Middle frontal gyrus		-36	54	18	4.76
B) Reduced activity in older compared to younger adults during navigation vs. control					
L Cerebellum	69	-36	-45	-35	4.91
L Precuneus	245	-9	-78	54	4.80
R Precuneus		12	-69	57	4.45
L Supramarginal gyrus	82	-48	-42	57	4.08
R Superior parietal lobe	70	39	-42	51	4.07
R Supramarginal gyrus	94	57	-30	41	4.01
R Postcentral gyrus		66	-18	37	3.30
R Insula	73	30	18	8	3.82
R Premotor cortex		48	6	14	3.66
C) Increased activity in older compared to younger adults during navigation vs. control					
R Superior frontal gyrus	2292	3	60	37	6.06
L Ventromedial prefrontal cortex		-3	63	18	5.56
L Orbitofrontal cortex	380	-36	33	-12	6.03
L Inferior frontal gyrus		-51	24	-9	4.54
R Middle temporal gyrus	471	69	-18	-15	5.81
		60	-9	-29	4.84
L Cerebellum	525	-42	-78	-38	5.71
L Visual cortex (extrastriate area)		-27	-78	-9	4.69
L Angular gyrus	368	-54	-66	28	5.38
R Orbitofrontal gyrus	232	30	33	-12	5.32
R Inferior frontal gyrus		42	36	-15	4.68
R Visual cortex (extrastriate area)	387	27	-84	-15	5.13
R Cerebellum		15	-87	-32	4.40
R Angular gyrus	245	45	-57	31	4.99
		54	-66	47	4.82
L Superior temporal sulcus	487	-63	-39	1	4.84
		-57	-3	-15	4.35
L Hippocampus	82	-21	-18	-12	4.76
		-30	-15	-22	4.21

Region	Size	x	y	z	t
Posterior cingulate cortex	192	0	-60	34	4.57
L Posterior cingulate cortex		-6	-57	21	4.32
L Premotor cortex	354	-39	12	24	4.55
L Middle frontal gyrus		-42	21	47	4.26
R Precentral gyrus	120	33	-15	28	4.23
		36	-15	41	4.00

D) Retrieval vs. encoding across the whole sample

Region	Size	x	y	z	t
R Caudate	8550	12	12	-2	Inf
L Premotor Cortex		-48	0	34	Inf
L Fusiform Gyrus/Inferior temporal gyrus		-42	-63	-12	Inf
L Parieto-occipital sulcus		-15	-72	24	7.81
L Lingual Gyrus		-21	-54	-2	7.79
R Cerebellum	241	6	-69	-22	5.73

E) Encoding vs. retrieval across the whole sample

Region	Size	x	y	z	t
L Visual cortex (extrastriate area)	9128	-6	-87	-9	Inf
R Visual cortex (extrastriate area)		12	-90	-9	Inf
R Superior frontal gyrus	387	30	39	51	4.89
		39	30	41	4.78
L Superior frontal gyrus	118	-36	30	51	4.78
		-24	27	51	4.00
L Superior frontal gyrus	101	-18	57	31	3.42
		-9	54	31	3.41
R Anterior cingulate cortex	86	3	21	24	4.15

F) Reduced activity in older compared to younger adults during retrieval vs. encoding

Region	Size	x	y	z	t
R Fusiform gyrus	144	27	-63	-12	4.56
		36	-78	-15	4.17
L Brain stem	92	-3	-45	-48	4.17
		0	-39	-38	3.81

G) Increased activity in older compared to younger adults during retrieval vs. encoding

Region	Size	x	y	z	t
R Supramarginal gyrus	2863	63	-24	24	6.23
R Inferior frontal gyrus		57	15	-2	5.16
L Postcentral gyrus	196	-24	-39	67	5.61
R Posterior cingulate cortex	438	6	-27	41	5.56
		9	-51	34	4.07
L Middle temporal gyrus	2422	-54	-54	-2	5.44
L Insula		-39	-15	-5	5.43
L Superior temporal gyrus		-66	-39	24	5.40
R Rostral prefrontal cortex	1180	9	54	-2	4.59
L Anterior cingulate cortex		-3	27	18	4.50
R Superior frontal gyrus		24	51	34	4.42
L Cerebellum	220	-27	-84	-32	4.49
		-39	-72	-42	4.22
L Superior frontal gyrus	99	-27	45	24	4.07

L Middle frontal gyrus		-33	57	21	3.62
H) Age-group differences in learning-related activity decreases					
L Ventromedial prefrontal cortex	202	-12	54	-2	4.04
		-3	42	-12	4.02
R Superior frontal gyrus	71	0	42	37	4.02
		9	45	41	3.82
I) Age-group differences in learning-related activity increases					
L Parieto-occipital sulcus	2257	-9	-66	24	5.93
		-27	-69	51	5.52
R Retrosplenial cortex		9	-57	4	4.82
Supplementary motor area	203	3	3	61	5.45
		-9	6	41	3.81
R Premotor cortex	125	30	0	51	4.81
		27	-3	67	4.44
L Premotor cortex	138	-24	3	57	4.57
		-30	-6	57	4.49
Visual cortex (striate area)	257	-6	-102	-2	4.54
		12	-102	11	3.96
J) Learning-group differences in learning-related activity changes within older adults					
R Lateral frontopolar cortex	117	33	48	-9	4.84
R Ventrolateral prefrontal cortex		39	36	-5	4.75
		51	36	-5	4.62
R Insula	76	33	18	-12	4.54
		33	18	1	4.15

Table S1, related to Table 1, Figure 4, and Figure 5: Spatial coordinates of the local maxima in the whole-brain fMRI analyses (p < 0.05, whole-brain FWE-corr.).

Data S1, related to Figure 3

Additional analyses in the behavioral experiment

Age-related differences in pointing performance depending on the characteristics of the VE were further analyzed by means of an ANOVA on the absolute pointing errors with intersection (I1-I4), direction (D1-D4), and target landmark (town hall, church) as repeated measures variables and age group (younger adults, older adults) as between-subjects variable. A significant interaction between the four factors suggested that the performance of the age groups was modulated by the respective intersection-direction-target landmark combination encountered in the VE during retrieval, $F(9, 288) = 2.05$, $p = .034$. Therefore, follow-up ANOVAs were conducted within the two age groups separately. In younger adults, a significant main effect of intersection, $F(3, 48) = 6.18$, $p = .005$ (Greenhouse-Geißer corrected), showed that performance was worse when they were located at I4 ($M = 48.6°$ ± $21.9°$) as compared to I1 ($M = 25.0°$ ± $19.7°$) or I2 ($M = 30.6°$ ± $25.7°$), all $p ≤ .010$ (Bonferroni-corrected). This was modulated by a significant interaction between intersection and target landmark, $F(3, 48) = 11.4$, $p < .001$. Pointing errors were smaller in this age group when they pointed towards the town hall ($M = 13.5°$ ± $14.5°$) as compared to the church ($M = 36.6°$ ± $29.3°$) at I1, which was the intersection adjacent to the town hall, and vice versa at I3, which was the intersection adjacent to the church (town hall: $M = 45.5°$ ± $35.5°$; church: $M = 25.8°$ ± $26.9°$), all $t ≥ 3.33$, all $p ≤ .004$. The directions from which the intersections were approached did not seem to have an influence on performance in this age group. In older adults, the same ANOVA also revealed an interaction between intersection and target landmark, $F(3, 48) = 3.38$, $p = .026$. When located at I3, pointing errors were smaller when the target landmark was the adjacent church ($M = 73.2°$ ± $27.4°$) as compared to the town hall ($M = 94.2°$ ± $19.9°$), $t(16) = 2.73$, $p = .015$. The corresponding comparison for I1 did not reach significance, $t(16) = 1.12$, $p = .281$. In addition, there was a significant interaction between direction and target landmark, $F(3, 48) = 3.75$, $p = .039$ (Greenhouse-Geißer corrected). Post-hoc t-tests showed that pointing towards the town hall ($M = 80.3°$ ± $18.1°$) tended to be easier as compared to pointing towards the church ($M = 94.5°$ ± $27.1°$) for the older adults when they approached the intersections from D4 (i.e., facing east), $t(16) = 1.96$, $p = .068$. In contrast, pointing towards the church ($M = 69.9°$ ± $19.6°$) tended to be easier than pointing towards the town hall ($M = 87.0°$ ± $23.3°$) when they approached the intersections from D2 (i.e., facing west), $t(16) = 1.99$, $p = .064$. This was modulated by an interaction between intersection, direction, and target landmark, $F(9, 144) = 2.25$, $p = .022$. Separate follow-up ANOVAs for each intersection with direction (D1-D4) and target landmark (town hall, church) as repeated measures variables revealed for I1 an interaction between the two factors that approached significance, $F(3, 48) = 3.21$, $p = .067$ (Greenhouse-Geißer corrected). Pointing towards the adjacent town hall ($M = 56.5°$ ± $41.3°$) was easier than pointing towards the church ($M = 96.9°$ ± $38.1°$) when participants were coming from D4 (i.e., facing east), $t(16) = 3.54$, $p = .003$. At I2, a main effect of direction, $F(3, 48) = 5.25$, $p = .003$, indicated that pointing generally tended to be easier from D2 (i.e., facing west; $M = 68.8°$ ± $32.7°$) as compared to D1 ($M = 94.0°$ ± $24.5°$) or D4 ($M = 95.8°$ ± $37.1°$), that is, when they were facing towards the dead-

ends at this intersection, all $p \leq .054$ (Bonferroni-corrected). At I3, a main effect of target landmark indicated that pointing towards the adjacent church (M = 73.2° ± 27.4°) was easier for the older adults than pointing towards the town hall (M = 94.2° ± 20.0°), $F_{(3, 48)} = 7.47$, $p = .015$. This was modulated by an interaction between direction and target landmark, $F_{(3, 48)} = 4.44$, $p = .008$. Pointing towards the church was easier when coming from D1 (i.e., facing south; town hall: M = 107.7° ± 31.5°; church: M = 65.6° ± 36.0°) or D2 (i.e., facing west; town hall: M = 98.0° ± 39.4°; church: M = 52.6° ± 40.8°), all $t \geq 3.19$, all $p \leq .006$. Finally, at I4, there was also an interaction between direction and target landmark, $F_{(3, 48)} = 3.74$, $p = .017$. Performance was better when participants pointed towards the church (M = 75.9° ± 30.8°) as compared to the town hall (M = 106.6° ± 31.4°) when approaching the intersection from D2 (i.e., facing west), $t_{(16)} = 2.59$, $p = .020$.

Taken together, this analysis supports the results from the analyses reported in the main text implying better navigational encoding in younger adults and a higher reliance on the specific sensory input in older adults. The directions from which they were approaching the intersections partly seemed to have an impact on their performance although variability in performance was generally quite high in this age group. One should note that a corresponding analysis restricted to the last learning blocks where participants were better able to navigate was not conducted due to a lack of statistical power. This would have also resulted in unequal numbers of trials that enter the analysis given the number of trials per condition and their randomization across the entire experiment.