Association of Hippocampal Asymmetry and Domain-Specific Cognitive Performance: a longitudinal study

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OBJECTIVE

To investigate whether the hemispheric hippocampal asymmetry at baseline visit and over follow-up years is associated with decline across different domains of cognitive function in dementia-free individuals.

CONCLUSION

- Hippocampal asymmetry can be used as a predictor for decline across different domains of cognitive function.
- Higher level of baseline CSF p-tau increases the effect of hippocampal asymmetry in predicting memory performance.
- Higher level of baseline CSF p-tau is associated with increased hippocampal asymmetry over time.

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INTRODUCTION

- Longitudinal Hippocampal volume change, measured with MRI, has huge potential as a marker for Alzheimer's disease (AD).
- The association between hippocampal volume and cognitive decline in AD has been frequently reported.
- Here we investigate whether the hemispheric hippocampal asymmetry over time is associated with cognitive decline.
- We also studied how baseline CSF AD biomarkers of Aβ and p-tau (AT classification) impacts the effect of hippocampal asymmetry on cognitive performance over time.
- We also investigated the impact of baseline AT biomarkers on the longitudinal changes in hippocampal asymmetry over 15 years of follow up.

METHODS

- **Participants:** 1335 individuals from Alzheimer's Disease Neuroimaging Initiative (ADNI), clinically diagnosed as cognitively normal (CN) or Mild cognitive impairment (MCI) at baseline visit.
- **Inclusion criteria:** subjects with available CSF biomarkers Aβ and p-tau at baseline visit, longitudinal structural MRI, and longitudinal cognitive scores in 4 domains: Memory (MEM), Language (LAN), Executive Functioning (EXF), and Visuo-Spatial Functioning (VSP).
- AT classification has been done based on CSF AD biomarkers of Aβ and p-tau.
- Harmonized cognitive domain scores (Range: -3 to +3) from the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP-PHC) were used.
- Asymmetry Index (AI) was defined as $\frac{|Left\ Hippocampus - Right\ Hippocampus|}{Left\ Hippocampus + Right\ Hippocampus}$
- Linear mixed effect models (LMM) were used to determine if baseline AI and AI measured over the follow-up years (longitudinal AI) are associated with the change in cognitive performance over time.
- In the LMM, a random intercept and slope were considered to account for the randomness across participants. Models were adjusted for baseline age, sex, and years of education.
- The regression coefficients for the baseline and longitudinal AI have been reported as the outcomes of interest.

RESULTS

- Baseline and longitudinal AI are associated with longitudinal MEM, LAN & EXF, not VSP (Table 2).
- Considering AT classes, AI is associated with MEM in all groups, with LAN in A-T- and A+T+, and with EXF in A-T- groups (Table 3).
- When the subjects are break down to CN and MCI, baseline AI is associated with cognitive performance only in MCI group (n=752, estimate for MEM -2.66, 95% CI -4.25 to -1.07, LAN -1.83, 95% CI -3.13 to -.53, EXF -1.50 95% CI -2.96 to -.03).
- Baseline Aβ do not affect association of AI on any cognitive domains but there was an interaction of baseline p-tau with both baseline and longitudinal AI association with MEM (Table 4).
- Higher baseline p-tau level, and not Aβ, over time is associated with increased longitudinal hippocampal asymmetry (Table 5).
- When sample was classified to CN & MCI groups, p-tau over time was associated with increased hippocampal asymmetry only in the CN group (n= 583, estimate .30, 95%. CI .10 to .50).

Table 1. Participants characteristics at baseline

Measure	Mean ± SD
n	1335
Age, y	72.58 ± 6.95
Female (n, %)	643 (48.2%)
Education, y	16.31 ± 2.63
Follow-up time, y (Median)	2
Aß42-baseline, pg/mL	1147.11 ± 636.84
p-tau-baseline, pg/mL	24.84 ± 13.04
Asymmetry Index - baseline	.03 ± .02
MEM-baseline	.57 ± .64
LAN-baseline	.59 ± .53
EXF- baseline	.53 ± .56
VSP- baseline	.46 ± .51

Abbreviations: Aβ42, Amyloid beta 42; p-tau, phosphorylated tau; MEM, memory; LAN, language; EXF, executive functioning; VSP, visuo-spatial functioning

Table 2. Association of hippocampal asymmetry with decline across 4 cognitive domains

	Baseline AI			Longitudinal AI		
	Estimate	Std. Error	P value	Estimate	Std. Error	P value
MEM	-3.07	.71	**<.001**	-.53	.21	**.011**
LAN	-1.94	.55	**<.001**	-.46	.23	**.045**
EXF	-1.20	.58	**.041**	-.60	.24	**.016**
VSP	-.16	.51	.749	-.27	.30	.375

Abbreviations: AI, asymmetry index; MEM, memory; LAN, language; EXF, executive functioning; VSP, visuo-spatial functioning

Table 3. Association of AI with longitudinal cognitive performance in AT groups

	A-T-						A-T+						A+T-						A+T+					
	AI baseline			AI longitudinal			AI baseline			AI longitudinal			AI baseline			AI longitudinal			AI baseline			AI longitudinal		
	Estimate	Std. Error	P value	Estimate	Std. Error	P value	Estimate	Std. Error	P value	Estimate	Std. Error	P value	Estimate	Std. Error	P value	Estimate	Std. Error	P value	Estimate	Std. Error	P value	Estimate	Std. Error	P value
MEM	-1.70	1.03	.098	-.80	.35	**.023**	-4.43	1.54	**.004**	.53	.60	.375	-1.19	1.44	.406	-1.35	.44	**.002**	-4.42	1.34	**.001**	-.16	.35	.644
LAN	-1.15	.85	.176	-.89	.39	**.022**	-1.15	1.22	.347	.15	.65	.817	-1.64	1.16	.162	-.74	.50	.139	-3.17	1.10	**.004**	-.02	.39	.956
EXF	-.98	.86	.275	-.87	.40	**.029**	-.54	1.28	.671	.02	.75	.975	-.45	1.23	.712	-.59	.52	.260	-2.02	1.17	.085	-.54	.42	.200
VSP	.13	.81	.868	.03	.49	.937	-2.44	1.25	**.050**	.93	.83	.263	-.16	1.13	.887	.09	.64	.887	.59	1.04	.568	-.91	.56	.108

Abbreviations: AI, asymmetry index; MEM, memory; LAN, language; EXF, executive functioning; VSP, visuo-spatial functioning

Table 4. Interaction of AD biomarkers with AI in predicting MEM decline.

	Aß-42			P_tau		
	Estimate	Std. Error	P value	Estimate	Std. Error	P value
AI baseline x Biomarker	.29	.00	.775	-.12	.05	**.014**
AI longitudinal x Biomarker	.59	.00	.071	.04	.01	**.019**

Abbreviations: AI, asymmetry index; Aβ42, Amyloid beta 42; p-tau, phosphorylated tau. Baseline levels of the biomarkers are used in the model.

Table 5. Association of AD biomarkers with hippocampal asymmetry over time.

	Aß-42			P_tau		
	Estimate	Std. Error	P value	Estimate	Std. Error	P value
Baseline level	-.17	.10	.086	.87	.50	.083
Baseline x Follow-up years	-.00	.02	.780	.35	.12	**.005**

Abbreviations: Aβ42, Amyloid beta 42; p-tau, phosphorylated tau. AI is the dependent variable in the linear mixed model.