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Structural equation modeling identifies differential links of pathologies and atrophy in dementia

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Question

Neuromodulatory systems exhibit particular vulnerability to protein pathologies in dementia[1]

Do brain areas more reliant on neuromodulation (higher receptor densities) show more atrophy linked to protein pathologies?

Method

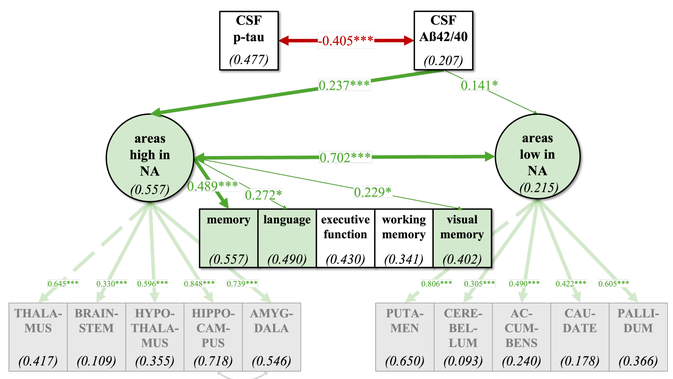
- Data from the DZNE DELCODE sample[2]
- N = 400 older adults split in 3 groups:
  - 122 Healthy controls (HC, 67.75 years (SD 4.97)
  - 152 subjective cognitive decline (SCD, 70.35 years (SD 5.77)
  - 126 MCI/AD, 72.88 years (SD 5.67)
- Volumes of brain areas split according to receptor densities high and low, based on: https://www.proteinatlas.org
- Structural equation modeling using lavaan[3] in R

Conclusions

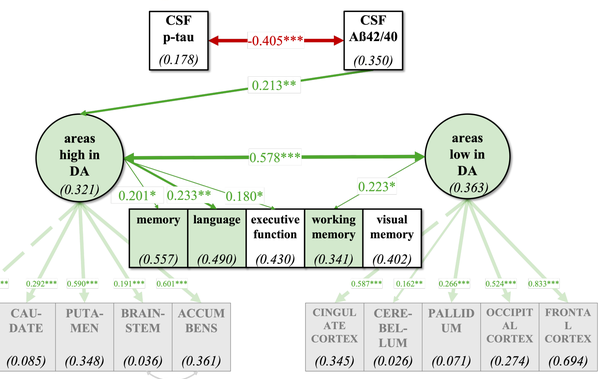
- Protein pathologies are in particular **linked to decline in areas high in NA** receptors
- Distinct links of cognitive function and atrophy across areas more dependent on NA, DA, SE or ACh
- Levels of tau & amyloid pathologies are correlated in SCD (and MCI/AD), but not in HC

Results

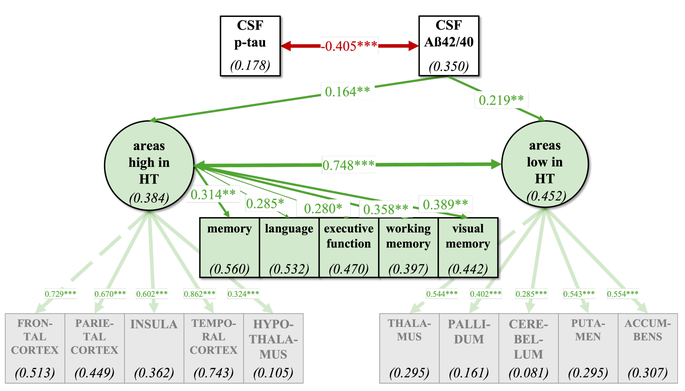
Noradrenaline (NA)



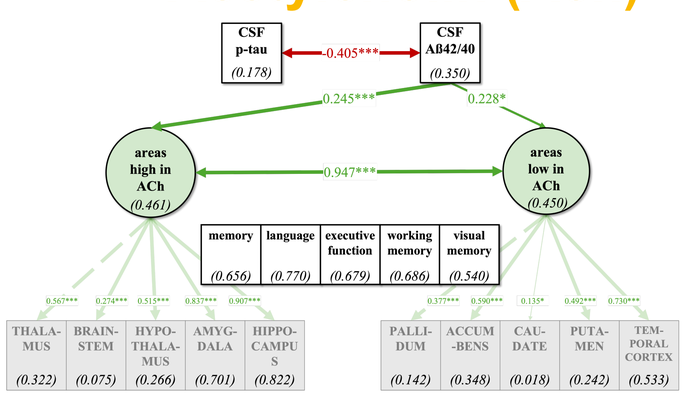
Dopamine (DA)



Serotonin (SE)



Acetylcholin (Ach)



Subgroups: Healthy controls (HC) & Subjective cognitive decline (SCD)/ Mild Cognitive Impairment (MIC) / Alzheimer's Disease (AD)

	Noradrenaline				Dopamine				Serotonin				Acetylcholin
	Whole sample (n = 400)	HC + relatives (n = 122)	SCD (n = 152)	MCI/AD (n = 126)	Whole sample (n = 400)	HC + relatives (n = 122)	SCD (n = 152)	MCI/AD (n = 126)	Whole sample (n = 400)	HC + relatives (n = 122)	SCD (n = 152)	MCI/AD (n = 126)	Whole sample (n = 400)
CFI	0.918		0.904		0.922		0.892		0.940		0.916		0.921
TLI	0.857		0.858		0.864		0.840		0.896		0.875		0.863
RMSEA	0.095		0.080		0.087		0.080		0.079		0.073		0.094
SRMR	0.081		0.086		0.072		0.088		0.057		0.077		0.068
p-tau ↔ Aß42/40	**-0.405*** **	-0.119[a]	-0.366***[a]	-0.424***[a]	**-0.405*** **	-0.119[a]	-0.366***[a]	-0.424***[a]	**-0.405*** **	-0.119[a]	-0.366***[a]	-0.424***[a]	**-0.405*** **
high areas ↔ low areas	**0.702*** **	**0.713*** **	**0.594*** **	**0.613*** **	**0.578*** **	**0.607*** **	**0.504*** **	**0.471*** **	**0.784*** **	**0.406**[a] **	**0.687***[a] **	**0.860***[a] **	**0.947*** **
p-tau → high areas	-0.066	0.004	0.006	0.010	-0.059	-0.027	-0.034	-0.056	-0.052	0.035	0.053	0.082	-0.082
p-tau → low areas	-0.050	-0.010	-0.011	-0.018	0.073	0.073*	0.110*	0.175*	-0.062	0.006	0.007	0.010	-0.108
Aß42/40 → high areas	0.237***	0.113*	0.127*	0.142*	0.213**	0.117	0.115	0.127	**0.164**	0.037	0.044	0.046	**0.245*** **
Aß42/40 → low areas	0.141*	0.071	0.066	0.069	0.103	0.015	0.018	0.019	**0.219**	0.114	0.119	0.108	**0.228** **
high areas → memory	**0.489*** **	0.156	0.147	0.092	**0.201***	0.171	0.185	0.118	**0.314** **	-0.010	-0.009	-0.006	-0.691
high areas → language	**0.272***	-0.004	-0.004	-0.003	**0.233** **	**0.200***	**0.223***	**0.141***	**0.285***	-0.066	-0.062	-0.042	-1.730
high areas → executive function	0.150	-0.065	-0.057	-0.040	**0.180***	0.160	0.161	0.114	**0.280***	-0.050	-0.042	-0.031	-1.726
high areas → working memory	0.086	-0.127	-0.114	-0.083	0.101	0.024	0.024	0.018	**0.358** **	0.096	0.081	0.064	-2.127
high areas → visual memory	**0.229***	-0.044	-0.041	-0.030	0.079	-0.020	-0.022	-0.016	**0.389** **	0.072	0.064	0.049	-1.211
low areas → memory	-0.081	0.017	0.020	0.013	0.148	-0.074	-0.066	-0.043	0.110	0.161	0.165	0.128	1.198
low areas → language	0.078	0.143	0.169	0.113	0.146	-0.060	-0.055	-0.036	0.164	**0.249***	**0.266***	**0.204***	2.185
low areas → executive function	0.122	0.159	0.169	0.126	0.159	-0.033	-0.027	-0.020	0.105	0.192	0.183	0.157	2.089
low areas → working memory	0.110	0.114	0.124	0.097	**0.223***	0.087	0.073	0.056	-0.002	0.022	0.021	0.019	2.446
low areas → visual memory	-0.034	0.020	0.023	0.017	0.147	-0.011	-0.010	-0.008	-0.114	-0.039	-0.039	-0.035	1.509
p-tau → memory	**-0.183*** **	**-0.116** **	**-0.155** **	**-0.163** **	**-0.210*** **	**-0.106** **	**-0.143** **	**-0.149** **	**-0.188*** **	**-0.117** **	**-0.158** **	**-0.167** **	-0.138
p-tau → language	**-0.154*** **	-0.070	-0.097	-0.102	**-0.173*** **	-0.061	-0.085	-0.089	**-0.151*** **	-0.070	-0.099	-0.104	-0.081
p-tau → executive function	**-0.140** **	-0.062	-0.077	-0.090	**-0.157*** **	-0.056	-0.070	-0.082	**-0.135** **	-0.062	-0.078	-0.092	-0.072
p-tau → working memory	**-0.152** **	-0.061	-0.077	-0.095	**-0.174*** **	-0.068	-0.086	-0.106	**-0.145** **	-0.066	-0.084	-0.103	-0.073
p-tau → visual memory	**-0.134** **	-0.058	-0.077	-0.092	**-0.153*** **	-0.057	-0.077	-0.091	**-0.134** **	-0.061	-0.081	-0.098	-0.083
Aß42/40 → memory	**0.185*** **	**0.110***	**0.116***	**0.082***	**0.231*** **	**0.111***	**0.118***	**0.082***	**0.214*** **	**0.107***	**0.115***	**0.081***	**0.185***
Aß42/40 → language	**0.221*** **	**0.120***	**0.132***	**0.092***	**0.232*** **	**0.108***	**0.119***	**0.083***	**0.214*** **	0.099	0.110	0.077	0.223
Aß42/40 → executive function	**0.251*** **	**0.157** **	**0.155** **	**0.121** **	**0.248*** **	**0.143***	**0.141***	**0.110***	**0.234*** **	**0.136***	**0.136***	**0.106***	**0.250***
Aß42/40 → working memory	**0.217*** **	0.094	0.095	0.078	**0.209*** **	0.084	0.085	0.070	**0.195*** **	0.081	0.082	0.067	0.217
Aß42/40 → visual memory	**0.205*** **	0.100	0.106	0.085	**0.222*** **	0.097	0.103	0.082	**0.215*** **	0.096	0.103	0.082	**0.207***

Figures above: Relationships between protein pathologies, brain volumes and cognitive functions are assessed while controlling for influences of interindividual differences in: ApoE4 Status, age, education level, white matter hyperintensities and gender (not shown here). Numbers in brackets indicate explained variance of respective variable /factor.

Table left: Multigroup analyses examine links from Figures above within HC, SCD, MCI/AD subgroups. Links between protein pathologies and areas high in NA and low in DA receptors prevailed also within subgroups. Higher levels in protein pathologies were generally linked to worse cognitive performance, also within subgroups (not shown in Figures above for the sake of clarity). Assessing subgroups in Ach was not possible as models did not coverge, likely due to subgroups not being sufficently different in variance patterns.

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