Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers and reflect diverse pathologies.

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Background: Aggregation of amyloid plaques and neurofibrillary tangles are classical hallmarks of Alzheimer's disease (AD) pathology. Loss of synaptic functionality has been recently identified as an early stage indicator of neuronal and psychiatric pathologies. In this cross-sectional cohort, we have studied the relationship between neurodegeneration and synaptic dysfunction in patients with AD, frontotemporal lobe dementia (FTD), and subjective cognitive decline (SCD).

Method: The cohort consisted of cerebrospinal fluid (CSF) samples (n=60) from patients diagnosed with AD (n=20), FTD (n=20), and SCD (n=20) from the Amsterdam Dementia Cohort. CSF Synaptosomal Associated Protein- 25 (SNAP25) was measured using a novel Simoa based immunoassay developed in-house. CSF vesicle-associated membrane protein-2 (VAMP2), neuronal pentraxin- 2 (NPTX2), and glutamate receptor-4 (GluR4) were measured on novel in-house ELISAs. All in-house immunoassays were validated and analytically qualified.

Results: Both SNAP25 and VAMP2 were significantly elevated in patients with AD and FTD compared to SCD. No significant change was observed for NPTX2 or GluR4 in any patient group (Table 1). CSF Tau and pTau correlated strongly to moderately with SNAP25 and VAMP2 in all three patient groups. However, this association was weak or lost with the biomarkers NPTX2 and GluR4. None of the synaptic biomarkers showed significant associations with CSF neurofilament light (NfL) in the clinical groups. SNAP25 and VAMP2 associated strongly with each other and moderately with NPTX2, but, this correlation was weakened or absent with GluR4 (Table 2).

Conclusion: The correlation of the synaptic biomarkers with pTau but the lack thereof with NfL imply that distinct pathological pathways are involved in synaptic and axonal degeneration. Furthermore, we find that the levels of SNAP25 and VAMP2 are not only increased in AD but also in FTD, unlike the well-established AD- specific synaptic biomarker neurogranin. To further verify the observed associations or the lack thereof, evaluation is ongoing in independent cohorts focusing on FTD (n= 240), AD with a history of traumatic brain injury (n= 224), and AD (n=12). In this cohort, we find 'proof of concept' that synaptic pathology is diverse and reflects distinct aspects of neurodegeneration.

Tabel 1: Multiple Comparisons of the clinical groups for each biomarker

Clinical Groups	AD vs SCD		FTD vs SCD		AD vs FTD	
Biomarker	AUC	P- Value	AUC	P- Value	AUC	P- Value
Aβ42	1	<0.0001	0.66	-	0.92	<0.0001
Tau	0.99	<0.0001	0.87	<0.0001	0.82	0.0005
pTau	1	<0.0001	0.8	0.001	0.83	0.0004
NfL	0.88	<0.0001	0.98	<0.0001	0.88	<0.0001
SNAP25	0.98	<0.0001	0.83	0.0003	0.74	0.009
VAMP2	0.82	0.0006	0.77	0.003	0.50	-
Ng	0.87	<0.0001	0.79	0.002	0.65	-
NPTX2	0.62	-	0.70	0.03	0.57	-
GluR4	0.60	-	0.51	-	0.60	-

Tabel 2: Correlation matrix of the biomarker immunoassays for the clinical groups

-1.00 -0.50 0.00 0.50 1.00

AD								
Spearman Rho	Aβ42	TAU	pTAU	SNAP25	VAMP2	Ng	NPTX2	GluR4	NfL
Aβ42									
TAU	-0.32								
pTAU	-0.31	***0.95***							
SNAP25	-0.36	***0.74***	***0.68***						
VAMP2	-0.10	***0.86***	***0.88***	***0.70***					
Ng	-0.28	***0.54***	***0.59***	***0.51***	***0.58***				
NPTX2	-0.16	0.39	0.42	***0.59***	***0.51***	***0.66***			
GluR4	0.14	0.28	0.34	0.21	0.41	0.28	0.34		
NfL	-0.21	***0.53***	0.43	0.30	***0.47***	0.03	-0.21	-0.03	

FTD								
Spearman Rho	Aβ42	TAU	pTAU	SNAP25	VAMP2	Ng	NPTX2	GluR4	NfL
Aβ42									
TAU	0.24								
pTAU	0.34	***0.78***							
SNAP25	0.35	***0.88***	***0.74***						
VAMP2	0.40	***0.68***	***0.74***	***0.68***					
Ng	0.40	***0.51***	***0.47***	***0.60***	***0.61***				
NPTX2	***0.55***	***0.46***	***0.62***	***0.53***	***0.69***	***0.63***			
GluR4	0.11	0.13	0.11	0.20	0.19	0.02	0.38		
NfL	0.16	0.40	0.00	0.31	0.12	0.29	-0.18	-0.27	

SCD								
Spearman Rho	Aβ42	TAU	pTAU	SNAP25	VAMP2	Ng	NPTX2	GluR4	NfL
Aβ42									
TAU	***0.68***								
pTAU	***0.71***	***0.86***							
SNAP25	***0.64***	***0.76***	***0.74***						
VAMP2	***0.72***	***0.90***	***0.91***	***0.83***					
Ng	***0.54***	***0.67***	***0.65***	***0.63***	***0.68***				
NPTX2	***0.61***	***0.67***	***0.60***	***0.69***	***0.67***	***0.50***			
GluR4	***0.47***	***0.52***	***0.44***	***0.52***	***0.49***	***0.53***	***0.46***		
NfL	0.05	0.38	0.19	0.31	0.34	0.06	0.26	-0.14	