CSF synaptic protein concentrations are raised in those with Alzheimer's disease pathology but not in those with FTD

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Background

Synapse dysfunction and/or loss occurs early in neurodegenerative disease. Fluid biomarkers for synaptic dysfunction may prove useful as measures of disease onset or progression in frontotemporal dementia (FTD) independent of the heterogeneous protein pathology found across genetic and clinical subtypes. A number of studies have reported increased CSF levels of the postsynaptic protein neurogranin in Alzheimer's disease (AD). CSF neurogranin correlates with total and phosphorylated tau but not $A\beta_{42}$ levels in CSF, although it correlates with post-mortem plaque pathology. The presynaptic proteins SNAP-25 and synaptotagmin have also been shown to be raised in CSF in AD. However, little is currently known about synaptic markers in frontotemporal dementia (FTD).

Methods

We measured the concentration of three different synaptic proteins in 85 CSF samples from the UCL Dementia Research Centre FTD cohort: Ng22 and Ng36 fragments of the postsynaptic protein neurogranin were measured using ELISAs and the presynaptic proteins SNAP-25 (total and long fragments) and synaptotagmin were measured using mass spectrometry.

Clinical phenotype	*N*	Gender *Male:Female*	Age at CSF (years) *Mean (SD)*
bvFTD	21	18:3	62.9 (7.3)
svPPA	11	7:4	61.5 (5.4)
nfvPPA	16	9:7	66.9 (5.9)
PPA-NOS	3	3:0	64.6 (5.4)
lvPPA	15	8:7	67.1 (6.2)
Healthy control	19	10:9	64.2 (7.1)

All patients were stratified based on their t-tau:$A\beta_{42}$ ratio into those likely to have AD pathology with a ratio>1 (AD biomarker group) and those likely to have FTLD pathology with a ratio<1 (FTD biomarker group). FTLD patients were also stratified into those likely to have tau or TDP-43 protein pathology.

Stratification	*N*	Gender *Male:Female*	Age at CSF (years) *Mean (SD)*
FTD biomarker group	48	34:14	64.0 (6.8)
AD biomarker group	18	11:7	66.4 (5.9)
Tau pathology	7	5:2	64.7 (8.9)
TDP-43 pathology	18	13:5	62.6 (5.6)

Results

Linear regression analyses with 95% bias-corrected bootstrapped confidence intervals with 1000 repetitions were used to compare CSF protein concentrations between all groups.

Synaptic concentrations by biomarker group

Four synaptic biomarkers were significantly increased in the AD biomarker group compared to the FTD biomarker group [mean (standard deviation): **Ng22** AD 232.2pg/ml (138.9), FTD 114.0 (117.5); **SNAP-25 total** AD 71.4pM (27.9), FTD 49.2 (16.7); **SNAP-25 long** AD 14.0pM (6.3), FTD 8.2 (3.4); **synaptotagmin** AD 287.7pM (156.0), FTD 197.1 (78.9)]. All synaptic biomarkers were increased in the AD biomarker group compared to the control group (figure 1).

Synaptic concentrations by pathological subtype

There were no significant differences in CSF synaptic protein concentrations between those with likely tau and TDP-43 pathology.

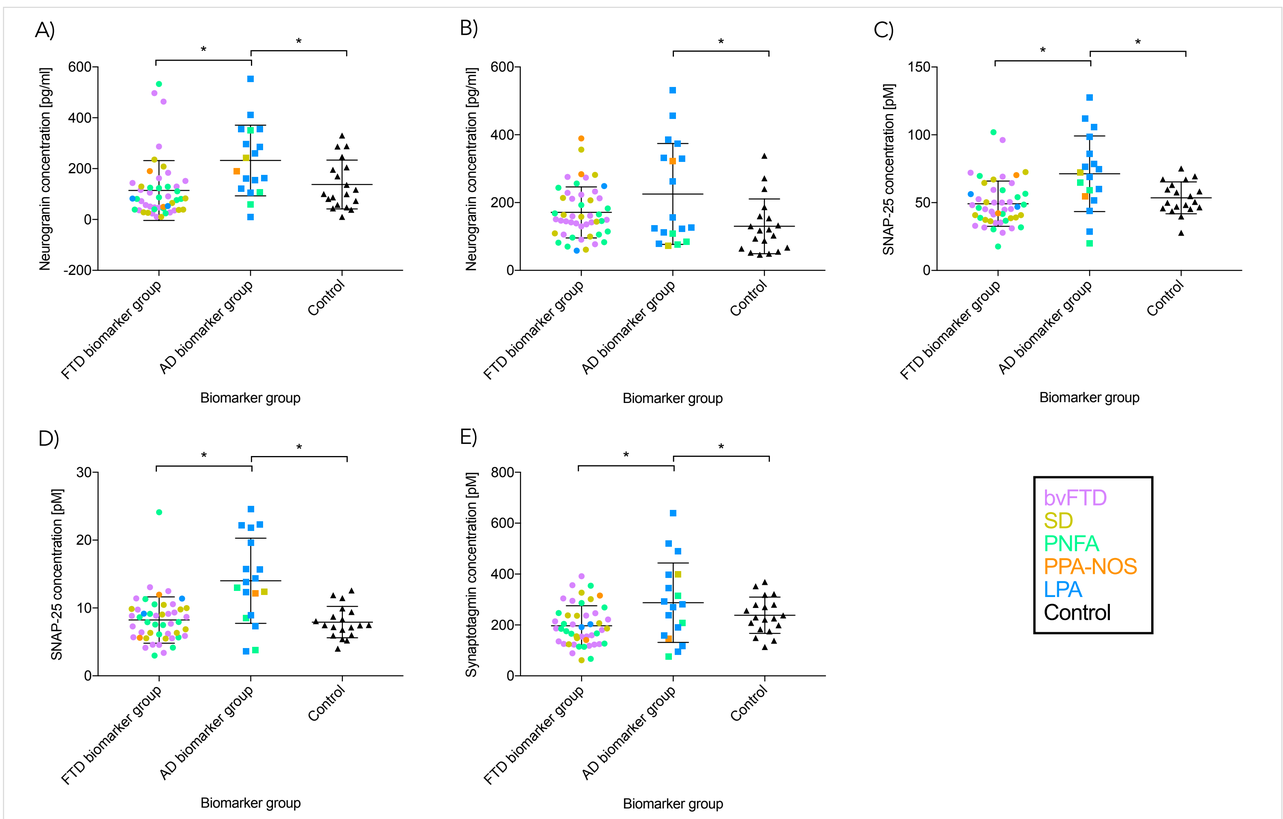

Figure 1. Synaptic concentrations for the five synaptic biomarkers in the AD biomarker group, FTD biomarker group and controls: A) Ng22, B) Ng36, C) SNAP-25 total, D) SNAP-25 long and E) synaptotagmin.

Correlations between biomarkers

Spearman's *r* tests revealed significant correlations between all biomarkers except Ng36 and synaptotagmin in all patients (figure 2).

All synaptic biomarkers, except Ng36, were significantly correlated with CSF t-tau concentrations in the FTD biomarker group (p = <0.0001) and AD biomarker group (p = <0.01). SNAP-25 (total and long) and synaptotagmin concentrations were significantly correlated with CSF $A\beta_{42}$ concentrations in the FTD biomarker group (p = <0.05).

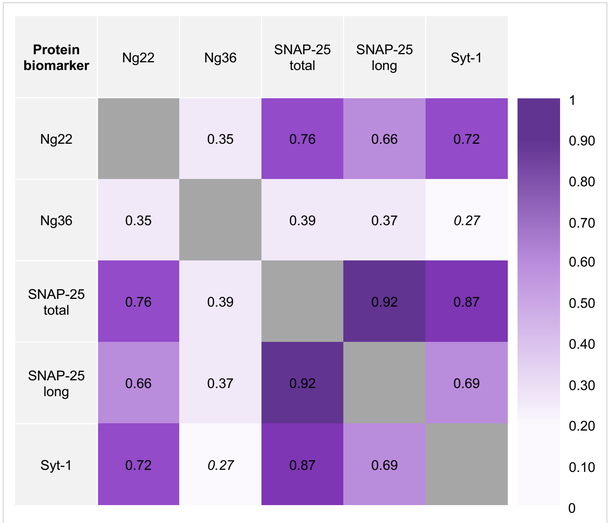

Figure 2. Matrix displaying correlation coefficients between protein concentrations of all synaptic biomarkers for all patients with dementia. The darker the the gradient, the greater the strength of the correlation. Syt1 = synaptotagmin.

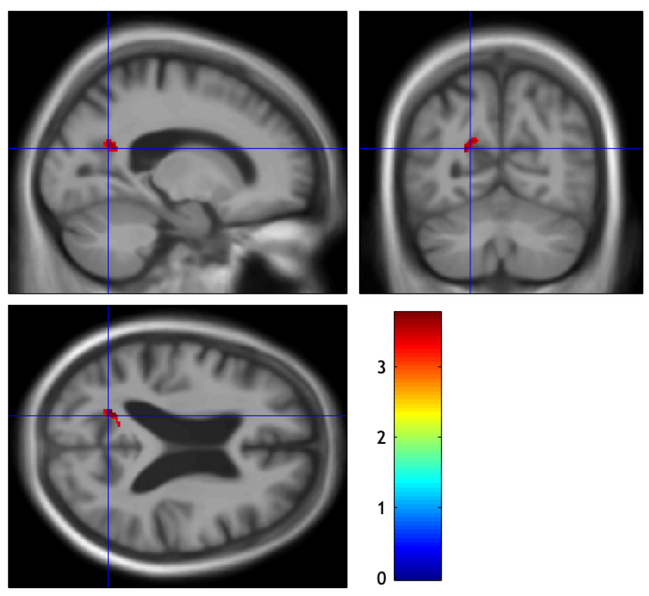

Figure 3. VBM revealed a significant association between CSF Ng22 concentration and volume loss in the left precuneus and posterior cingulate.

Correlations with brain volumes

Voxel-based morphometry (VBM) using multiple regression identified neuroanatomical correlates of CSF Ng22, Ng36 and SNAP-25 total.

Increased Ng22 concentration was associated with grey matter loss in the left precuneus and posterior cingulate (p = <0.001; figure 3). Increased Ng36 was associated with grey matter loss in left and right parietal regions (p = <0.001). Increased SNAP-25 total was associated with right middle temporal volume loss (p = <0.001).

Conclusions

These results suggest that higher synaptic protein concentrations in CSF may be related to AD pathology but not FTLD pathology. Consistent with this, neuroanatomical correlates are consistent with areas of early grey matter loss in AD. More work is needed to examine these markers in a larger FTD group, and to investigate CSF concentrations of other synaptic proteins.

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