DAY 5
ABSTRACT 2

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Serum biomarkers for prognosis and monitoring in asymptomatic Alzheimer's Disease

Abstract:

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Background:

Prognostic and monitoring capabilities of blood-based biomarkers for early cognitive decline, amyloid-β (Aβ) accumulation and grey matter (GM) loss in the asymptomatic phase of Alzheimer disease require further investigation over extended time periods. This longitudinal study investigated serum glial fibrillary acidic protein (GFAP), neurofilament light (NfL) and Aβ1-42/Aβ1-40 as potential prognostic and monitoring biomarkers in cognitively unimpaired (CU) elderly.

Method:

We included 184 CU older adults (Table 1) who underwent baseline serum sampling and 2-yearly neuropsychological assessment for up to 10 years (median: 6 years, Figure 1). A subset (N=109) underwent serial blood sampling,

Aβ-PET and structural MRI at 2 (N=73), 3 (N=34), or 4 (N=2) time points (time interval: 2-10 years, median: 6 years). Cognition was evaluated in memory, language and executive functioning domains through conversion of neuropsychological tests scores to standardised z-scores and subsequent averaging per domain. Aβ-accumulation and GM loss were analysed in a voxelwise manner using Voxelstats with cluster-level pRFT<.05 and voxel-level puncorrected<.001 significance thresholds.[1] Aβ1-42/Aβ1-40 was inverted to facilitate biomarker comparison. Linear-mixed effects models were used to (i) identify the predictive value of serum biomarkers for longitudinal cognitive decline, Aβ-accumulation and GM loss, (ii) calculate annual serum biomarker rates of change and (iii) investigate associations between longitudinal biomarker changes and longitudinal changes in cognition, Aβ-PET and GM volume.

Result:

High baseline GFAP and NfL predicted a longitudinal decline in memory (βGFAP*time=-0.020, pFDR=0.03; βNfL*time=-0.031, pFDR=0.002) and language (βGFAP*time=-0.025, pFDR<0.001, βNfL*time=-0.017, pFDR=0.04), and longitudinal GM loss within the hippocampus. Low Aβ1-42/Aβ1-40 predicted memory decline (βAβ1-42/Aβ1-40*time=-0.022, pFDR=0.03) as well as Aβ accumulation within Aβ-vulnerable regions (Figure 1). Serum GFAP (βtime=0.022, pFDR<.001) and NfL (βtime=0.040, pFDR<.001) increased over time. Longitudinal serum NfL increases were associated with a concomitant decline in memory (βΔNfL*time=-0.031, pFDR=.004), language (βΔNfL*time=-0.022, pFDR=.01) and GM volume (Figure 2). Serum GFAP increases were associated with precuneal Aβ accumulation. Aβ1-42/Aβ1-40 decreases were stronger in Aβ- subjects (pFDR<.001) and did not associate with Aβ accumulation, nor any other longitudinal marker.

Conclusion:

Serum GFAP, NfL and Aβ1-42/Aβ1-40 are prognostic and/or monitoring biomarkers providing complementary information by reflecting different Aβ-dependent or -independent pathophysiological processes.

Reference:

[1] Mathotaarachchi et al. Front Neuroinform 2016.

Table 1. Baseline demographic data

Characteristic	All	Aβ+	Aβ-	*P value*
Number, N	184	23	161	
Age, y	69 ± 6	71 ± 5	69 ± 7	***.03***
Sex, female	98 (53)	8 (35)	80 (50)	*.26*
APOE-ε4 carriers, n (%)	83 (45)	17 (74)	66 (41)	***.006***
Education, y	15 [5]	15 [5]	15 [5]	*.98*
Aβ-PET load (CL)	6.0 [13.0]	43.7 [39.6]	4.1 [9.9]	***<.001***
CDR (/3)	0 [0]	0 [0]	0 [0]	*1.00*
MMSE (/30)	29 [1]	29 [1]	29 [1]	*.99*
Serum GFAP (pg/mL)	122 [70]	150 [67]	117 [67]	***.01***
Serum NfL (pg/mL)	16.4 [9.6]	17.2 [11.7]	16.2 [8.5]	*.13*
Serum Aβ1-42/Aβ1-40	0.062 [0.013]	0.050 [0.009]	0.063 [0.012]	***<.001***

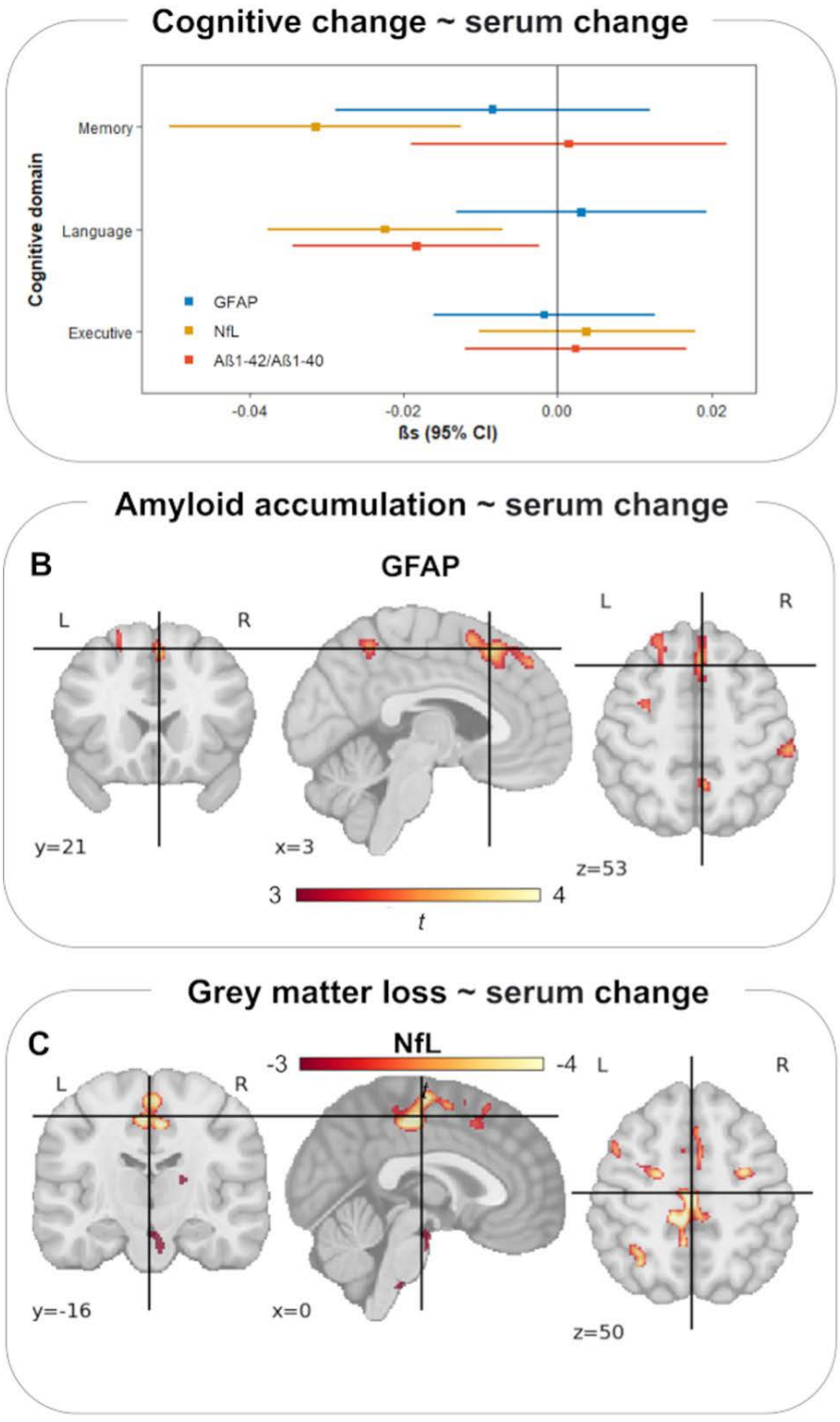

Figure 2. Monitoring capabilities of serum biomarkers for cognitive decline (A), amyloid-β accumulation (B) and grey matter loss (C)

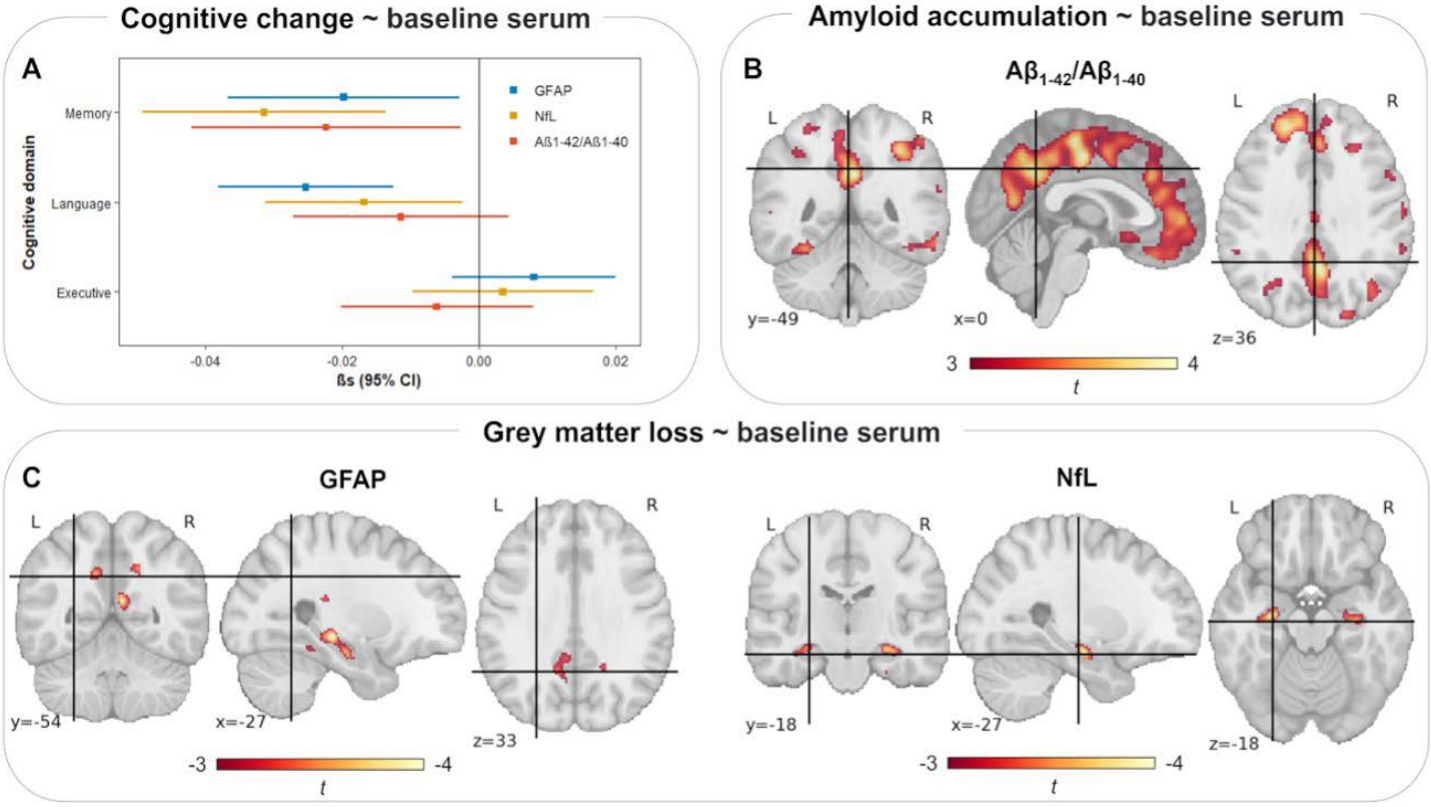

Figure 1. Prognostic capabilities of serum biomarkers for cognitive decline (A), amyloid-β accumulation (B) and grey matter loss (C)