Predicting brain age as a biomarker for risk of dementia

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MRI are used first. A diagnosis could be made in 358 patients (PCC>0.7, Figure 1). For the remaining 177 patients, adding Ab biomarkers was simulated: PCC was recomputed by testing if the patient had positive (median of AD group: 504 pg/ml) or negative (median of SCD group: 959 pg/ml) Ab value. Either of these simulated PCC values reached the cutoff in 130 patients. When we added actual CSF results to these patients, a diagnosis could be made in additional 79 patients. In total, 82 % of patients ((358+79)/535)) were diagnosed with accuracy of 90 % but CSF was measured only in 24 % of patients (130/535). For comparison, when CSF was measured for all patients (535/535), accuracy was 92 % and a diagnosis was made in 75 % of patients (401/535). Figure 2 shows share of patients diagnosed, classification accuracy and share of patients with CSF measured for different PCC cutoffs. **Conclusions:** This study demonstrates that a stepwise approach enables decreasing the number of CSF measurements by >70 % without compromising accuracy. Reference: [1] A. Tolonen et al. *Frontiers in Aging Neuroscience* 10:111, 1-11, 2018.

Table 1. Characteristics of patient data.

Diagnosis	N	Females (%)	Age (years)	MMSE
ALL	535	49	64.9 ± 7.9	23.7 ± 4.9
SCD	139	43	61.8 ± 7.8	28.4 ± 1.5
AD	286	55	66.5 ± 7.7	21.2 ± 4.6
FTD	82	44	62.5 ± 6.0	24.2 ± 4.3
VaD	28	29	69.7 ± 7.7	23.9 ± 3.9

The columns "Age" and "MMSE" show the average and standard deviation. Abbreviations: N=number of subjects, MMSE=mini-mental state examination, CN=cognitively normal, AD=Alzheimer's disease, FTD=frontotemporal dementia, VaD=vascular dementia.

O2-02-04 CSF BIOMARKERS IN DOWN SYNDROME

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Background: Nearly all individuals with Down Syndrome (DS) will develop Alzheimer Disease (AD) neuropathology by the age of 40, and up to 80% will develop cognitive decline consistent with AD dementia. Characterization of CSF biomarkers in DS is critical for the advancement of diagnostic tools and therapeutic interventions for AD in these individuals. To this end, CSF biomarkers were analyzed in a cohort from the Alzheimer's Biomarkers Consortium-Down Syndrome (ABC-DS) study. **Methods:** Forty-two participants with DS (mean age 48±6 years) underwent CSF collection and a clinical evaluation that assessed for the presence or absence of dementia. Established CSF biomarkers for AD (Aβ40, Aβ42, total tau [tTau], and phosphorylated tau-181 [pTau]) were measured with the LUMIPULSE G1200 automated assay platform. Additional emerging biomarkers of neuronal and synaptic injury (VILIP-1, NfL, SNAP-25, neurogranin) and gliosis/neuroinflammation (sTREM2, YKL-40) will be measured via Erenna or plate-based ELISAs. Mean analyte levels were compared between asymptomatic (no MCI, no dementia) and symptomatic (MCI or dementia) individuals by Student's t-test and ANCOVA, and the relationship between biomarkers and age was evaluated by Pearson correlation. **Results:** Twenty-seven individuals were asymptomatic and 15 were symptomatic (8 MCI, 7 AD dementia). In the cohort as a whole, CSF Aβ42 (r=-0.44, p=0.003) and Aβ42/Aβ40 (r=-0.50, p=0.0005) decreased significantly with older age, whereas pTau (r=0.44, p=0.003), tTau/Aβ42 (r=0.35, p=0.02) and pTau/Aβ42 (r=0.45, p=0.002) increased with age. Symptomatic individuals had significantly lower CSF Aβ42 (p=0.003) and Aβ42/Aβ40 (p=0.02) and higher pTau (p=0.02), tTau/Aβ42 (p=0.01) and pTau/Aβ42 (p=0.005). After controlling for age, CSF Aβ42 remained significantly lower in the symptomatic group (p<0.05), whereas only trends (p=0.05-0.15) remained for differences in the other biomarkers, likely due to inadequate statistical power in this small cohort. **Conclusions:** Individuals with DS exhibit patterns of established AD-related CSF biomarkers similar to those observed in studies of late-onset AD and autosomal-dominant AD, although the patterns are influenced by age in this cohort. Additional studies of prevalent and incident cases with larger numbers are needed to confirm the potential utility of these and other CSF biomarkers for the detection of AD pathology in DS in clinical practice and clinical trials.

O2-02-05 PREDICTING BRAIN AGE AS A BIOMARKER FOR RISK OF DEMENTIA

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Background: The gap between predicted brain age using magnetic resonance imaging (MRI) and chronological age may serve as biomarker for dementia. We aimed to investigate the utility of such a gap as a risk biomarker for incident dementia in a general elderly population, using a deep learning (DL) approach for predicting brain age based on MRI-derived grey matter maps. **Methods:** From the population-based Rotterdam Study, 5656 dementia-free and stroke-free participants (mean age 64.67±9.82, 54.73% women) underwent brain MRI at 1.5T, including three-dimensional T1-weighted sequence, between 2006 and 2015. All

participants were followed for incident dementia until 2016. During 6.66±2.46 years of follow-up, 159 subjects developed dementia. Subjects were split into control (N=5497) and incident dementia (N=159) groups. Control group data was split into training, validation and test sets, and used to train a convolutional neural network (CNN) model to predict brain age. We built a CNN model to predict brain age based on its MRI. We used mean absolute error (MAE) to measure model performance in predicting brain age. Reproducibility of prediction was tested using the intraclass correlation coefficient (ICC) computed on a subset of 80 subjects. Cox proportional hazards models were used to assess the association of the age gap with incident dementia, adjusted for years of education, ApoEe4 allele carriership, grey matter volume and intracranial volume. Additionally, we computed the Grad-CAM attention maps of CNN, which shows which brain regions are important for age prediction. **Results:** MAE of brain age prediction was 4.45±3.59 years and ICC was 0.97 (95% confidence interval CI=0.96-0.98). Cox proportional hazards models showed that the age gap was significantly related to incident dementia (hazard ratio HR=1.11 and 95% CI=1.06-1.15). Attention maps indicated that grey matter density around the amygdalae and hippocampi primarily drive the age estimation. These brain regions are relevant to brain aging and are also affected by neurodegenerative processes. **Conclusions:** We show that the gap between DL-derived predicted brain age on brain imaging and chronological brain age is a biomarker associated with risk of dementia development. This suggests that it can be used as a biomarker, complimentary to those that are known, for dementia risk screening.

Table 1. Characteristics of data sets derived from the population-based Rotterdam Study.

	Train	Validation	Test**	Incident dementia**
N_{subj}	3688	1099	550	159
N_{img}	5865	2353	550	159
Mean age* (years±sd)	66.09±10.76	64.84±9.69	64.85±10.82	77.33±7.15
Sex proportion* (female/male)	0.55/0.45	0.54/0.46	0.55/0.45	0.58/0.42
Education* (years±sd)	12.64±3.89	12.63±3.81	12.58±4.00	11.43±3.57
GM volume* (liters±sd)	0.60±0.06	0.60±0.06	0.60±0.06	0.55±0.05
ICV* (liters±sd)	1.48±0.16	1.47±0.16	1.48±0.16	1.45±0.17
ApoE4 carriership* (0/1/2)	0.72/0.26/0.02	0.72/0.25/0.02	0.74/0.23/0.03	0.57/0.36/0.06
Follow-up time* (years±sd)	5.42 ±2.81	4.93±2.80	6.68±2.29	4.29±2.26

* Values are based on N_{img}.
** Selection only includes baseline image of subjects.
Abbreviations: number of subjects (N_{subj}); number of images (N_{img}); grey matter (GM); intracranial volume (ICV)

Table 2. Association of gap between brain age and chronological age with incident dementia assessed by Cox proportional hazards models, both in the total study sample and in a subsample with a minimum follow-up time of 5 years.

Model	Cox Regression		
	n/N	HR (95% CI)	p-value
Total sample			
Model I	159/1808	1.15 (1.11-1.20)	1.02×10^{-12}
Model II	154/1790	1.11 (1.07-1.16)	4.59×10^{-7}
Model III	150/1714	1.11 (1.06-1.15)	1.23×10^{-6}
Sample follow-up time > 5 years			
Model I	62/1366	1.13 (1.06-1.20)	1.38×10^{-4}
Model II	60/1352	1.10 (1.03-1.17)	3.20×10^{-3}
Model III	58/1305	1.09 (1.02-1.17)	7.24×10^{-3}

Model I: age + sex.
Model II: model I + grey matter volume + intracranial volume.
Model III: model II + years of education + APOEe4 carrier status.
Abbreviations: confidence interval (CI); odds ratio (OR); hazard ratio (HR); number of cases (n); total number of participants (N).

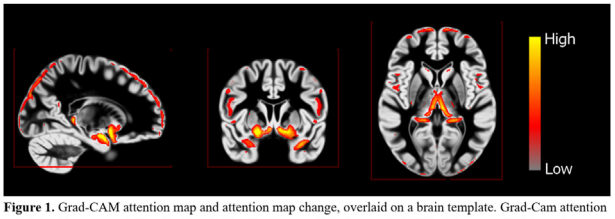

Figure 1. Grad-CAM attention map and attention map change, overlaid on a brain template. Grad-Cam attention map intensity per voxel. Voxel values in the attention map have been set at 0.65 minimum and 0.95 maximum threshold to exclude background values and focus on more important regions.

O2-02-06 CEREBROSPINAL-FLUID-BASED BIOMARKER EVIDENCE OF AMYLOIDOGENESIS IN DEMENTIA WITH LEWY BODIES DEPENDS UPON *APOE*-ε4 CARRIER STATUS

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Background: Amyloidogenesis may cause earlier onset of dementia with Lewy bodies (DLB) as well as Alzheimer's dementia (AD), whereas the angiotensin-converting enzyme (ACE-1) is an amyloid-β-degrading enzyme. **Methods:** Consecutive outpatients with probable DLB (fourth consensus report of the DLB Consortium) were paired with outpatients with late-onset AD (National Institute on Aging – Alzheimer's Association) by gender, Clinical Dementia Rating (CDR) and Mini-Mental State Examination scores, and with cognitively healthy controls by gender and age (±1 year). Genotyping for rs7412 and rs429358 (*APOE*) was undertaken with TaqMan® Real-Time PCR technology. Cerebrospinal fluid concentrations of amyloid ($A\beta_{42}/A\beta_{40}/A\beta_{38}$), ACE-1, *tau* and phospho-*tau* Thr181 were assessed by enzyme-linked immunosorbent assays, significance at $p<0.05$. **Results:** Overall, 27 participants with DLB (78.48±9.0 years-old, CDR sum-of-boxes 10.96±3.8, eleven *APOE*-ε4 carriers) were paired with 27 participants with AD (81.00±5.8 years-old, CDR sum-of-boxes 10.44±3.9, twelve *APOE*-ε4 carriers) and 27 controls (78.48±8.7 years-old, CDR sum-of-boxes 0.30±0.8, four *APOE*-ε4 carriers); two thirds were women. For *APOE*-ε4 carriers: $A\beta_{42}/A\beta_{40}$ 0.08±0.0 for DLB, 0.06±0.0 for AD, 0.08±0.0 for controls, p=0.898; $A\beta_{42}/A\beta_{38}$ 0.23±0.1 for DLB, 0.19±0.1 for AD, 0.50±0.5 for controls, p=0.341; *tau*/phospho-*tau* 4.37±5.7 for DLB, 4.01±4.0 for AD, 1.74±0.3 for controls, p=0.235; ACE-1 levels (ng/ml) 2.32±1.5 for DLB, 1.94±1.4 for AD, 2.51±2.0 for controls, p=0.779. For *APOE*-ε4 non-carriers: $A\beta_{42}/A\beta_{40}$ 0.10±0.1 for DLB, 0.07±0.0 for AD, 0.08±0.0 for controls, p=0.274; $A\beta_{42}/A\beta_{38}$ 0.36±0.2 for DLB, 0.20±0.1 for AD, 0.30±0.1 for controls, p=0.009; *tau*/phospho-*tau* 1.90±1.2 for DLB, 4.33±9.0 for AD, 2.47±1.4 for controls, p=0.101; ACE-1 levels (ng/ml) 2.05±1.8 for DLB, 2.34±1.3 for AD, 2.32±1.7 for controls, p=0.596. Use of ACE inhibitors did not affect ACE-1 levels. **Conclusions:** Most patients were in earlier dementia stages, translating into many non-significant comparisons. $A\beta_{42}/A\beta_{38}$ was significantly higher only for *APOE*-ε4 non-carriers with DLB, whereas $A\beta_{42}/A\beta_{40}$ and $A\beta_{42}/A\beta_{38}$ were lower for *APOE*-ε4 carriers with DLB than for *APOE*-ε4 non-carriers with DLB; *tau* pathology in DLB followed *tau* pathology in AD more closely for *APOE*-ε4 carriers. ACE-1 levels