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BIOMARKERS

POSTER PRESENTATION

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NEUROIMAGING

Multimodal phenotyping of successful cognitive aging

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Abstract

Background: While some memory decline in old age is "normal", there are some older individuals with maintained high cognitive performance. Using a multimodal approach including neuroimaging, fitness, genetic and questionnaire data (Figure 1A), we aimed to identify factors that are related to successful cognitive aging and whether these differ between sexes.

Method: We analyzed 165 cognitively normal older adults age ≥ 60 years from an ongoing study (SFB1436) (age=71±8years, 43% female). For all participants, we determined plasma $Abeta_{1-42}/Abeta_{1-40}$. Temporal lobe tau burden was estimated by [^{18}F]PI-2620 in a subsample (see Figure 1A for sample sizes). We assessed global white matter hyperintensity (WMH) volumes and gray matter thickness for medial temporal lobe (MTL), anterior cingulate cortex (ACC) and whole brain. We measured aerobic and muscular capacity (and blood pressure) by fitness assessment and trait/state anxiety by self-reports. Genetic profiling included KLOTHO and KIBRA polymorphisms and APOE genotype. To phenotype successful cognitive aging, we i) grouped individuals age ≥ 79.5 years into SuperAgers (N=18) based on delayed verbal recall performance ≥ normative values at age of 50-60 years versus typical agers (N=19). For the whole sample we ii) calculated cognitive age gap (CAG) as the difference between cognition-predicted age and chronological age (Figure 3A). We assessed how markers of pathology, brain structure, fitness, mental health and genetics were related to CAG, covarying for chronological age, sex and education.

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Result: SuperAgers and typical agers did not differ in age, sex, education, fitness, anxiety or Abeta42/40 (all p-values>0.1). However, SuperAgers had less WMH volume, higher ACC thickness, lower blood pressure and less temporal lobe tau-tracer binding (small subgroup;). In the whole sample, younger cognitive age related to higher MTL and global cortical thickness, less temporal tau-tracer binding, less anxiety (all p<0.05; Figure 3B) and marginally to higher muscular capacity (p=.06). Only the association between anxiety measures and CAG was moderated by sex (Figure 3B). CAG was not related to genotype.

Conclusion: Our results suggest that successful cognitive aging is related to resistance against age-related pathology and higher brain integrity. Younger cognitive age is linked to better mental health, especially in females.

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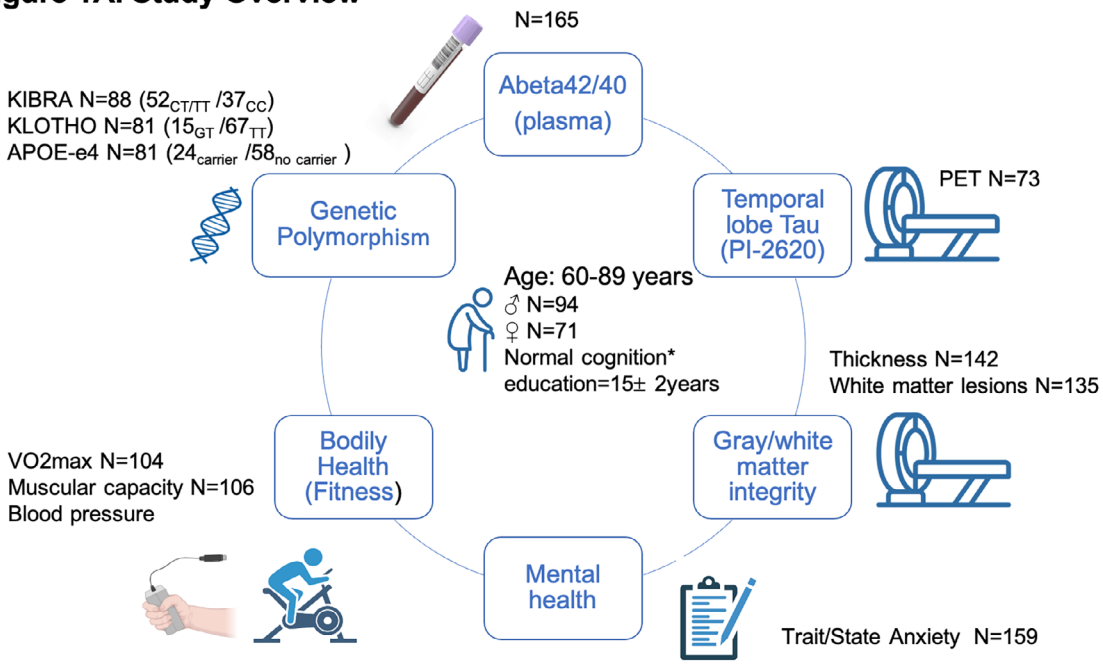
Figure 1A. Study Overview



Normal cognition*: based on age, sex and education adjusted scores on the CERAD-PLUS battery

B. Methods

Target	Modality	Method	Regions/ measure
Abeta42/40	Blood Plasma	Assay: *Lumipulse G Fujirebio*	$Abeta_{1-42}/Abeta_{1-40}$
Tau burden	PET- ^{18}F-PI2620 (60min-dynamic)	*Multilinear Reference Tissue Model2*, reference: inferior cerebellum	Distribution volume ratio (DVR) in temporal lobe ("Jack" –composite region)
White matter lesions	MRI-FLAIR	Segmentation via *lesion segmentation toolbox* (LPA algorithm)	Whole brain white matter hyperintensity volume (log-transformed)
Gray matter Thickness	MRI-T1 (0.8×0.8×0.8 mm^3	*FreeSurfer* segmentation	Anterior cingulate, medial temporal lobe (entorhinal, parahipp., fusiform), whole brain
Cardiovascular fitness	Fitness assessment	Spiroergometry- Maximal oxygen consumption (VO2max)	Aerobic capacity (VO2max)
Muscular capacity	Fitness assessment	Muscle strength by hand grip test Muscle quantity by Bioelectrical impedance analysis Physical performance by *Timed-up-and-go test*	Composite of hand grip strength, appendicular skeletal muscle mass, and walking performance
Mental health	Questionnaire	State-Trait Anxiety Inventory	Trait and State Anxiety
Genetic Polymorphism	Blood	Single nucleotide polymorphism: Klotho: rs9536314; KIBRA: rs17070145 APOE genotype	*KLOTHO* SNP(GT vs TT) *KIBRA* SNP (CT/TT vs CC) APOE*e4* carrier vs non-carrier

Figure 2. Differences in age-related pathology and brain structure between SuperAgers and Typical Agers

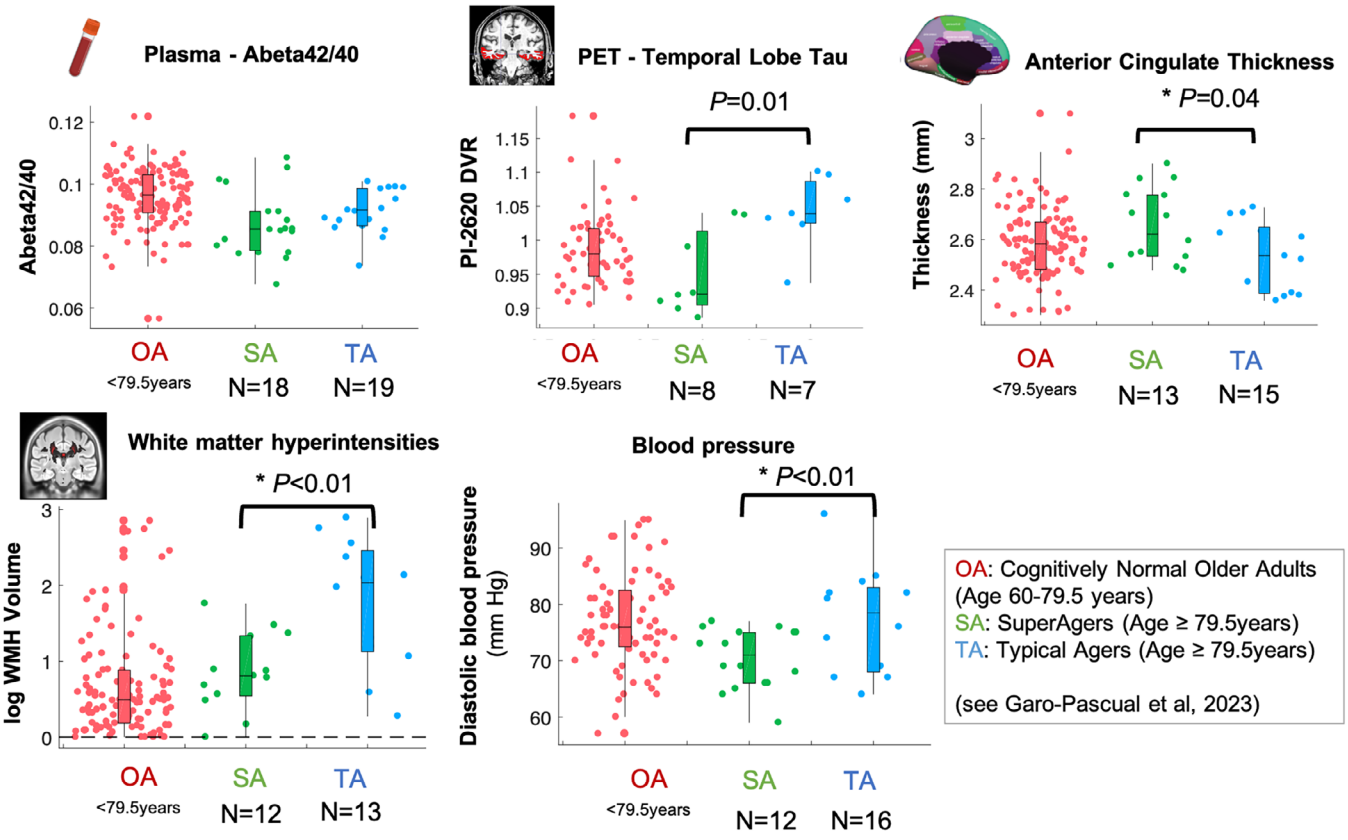


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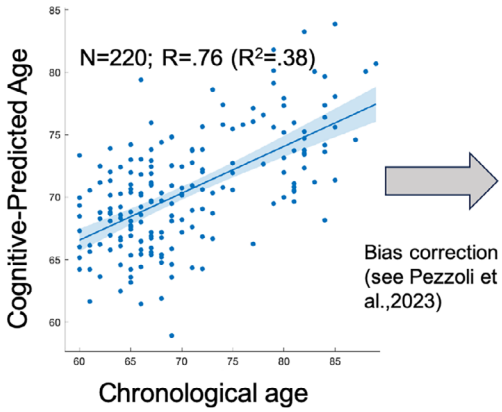
Figure 3A. Cognitive Age Gap (CAG)

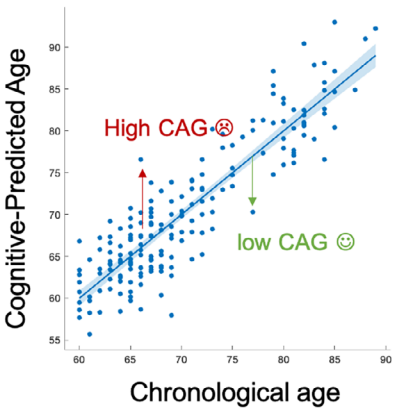
Cognitive age gap (CAG)=
cognitive-predicted age –chronological age

Partial least square regression in 220 older adults

Tests (predictors):
Verbal learning & memory
Symbol digit modalities
Semantic fluency
Rey Figure
Free and cued selective reminding
Logical memory

Model: 5 components





B. Cognitive Age Gap (CAG) related to brain thickness, tau measures and mental health