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Comparison between amyloid-PET and CSF amyloid-β biomarkers in a clinical cohort with memory deficits

Caroline Bouter[a,*,1], Jonathan Vogelgsang[b,1], Jens Wiltfang[b,c,d]

[a] University Medical Center Goettingen (UMG), Georg-August-University, Dept. of Nuclear Medicine, Robert-Koch-Str. 40, D-37075 Goettingen, Germany
[b] University Medical Center Goettingen (UMG), Georg-August-University, Dept. of Psychiatry and Psychotherapy, Von-Siebold-Str. 5, D-37075 Goettingen, Germany
[c] German Center for Neurodegenerative Diseases (DZNE), Von-Siebold-Str. 3a, D-37075 Goettingen, Germany
[d] iBiMED, Medical Science Department, University of Aveiro, Portugal

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ABSTRACT

With increasing prevalence of Alzheimer's disease (AD) and advances in research of therapeutic approaches, an early and accurate *in-vivo* diagnosis is crucial. Different biomarkers that are able to identify AD are currently in focus. However, whether and to which extend results of cerebrospinal fluid (CSF) and imaging biomarkers are comparable, is unclear. This study aims to correlate CSF and amyloid imaging biomarkers comparing them to cognitive measurements in order to determine whether these methods provide identical or complementary information.

The study comprises 33 consecutive patients with suspected cognitive decline that underwent lumbar puncture for CSF biomarker analysis and Amyloid-PET/CT within the diagnostic evaluation of memory impairment. Amyloid PET/CTs were evaluated visually and quantitatively. CSF and imaging data were retrospectively evaluated and results were compared to cognition tests, age, gender, and ApoE status.

Global cortex SUVr levels correlated highly with CSF $A\beta_{42/40}$ and moderately with $A\beta_{42}$ but not with $A\beta_{40}$. Global cortex SUVr and $A\beta_{42/40}$ correlated with mini mental status examination.

This study indicates that Amyloid-PET and CSF biomarkers might not reflect identical clinical information and a combination of both seems to be the most accurate way to characterize clinically unclear cognitive decline.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia with an increasing incidence. Currently, AD affects about 35 million people worldwide. This number is expected to increase to over 100 million until 2050 [1].

To date, the definite confirmation of the diagnosis of AD can only be made histopathologically. However, growing evidence suggests that pathological changes leading to AD begin many years before first clinical symptoms appear [2]. Next to neuropsychological testing, several biomarkers for diagnosis of AD are under investigation to establish a probable diagnosis of AD. These include specific proteins in cerebrospinal fluid (CSF) or blood and neuroimaging. Currently, the CSF biomarkers Amyloid-β_{42} ($A\beta_{42}$), total-Tau (tTau), and phospho-181-Tau (pTau) as well as positron-emission-tomography (PET) imaging are clinically validated and recommended [3–6].

At the current stage, AD therapy is limited to symptomatic treatments. Since degenerative processes are leading to typical symptoms of MCI or dementia, an effective treatment of AD should be initiated at an early stage [7] for what an early diagnosis is crucial.

1.1. Fluid biomarkers

During the diagnostic process of cognitive deficits and dementia, the detection of Aβ pathology can be supported by different biomarkers. At the beginning of the 21st century, novel CSF biomarker assays were developed in order to detect Aβ species, namely $A\beta_{1-42}$ [8]. The C-terminal elongated $A\beta_{42}$ is a highly aggregating Aβ peptide which is mainly accumulating in plaques. Thus, decrease of $A\beta_{42}$ in CSF is a biomarker for AD pathology. More recent studies suggest, that the $A\beta_{42}$ to $A\beta_{40}$ ratio ($A\beta_{42/40}$) outperforms $A\beta_{42}$ as a biomarker for Aβ pathology in CSF [9,10].

Besides $A\beta_{42}$ or $A\beta_{42/40}$, tTau and pTau are elevated in CSF of AD patients [11].

* Corresponding author.
E-mail address: caroline.bouter@med.uni-goettingen.de (C. Bouter).
[1] These authors contributed equally.

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1.2. PET-imaging

Molecular imaging of the brain is considered a diagnostic biomarker supporting neuropsychological testing and CSF biomarkers. Pathological aggregation of β-amyloid is a pathophysiological hallmark of AD and histopathological proof of β-amyloid *post-mortem* displays the gold standard of AD diagnosis. Non-invasive molecular imaging of β-amyloid *in-vivo* was developed within the last years. Several PET-tracers that detect β-amyloid-plaques are commercially available including: Pittsburgh Compound B (^{11}C-PiB), ^{18}F-Florbetaben (Piramal Healthcare), ^{18}F-Florbetapir (Eli Lilly and Company/Avid Radiopharmaceuticals) and ^{18}F-Flourmetamol (GE Healthcare). These tracers were excessively validated comparing PET-results with histopathological findings [12–17]. A strong correlation between tracer uptake *in-vivo* and amyloid pathology in brain tissues could be shown and amyloid imaging became an established biomarker for AD. Cortical uptake of ^{11}C-PiB correlates with uptake of ^{18}F-Amyloid tracers [18,19]. Amyloid-PET is used to assess cortical amyloid load in patients with cognitive decline.

1.3. Clinical relevance

The clinical state of cognition (normal, MCI or dementia) is diagnosed using standardized neuropsychological testing and clinical examination. Biomarkers, both CSF and PET imaging, are important to state an Alzheimer specific pathology [4]. There is still inconsistent literature on the question whether CSF Aβ-levels correspond to cognitive decline [20,21].

It is unclear, whether CSF and PET supply identical or perhaps complementary information. Addressing this issue, we compared CSF Aβ biomarkers with quantified Amyloid-PET data in this study. CSF and PET biomarkers were correlated with the cognitive state of the participants and the impact of systemic factors on these biomarkers was examined.

2. Material & methods

2.1. Study population

The current study was performed with patients from the biobank of the Department of Psychiatry and Psychotherapy, University Medical Center Goettingen (ethical vote 9/2/16) between July 2016 and November 2017. Patients were at a mean age of 63.0 ± 15.4 years. 48 patients were female and 72 patients were male. The mean mini mental state examination (MMSE) and clock-drawing test (CDT) scores were 25.6 ± 3.9 and 2.2 ± 1.2, respectively. CSF Aβ concentrations were 6830 ± 3476 pg/ml, 550 ± 359 pg/ml and 0.079 ± 0.025 for $Aβ_{40}$, $Aβ_{42}$, and $Aβ_{42/40}$.

A subgroup of 33 patients underwent Amyloid PET/CT using ^{18}F-Florbetaben. These patients were at a mean age of 68.4 ± 10.3 years. 13 patients were female and 20 patients were male. The mean mini mental state examination (MMSE) and clock-drawing test (CDT) scores were 25.2 ± 3.0 and 2.4 ± 1.2. PET imaging was performed during routine clinical diagnostics. Amyloid-PETs of 18 participants (54.5%) were diagnosed as abnormal with a mean SUVr of 1.62 (Table 1).

2.2. Multiplex Aβ immunoassay

CSF was collected and prepared according to the local standard operating procedures [22]. Briefly, CSF samples were centrifuges for 10 min at 2000 ×*g* at room temperature and stored at −80 °C. CSF samples were stored as 110 µl up to 18 months. All patients gave their informed consent prior to the inclusion to the biobank.

CSF $Aβ_{40}$ and $Aβ_{42}$ concentrations – and out of it the calculated $Aβ_{42/40}$ CSF ratio – were measured using a recently validated chemiluminescence multiplex immunoassay (V-PLEX Aβ (6E10) Mesoscale) [23]. Briefly, the assay plate was blocked with 150 µl blocking buffer followed by three consecutive washing steps. CSF was diluted with dilution buffer to a final dilution of 1:16. 25 µl diluted samples or standards were incubated for 120 min at room temperature together with 25 µl detection antibody solution, consisting of 2% sulfo-tag labelled anti-Aβ antibody (6E10) and 1% $Aβ_{40}$ blocker. The assay plate was washed three times and 150 µl read buffer was added before measuring the plate using the MESO QuickPlex SQ 120 reader (Mesoscale).

Table 1
Cohort characteristics.

		PET cohort	Biobank cohort
Cases *n*		33	120
Mean age *years* (SD)		68.4 (10.3)	63.0 (15.4)
Female *n* (%)		13 (39.4%)	48 (40.0%)
Mean MMSE points (SD)		25.2 (3.0)	25.6 (3.9)
Mean CDT points (SD)		2.4 (1.2)	2.2 (1.2)
CSF	$Aβ_{40}$*pg/ml* (SD)	5517 (3259)	6830 (3476)
	$Aβ_{42}$*pg/ml* (SD)	398 (262)	550 (359)
	$Aβ_{42/40}$*pg/ml* (SD)	0.074 (0.024)	0.079 (0.025)
PET	Abnormal Amyloid-PET *n* (%)	18 (54.5%)	
	SUVr Amyloid-PET (SD)	1.39 (0.33)	
	SUVr abnormal Amyloid-PET (SD)	1.62 (0.28)	
	SUVr normal Amyloid-PET (SD)	1.12 (0.08)	

2.3. Amyloid-PET/CT

Amyloid PET/CT with ^{18}F-Florbetaben was performed on a Philips Gemini TF16 PET/CT-scanner (Philips Medical Systems, Cleveland, OH, USA) with a 128 × 128 matrix with 2 mm slice thickness. Low-dose-CT with a 512 × 512 matrix with 2 mm slice thickness was used for attenuation correction (CTAC-SG algorithm). Reconstruction was performed using the LOR-TF-RAMLA ("BLOB-OS-TF") algorithm. ^{18}F-Florbetaben (Piramal Imaging Ltd., Cambridge, UK) was used in all 33 patients.

300 (± 20%) MBq ^{18}F-Florbetaben was administered intravenously and PET/CT was performed 90 min post injection with an acquisition time of 20 min according to the manufacturer's protocol. PET/CTs were visually assed by an experienced nuclear medicine physician that underwent a specific reader training for amyloid imaging. Scans were visually scored 'negative' if the tracer uptake was within the physiological range with non-specific uptake in the white matter and clear grey/white matter contrast and scored 'positive' if tracer uptake in the grey matter was increased in at least two cortical areas loosing grey/white matter contrast (Fig. 1A–B). The interval between lumbar puncture for CSF analysis and PET/CT was between 1 day and 5.5 months (44 ± 48 days).

Amyloid uptake was assed semi-quantitatively using CortexID Suite (GE Healthcare, Little Chalfont, UK). In brief, automated grey matter segmentation was performed after anatomic normalization using a T1-weighted MRI-template and nine reference regions were defined (frontal cortex, anterior and posterior cingulate cortex, mesial and lateral temporal cortex, parietal cortex, occipital cortex, whole cortex and cerebellar cortex, Fig. 1C–D). Standardized uptake values of these regional volumes were obtained and standardized uptake value ratios (SUVr) were calculated using the whole cerebellum as reference as histopathological findings showed low or absent amyloid-β deposition in the cerebellar cortex [24].

2.4. Statistical analysis

Unpaired *t*-tests, Mann-Whitney test, and nonparametric correlation (Spearman) were used for statistical evaluation. All statistics were calculated using Microsoft Excel or Prism (GraphPad Software), version 8 for Windows (Microsoft).

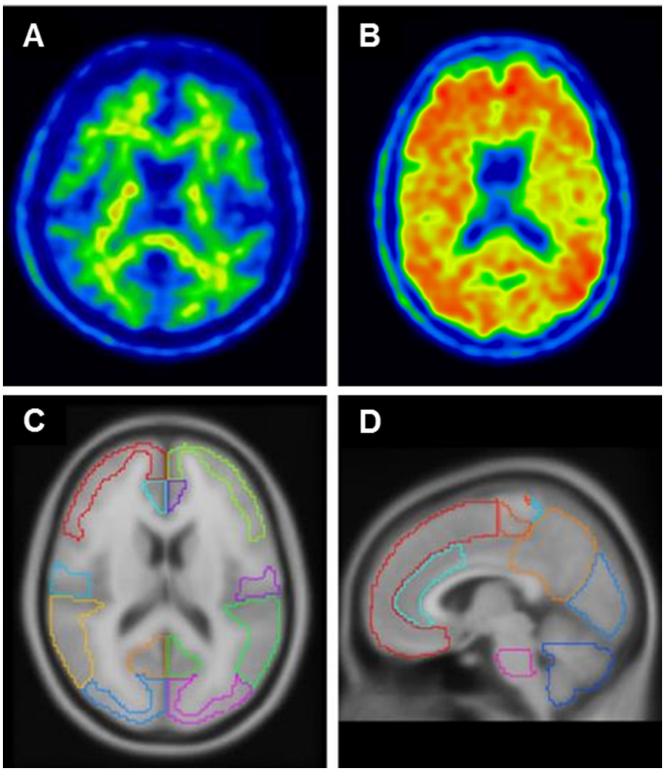

Fig. 1. Amyloid PET/CT. (A) Negative Amyloid scan with non-specific uptake in the white matter. (B) Positive Amyloid scan with increased uptake in the frontal, parietal, posterior cingulate and occipital cortex. (C-D) MRI template with marked regions, transversal (C) and sagittal (D) view.

3. Results

3.1. Amyloid uptake

Amyloid-PET/CT was visually positive in 18 cases and negative in 15 cases. Amyloid uptake was analysed semi-quantitatively and SUVr was compared between global cortex and seven different cerebral areas. Cortical areas did not show significant differences of SUVr ($p > 0.35$), except of the temporal mesial cortex. SUVr within the temporal mesial cortex was lower compared to global cortex and other cortical areas ($p < 0.0001$). There was no significant difference of SUVr between right and left hemisphere in all areas ($p > 0.16$). Therefore, further comparisons were performed using SUVr of the global cortex.

Visually negative scans showed significantly lower uptake in all cortical areas compared to scans that were rated positive (95% confidence interval 0.3582 to 0.6417; $p < 0.0001$, Fig. 2).

3.2. Correlation between amyloid PET/CT and fluid biomarkers

CSF $A\beta_{40}$ showed no correlation to SUVr of the global cortex (95% confidence interval − 0.4524 to 0.3566; $p > 0.79$), whereas $A\beta_{42}$ (95% confidence interval − 0.7055 to −0.01746; $p < 0.0366$; $r = -0.42$) and $A\beta_{42/40}$ (95% confidence interval − 0.7961 to −0.2233; $p < 0.0025$; $r = -0.58$) correlated with SUVr levels (Fig. 3).

3.3. Impact of age, gender and ApoE status

We analysed the impact of ApoE on CSF and PET biomarkers by comparing ApoE4 with non-ApoE4 carriers. SUVr was significantly higher in ApoE4 carriers (SUVr: 1.489, 95% confidence interval 1.334 to 1.643) compared to non-carriers (SUVr: 1.313, 95% confidence interval 1.141 to 1.486; $p = 0.0371$). CSF $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42/40}$ was lower in ApoE4 carriers. ApoE4 carriers had CSF $A\beta_{40}$ levels of 5670 pg/ml (95% confidence interval 4824 pg/ml to 6516 pg/ml), CSF $A\beta_{42}$ levels of 356.0 pg/ml (95% confidence interval 292.3 pg/ml to 419.7 pg/ml), and CSF $A\beta_{42/40}$ levels of 0.0642 (95% confidence interval 0.0573 to 0.0711). Non-ApoE4 carriers had CSF $A\beta_{40}$ levels of 7502 pg/ml (95% confidence interval 6663 pg/ml to 8341 pg/ml; $p = 0.0173$), CSF $A\beta_{42}$ levels of 662.8 pg/ml (95% confidence interval 576.1 pg/ml to 749.5 pg/ml; $p < 0.0001$), and CSF $A\beta_{42/40}$ levels of 0.0877 (95% confidence interval 0.0828 to 0.0925; $p < 0.0001$).

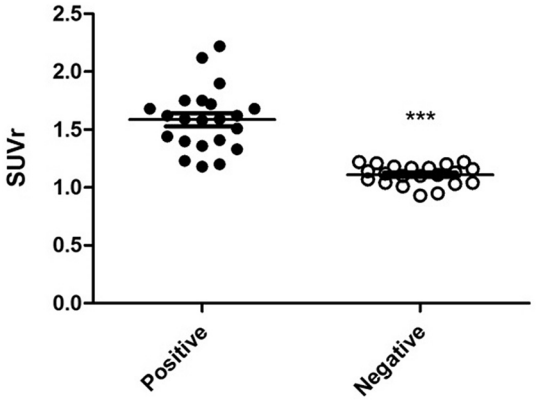

Fig. 2. Visual Amyloid-PET analysis. SUVr of global cortex. SUVr of visually positive cases was significantly higher compared to visually negative cases. ***$p < 0.0001$, *t*-test.

Interestingly, age correlated negatively with CSF $A\beta_{42}$ (95% confidence interval − 0.3934 to −0.0427; $p = 0.0133$, $r = -0.23$) and CSF $A\beta_{42/40}$ (95% confidence interval − 0.5714 to −0.2696; $p < 0.0001$, $r = -0.43$) but did not affect the SUVr (global cortex, 95% confidence interval − 0.1939 to 0.4933; $p > 0.34$) or CSF $A\beta_{40}$ (95% confidence interval − 0.1337 to 0.2342; $p > 0.57$).

No effect of gender on any biomarker could be observed (PET: $p > 0.15$; CSF $A\beta_{42}$: $p > 0.91$; CSF $A\beta_{42/40}$: $p > 0.60$).

3.4. Correlation between cognition and amyloid PET/CT and CSF biomarkers

Global cortex SUVr showed a strong correlation with MMSE (95% confidence interval − 0.7244 to −0.1779; $p = 0.0031$, $r = -0.5$; Fig. 4) but not with CDT (95% confidence interval − 0.03819 to 0.6116; $p = 0.0700$; $r = 0.32$).

MMSE did not correlate with the biomarkers $A\beta_{42}$ (95% confidence interval − 0.1129 to 0.2940; $p > 0.35$) or $A\beta_{40}$ (95% confidence interval − 0.2769 to 0.1312; $p > 0.45$) but with $A\beta_{42/40}$ (95% confidence interval 0.1151 to 0.4868; $p = 0.0018$; $r = 0.31$; Fig. 5A–C). CDT showed no correlation with $A\beta_{40}$, $A\beta_{42}$ or $A\beta_{42/40}$ (95% confidence interval − 0.3009 to 0.1192; $p > 0.36$, −0.3569 to 0.0569; $p > 0.13$, and − 0.3599 to 0.00534; $p > 0.12$; Fig. 5D–F).

4. Discussion

Due to the increasing prevalence of AD and advances in research of therapeutic approaches, the development of biomarkers that are able to identify the disease *in-vivo* are currently in focus. Early and accurate detection and prediction whether a patient with MCI proceeds into AD is crucial. Therefore, biomarkers (fluid and imaging biomarkers) are not only essential for confirming the diagnosis of AD but also for identifying patients at great risk for AD development and possible therapy responders as well as for therapy monitoring and inclusion of suitable patients for clinical studies.

Whereas CSF analysis is a medium invasive but well tolerated and rather cheap procedure, the performance of PET imaging is expensive

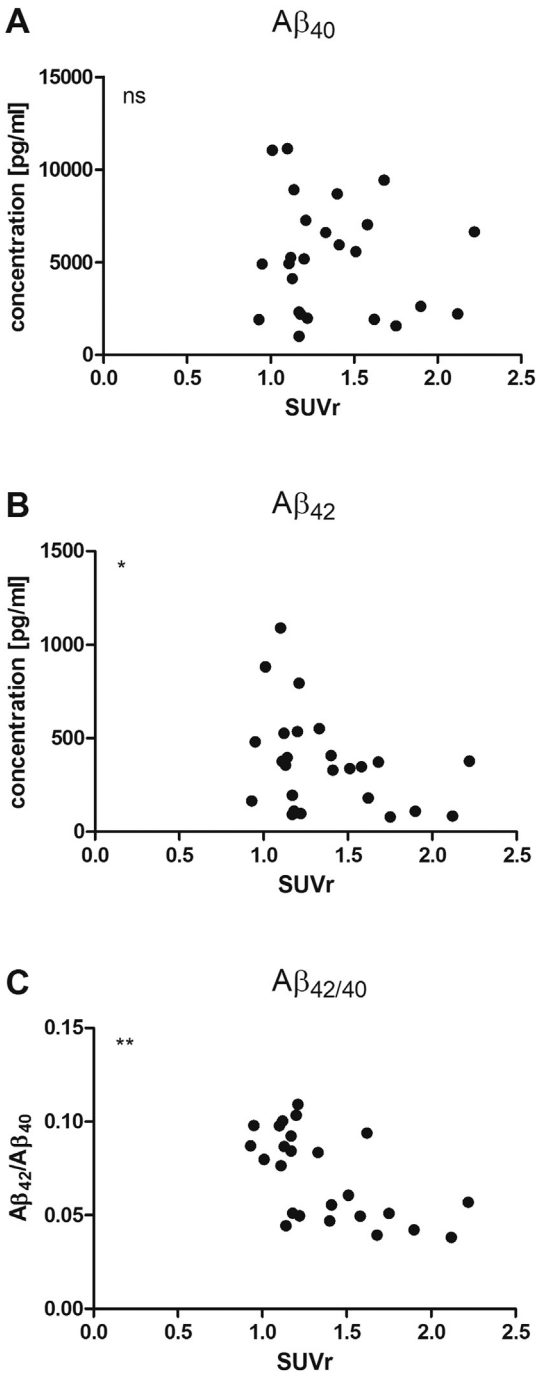

Fig. 3. Correlation between Amyloid PET/CT and CSF. CSF $A\beta_{40}$ showed no correlation to SUVr of the global cortex, whereas $A\beta_{42}$ and $A\beta_{42/40}$ correlated with SUVr levels.

and limited to big diagnostic centres due to the complex infrastructure (PET/CT scanner, availability of tracers *etc.*).

4.1. PET and CSF biomarkers

In the current study, we describe the relation between Amyloid-PET and CSF Aβ biomarkers in a cohort of 33 patients.

Results in our study show a correlation between the amyloid tracer uptake in PET with decreased $A\beta_{42}$ and $A\beta_{42/40}$ ratio in CSF. These findings are in line with previous studies [25–30]. Furthermore, histopathological studies were able to show a good negative correlation between amyloid plaque deposition in the neocortex and hippocampus

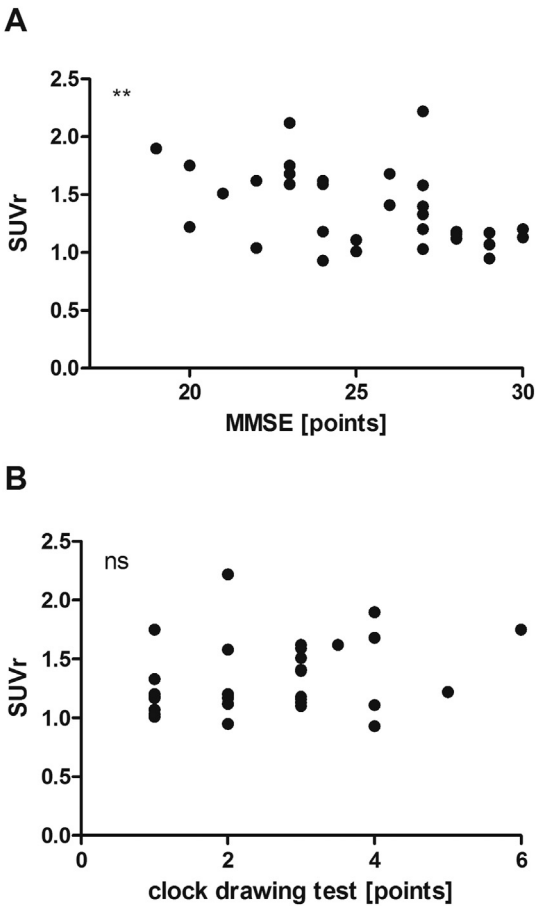

Fig. 4. Correlation of Amyloid PET/CT and cognition tests. Global cortex SUVr showed a correlation with both, MMSE and CDT.

with $A\beta_{42}$ levels in CSF [31].

In accordance to earlier studies, we could demonstrate a higher correlation between amyloid-tracer uptake and $A\beta_{42/40}$ than $A\beta_{42}$ [32–34]. These findings indicate that $A\beta_{42/40}$ better depicts central amyloid load than $A\beta_{42}$ alone. In combination with previously published data comparing $A\beta_{42}$ and $A\beta_{42/40}$ [9,10,34], this study clearly supports the clinical implementation of $A\beta_{42/40}$.

In recent years, amyloid imaging became an established biomarker for AD with an almost identical diagnostic accuracy compared to CSF biomarkers [35]. Both biomarkers, CSF $A\beta_{42}$ or $A\beta_{42/40}$ and amyloid imaging, seem to reliably display plaque pathology. However, it remains unclear whether Amyloid-PET and amyloid in CSF provide independent information or even partially different aspects of amyloid metabolism [36]. Recent findings suggest that CSF $A\beta_{42}$ might be the earliest biomarker showing a positive result even before PET [37]. However, this finding is still controversial as other results of longitudinal studies could not confirm any evidence of CSF Aβ abnormalities preceding changes in amyloid imaging [29].

4.2. Cognitive status

MMSE and CDT are widely used clinical screening tools for follow-up measurements of a patient's cognitive status. In the current study, we were able to show a correlation between both tests and CSF $A\beta_{42/40}$ ratio but not with CSF $A\beta_{40}$ or $A\beta_{42}$. Patients' amyloid load correlated to MMSE in contrast to earlier findings using the amyloid tracer ^{11}C-PiB or ^{18}F-Florbetaben that could not show a correlation between MMSE and amyloid burden [38,39]. However, a Phase 0 study of ^{18}F-Florbetaben described a correlation between obtained z-scores (amyloid uptake in relation to normal controls) and MMST and CDT [40]. *Post mortem*

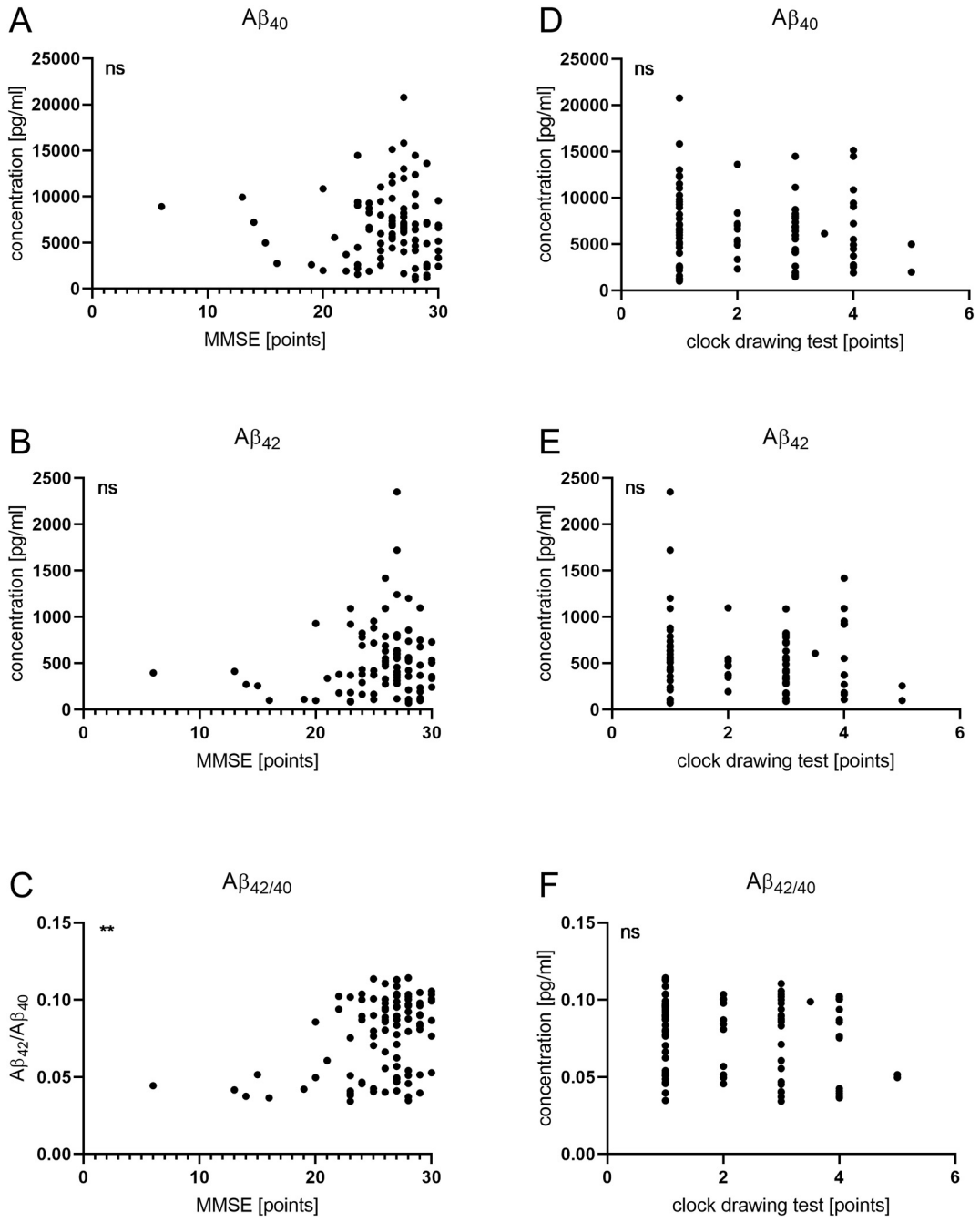

Fig. 5. Correlation between cognition tests and CSF biomarkers. MMSE did not correlate with the biomarkers $A\beta_{40}$ or $A\beta_{42}$ but with $A\beta_{42/40}$. CDT showed no correlation with $A\beta_{40}$, $A\beta_{42}$ or $A\beta_{42/40}$.

studies could not demonstrate a relationship between the density of amyloid plaques and the severity of cognitive impairment [41,42]. As amyloid deposition is suggested as an early event years before cognitive deficits occur, pathological biomarkers might not always be able to reflect the cognitive state of a patient. Therefore, pathological biomarkers have to be interpreted considering the cognitive status.

4.3. Influencing factors

The biomarker supported diagnosis of Alzheimer's disease is highly recommended accorded to novel guidelines [4]. Unfortunately, measurement of Aβ in CSF is a complex technique. In particular, pre-analytical procedures of CSF handling and laboratory variances seem to have a major impact on the analysis of Aβ [10,43]. Besides pre-analytical and analytical difficulties in the detection of CSF Aβ, there are different systemic factors that affect $A\beta_{42}$ levels.

In our study, $A\beta_{42}$ concentrations were affected by age. Results of age-dependent changes of $A\beta_{42}$ concentrations in CSF are somewhat controversial. Several studies reported a linear decrease of CSF $A\beta_{42}$ with age [44–46] while other studies showed no changes or an increase of $A\beta_{42}$ [47–50]. However, several factors that might influence $A\beta_{42}$ findings in CSF have to be taken into account that might explain those diametrical findings as sleep cycle and handling and storage of samples [51,52]. Age might be an influencing factor of Aβ analysis that has to be considered in the interpretation of CSF measurements. Furthermore, reduced $A\beta_{42}$ in CSF was also reported in several disorders without Aβ plaque pathologies as amyotrophic lateral sclerosis, Creutzfeldt-Jacob disease and multiple system atrophy [53,54] suggesting that other

factors can also influence $A\beta_{42}$ CSF-levels.

In addition, it has been reported that the ApoE genotype influences Aβ levels in CSF [55–57]. Since the ApoE genotype has a minor relevance in the diagnostic of AD in clinical routine, the regular diagnostic determination of the ApoE genotype is currently not recommended [58]. But the interpretation of Aβ levels in CSF without the knowledge of the ApoE genotype can be difficult and therefore ApoE status should also be considered especially in difficult cases. In the present data we could compare the effect of age and ApoE on both, Aβ biomarkers in CSF and cerebral amyloid deposition by Amyloid-PET. We were able to confirm that ApoE4 is correlated with lower CSF Aβ levels [55–57]. Interestingly, CSF Aβ levels are affected by both, age and ApoE genotype. However, we could demonstrate that cerebral Amyloid deposition as quantified by Amyloid-PET is only affected by the ApoE genotype but not by age. ApoE4 is associated with an about 13.5% higher Amyloid SUVr in the cortex. This finding corresponds to the well-studied association between ApoE4 and AD [59]. Grupe et al. could identify in their genome-wide association study ApoE as the most prominent risk factor for the development of AD [60]. Thus, the diagnostic application of an Amyloid-PET might be superior to a CSF analysis as it is not as susceptible to influencing factors. However, we have not addressed the question if these correlations correspond to specific diagnostic entities, *i.e.* if there are differences in patients with AD, LBD of FTLD. Further studies with more specific neurodegenerative entities and, if possible, *post mortem* neuropathological confirmation should be performed.

5. Conclusion

Biomarkers for AD diagnostics become more and more essential for accurate diagnosis of AD, prediction of AD development and identification of possible therapy responders. Our results strengthen previous findings that CSF and PET reliably show amyloid plaque pathology. CSF seems to be more susceptible to influencing factors whereas it is suggested to show amyloid pathology even before PET can identify elevated cerebral amyloid load. A combination of CSF and imaging biomarkers in clinically and neuropsychologically confirmed cognitive impairment considering the cognitive status seems to be the most accurate way to characterize AD patients to date.

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