# Ⅲ. 研究成果の刊行に関する一覧表

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
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# Ⅳ. 研究成果の刊行物・別冊

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# Interrelations between CSF Soluble AβPPβ, Amyloid-β 1-42, SORL1, and Tau Levels in Alzheimer's Disease

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**Abstract.** Recently, light has been shed on possible interrelations between the two most important pathological hallmarks of Alzheimer's disease (AD): the amyloid cascade and axonal degeneration. In this study, we investigated associations between sβAPPβ, a product of the cleavage of the amyloid-β protein precursor (AβPP) by β-secretase, amyloid-β 1-42 ($A\beta_{42}$), soluble SORL1 (also called LR11 or SORLA), a receptor that is involved in AβPP processing, and the marker of axonal degeneration tau in the cerebrospinal fluid (CSF) of 76 patients with mild cognitive impairment (MCI), 61 patients with AD, and 17 patients with frontotemporal dementia, which neuropathologically is not related to the amyloid pathology. In the AD group, significant associations between sAβPPβ, tau ($p < 0.001$), and soluble SORL1 ($p < 0.001$) were detected according to linear regression models. In patients with MCI, sAβPPβ correlated significantly with tau ($p < 0.001$) and soluble SORL1 ($p = 0.003$). In the FTD group, only SORL1 ($p = 0.011$) was associated with sAβPPβ and not tau. $A\beta_{42}$ was found to be significantly related to tau levels in CSF in the MCI group ($p < 0.001$) and they tended to be associated in the AD group ($p = 0.05$). Our results provide further evidence for a link between the two facets of AD pathology, which is likely to be mediated by the binding of Aβ oligomers to specifically targeted neurons, resulting in stimulating tau hyperphosphorylation and neurodegeneration.

Keywords: Alzheimer's disease, amyloid, amyloid-β 1-42, association, soluble AβPPβ, SORL1, tau

## INTRODUCTION

The pathological hallmarks of Alzheimer's disease (AD) comprise extracellular fibrillar amyloid-β (Aβ) deposits and soluble Aβ oligomers (both products of the amyloid cascade), intracellular neurofibrillary tangles formed by abnormally phosphorylated tau protein, astrocytosis, and synaptic as well as neuronal loss [1]. It is an important and tempting research task to

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unveil how the multiple facets of AD pathology are interlinked.

The proteolytic breakdown of the amyloid-β protein precursor (AβPP) by β-secretase generates the β-secretase cleaved soluble AβPP (sAβPPβ) and the peptide C99. The subsequent proteolysis of C99 by γ-secretase results in the generation of several isoforms of Aβ. The fibrillar forms of Aβ, mainly consisting of the isoform $Aβ_{42}$ which is one of the main constituents of amyloid plaques, were initially considered to be the drivers of neuronal damage [2]. However, new observations provide evidence that small soluble Aβ oligomers which have no propensity for aggregation represent the most synaptotoxic species of the peptide [2]. Aβ oligomers are generated by the ability of β- and γ-secretase to execute proteolytic cleavage at different positions in AβPP, as well as by the probable involvement of other AβPP- and Aβ-degrading proteases. Interestingly, Aβ oligomers have been shown to be increased in the brain and in the cerebrospinal fluid (CSF) of patients with AD and to correlate with neurofibrillary tangle density [3-4]. According to findings of cell culture studies, they attach to synapses in the central nervous system and inhibit long-term potentiation, enhance long term depression, induce oxidative stress and abnormal phosphorylation of tau, and subsequently foster axonal degeneration [5–7]. It is known that Aβ oligomers activate glycogen synthase kinase-3β (GSK3β), Src family tyrosine kinases and phosphatidylinositol 3-kinase (PI3K), which are involved in the pathological hyperphosphorylation of tau [5, 8]. Intrahippocampal injection of an anti-oligomer antibody unexpectedly resulted in the clearing of both Aβ and tau pathology in a triple transgenic mouse model harboring mutant human AβPP, tau, and presenilin 1 [9]. Moreover antibodies against Aβ lead to a reduction of soluble Aβ oligomers, but not insoluble Aβ and lead to a decline of both GSK3β activation and tau phosphorylation [10]. However, the link between the amyloid cascade and tau pathology in AD still remains elusive, especially in the absence of data from patients suffering from AD.

In recent years, the sortilin-related receptor with A-type repeats (SORL1, also called LR11 or SORLA), a member of the apolipoprotein E and low-density lipoprotein receptor family, has captured scientific attention as a factor that is crucially implicated in the sorting of AβPP and in its interactions with secretases [11]. SORL1 is diffusely expressed throughout the brain and acts as an intracellular sorting receptor that engages in the Golgi apparatus-endosome transport [12]. SORL1 promotes the retention of AβPP in subcellular compartments which are less favorable for secretase processing and thereby reduces the extent of proteolytic breakdown into both amyloidogenic and non-amyloidogenic products [13]. The interaction between AβPP and SORL1 is not limited to the formation of complexes, but also comprises SORL1-dependent translocation of AβPP and a concomitant drastic decrease of AβPP cleavage [12]. Reduction of SORL1 levels in specific cell compartments leads to overproduction of Aβ [14], since the reduction of SORL1 switches AβPP away from the retromer recycling pathway and instead exposes AβPP to α- and β-secretase cleavage [12]. In line with these findings, the neuronal expression of SORL1 is dramatically decreased in AD brains [15–17]. However, SORL1 expression is not decreased in familial AD, suggesting that diminished SORL1 expression is not a consequence of amyloid accumulation [15]. Furthermore, SORL1 gene variants are assumed to be among the strongest genetic predisposition factors for AD [14, 18]. Nonetheless, no general consensus on the role of SORL1 genetic variants as risk factors for AD exists, since other investigations found only weak or no associations between SORL1 genetic variants and AD [19–24].

sAβPPβ is not prone to aggregation, and since it can be detected in the CSF, its levels in CSF do not reflect the generation only of $Aβ_{42}$ but of all Aβ peptides. The CSF is in direct contact with the central nervous system, therefore many alterations in the biochemical composition of brain parenchyma are reflected in the CSF, owing to the free exchange of molecules between the brain and the CSF [25]. The present study aimed to investigate possible associations between CSF levels of sAβPPβ, $Aβ_{42}$, and tau in patients with mild dementia in AD, patients with mild cognitive impairment (MCI), which in many cases represents a prodromal phase of AD [26], and patients with frontotemporal dementia (FTD) [27], a form of neurodegeneration which does not involve amyloid pathology. Since increased sAβPPβ may be associated with higher levels of Aβ oligomers, which might foster hyperphosphorylation of tau and subsequently axonal degeneration, a positive correlation between tau and sAβPPβ in patients with AD and possibly in the MCI group, but not in patients with FTD was expected. A further aim of the study was to elucidate possible relations between CSF SORL1 concentrations and sAβPPβ and $Aβ_{42}$, since according to the observations of cell culture studies SORL1 influences the cleavage of AβPP by secretases, resulting in the generation of sAβPPβ among further molecules. As a result, a negative correlation between

SORL1 and sAβPPβ and a positive between SORL1 and $A\beta_{42}$ in CSF possibly in all groups of participants was expected.

## METHODS

The study protocol was approved by the ethics committee of the Faculty of Medicine at Technische Universität München. The study was conducted in accordance with the 1964 Declaration of Helsinki. All participants gave their written informed consent after an extensive description of the study aims and procedures.

### *Participants*

The study encompassed 76 patients with MCI, 61 patients with mild dementia in AD, and 17 patients with FTD, who were recruited at the Department of Psychiatry and Psychotherapy at Technische Universität München. The examination of the patients included a history from the patient and from an informant, medical, neurological, and psychiatric examination, laboratory screening, structural brain imaging (MRI or CT), and a neuropsychological examination based on the German version of the Consortium to Establish a Registry for AD neuropsychological assessment battery (CERAD-NAB) [28]. The diagnosis of dementia was based on the criteria of the ICD-10 classification system [29]. To ensure that patients with dementia had not crossed the threshold to moderate dementia, patients with a score below 15 points on the MMSE were excluded from the study. This score has been found to discriminate mild from moderate dementia [30]. MMSE staging has been proven to be an effective clinical instrument for tracking the stages of dementia [30]. Patients with AD fulfilled the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) for probable AD [31]. Patients with MCI met the revised consensus criteria of the International Working Group on MCI [32]. The diagnosis of FTD was established according to the revised Lund-Manchester criteria [33].

### *CSF sampling and analyses*

CSF was collected in sterile polypropylene tubes, using atraumatic canulas placed in the L3/L4 or L4/L5 intervertebral space, and gently mixed. The CSF was centrifuged at 1800 g (4°C) for 10 min to remove cells and aliquots of the remaining CSF supernatants were stored in polypropylene tubes at −80°C.

### *Determination of tau, $A\beta_{42}$, and sAβPPβ levels*

CSF $A\beta_{42}$, total tau (Innogenetics, Ghent, Belgium), and sAβPPβ (IBL, Gunma, Japan) in CSF were measured in duplicate with commercially available enzyme-linked immunosorbent assays (ELISA) according to the manufacturers' instructions as described previously in detail [34–36].

### *SORL1 concentrations*

SORL1 concentrations in CSF were determined using ELISA by Sekisui Medical Co Ltd. (Ryugasaki, Japan) as described previously [37]. Briefly, 10 µl CSF was diluted with 100 µl sample buffer and added to the plate coated with mouse monoclonal antibody M3 [38]. Subsequently, after incubating with the biotinylated rat monoclonal antibody R14, the SORL-antibody complex reacted with horseradish peroxidase-conjugated streptavidin and substrate. A standard curve was constructed using a purified SORL1 protein. The final absorbance of each sample was measured at 450 nm. The intraassay and interassay coefficients of variation were 3.7% and 10.5% respectively [37]. SORL1 concentrations were determined in 57 patients with MCI, in 42 with AD, and in all patients with FTD.

### *Statistical analyses*

Statistical analyses were implemented in IBM SPSS Statistics 19.0 for Windows. The normal distribution of data was checked using the Kolmogorov-Smirnov test. Differences between the groups with regard to age, sAβPPβ, $A\beta_{42}$, SORL1, and MMSE were tested by analysis of variance (ANOVA), and with regard to tau CSF concentrations with the Kruskal-Wallis test. Pairwise comparisons were performed using the Bonferroni's test or the *T*-test (normally distributed data) and the Mann-Whitney test (data not normally distributed). $X^2$ tests were employed for nominal (categorical) data. Possible associations between CSF tau on the one hand and sAβPPβ and $A\beta_{42}$ on the other hand in each of the three groups of the study sample were investigated with linear regression analysis models, into which tau concentrations were fed as dependent variable and sAβPPβ, $A\beta_{42}$, age, and gender as explanatory variables. The MCI group was dichotomized with regard to tau values, as markers of neurodegeneration, in order to investigate

Table 1
Characteristics of the study sample. Data presented as mean (SD)

| | MCI | AD | FTD |
|---|---|---|---|
| *n* | 76 | 61 | 17 |
| Age (in years) | 65.5 (9.4) | 66.9 (9.5) | 62.9 (6.2) |
| Gender (men/women) | 38/38 | 32/29 | 7-Oct |
| MMSE (standard deviation) [range] | 26.89 (2.08) [22–30] | 22.54 (2.86) [16–27]* | 24.18 (3.58) [17–29]# |
| Tau (ng/ml) | 405.18 (270.43) | 599.93 (360.25)* | 214.35 (103.00)#‡ |
| Soluble AβPPβ (ng/ml) | 1059.94 (479.68) | 836.27 (383.71)* | 203.71 (103.94)#‡ |
| SORL1 (ng/ml) | (*n* = 57), 11.92 (4.28) | (*n* = 42), 11.89 (4.74) | (*n* = 17) 10.38 (3.35) |
| Amyloid-$\beta_{1-42}$ (ng/ml) | 737.46 (333.37) | 536.49 (235.43)* | 934.12 (345.24)#‡ |

MCI: Mild cognitive impairment, AD: Alzheimer's disease, FTD: Frontotemporal dementia, MMSE: Mini- mental state examination, SORL1: Sortilin-related receptor with A-type repeats; *Statistically significant differences between the MCI and AD groups, $p < 0.05$; #Statistically significant differences between the MCI and FTD groups, $p < 0.05$; ‡Statistically significant differences between the AD and FTD groups, $p < 0.05$.

possible differences in the relationship between tau and $A\beta_{42}$ and sAβPPβ between patients with MCI, developing on a neurodegenerative basis (>253 ng/L)

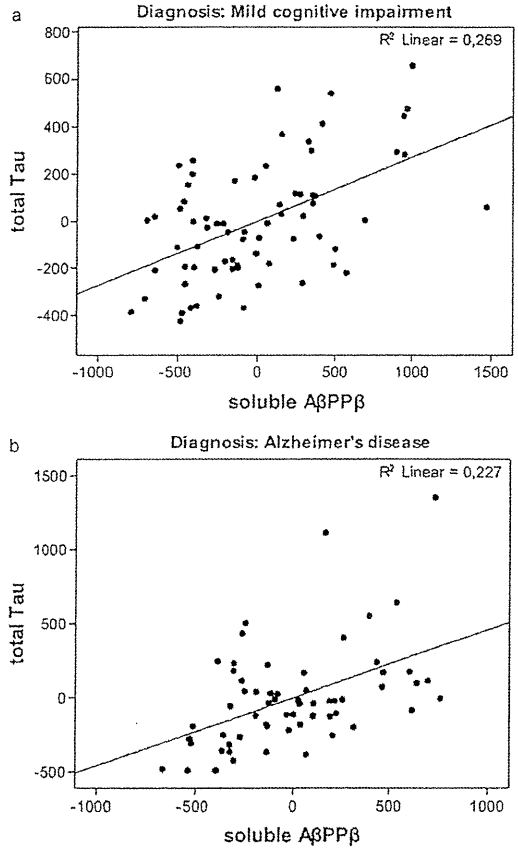


Fig. 1. Partial regression diagrams of total tau and soluble AβPPβ concentrations in cerebrospinal fluid in (a) patients with mild cognitive impairment and in (b) patients with Alzheimer's disease. Values are standardized and at zero centered.

[39] and those with non-degenerative MCI. The regression analysis with tau as dependent variable included sAβPPβ, $A\beta_{42}$, age, and gender as explanatory factors. The relations between CSF sAβPPβ and $A\beta_{42}$ and SORL1 concentrations were studied with linear regression models which included sAβPPβ or $A\beta_{42}$ as dependent factor and SORL1, age and gender as independent parameters. *P* values of less than 0.05 were considered statistically significant.

## RESULTS

Statistically significant differences across diagnostic groups regarding MMSE scores and CSF parameters were detected and are presented in Table 1. The linear regression analysis in the MCI group revealed statistically significant correlations of both sAβPPβ (standardized coefficient B = 0.486; $p < 0.001$) (Fig. 1) and $A\beta_{42}$ (standardized coefficient B = −0.465; $p < 0.001$) (Fig. 2) with tau, whereas neither age (standardized coefficient B = 0.083, $p = 0.421$) nor gender (standardized coefficient B = −0.045; $p = 0.648$) were associated with tau levels in CSF. Moreover, demographic, clinical, and biomarker data of the degenerative and non-degenerative MCI subgroups are presented in Table 2. The regression analysis with tau as dependent variable and sAβPPβ, $A\beta_{42}$, age, and gender as explanatory factors showed that tau correlated significantly in the degenerative MCI subsample with both $A\beta_{42}$ (standardized coefficient B = −0.506; $p = 0.001$) and sAβPPβ (standardized coefficient B = 0.370; $p = 0.008$). Unexpectedly, in the non-degenerative MCI subsample tau did positively correlate with CSF $A\beta_{42}$ (standardized coefficient B = 0.617; $p = 0.004$), while sAβPPβ did not (standardized coefficient B = 0.201; $p = 0.34$). In patients with AD, sAβPPβ (standardized coefficient B = 0.487; $p < 0.001$) (Fig. 1) was

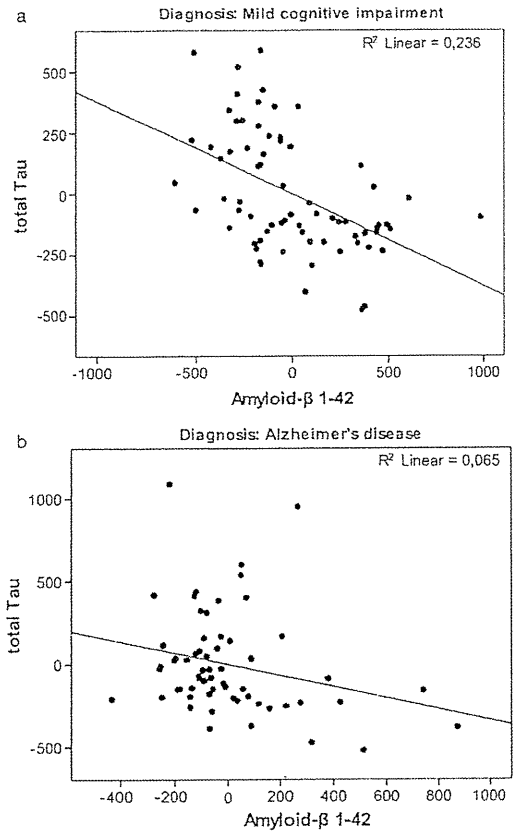


Fig. 2. Partial regression diagrams of total tau and amyloid-β 1-42 concentrations in cerebrospinal fluid in (a) patients with mild cognitive impairment and in (b) patients with Alzheimer's disease. Values are standardized and at zero centered.

significantly associated with tau. The association between $A\beta_{42}$ and tau strongly tended to be statistically significant (standardized coefficient B = −0.221, $p = 0.05$) (Fig. 2), whereas age (standardized coefficient B = −0.096; $p = 0.409$) and gender (standardized coefficient B = 0.080; $p = 0.51$) were not related to tau. In the FTD group neither sAβPPβ (standardized coefficient B = 0.350, $p = 0.199$) nor $A\beta_{42}$ (standardized coefficient B = 0.379, $p = 0.175$) were related to tau levels. No associations were detected between age (standardized coefficient B = 0.147, $p = 0.689$) and gender (standardized coefficient B = 0.142, $p = 0.532$) and tau concentrations in CSF. In all models, tolerance values were not less than 0.57. Tolerance values less than 0.2 are usually considered to indicate collinearity [40].

According to the regression analysis, CSF sAβPPβ levels correlated significantly with SORL1 concentrations (standardized coefficient B = 0.379; $p = 0.003$) in patients with MCI (Fig. 3) and were not influenced by age (standardized coefficient B = −0.158; $p = 0.202$) or gender (standardized coefficient B = 0.211; $p = 0.09$). In the AD group, significant associations between sAβPPβ and SORL1 (standardized coefficient B = 0.551; $p < 0.001$) (Fig. 3) and gender (standardized coefficient B = 0.398; $p = 0.003$) were observed, while age was not associated with SORL1 levels (standardized coefficient B = −0.045; $p = 0.734$). In patients with FTD, only SORL1 was found to be related to sAβPPβ levels in CSF (standardized coefficient B = 0.708; $p = 0.011$) (Fig. 3), whereas age (standardized coefficient B = −0.211; $p = 0.402$) and gender (standardized coefficient B = 0.347; $p = 0.141$) were not. Regarding relations between $A\beta_{42}$ and SORL1, the regression analysis did not reveal any associations between $A\beta_{42}$ and SORL1, age, or gender either in the MCI group (standardized coefficient B = 0.074, −0.201, 0.037, $p = 0.582$, 0.140, 0.785, respectively), or in the AD group (standardized coefficient B = −0.059, 0.096, 0.033, $p = 0.726$, 0.570, 0.838) respectively). The analysis did not show any

Table 2
Characteristics of patients with degenerative mild cognitive impairment (MCI) and with non degenerative MCI. Data presented as mean (SD)

| | Degenerative MCI | Non-degenerative MCI |
|---|---|---|
| *n* | 47 | 29 |
| Age (in years) | 67.3 (9.0) | 62.7 (9.4)* |
| Gender (men/women) | 23/24 | 15/14 |
| MMSE (standard deviation) [range] | 26.73 (2.22) [22–30] | 27.14 (1.84) [23–30]* |
| Tau (ng/ml) | 549.64 (247.08) | 171.07 (61.65)* |
| Soluble AβPPβ (ng/ml) | 1156.62 (491.57) | 903.26 (422.17)* |
| SORL1 (ng/ml) | (*n* = 32), 12.01 (5.16) | (*n* = 25), 11.80 (2.88) |
| Amyloid-$\beta_{1-42}$ (ng/ml) | 659.55 (314.33) | 863.72 (329.63)* |

MMSE: Mini-mental state examination, SORL1: Sortilin-related receptor with A-type repeats; *Statistically significant differences, $p < 0.05$.

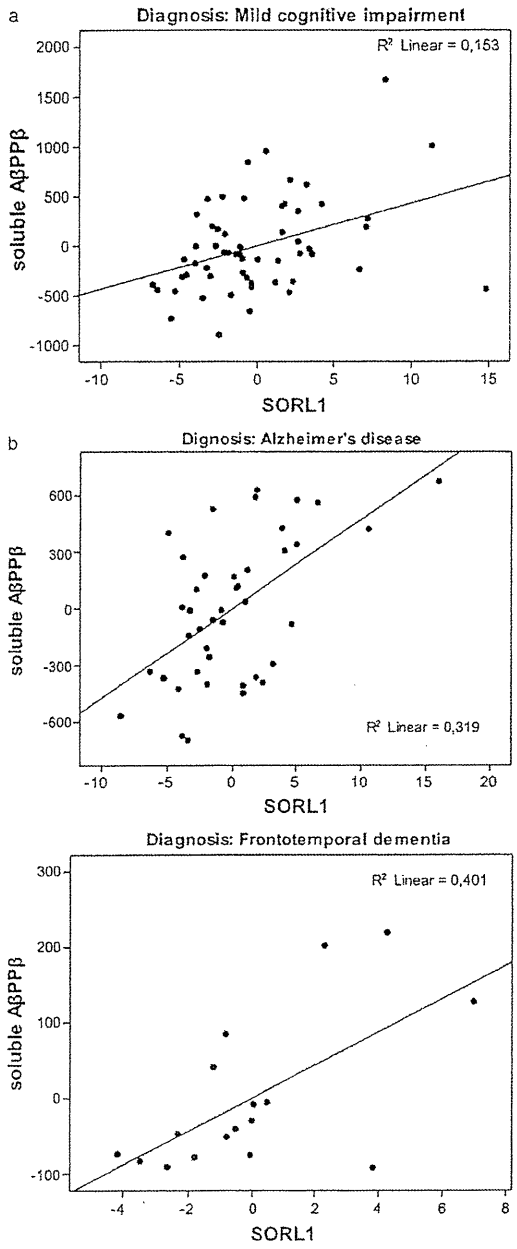


Fig. 3. Partial regression diagrams of soluble AβPPβ and SORL1 concentrations in cerebrospinal fluid in (a) patients with mild cognitive impairment, in (b) patients with Alzheimer's disease, and in (c) patients with frontotemporal dementia. Values are standardized and at zero centered.

statistically significant relations between $A\beta_{42}$ and SORL1 (standardized coefficient $B=0.514$, $p=0.077$), age ($B=-0$–$030$, $p=0.915$), or gender (standardized coefficient $B=0.382$, $p=0.146$) in patients with FTD too. Tolerance values were not less than 0.73.

## DISCUSSION

The main findings of the present study are the statistically significant positive correlations between sAβPPβ and tau in patients with AD and MCI, but not in the group of FTD patients, and the significant associations between sAβPPβ and soluble SORL1 in all groups of participants.

The positive correlation between sAβPPβ and tau in CSF of patients with AD and MCI, especially with MCI developing on a neurodegenerative basis, and the absence of such an association in the non-degenerative MCI subgroup are observations, which further support the concept of an interrelation between amyloid and tau pathology in AD, even though they do not establish any straightforward facilitatory causal effect of sAβPPβ on the increase of tau concentrations in CSF. These findings are in line with the reported positive correlation between tau levels and total soluble AβPP in CSF [41, 42], as well as with the association between β-secretase activity and tau levels [43]. One plausible explanation for this result is that the link between the two facets of AD pathology is possibly mediated by the binding of Aβ oligomers to neuronal target receptors, which aberrantly activates trophic signaling and activates an incomplete set of downstream events (e.g., increased Akt activation, hyperphosphorylation of critical Akt substrates, excessive activation of the PI3K/Akt pathway, leading to tau hyperphosphorylation, and neuronal degeneration [5]. Alternatively, the positive correlation between sAβPPβ and tau in CSF in AD and MCI could be attributable to an unspecific protein release from dying neurons and axons [43]. In line with the hypothesis that Aβ oligomers induce tau hyperphosphorylation and subsequently neurodegeneration, we detected an association between tau levels and sAβPPβ, mirroring the generation of all Aβ peptides, and not only of $A\beta_{42}$. However, it should be underscored that there is no experimental evidence for a relation between sAβPPβ and Aβ oligomers.

$A\beta_{42}$ was found to be associated with tau in the MCI group and marginally in the AD. Previous studies found a correlation between $A\beta_{42}$ and tau in CSF

in healthy elderly individuals and in patients with non-neurodegenerative MCI, but not in patients suffering from AD pathology [41, 44]. Our MCI group was not restricted to patients with MCI due to neurodegeneration, since patients with MCI were recruited according to clinical criteria and not values of markers of degeneration. Nonetheless, the dichotomization of the MCI group with regard to values of the neurodegeneration marker tau revealed a significant negative correlation between tau and $A\beta_{42}$ in the degenerative MCI subsample, whereas in the non-degenerative MCI subsample tau was found to correlate positively with CSF $A\beta_{42}$. These findings in conjunction with the presence only of a tendency to a correlation between $A\beta_{42}$ and tau in CSF in patients with AD possibly indicate that the progression of AD pathology is likely to result in the attenuation of the association between $A\beta_{42}$ and tau possibly via deficient clearance mechanisms of $A\beta_{42}$ or high rates of $A\beta_{42}$ aggregation in amyloid plaques [1]. The observed discrepancies, concerning the relationship between tau and $A\beta_{42}$ in CSF in the patients with AD and MCI, obviously warrant further investigation, especially in the light of the limited size of the non-degenerative MCI subgroup in our study.

The regression analysis model revealed an impact of gender on CSF sAβPPβ levels in patients with AD. This observation implies a sexual dimorphism. Interestingly, recent reports from AD transgenic animal models have reported higher β-secretase activity and a more aggressive Aβ pathology in female than male mice [45]. Such findings are compatible with previous observations, which indicate an upregulation of both α- and β- pathways in women compared with men with AD [46]. Moreover, it is noteworthy that epidemiological studies have shown that women have higher risk of AD even after adjustment for age [47, 48]. Nonetheless, the influence of gender on CSF sAβPPβ concentrations needs to be replicated in studies including larger samples.

To our knowledge this is the first study to elucidate a correlation between SORL1 concentrations and sAβPPβ in CSF of patients with AD, MCI, and FTD. SORL1 was previously found to be reduced in the Golgi and early endosomal compartments in AD [49–51], allowing or fostering AβPP to be processed by β- and α-secretase, resulting in the generation of sAβPPβ [12, 52, 53]. The positive correlation in our study seems to be a contradiction in this regard. However, the employed ELISA determines the soluble form of SORL1, which is the product of SORL1 processing by proteases. It consists of the extracellular domain of the membrane-spanning SORL1 protein [37], which was found to be elevated in patients with AD [54] and is assumed to be less efficient than full-length SORL1 with regard to mediating AβPP transport through the Golgi-apparatus [53]. However, a hypothesis claiming that in AD the intracellular decline in full-length SORL1 levels is caused by an elevation in the endoproteolytical cleavage of SORL1, resulting in an elevation of the concentrations of the less efficient soluble SORL1, which can be detected in CSF, is quite unlikely especially in the light of the absence of statistically significant differences in CSF SORL1 concentrations amid the three study groups. A further possible explanation for the detected positive correlation is the direct interaction of soluble SORL1 with sAβPPβ in CSF in association with apolipoprotein E, since SORL1 levels in CSF are particularly increased in patients with AD carrying the *APOE* ϵ4 allele [54], and SORL1 is a membrane receptor for APOE-containing lipoproteins in CSF [55]. Though in participants in whom CSF SORL1 was determined ($n = 116$), no differences were elucidated in SORL1 levels between *APOE* ϵ4 allele carriers and non carriers either in the AD or MCI and FTD groups (data not shown); in the regression analysis the interaction term *APOE* ϵ4 × SORL1 levels showed a significant effect on sAβPPβ concentrations (independent variable) in the MCI and AD group (standardized coefficient $B = 0.46$, 0.391, and $p < 0.001$, $p = 0.01$ respectively), while in patients with FTD, the association did not attain statistical significance (standardized coefficient $B = 0.085$, $p = 0.747$). Interestingly, the positive correlation between SORL1 and sAβPPβ was also found in FTD. This observation indicates that the association between the two molecules is not restricted to patients suffering from amyloid pathology. Therefore, future studies investigating the associations between the two molecules in further clinical entities, that are associated with alterations in processing of AβPP (e.g., multiple sclerosis, lyme neuroborreliosis) [56, 57], as well as in healthy subjects are required, since it is possible that the detected relation can be observed not only in patients with neurodegeneration.

Despite the detected significant association between CSF SORL1 and sAβPPβ levels in CSF in all study groups, the analysis did not reveal such an association between SORL1 and $A\beta_{42}$, possibly owing to the aggregation of $A\beta_{42}$ in amyloid plaques and/or impaired $A\beta_{42}$ clearance mechanisms, resulting in the undermining of a potential association between the two peptides in the CSF.

The present study should be viewed in the light of a number of limitations. The size of the study sample was relatively small and no control group was included. As a consequence, we were not in the position to explore possible associations between sAβPPβ, tau and SORL1 in physiological aging. However, a group of patients with FTD, which is pathologically not characterized by amyloid pathology, was included in the study. Only a few proteins related to amyloid metabolism were determined. Thus our analysis and the detected associations do not provide experimental evidence for causal effects. Unfortunately, *APOE* genotype data were not available for all study participants. As a result this genetic factor could not be included in the regression analysis as residual. Our investigation encompassed a sample which was restricted to participants recruited at university centers. Hence, the generalization of the results warrants further investigation. No pathological verification of diagnoses was available, but current diagnostic criteria for AD have been shown to be very accurate for populations recruited at specialized centers [58].

AD is a clinical entity which is assumed to reach the dimension of a health scourge in the near future. As a result it is worth trying to unravel the pathomechanisms underlying the disease in order to facilitate the development of new effective disease-modifying therapies. The elucidated interrelations between the amyloid cascade and axonal degeneration as well as between soluble SORL1 and sAβPPβ contribute to our understanding of the genesis of AD and probably to the developing of novel therapeutic strategies.

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