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RESEARCH ARTICLE

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Distinct cerebrospinal fluid amyloid β peptide signatures in sporadic and *PSEN1* A431E-associated familial Alzheimer's disease

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Abstract

Background: Alzheimer's disease (AD) is associated with deposition of amyloid β ($A\beta$) in the brain, which is reflected by low concentration of the $A\beta$ 1-42 peptide in the cerebrospinal fluid (CSF). There are at least 15 additional $A\beta$ peptides in human CSF and their relative abundance pattern is thought to reflect the production and degradation of $A\beta$. Here, we test the hypothesis that AD is characterized by a specific CSF $A\beta$ isoform pattern that is distinct when comparing sporadic AD (SAD) and familial AD (FAD) due to different mechanisms underlying brain amyloid pathology in the two disease groups.

Results: We measured $A\beta$ isoform concentrations in CSF from 18 patients with SAD, 7 carriers of the FAD-associated presenilin 1 (*PSEN1*) A431E mutation, 17 healthy controls and 6 patients with depression using immunoprecipitation-mass spectrometry. Low CSF levels of $A\beta$ 1-42 and high levels of $A\beta$ 1-16 distinguished SAD patients and FAD mutation carriers from healthy controls and depressed patients. SAD and FAD were characterized by similar changes in $A\beta$ 1-42 and $A\beta$ 1-16, but FAD mutation carriers exhibited very low levels of $A\beta$ 1-37, $A\beta$ 1-38 and $A\beta$ 1-39.

Conclusion: SAD patients and *PSEN1* A431E mutation carriers are characterized by aberrant CSF $A\beta$ isoform patterns that hold clinically relevant diagnostic information. *PSEN1* A431E mutation carriers exhibit low levels of $A\beta$ 1-37, $A\beta$ 1-38 and $A\beta$ 1-39; fragments that are normally produced by γ -secretase, suggesting that the *PSEN1* A431E mutation modulates γ -secretase cleavage site preference in a disease-promoting manner.

Background

Pathological hallmarks of Alzheimer's disease (AD) include synaptic and neuronal degeneration along with extracellular deposits of amyloid β protein ($A\beta$) in senile plaques in the cerebral cortex [1]. These changes are reflected *in vivo* by elevated tau protein concentrations and reduced levels of the aggregation prone 42 amino acid isoform of $A\beta$ ($A\beta$ 1-42) in the cerebrospinal fluid (CSF) [2,3]. The mechanism underlying CSF $A\beta$ 1-42 reduction in AD is thought to be sequestration of the peptide in senile plaques. Accordingly, studies have found a strong correlation between low $A\beta$ 1-42 in CSF

and high numbers of plaques in the neocortex and hippocampus [4], as well as high retention of Pittsburgh Compound-B (PIB) in positron emission tomography (PET) scans that directly reflect plaque pathology in the brain [5,6]. $A\beta$ peptides are generated through proteolytic processing of the transmembrane amyloid precursor protein (APP). In the amyloidogenic pathway, APP is cleaved by two aspartyl proteases, first by β -secretase within its ectodomain and subsequently by γ -secretase within its transmembrane domain [7]. Certain forms of $A\beta$ 1-42 may act early in the disease process by disrupting synaptic plasticity mechanisms that are believed to underlie memory in the hippocampal network [8,9].

γ -Secretase is a multiprotein complex with the presenilin (PS) proteins at its enzymatic core [10]. Because of imprecise cleavage specificity, γ -secretase generates $A\beta$

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peptides of variable length at the carboxyl terminus. Mutations in the PS-encoding *PSEN1* and *PSEN2* genes that accelerate brain amyloid plaque pathology and cause early onset familial AD (FAD) increase the A β 1-42/A β 1-40 ratio in primary fibroblasts and plasma of affected individuals, in transfected cells, and in transgenic animals, but this effect is modest and not always reproducible [11,12]. To date, more than 160 distinct AD-promoting missense mutations have been identified in *PSEN1* and three in *PSEN2*.

In addition to A β 1-42 and A β 1-40, there are several shorter isoforms of A β [13]. We recently identified a set of 18 N- and C-terminally truncated A β peptides in CSF using immunoprecipitation-mass spectrometry (IP-MS) [14,15]. Their relative abundance pattern distinguished AD from controls with an accuracy of 86% [16]. Here, we test the hypotheses that (i) sporadic AD patients are different from controls and patients with depression with regards to their CSF A β isoform pattern, (ii) SAD patients and FAD mutation carriers differ in their A β isoform pattern as a reflection of different mechanisms underlying brain amyloid deposition in the two disease groups, and (iii) the AD-associated A β 1-16 fragment affects hippocampal synaptic plasticity.

Results and Discussion

Patient characteristics

Study participants were recruited at three specialized memory clinics, one in Munich, Germany, and two in California in the USA (UCSD and UCLA). The Munich study groups included 6 patients with SAD and 6 patients with major depression. The California study groups were comprised of 7 subjects carrying the FAD-associated *PSEN1* A431E mutation, 12 patients with SAD and 17 healthy controls (Table 1). The A431E mutation in persons of Mexican origin represents a founder effect arising from Jalisco State [17,18]. This mutation causes an aggressive form of AD with a mean age of onset in the early 40's that is sometimes associated with spastic tetraparesis and "cotton-wool" amyloid plaques on pathology [19]. Of the 7 *PSEN1* A431E mutation carriers, 5 were completely asymptomatic (CDR scores of 0) and had a mean age of 26 years, whereas the other two had some degree of cognitive impairment (CDR scores of 0.5 and 2, respectively, Table 2). Prior studies have demonstrated that this mutation is associated with increased levels of A β 1-42 in the plasma of presymptomatic persons and a decreased A β 1-42/A β 1-40 ratio in CSF [20].

CSF A β isoform patterns are distinct across groups

Representative CSF A β isoform mass spectra for SAD patients, FAD mutation carriers and controls are shown in Figure 1. Normalized CSF A β isoform intensities (Figure 2) were compared across the three groups using

multivariate discriminant analysis (Figure 3). FAD patients were clearly separated from SAD and non-AD (controls and depression), and the latter two groups were also segregated from each other, although to a lesser extent. In order to ease the interpretation, subsequent pairwise discriminant analysis were performed for SAD patients vs. non-AD and SAD vs. FAD. Low levels of A β 1-42 and high levels of A β 1-16 were the main contributors for the separation of SAD from non-AD (Figure 4). A β 1-34, A β 1-17, A β 1-13 and A β 1-14 contributed weakly to the separation. Low CSF A β 1-42 is a well-replicated finding in AD [21]. However, elevated A β 1-16 in AD is less well known. The data presented herein, along with earlier results from independent data sets [16], show that SAD patients tend to express high levels of A β 1-16 in their CSF at the group level, which also seems to hold true for *PSEN1* A431E mutation carriers (Figure 2). Two SAD patients had very high A β 1-16 levels (Figure 2). These patients, one male and one female, were 77 and 79 years old and did not differ from other SAD patients with regards to cognitive scores or A β 1-42 concentrations. The reason for their very high A β 1-16 levels is at present unknown.

Recent cell culture experiments using different secretase inhibitors suggest that A β 1-16 is derived from concerted cleavages of APP by β - and α -secretase, thus reflecting a third metabolic pathway for APP [22]. Curiously, depressed patients in this study also had higher A β 1-16 levels than the healthy controls (Figure 2). Pending confirmation in independent and larger patient materials, this result may provide clues regarding altered APP metabolism in depression. There were no other A β -related changes in common in depression and SAD vs. controls.

FAD mutation carriers express low levels of A β 1-37, A β 1-38 and A β 1-39 in CSF

The reason for the distinct subgrouping of SAD patients and FAD mutation carriers in Figure 3A was analyzed in detail by comparing their CSF A β isoform patterns specifically (Figure 5A). Both disease groups were characterized by similar levels of A β 1-42 and A β 1-40, implying similar degrees of amyloid pathology in their brains [4,5]. However, FAD mutation carriers had very low concentrations of A β 1-37, A β 1-38 and A β 1-39 and high A β 1-20 compared with SAD patients (Figure 2). These deviations separated the two groups completely (Figure 5B and 5C). Similar A β 1-37, A β 1-38 and A β 1-39 changes have been seen in media from cell lines expressing the *PSEN1* Δ 9 or L166P mutation, or the *PSEN2* N141I mutation [11]. The A β 1-37, A β 1-38 and A β 1-39 isoforms are normally produced by γ -secretase, suggesting that certain *PSEN1* and *PSEN2* mutations may modulate γ -secretase function by inhibiting cleavage at Gly37, Gly38 and Val39, without affecting the

Table 1 Demographic characteristics of patients and controls^a

	SAD patients (n = 18)	<i>PSEN1</i> A431E mutation carriers (n = 7)	Healthy controls (n = 17)	Patients with depression (n = 6)
Age (years)	74 (8.9)	33 (10)	55 (17)	68 (4.9)
Gender (m/f)	10/8	3/4	7/10	0/6
MMSE scores ^b	22 (4.4)	24 (9.1)	30 (0.5)	28 (1.9)

^aData are presented as mean (standard deviation, SD).

^bMMSE is Mini-Mental State Examination score.

production of A β 1-42 and A β 1-40 significantly. It is tempting to speculate that A β 1-37, A β 1-38 and A β 1-39 may inhibit A β 1-42 oligomerization by forming less aggregation-prone heterocomplexes with A β 1-42. Such a protective effect has recently been described for A β 1-40 [23,24]. The key AD-promoting effect of *PSEN1* A431E, and possibly several other FAD-associated *PSEN* mutations, may thus be a tweaked γ -secretase cleavage site preference that results in loss of C-terminally truncated A β species. Modulating γ -secretase function to boost cleavages at Gly37, Gly38 and Val39 would in that case be a novel approach to prevent AD-associated A β aggregation. However, prior to such a claim, the hypothesis that A β 1-37, A β 1-38 and A β 1-39 indeed inhibit A β 1-42 oligomerization and toxicity must be tested in additional studies.

AD-associated A β 1-16 does not inhibit long-term potentiation

One of the hallmark synaptotoxic effects of A β 1-42 is the inhibition of long-term potentiation (LTP) [25]. Results presented here, together with earlier data from our group [16], showing elevated CSF levels of A β 1-16 in AD, prompted us to test whether the A β 1-16 peptide *per se* inhibits LTP. To that end, we exposed acute rat hippocampal slices to A β 1-16 and elicited LTP at the glutamatergic synapses in the CA1 region. Under our control conditions, a strong LTP-inducing protocol

(three times 20 impulses at 50 Hz during blockade of GABA_A receptors) resulted in LTP that amounted to $130 \pm 7.3\%$ (presynaptic volley = $97 \pm 3.5\%$, n = 7) 60 minutes after the induction (Figure 6A, D). As a positive control, we exposed the slice to A β 1-42 oligomers (prepared from 1 μ M monomeric A β 1-42, see Methods) for 30-60 minutes before the induction of LTP. Under these conditions the LTP was $103 \pm 5.9\%$ (presynaptic volley = $90.5 \pm 1.6\%$, n = 6), which was significantly smaller than control ($P = 0.017$) (Figure 6B, D). To test whether A β 1-16 affects the generation of LTP, we exposed the slice to A β 1-16 (1 μ g/L) for 60 minutes before the induction. The absolute endogenous concentration of A β 1-16 in human CSF is 10-50 ng/L [15], but the synaptic concentration is not known. Therefore, to ascertain a not too low synaptic concentration of A β 1-16, we used a concentration 20-100 times the absolute endogenous concentration of A β 1-16 in human CSF. In the presence of A β 1-16, LTP was $141 \pm 3.6\%$ (presynaptic volley = $100 \pm 2.5\%$, n = 12) (Figure 6C, D), which is not significantly different from the control ($P = 0.12$). Hence, we conclude that A β 1-16 does not inhibit LTP at hippocampal CA3-CA1 synapses.

Limitations

Although the findings of this study are intriguing, there are some limitations that should be mentioned.

First, the study is small and the important findings, i. e., the increased levels of A β 1-16 in AD and depression and the reduced levels of A β 1-37, A β 1-38 and A β 1-39 in *PSEN1* A431E-caused FAD, are in need of replication.

Second, CSF samples were obtained at different centers. However, no center effects on A β isoform levels were detected. Further, when levels of the various A β peptides were compared between the 7 FAD mutation carriers and their 3 similarly aged non-mutation carrying kin from whom CSF was obtained at the same center, levels of A β 1-37, A β 1-38 and A β 1-39 but not of other A β peptides were significantly lower ($P \leq 0.003$) and non-overlapping. In fact, differences in these levels were greater than that of A β 1-42, which was non-significant in this small subpopulation. The finding of decreased levels of A β 1-37, A β 1-38 and A β 1-39 in the CSF of persons with the A431E *PSEN1* mutation therefore appears to be a robust finding. How this might be related to the cotton wool plaque pathology that has

Table 2 Summary of the 7 subjects with the *PSEN1* A431E mutation

Case	APOE Genotype	Relative age ^a	CDR ^b	MMSE ^c
1	3/3	-16	0	29
2	3/3	-1	0.5	27
3	3/3	-18	0	29
4	3/3	2	2	5
5	3/3	-22	0	30
6	2/3	-19	0	28
7	2/3	-15	0	29

^aRelative age is the number of years prior to the typical family-specific age of dementia diagnosis. Absolute age and gender are not shown to protect confidentiality with regard to subjects' identity and mutation status.

^bCDR is the Clinical Dementia Rating scale score (0 = asymptomatic, 0.5 is questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia).

^cMMSE is Mini-Mental State Examination score.

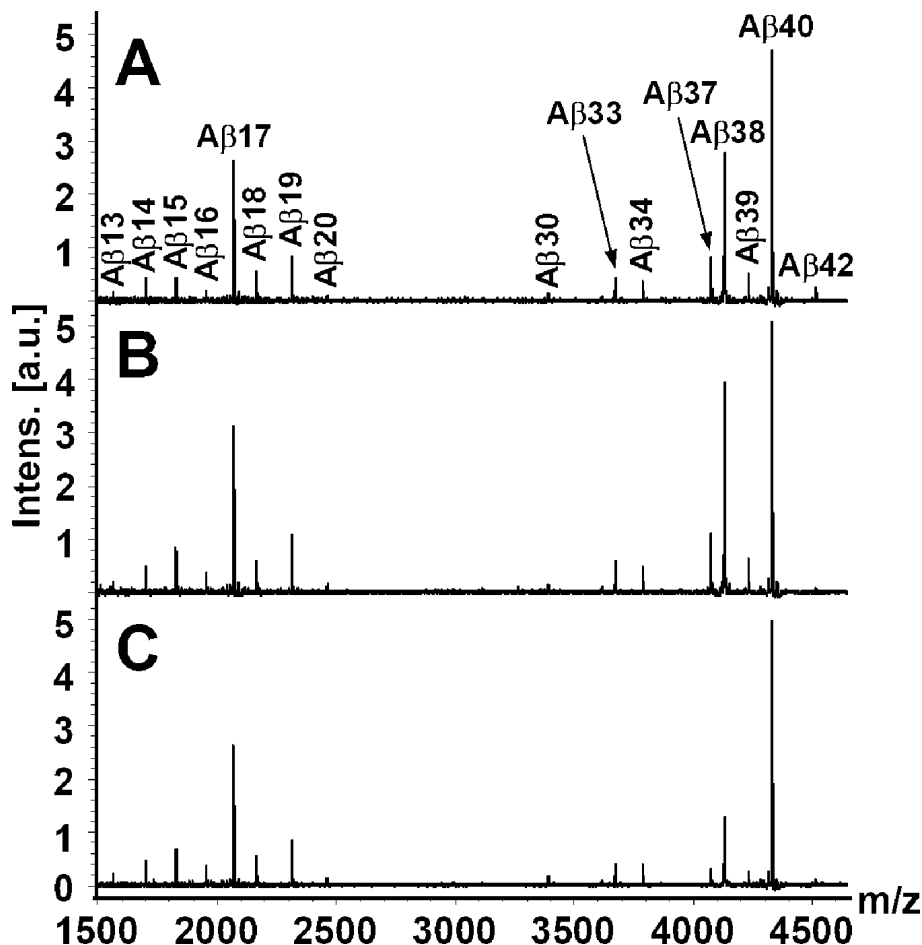


Figure 1 Representative mass spectra showing C-terminally truncated A β peptides immunoprecipitated from cerebrospinal fluid using antibody 6E10. (A) Representative A β isoform pattern in a control individual. (B) Representative A β isoform pattern in a patient with sporadic Alzheimer's disease. (C) Representative A β isoform pattern in a carrier of the FAD-associated *PSEN1* A431E mutation.

been demonstrated to consist of increased amounts of N-terminally truncated forms of A β 42 in persons with other *PSEN1* mutations [26] is unclear.

Third, the age distribution differed between the different groups. Of all the A β isoforms, in all study groups, only A β 1-34 in the controls correlated with age ($r_s = -0.61$, $P = 0.01$). However, A β 1-34 is higher in the AD group compared with the controls, which is opposite to what would have been expected if the difference were due to an age effect. This makes age an unlikely confounder.

Conclusions

The findings presented here show that (i) SAD patients differ from cognitively normal individuals and depressed patients with regards to their CSF A β isoform pattern and (ii) carriers of the FAD-associated *PSEN1* A431E mutation have low CSF levels of C-terminally truncated A β peptides shorter than A β 1-40, suggesting a loss of

function effect that leads to a relative abundance of aggregation-prone A β 1-42. The influence of A β 1-37, A β 1-38 and A β 1-39 reductions on A β 1-42 oligomerization and toxicity needs to be examined in experimental studies. CSF A β 1-16 may be a positive biomarker for AD but its specificity against depression must be tested further.

Methods

Study participants

Patients with SAD and major depression were diagnosed according to DSM-III-R criteria [27]. SAD patients fulfilled the criteria of probable AD defined by NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders - Stroke/Alzheimer's Disease and Related Disorders Association) [28]. The seven persons carrying the A431E mutation in *PSEN1* [17] were participants in a study of symptomatic persons affected by ($n = 2$), and asymptomatic persons at-risk for ($n = 5$) FAD

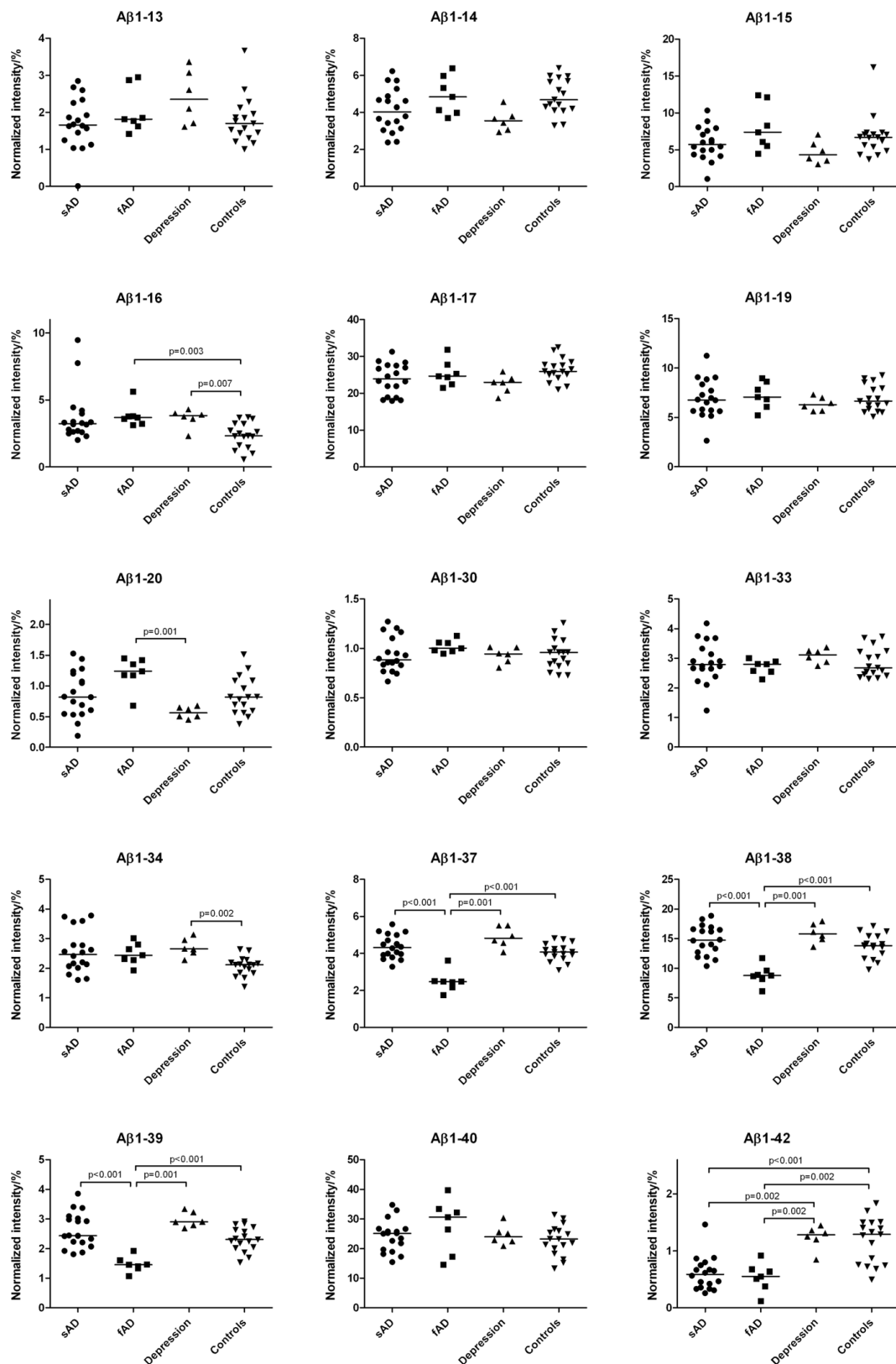


Figure 2 Scatter plots of normalized Aβ fragment intensities derived from IP-MS in the different disease and control groups. Thin horizontal lines indicate medians. Significant differences are indicated.

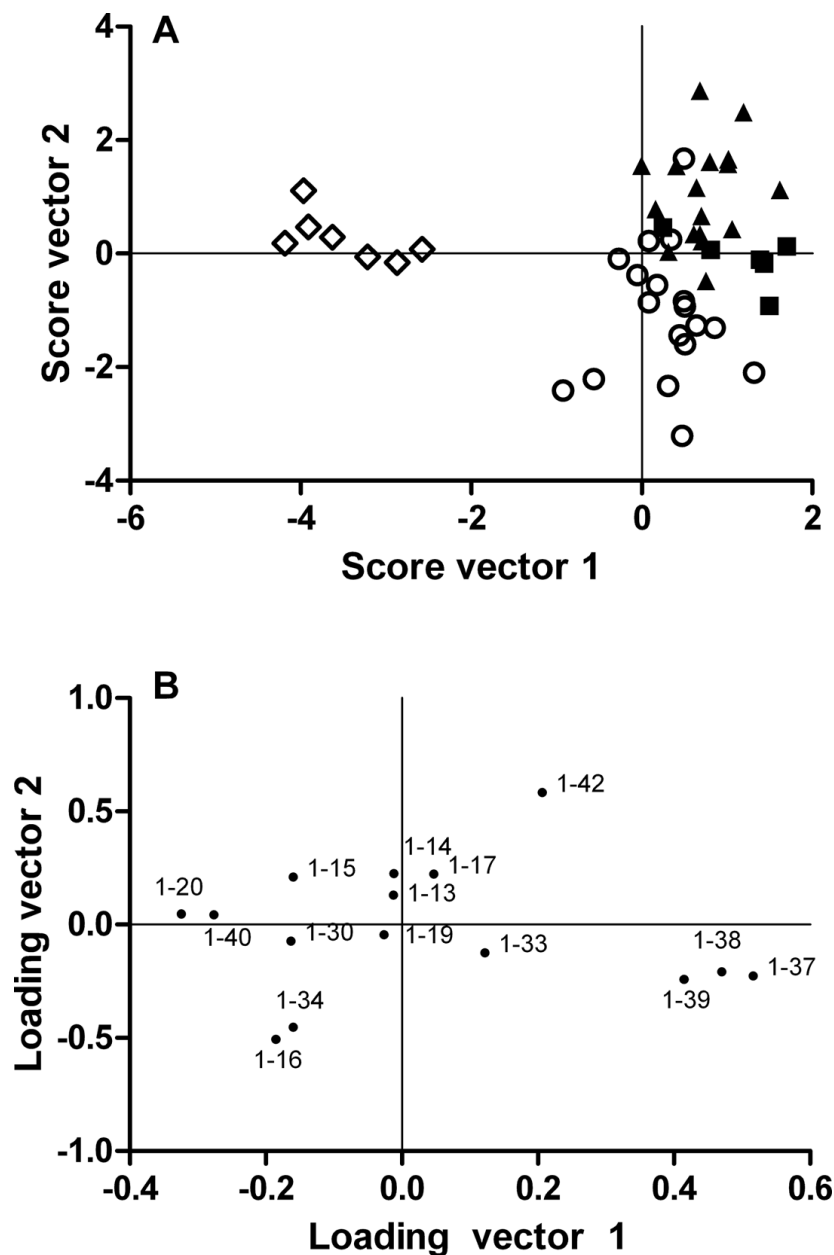
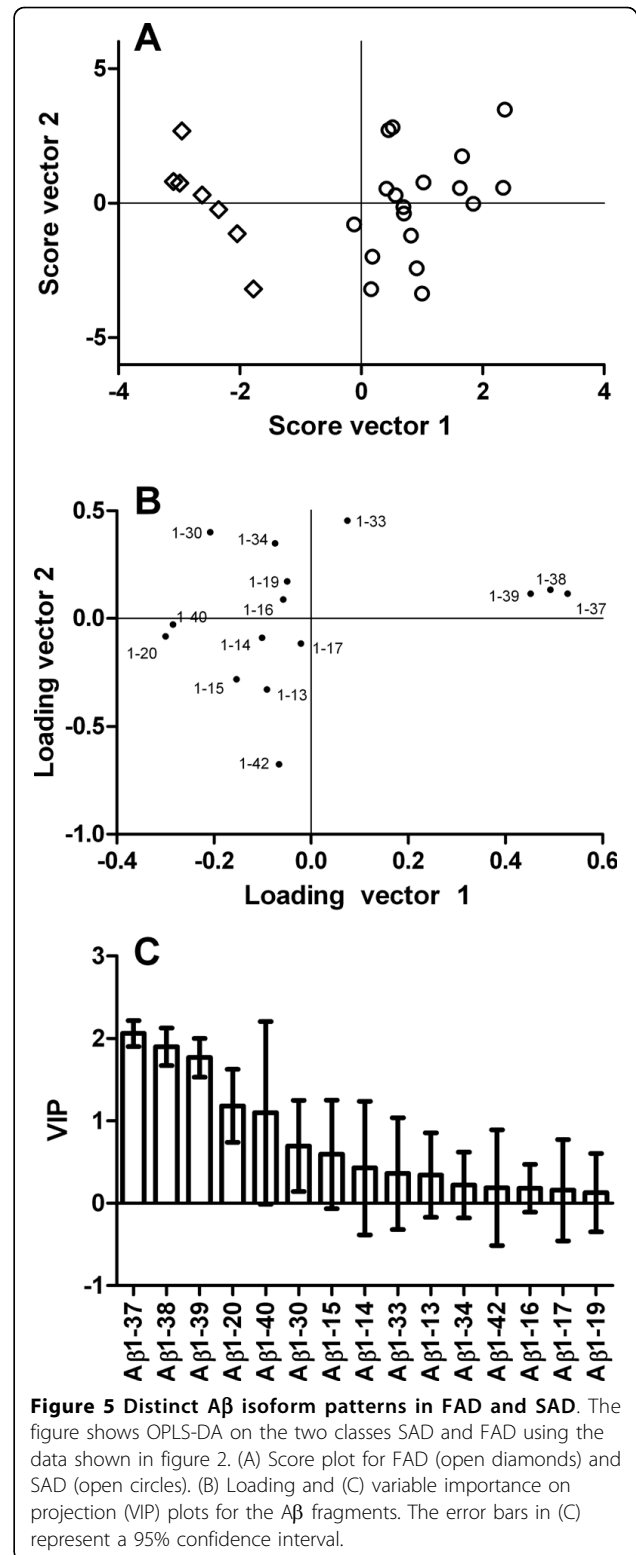
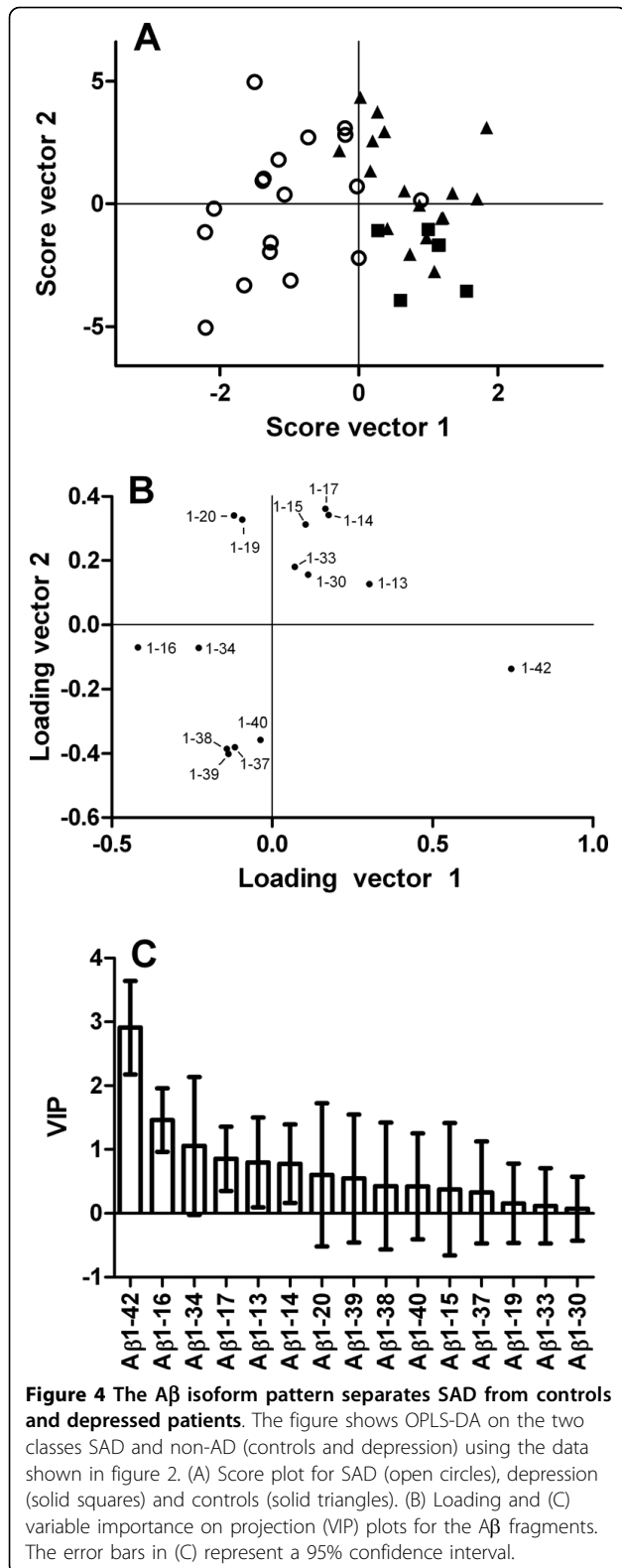
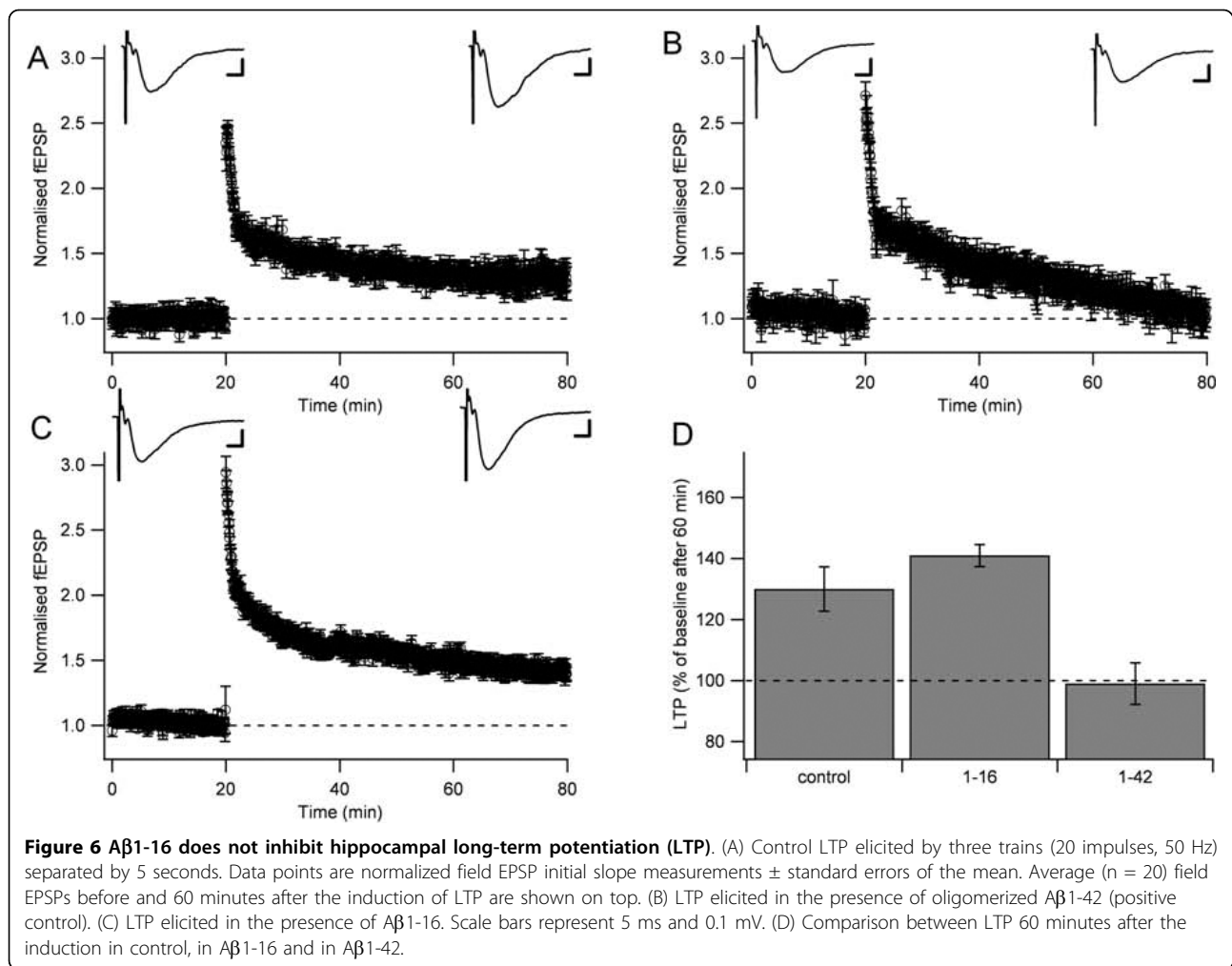


Figure 3 Distinct A β isoform patterns in FAD compared to SAD and non-AD. The figure shows OPLS-DA on the three classes FAD, SAD, and non-AD (controls and depression) using the data shown in figure 2. (A) Score plot for FAD (open diamonds), SAD (open circles), depression (solid squares), and controls (solid triangles). (B) Loading and plot for the A β fragments.

being conducted at UCLA. Subjects seen at UCLA underwent a comprehensive clinical evaluation by investigators blind to their genetic status that included the Clinical Dementia Rating scale [29]. Three of the 17 controls were non-mutation carrying family members also enrolled in this study. The healthy controls were mainly recruited from senior citizen organizations and through information meetings on dementia. A few controls were spouses of subjects in the study. Inclusion

criteria for controls were that they should be physically and mentally healthy and not experiencing or exhibiting any cognitive impairment. All controls were thoroughly interviewed about their somatic and mental health by researchers before inclusion in the study. Mini-mental state examination (MMSE) was used as a global measure of cognitive functioning [30]. The study was approved by the ethics committees of Ludwig-Maximilian University, Germany, and UCLA and UCSD, USA.





CSF sampling and biochemical analyses

CSF samples were collected in the morning by lumbar puncture (LP) through the L3/L4 or L4/L5 interspace. CSF was collected in polypropylene tubes in 500 μ L aliquots that were centrifuged, frozen and stored at -80°C pending biochemical analyses, without being thawed and re-frozen. The immunoprecipitation and mass spectrometric analysis were conducted as described before [15]. Briefly, 8 μ g of the monoclonal antibody 6E10 (epitope 4-9, Signet Laboratories Inc., Dedham, USA) was used together with magnetic Dynabeads (Sheep anti-mouse IgG) for immunoprecipitating C-terminally truncated A β peptides from 1 mL CSF. The samples were analyzed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS, Autoflex, Bruker Daltonics, Bremen, Germany) operating in reflector mode. An in house MATLAB[®] program (Mathworks Inc. Natick, MA, USA) was used for integration of the peaks for each spectrum and the integration limits were from -2 to +5 m/z relative to the monoisotopic peak.

Prior to the statistical analysis the peak areas were normalized to the sum of the integrated peaks.

Electrophysiology

Electrophysiological experiments were performed on hippocampal slices from 35-60 day-old male Wistar rats. The rats were anesthetized with isoflurane (Abbott) prior to decapitation. The brain was removed and placed in an ice-cold solution containing (in mM): 140 cholineCl, 2.5 KCl, 0.5 CaCl₂, 7 MgCl₂, 25 NaHCO₃, 1.25 NaH₂PO₄, 1.3 ascorbic acid and 7 dextrose. Transverse hippocampal slices (400 μ m thick) were cut with a vibratome (HM 650 V Microm, Germany) in the same ice-cold solution and were subsequently stored in artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 3 KCl, 2 CaCl₂, 4 MgCl₂, 26 NaHCO₃, 1.25 NaH₂PO₄, 0.5 ascorbic acid, 3 myo-inositol, 4 D, L-lactic acid, and 10 D-glucose. After at least one hour of storage at 25°C , a single slice was transferred to a recording chamber where it was kept submerged in a constant flow (~ 2 ml min^{-1}) at 30 - 32°C . The perfusion fluid

contained (in mM) 124 NaCl, 3 KCl, 4 CaCl₂, 4 MgCl₂, 26 NaHCO₃, 1.25 NaH₂PO₄, and 10 D-glucose. Picrotoxin (100 μM, Sigma-Aldrich Stockholm, Sweden) was always present in the perfusion fluid to block GABA_A receptor-mediated activity. All solutions were continuously bubbled with 95% O₂ and 5% CO₂ (pH ~7.4). The higher than normal Ca²⁺ and Mg²⁺ concentrations were used to inhibit spontaneous network activity. ACSF was spiked with synthetic Aβ1-16 (Bachem, Weil am Rhein, Germany) in water solution to a final concentration of 1 μg/L. Aβ1-42 oligomers were prepared according to a standard protocol [31]. Briefly, 1 μM Aβ1-42 was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) on ice and incubated for 90 minutes in room temperature. HFIP was removed using speedvac and the remaining Aβ1-42 peptide film was stored at -80°C. The film was dissolved in DMSO to 5 mM, sonicated, further diluted in PBS containing 0.2% SDS to 400 μM and incubated for six hours at 37°C. Water was added to a concentration of 100 μM and this solution was incubated for 18 hours at 37°C. Finally, the solution was centrifuged at 3000 g for 20 minutes and stored for no more than three days at 4°C.

Electrical stimulation of Schaffer collateral/commissural axons and recordings of synaptic responses were carried out in the stratum radiatum of the CA1 region. Stimuli consisted of biphasic constant current pulses (15–80 μA, 200 μs, STG 1002 Multi Channel Systems MCS GmbH, Reutlingen, Germany) delivered through tungsten wires (resistance ~0.1 MΩ). The synaptic input was activated every 5 s. Field excitatory postsynaptic potentials (EPSPs) were recorded with a glass micropipette (1 M NaCl, resistance ~4 MΩ). Field EPSPs were sampled at 10 kHz with an EPC-9 amplifier (HEKA Elektronik, Lambrrecht, Germany) and filtered at 1 kHz. Evoked responses were analyzed off-line using custom-made IGOR Pro (WaveMetrics, Lake Oswego, OR) software. Field EPSP magnitude was estimated by linear regression over the first 0.8 ms of the initial slope. The presynaptic volley was measured as the slope of the initial positive-negative deflection, and it was not allowed to change by more than 15% during the experiment.

Statistical analyses

Multivariate discriminant analysis (DA) was performed using the orthogonal projection to latent structure (OPLS) algorithm [32] implemented in the software SIMCA P+ v. 12 (Umetrics, Umeå, Sweden). In general, OPLS-DA finds the direction (score vector) in the multi-dimensional orthogonal space created by the different measured variables that best separate the predefined classes. To visualize the result from an OPLS-DA, the observations are projected onto a plane spanned by the score vectors. The contribution of the different variables to the score vectors is presented in a loading plot. A

vector from the origin to a variable in the loading plot points in the direction that an observation in the score plot will be displaced if the value of the variable is increased. Also, the extent of the displacement is proportional to the magnitude of the vector [33]. Comparisons between groups with regards to individual, normalized Aβ isoform intensities were performed using nonparametric Kruskal-Wallis test, followed by the Mann-Whitney test. P-values for the Mann-Whitney test were reported given that (i) the p-value for the Kruskal-Wallis test was below 0.05 after Bonferroni correction (15 tests) and (ii) the difference was significant at p < 0.05 using Dunn's post hoc test for multiple comparisons. Electrophysiological data were evaluated using Student's t-test.

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Authors' contributions

EP participated in the design of the study and carried out mass spectrometric analyses. UA participated in the design of the study and performed statistical analyses. JMR characterized patients and contributed samples. KBU characterized patients and contributed samples. JD performed electrophysiological experiments. PB and OH participated in the design of the study. AH performed electrophysiological experiments. MKG carried out mass spectrometric analyses. EH performed electrophysiological experiments. DG and HH characterized patients and contributed samples. KBI participated in the design of the study and its coordination. HZ participated in the design of the study and its coordination, and drafted the manuscript. All authors interpreted the data, revised the manuscript for important intellectual content and read and approved the final manuscript version.

Competing interests

The authors declare that they have no competing interests.

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