

RESEARCH ARTICLE

Open Access

Heart fatty acid binding protein and A β -associated Alzheimer's neurodegeneration

Rahul S Desikan^{1*}, Wesley K Thompson², Dominic Holland³, Christopher P Hess⁴, James B Brewer^{1,3}, Henrik Zetterberg^{5,6}, Kaj Blennow⁵, Ole A Andreassen^{2,7}, Linda K McEvoy¹, Bradley T Hyman^{8†}, Anders M Dale^{1,2†} and For the Alzheimer's Disease Neuroimaging Initiative

Abstract

Background: Epidemiological and molecular findings suggest a relationship between Alzheimer's disease (AD) and dyslipidemia, although the nature of this association is not well understood.

Results: Using linear mixed effects models, we investigated the relationship between CSF levels of heart fatty acid binding protein (HFABP), a lipid binding protein involved with fatty acid metabolism and lipid transport, amyloid- β (A β), phospho-tau, and longitudinal MRI-based measures of brain atrophy among 295 non-demented and demented older individuals. Across all participants, we found a significant association of CSF HFABP with longitudinal atrophy of the entorhinal cortex and other AD-vulnerable neuroanatomic regions. However, we found that the relationship between CSF HFABP and brain atrophy was significant only among those with low CSF A β ₁₋₄₂ and occurred irrespective of phospho-tau_{181p} status.

Conclusions: Our findings indicate that A β -associated volume loss occurs in the presence of elevated HFABP irrespective of phospho-tau. This implicates a potentially important role for fatty acid binding proteins in Alzheimer's disease neurodegeneration.

Keywords: Alzheimer's disease, Fatty acids, Lipids, Amyloid, Tau, Brain atrophy

Background

A growing number of epidemiological and experimental studies suggest an association between Alzheimer's disease (AD) and dyslipidemia. In observational studies, high serum cholesterol levels have been associated with increased risk of AD [1,2]. Genetic linkage and genome-wide association studies have identified a number of genes involved with cholesterol metabolism and transport as AD susceptibility loci [3,4] and cellular and molecular biology research has indicated a critical role for neuronal membrane phospholipids ('lipid rafts') in modulating AD-associated pathogenesis [5]. However, in animal models, apolipoprotein E modulates the relationship between low-density lipoproteins and amyloid- β (A β) deposition [6,7] suggesting an indirect effect of intra-cranial cholesterol on Alzheimer's pathology. Furthermore, conflicting evidence from epidemiological

studies shows an unclear association between elevated cholesterol levels and AD risk [8,9], protein levels of fatty acid binding proteins have been noted to be decreased in brains of AD patients [10], and randomized clinical trials have not shown a clear benefit of lipid-lowering therapy on AD onset [2]. Thus there is a need for additional research evaluating the relationship between lipid biology and neurodegeneration in individuals at risk for AD.

In humans, structural MRI and CSF biomarkers allow for the indirect assessment of the cellular changes underlying AD *in vivo*. Structural MRI provides measures of brain atrophy, which reflect loss of dendrites, synapses [11] and neurons [12]. Low CSF levels of A β strongly correlate with intracranial amyloid plaques and high concentrations of CSF phospho-tau (p-tau) correlate with tau-associated neurofibrillary tangles [13,14]. Recent work suggests that CSF levels of heart fatty acid binding protein (HFABP or FABP3), a lipid binding protein involved with fatty acid metabolism and lipid transport [15] may have diagnostic and prognostic value in the earliest stages of AD [16-20]. Here,

* Correspondence: rdesikan@ucsd.edu

†Equal contributors

¹Department of Radiology, University of California, San Diego, 8950 Villa La Jolla Drive, Suite C101, La Jolla, CA 92037-0841, USA

Full list of author information is available at the end of the article

among non-demented older individuals at risk for AD and demented participants diagnosed with probable AD, we investigated whether CSF HFABP is associated with brain atrophy over time and whether interactions between high CSF HFABP and low CSF $A\beta_{1-42}$ and high CSF HFABP and high CSF p-tau_{181p} are associated with brain atrophy over time. We also evaluated the relationship between CSF HFABP and other lipid binding proteins including Apolipoprotein (Apo) C III, Apo D, and Apo E.

Results

CSF HFABP and brain atrophy rates

In our initial analyses, we used linear mixed effects models, co-varying for baseline age, sex, presence (“carriers”) or absence (“non-carriers”) of at least one $\epsilon 4$ allele of apolipoprotein E (APOE $\epsilon 4$), diagnostic status (AD vs mild cognitive impairment (MCI) vs healthy elderly controls (HC)), and disease severity (CDR-Sum of Boxes score at baseline) to examine whether CSF HFABP levels are associated with longitudinal atrophy of the entorhinal cortex and other AD-vulnerable regions of interest (‘AD vulnerable ROI’ – for additional details see Methods) (Figure 1). We found a significant relationship between CSF HFABP, time, and atrophy rate of the entorhinal cortex (β -coefficient = -0.007 , standard error (SE) = 0.003 , p -value = 0.013) and the AD-vulnerable ROI (β -coefficient = -0.005 , SE = 0.002 , p -value = 0.017), indicating increased volume loss with elevated CSF HFABP levels.

CSF HFABP, CSF $A\beta_{1-42}$, CSF p-tau_{181p}, and brain atrophy rates

Next, we asked whether statistical interactions between CSF HFABP and CSF $A\beta_{1-42}$ and between CSF HFABP and CSF p-tau_{181p} are associated with brain atrophy over time. These linear mixed effects models included the main and interactive effects of CSF HFABP, CSF $A\beta_{1-42}$, status and CSF p-tau_{181p} status, and co-varied for the demographic and clinical variables mentioned previously (see Methods for further details on the model). Key results from these models are shown in Table 1.

As illustrated in Table 1, with the interaction terms of the three CSF biomarkers in the model, the association of CSF HFABP with brain atrophy over time was not significant. However, there were significant interactive effects between CSF HFABP x CSF $A\beta_{1-42}$ status x time and CSF HFABP x CSF p-tau_{181p} status x time on atrophy of both the entorhinal cortex and the AD-vulnerable ROI. The only CSF biomarker to show a significant association with atrophy over time in the entorhinal cortex and AD-vulnerable ROI was CSF p-tau_{181p}. Of the co-variates, the interaction of time by diagnostic status and APOE $\epsilon 4$ carrier status were significant for both entorhinal cortex atrophy (diagnostic status x time: β -coefficient = -0.007 , SE = 0.002 , p -value = 0.0005 ; APOE $\epsilon 4$ carrier status x time (β -coefficient = -0.004 , SE = 0.002 , p -value = 0.03) and AD-vulnerable ROI atrophy (diagnostic status x time: β -coefficient = -0.006 , SE = 0.002 , p -value = 0.0003 ; APOE $\epsilon 4$ carrier status x time (β -coefficient = -0.003 , SE = 0.001 , p -value = 0.02). None of the

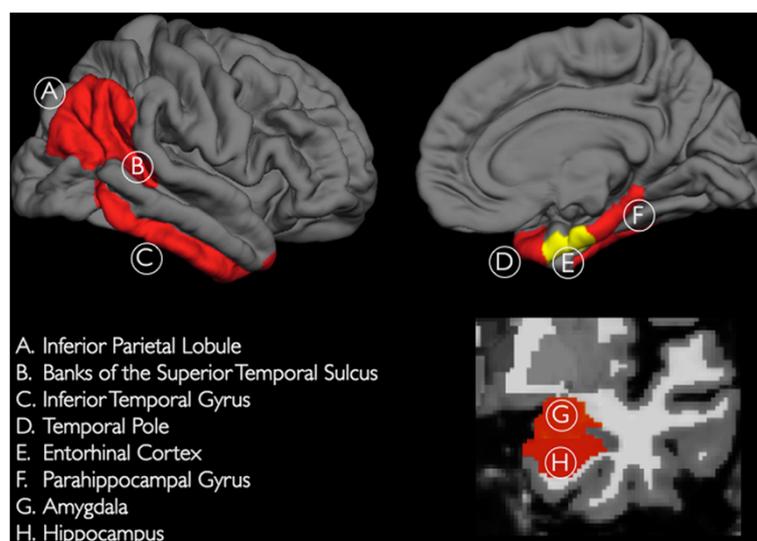


Figure 1 Three-dimensional representations of the neuroanatomic regions examined in the current study (only one hemisphere is shown). All of the examined neocortical regions are illustrated in the lateral and medial views of the gray matter surface (top row). The two non-neocortical regions (i.e., the hippocampus and amygdala) are illustrated in the coronal view of a T1-weighted MRI image (bottom row). Regions illustrated in red constitute the ‘AD-vulnerable ROI’ (for further details please see manuscript text).

Table 1 Linear mixed effects model results for analyses involving all 295 participants

	Main effect	Interaction with time	Interaction with HFABP and time
Entorhinal Cortex			
CSF HFABP	0.005 (0.15)	-0.005 (0.34)	N/A
CSF A β_{1-42} status	0.003 (0.17)	-0.0004 (0.88)	-0.017 (0.003)
CSF p-tau _{181p} status	-0.004 (0.15)	-0.01 (0.0007)	0.020 (0.0005)
AD-Vulnerable ROI			
CSF HFABP	0.003 (0.21)	-0.003 (0.51)	N/A
CSF A β_{1-42} status	0.001 (0.44)	-0.0000 (0.99)	-0.013 (0.002)
CSF p-tau _{181p} status	-0.002 (0.10)	-0.0007 (0.002)	0.014 (0.001)
		Time by HFABP Entorhinal cortex	Time by HFABP AD Vulnerable ROI
Low CSF A β_{1-42} (n = 211)		-0.009 (0.007)	-0.007 (0.007)
High CSF A β_{1-42} (n = 86)		0.001 (0.75)	0.003 (0.22)
High CSF p-tau _{181p} (n = 197)		-0.002 (0.58)	-0.002 (0.47)
Low CSF p-tau _{181p} (n = 98)		-0.006 (0.21)	-0.002 (0.35)

Beta-coefficients with p-values indicated in parenthesis. Please see text for additional details.

other variables showed significant main or interactive effects.

To further investigate the three-way interactions, we performed follow-up analyses after stratifying on the basis of CSF A β_{1-42} status (i.e. low and high status) and CSF p-tau_{181p} status (i.e. high and low status). We found a significant CSF HFABP by time interaction on entorhinal cortex and AD-vulnerable ROI atrophy rate only among individuals with low CSF A β_{1-42} levels (Table 1, Figure 2A) Among individuals with high CSF A β_{1-42} levels and high or low CSF p-tau_{181p} levels, we found no effect of CSF HFABP by time on brain atrophy (Table 1, Figure 2A, 2B). This indicates elevated volume loss with elevated CSF HFABP and low CSF A β_{1-42} irrespective of CSF p-tau_{181p} status.

We also evaluated whether interactions between high CSF HFABP and low CSF A β_{1-42} and high CSF HFABP and high CSF p-tau_{181p} are associated with longitudinal clinical decline as assessed with the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). In these analyses, neither the interaction between CSF HFABP, CSF A β_{1-42} status and time nor the interaction between CSF HFABP, CSF p-tau_{181p} status and time was significantly associated with longitudinal change in ADAS-cog (see Additional file 1).

CSF HFABP and other lipid binding proteins

We next used generalized linear models to investigate the relationship between CSF HFABP and CSF p-tau_{181p}, and levels of other lipid binding proteins including Apolipoprotein (Apo) C III, Apo D, and Apo E at baseline. The relation of each of these apolipoproteins with CSF HFABP was assessed in separate models; all models controlled for age, sex, APOE $\epsilon 4$ carrier status, diagnostic status, and CDR-Sum of Boxes score.

We found significant associations between CSF HFABP and CSF p-tau_{181p} (β -coefficient = 0.008, SE = 0.001, p-value = $< 2.0 \times 10^{-16}$), CSF levels of Apo C III (β -coefficient = 0.29, SE = 0.07, p-value = 4.2×10^{-5}), ApoD (β -coefficient = 0.35, SE = 0.09, p-value = 2.8×10^{-4}), and ApoE (β -coefficient = 0.86, SE = 0.12, p-value = 2.9×10^{-16}) (Figure 3).

Using the same linear mixed effects framework described above, we additionally evaluated whether statistical interactions between CSF HFABP and the other lipid binding proteins are associated with brain atrophy over time. We found a significant interaction only between CSF HFABP and CSF Apo C III on entorhinal cortex atrophy rate (β -coefficient = 0.02, SE = 0.009, p-value = 0.02). None of the other lipid binding proteins demonstrated a significant interaction with CSF HFABP on atrophy rates of the entorhinal cortex and the AD-vulnerable ROI (p-values > 0.2).

Discussion

Here, we demonstrate that in non-demented older individuals at risk for AD and in mild AD participants, HFABP is associated with volume loss in brain areas selectively affected in the earliest stages of AD. However, we found that the relationship between HFABP and brain atrophy is present only among individuals with low CSF A β_{1-42} , and occurs irrespective of phospho-tau levels. Considered together, these results suggest a potentially important role for fatty acid binding proteins in early Alzheimer's disease pathobiology.

Our findings also indicate that rather than simply representing a generalized marker of neuronal degeneration, elevated CSF levels of HFABP may reflect central nervous system lipid dyshomeostasis. Consistent with prior studies [16,18], we found a significant association

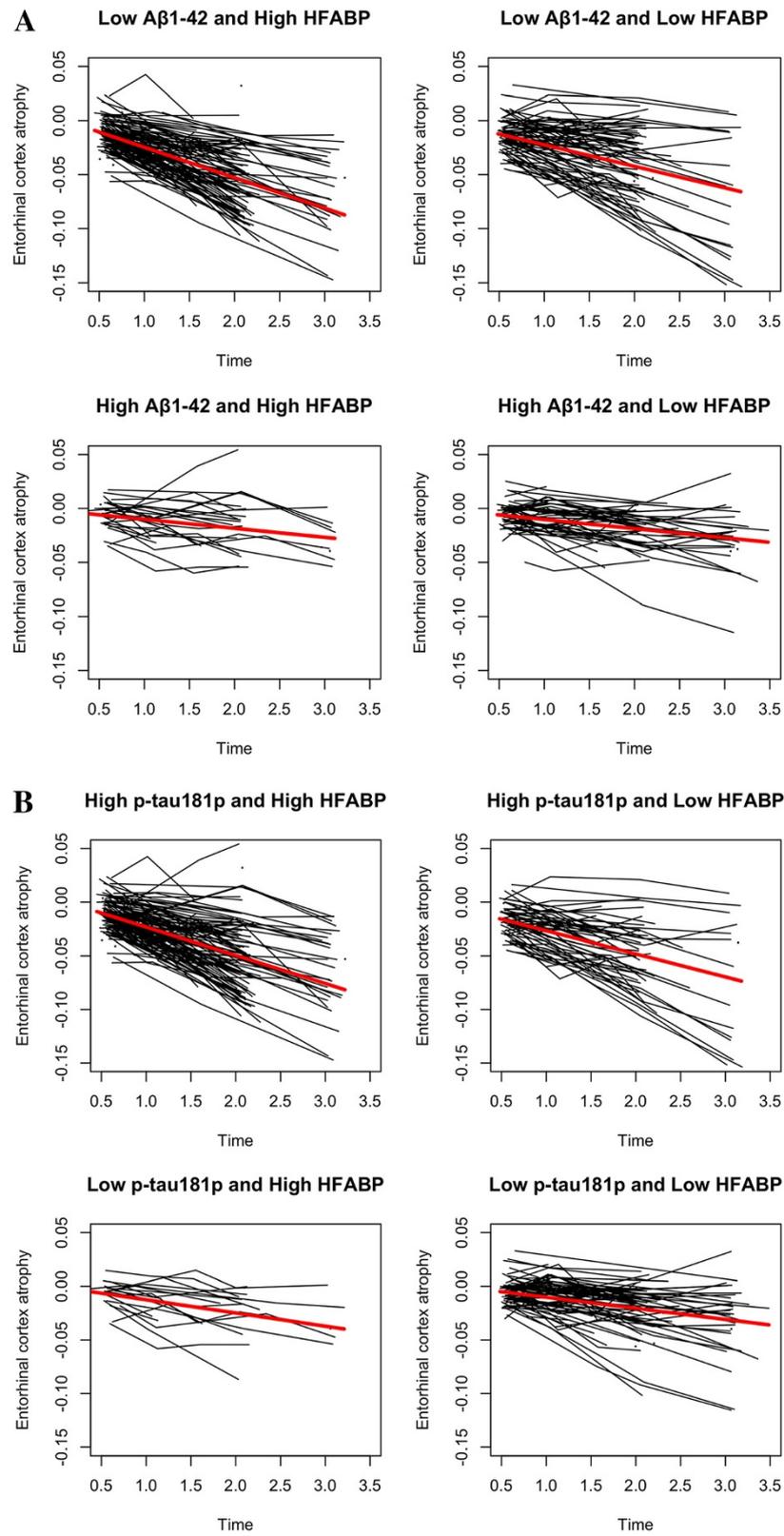


Figure 2 (See legend on next page.)

(See figure on previous page.)

Figure 2 (A) Spaghetti plots illustrating atrophy of the entorhinal cortex among all participants classified as low $A\beta_{1-42}$ and high HFABP (based on median value of FABP) (top left panel), low $A\beta_{1-42}$ and low HFABP (top right panel), high $A\beta_{1-42}$ and high FABP (bottom left panel), and high $A\beta_{1-42}$ and low FABP (bottom right panel). The red line indicates the mean atrophy rate for the four respective groups (i.e. low $A\beta_{1-42}$ and high FABP, low $A\beta_{1-42}$ and low FABP, high $A\beta_{1-42}$ and high FABP and high $A\beta_{1-42}$ and low FABP). As illustrated, the slopes of the red lines are significantly different depending on CSF $A\beta_{1-42}$ status (please see text for further details). **(B)** Spaghetti plots illustrating atrophy of the entorhinal cortex among all participants classified as high p-tau_{181p} and high HFABP (based on median value of FABP) (top left panel), high p-tau_{181p} and low HFABP (top right panel), low p-tau_{181p} and high FABP (bottom left panel), and low p-tau_{181p} and low FABP (bottom right panel). The red line indicates the mean atrophy rate for the four respective groups (i.e. high p-tau_{181p} and high FABP, high p-tau_{181p} and low FABP, low p-tau_{181p} and high FABP and low p-tau_{181p} and low FABP). As illustrated, the slopes of the red lines are not significantly different depending on CSF p-tau_{181p} status (please see text for further details).

between HFABP and phospho-tau. However, we also found a strong relationship between HFABP and a number of apolipoproteins including ApoE, as well as an interaction between HFABP and ApoC III on volume loss. Together, these findings support the hypothesis that intra-cranial lipid biology may influence Alzheimer's neurodegeneration [5].

Our results suggest that the relationship between neuronal lipid biology and neurodegeneration may be influenced by amyloid pathology even after controlling

for the effects of APOE $\epsilon 4$. An important aspect of our findings is the specific relationship between HFABP and $A\beta$ deposition, where volume loss occurs only in the presence of elevated HFABP and decreased $A\beta$ (i.e. increased $A\beta$ deposition in the brain). A growing body of experimental evidence from various model systems indicates that phospholipids play an integral role in regulating amyloidogenesis. Enriched cholesterol and lipid microenvironments ('lipid rafts') within the plasma membrane and the

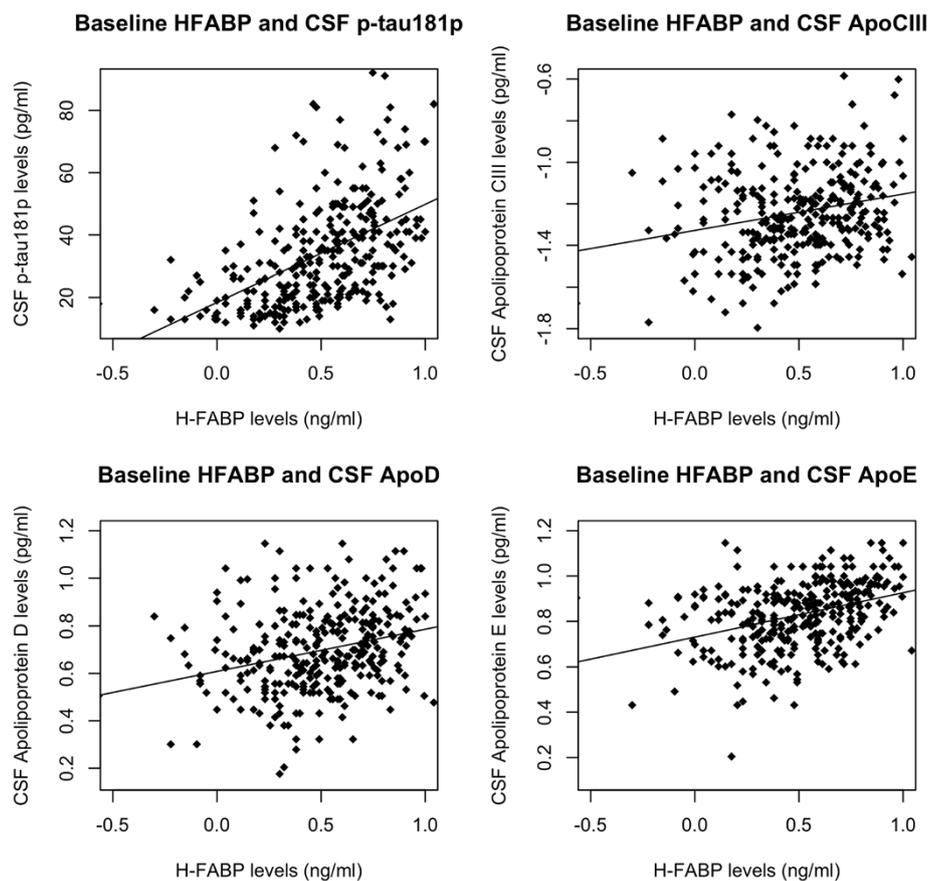


Figure 3 Scatter plots demonstrating the relationship between baseline CSF levels of HFABP (quality-controlled, transformed values as described in reference 18) CSF p-tau_{181p} (top left), CSF ApoC III (top right), CSF ApoD (bottom left) and CSF ApoE (bottom right). The black line represents the best-fit regression line.

Table 2 Demographic, clinical, and imaging data for all participants in this study

	HC (n = 90)	MCI (n = 139)	AD (n = 66)
Age, Mean (SE)	76.0 (0.6)	75.1 (0.7)	75.4 (0.9)
Female, %	51	33	41
Education Years, Mean (SE)	15.6 (0.3)	16.1 (0.2)	15.1 (0.4)
MMSE, Mean (SE)	29.1 (0.1)	26.7 (0.1)	23.4 (0.2)
CDR-SB, Mean (SE)	0.03 (0.01)	1.5 (0.07)	4.2 (0.2)
APOE ε4 carriers (%)	24	54	71
CSF H-FABP level (ng/ml), Mean (SE)	0.38 (0.03)	0.54 (0.02)	0.58 (0.03)
CSF Aβ ₁₋₄₂ level (pg/ml), Mean (SE)	207.8 (5.6)	157.5 (4.1)	141.5 (2.6)
CSF p-tau _{181p} level (pg/ml), Mean (SE)	24.7 (1.4)	36.8 (1.3)	41.7 (2.6)
Entorhinal Cortex APC, Mean (SE)	-0.8 (0.1)	-2.4 (0.1)	-2.9 (0.2)
AD-vulnerable ROI APC, Mean (SE)	-1.1 (0.1)	-3.2 (0.2)	-3.9 (0.3)

MCI; mild cognitive impairment, HC; cognitively normal older adults, AD; Alzheimer's disease, MMSE; Mini-mental status exam, CDR-SB; Clinical dementia rating-sum of boxes score, APC; Annualized percent change, SE; Standard error of the mean.

mitochondria-associated endoplasmic reticulum membrane promote γ -secretase activity resulting in increased A β production [5,21]. In comparison, outside lipid rafts, amyloid-precursor protein (APP) processing occurs predominantly via the non-amyloidogenic α -secretase pathway [22]. Membrane phospholipids also influence A β aggregation and clearance [5] and through release of arachidonic acid via the phospholipase 2 pathway, may additionally serve as critical mediators in A β -induced synaptotoxicity, leading to learning, memory, and behavioral impairments in mouse models of AD [23]. Our results are consistent with these observations and suggest that phospholipids and lipid binding proteins may affect Alzheimer's neurodegeneration primarily via A β -associated mechanisms.

One potential concern is that our current findings do not explain the previously noted relationships observed between HFABP and non-AD neurodegenerative diseases such as vascular dementia, Creutzfeldt-Jakob disease, Parkinson's disease, and dementia with Lewy bodies [18,24-27]. Though we did not explicitly evaluate the role of HFABP in other neurodegenerative conditions or as a differential disease marker of AD, our findings may help provide insights into common mechanisms underlying an array of protein misfolding neurologic disorders. For example, lipid metabolism may play an important role in synaptic degeneration and regeneration [28] and as such, may be involved in a number of neurodegenerative diseases. Another intriguing notion is that in addition to APP and A β , phospholipid rich lipid rafts may play an important role in mediating pathogenesis associated with a number of proteins including α -synuclein [29,30] and prions [31,32] thus raising the possibility that lipid dyshomeostasis may represent an early

trigger for a number of protein misfolding neurodegenerative disorders.

A limitation of our study is its observational nature, which precludes conclusions regarding causation. Our results cannot differentiate whether elevated HFABP causes, results from, or is simply correlated with amyloid deposition and volume loss. Additionally, our findings require further validation on a larger, independent population-based cohort.

Conclusions

In summary, our results suggest that CSF HFABP reflects intra-cranial lipid biology and associates with A β -associated neurodegeneration irrespective of tau. Clinically, our findings suggest that HFABP may represent an important modifier of progression from amyloid deposition to neurodegeneration. Considered together with our prior findings [33,34], this suggests that in addition to phospho-tau, the HFABP/A β /neurodegeneration axis may represent an important area for further investigation. Using experimental models, it would be helpful to better understand the precise relationship between HFABP and A β dyshomeostasis and whether proteins influence or modulate this association. The results of these studies could provide insights into whether fatty acids and lipids represent a viable therapeutic target for individuals in the presymptomatic and very mildly symptomatic phase of the disease process.

Methods

We evaluated cognitively normal older adults (HC = 90), individuals diagnosed with amnesic MCI (n = 139), and probable AD (n = 66) from the Alzheimer's Disease Neuroimaging Initiative (ADNI; see Additional file 1 for further details). From a total of 415 demented and non-demented older individuals who underwent longitudinal MR imaging

and CSF lumbar puncture, we restricted our analyses to those participants with quality-assured baseline and at least one follow-up MRI scan (Table 2).

We evaluated baseline CSF HFABP levels analyzed using a multiplex-based immunoassay panel. This immunoassay panel, based on Luminex xMAP immunoassay technology and developed by Rules Based Medicine (MyriadMBM), measures a range of lipid, inflammatory, metabolic, and other AD-relevant indices (for further details, please see reference 18). We also examined baseline CSF $A\beta_{1-42}$ and CSF p-tau_{181p} levels, determined using the AlzBio3 Luminex xMAP immunoassay (Innogenetics, Ghent, Belgium). Using previously proposed CSF cutoffs¹⁹ we classified participants based on low (<192 pg/ml) and high (>192 pg/ml) $A\beta_{1-42}$ levels and high (>23 pg/ml) and low (<23 pg/ml) p-tau_{181p} levels.

We examined 1205 T₁-weighted MRI scans. We performed quantitative volume and surface-based analysis of all baseline MRI scans using automated region-of-interest (ROI) labeling techniques [35,36], primarily focusing on the entorhinal cortex, a medial temporal lobe region that is selectively affected in the earliest stages of AD [37] (Figure 1). To additionally investigate neuroanatomic regions that are involved in the later stages of the disease process [37,38], and to minimize multiple comparisons, we averaged longitudinal volume change in the temporal pole, parahippocampal gyrus, inferior temporal gyrus, banks of the superior temporal sulcus, inferior parietal lobule, amygdala, and hippocampus to create an 'AD-vulnerable' ROI [33,34] (Figure 1). Using an image-analysis method developed within our laboratory [39], we assessed longitudinal sub-regional change in gray matter volume (atrophy) on serial MRI scans (see Additional file 1 for additional details).

For the primary analyses, we used linear mixed effects models to examine the associations of CSF HFABP, CSF $A\beta_{1-42}$ status, and CSF p-tau_{181p} status on atrophy rate of the entorhinal cortex, and of the AD-vulnerable ROI. All analyses co-varied for the effects of the baseline age, sex, presence ("carriers") or absence ("non-carriers") of at least one $\epsilon 4$ allele of apolipoprotein E (APOE $\epsilon 4$), diagnostic status (AD vs MCI vs HC), and disease severity (CDR-Sum of Boxes score at baseline).

Specifically, our initial model was:

$$\Delta v = b_0 + b_1 \Delta t + b_2 \text{CSF_HFABP} \times \Delta t + \text{covariates} \times \Delta t + e \quad (1)$$

Here, Δv is the entorhinal cortex or AD-vulnerable ROI thickness change from baseline (millimeters³) and Δt is the change in time from baseline MRI scan (years).

Next, investigated whether interactions of CSF HFABP with CSF $A\beta_{1-42}$ status, and CSF p-tau_{181p} status were significantly associated with atrophy over time. Specifically:

$$\begin{aligned} \Delta v = & \beta_0 + \beta_1 \Delta t + \beta_2 \text{CSF_HFABP} \times \Delta t \\ & + \beta_3 \text{CSF_Ab}_{1-42}\text{-status} \times \Delta t \\ & + \beta_4 \text{CSF_p-tau}_{181p}\text{-status} \times \Delta t \\ & + \beta_5 [\text{CSF_HFABP} \times \text{CSF_Ab}_{1-42}\text{-status} \times \Delta t] \\ & + \beta_6 [\text{CSF_HFABP} \times \text{CSF_p-tau}_{181p}\text{-status} \times \Delta t] \\ & + \text{covariates} \times \Delta t + e \end{aligned} \quad (2)$$

In both models, the main effects of all variables were also included. For brevity, we focus above on the effects of interest.

Additional file

Additional file 1: Methods and results.

Abbreviations

HFABP: Heart fatty acid binding protein; $A\beta$: Amyloid- β ; p-tau_{181p}: Phospho-tau; AD: Alzheimer's disease; MCI: Mild cognitive impairment; HC: Healthy older controls; AD-vulnerable ROI: Neocortical and subcortical regions affected in the later stages of Alzheimer's disease.

Competing interests

Dr. Anders M. Dale is a founder and holds equity in CorTechs Labs, Inc, and also serves on the Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

Dr. Linda K. McEvoy's has stock options in CorTechs Labs, Inc.

Dr. James B. Brewer holds stock options in CorTechs Labs, Inc and serves on the advisory board and receives financial support from the Eli Lilly Biomarker Unit (Amyvid). Dr. Brewer also receives research support from General Electric and Janssen Alzheimer Immunotherapy.

Dr. Kaj Blennow has served on the advisory boards for Innogenetics, Lilly, Pfizer and Roche.

Authors' contributions

Drs. D, McE, H and D were involved with conception, design, and interpretation of data. Drs. D, McE, H and D provided general overall supervision of the study. Drs. D and T were involved with data analysis. Drs. D, B, McE, A, and D acquired funding. All authors contributed to drafting and critical revision of the manuscript and have given final approval of the version to be published.

Acknowledgements

This research was supported by grants from the National Institutes of Health (R01AG031224; K01AG029218; K02 NS067427; T32 EB005970), the Research Council of Norway (183782/V50) and the South East Norway Health Authority (2010-074). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging;

Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129 and K01 AG030514.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Author details

¹Department of Radiology, University of California, San Diego, 8950 Villa La Jolla Drive, Suite C101, La Jolla, CA 92037-0841, USA. ²Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA. ³Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA. ⁴Neuroradiology Section, Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA. ⁵Clinical Neurochemistry Laboratory, The Sahlgrenska Academy at Göteborg University, Gotheburg, Mölndal 40530, Sweden. ⁶UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK. ⁷Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ⁸Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.

Received: 4 May 2013 Accepted: 23 September 2013

Published: 2 October 2013

References

- Shepardson NE, Shankar GM, Selkoe DJ: **Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies.** *Arch Neurol* 2011, **68**:1239–1244.
- Shepardson NE, Shankar GM, Selkoe DJ: **Cholesterol level and statin use in Alzheimer disease: II. Review of human trials and recommendations.** *Arch Neurol* 2011, **68**:1385–1392.
- Jones L, Holmans PA, Hamshere ML, Harold D, Moskva V, Ivanov D, Pocklington A, Abraham R, Hollingworth P, Sims R, Gerrish A, Pahwa JS, Jones N, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schürmann B, Heun R, Kölsch H, van den Bussche H, Heuser I, Peters O, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel KH, Klopp N, Wichmann HE, Ruther E, Carrasquillo MM, Pankratz VS, Younkin SG, Hardy J, O'Donovan MC, Owen MJ, Williams J: **Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease.** *PLoS One* 2010, **5**:e13950.
- Jones L, Harold D, Williams J: **Genetic evidence for the involvement of lipid metabolism in Alzheimer's disease.** *Biochim Biophys Acta* 2010, **1801**:754–761.
- Di Paolo G, Kim TW: **Linking lipids to Alzheimer's disease: cholesterol and beyond.** *Nat Rev Neurosci* 2011, **12**:284–296.
- Wahrle SE, Jiang H, Parsadanian M, Kim J, Li A, Knoten A, Jain S, Hirsch-Reinshagen V, Wellington CL, Bales KR, Paul SM, Holtzman DM: **Overexpression of ABCA1 reduces amyloid deposition in the PDAPP mouse model of Alzheimer disease.** *J Clin Invest* 2008, **118**:671–682.
- Castellano JM, Deane R, Gottesdiener AJ, Verghese PB, Stewart FR, West T, Paoletti AC, Kasper TR, DeMattos RB, Zlokovic BV, Holtzman DM: **Low-density lipoprotein receptor overexpression enhances the rate of brain-to-blood A β clearance in a mouse model of β -amyloidosis.** *Proc Natl Acad Sci USA* 2012, **109**:15502–15507.
- Reitz C, Luchsinger J, Tang MX, Manly J, Mayeux R: **Impact of plasma lipids and time on memory performance in healthy elderly without dementia.** *Neurology* 2005, **64**:1378–1383.
- Reitz C, Tang MX, Manly J, Schupf N, Mayeux R, Luchsinger JA: **Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment.** *Dement Geriatr Cogn Disord* 2008, **25**:232–237.
- Cheon MS, Kim SH, Fountoulakis M, Lubec G: **Heart type fatty acid binding protein (H-FABP) is decreased in brains of patients with Down syndrome and Alzheimer's disease.** *J Neural Transm Suppl* 2003, **67**:225–34.
- Freeman SH, Kandel R, Cruz L, Rozkalne A, Newell K, Frosch MP, Hedley-Whyte ET, Locascio JJ, Lipsitz LA, Hyman BT: **Preservation of neuronal number despite age-related cortical brain atrophy in elderly subjects without Alzheimer disease.** *J Neuropathol Exp Neurol* 2008, **67**:1205–1212.
- Bobinski M, de Leon MJ, Wegiel J, Desanti S, Convit A, Saint Louis LA, Rusinek H, Wisniewski HM: **The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease.** *Neuroscience* 2000, **95**:721–725.
- Blennow K, Hampel H, Weiner M, Zetterberg H: **Cerebrospinal fluid and plasma biomarkers in Alzheimer disease.** *Nat Rev Neurol* 2010, **6**:131–144.
- Fagan AM, Holtzman DM: **Cerebrospinal fluid biomarkers of Alzheimer's disease.** *Biomark Med* 2010, **4**:51–63.
- Moullé VS, Cansell C, Luquet S, Cruciani-Guglielmacci C: **The multiple roles of fatty acid handling proteins in brain.** *Front Physiol* 2012, **3**:385.
- Chiasserini D, Parnetti L, Andreasson U, Zetterberg H, Giannandrea D, Calabresi P, Blennow K: **CSF levels of heart fatty acid binding protein are altered during early phases of Alzheimer's disease.** *J Alzheimers Dis* 2010, **22**:1281–1288.
- Rosén C, Mattsson N, Johansson PM, Andreasson U, Wallin A, Hansson O, Johansson JO, Lamont J, Svensson J, Blennow K, Zetterberg H: **Discriminatory Analysis of Biochip-Derived Protein Patterns in CSF and Plasma in Neurodegenerative Diseases.** *Front Aging Neurosci* 2011, **3**:1.
- Olsson B, Hertze J, Ohlsson M, Nägga K, Höglund K, Basun H, Annas P, Lannfelt L, Andreasen N, Minthon L, Zetterberg H, Blennow K, Hansson O: **Cerebrospinal Fluid Levels of Heart Fatty Acid Binding Protein are Elevated Prodromally in Alzheimer's Disease and Vascular Dementia.** *J Alzheimers Dis* 2012, Dec 19.
- Olsson B, Hertze J, Ohlsson M, Nägga K, Höglund K, Basun H, Annas P, Lannfelt L, Andreasen N, Minthon L, Zetterberg H, Blennow K, Hansson O: **Cerebrospinal fluid levels of heart fatty acid binding protein are elevated prodromally in Alzheimer's disease and vascular dementia.** *J Alzheimers Dis* 2013, **34**(3):673–9.
- Shaw LM, Vanderstichele H, Knopik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ: **Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects.** *Ann Neurol* 2009, **65**:403–13.
- Schon EA, Area-Gomez E: **Mitochondria-associated ER membranes in Alzheimer disease.** *Mol Cell Neurosci* 2013, **55**:26–36.
- Vetrivel KS, Thinakaran G: **Membrane rafts in Alzheimer's disease beta-amyloid production.** *Biochim Biophys Acta* 2010, **1801**:860–7.
- Sanchez-Mejia RO, Mucke L: **Phospholipase A2 and arachidonic acid in Alzheimer's disease.** *Biochim Biophys Acta* 2010, **1801**:784–90.
- Steinacker P, Mollenhauer B, Bibl M, Cepek L, Esselmann H, Brechlin P, Lewczuk P, Poser S, Kretzschmar HA, Wiltfang J, Trenkwalder C, Otto M: **Heart fatty acid binding protein as a potential diagnostic marker for neurodegenerative diseases.** *Neurosci Lett* 2004, **370**:36–9.
- Mollenhauer B, Steinacker P, Bahn E, Bibl M, Brechlin P, Schlossmacher MG, Locascio JJ, Wiltfang J, Kretzschmar HA, Poser S, Trenkwalder C, Otto M: **Serum heart-type fatty acid-binding protein and cerebrospinal fluid tau: marker candidates for dementia with Lewy bodies.** *Neurodegener Dis* 2007, **4**:366–75.
- Wada-Isoe K, Imamura K, Kitamura M, Kowa H, Nakashima K: **Serum heart-fatty acid binding protein levels in patients with Lewy body disease.** *J Neurol Sci* 2008, **266**:20–24.
- Ohrfelt A, Andreasson U, Simon A, Zetterberg H, Edman A, Potter W, Holder D, Devanarayan V, Seeburger J, Smith AD, Blennow K, Wallin A: **Screening for new biomarkers for subcortical vascular dementia and Alzheimer's disease.** *Dement Geriatr Cogn Dis Extra* 2011, **1**:31–42.
- Mauch DH, Nägler K, Schumacher S, Göritz C, Müller EC, Otto A, Pflieger FW: **CNS synaptogenesis promoted by glia-derived cholesterol.** *Science* 2001, **294**:1354–7.

29. Fortin DL, Troyer MD, Nakamura K, Kubo S, Anthony MD, Edwards RH: **Lipid rafts mediate the synaptic localization of alpha-synuclein.** *J Neurosci* 2004, **24**:6715–23.
30. Büttner S, Delay C, Franssens V, Bammens T, Ruli D, Zauschirm S, de Oliveira RM, Outeiro TF, Madeo F, Buée L, Galas MC, Winderickx J: **Synphilin-1 enhances α -synuclein aggregation in yeast and contributes to cellular stress and cell death in a Sir2-dependent manner.** *PLoS One* 2010, **5**:e13700.
31. Taylor DR, Hooper NM: **The prion protein and lipid rafts.** *Mol Membr Biol* 2006, **23**:89–99.
32. Westaway D, Jhamandas JH: **The P's and Q's of cellular PrP-A β interactions.** *Prion* 2012, **6**:359–63.
33. Desikan RS, McEvoy LK, Thompson WK, Holland D, Roddey JC, Blennow K, Aisen PS, Brewer JB, Hyman BT, Dale AM: **Alzheimer's Disease Neuroimaging Initiative. Amyloid- β associated volume loss occurs only in the presence of phospho-tau.** *Ann Neurol* 2011, **70**:657–61.
34. Desikan RS, McEvoy LK, Holland D, Thompson WK, Brewer JB, Aisen PS, Andreassen OA, Hyman BT, Sperling RA, Dale AM: **For the Alzheimer's Disease Neuroimaging Initiative. Apolipoprotein E {varepsilon}4 Does Not Modulate Amyloid- β -Associated Neurodegeneration in Preclinical Alzheimer Disease.** *AJNR Am J Neuroradiol* 2013, **34**:505–10.
35. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM: **Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain.** *Neuron* 2002, **33**:341–55.
36. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ: **An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest.** *Neuroimage* 2006, **31**:968–80.
37. Braak H, Braak E: **Neuropathological staging of Alzheimer-related changes.** *Acta Neuropathol* 1991, **82**:239–59.
38. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW: **The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease.** *Cereb Cortex* 1991, **1**:103–16.
39. Holland D, Dale AM: **Nonlinear registration of longitudinal images and measurement of change in regions of interest.** *Med Image Anal* 2011, **15**:489–97.

doi:10.1186/1750-1326-8-39

Cite this article as: Desikan *et al.*: Heart fatty acid binding protein and A β -associated Alzheimer's neurodegeneration. *Molecular Neurodegeneration* 2013 **8**:39.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

