Publications abstracts

Association of brain network dynamics with plasma biomarkers in subjective memory complainers.

Chiesa PA, Houot M, Vergallo A, Cavedo E, Lista S, Potier MC, Zetterberg H, Blennow K, Vanmechelen E, De Vos A, Dubois B, Hampel H; INSIGHT-preAD study group; Alzheimer Precision Medicine Initiative (APMI). Neurobiol Aging. 2020 Apr;88:83-90. doi: 10.1016/j.neurobiolaging.2019.12.017. Epub 2019 Dec 23. PMID: 32087948

Abstract

Using a single integrated analysis, we examined the relationship between brain networks and molecular pathways in a cohort of elderly individuals at risk for Alzheimer's disease. In 205 subjective memory complainers (124 females, mean age: 75.7 ± 3.4), individual functional connectome was computed for a total of 3081 functional connections (set A) and 6 core plasma biomarkers of Alzheimer's disease (set B) were assessed. Partial least squares correlation analysis identified one dimension of population covariation between the 2 sets ($p < 0.006$), which we named bioneural mode. Five core plasma biomarkers and 190 functional connections presented bootstrap ratios greater than the critical value |1.96|. T-tau protein showed a trend toward significance (bootstrap resampling = 1.64). The salience, the language, the visuospatial, and the default mode networks were the strongest significant networks. We detected a strong association between network dynamics and core pathophysiological blood biomarkers. Innovative composite biomarkers, such as the bioneural mode, are promising to provide outcomes and better inform drug development and clinical practice for neurodegenerative diseases.

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Plasma tau correlates with basal forebrain atrophy rates in people at risk for Alzheimer disease.

Cavedo E, Lista S, Houot M, Vergallo A, Grothe MJ, Teipel S, Zetterberg H, Blennow K, Habert MO, Potier MC, Dubois B, Hampel H; INSIGHT-preAD Study Group, Alzheimer Precision Medicine Initiative. Neurology. 2020 Jan 7;94(1):e30-e41. doi: 10.1212/WNL.0000000000008696. Epub 2019 Dec 4. PMID: 31801830

Abstract

Objective: To investigate whether baseline concentrations of plasma total tau (t-tau) and neurofilament light (NfL) chain proteins are associated with annual percent change (APC) of the basal forebrain cholinergic system (BFCS) in cognitively intact older adults at risk for Alzheimer disease (AD).

Methods: This was a large-scale study of 276 cognitively intact older adults from the monocentric INSIGHT-preAD (Investigation of Alzheimer's Predictors in Subjective Memory Complainers) cohort. Participants underwent baseline assessment of plasma t-tau and NfL concentrations as well as baseline and 24-month follow-up MRI scans. Linear models with and without influential observations (calculated using the Cook distance) were carried out to investigate the effect of plasma NfL and t-tau concentrations, and their interaction effect with β-amyloid status and *APOE* genotype, on the APC of the whole BFCS and its anterior (Ch1/2) and posterior (Ch4) subdivisions separately.

Results: Higher plasma t-tau concentrations at baseline were associated with higher BFCS rate of atrophy (model without influencers: n = 251, F value = 4.6815; *p* value = 0.031). Subregional analyses showed similar results for both the APC of the Ch1/2 (model without influencers: n = 256, F value = 3.9535, *p* corrected = 0.047) and Ch4 BFCS sectors (model without influencers: n = 253, F value = 4.9090, *p* corrected = 0.047). Baseline NfL, β-amyloid load, and *APOE ε4* carrier status did not affect APC of the BFCS.

Conclusion: Increased concentrations of baseline plasma t-tau may predict in vivo structural BFCS atrophy progression in older adults at risk for AD, independently of β-amyloid status and *APOE* genotype.

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Plasma amyloid β 40/42 ratio predicts cerebral amyloidosis in cognitively normal individuals at risk for Alzheimer's disease.

Vergallo A, Mégret L, Lista S, Cavedo E, Zetterberg H, Blennow K, Vanmechelen E, De Vos A, Habert MO, Potier MC, Dubois B, Neri C, Hampel H; INSIGHT-preAD study group; Alzheimer Precision Medicine Initiative (APMI). Alzheimers Dement. 2019 Jun;15(6):764-775. doi: 10.1016/j.jalz.2019.03.009. Epub 2019 May 18. PMID: 31113759

Abstract

Introduction: Blood-based biomarkers of pathophysiological brain amyloid β (Aβ) accumulation, particularly for preclinical target and large-scale interventions, are warranted to effectively enrich Alzheimer's disease clinical trials and management.

Methods: We investigated whether plasma concentrations of the $A\beta_{1-40}/A\beta_{1-42}$ ratio, assessed using the single-molecule array (Simoa) immunoassay, may predict brain Aβ positron emission tomography status in a large-scale longitudinal monocentric cohort (N = 276) of older individuals with subjective memory complaints. We performed a hypothesis-driven investigation followed by a no-a-priori hypothesis study using machine learning.

Results: The receiver operating characteristic curve and machine learning showed a balanced accuracy of 76.5% and 81%, respectively, for the plasma $A\beta_{1-40}/A\beta_{1-42}$ ratio. The accuracy is not affected by the apolipoprotein E (APOE) ε4 allele, sex, or age.

Discussion: Our results encourage an independent validation cohort study to confirm the indication that the plasma $A\beta_{1-40}/A\beta_{1-42}$ ratio, assessed via Simoa, may improve future standard of care and clinical trial design.

Keywords: Alzheimer's disease; Amyloid PET; Classification and regression trees (CART); Machine learning; Plasma amyloid β; Simoa immunoassay; Subjective memory complainers.

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Resting-state posterior alpha rhythms are abnormal in subjective memory complaint seniors with preclinical Alzheimer's neuropathology and high education level: the INSIGHT-preAD study.

Babiloni C, Lopez S, Del Percio C, Noce G, Pascarelli MT, Lizio R, Teipel SJ, González-Escamilla G, Bakardjian H, George N, Cavedo E, Lista S, Chiesa PA, Vergallo A, Lemercier P, Spinelli G, Grothe MJ, Potier MC, Stocchi F, Ferri R, Habert MO, Fraga FJ, Dubois B, Hampel H; INSIGHT-preAD Study Group.

Neurobiol Aging. 2020 Jun;90:43-59. doi: 10.1016/j.neurobiolaging.2020.01.012. Epub 2020 Feb 1. PMID: 32111391

Abstract

Cognitive reserve is present in Alzheimer's disease (AD) seniors with high education attainment making them clinically resilient to extended brain neuropathology and neurodegeneration. Here, we tested whether subjective memory complaint (SMC) seniors with AD neuropathology and high education attainment of the prospective INSIGHT-preAD cohort (Paris) may present abnormal eyes-closed resting state posterior electroencephalographic rhythms around individual alpha frequency peak, typically altered in AD patients. The SMC participants negative to amyloid PET AD markers (SMCneg) with high (over low-moderate) education level showed higher posterior alpha 2 power density (possibly "neuroprotective"). Furthermore, amyloid PET-positive SMC (SMCpos) participants with high (over low-moderate) education level showed higher temporal alpha 3 power density (possibly "neuroprotective") and lower posterior alpha 2 power density (possibly "compensatory"). This effect may reflect cognitive reserve as no differences in brain gray-white matter, and cognitive functions were observed between these SMCpos/SMCneg subgroups. Preclinical Alzheimer's neuropathology may interact with education attainment and neurophysiological mechanisms generating cortical alpha rhythms around individual alpha frequency peak (i.e., alpha 2 and 3) in quiet wakefulness.

Keywords: Alpha rhythms; INSIGHT-preAD study; Preclinical Alzheimer's disease (AD); Preclinical Alzheimer's neuropathology; Resting state EEG rhythms; Subjective memory complaint (SMC).

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EEG evidence of compensatory mechanisms in preclinical Alzheimer's disease.
Gaubert S, Raimondo F, Houot M, Corsi MC, Naccache L, Diego Sitt J, Hermann B, Oudiette D, Gagliardi G, Habert MO, Dubois B, De Vico Fallani F, Bakardjian H, Epelbaum S; Alzheimer's Disease Neuroimaging Initiative.
Brain. 2019 Jul 1;142(7):2096-2112. doi: 10.1093/brain/awz150. PMID: 31211359 Free article.

Abstract

Early biomarkers are needed to identify individuals at high risk of preclinical Alzheimer's disease and to better understand the pathophysiological processes of disease progression. Preclinical Alzheimer's disease EEG changes would be non-invasive and cheap screening tools and could also help to predict future progression to clinical Alzheimer's disease. However, the impact of amyloid-β deposition and neurodegeneration on EEG biomarkers needs to be elucidated. We included participants from the INSIGHT-preAD cohort, which is an ongoing single-centre multimodal observational study that was designed to identify risk factors and markers of progression to clinical Alzheimer's disease in 318 cognitively normal individuals aged 70-85 years with a subjective memory complaint. We divided the subjects into four groups, according to their amyloid status (based on 18F-florbetapir PET) and neurodegeneration status (evidenced by 18F-fluorodeoxyglucose PET brain metabolism in Alzheimer's disease signature regions). The first group was amyloid-positive and neurodegeneration-positive, which corresponds to stage 2 of preclinical Alzheimer's disease. The second group was amyloid-positive and neurodegeneration-negative, which corresponds to stage 1 of preclinical Alzheimer's disease. The third group was amyloid-negative and neurodegeneration-positive, which corresponds to 'suspected non-Alzheimer's pathophysiology'. The last group was the control group, defined by amyloid-negative and neurodegeneration-negative subjects. We analysed 314 baseline 256-channel high-density eyes closed 1-min resting state EEG recordings. EEG biomarkers included spectral measures, algorithmic complexity and functional connectivity assessed with a novel information-theoretic measure, weighted symbolic mutual information. The most prominent effects of neurodegeneration on EEG metrics were localized in frontocentral regions with an increase in high frequency oscillations (higher beta and gamma power) and a decrease in low frequency oscillations (lower delta power), higher spectral entropy, higher complexity and increased functional connectivity measured by weighted symbolic mutual information in theta band. Neurodegeneration was associated with a widespread increase of median spectral frequency. We found a non-linear relationship between amyloid burden and EEG metrics in neurodegeneration-positive subjects, either following a U-shape curve for delta power or an inverted U-shape curve for the other metrics, meaning that EEG patterns are modulated differently depending on the degree of amyloid burden. This finding suggests initial compensatory mechanisms that are overwhelmed for the highest amyloid load. Together, these results indicate that EEG metrics are useful biomarkers for the preclinical stage of Alzheimer's disease.

Keywords: EEG; amyloid load; functional connectivity; neurodegeneration; preclinical Alzheimer's disease.

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Aptamers as **biomarkers** for **neurological disorders**. Proof of concept in transgenic mice.

Lecocq S, Spinella K, Dubois B, Lista S, Hampel H, Penner G. PLoS One. 2018 Jan 5;13(1):e0190212. doi: 10.1371/journal.pone.0190212. eCollection 2018. PMID: 29304088 Free PMC article.

Abstract

The act of selecting aptamers against blood serum leads to deep libraries of oligonucleotide sequences that bind to a range of epitopes in blood. In this study we developed an enriched aptamer library by performing positive selection against a pool of blood serum samples from transgenic mice (P301S) carrying the human tau gene and counter selecting against pooled blood serum from negative segregant (wild type) mice. We demonstrated that a large proportion of the aptamer sequences observed with next generation sequence (NGS) analysis were the same from selection round 5 and selection round 6. As a second step, we applied aliquots of the selection round 5 enriched library to blood serum from 16 individual mice for a single round of selection. Each of these individual libraries were characterized through NGS analysis and the changes in relative frequency in aptamers from transgenic mice versus wild type were used to construct a diagnostic fingerprint of the effect of the action of the transgene on the composition of blood serum. This study serves as a model for similar applications with human subjects.

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Aptamarker prediction of brain amyloid-beta status in cognitively normal individuals at risk for Alzheimer's disease.

Penner G, Lecocq S, Chopin A, Vedoya X, Lista S, Vergallo A, Cavedo E, Lejeune FX, Dubois B, Hampel H; INSIGHT-preAD study group; Alzheimer Precision Medicine Initiative (APMI). PLoS One. 2021 Jan 4;16(1):e0243902. doi: 10.1371/journal.pone.0243902. eCollection 2021. PMID: 33395442 Free PMC article.

Abstract

Introduction: This review is focused on the methods used for biomarker discovery for Alzheimer's disease (AD) in blood rather than on the nature of the biomarkers themselves. **Areas covered**: All biomarker discovery programs explicitly rely on contrasts in phenotype as a basis for defining differences. In this review, we explore the basis of contrasting choices as a function of the type of biomarker (genetic, protein, metabolite, non-coding RNA, or pathogenic epitope). We also provide an overview of the capacity to identify pathogenic epitopes with our new platform called Aptamarkers. It is suggested that a pre-existing hypothesis regarding the pathophysiology of the disease can act as a constraint to the

development of biomarkers. **Expert opinion**: Limiting putative biomarkers to those that have a postulated role in the pathophysiology of disease imposes an unrealistic constraint on biomarker development. The understanding of Alzheimer's disease would be accelerated by agnostic, non-hypothesis-based biomarker discovery methods. There is a need for more complex contrasts and more complex mathematical models.

Keywords: Alzheimer’s disease; Aptamarkers; Aptamers; blood-based biomarkers.