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Research Report

Cognitive Trajectories in Preclinical and Prodromal Alzheimer's Disease Related to Amyloid Status and Brain Atrophy: A Bayesian Approach

Stefan J. Teipel^{a,b,*}, Martin Dyrba^a, Fedor Levin^a, Slawek Altenstein^{c,d}, Moritz Berger^c, Aline Beyle^f, Frederic Brosseron^f, Katharina Buerger^{g,h}, Lena Burowⁱ, Laura Dobisch^j, Michael Ewers^{g,h}, Klaus Fließbach^{f,k}, Ingo Frommann^{f,k}, Wenzel Glanz^j, Doreen Goerss^{a,b}, Daria Gref^l, Niels Hansen^m, Michael T. Heneka^f, Enise I. Incesoy^{j,n,o}, Daniel Janowitz^h, Deniz Keles^l, Ingo Kilimann^{a,b}, Christoph Laske^{p,q}, Andrea Lohse^d, Matthias H. Munk^{p,r}, Robert Perneczky^{g,i,s,t}, Oliver Peters^{c,l}, Lukas Preis^l, Josef Priller^{c,d,u,v}, Ayda Rostamzadeh^w, Nina Roy^f, Matthias Schmid^{e,f}, Anja Schneider^{f,k}, Annika Spottke^{f,x}, Eike Jakob Spruth^{c,d}, Jens Wiltfang^{m,y,z}, Emrah Düzel^{l,n}, Frank Jessen^{f,w}, Luca Kleineidam^k and Michael Wagner^{f,k}, for the DELCODE study group and the Alzheimer's Disease Neuroimaging Initiative¹

^aGerman Center for Neurodegenerative Diseases (DZNE), Rostock, Germany

^bDepartment of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany

^cGerman Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

^dDepartment of Psychiatry and Psychotherapy, Charité, Berlin, Germany

^eInstitute for Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany

^fLuxembourg Centre for Systems Biomedicine, University of Luxembourg, Belvaux, Luxembourg

^gGerman Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany

^hInstitute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany

ⁱDepartment of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

^jGerman Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

^kUniversity of Bonn Medical Center, Department of Neurodegenerative Disease and Geriatric Psychiatry/Psychiatry, Bonn, Germany

^lCharité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin-Institute of Psychiatry and Psychotherapy, Berlin, Germany

^mDepartment of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Goettingen, Germany

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*Correspondence to: Stefan J. Teipel, MD, Department of Psychosomatic Medicine, University of Rostock, and DZNE Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany. Tel.: +49 01149 381 494 9470; Fax: +49 01149 381 494 9472; E-mail: stefan.teipel@med.uni-rostock.de.

¹*Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany*

²*Department for Psychiatry and Psychotherapy, University Clinic Magdeburg, Magdeburg, Germany*

³*German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany*

⁴*Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany*

⁵*Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany*

⁶*Munich Cluster for Systems Neurology (SyNergy) Munich, Munich, Germany*

⁷*Ageing Epidemiology Research Unit (AGE), School of Public Health, Imperial College London, London, UK*

⁸*School of Medicine, Technical University of Munich; Department of Psychiatry and Psychotherapy, Munich, Germany*

⁹*University of Edinburgh and UK DRI, Edinburgh, UK*

¹⁰*Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany*

¹¹*Department of Neurology, University of Bonn, Bonn, Germany*

¹²*German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany*

¹³*Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal*

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Abstract.

Background: Cognitive decline is a key outcome of clinical studies in Alzheimer's disease (AD).

Objective: To determine effects of global amyloid load as well as hippocampus and basal forebrain volumes on longitudinal rates and practice effects from repeated testing of domain specific cognitive change in the AD spectrum, considering non-linear effects and heterogeneity across cohorts.

Methods: We included 1,514 cases from three cohorts, ADNI, AIBL, and DELCODE, spanning the range from cognitively normal people to people with subjective cognitive decline and mild cognitive impairment (MCI). We used generalized Bayesian mixed effects analysis of linear and polynomial models of amyloid and volume effects in time. Robustness of effects across cohorts was determined using Bayesian random effects meta-analysis.

Results: We found a consistent effect of amyloid and hippocampus volume, but not of basal forebrain volume, on rates of memory change across the three cohorts in the meta-analysis. Effects for amyloid and volumetric markers on executive function were more heterogeneous. We found practice effects in memory and executive performance in amyloid negative cognitively normal controls and MCI cases, but only to a smaller degree in amyloid positive controls and not at all in amyloid positive MCI cases.

Conclusions: We found heterogeneity between cohorts, particularly in effects on executive functions. Initial increases in cognitive performance in amyloid negative, but not in amyloid positive MCI cases and controls may reflect practice effects from repeated testing that are lost with higher levels of cerebral amyloid.

Keywords: Alzheimer's disease, executive function, longitudinal, memory, mild cognitive impairment, non-linear, practice effects, subjective cognitive decline

INTRODUCTION

Rates of cognitive decline are a key outcome for longitudinal follow-up and monitoring the effect of interventions in Alzheimer's disease (AD). In addition, cognitive decline serves as a reference for assessing the predictive accuracy of biomarkers such as pathological accumulation of amyloid or brain

atrophy. In addition to linear trajectories, loss of initial increases in performance representing practice effects from repeated testing may be a sensitive indicator of early pathology [1–4]. Thus, cognitive decline does not necessarily follow a linear course, and the effects of external predictors or effectors of change may also be nonlinear. Therefore, allowing for

non-linearity both in trajectories of cognitive decline and in effects of external variables may increase the ability to uncover biologically meaningful effects, including practice effects.

Bayesian approaches have become increasingly popular for modeling change in imaging biomarkers of AD [5], and have been applied to study trajectories of atrophy [6], or functional connectivity [7] over time. Bayesian analysis has major advantages over classical frequentist analysis [8]. It allows explicit modelling and checking a priori assumptions on the shape of cognitive trajectories and predictive parameters. This is particularly interesting if one uses several cohorts so that the shape parameters from one cohort can be used as a prior for another cohort. In addition, Bayesian analysis allows for a direct evaluation of the evidence in favor and against competing hypotheses [9, 10].

In the current study, we used Bayesian linear and nonlinear joint mixed effect models with selected distribution functions to determine the association of key pathological markers of AD with longitudinal rates of cognitive decline as well as practice effects in cognitively healthy people and people with mild cognitive impairment (MCI) or subjective cognitive decline (SCD). Specifically, we tested the association of amyloid load as potential upstream event of AD pathology [11–13], as well as atrophy of cholinergic basal forebrain [1] and hippocampus as potential downstream markers of neurodegeneration [14] with rates of memory and executive function change. To allow testing the generalizability of findings assessments included three independent samples, one from the ADNI cohort [15], one from the AIBL cohort [16] and one from the DELCODE cohort [17], with a total of 1,514 participants.

We tested the following two sets of hypotheses:

First, we expected that amyloid positivity as well as basal forebrain atrophy would be associated with less favorable cognitive performance over time in executive [18, 19] and memory function [1, 20], whereas hippocampus atrophy was expected to be predominantly associated with memory function decline [21, 22]. We used Bayesian random effects meta-analysis to determine replicability and heterogeneity of results across cohorts [23].

Secondly, based on previous assessments of practice effects [1–4], we expected that cognitively normal individuals would show benefits from repeated testing, which could be captured by polynomial rather than linear models of change. We also expected that this effect would be attenuated in the

presence of amyloid positivity [24] and brain volume reductions. Considering these effects eventually will help increasing the power of studies monitoring effects of disease or interventions on cognitive decline.

MATERIAL AND METHODS

Data sources

Part of the data was obtained from the ADNI-1, ADNI-GO, and ADNI-2 cohorts from the ADNI database (<http://adni.loni.usc.edu/>). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations, with the primary goal of testing whether neuroimaging, neuropsychological, and other biologic measurements can be used as reliable *in-vivo* markers of AD pathogenesis [15]. A comprehensive description of ADNI and up-to-date information is available at [HTTP://www.adni-info.org](http://www.adni-info.org). All procedures performed in the ADNI studies involving human participants were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the ADNI studies.

Another part of the data was obtained from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) [16]. This study was launched in 2006. Data were obtained from the AIBL LONI website (<https://ida.loni.usc.edu/login.jsp?project=AIBL&page=HOME>). Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the AIBL study.

Finally, another part of the data was obtained from the DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) study, conducted by the Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) [17]. DELCODE is an ongoing German multicenter observational study initiated in 2014 on predementia AD that aims to characterize early disease stages, in particular SCD, improve upon prognostics of disease progres-

sion and identify new markers for preclinical AD (<https://www.dzne.de/forschung/studien/klinische-studien/delcode/>). All participants or their representatives provided written informed consent. The study protocol was approved by the local institutional review boards and ethical committees of the participating centers. It was conducted in accord with the Helsinki Declaration of 1975 and its later amendments.

Participants

From the ADNI cohort we identified cognitively normal subjects and participants with MCI with amyloid PET and MRI scans available at baseline and at least one cognitive follow-up. Detailed inclusion criteria for diagnostic categories can be found at the ADNI web site (<http://adni.loni.usc.edu/methods/>). Cognitively normal subjects had MMSE scores between 24–30 (inclusive), a CDR=0, were non-depressed, non-MCI, and non-demented, and reported no subjective memory concerns. MCI subjects had MMSE scores between 24–30 (inclusive), a subjective memory concern reported by subject, informant, or clinician, objective memory loss measured by education and age adjusted scores on delayed recall, a CDR = 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Starting with ADNI-GO, MCI cases were further divided into late and early stages of MCI based on the WMS-R Logical Memory II Story A score. Here, we combined both subtypes into a single category of MCI to be consistent with ADNI-1 cases. ADNI participants are followed-up yearly using clinical, neuropsychological, and imaging assessment.

For replication purposes we used baseline and longitudinal data from AIBL and DELCODE. From AIBL we identified cognitively normal participants and MCI cases with MRI and amyloid PET scans available at baseline and at least one cognitive follow-up. Different to ADNI and DELCODE, AIBL MCI participants fulfilled criteria by Winblad et al. [25] and Petersen et al. [26], including not only amnesic, but also non-amnesic MCI cases. Major exclusion criteria for AIBL were age < 60 years, a history of non-AD dementia, schizophrenia, bipolar disorder, current depression with a short Geriatric Depression Scale score above 5/15 (for cognitively normal individuals), Parkinson's disease, symptomatic stroke, current uncontrolled or life threatening medical ill-

ness, diagnosed obstructive sleep apnea, past head injury with over one hour of post-traumatic amnesia, or alcohol use above two standard drinks per day for women or four per day for men. AIBL participants are followed-up every 18 months using clinical, neuropsychological and imaging assessment.

From DELCODE we derived two samples. One sample with MRI scans available at baseline and at least one cognitive follow-up and one subsample with cerebrospinal fluid (CSF) available at baseline and at least one cognitive follow-up. Both samples consisted of older healthy controls, cognitively normal first degree relatives of patients with dementia, and participants with amnesic MCI or subjective cognitive decline (SCD). Participants with AD dementia from DELCODE were excluded from our analyses. DELCODE excluded people with a current major depressive episode, past or present major psychiatric disorders, neurological diseases other than AD, or unstable medical conditions [17]. SCD was defined as a persistent self-perceived cognitive decline in the absence of objective cognitive impairment as measured by the CERAD test battery, lasting at least for 6 months and being unrelated to an acute event [27]. The MCI patients met the core clinical criteria for MCI according to National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup guidelines [28]. The control participants had no objective cognitive impairment in cognitive tests, no history of neurological or psychiatric disease and did not report self-perceived cognitive decline. Relatives were defined as cognitively normal people with at least one confirmed AD case in their direct kinship. DELCODE participants are followed-up yearly using clinical, neuropsychological, and imaging assessment.

The sample size was not based on a priori power calculation but used data available from the three cohorts fulfilling the inclusion criteria.

Neuropsychological assessment

For the ADNI cohort, we used two previously defined composite measures for the investigation of memory (ADNI memory score) [29] and executive functions (ADNI executive score) [30].

For the AIBL cohort, we used the delayed recall of logical memory of the Wechsler Memory Scale-Third edition [31]. We had no access to a measure of executive function in the AIBL data repository made available to us.

For the DELCODE cohort we used the delayed recall of logical memory of the Wechsler Memory Scale-Revised as a measure of memory function, and the Wechsler Memory Scale-Revised digit span (average of digit span forward and backward) as measure of executive function. In a sensitivity analysis, we used the ratio of the trail making test B to A (TMTB/A) as measure of executive function [32].

Amyloid PET data acquisition

For the ADNI data, amyloid positivity was determined using amyloid-sensitive ^{18}F -florbetapir PET scans. Detailed acquisition and standardized pre-processing steps of ADNI imaging data are available at the ADNI website (<https://adni.loni.usc.edu/methods/>). Amyloid-PET data was collected during a 50- to 70-min interval following a 370 MBq bolus injection of ^{18}F -Florbetapir. To account for the multicentric acquisition of the data across different scanners and sites, all PET scans undergo standardized pre-processing steps within ADNI. For anatomical reference and pre-processing of the PET scans we used the corresponding structural MRI scan that was closest in time to the Florbetapir PET scan.

For the AIBL sample, each participant had an amyloid sensitive PET scan from one of the following three tracers: ^{11}C -Pittsburgh compound-B (PIB), ^{18}F -florbetapir, and ^{18}F -flutemetamol. Amyloid-PET scans were collected as three to six frames of 5 min starting 40, 50, or 90 min post injection of the respective tracer. Detailed acquisition information is available at <https://aibl.csiro.au/adni/imaging.html>. The frames were averaged and matched to the corresponding structural MRI scan for further processing.

MRI data acquisition

In the ADNI sample MRI data were acquired on multiple 3T MRI scanners using scanner-specific T1-weighted sagittal 3D MPRAGE sequences. Similar to the PET data, MRI scans undergo standardized preprocessing steps aimed at increasing data uniformity across the multicenter scanner platforms (see <https://adni.loni.usc.edu/methods/> for detailed information on multicentric MRI acquisition and pre-processing in ADNI).

In the AIBL sample, MRI data were acquired at two sites equipped with Siemens 3T MRI scanners using ADNI-compliant T1-

weighted sagittal MPRAGE sequences. See <https://aibl.csiro.au/adni/imaging.html> for details.

For DELCODE the MRI data were acquired from nine Siemens 3.0 Tesla MRI scanners (4 Verio, 1 Skyra, 3 TimTrio and 1 Prisma system) using identical acquisition parameters and harmonized instructions as previously described [33]. To ensure high image quality throughout the acquisition phase, all scans had to pass a semi-automated quality check during the study conduction, so that protocol deviations could be reported to the study sites, and the acquisition at the respective site could be adjusted. High-resolution T1-weighted anatomical images were obtained using a sagittal magnetization-prepared rapid gradient echo (MPRAGE) sequence (field of view 256×256 mm, matrix size 256×256 , isotropic voxel size 1 mm, echo time 4.37 ms, flip angle 7° , repetition time 2500 ms, number of slices 192, parallel imaging acceleration factor 2).

Amyloid PET data pre-processing

Images were preprocessed using Statistical Parametric Mapping software version 8 (SPM8) (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London) implemented in Matlab 2013. The pre-processing pipeline followed the routine previously described in [34]. First, each subject's averaged PET frames were coregistered to their corresponding T1-weighted MRI scan. The coregistered PET images were spatially normalized to an aging/AD-specific reference template using the deformation parameters derived from the normalization of their corresponding MRI.

The regional ^{18}F -Florbetapir-PET mean uptake values were estimated for 52 brain regions defined by the Harvard-Oxford structural atlas [35], including both cortical and subcortical regions (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>). Standard uptake value ratios (SUVR_{Cer}) were computed for the 52 brain regions by dividing the mean uptake values by the mean uptake value of the whole cerebellum [34, 36–38].

For ADNI data, we used the widely used global signal cutoffs for ^{18}F -Florbetapir-PET SUVRS of $\text{SUVR}_{\text{Cer}} = 1.17$ [39, 40].

For the AIBL amyloid scans, we followed the Centiloid SPM pre-processing pipeline [37], which established procedures to harmonize measures obtained from multi-tracer PET studies. First, all amyloid scans were coregistered to their corresponding T1-weighted MRI scans and spa-

Table 1
Demographic characteristics

ADNI (N = 548)	N(f/m) ¹	Age [y] ² mean (95% CI)	MMSE ³ mean (95% CI)	Education [y] ⁴ mean (95% CI)	Follow-up [y] ⁵ mean (95% CI)
Controls	87/205	73.6 (72.7 – 74.6)	29.1 (28.9 – 29.2)	16.6 (16.3 – 17.0)	4.4 (4.2 – 4.7)
MCI	85/171	71.9 (71.1 – 72.6)	28.1 (27.9 – 28.3)	16.1 (15.8 – 16.4)	4.0 (3.8 – 4.1)
AIBL (N = 265)	N(f/m) ⁶	Age [y] ⁷ mean (95% CI)	MMSE ⁸ mean (95% CI)	Education [y] ⁹ mean (95% CI)	Follow-up [y] ¹⁰ mean (95% CI)
Controls	131/100	72.4 (71.6 – 73.2)	28.9 (28.7 – 29.0)	–	2.0 (1.8 – 2.1)
MCI	14/20	74.2 (72.0 – 76.5)	27.0 (26.2 – 27.7)	–	2.7 (2.3 – 3.2)
DELCODE (N = 416) amyloid	N(f/m) ¹¹	Age [y] ¹² mean (95% CI)	MMSE ¹³ mean (95% CI)	Education [y] ¹⁴ mean (95% CI)	Follow-up [y] ¹⁵ mean (95% CI)
Controls	67/58	68.3 (67.4 – 69.2)	29.4 (29.3 – 29.6)	14.5 (14.0 – 14.9)	2.9 (2.6 – 3.1)
SCD	85/111	71.4 (70.6 – 72.2)	29.2 (29.0 – 29.3)	14.8 (14.4 – 15.2)	2.6 (2.4 – 2.8)
MCI	41/54	72.4 (71.3 – 73.5)	27.0 (26.5 – 27.5)	13.9 (13.3 – 14.5)	2.6 (2.3 – 2.9)
DELCODE (N = 701) volumes	N(f/m) ¹⁶	Age [y] ¹⁷ mean (95% CI)	MMSE ¹⁸ mean (95% CI)	Education [y] ¹⁹ mean (95% CI)	Follow-up [y] ²⁰ mean (95% CI)
Controls	148/108	68.7 (68.1 – 69.4)	29.5 (29.4 – 29.6)	14.7 (14.3 – 15.0)	3.1 (2.9 – 3.2)
SCD	160/172	71.3 (70.6 – 71.9)	29.2 (29.1 – 29.3)	14.7 (14.4 – 15.1)	2.4 (2.3 – 2.6)
MCI	49/64	73.3 (72.2 – 74.3)	28.0 (27.7 – 28.4)	14.2 (13.7 – 14.8)	2.2 (2.0 – 2.5)

¹Bayes factor in favor of no group effect ($BF_{10} = 0.143$); i.e., a group effect is 0.143 times less likely than the absence of such an effect. ²Bayes factor moderately in favor of a group effect ($BF_{10} = 3.291$). ³Bayes factor extremely in favor of a group effect ($BF_{10} = 2.4 * 10^8$). ⁴Bayes factor shows no conclusive evidence of a group effect ($BF_{10} = 0.90$). ⁵Bayes factor moderately in favor of a group effect ($BF_{10} = 7.6$). ⁶Bayes factor in favor of the absence of a group effect ($BF_{10} = 0.26$). ⁷Bayes factor in favor of a group effect ($BF_{10} = 8.6$). ⁸Bayes factor in favor of a group effect ($BF_{10} = 2.6 * 10^{56}$). ⁹Data on education years were not available through the AIBL LONI website. ¹⁰Bayes factor strongly in favor of a group effect ($BF_{10} = 21.2$). ¹¹Bayes factor in favor of the absence of a group effect ($BF_{10} = 0.14$). ¹²Bayes factor extremely in favor of a group effect ($BF_{10} = 5.73 * 10^6$). ¹³Bayes factor extremely in favor of a group effect ($BF_{10} = 1.6 * 10^{28}$). ¹⁴Bayes factor in favor of the absence of a group effect ($BF_{10} = 0.72$). ¹⁵Bayes factor in favor of the absence of a group effect ($BF_{10} = 0.37$). ¹⁶Bayes factor shows no conclusive evidence of a group effect ($BF_{10} = 0.80$). ¹⁷Bayes factor extremely in favor of a group effect ($BF_{10} = 3.9 * 10^9$). ¹⁸Bayes factor extremely in favor of a group effect ($BF_{10} = 1.5 * 10^{23}$). ¹⁹Bayes factor in favor of the absence of a group effect ($BF_{10} = 0.07$). ²⁰Bayes factor extremely in favor of a group effect ($BF_{10} = 1.14 * 10^9$).

tially normalized to the MNI reference space as described above. Then, the tissue masks provided at <https://www.gaain.org/centiloid-project> were used to calculate the standard uptake value ratios ($SUVR_{CL}$). $SUVR_{CL}$ measures were converted to Centiloid values as recommended for the different amyloid PET traces [37, 41, 42]. Finally, amyloid status of the participants was determined using the cutoff 24.1 CL [41].

Brain volume measurements

The T1-weighted anatomical images were preprocessed using the Computational Anatomy Toolbox (CAT12, v9.6/r7487[43] for Statistical Parametric Mapping 12 (SPM12, v12.6/r1450, Wellcome Centre for Human Neuroimaging, London, UK). The images were segmented into grey matter, white matter, and CSF, followed by spatial normalization to the default CAT12 brain template in Montreal

Neurological Institute (MNI) reference space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm. During this step, the images were resliced to an isotropic voxel size of 1.5 mm, and modulated to adjust for expansion and shrinkage of the grey matter tissue. For basal forebrain volumetry, we applied a mask containing the cholinergic nuclei of the basal forebrain [44] to derive the raw basal forebrain volumes. For hippocampus volumetry we used the harmonized hippocampus segmentation protocol, an internationally driven effort under the auspices of the Alzheimer's Association [45], implemented into an automated volumetry pipeline to ease processing of larger numbers of cases [46]. The raw basal forebrain and hippocampus volume estimates were proportionally scaled to total intracranial volume, i.e., the sum of the grey matter, white matter and CSF maps from the CAT12 segmentation, to adjust for head size.

We dichotomized the brain volumes according to the following procedure: We determined volume W-scores by regressing out age and sex, and used the 15% percentile of the volume W-scores in the healthy control group as threshold for the binary split; i.e., values corresponding to W-scores below the 15% percentile of the control group were classified as smaller and volumes corresponding to W-scores above the 15% percentile as larger volumes.

CSF sampling and AD biomarker assessment

For the DELCODE data, amyloid positivity was determined using CSF A β ₄₂ levels. Biomaterial sampling procedures and biomarker measurements for DELCODE have been described elsewhere [17]. In brief, material was sampled by trained study personal following standard operating procedures (SOP) for collection and storage of samples. CSF samples were aliquoted after centrifugation and stored at -80°C until analysis.

AD markers had been determined using commercially available kits according to vendor specifications: V-PLEX A β Peptide Panel 1 (6E10) Kit (K15200E) and V-PLEX Human Total Tau Kit (K151LAE) (MesoScale Diagnostics LLC,

Rockville, USA), and Innostest Phospho-Tau(181P) (81581; Fujirebio Germany GmbH, Hannover, Germany). Amyloid positivity was determined based on CSF A β ₄₂ levels in the DELCODE data. The cut-off for abnormal concentrations of A β ₄₂ (<496 pg/ml) was derived from the literature, which applied the respective assays [47].

Statistical analysis

Demographic characteristics were compared between diagnostic groups using Bayesian ANOVA and contingency tables as appropriate. We used Jeffreys' Amazing Statistics Program (JASP Version 0.11), available at jasp-stats.org, to calculate the models. We report the Bayes Factor (BF₁₀) quantifying evidence against the null hypothesis.

Prediction of cognitive change by amyloid status and volumes was done using Bayesian generalized mixed effects models with time nested within individuals with random slope and intercept terms, and longitudinal cognitive scores as outcomes. We compared fit of non-Gaussian versus Gaussian models for the dependent variables using posterior predictive checks. We compared 3rd (and 2nd) degree poly-

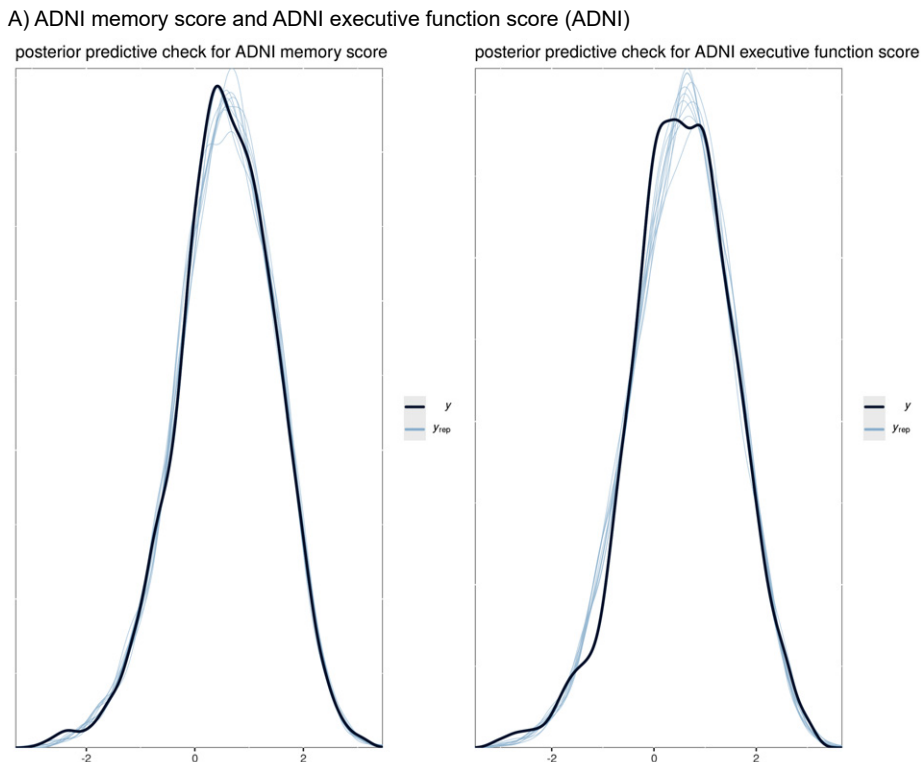
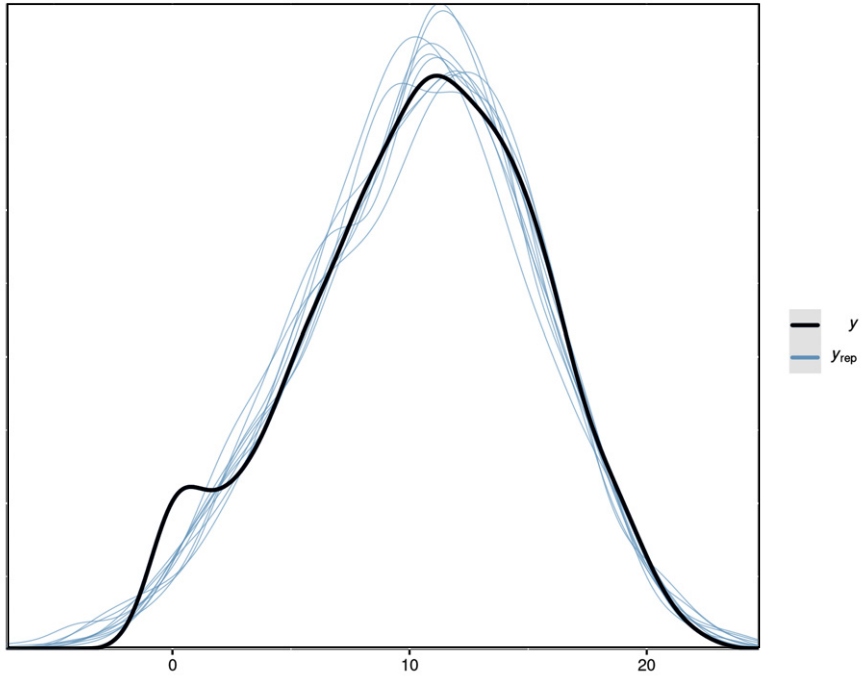


Fig. 1. (Continued)

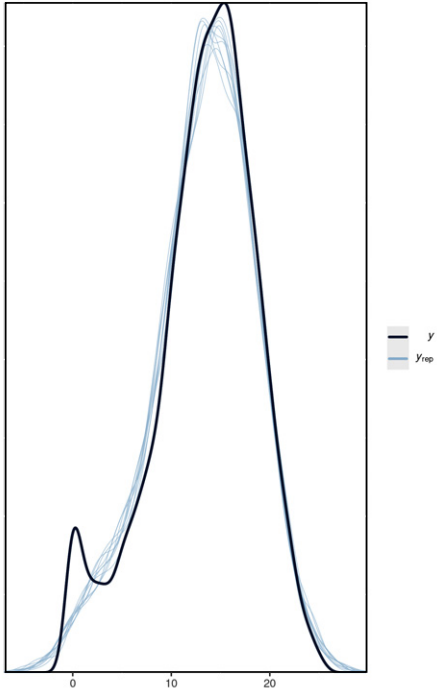
B) Delayed recall score (AIBL)

posterior predictive check for delayed recall



C) WMS logical memory and digit span (DELCODE)

posterior predictive check for WMS logical memory



posterior predictive check for WMS digit span

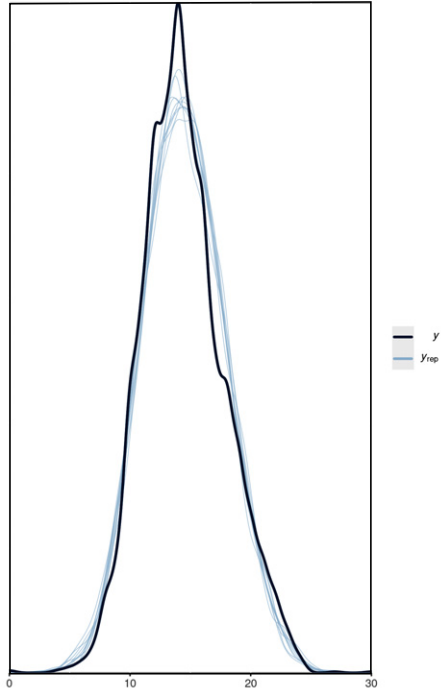


Fig. 1. (Continued)

nomial interaction terms of time by amyloid (and volume) with only a linear interaction term for time using leave one out cross validation in the R library “loo”. These analyses were conducted using library “brms” in R, accessed through R Studio, version 1.1.463. We used the “brms” default uninformative flat priors and in a sensitivity analysis compared outcomes when using very weakly informed priors with a normal distribution of mean 0 and standard deviation of 10.

We derived the individual degree of a practice effect as the slope of the individual cognitive trajectory at baseline. More formally, the slope of the trajectory at $t=0$ equals the value of the first derivative of the cubic function at $t=0$. If the basis function is $a + bt + ct^2 + dt^3$, then its 1st derivative is $b + 2ct + 3dt^2$. Consequently, the derivative at $t=0$ (i.e. the slope of the trajectory at baseline) is equal to the linear component coefficient b . This analysis was only meaningful for the ADNI data where we could fit a cubic function for the cognitive trajectories. Associations of the individual slopes of the trajectory at $t=0$ with age (controlling for amyloid status) and with amyloid and volumes (controlling for age and sex) were conducted using Bayesian ANCOVA models in JASP.

We used a Bayesian random-effects meta-analysis [23] to determine domain specific effects of amyloid (and volumes) on rates of cognitive change across the three cohorts. Rates of cognitive change within each cohort were estimated from generalized mixed effects models with random slope and intercept terms, and age, sex, and diagnosis main effects as confounders. Rates of cognitive change were z-standardized within each cohort. Bayesian random effects meta-analysis was conducted using library “bayesmeta” in R [23]. For the effect size estimates we chose a weakly informed normally distributed prior with mean 0 and standard deviation of 4. The prior for the heterogeneity parameter τ was chosen as a weakly informed half-normal distribution with a standard deviation of 0.5, consistent with a previous systematic review of heterogeneity estimates across a large range of meta-analyses from the Cochrane library [48]. In a sensitivity analysis, we compared effects when using

an uninformative Jeffreys prior for heterogeneity.

Details of the Bayesian analysis are summarized according to the Checklist of Bayesian Analysis Reporting Guidelines [49] in Supplementary Table 1.

RESULTS

Demographic data

We had overall 1,514 cases divided into 548 cases from ADNI, 265 cases from AIBL, and 701 cases from DELCODE (with volume measures available). From the DELCODE sample, we separately analyzed a subset of 416 cases with additionally CSF amyloid measures available. All cases had at least one follow-up cognitive testing. Detailed demographic characteristics are summarized in Table 1. Overall, age was well matched between diagnostic groups within cohorts, except for a maximum mean difference of 4.6 years in the DELCODE sample. Education and sex were very well matched between diagnostic groups across all cohorts. Follow-up times were unbalanced between diagnostic groups within cohorts with a maximum mean difference of 0.9 years in the DELCODE volume sample. AIBL data were unbalanced in respect to diagnostic groups with 231 healthy controls, but only 34 MCI cases.

Gaussian versus non-Gaussian distribution of the dependent variables

We used posterior predictive checks of the draws from the posterior distributions to check if a Gaussian function sufficiently fitted the cognitive outcomes. The posterior predictive checks showed very good fit by a Gaussian distribution for all cognitive outcomes (ADNI memory score, ADNI executive function score, WMS logical memory, WMS logical memory, WMS digit span), see Fig. 1.

Linear versus polynomial function of the predictors

Leave one out cross-validation suggested that a cubic model provided a better fit than a linear model for the ADNI amyloid and volume data (Table 2). In contrast, a cubic model did not provide a better fit than

Fig. 1. Posterior predictive checks for cognitive outcomes. Plots comparing the observed outcome variables y (black line) to simulated datasets y_{rep} (blue lines) from the posterior predictive distribution. The plots show the dependent variables ADNI memory score and ADNI executive function score (ADNI, A), delayed recall score (AIBL, B), and WMS logical memory and digit span (DELCODE, C), and 10 samples each from the posterior distribution. The posterior distribution was assessed from mixed effect regression models, predicting cognitive scores by diagnosis and its interaction term with time and age and sex with random intercept and slope, nested within individuals. We used a Gaussian distribution for all dependent variables.

Table 2
Leave-one-out model fit

ADNI	amyloid		basal forebrain		hippocampus	
	ELPD	SE	ELPD	SE	ELPD	SE
Linear model	-2727.0	77.2	-2744.2	77.9	-2749.0	78.3
Cubic model	-2627.4	77.1	-2634.6	75.1	-2643.8	76.2
Diff (cubic versus linear)	99.6	14.3	109.5	15.8	105.1	14.4
AIBL	amyloid		basal forebrain		hippocampus	
	ELPD	SE	ELPD	SE	ELPD	SE
Linear model	-2610.8	23.8	-2627.2	23.5	-2623.9	23.9
Cubic model	-2613.8	23.5	-2632.2	22.9	-2626.5	23.0
Diff (cubic versus linear)	-3.0	4.2	-5.0	3.5	-2.7	4.1
DELCODE	amyloid		basal forebrain		hippocampus	
	ELPD	SE	ELPD	SE	ELPD	SE
Linear model	-3503.4	26.4	-13978.0	70.5	-13972.4	70.0
Cubic model	-3526.6	26.3	-13991.1	70.0	-13.976.6	69.6
Diff (cubic versus linear)	-18.6	6.0	-13.1	6.3	-4.3	7.2

ELPD, expected log posterior density; SE, standard error; Diff, difference in ELPD between cubic and linear model. Positive values for the ELPD difference between cubic and linear model indicate superior fit of the cubic compared with the linear model, negative values indicate superior fit of the linear model. Only ELPD differences substantially exceeding the SE of the difference should be considered to be relevant [65]. No threshold for this has been established, some authors suggest as a rule of thumb $|\text{ELPD}_{\text{diff}}/\text{SE}_{\text{diff}}| > 4$, highlighted in the table in bold font.

a linear model for either the AIBL or the DELCODE cohort data (Table 2). This was also true, when we fitted quadratic instead of cubic models to the AIBL and DELCODE data (data not shown).

Cognitive change associated with baseline amyloid and volumes

The trajectories of cognitive change, controlled for age and sex, according to diagnosis by amyloid status and volumes, respectively, are shown in Figs. 2–4. We used the best fitting models, i.e., cubic models in time for ADNI, and linear models in time for AIBL, and DELCODE data.

In the ADNI data (Fig. 2A), the amyloid positive MCI cases showed low baseline values of memory and executive function followed by immediate cognitive decline. The amyloid positive cognitively normal controls showed an initial increase of performance followed by pronounced cognitive decline. In contrast, MCI amyloid negative cases remained cognitive stable, whereas the amyloid negative controls showed an initial increase with reversion to baseline levels. A similar pattern arose for the AIBL delayed logical memory recall (Fig. 2B), with decline both in amyloid positive MCI and control cases, and cognitive stability or even increase in the amyloid negative MCI and control cases. Due to the linear models, we could not assess initial increases. Also, the DELCODE data for WMS logical memory recall (Fig. 2C) showed a decline both for amyloid pos-

itive MCI and SCD cases that was separated from the trajectory of the amyloid negative healthy control reference group according to the 95% credibility interval of the regression estimates. MCI amyloid negative cases also showed more pronounced decline than the amyloid negative controls. Different to the ADNI and AIBL findings, logical memory scores were widely stable or even increasing even for amyloid positive healthy controls. The digit span showed decline only for the MCI amyloid positive cases, and relatively stable to increasing performance in the other groups. Similar to the amyloid effects in the ADNI cohort, we found declining trajectories (after an intermediate increase in the controls) for the MCI and control cases with smaller basal forebrain volume, both for memory and executive function scores (Fig. 3A). Only slight decline, after intermediate improvement, occurred in the MCI and control cases with larger basal forebrain volume. In contrast, in the AIBL cohort basal forebrain volume did not differentiate trajectories of delayed recall within the MCI and the healthy controls, respectively (Fig. 3B). In the DELCODE cohort, logical memory showed more decline in amyloid MCI cases with smaller basal forebrain volumes, with stable estimates for MCI cases with larger basal forebrain volumes and increases of performance in healthy controls and SCD cases irrespective of basal forebrain volume (Fig. 3C). Digit span declined in MCI cases irrespective of basal forebrain volume, with increases in the other groups.

For hippocampus volume, in the ADNI cohort trajectories of memory and executive function showed more pronounced decline for MCI cases with smaller hippocampus volumes. All other groups declined as well, however, MCI cases with larger hippocampus volume and healthy controls irrespective of hippocampus volume showed less pronounced cognitive decline (Fig. 4A). Even the healthy controls with large hippocampus volume showed some degree of memory decline, but not of executive function decline. Both control groups, irrespective of hippocampus volume showed initial improvements in performance. In the AIBL cohort, smaller hippocampus volume separated between more or less pronounced decline in

delayed recall both in the controls and the MCI cases (Fig. 4B). In the DELCODE cohort, similar to the basal forebrain volume, logical memory score decline was more pronounced in the MCI cases with smaller hippocampus volume (Fig. 4C). Digit span declined in MCI cases with smaller hippocampus volume, was stable in MCI cases with larger hippocampus volume and increased in the other groups.

When we considered the combination of diagnosis with amyloid status and volume, we found that amyloid positive MCI (control) cases with smaller basal forebrain or hippocampus volumes had most more pronounced rates of memory or executive function decline compared with amyloid negative MCI

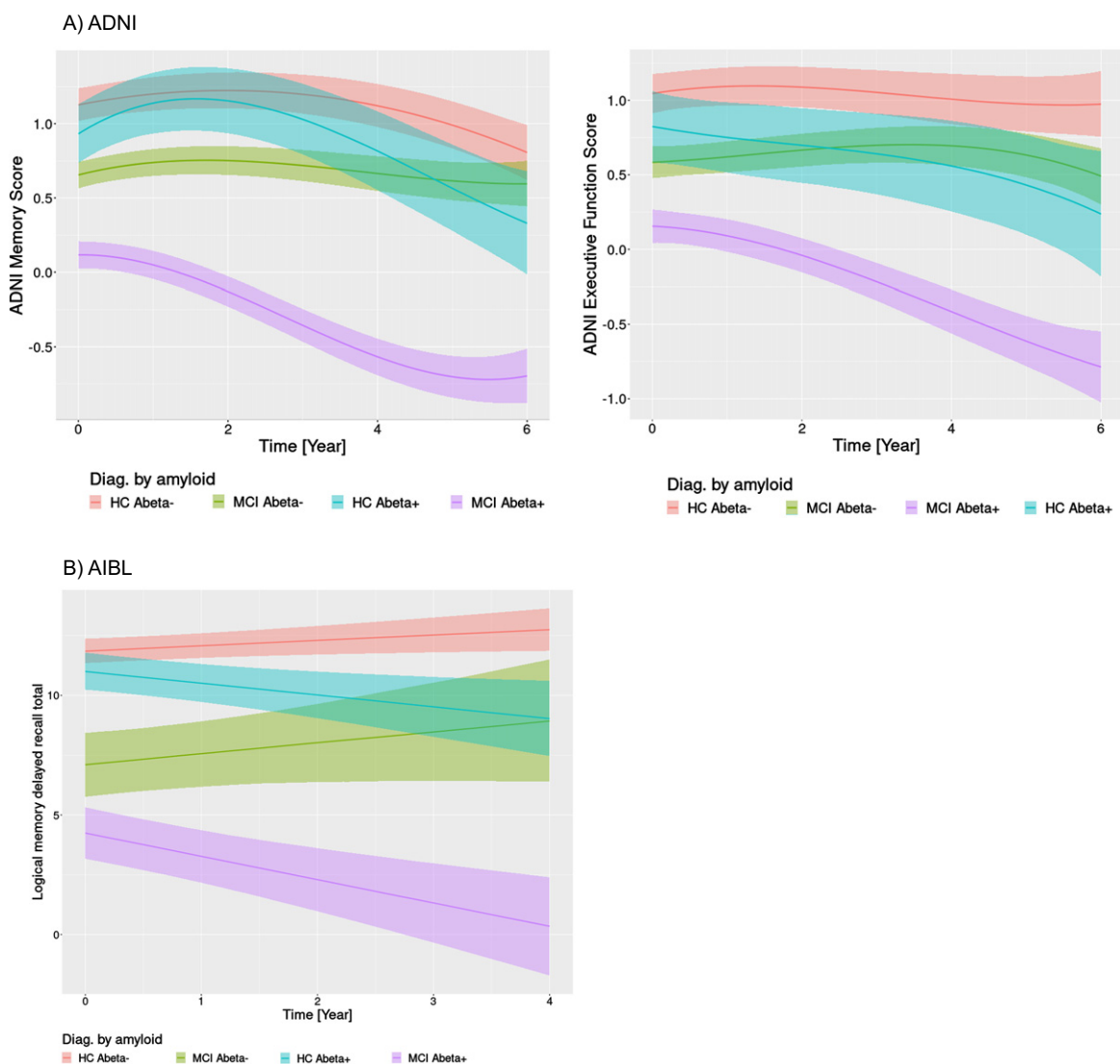


Fig. 2. (Continued)

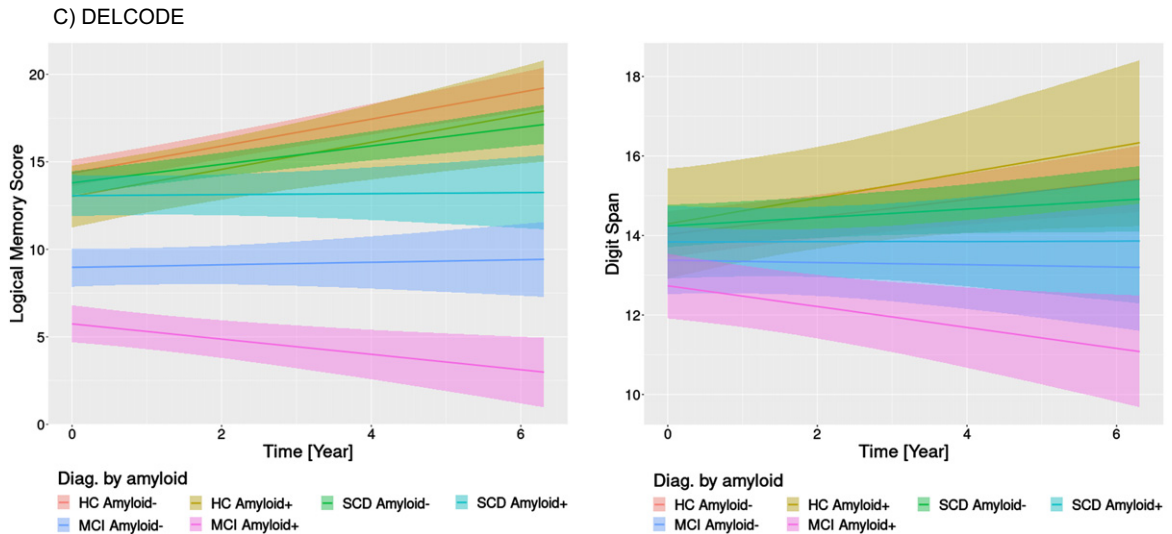


Fig. 2. Cognitive change by diagnosis and amyloid status. Marginal interaction effects of time with amyloid status and diagnosis for ADNI memory and executive function in the ADNI cohort (A), delayed recall of logical memory in the AIBL cohort (B), and delayed recall of logical memory in the DELCODE cohort (C) as dependent variables in generalized mixed effect models predicting cognitive scores by diagnosis, amyloid status, and their interaction with time with random slope and intercept terms, nested within individuals. Trajectories feature the 95% credibility intervals for estimates of change. HC Aβeta-, amyloid negative healthy controls; HC Aβeta+, amyloid positive healthy controls.

(control) cases with larger brain volumes, suggesting an additive effect of pathologies (corresponding trajectories for the ADNI cohort are shown in Supplementary Figures 1 and 2).

Practice effects

We found extreme evidence for an association between age and estimates of practice effects for both memory and executive functions, with lower estimates of the linear slope component at older ages, even after controlling for the effects of group and sex (Supplementary Tables 2A and 3B, Supplementary Figure 3). We found even stronger evidence for a group (diagnosis by amyloid or volume) effect, with lower estimates for amyloid-positive cases and for MCI cases compared with control cases, after controlling for the effects of age and sex (Supplementary Tables 2B and 3B, Supplementary Figure 4).

Meta-analysis

As shown in Fig. 5, mean effect size estimates across the three cohorts for the memory domain and the two cohorts for the executive function domain were in favor of an effect for amyloid and hippocampus volume on memory. The other effects size estimates included zero. In addition, the heterogene-

ity parameter tau was small for hippocampus and memory and medium for amyloid and memory, but was high for the other models, reflecting the small number of studies and suggesting relatively large heterogeneity across the cohorts. All results were preserved when using an uninformative Jeffreys prior for heterogeneity instead of the weakly informative prior (data not shown).

DISCUSSION

We studied trajectories of cognitive decline across three independent cohorts to determine whether amyloid status and basal forebrain and hippocampus volumes were associated with domain specific cognitive decline and differences in practice effects from repeated cognitive testing [50] in healthy older people and preclinical and prodromal AD cases.

Across all cohorts, cognitive outcomes for memory and executive function were fit very well by a normal distribution. This indicates that ADNI memory and executive function score as well as WMS-R/IV delayed recall of logical memory and digit span showed little floor and ceiling effects in older cognitively normal people and prodromal AD patients. Results would likely have been different if AD dementia cases with possible floor effects or high-

performing younger individuals with possible ceiling effects had been included.

Consistent with our first hypothesis and in agreement with previous studies [51, 52], we found associations of amyloid status and brain volumes with rates of cognitive decline across the three cohorts. Confirming previous studies that pooled data across cohorts [52], here we used a Bayesian random-effects meta-analysis to determine heterogeneity of results across cohorts. Amyloid status and hippocampus volume were associated with change in memory with a strong mean effect. Here, the heterogeneity parameter tau indicated small to medium heterogeneity across studies. Heterogeneity was high among executive function models. These results suggest that apparently well-established associations of amyloid and

brain volumes with rates of executive function were heterogeneous across cohorts. As one potential factor, a clinical-neuropathological study suggested that episodic memory is sensitive to many neuropathologies, including AD pathology but also Lewy body disease and TDP-43 pathology, whereas working memory as measure of executive function was only late affected by the different pathologies and less consistently than episodic memory [53]. This would suggest that differences between cohorts for example in respect to stages of disease and underlying pathologies may have less effect on the heterogeneity between cohorts in estimates of rates of episodic memory than executive function change.

Meta-analysis across several cohorts allows assessing how stable effects are across cohorts which

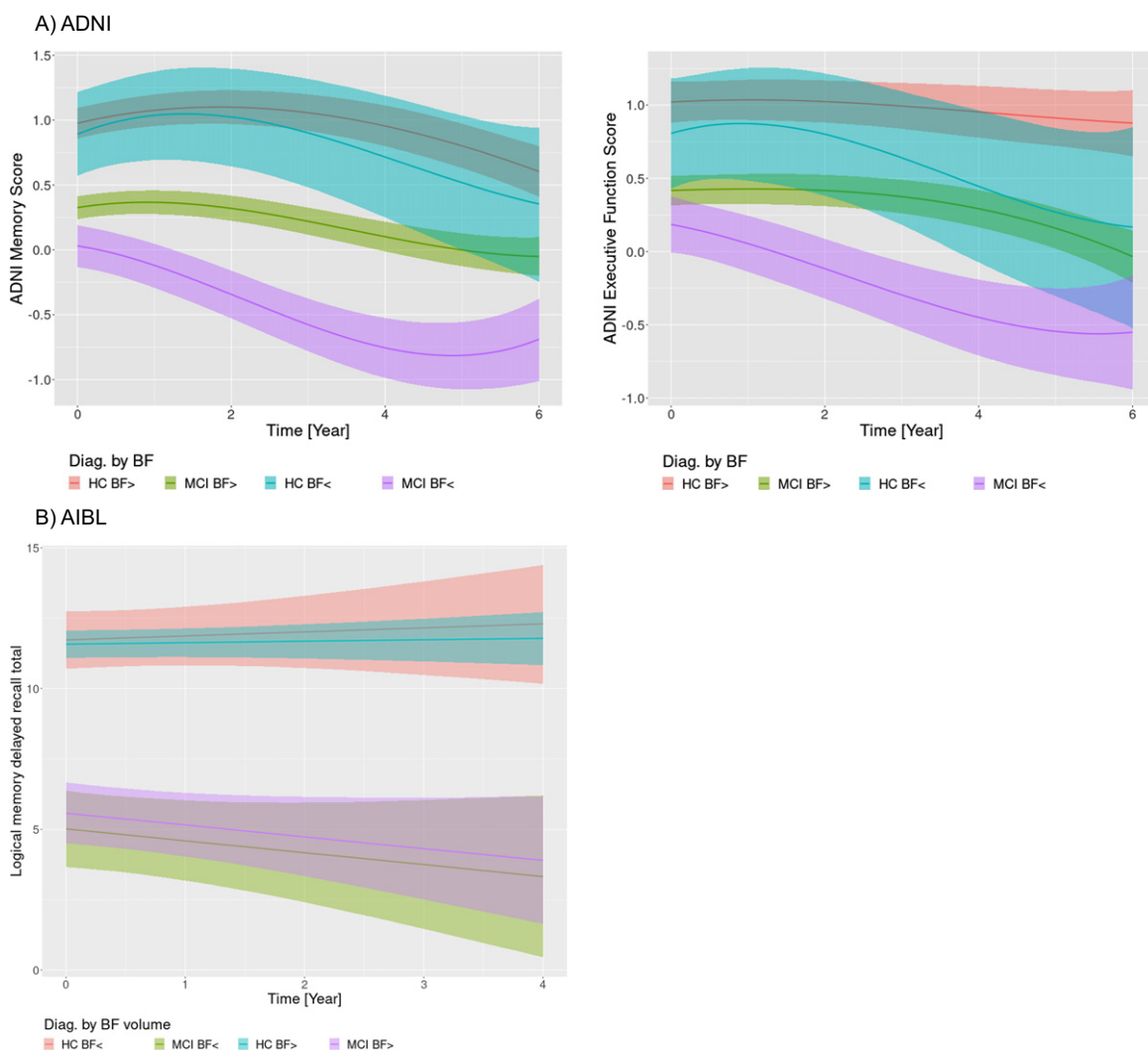


Fig. 3. (Continued)

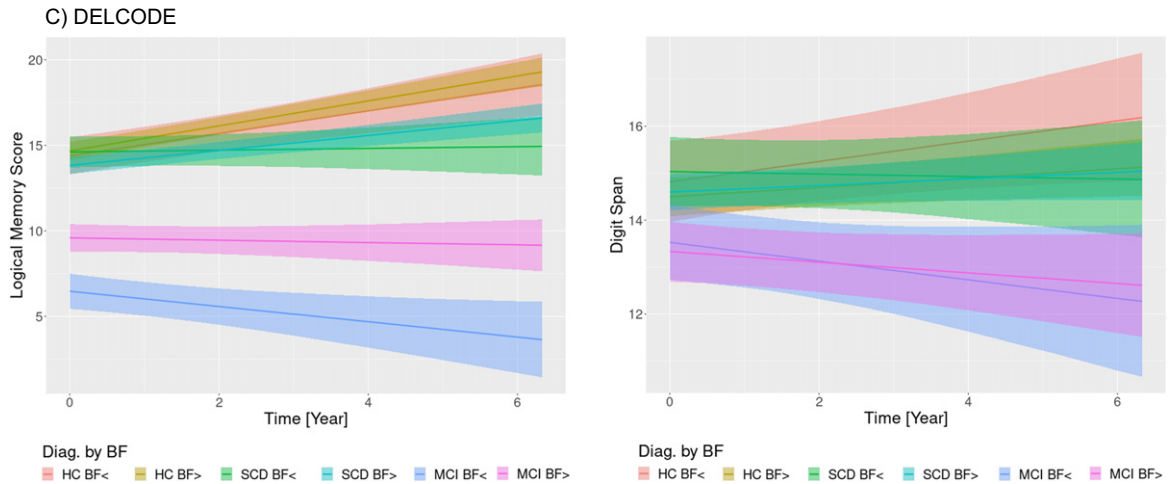


Fig. 3. Cognitive change by diagnosis and basal forebrain volume. Marginal interaction effects of time with basal forebrain volume (atrophy versus no atrophy) and diagnosis for ADNI memory and executive function in the ADNI cohort (A), delayed recall of logical memory in the AIBL cohort (B), and delayed recall of logical memory in the DELCODE cohort (C) as dependent variables in generalized mixed effect models predicting cognitive scores by diagnosis, basal forebrain volume, and their interaction with time with random slope and intercept terms, nested within individuals. Trajectories feature the 95% credibility intervals for estimates of change. HC BF>, healthy controls without basal forebrain atrophy; HC BF<, healthy controls with basal forebrain atrophy.

is particularly relevant for heterogeneous outcomes such as executive function. The WMS delayed logical memory scores and the ADNI composite measures of memory and executive function provided a good separation of trajectories across the three cohorts. In contrast, only the amyloid positive MCI cases had a distinct trajectory in WMS digit span, whereas the credibility intervals for the executive function trajectories of other groups in DELCODE largely overlapped. In a sensitivity analysis we used the ratio of TMT-B to A as alternative measure of executive function [32], but the overlap of trajectories was even more pronounced than for digit span. One solution to this problem could be the use of composite measures of executive function, such as the ADNI executive composite, to compensate for the high intraindividual variability of single scores. Such composite scores derived from a confirmatory factor analysis are available for the DELCODE baseline data [54, 55], but are still in progress for the longitudinal data.

Consistent with our expectation, a nonlinear model of cognitive change was superior to a linear model in the ADNI data. We found extreme evidence for an association of memory and executive function practice effects with age and amyloid and brain volume status. The amyloid negative and positive healthy controls and the amyloid negative MCI cases showed an initial increase of memory performance, indicating practice effects from repeated testing that was lost in amyloid positive MCI cases. For executive func-

tion, only amyloid negative controls and MCI cases showed evidence for a practice effect that was lost in amyloid positive controls and MCI cases. Results were similar for basal forebrain and hippocampus volumes with absence of practice effects in MCI cases with smaller volumes. These findings are consistent with the observation of a previous study that only cognitively normal people who remained cognitively stable over several years of follow up showed practice effects compared with cognitively normal people who later developed AD type cognitive impairment [3]. This previous study [3] had used linear least square estimates of slope, whereas in the current study we used the first derivative from the cubic trajectory of the individual-level change at baseline to identify practice effects. The former approach is more accessible, whereas the latter approach accounts for the likely nonlinear nature of cognitive decline and assesses the slope at baseline rather than over all or most of the observation period. Another study used continuous time structural equation modeling to determine practice effect components in longitudinal change of memory performance in aging and AD spectrum cases [56]. This approach describes cognitive change through latent factors, where the practice effect factor is partly estimated from repeated tests at each time point. This approach is more explicit in the operationalization of the practice effect than our or previous approaches; however, it requires repeated measures at each time point which are not available

from all cohort repositories and not for composite measures. At the same time, it will be interesting to compare different approaches for assessing practice effect in future studies.

Another study found that absence of practice effects was predictive of more pronounced cognitive decline in MCI cases [3, 57]. Again, our finding of smaller practice effects in amyloid positive compared with amyloid negative cases agrees with this previous report, suggesting that prodromal AD cases, characterized by the presence of amyloid or progressive cognitive decline, lose the practice effect for episodic memory. In addition, we found lower practice effects with higher age, even when controlling for amyloid and diagnosis, consistent with some [56, 58], but not all [59] previous reports.

When stratifying according to basal forebrain volume, healthy controls with a larger basal forebrain volume had a higher probability for a practice effect for memory and executive performance compared with MCI cases, but not compared with controls with smaller basal forebrain volume. This indicates that not basal forebrain volume but rather control of MCI status was driving differences in practice effect. In contrast, when using hippocampus volume, only healthy controls with larger hippocampus volume showed practice effects for memory performance which was lost in MCI patients irrespective of hippocampus volume and in healthy controls with smaller hippocampus volume. This effect of hippocampus volume was much less pronounced for executive function. These findings are consistent with

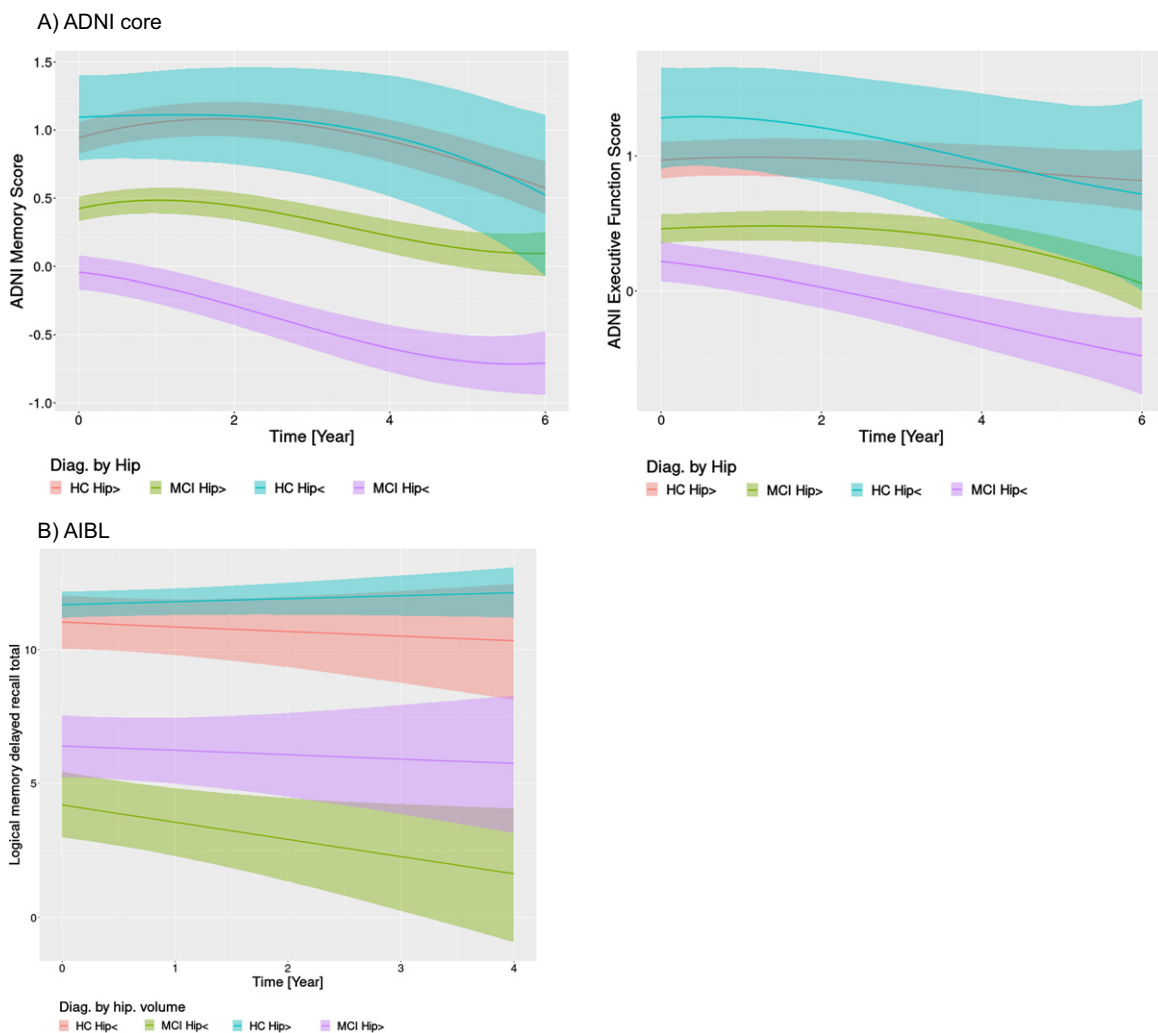


Fig. 4. (Continued)

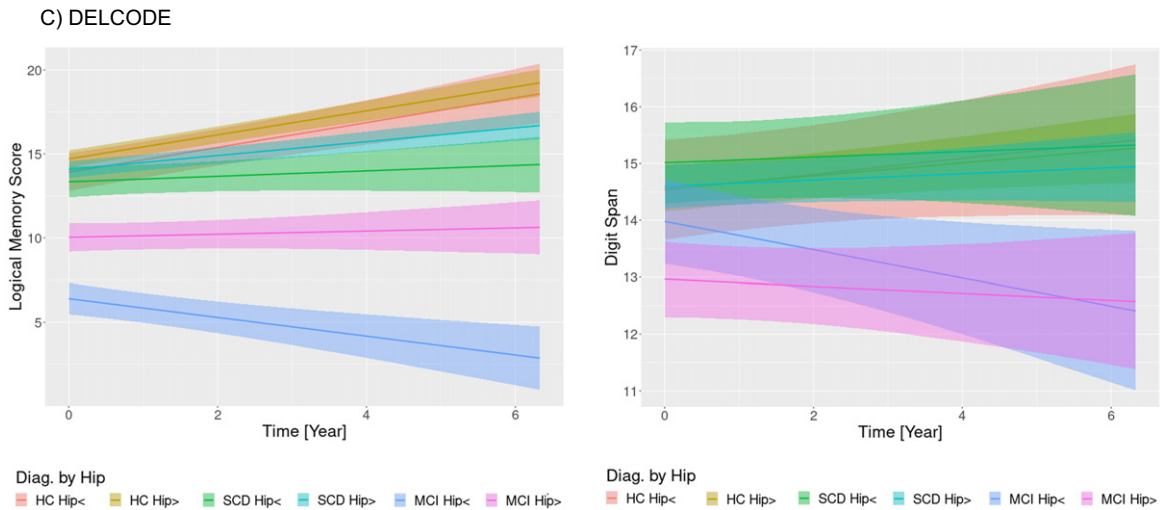


Fig. 4. Cognitive change by diagnosis and hippocampus volume. Marginal interaction effects of time with hippocampus volume (atrophy versus no atrophy) and diagnosis for ADNI memory and executive function in the ADNI cohort (A), delayed recall of logical memory in the AIBL cohort (B), and delayed recall of logical memory in the DELCODE cohort (C) as dependent variables in generalized mixed effect models predicting cognitive scores by diagnosis, hippocampus volume, and their interaction with time with random slope and intercept terms, nested within individuals. Trajectories feature the 95% credibility intervals for estimates of change. HC Hip>, healthy controls without hippocampus atrophy; HC Hip<, healthy controls with hippocampus atrophy.

the association of hippocampus volume with episodic memory function [60]. They may indicate that in cognitively normal older people absence of a practice effect for episodic memory may point to hippocampal volume loss, although other factors can of course account for it as well. In a cohort of 190 cognitively normal people absence of practice effect was associated with a metabolic signature suggestive of AD type neurodegeneration in FDG-PET, irrespective of amyloid status [61]. Here, we found that practice effects for memory in healthy controls depended on hippocampus atrophy. Both FDG-PET and hippocampal volume may serve as proxy markers of neurodegeneration [62] and were associated with loss of practice effect for memory performance in cognitively healthy controls.

Interestingly, in the AIBL and DELCODE cohorts a cubic and a quadratic model were not superior or even inferior to a linear model. We can speculate that the overall increase of performance in the healthy controls and the amyloid negative MCI and (in the DELCODE sample) amyloid negative SCD cases may reflect an underlying practice effect. However, we would be reluctant to evaluate a positive slope of a linear trajectory over the entire observation period as a practice effect. This is different from an initial increase in performance after baseline, as identified by the first derivative of the polynomial trajectory of change. Factors other than a practice effects could

cause positive linear slopes in performance, such as a survival effect that occurs later in the observation period.

The discrepancy findings between the ADNI cohort and the other two cohorts in the fit of linear and non-linear models may point to a requirement of non-linear models: the need of a sufficient number of time points to allow a reliable estimate of a non-linear effect. Even with a Bayesian approach we could not obtain a stable polynomial estimate for the AIBL and DELCODE samples which had at least one observation time point less compared with the ADNI data.

Our study has several limitations. First, there was no consistent outcome measure for the memory and executive domain across the three cohorts. This limited the comparability of findings between the cohorts and is mirrored in the heterogeneity estimates of the meta-analysis. At the same time, this degree of heterogeneity is prevalent across clinical cohort studies and needs to be considered by the analysis strategy. Here, we chose explicit modeling of this heterogeneity in the Bayesian random effect meta-analysis, using a sensitivity analysis for the heterogeneity prior. Improving the replicability of clinical research [63] will require a major effort in harmonizing study and analysis designs and in using analyses capable of modeling heterogeneity itself. Therefore, the inclusion of multiple cohorts and the use of meta-analyses

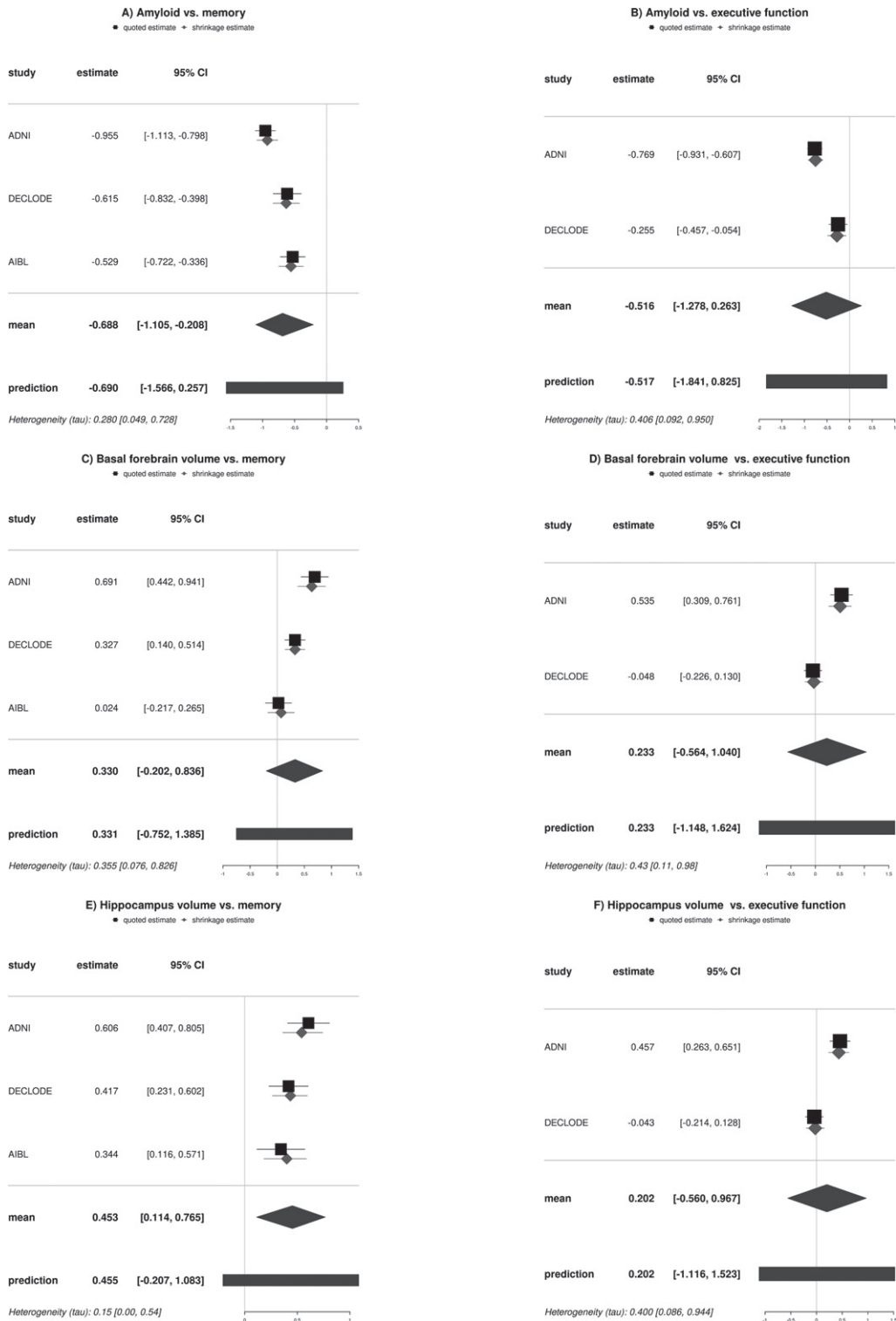


Fig. 5. Forest plots of amyloid and volume effects on cognitive outcomes. The forest plots feature the direct and indirect estimates of amyloid and volume effects separated for memory and executive outcomes across the cohorts. Estimates are based on Bayesian random effect meta-analysis models with weakly informative effect priors (normal (mean=0, standard deviation=4)) and heterogeneity priors (halfnormal (scale=0.5)). 95% CI, 95% credibility interval.

and Bayesian approaches to test the impact of a priori assumptions may help improving replicability in the future. Secondly, access to data from the AIBL cohort was limited so that we could not model executive domain changes. In future, full access to all publicly funded cohorts will be required in order to achieve maximum output for clinical research. However, it should be noted that access to German DELCODE data is also currently restricted, so we still have a long way to go to implement FAIR data sharing principles [64]. Thirdly, the method to determine amyloid status varied between cohorts. In ADNI and AIBL, we used amyloid PET data, in DELCODE CSF A β ₄₂ levels. This will likely have contributed to heterogeneity, at the same time it encourages us to believe that the consistent findings for memory across cohorts reflect robust effects.

In summary, we found robust effects of amyloid status and hippocampus volume on change in memory performance across three independent cohorts, but more heterogeneous effects of basal forebrain and of all markers on executive function. Modeling non-linear trajectories of cognitive change in the ADNI data suggested initial increases of cognitive performance, possibly reflecting practice effects, in healthy controls and partly in MCI cases who were amyloid negative or had intact brain volumes. Similar effects could not be tested in the AIBL and DELCODE cohorts because the available number of time points did not allow for stable estimation of polynomial effects even in a Bayesian framework. We hope that our analyses have illustrated the power of Bayesian analysis not only to test likelihood for the absence of an effect but to directly quantify the evidence in favor or against the presence of an effect, to assess the degree of heterogeneity, and to conduct sensitivity analyses to estimate to which degree prior assumptions may influence the outcome.

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CONFLICTS OF INTEREST

SJT participated in scientific advisory boards of Roche Pharma AG, Biogen, Grifols, and Eisai and is member of the independent data safety and monitoring board of the Study ENVISION (Biogen).

DATA AVAILABILITY

Anonymized data from DELCODE used in this article will be made available by request from any qualified investigator through the DELCODE Steering Board for purposes of replicating procedures and results. The data from ADNI and AIBL are available through the central data repository hosted on LONI (<https://ida.loni.usc.edu/login.jsp>). Metrics derived from these public data for the current study, such as basal forebrain and hippocampus volumes, will be made available by request from any qualified investigator by the corresponding author.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/ADR-230027>.

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