Neuronal injury biomarkers for assessment of the individual cognitive reserve in clinically suspected Alzheimer’s disease

Leonie Beyera,1, Jonas Schnabela,1, Philipp Kazmierczab, Michael Ewersc, Sonja Schöneckerd, Catharina Prid, Johanna Meyer-Wilmesa, Marcus Unterrainera, Cihan Catake, Oliver Pogarelf, Robert Perneckyc,f,h,i, Nathalie L. Albertj, Peter Bartensteina,j, Adrian Danekd, Katharina Buерgerc,e, Johannes Levind, Axel Romingera,g,j, Matthias Brendela,j,⁎

⁎ Corresponding author at: Department of Nuclear Medicine, University of Munich, LMU Munich, Marchioninistraße 15, 81377 Munich, Germany.
E-mail address: matthias.brendel@med.uni-muenchen.de (M. Brendel).
1 Contributed equally.

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ABSTRACT

Objectives: Many predictive or influencing factors have emerged in investigations of the cognitive reserve model of patients with Alzheimer’s disease (AD). For example, neuronal injury, which correlates with cognitive decline in AD, can be assessed by [18F]-fluorodeoxyglucose positron-emission-tomography (FDG-PET), structural magnetic resonance imaging (MRI) and total tau in cerebrospinal fluid (CSFtotal tau), all according to the A/T/N-classification. The aim of this study was to calculate residual cognitive performance based on neuronal injury biomarkers as a surrogate of cognitive reserve, and to test the predictive value of this index for the individual clinical course.

Methods: 110 initially mild cognitive impaired and demented subjects (age 71 ± 8 years) with a final diagnosis of AD dementia were assessed at baseline by clinical mini-mental-state-examination (MMSE), FDG-PET, MRI and CSFtotal tau. All neuronal injury markers were tested for an association with clinical MMSE and the resulting residuals were correlated with years of education. We used multiple regression analysis to calculate the expected MMSE score based on neuronal injury biomarkers and covariates. The residuals of all neuronal injury biomarker regressions correlated significantly with education level, indicating them to be surrogates of cognitive reserve. A positive residual was associated with faster cognitive deterioration at follow-up for the residuals of stand-alone FDG-PET (R = −0.36, p = .01) and the combined residualized memory function model (R = −0.35, p = .02).

Conclusions: These findings suggest that subjects with higher cognitive reserve had accumulated more pathology, which subsequently caused a faster cognitive decline over time. Together with previous findings suggesting that higher reserve is associated with slower cognitive decline, we propose a biphasic reserve effect, with an initially protective phase followed by more rapid decomposition once the protection is overwhelmed.

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1. Introduction

Alzheimer’s disease (AD), being the most common form of neurodegenerative dementia, is having an enormous impact on health care systems in societies with aging populations (Ziegler-Graham et al., 2008). In the majority of clinical routine settings, the diagnosis of AD is still based on clinical and behavioural changes and exclusion of other medical causes. Classically, a firm diagnosis of AD required post mortem neuropathological findings of intracellular neurofibrillary tangles and extracellular amyloid plaques (Braak and Braak, 1991) but in recent years, in vivo biomarkers are emerging as sufficient diagnostic criteria for AD (Dubois et al., 2014; McKhann et al., 2011; Jack Jr et al., 2018). This diagnosis derives from the non-invasive detection of the hallmark pathologies of β-amyloid (Aß) and tau-positivity, plus neurodegeneration/neuronal injury, which are together known as the A/T/N classification scheme (Jack Jr et al., 2016).

In the A/T/N scheme, positron emission tomography (PET) with specific ligands for Aß or tau and/or cerebrospinal fluid (CSF) measurements give readouts for abnormal protein aggregates in living brain. Neurodegeneration/neuronal injury is detected by T1-weighted magnetic resonance imaging (MRI), providing a measure of grey matter atrophy in key regions such as the hippocampus, ventricular dilation, or sulcal widening (Jack et al., 2010). Alternately, measurement of total soluble tau proteins in the CSF serves as an indicator of global neuronal injury (Bartlett et al., 2012). Finally, PET with [18F]-fluorodeoxyglucose (FDG) can reveal reduced cortical glucose utilization, which is indicative of the impaired synaptic dysfunction in AD subjects compared to age-matched healthy controls (Mosconi et al., 2008). In general, scores for the several biomarkers of neurodegeneration/neuronal injury all correlate with the severity of AD pathology post mortem (Landau et al., 2010), supporting their use in diagnostics. Nonetheless, results of a recent investigation underlined the limited agreement between binarized read-outs of neuronal injury biomarkers (Alexopoulos et al., 2014).

The contemporary concept of cognitive reserve as a moderating factor between the extent of neurodegeneration and clinical deterioration entails a complex model wherein many different protective environmental factors contribute to cognitive reserve, in particular the number of years of education (YoE) (Yoon et al., 2016), but also occupational complexity (Andel et al., 2006; Potter et al., 2008), extent of intellectual activities during leisure time (Wilson et al., 2002; Verghese et al., 2003), or higher physical fitness (Okonkwo et al., 2014; Tolpapanen et al., 2015; Duzel et al., 2016). Different imaging findings suggest that both structural and functional brain differences may underlie cognitive reserve, e.g. a larger premorbid brain volume (Perneckzy et al., 2010) or greater left frontal cortex connectivity (Franzmeier et al., 2018).

How exactly to quantify cognitive reserve is another matter. Cognitive reserve is conceptualized as the extent to which cognitive performance exceeds what might be expected from the level of brain pathology. Residualized cognitive performance (after regression of pathology markers) has been previously suggested as an objective marker of reserve predictive for future cognitive changes in aging and AD (Reed et al., 2010). However, it remains uncertain which marker(s) of brain pathology should be used to estimate the expected level of cognitive performance. Here, we propose to use the neurodegeneration biomarkers that were recently introduced for the purely biomarker-based A/T/N staging system of AD (Jack Jr et al., 2016), where “A” stands for PET assessment of amyloidosis, “T” for CSF assessment of total tau pathology (CSFtau), and “N” stands for neurodegeneration illustrated by structural MRI.

Thus, we first correlated biomarkers for neuronal injury in a series of patients with their individual cognitive status measured by MMSE and tested for an association of individual residuals with YoE as a predictor of cognitive reserve. We then created a model based on biomarkers of neuronal injury along with relevant covariates for AD to calculate the expected individual cognitive performance. Finally, we tested if the discrepancy between measured and model-derived cognitive performance, as a surrogate of cognitive reserve, could predict cognitive deterioration in later follow-up at the single patient level.

2. Methods

2.1. Study design and patient enrollment

The study included patients with mild cognitive impairment (MCI) or mild to moderate AD dementia, all confirmed as having AD dementia in clinical follow-up (27 ± 13 months). The subjects were recruited and scanned in a clinical setting at the University of Munich Department of Nuclear Medicine between 2010 and 2016. Patients had been referred by the Departments of Neurology, Psychiatry and Institute for Stroke and Dementia Research. The local ethics committee approved analysis of the anonymized data (application 399–09). All subjects underwent clinical dementia workup, including detailed cognitive testing, structural MRI, CSF-examination, and FDG-PET. Requirements for inclusion were clinically suspected AD, an available structural MRI, and a CSF-examination. Confirmation of AD during a clinical follow-up of ≥12 months was obligatory for inclusion. Patients with insufficient clinical data (e.g. no clinical follow-up confirming the suspected diagnosis) were excluded. Further exclusion criteria were stroke, major depression, cerebral manifestation of malignancies, and other severe neurological or psychiatric disorders.

2.2. Clinical assessment and cognitive testing

We first conducted a clinical neurological examination and neuropsychological testing consisting of the CERAD plus battery which includes the Mini-Mental-State Examination (MMSE) (Folstein et al., 1975), Trail-Making Test A and B, as well as verbal fluency tests (Morris et al., 1989; Chandler et al., 2005). A summed CERAD score was assembled according to (Chandler et al., 2005). YoE was recorded, and laboratory parameters for metabolic causes of cognitive impairment (vitamin B12, thiamine and folate levels, thyroid and liver function) were assessed.

2.3. MRI

MRI was performed (1.5/3.0 Tesla magnets) using a T1w sequence for atrophy assessment and a T2w-FLAIR sequence for screening of leukoencephalopathy. The hippocampal atrophy as a biomarker for neuronal injury was rated visually by an expert in Radiology, using the Scheltens-Scale for medial temporal lobe atrophy, which ranges from 0 to 4 (for representative T1 MRI images see Fig. 1) (Scheltens et al., 1992). A summed score was assembled for both hemispheres. In addition, white matter lesions visible on T2 MRI images were assessed using the Fazekas-Score (ranging from 0 to 3) by the same expert (Fazekas et al., 1987; Kim et al., 2008).

2.4. CSF

Lumbar CSF was collected for measurement of phosphorylated tau (previously established threshold for abnormal p-tau: 61 pg/ml) and total tau by radioimmunoassay (previously established threshold: 450 pg/ml) (Meredith Jr et al., 2013).

2.5. FDG-PET imaging

2.5.1. FDG PET acquisition

FDG was purchased commercially. FDG-PET images were acquired using a 3-dimensional GE Discovery 690 PET/CT scanner or a Siemens ECAT EXACT HR + PET scanner. All patients fasted for at least six hours, and had a plasma glucose level < 120 mg/dl (6.7 mM) at time of
tracer administration, when a dose of 140 ± 7 MBq [18F]-FDG was injected as a slow intravenous bolus while the subject sat quietly in a room with dimmed light and low noise level. A static emission frame was acquired from 30 min to 45 min p.i. for the GE Discovery 690 PET/CT, or from 30 min to 60 min p.i. for the Siemens ECAT EXACT HR+ PET scanner. A low-dose CT scan (GE) or a transmission scan with external 68Ge-sources (Siemens) was performed prior to the static acquisition for attenuation correction. PET data were reconstructed iteratively (GE) or with filtered back-projection (Siemens).

2.5.2. Visual analysis of FDG PET

For visual image interpretation of FDG-PET images, three-dimensional stereotactic surface projections (3D-SSP) (Minoshima et al., 1995) were generated using the software Neurostat (Department of Radiology, University of Washington, Seattle, WA, U.S.A.). An expert in Nuclear Medicine visually assessed the 3D-SSP images using tracer uptake and Z-score maps (with global mean scaling). Voxel-wise Z-scores were calculated in Neurostat by comparing the individual tracer uptake to historical FDG-PET images from a healthy age-matched cohort (n = 18). The reader had access to clinical information and structural imaging, which was conducted in all cases. To allow a visual based quantification, we applied a simplified approach of the t-sum method published by Herholz and coworkers (Herholz et al., 2002). Preselected AD-typical regions in FDG-PET (bilateral parietal lobe, temporal lobe and posterior cingulate cortex) were rated based on the surface projections into four grades of neuronal injury ranging from 0 (no neuronal injury) to 3 (severe neuronal injury), with representative images shown in Fig. 2. A combined FDG-PET Score (0–18) was calculated by summing the values for all six regions.

2.5.3. Semiquantitative analysis of FDG PET

Semi-quantitative analysis of FDG uptake was performed to validate the visual findings. All individual FDG-PET image volumes were registered to an in-house FDG-PET template within the MNI space (Daerr et al., 2017) using PMOD software (version 3.5, PMOD Technologies Ltd., Zürich, Switzerland). We measured the mean activity within bilateral parietal and temporal volumes of interest (VOIs: posterior cingulate gyrus, superior parietal gyrus, remaining parietal lobe, posterior temporal lobe, middle temporal gyrus) of the Hammers atlas (Hammers et al., 2003), corresponding to the affected regions seen in Fig. 2. Measured regional activities were scaled to standardized uptake value ratios relative to a cerebellum reference region.

2.6. Calculations and statistical analysis

Scheltens-Scale scores, CSF\textsubscript{1\textsubscript{tau}} concentrations and FDG-PET readouts were correlated with clinical MMSE-Scores (MMSEOBSERVED), corrected for age, gender and the severity of white matter lesions (Fazekas-Score) and the residuals (RES\textsubscript{PET}, RES\textsubscript{MRI}, RES\textsubscript{CSF}) were archived. The residuals of all regression analyses were correlated with YoE.

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Fig. 1. Evaluation scheme for magnetic resonance imaging. Representative T1 structural MR images for a Scheltens-Score 0 (no atrophy), 1 (only widening of choroid fissure), 2 (also widening of temporal horn of lateral ventricle), 3 (moderate loss of hippocampal volume, decrease in height) to 4 (severe volume loss of hippocampus).

Fig. 2. Evaluation scheme for positron emission tomography. Representative three-dimensional stereotactic surface projections (3D-SSP) of normalized tracer uptake from right lateral (upper row) and left medial (bottom row) for no (0), mild (1), moderate (2) and severe neuronal injury (3) in all six Alzheimer’s disease typical regions.
A regression analysis was performed by a model including the three A/T/N biomarkers of neuronal injury, YoE, and covariates (age, gender, leukoencephalopathy) as predictors to anticipate the MMSE score and calculate a MMSE score based on the biomarkers of neuronal injury (MMSEPREDICTED = MMSE neuronal injury). A surrogate score for the individual cognitive reserve was calculated by ΔMMSE = MMSEOBSERVED - MMSEPREDICTED. ΔMMSE was compared to the natural variance of the MMSE methods using standard deviations (SD) of historical test-retest analyses (Tombaugh, 2005).

Clinical deterioration was measured by clinical follow-up assessment of at least 12 months. Each subject’s annual rate of decline in MMSE-score was correlated with the residuals using only a single method of the MMSE methods using standard deviations (ΔMMSE, see Fig. 4). When comparing the individual surrogate score to the published SD of an MMSE test-retest (Tombaugh, 2005), 49.0% of subjects had surrogate score magnitudes exceeding more than one SD (± 2.37) and 15.5% more than two SDs (± 4.74).

Importantly, age had no impact on the observed distribution of surrogate scores of cognitive reserve (R = 0.00, p = .99; see Supplement Figure 3).

3.4. Prediction of individual cognitive decline by neuronal injury based residualized memory function

Finally, we asked if the calculated surrogate score for cognitive reserve in the single subject has clinical relevance for predicting disease progression. The mean annual MMSE change (n = 110) was −1.55 (± 2.41). ΔMMSE (β = −0.35, p = .02) and RESPET (β = −0.36, correlations for CERAD plus battery scores are presented in Supplement Figure 1). Visual and semi-quantitative FDG-PET read-outs likewise showed highly congruent results (R = 0.70, p < .01, see Supplement Figure 2), so we elected to use the clinically common visual read-out of surface projections in the regions known to be affected in AD for further analyses.

FDG-PET grading showed the highest association with the MMSEOBSERVED score (β = −0.49, p < .001) than did grading of the hippocampal volume in MRI (β = −0.15, p = .14) and the CFSF-tau level (β = −0.12, p = .22; see Fig. 3A–C); FDG-PET, age, gender, and leukoencephalopathy accounted for 21% of the variance in MMSEOBSERVED (F(4,106) = 8.2, p < .01, R² = 0.24, R²(Adjusted) = 0.21). The hippocampal volume in MRT together with age, gender, and leukoencephalopathy accounted for 1% of the variance in MMSEOBSERVED (F(4,106) = 1.4, p = .24, R² = 0.05, R²(Adjusted) = 0.01).

The correlation of regression residuals (RESPET, RESMRID, RESCSF) with the YoE revealed significant positive associations for all three biomarkers (MRI: R = 0.35, p < .01; CSF: R = 0.35, p < .01; PET: R = 0.39, p < .01) (see Fig. 3D–F), indicating that the discrepancies between biomarker results and clinically assessed MMSE may also serve as a proxy of cognitive reserve.

Leukoencephalopathy, as assessed with the Fazekas-Score, did not have a significant correlation with baseline cognitive performance (R = 0.08, p = .42).

3.3. Regression model of neuronal injury based cognitive performance

3.3.1. Multiple regression model

Next, we computed a regression model to assess the factors influencing the current cognitive performance. FDG-PET and YoE significantly explained some of the variance in the calculation of MMSEPREDICTED score predicted by the model of neuronal injury biomarkers and covariates (for details see Table 2).

Using the calculated weighting factors, the individually predicted MMSEPREDICTED score was generated using the following formula:

\[
\text{MMSEPREDICTED} = 20.810 - (0.592 \times \text{FDG}) - (0.046 \times \text{Scheltens}) - (0.0004 \times \text{CSF}) - (0.028 \times \text{Fazekas}) - (0.483 \times \text{YoE}) - (0.499 \times \text{Gender}) - (0.002 \times \text{Age})
\]
indicated a significant negative association with the annual MMSE change upon clinical follow-up (see Fig. 5). ΔMMSE, age, and gender together accounted for 16% of the variance in annual MMSE change ($F(3,107)=4.0$, $p=.01$, $R^2=0.21$, $R^2_{\text{Adjusted}}=0.16$); RES PET, age and gender likewise accounted for 17% of the variance in annual MMSE change ($F(3,107)=4.3$, $p=.01$, $R^2=0.23$, $R^2_{\text{Adjusted}}=0.17$). Single RES MRI ($\beta=-0.23$, $p=.10$) and RES CSF ($\beta=-0.23$, $p=.11$) did not show a significant correlation with the annual MMSE change.

Thus, patients whose present cognition seemed at odds with their manifest signs of neuronal injury by biomarker grading showed worse cognitive deterioration in the clinical follow up. Among single neuronal injury markers, the residuals of FDG-PET indicated the strongest predictive value.

### Table 2

Regression coefficients of the biomarker based model. Regression coefficients, $\beta$-values and significance levels of the multiple regression analysis for the calculation of the neuronal injury biomarker based anticipated mini mental status examination.

| Regression coefficient | $\beta$ | $p$ |
|------------------------|---------|-----|
| Constant               | 20.810  | .000|
| FDG-PET visual         | -0.592  | -0.505| .000|
| Scheltens-Score        | 0.046   | 0.021| .814|
| CSF totaltau           | 0.0004  | 0.030| .723|
| Fazekas score          | -0.028  | 0.003| .967|
| Years of Education     | 0.483   | 0.355| .000|
| Gender                 | -0.499  | -0.058| .490|
| Age (y)                | 0.002   | 0.004| .968|

$p = .01$ indicated a significant negative association with the annual MMSE change upon clinical follow-up (see Fig. 5). ΔMMSE, age, and gender together accounted for 16% of the variance in annual MMSE change ($F(3,107)=4.0$, $p=.01$, $R^2=0.21$, $R^2_{\text{Adjusted}}=0.16$); RES PET, age and gender likewise accounted for 17% of the variance in annual MMSE change ($F(3,107)=4.3$, $p=.01$, $R^2=0.23$, $R^2_{\text{Adjusted}}=0.17$). Single RES MRI ($\beta=-0.23$, $p=.10$) and RES CSF ($\beta=-0.23$, $p=.11$) did not show a significant correlation with the annual MMSE change.

Thus, patients whose present cognition seemed at odds with their manifest signs of neuronal injury by biomarker grading showed worse cognitive deterioration in the clinical follow up. Among single neuronal injury markers, the residuals of FDG-PET indicated the strongest predictive value.
4. Discussion

We demonstrate that neuronal injury biomarker readouts in relation to clinical scoring of cognition can serve to assess the individual cognitive reserve in MCI and AD subjects, which is predictive of future decline. Among the neuronal injury biomarkers, FDG-PET correlated better with clinical scoring by MMSE than did measures of hippocampal atrophy by structural MRI or total-tau by CSF analysis. By creating a composite model based on neuronal injury biomarkers and relevant covariates for AD, we further investigated the manner in which cognitive performance predicted by modelling of biomarker findings differed from the individual clinical observations in many patients. The difference between the two cognitive scores (MMSE\textsubscript{observed} and MMSE\textsubscript{predicted}) represents a surrogate for the individual cognitive reserve. Importantly, this individual cognitive reserve forecasts the cognitive deterioration to follow-up, independent from the extent of cognitive deterioration at baseline.

A range of neuronal injury biomarkers (FDG-PET, MRI, CSF\textsubscript{total-tau}) are currently recommended to substantiate the working hypothesis of an AD diagnosis (Jack Jr et al., 2016). In previous studies, all three of these biomarkers correlated independently with cognitive performance (Nathan et al., 2017; Forster et al., 2010). Nevertheless, their relationship with the extent of neuronal injury is complex, and has poor agreement within the A/T/N triad of biomarkers (Alexopoulos et al., 2014). This may be due to the distinct aspects of neuronal injury captured by PET, MRI and CSF measurements; whereas FDG-PET primarily depicts net synaptic dysfunction, the hippocampal atrophy in MRI indicates region specific neuronal and neuropil loss, and elevated total-tau in CSF is a non-specific marker of different forms of neuronal damage (Jack et al., 2010). Furthermore, current thinking holds that tau pathophysiology precedes onset of hypometabolism or hippocampal atrophy in the course of AD (Jack Jr et al., 2013; Bateman et al., 2012). If so, tau levels in CSF may bear only a transient relationship with the extent of neuronal injury and cognitive decompensation. Nonetheless,
current practice recommends all three biomarkers equally for assessment of neurodegeneration/neuronal injury by current AD classification schemes (Jack Jr et al., 2016). Our present data entails the hitherto first head-to-head comparison of FDG-PET, MRI, and CSF biomarkers as predictors of current and future cognitive function in a mixed population of MCI and AD patients. We find that reduced relative FDG uptake in AD-related cortical regions correlated best with MMSE scores, whereas hippocampal atrophy or total tau in CSF showed only a poor agreement. Thus, freestanding FDG-PET is a good predictor for cognitive function in this population, with little additional benefit derived from considering MRI and CSF results. This finding may prove particularly useful in the diagnosis of AD in aphasic or otherwise unresponsive patients (Rogalski et al., 2016). Furthermore, we were able to show that a simple scoring system, based on neuronal injury as depicted by surface projections of FDG-PET, gave equivalent prediction of cognitive function when compared to a semi-quantitative approach. This enables taking the previously vague concept of cognitive reserve into consideration when FDG-PET is used for evaluation of possible AD in clinical routine at tertiary centers.

Many different factors have been shown to influence the individual cognitive reserve of the individual patient. Above all, higher YoE seems to be the best predictor for a higher cognitive reserve (Yoon et al., 2016). Importantly, residuals deriving from separate regression analyses between neuronal injury biomarker results and the clinically observed MMSE correlated significantly with the YoE, indicating that these residuals are indeed a surrogate for the individual cognitive reserve. By implication, the neuronal injury biomarkers can also serve as a surrogate of cognitive reserve, as has already been shown for a larger premorbid brain volume (Pernecký et al., 2010) or greater left frontal cortex connectivity (Franzmeier et al., 2018).

The main objective of this study was to create a model including several established biomarkers for neuronal injury and relevant covariates such as age and YoE to compute the residualized memory function. All of the selected parameters are known to impact in- variates such as age and YoE to compute the residualized memory function in this population, with little additional benefit derived from considering MRI and CSF results. This finding may prove particularly useful in the diagnosis of AD in aphasic or otherwise unresponsive patients (Rogalski et al., 2016). Furthermore, we were able to show that a simple scoring system, based on neuronal injury as depicted by surface projections of FDG-PET, gave equivalent prediction of cognitive function when compared to a semi-quantitative approach. This enables taking the previously vague concept of cognitive reserve into consideration when FDG-PET is used for evaluation of possible AD in clinical routine at tertiary centers.

Among the limitations of this study, we note that the MMSE is a commonly used instrument for detection of cognitive impairment in patients with suspected AD, but it cannot replace detailed neuropsychological testing, and does not represent all aspects of cognitive decline. For this reason, we also administered the CERAD test in most of our subjects, which showed comparable results (see Supplement Figure 1). For facile implementation in a clinical routine, the present calculated grading of neuronal injury is based rather on the MMSE, aiming to provide a standardized, widely accepted index. We focused on covariates that are recommended in the guidelines for supporting the diagnosis of AD, but we were not able to cover the full range of environmental factors, co-morbidities, and ApoE-status, which might have had impact in this analysis. Current standards for diagnosis of AD in living patients call for evidence of Aβ and tau pathology to either CSF analysis or PET (Jack Jr et al., 2016). While p-tau content of CSF was available for our patients, which showed comparable results (see Supplement Figure 1). For facile implementation in a clinical routine, the present calculated grading of neuronal injury is based rather on the MMSE, aiming to provide a standardized, widely accepted index. We focused on covariates that are recommended in the guidelines for supporting the diagnosis of AD, but we were not able to cover the full range of environmental factors, co-morbidities, and ApoE-status, which might have had impact in this analysis. Current standards for diagnosis of AD in living patients call for evidence of Aβ and tau pathology to either CSF analysis or PET (Jack Jr et al., 2016). While p-tau content of CSF was available for our patients, which showed comparable results (see Supplement Figure 1). For facile implementation in a clinical routine, the present calculated grading of neuronal injury is based rather on the MMSE, aiming to provide a standardized, widely accepted index. We focused on covariates that are recommended in the guidelines for supporting the diagnosis of AD, but we were not able to cover the full range of environmental factors, co-morbidities, and ApoE-status, which might have had impact in this analysis. Current standards for diagnosis of AD in living patients call for evidence of Aβ and tau pathology to either CSF analysis or PET (Jack Jr et al., 2016). While p-tau content of CSF was available for our patients, which showed comparable results (see Supplement Figure 1). For facile implementation in a clinical routine, the present calculated grading of neuronal injury is based rather on the MMSE, aiming to provide a standardized, widely accepted index. We focused on covariates that are recommended in the guidelines for supporting the diagnosis of AD, but we were not able to cover the full range of environmental factors, co-morbidities, and ApoE-status, which might have had impact in this analysis. Current standards for diagnosis of AD in living patients call for evidence of Aβ and tau pathology to either CSF analysis or PET (Jack Jr et al., 2016). While p-tau content of CSF was available for our patients, which showed comparable results (see Supplement Figure 1). For facile implementation in a clinical routine, the present calculated grading of neuronal injury is based rather on the MMSE, aiming to provide a standardized, widely accepted index. We focused on covariates that are recommended in the guidelines for supporting the diagnosis of AD, but we were not able to cover the full range of environmental factors, co-morbidities, and ApoE-status, which might have had impact in this analysis. Current standards for diagnosis of AD in living patients call for evidence of Aβ and tau pathology to either CSF analysis or PET (Jack Jr et al., 2016). While p-tau content of CSF was available for our patients, which showed comparable results (see Supplement Figure 1). For facile implementation in a clinical routine, the present calculated grading of neuronal injury is based rather on the MMSE, aiming to provide a standardized, widely accepted index. We focused on covariates that are recommended in the guidelines for supporting the diagnosis of AD, but we were not able to cover the full range of environmental factors, co-morbidities, and ApoE-status, which might have had impact in this analysis. Current standards for diagnosis of AD in living patients call for evidence of Aβ and tau pathology to either CSF analysis or PET (Jack Jr et al., 2016). While p-tau content of CSF was available for our patients, which showed comparable results (see Supplement Figure 1).
memory function. Importantly, this concept can be established by simple visual and laboratory read-outs without use of highly sophisticated quantification methods. The established surrogate score of cognitive reserve by neuronal injury biomarkers predicts future cognitive progression at the single patient level and should therefore serve to adjust for heterogeneous clinical progression independent of treatment arm in therapeutic trials.

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Conflict of interest

The authors do not report conflicts of interest.

Appendix A. Supplementary data

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