Brain Imaging and Behavior (2019) 13:162–171
https://doi.org/10.1007/s11682-018-9870-8

ORIGINAL RESEARCH

A methodological approach to studying resilience mechanisms: demonstration of utility in age and Alzheimer's disease-related brain pathology

Dominik Wolf[1] · Florian Udo Fischer[1] · Andreas Fellgiebel[1] · for the Alzheimer's Disease Neuroimaging Initiative

Published online: 1 May 2018

Abstract
The present work aims at providing a methodological approach for the investigation of resilience factors and mechanisms in normal aging, Alzheimer's disease (AD) and other neurodegenerative disorders. By expanding and re-conceptualizing traditional regression approaches, we propose an approach that not only aims at identifying potential resilience factors but also allows for a differentiation between general and dynamic resilience factors in terms of their association with pathology. Dynamic resilience factors are characterized by an increasing relevance with increasing levels of pathology, while the relevance of general resilience factors is independent of the amount of pathology. Utility of the approach is demonstrated in age and AD-related brain pathology by investigating widely accepted resilience factors, including education and brain volume. Moreover, the approach is used to test hippocampal volume as potential resilience factor. Education and brain volume could be identified as general resilience factors against age and AD-related pathology. Beyond that, analyses highlighted that hippocampal volume may not only be disease target but also serve as a potential resilience factor in age and AD-related pathology, particularly at higher levels of tau-pathology (i.e. dynamic resilience factor). Given its unspecific and superordinate nature the approach is suitable for the investigation of a wide range of potential resilience factors in normal aging, AD and other neurodegenerative disorders. Consequently, it may find a wide application and thereby promote the comparability between studies.

Keywords Resilience mechanisms · Homeodynamics · Methodological approach · Normal aging · Mild cognitive impairment · Alzheimer's disease

Introduction

The brain is a self-organizing and adaptive system that shows robustness in the sense of sustained cognitive functioning in spite of gradual or sudden impairment of its components. This remarkable property derives from complex maintenance, repair and compensatory mechanisms, also labelled as resilience mechanisms. The traditional conceptual model to describe the tendency to relative constancy (i.e. stable steady states) is the concept of homeostasis (Cannon 1932). However, homeostasis fails taking into account that the internal milieu of the brain is not permanently fixed. It exhibits dynamic regulation and interaction among various levels of organization and a dynamic and constantly changing nature of growth, development, maturation and aging. A concept that accounts for both the tendency towards relative constancy of physiological status as well as the dynamic nature of brain development and adaption is the concept of homeodynamics (Lloyd et al. 2001; Yates 1994). Resilience mechanisms enabling relative constancy and robustness can therefore be considered as one part of the homeodynamic processes.

Despite the tendency to constancy and robustness, marked individual variability of cognitive phenotypes at given levels of brain pathology, damages, or impairments have been observed (e.g. in normal aging and Alzheimer's disease (AD)) (Davis et al. 1999; Katzman et al. 1988; Riley et al. 2002). These observations imply strong variations in the degree of

✉ Dominik Wolf
dominik.wolf@unimedizin–mainz.de

[1] Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Untere Zahlbacher Str. 8, 55131 Mainz, Germany

brain resilience and suggest an intrinsically continuous nature of resilience, as shown in Figure 1. Mechanisms underlying resilience operate and interact among different micro- and macrostructural levels (from genes over proteins and cells up to micro- and macrocircuits). Moreover, they can be subdivided in passive and active mechanisms. Passive mechanisms define resilience as the amount of damage that can be sustained before reaching a threshold for clinical expression. Active mechanisms define resilience as an active attempt to compensate for brain damage (Stern 2002). In the field of brain research, passive mechanisms have been subsumed under the term brain reserve while active mechanisms have been subsumed under the term cognitive reserve (Stern 2009). Beyond that, resilience mechanisms can be distinguished based on their association with pathology. While the importance of some mechanisms varies as a function of the amount of pathology (i.e. dynamic resilience mechanisms; e.g. increasing importance of a resilience mechanism with higher levels of pathology), the importance of others is independent of the amount of pathology (i.e. general resilience mechanisms). These complex characteristics of resilience mechanisms make it challenging to identify, characterize and disentangle such mechanisms.

A better understanding of resilience mechanisms leads to a deeper comprehension of homeodynamic processes, which ultimately determine the clinical phenotypes in normal aging and neurodegenerative diseases, such as AD. This is a necessary step towards more accurate prediction of cognitive decline in normal aging and neurodegenerative diseases as well as for the identification of possible prevention and treatment strategies. The present work aims at introducing a methodological approach for the investigation of resilience mechanisms that extends and re-conceptualizes existing approaches. Given its unspecific and superordinate nature it is applicable to a wide range of research questions within the field of resilience research and may therefore promote the comparability between studies.

First, we introduce the methodological approach and its theoretical background. Thereafter, utility of the approach is demonstrated in age and Alzheimer's disease (AD)-related brain pathology, by investigating widely accepted resilience factors, including education and brain volume. In an explorative analysis, we subsequently investigated the potential of hippocampal volume to serve as resilience factor. Hippocampal atrophy is one of the core characteristics in aging and AD and is closely related to disease-typical memory deficits (Jack et al. 2000; Shi et al. 2009). However, some studies showed an association between higher hippocampal volumes and preserved cognitive functioning in the presence of AD-related brain pathology, indicating that the hippocampus might also represent a promising resilience factor (Chételat et al. 2010; Erten-Lyons et al. 2009).

Methods

Introduction of the approach to studying resilience mechanisms

The investigation of resilience mechanisms requires, at minimum, a measure of a resilience factor, a measure of pathology or brain damage, and a measure of cognitive outcome. In the literature on resilience research this full model is only rarely tested. Studies that considered all 3 components usually applied regression approaches where cognitive performance was set as outcome variable and an interaction term between pathology and resilience factor was set as predictor variable. Traditionally, a significant interaction term was considered necessary to support the claim of resilience (Christensen et al. 2008).

By expanding and re-conceptualizing such traditional regression approaches we propose an approach that not only

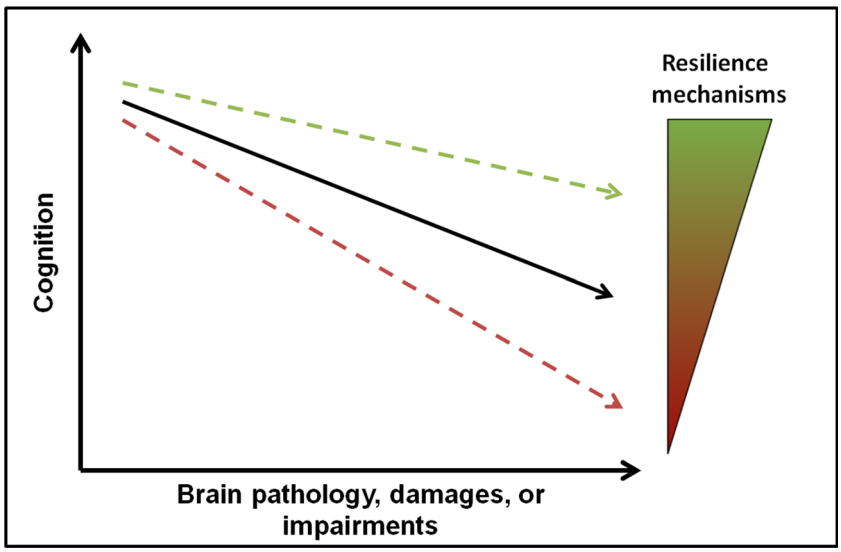

Fig. 1 Brain pathology, damages or impairments are associated with cognitive decline as shown by the black arrow. This association is modulated by resilience mechanisms. High resilience (green part of the colored triangle) counteracts brain pathology and preserves cognition or reduces cognitive decline (green arrow). Low resilience (red part of the colored triangle) leads to accelerated cognitive decline (red arrow)

aims at the identification of potential resilience factors but also allows for a differentiation between general and dynamic resilience factors in terms of their association with pathology (dynamic resilience factor: increasing importance of a resilience factor with higher levels of pathology; general resilience factor: the importance of the resilience factor is independent of the amount of pathology). The model is described in the following equation.

$$COG = \beta 0 + \beta 1 * PATH + \beta 2 * RES_{FACTOR} + \beta 3 * (RES_{FACTOR} * PATH) + \varepsilon \quad (1)$$

In this model, a pathology measure (PATH), a potential resilience factor (RES_{FACTOR}, e.g. brain volume), and the interaction between resilience factor and pathology measure (RES_{FACTOR} *PATH) are regressed against cognitive performance (COG). Since pathology is entered as predictor variable, the variance in cognition as outcome variable is adjusted for the effect of pathology. The remaining variance in cognition which is not explained by pathology (in other words: cognitive performance which deviates from the performance that would be expected based on the amount of pathology) can be seen as a measure of resilience. In order to improve the comprehensibility and readability hereinafter, the outcome variable is referred to as "resilience". Several pathology measures as well as their interaction terms with the resilience factor can be added to the model. Moreover, the model can be complemented by control variables. All continuous predictor variables in the model should be mean-centered in order to reduce collinearity among predictors. In case of outliers, a robust regression model should be applied in addition to/instead of the linear model.

Resilience factors are supported by the model in the following cases:

(i) General resilience factor: Positive main effect of the resilience factor on resilience. No association between the interaction term (RES_{FACTOR}*PATH) and resilience.

This result indicates that the resilience factor is associated with resilience, irrespective of the amount of pathology.

(ii) Dynamic resilience factor: Significant association between the interaction term (RES_{FACTOR}*PATH) and resilience, such that the resilience factor is positively related with resilience whereby the strength of this association differs at low and high levels of the pathology measure. No main (independent) effect of the resilience factor on resilience.

This result indicates a dynamically changing association between resilience factor and resilience as a function of the amount of pathology, whereby the resilience factor is not independently associated with resilience.

(iii) General and dynamic resilience factor: Positive main (independent) effect of the resilience factor on resilience. Significant association between the interaction term (RES_{FACTOR}*PATH) and resilience, such that the resilience factor is positively related to resilience whereby the strength of this association differs at low and high levels of pathology.

This result indicates that the resilience factor is associated with resilience, irrespective of the amount of pathology, whereby the strength of this association dynamically changes as a function of the amount of pathology.

Demonstration of utility

Utility of the approach is demonstrated in age and AD-related brain pathology. Pathology was quantified using cerebrospinal fluid (CSF) measurements of p- and t-tau, positron emission tomography (PET)-based measurements of cerebral amyloid load, and magnetic resonance imaging-based measures of white matter hyperintensity volume (WMHV). Initially, we investigated widely accepted resilience factors, including education and brain volume. Thereafter, we applied our model to investigate the potential of hippocampal volume to serve as resilience factor.

Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The present study sample consisted of 457 older individuals without dementia from the ADNI-2 cohort, including 158 cognitively normal (CN) and 299 MCI participants. Detailed diagnostic criteria have been published on the ADNI website (adni.loni.usc.edu/methods). Eligibility criteria for the present study included availability of AV45-PET, high-resolution structural MRI acquisitions, cognitive assessment, and CSF-Tau measurement from the same study time point. Demographical and clinical data of the subjects are shown in Table 1.

Standard protocol approvals, registrations, and patient consents

Data collection and sharing in ADNI were approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from all participants.

Table 1 Demographical and clinical data of diagnostic subgroups

	CN	MCI
N	158	299
Age (yr)	74 (6)	72 (7)
Gender (F/M)	80/78	136/163
Education (yr)	17 (2)	16 (3)
ADNI-mem	1.1 (0.6)	0.3 (0.7)
ADAS-cog	9.2 (4.6)	15.8 (7.2)
AV45 uptake	1.1 (0.2)	1.2 (0.2)
WMHV	4.2 (3.3)	4.6 (3.6)
p-tau$_{181p}$	33.3 (15.7)	43.0 (24.8)
t-tau	67.5 (33.8)	87.3 (52.7)
APOE ε4 (−/+)	116/42	148/151
Norm. Hipp-vol right	2308.4 (176.4)	2155.8 (272.3)
Norm. Hipp-vol left	2100.8 (197.0)	1926.1 (287.2)

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADNI-mem = ADNI memory composite score; AV45 uptake = cerebral amyloid load (standard uptake value ratio); WMHV = white matter hyperintensity; p-tau$_{181p}$ = tau phosphorylated at the threonine 181 position (pg/ml); t-tau = total tau (pg/ml); Norm. Hipp-vol right = TIV-normalized hippocampus volume right, expressed in mm^3 ; Norm. Hipp-vol left = TIV-normalized hippocampus volume left, expressed in mm^3 ; yr. = years; F/M = female/male

Imaging data

Acquisition and standardized processing steps of the multicentric MRI and PET data have been described in detail on the ADNI website (adni-loni.usc.edu/methods). Briefly, structural MRI data were acquired on 3 T scanning platforms using T1-weighted sagittal 3-dimensional magnetization-prepared rapid acquisition gradient echo sequences. AV45-PET scans were acquired according to a standard dynamic 50–70 min protocol following the intravenous injection of 370 ± 37 MBq of [^{18}F]-AV45. All ADNI image data undergo standardized processing steps to increase data uniformity across multicenter imaging data.

MRI data were processed using statistical parametric mapping (SPM8, Wellcome Trust Center for Neuroimaging) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm). First, images were segmented into partitions of gray matter (GM), white matter (WM), and CSF using the tissue free segmentation routine of the VBM8-toolbox. The resulting GM and WM partitions were then high-dimensionally registered to MNI standard space using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner 2007). Voxel values were modulated to preserve the original amount of GM and WM present before normalization.

In the literature, a variety of indicators of brain size have been used, including head circumference, intracranial volume (sum of GM, WM, and CSF volumes) or brain tissue volume (sum of GM and WM volumes) (Christensen et al. 2008). Since we were specifically interested in resilience properties of the current brain size, brain volume was quantified by the sum of GM and WM volume. In order to delineate the raw brain volume from brain atrophy, we also quantified the normalized brain volume by dividing the raw brain volume through the total intracranial volume (TIV). TIV as well as WMHV were calculated at the ADNI core laboratories from T1-weighted and FLAIR data using published segmentation methods (DeCarli et al. 2005; Fletcher et al. 2012).

Raw hippocampal volumes (bilateral) were calculated by summing up all GM voxel values within newly created reference MNI-standard space hippocampal labels. These labels result from segmentations of the high resolution MNI152-template by four expert tracers following the newly established Harmonized Protocol (Frisoni et al. 2015). The labels were designed as consensus labels, wherein all voxels were included that had been segmented as hippocampal tissue by all four tracers (Wolf et al. 2017). Normalized hippocampal volumes were calculated by dividing the raw hippocampal volumes through the TIV.

Individual AV45-PET standardized uptake value ratios (SUVRs) were calculated by ADNI PET core laboratories (http://adni.loni.usc.edu/methods/pet-analysis). Briefly, cerebral AV45 uptake was quantified by the mean uptake within a composite mask including frontal, angular/posterior cingulate, lateral parietal, and lateral temporal regions, divided by the mean uptake within the cerebellum.

CSF measurement

All CSF biomarkers collected at different centers were stored and analyzed at the Penn ADNI Biomarker Core Laboratory at the University of Pennsylvania, Philadelphia. CSF

concentrations of p-tau and t-tau were measured in the baseline CSF samples using the multiplex xMAP Luminex platform (Lumnix Corp., Austin, TX). More details on data collection and processing of the CSF samples can be found elsewhere (Shaw et al. 2009) (http://adni.loni.usc.edu/methods).

APOE genotype

APOE genotype was determined by genotyping the two single nucleotide polymorphisms that define the APOE ε2, ε3, and ε4 alleles (rs429358, rs7412) with DNA extracted by Cogenics from a 3-ml aliquot of EDTA blood (adni.loni.usc.edu/data-samples/genetic-data).

Neuropsychological assessment

Cognitive ability was assessed using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog, 13-item version) (Rosen et al. 1984) and the ADNI-memory composite score (ADNI-mem) (Crane et al. 2012). Both scores were chosen given their sensitivity to age and AD-related brain pathology. While ADAS-cog assesses various domains of cognition, the ADNI-mem score specifically reflects memory deficits. Performances were downloaded from the ADNI Web page (http://adni.loni.ucla.edu).

Statistics

In the proposed resilience regression approach, ADAS-cog and ADNI-mem scores were set as outcome variables. ADAS-cog scores were inverted so that lower scores indicated lower performance. Pathology measures (p- and t-tau, AV45 uptake, and WMHV), resilience factors of interest (education, raw brain volume, normalized brain volume, raw hippocampal volume, and normalized hippocampal volume), and the interactions between pathology markers and resilience factors were set as predictor variables (separate regression models were applied for each resilience factor). Moreover, age, gender, and APOE4 status (APOE4 positivity on at least one ε4 allele vs. APOE4 negativity) were included as control variables. All continuous predictor variables were mean-centered in order to reduce collinearity among predictors. The interaction terms between pathology markers and resilience factor of interest were calculated from the mean centered variables. All regression analyses were repeated using robust regression models to control the influence of potential outliers (based on an M estimator). Statistical analyses were carried out using the statistical software package R 3.0.2.

Results

Investigation of traditional resilience factors: Brain volume and education

Results of the regression analyses including raw brain volume, normalized brain volume, and education as resilience factors of interest are shown in Table 2. For ADAS-cog resilience, parametric linear regression analyses showed a positive main effect of raw and normalized brain volume (raw volume: $p = .007$; normalized volume: $p < .001$). A main effect of education has not been found. Moreover, none of the interaction effects were significant.

For ADNI-mem resilience, parametric linear regression analyses showed positive main effects of raw and normalized brain volume (raw volume: $p = .002$; normalized volume: $p < .001$) as well as of education ($p = .005$). No interaction effects have been found.

Robust regression analyses confirmed all positive main effects of the linear regression analyses. For ADAS-cog resilience, robust regression showed a trend towards a positive main effect of education ($p = .071$) that has not been found in the parametric linear regression model. No interaction effects (neither for ADAS-cog resilience nor for ADNI-mem resilience) have been found.

Explorative investigation of hippocampal volume as potential resilience factor

Results of the regression analyses including raw- and normalized hippocampal volumes as resilience factors of interest are shown in Table 3. For ADAS-cog resilience, parametric linear regression analyses showed positive main effects of the left and right raw and normalized hippocampal volumes (raw volume left: $p < .001$, normalized volume left: $p < .001$; raw volume right: $p < .001$, normalized volume right: $p < .001$). Moreover, interaction effects between raw and normalized hippocampal volumes (left and right) and t-tau have been found (raw volume left: $p = .025$, normalized volume left: $p = .013$; raw volume right: $p = .019$, normalized volume right: $p = .008$).

For ADNI-mem resilience, parametric linear regression analyses showed positive main effects of the left and right raw and normalized hippocampal volumes (raw volume left: $p < .001$, normalized volume left: $p < .001$; raw volume right: $p < .001$, normalized volume right: $p < .001$). Moreover, interaction effects between normalized hippocampal volumes (left and right) and t-tau have been found (left: $p = .008$, right: $p = .010$).

Robust regression analyses confirmed all main- and interaction effects that have been found in the parametric linear regression analyses. Moreover, robust regression analyses showed a trend towards an interaction between the raw hippocampal volumes (left and right) and t-tau on ADAS-mem resilience (left: $p = .066$; right: $p = .089$). As shown in

Table 2 Investigation of brain volume and education as resilience factors

	General linear model				Robust regression			
	ADAS-cog resilience		ADNI-mem resilience		ADAS-cog resilience		ADNI-mem resilience	
	beta	*p*	beta	*p*	beta	*p*	beta	*p*
Education	.060	.153	.116	**.005**	.076	.071	.114	**.007**
Education x t-tau	.046	.437	−.015	.797	.020	.734	−.036	.547
Education x p-tau	−.038	.513	−.018	.751	−.036	.540	−.021	.721
Education x AV45	−.019	.714	.016	.756	.021	.692	.042	.428
Education x WMHV	−.037	.387	−.021	.605	−.019	.657	−.025	.564
Raw brain volume	.137	**.007**	.152	**.002**	.156	**.003**	.156	**.003**
Raw brain volume x t-tau	.060	.327	−.015	.801	.015	.811	.003	.968
Raw brain volume x p-tau	−.026	.657	.026	.656	.006	.919	.023	.699
Raw brain volume x AV45	−.045	.371	−.001	.989	.002	.971	.007	.885
Raw brain volume x WMHV	−.030	.468	−.018	.658	−.024	.568	−.009	.833
Norm. Brain volume	.226	**<.001**	.240	**<.001**	.219	**<.001**	.236	**<.001**
Norm. Brain volume x t-tau	.059	.310	.041	.470	.071	.225	.059	.310
Norm. Brain volume x p-tau	−.079	.163	−.104	.061	−.079	.159	−.100	.077
Norm. brain volume x AV45	.016	.748	.008	.876	.024	.640	.001	.986
Norm. brain volume x WMHV	.066	.126	.030	.479	.052	.226	.021	.626

Note: ADAS-cog and ADNI-mem scores were set as outcome variables. Pathology measures (t-tau, p-tau, AV45, WMHV) were set as predictor variables in all regression analyses to adjust the variance in cognition for the effect of pathology. Brain volume (raw and normalized) and its interaction with pathology measures as well as education and its interaction with pathology measures were set predictor variables of interest (in separate regression analyses). Age, gender, and APOE4 status were set as control variables in all regression analyses (control variables are not shown in the table). Abbreviations: ADAS-cog resilience = pathology-adjusted variance of the Alzheimer's Disease Assessment Scale-cognitive subscale; ADNI-mem resilience = pathology-adjusted variance of the ADNI-memory composite score; AV45 = cerebral amyloid load (standard uptake value ratio); WMHV: white matter hyperintensity volume; beta: standardized beta coefficients

Figure 2, the interactions between hippocampal volume and t-tau were such that ADAS-cog resilience and ADNI-mem resilience were more positively associated with hippocampal volumes at high levels of t-tau than at low levels of t-tau.

Discussion

In the present work, we introduced a methodological approach for the investigation of resilience factors, followed by a demonstration of utility using the example of age and AD-related brain pathology.

Introduction of a methodological approach to studying resilience factors

General aspects of strategies to studying resilience factors

Different methodological approaches have been developed to investigate resilience factors. The investigation of such factors requires at least 3 features: (i) a measure of resilience, (ii) a measure of pathology or brain damage, and (iii) a measure of cognitive outcome. In the literature on resilience research such a specification is rarely achieved. Several approaches investigate the association between a resilience factor of interest and a common proxy for resilience, such as education, without taking into account cognitive performance. Such approaches provide supporting evidence for the claim of resilience but do not test it (Christensen et al. 2008). Approaches that investigate the full model often compare subjects who remain cognitively intact with those who develop cognitive dysfunctions in the face of significant pathology. Such an artificial dichotomization of the cognitive outcome ignores the intrinsically continuous nature of resilience and has potential limitations, including loss of power, spurious statistical significance and decrease in reliability (Cohen 1983). Another set of strategies included the application of regression approaches where cognitive performance is set as outcome variable and an interaction between pathology and resilience factor on cognition is considered necessary to support the claim of resilience (Christensen et al. 2008; Ewers et al. 2013). Such models take all of 3 features that are necessary to investigate resilience factors into account. More recent approaches investigated resilience factors by integrating a measure of resilience into a latent variable model of resilience using path analyses (Hohman et al. 2016).

Table 3 Investigation of hippocampal volume as potential resilience factor

	General linear model				Robust regression			
	ADAS-cog resilience		ADNI-mem resilience		ADAS-cog resilience		ADNI-mem resilience	
	beta	*p*	beta	*P*	beta	*p*	beta	*p*
Raw hipp-vol left	.301	**<.001**	.295	**<.001**	.304	**<.001**	.296	**<.001**
Raw hipp-vol left x t-tau	.136	**.025**	.105	.078	.135	**−.025**	.111	.066
Raw hipp-vol left x p-tau	−.058	.344	−.041	.501	−.071	.248	−.046	.450
Raw hipp-vol left x AV45	−.014	.790	−.008	.882	.030	.577	−.009	.874
Raw hipp-vol left x WMHV	.028	.474	.029	.450	.039	.320	.025	.528
Raw hipp-vol right	.232	**<.001**	.233	**<.001**	.229	**<.001**	.237	**<.001**
Raw hipp-vol right x t-tau	.139	**.019**	.091	.118	.133	**.027**	.101	.089
Raw hipp-vol right p-tau	−.026	.655	.001	.994	−.025	.676	.009	.876
Raw hipp-vol right AV45	−.045	.376	−.035	.485	−.003	.952	−.044	.385
Raw hipp-vol right WMHV	.045	.257	.001	.979	.066	.552	.031	.779
Norm. Hipp-vol left	..283	**<.001**	.278	**<.001**	.287	**<.001**	.271	**<.001**
Norm. Hipp-vol left x t-tau	.135	**.013**	.142	**.008**	.148	**.006**	.133	**.013**
Norm. Hipp-vol left x p-tau	−.080	.173	−.097	.094	−.098	.100	−.093	.112
Norm. Hipp-vol left x AV45	.031	.558	.003	.961	.044	.400	−.010	.850
Norm. Hipp-vol left x WMHV	.066	.093	.045	.252	.072	.068	.029	.461
Norm. Hipp-vol right	.208	**<.001**	.205	**<.001**	.201	**<.001**	.217	**<.001**
Norm. Hipp-vol right x t-tau	.151	**.008**	.146	**.010**	.157	**.006**	.143	**.011**
Norm. Hipp-vol right x p-tau	−.049	.429	−.055	.365	−.054	.382	−.040	.513
Norm. Hipp-vol right x AV45	.011	.835	−.026	.612	.021	.693	−.048	.362
Norm. Hipp-vol right x WMHV	.062	.118	.033	.404	.066	.102	.025	.532

Note: ADAS-cog and ADNI-mem scores were set as outcome variables. Pathology measures (t-tau, p-tau, AV45, WMHV) were set as predictor variables in all regression analyses to adjust the variance in cognition for the effect of pathology. Hippocampal volumes (raw and normalized) and their interactions with pathology measures were set as predictor variables of interest. Age, gender, and APOE4 status were set as control variables in all regression analyses (control variables are not shown in the table). Abbreviations: ADAS-cog resilience = pathology adjusted variance of the Alzheimer's Disease Assessment Scale-cognitive subscale; ADNI-mem resilience = pathology-adjusted variance of the ADNI-memory composite score; AV45 = cerebral amyloid load (standard uptake value ratio); WMHV: white matter hyperintensity volume; beta: standardized beta coefficients

Strengths and limitations of the proposed approach to studying resilience factors

Our approach aims at extending and re-conceptualizing traditional regression approaches, where cognitive performance was set as outcome variable and an interaction between pathology and resilience factor was set as predictor variable. The approach is based on a systematic consideration of (i) effects of a resilience factor on resilience and (ii) interaction effects between a resilience factor and pathology on resilience. In the proposed model, a significant interaction is not considered necessary to support the claim of resilience but indicates a dynamically changing importance of a resilience factor with increasing pathology (i.e. dynamic resilience factor). On the other hand, the lack of an interaction in the presence of a main effect of the resilience factor indicates a general resilience factor that is independent of the amount of pathology. Thus, besides the determination of potential resilience factors our model allows for a differentiation of general and dynamic resilience factors in terms of their association with pathology. The model takes all 3 features into account that are necessary to investigate resilience factors. Moreover, it avoids artificial dichotomization/aggregation of continuous variables. It can be complemented by control variables (e.g. age and gender) and extended by resilience factors that have been found in previous studies, enabling the investigation of the independence of a resilience factor of interest from already known factors. Together with its unspecific and superordinate nature it may find a wide application and thereby promote the comparability between studies within the field of resilience research.

Our approach has some limitations. As all linear regression models, our model is sensitive to outliers. In case of outliers, a robust regression model should be applied in addition to/instead of the proposed linear model. Moreover, the model is sensitive to overfitting which results in the modeling of the random error in the data rather than of the relationship

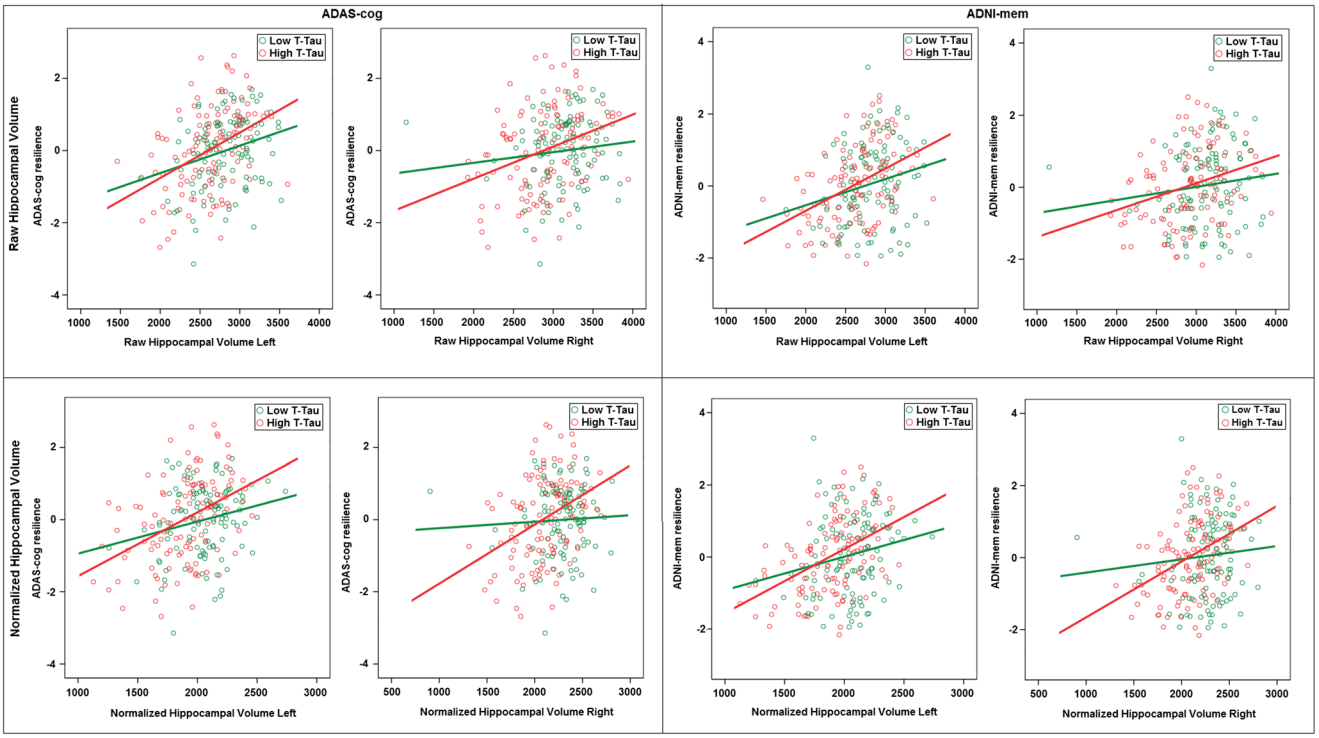

Fig. 2 Scatterplots of the relationship between hippocampal volumes (upper row: raw hippocampal volumes; lower row: normalized hippocampal volumes) and resilience (left side: pathology-adjusted ADAS-cog scores; right side: pathology-adjusted ADNI-mem scores) separated for t-tau extreme groups using quartile splits (low t-tau: lower quartile, $N = 115$; high t-tau: upper quartile, $N = 114$). Associations between hippocampal volumes and ADAS-cog/ADNI-mem resilience are given in colored lines (green lines: relationship between both variables at low levels of t-tau; red lines: relationship between both variables at high levels of t-tau)

between outcome and predictor variables. Overfitting commonly arises when too many predictors (compared to the number of samples) are included in the regression model. Finally, linear regression models are meant to describe linear relationships between predictors and outcome variables. Thus, the proposed model is limited in the detection of non-linear resilience effects.

Demonstration of utility of the approach

Utility of the approach was demonstrated in age and AD-related brain pathology. Pathology was quantified using CSF measures of p- and t-tau, PET-based measures of cerebral amyloid load, and MRI-based measures of WMHV.

Brain volume and education

In a first step, the proposed approach has been applied to investigate widely accepted resilience factors in the aging and AD literature, including education and brain volume. In addition to the raw brain volume the TIV-normalized brain volume has been investigated, which is typically seen as a measure of atrophy.

In line with previous studies (Ewers et al. 2013; Stern 2006, 2012), education could be identified as resilience factor against age and AD-related brain pathology (main effect of education on ADNI-mem resilience and trend towards a main effect on ADAS-cog resilience in the robust regression analysis). Regression analyses further indicated that the association of education with resilience is independent of the amount of pathology (non-significant interactions between resilience factors and pathology measures), suggesting that education represents a general resilience factor. From a mechanistic perspective, it has been suggested that education is related to processes that actively compensate brain damage to preserve cognitive functioning (Stern 2006, 2012).

In line with education, current brain volume could be confirmed as resilience factor against age and AD-related brain pathology. Interestingly, regression analyses demonstrated that both raw- and normalized brain volumes were positively associated with resilience. It has been suggested that brain volume acts as a passive reserve factor insofar as larger brains might simply tolerate more pathology (Stern 2006, 2012). Normalized brain volume is typically seen as a measure of atrophy. The observed associations between normalized brain volume and resilience suggest that resilience might also be manifested by less brain atrophy (respectively higher brain health) at a given level of pathology. In line with education, regression analyses further suggest that the association between brain volume (raw- and normalized volumes) and resilience is independent of the amount of pathology, indicating

that raw- and normalized brain volume represent general resilience factors.

Hippocampal volume

In explorative analyses, the proposed approach was used to investigate hippocampal volume as potential resilience factor. Robust regression analyses showed that both raw- and normalized hippocampal volumes (left and right) are positively associated with resilience (main effect of hippocampal volume on ADAS-cog resilience and ADNI-mem resilience), indicating a general resilience effect of hippocampal volume on age and AD-related pathology. These findings are in line with previous studies indicating that the hippocampus might not only be target of AD-related pathology but also serve as a potential resilience factor (Chételat et al. 2010; Erten-Lyons et al. 2009). Resilience properties of raw hippocampal volume might be explained by a passive reserve mechanism, similar to the potential mechanism of raw brain volume. Subjects with higher hippocampal volumes may tolerate more pathology leading to less severe cognitive decline. In line with normalized brain volume, normalized hippocampal volume is typically seen as a measure of atrophy. Resilience properties of normalized hippocampal volume might be explained by underlying active compensatory processes, which might attenuate hippocampal atrophy and maintain hippocampal function. An increase in hippocampal neurotrophin levels has been observed especially in MCI and early AD stages (Mufson et al. 2015). Moreover, hippocampal hypertrophy of neuronal nuclei, cell bodies and nucleoli has been found at autopsy in brains of cognitively healthy elderly with ß-amyloid plaques compared to cognitively healthy elderly without ß-amyloid plaques and to MCI and AD patients (Iacono et al. 2009; Riudavets et al. 2007). These results have been interpreted as reflecting active compensatory cellular responses to injury.

Beyond the main effects of hippocampal volume on ADAS-cog resilience and ADNI-mem resilience, regression analyses showed significant interaction effects between hippocampal volume (raw and normalized, left and right) and t-tau on ADAS-cog resilience and ADNI-mem resilience, suggesting that the association between hippocampal volume and resilience dynamically increases with increasing t-tau levels (see Figure 2). Tau pathology in aging and early AD-stages has mainly been found in medial temporal and hippocampal regions (Braak and Braak 1995; de Calignon et al. 2012; Johnson et al. 2016). This spatial proximity of tau pathology to the hippocampus (respectively spatial overlap) may explain the particular importance of hippocampal resilience properties with increasing tau pathology. Of note, both the main effects of hippocampal volume on ADAS-cog resilience and ADNI-mem resilience and the interaction effects between hippocampal volume and t-tau on ADAS-cog resilience and ADNI-mem resilience remained unchanged when controlling for brain volume and education as already known resilience factors, suggesting that hippocampal volume represents an independent resilience factor (data not shown).

Conclusion

With the present work, we aimed at providing a methodological approach for the investigation of resilience factors that extends and re-conceptualizes existing regression approaches. Besides the identification of potential resilience factors it aims at the differentiation of general and dynamic resilience factors in terms of their association with pathology. Given its unspecific and superordinate nature it may find a wider application and thereby increase the comparability between studies. Utility of the approach has been demonstrated in age and AD-related brain pathology. Widely accepted resilience factors in the aging and AD research field, including education and brain volume, could be reproduced by the model. Moreover, analyses highlighted hippocampal volume as a promising resilience factor against age and AD-related brain pathology, particularly in case of elevated tau-pathology.

Acknowledgements Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage, 38*(1), 95–113.

Braak, H., & Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging, 16*(3), 271–278.

Cannon, W. B. (1932). *The wisdom of the body*. New York: W.W. Norton and Co..

Chételat, G., Villemagne, V. L., Pike, K. E., Baron, J.-C., Bourgeat, P., Jones, G.,. .. Szoeke, C. (2010). Larger temporal volume in elderly with high versus low beta-amyloid deposition. Brain, awq 187.

Christensen, H., Anstey, K. J., Leach, L. S., & Mackinnon, A. J. (2008). Intelligence, education, and the brain reserve hypothesis. *The Handbook of Aging and Cognition, 3*.

Cohen, J. (1983). The cost of dichotomization. *Applied Psychological Measurement, 7*(3), 249–253.

Crane, P. K., Carle, A., Gibbons, L. E., Insel, P., Mackin, R. S., Gross, A., et al. (2012). Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging and Behavior, 6*(4), 502–516.

Davis, D., Schmitt, F., Wekstein, D., & Markesbery, W. (1999). Alzheimer neuropathologic alterations in aged cognitively normal subjects. *Journal of Neuropathology & Experimental Neurology, 58*(4), 376–388.

de Calignon, A., Polydoro, M., Suárez-Calvet, M., William, C., Adamowicz, D. H., Kopeikina, K. J., et al. (2012). Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron, 73*(4), 685–697.

DeCarli, C., Fletcher, E., Ramey, V., Harvey, D., & Jagust, W. J. (2005). Anatomical mapping of white matter hyperintensities (WMH). *Stroke, 36*(1), 50–55.

Erten-Lyons, D., Woltjer, R., Dodge, H., Nixon, R., Vorobik, R., Calvert, J., et al. (2009). Factors associated with resistance to dementia despite high Alzheimer disease pathology. *Neurology, 72*(4), 354–360.

Ewers, M., Insel, P. S., Stern, Y., Weiner, M. W., & Initiative, A. s. D. N. (2013). Cognitive reserve associated with FDG-PET in preclinical Alzheimer disease. *Neurology, 80*(13), 1194–1201.

Fletcher, E., Singh, B., Harvey, D., Carmichael, O., & DeCarli, C. (2012). *Adaptive image segmentation for robust measurement of longitudinal brain tissue change.* Paper presented at the Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE.

Frisoni, G. B., Jack, C. R., Bocchetta, M., Bauer, C., Frederiksen, K. S., Liu, Y., et al. (2015). The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: evidence of validity. *Alzheimer's & Dementia, 11*(2), 111–125.

Hohman, T. J., McLaren, D. G., Mormino, E. C., Gifford, K. A., Libon, D. J., Jefferson, A. L., et al. (2016). Asymptomatic Alzheimer disease Defining resilience. *Neurology, 87*(23), 2443–2450.

Iacono, D., Markesbery, W., Gross, M., Pletnikova, O., Rudow, G., Zandi, P., & Troncoso, J. (2009). The Nun Study Clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. *Neurology, 73*(9), 665–673.

Jack, C., Petersen, R. C., Xu, Y., O'brien, P., Smith, G. E., Ivnik, R. J., et al. (2000). Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology, 55*(4), 484–490.

Johnson, K. A., Schultz, A., Betensky, R. A., Becker, J. A., Sepulcre, J., Rentz, D., et al. (2016). Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Annals of Neurology, 79*(1), 110–119.

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., et al. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology, 23*(2), 138–144.

Lloyd, D., Aon, M. A., & Cortassa, S. (2001). Why homeodynamics, not homeostasis? *The Scientific World Journal, 1*, 133–145.

Mufson, E. J., Mahady, L., Waters, D., Counts, S. E., Perez, S. E., DeKosky, S. T., et al. (2015). Hippocampal plasticity during the progression of Alzheimer's disease. *NeuroScience, 309*, 51–67.

Riley, K. P., Snowdon, D. A., & Markesbery, W. R. (2002). Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Annals of Neurology, 51*(5), 567–577.

Riudavets, M. A., Iacono, D., Resnick, S. M., O'Brien, R., Zonderman, A. B., Martin, L. J., et al. (2007). Resistance to Alzheimer's pathology is associated with nuclear hypertrophy in neurons. *Neurobiology of Aging, 28*(10), 1484–1492.

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. The American journal of psychiatry.

Shaw, L. M., Vanderstichele, H., Knapik-Czajka, M., Clark, C. M., Aisen, P. S., Petersen, R. C., et al. (2009). Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Annals of Neurology, 65*(4), 403–413.

Shi, F., Liu, B., Zhou, Y., Yu, C., & Jiang, T. (2009). Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus, 19*(11), 1055–1064.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society, 8*(03), 448–460.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Disease & Associated Disorders, 20*(2), 112–117.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015–2028.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006–1012.

Wolf, D., Bocchetta, M., Preboske, G. M., Boccardi, M., Grothe, M. J., & Initiative, A. s. D. N. (2017). Reference standard space hippocampus labels according to the EADC-ADNI harmonized protocol: Utility in automated volumetry. In *Alzheimer's & Dementia*.

Yates, F. E. (1994). Order and complexity in dynamical systems: homeodynamics as a generalized mechanics for biology. *Mathematical and Computer Modelling, 19*(6), 49–74.