Neurobiology of Aging xxx (2019) 1–3

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Negative Results

Education does not protect cognitive function from brain pathology in the ADNI 2 cohort

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ARTICLE INFO

Article history:
Received 26 June 2019
Received in revised form 30 October 2019
Accepted 22 November 2019

Keywords:
Education
Cognitive reserve
Alzheimer's disease
Cognition
Biomarkers

ABSTRACT

Educational attainment is widely accepted as a cognitive reserve variable. However, few studies have demonstrated that education statistically moderates the effects of pathology on cognition. Here, we explored this issue in a sample of 441 Alzheimer's disease (AD) and mild cognitive impairment participants from the Alzheimer's Disease Neuroimaging Initiative cohort who had AD markers ($A\beta_{42}$, tau, structural brain volumes) at baseline and underwent cognitive testing at baseline and at 6-month, 12-month, and 24-month time points. An AD-related biomarker (atrophy/pathology) composite at baseline was developed using stepwise backward linear regression. Potential moderation effects of education on the relationship between AD biomarkers and cognition were explored using linear mixed models. Education was positively correlated with cognition, and biomarkers were negatively correlated with cognition, across domains and diagnostic groups. However, education generally did not moderate the effects of biomarkers on baseline or longitudinal cognition. Our results do not support the hypothesis that education protects cognitive function from brain pathology in the Alzheimer's Disease Neuroimaging Initiative cohort, questioning its accepted status as a reserve variable.

1. Introduction

Educational attainment and its correlates have positive effects on cognitive performance across the life span (Brewster et al., 2014; Salthouse, 1991a,b). Such findings have raised the possibility that education may promote cognitive reserve (CR) (Stern, 2002). A number of studies have provided apparent support for education as a CR variable, reporting more severe Alzheimer's disease (AD) pathology in those with higher versus lower education (Garibotto et al., 2008; Kemppainen et al., 2008). However, new consensus guidelines concerning CR research (Stern et al., 2018) suggest that conclusions concerning CR variables should be based on statistical moderation between pathology and clinical/cognitive status variables. That is, cognitive performance should be predicted by the interaction between a purported CR variable and brain status.

Only a few studies with large sample sizes have reported such statistical moderation (Bennett et al., 2005, 2003, Stern et al., 1995, 1992). Furthermore, these findings are counterbalanced by several null results (Koepsell et al., 2008; Roe et al., 2007; Stern et al., 1999). Potential discrepancies between previous results could include the clinical status of participants, the cognitive domain tested, and the use of cross-sectional versus longitudinal designs. Here, we comprehensively explored these possibilities by examining if education moderates the effects of pathology on either baseline or longitudinal memory (MEM) and/or executive function (EF) in mild cognitive impairment (MCI) and/or AD clinical groups.

2. Materials and methods

We accessed data from 441 participants with MCI or AD from Alzheimer's Disease Neuroimaging Initiative 2 that had summary measures of MRI regional volumes, cerebrospinal fluid AD pathology (n = 426), composite scores of MEM (Crane et al., 2012) and EF (Gibbons et al., 2012), and basic demographic information (Table 1) at baseline (Figure S1). Composite measures of baseline atrophy/pathology were derived empirically based on their association with

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[1] 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/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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https://doi.org/10.1016/j.neurobiolaging.2019.11.017

Table 1
Participant demographics at baseline

Characteristic	Total (N = 441)	MCI (N = 313)	AD (N = 128)	*p*-value
Age (y)	72.5 (7.7)	71.7 (7.3)	74.4 (8.4)	0.001
Female (n, %)	191 (43.3)	140 (44.7)	51 (39.8)	0.347
Education (y)	16.2 (2.6)	16.4 (2.6)	15.8 (2.6)	0.021
Tau/Aβ_{42} ratio[a]	0.73 (0.55)	0.60 (0.47)	1.05 (0.60)	<0.001
MEM cognitive composite	−0.073 (0.82)	0.25 (0.70)	−0.88 (0.49)	<0.001
EF cognitive composite	−0.028 (1.07)	0.32 (0.92)	−0.87 (0.96)	<0.001
MEM pathology composite	0 (0.34)	−0.12 (0.30)	0.27 (0.27)	<0.001
EF pathology composite	0 (0.45)	−0.14 (0.40)	0.34 (0.36)	<0.001

Demographic, pathology, and performance information is displayed for all participants. Reported values are mean with standard deviation, beside gender. Those with AD were significantly older, had greater AD pathology burden, were less educated, and performed worse on neurocognitive testing than those with MCI.
Key: MCI, mild cognitive impairment; AD, Alzheimer's disease; MEM, memory; EF, executive function.
[a] A total of 15 participants were missing data on this component of the pathology composite.

scores per cognitive domain. Baseline composite measures of atrophy/pathology here included both structural volumes and concentration ratio of tau/Aβ_{42} in the cerebrospinal fluid (Bakkour et al., 2009; Fagan et al., 2007; Shaw et al., 2009). Individual structures were ICV-normalized, and both structural volumes and tau/Aβ_{42} ratio were z-scored relative to the group mean before they were entered into the composites. Backward elimination was used to remove the least significant predictor one at a time until only z-scored predictors with $p < 0.05$ were remaining, which were averaged to form the cognitive domain-specific composites.

Using SPSS, linear mixed models were then used to determine if baseline pathology and education predict cognitive scores at baseline and longitudinally for both MCI and AD groups at $p < 0.05$, with MEM or EF scores as the dependent variables. Models included all possible interactions excluding age and gender (pathology × time, education × time, pathology × education, and pathology × education × time).

3. Results

There was a main effect of education on both cognitive domains in the AD and MCI groups (Tables 2 and 3). There were no significant education × time interactions in either cognitive domain, for either group (Tables 2 and 3).

The specific pathology variables predictive of each cognitive composite variable are listed in Table S1. The MEM and EF pathology composite measures were highly significant predictors of their respective baseline cognitive domain scores as listed in Tables 2 and 3 (all *p* values ≤0.001).

There were no significant education × pathology or education × pathology × time interactions in either cognitive domain for either diagnostic group (Tables 2 and 3). Further investigation using an age median split yielded the same conclusion for MEM (Tables S2, S3) with a mixed conclusion for EF (Tables S2, S3; Figure S2).

Table 2
Alzheimer's disease

Category	Beta	Memory F-value	*p*-value	Beta	EF F-value	*p*-value
Age	−0.001	0.019	0.889	0.003	0.116	0.734
Gender	−0.155	3.465	0.065	−0.159	1.180	0.280
Education	0.063	5.006	0.027	0.154	6.586	0.012
Pathology composite	−0.837	39.523	<0.001	−1.216	41.90	<0.001
Time	−0.446	34.772	<0.001	−0.780	19.87	<0.001
Path composite × time	−0.034	5.257	0.003	0.191	2.135	0.103
Education × path	−0.140	1.712	0.193	−0.198	0.490	0.486
Education × time	0.141	2.374	0.078	0.174	1.419	0.245
Education × path × time	−0.313	1.118	0.348	−0.003	0.916	0.438

Unstandardized beta, F and *p* values are reported for linear mixed models for both MEM and EF in those with AD. There were no education × pathology interactions either at baseline or longitudinally through 2 y.
Key: EF, executive function.

Table 3
Mild cognitive impairment

Category	Beta	Memory F-value	*p*-value	Beta	EF F-value	*p*-value
Age	−0.008	3.222	0.074	−0.027	15.372	<0.001
Gender	−0.215	12.227	0.001	−0.104	1.341	0.248
Education	0.076	4.805	0.029	0.132	4.757	0.030
Pathology composite	−1.244	156.122	<0.001	−0.789	58.864	<0.001
Time	−0.107	18.210	<0.001	−0.072	1.918	0.127
Path composite × time	−0.538	13.794	<0.001	−0.357	5.692	0.001
Education × path	0.053	0.070	0.792	−0.151	3.753	0.054
Education × time	0.006	0.158	0.924	−0.076	1.376	0.250
Education × path × time	−0.122	1.236	0.297	−0.176	0.960	0.412

Unstandardized beta, F, and *p* values are reported for linear mixed models for both MEM and EF in those with MCI. There were no education × pathology × time interactions through 2 y, although there was a trend for an education × pathology interaction at baseline for EF. However, in this interaction, EF scores were not as negatively affected by pathology in lower education than those with higher education, which the opposite direction expected using cognitive reserve theory.
Key: MCI, mild cognitive impairment; MEM, memory; EF, executive function.

4. Discussion

Our results indicate that higher educational attainment was associated with better cognitive functioning in MCI and AD, in both MEM and EF domains. However, education generally did not moderate the effects of atrophy/pathology, time or their interaction on cognitive function. Only in a subgroup of younger AD participants was a moderating effect of education observed and this effect was selective to EF. These results are consistent with other studies with large samples (Koepsell et al., 2008; Roe et al., 2007; Vemuri et al., 2011). Overall, our results suggest that education is an insufficient proxy for CR. However, the selective CR effect we observed in a younger AD subgroup leaves open the possibility that education may protect EF against significant pathology before additional brain declines associated with advanced aging (see Supplementary Material for the complete version of this article).

Disclosure

The authors report no disclosures.

Acknowledgements

ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc; Piramal Imaging; Servier;

Takeda Pharmaceutical Company; and Transition Therapeutics. 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 Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

This work was supported 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) and the National Institutes of Health (R01 AG055449).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.11.017.

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