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## Education does not Protect Cognitive Function from Brain Pathology in the ADNI 2 Cohort

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### 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 (MCI) participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI2) 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 timepoints. An AD-related atrophy/pathology composite at baseline was developed using stepwise backward linear regression. Potential moderation effects of education on the relationship between pathology and memory and executive function were explored using linear mixed models. Education was positively correlated with cognition, and pathology was negatively correlated with cognition, across domains and diagnostic groups. However, education generally did not moderate the effects of pathology on baseline or longitudinal cognition. Our results do not support the hypothesis that education protects cognitive function from brain pathology in the ADNI 2 cohort, questioning its accepted status as a reserve variable.

### Keywords

Education; Cognitive Reserve; Alzheimer's Disease; Cognition; Biomarkers

## 1. Introduction

Educational attainment and its correlates have positive effects on cognitive performance across the lifespan (Brewster et al., 2014; Salthouse, 1991a, 1991b). Such findings have

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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 AD pathology in those with higher versus lower education (Garibotto et al., 2008; Kempainen 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). Further, these findings are counterbalanced by several null results (Koeppel 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 and/or executive function in 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 (ADNI2) that had summary measures of MRI regional volumes, CSF AD pathology (n=426), composite scores of memory (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 scores per cognitive domain. Baseline composite measures of atrophy/pathology here included both structural volumes and concentration ratio of tau/A $\beta$ <sub>42</sub> in the CSF (Bakkour et al., 2009; Fagan et al., 2007; Shaw et al., 2009). Individual structures were ICV-normalized, and both structural volumes and tau/A $\beta$ <sub>42</sub> 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  $\times$  time, education  $\times$  time, pathology  $\times$  education, and pathology  $\times$  education  $\times$  time).

## 3. Results

There was a main effect of education on both cognitive domains in the AD and MCI groups (Tables 2, 3). There were no significant education  $\times$  time interactions in either cognitive domain, for either group (Tables 2, 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, 3 (all p values < 0.001).

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

## 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 (Koeppel et al., 2008; Roe et al., 2007; Vemuri et al., 2011). Overall, our results are consistent with a view that education is an insufficient proxy for cognitive reserve. However, the selective CR effect we observed in a younger AD subgroup leaves open the possibility that education may protect EF against significant pathology prior to additional brain declines associated with advanced aging (See Supplementary Material for the complete version of this manuscript).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

<b>ADNI</b>	Alzheimer's Disease Neuroimaging Initiative
<b>AD</b>	Alzheimer's Disease
<b>MCI</b>	Mild Cognitive Impairment
<b>CR</b>	Cognitive Reserve
<b>MRI</b>	Magnetic Resonance Imaging
<b>MEM</b>	Memory
<b>EF</b>	Executive Function
<b>CSF</b>	Cerebrospinal Fluid
<b>A<math>\beta</math><sub>42</sub></b>	Amyloid-Beta 42
<b>ICV</b>	Intracranial Volume
<b>LMM</b>	Linear Mixed Models

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**Table 1**

## Participant Demographics at Baseline

Characteristic	Total (N=441)	MCI (N=313)	AD (N=128)	<i>p</i> -value
Age (Years)	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 (Years)	16.2 (2.6)	16.4 (2.6)	15.8 (2.6)	0.021
Tau/A $\beta$ <sub>42</sub> ratio *	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.

\* A total of 15 participants were missing data on this component of the pathology composite.

**Table 2:**

AD

Category	Memory			EF		
	Beta	F-value	p-value	Beta	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 x Path x 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 x pathology interactions either at baseline or longitudinally through 2 years.

**Table 3:**

MCI

Category	Memory			EF		
	Beta	F-value	<i>p</i> -value	Beta	F-value	<i>p</i> -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 x Path x 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 x pathology x time interactions through 2 years, although there was a trend for an education x 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.