Published in final edited form as:

Parkinsonism Relat Disord. 2015 August ; 21(8): 899–904. doi:10.1016/j.parkreldis.2015.05.020.

Cognitive reserve and β -amyloid pathology in Parkinson disease

Carolyn Lucero, MS^{d,g}, Meghan C. Campbell, PhD^{a,b}, Hubert Flores, MS^a, Baijayanta Maiti, MD, PhD^a, Joel S. Perlmuter, MD^{a,b,c,d,e}, and Erin R. Foster, OTD^{a,d,f,*}

Carolyn Lucero: carolynlucero33@gmail.com; Meghan C. Campbell: meghanc@npg.wustl.edu; Hubert Flores: floresh@npg.wustl.edu; Baijayanta Maiti: maitib@neuro.wustl.edu; Joel S. Perlmuter: joel@npg.wustl.edu

^aDepartment of Neurology, Washington University School of Medicine, St. Louis, MO, USA

^bDepartment of Radiology, Washington University School of Medicine, St. Louis, MO, USA

^cDepartment of Anatomy & Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

^dProgram in Occupational Therapy, Washington University School of Medicine, St. Louis, MO, USA

^eProgram in Physical Therapy, Washington University School of Medicine, St. Louis, MO, USA

^fDepartment of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

^gOccupational Therapist, Bethel Public Schools, Spanaway, WA, USA

Abstract

Introduction—Dementia in Parkinson disease (PD) is associated with abnormal accumulation of proteins, including β -amyloid, in cortical regions. High cognitive reserve capacity may protect cognition from β -amyloid and delay the onset of dementia. We tested the cognitive reserve theory in PD by determining whether educational attainment, a proxy for cognitive reserve, modifies the correlation between cortical β -amyloid accumulation and cognitive impairment.

Methods—PD participants (N=155) underwent MRI to quantify brain volume and [¹¹C] PiB PET imaging to quantify fibrillar β -amyloid deposition. Mean cortical binding potentials (MCPB) were calculated for each participant, with higher scores indicating more fibrillar β -amyloid. Global cognitive function was assessed using the Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE). Multiple linear regression analysis was used to determine whether education modified the relationship between MCPB and cognitive function after controlling for brain volume.

Results—MCPB interacted with educational attainment to predict scores on each of the cognitive outcome measures ($p < 0.02$). Post-hoc analysis revealed that the effect of MCPB on

*Corresponding author: Erin R. Foster, OTD, Washington University School of Medicine, Campus Box 8111, 660 South Euclid Avenue, St. Louis, MO 63110, Telephone: (314) 286-1638, Fax: (314) 747-3258, erfoster@wustl.edu.

The authors declare no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

cognitive function changed once the level of education reached 16 years. For participants with less than 16 years of education ($n=68$), higher MCBP correlated with worse cognitive function, with MCBP accounting for 8-30% of the variance in MMSE and CDR scores ($ps < 0.02$). For participants with at least 16 years of education ($n=87$), MCBP did not correlate with MMSE or CDR scores ($R^2s < 0.02$, $ps > 0.17$).

Conclusion—These findings provide support for the cognitive reserve theory in PD and suggest that education may protect PD patients' cognition against cortical β -amyloid pathology.

Keywords

Parkinson's disease; dementia; cognition; cognitive reserve; education

Dementia commonly occurs in people with Parkinson disease (PD). Point prevalence estimates of dementia in PD are about 30%(1), and at least 80% of people who survive more than 20 years with PD develop dementia(2). Accumulation of cortical synucleinopathy including Lewy bodies and Lewy neurites (aggregated α -synuclein) in the cerebral cortex and limbic system is likely the primary substrate of dementia in PD(3). However, abnormal accumulation of β -amyloid also occurs in more than half of PD with dementia (4) and can be measured *in vivo* using [^{11}C] PiB PET imaging (5). Abnormally elevated cortical [^{11}C] PiB binding in patients with PD correlates with greater cognitive impairment and cognitive decline over time (5, 6).

Autopsy data often demonstrate a mismatch between an individual's level of neuropathology thought to contribute to dementia and the clinical severity of the cognitive impairment. For example, abnormal β -amyloid deposition and abnormal tau deposition in the form of neurofibrillary tangles are typically found in people with Alzheimer's disease (AD) once dementia develops clinically; however, studies have shown that 33-67% of people who are cognitively normal at death have these pathologic changes(7-9). Similarly, people with PD that do not have cognitive impairment may have abnormal cortical PiB uptake (5). The concept of cognitive reserve arose to explain this mismatch (10). Cognitive reserve refers to the ability to make flexible, adaptable and efficient use of brain networks or alternate cognitive processing strategies that permits individuals to functionally compensate for neuropathology (10). Individual differences in reserve capacity could confer differential susceptibility to the effects of brain damage. Individuals with high cognitive reserve maintain function despite brain damage, but individuals with low cognitive reserve cannot compensate for an equivalent degree of brain damage and thus express cognitive impairment. Life experiences can influence reserve capacity, particularly those that are mentally stimulating (11). This notion is supported by studies showing, that engagement in mentally stimulating activities inversely relates to the development of dementia (11, 12).

Substantial evidence supports the existence of cognitive reserve in the context of normal aging and AD. Educational attainment is the most commonly used indicator of cognitive reserve in this literature. Older adults with higher education maintain cognitive function despite β -amyloid accumulation measured postmortem (13) and *in vivo*(14), whereas cognition among those with lower education is negatively affected by β -amyloid accumulation. A large population-based autopsy study ($N = 872$) found that while education

does not protect against the development of various neurodegenerative or vascular pathologies, it does mitigate the impact of these pathologies on the expression of dementia, thus providing further support for the functional compensatory role of cognitive reserve(15). Finally, a recent meta-analysis (N = 437,477) provides robust support for a number of postulates of the cognitive reserve hypothesis, including the association of low education and increased risk of dementia and the observation that cognitive impairment in highly educated people requires more neuropathology(16). Interestingly, education may be less relevant to the relationship between tau pathology and cognitive impairment (13, 15).

The mechanism by which education exerts these effects remains unclear. Greater educational attainment may be indicative of early cognitive enrichment or may lead to higher lifelong cognitive enrichment, both of which may promote neurogenesis, neuronal signaling, and synaptic plasticity in animals (17, 18). Further, lifelong cognitive enrichment may induce functional network changes and the increased availability of compensatory networks (18). Alternatively, educational attainment may simply be a marker for those with high pre-existing neural or cognitive capacity due to, for example, genetic factors.

The cognitive reserve hypothesis also may apply to PD. Although not a universal finding, several studies demonstrate a relationship between level of education and cognitive function in PD(19, 20). For example, higher education relates to better cognitive performance in PD after controlling for symptom severity and disease duration(21), and lower education predicts dementia(22) and greater cognitive decline over time(19, 23). However, these studies cannot determine whether education protects cognition against neuropathology or simply provides an advantage on cognitive tests. Direct measures of neuropathology must be included in statistical models to ascertain the protective role of education and cognitive reserve in PD.

We investigated cognitive reserve in PD using [^{11}C] PiB PET imaging to quantify cortical β -amyloid neuropathology in a large and well-characterized sample of PD participants. We used moderation analysis to determine if educational attainment influences the relationship between cortical β -amyloid and cognitive function in PD after controlling for brain volume. In accordance with the cognitive reserve theory, we hypothesized that education protects against the effects of neuropathology such that cortical β -amyloid would be less predictive of cognitive impairment in individuals with higher education compared to those with lower education.

Methods

This study was approved by the Human Research Protection Office and Radioactive Drug Research Committee at Washington University School of Medicine (WUSM) and was completed in accordance with the Helsinki Declaration. Written informed consent was obtained for all participants.

Design and Participants

Participants with PD were recruited through the Movement Disorders Center at WUSM (consecutive patients were asked) and the community (advertisements in the Greater St.

Louis, Chapter of the American Parkinson Disease Association newsletter and at educational events) between October 2006 and February 2014. Inclusion criteria included no major neurologic or psychiatric diseases other than PD, ability to lie still for 90 minutes of neuroimaging, no contraindications to magnetic resonance imaging (MRI), and consent to brain donation. Participants were diagnosed with PD based on modified United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria with clear clinical response to levodopa. Participants underwent structural MRI, PiB PET imaging, clinical interview and neurologic examination. Movement disorders specialists performed the clinical and neurological evaluations. Motor evaluations (Unified Parkinson's Disease Rating Scale Part III; UPDRS) were first completed off antiparkinsonian medications overnight and then repeated following medication administration.

Measures

Educational attainment, obtained via self-report, was used as the proxy measure of cognitive reserve. The Clinical Dementia Rating scale (CDR)(24) was used to quantify the presence and severity of dementia. The CDR is a structured interview that assesses cognition and function in six categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The global CDR score is a weighted average of the category ratings, where CDR 0 indicates no dementia, CDR 0.5 indicates cognitive decline (not meeting criteria for dementia), and CDR 1, 2, and 3 indicate mild, moderate, and severe dementia, respectively. The "sum of boxes" score (CDR-SB) is the sum of the category ratings and can range from 0 to 18. The Mini-Mental State Examination (MMSE) was used to measure global cognitive function. Scores on the MMSE range from 0 to 30, with lower scores indicating, worse cognitive function. These assessments were conducted while participants were on antiparkinsonian medication.

Magnetic resonance images were obtained in a Siemens 3T TRIO scanner equipped with a standard 12-channel head coil. Anatomical imaging included one sagittal T1-weighted magnetization-prepared rapid gradient echo (MP-RAGE) scan (repetition time (TR) = 2400 ms; inversion time (TI) = 1000 ms, echo time (TE) = 16 ms, flip angle=8°, 0.9 mm³ voxels) and T2-weighted MR scan (TE = 455 ms, TR = 3200 ms, 1mm³ voxels). Automated cortical reconstruction and volumetric segmentation was performed with Freesurfer image analysis suite (version 5.3, <http://sufer.nmr.mgh.harvard.edu/>) as previously outlined(25). The resultant images were visually inspected for accuracy and manual pial surface edits were employed if necessary. The total brain volume as automatically computed by FreeSurfer consists of gray and white matter, excluding brainstem, ventricles, cerebrospinal fluid, and choroid plexus. Brain volume was corrected for individual differences in head size by using the estimated total intracranial volume.

[¹¹C]-PiB PET imaging was used to measure fibrillar β -amyloid deposition in the brain. [¹¹C]-PiB synthesis, PET imaging and data analyses were done as previously described (5, 26). Binding potentials (BP) were calculated from the tracer distribution volume (DV) as $BP = DV - 1$. Mean cortical binding potentials (MCBP) were calculated for each participant as the average of BPs from four cortical regions (prefrontal cortex, gyrus rectus, lateral

temporal cortex and precuneus), with higher scores indicating more fibrillar β -amyloid. MCBP values ≥ 0.18 are considered abnormally elevated (27).

Statistical Analysis

First, multiple linear regression models were used to examine the independent associations of brain volume, MCBP and education with cognitive function (Model 1). Then an interaction term (education $\times$ MCBP) was added to these models to test whether education moderated the relationship of MCBP and cognitive function (Model 2), whereby a significant interaction would indicate moderation. Separate models were run for each cognitive outcome variable (MMSE, CDR, and CDR-SB). Significant interactions were probed using the Johnson-Neyman technique to determine the value along the continuum of education at which the association of MCBP and cognitive function transitioned between statistically significant and not significant (28). In a secondary analysis, these steps were repeated with a block of clinical predictors entered first (described below). All tests were 2-tailed, and $p < 0.05$ was considered significant.

Results

The final sample included 155 participants with PD. Demographic and clinical characteristics of the sample are presented in Table 1. The majority of participants had a low cortical β -amyloid burden (16% were PIB+) and mild, if any, cognitive impairment (84% had CDR ≥ 0 or 0.5). Of the participants with dementia (CDR < 1), 10 had Dementia with Lewy Bodies (DLB) and 15 had Parkinson Disease Dementia (PDD) based on timing of onset of dementia with respect to onset of motor manifestations of PD. In addition, 14 participants (5 CDR 0.5, 9 CDR < 1) were on or had taken an anti-dementia drug (primarily donepezil).

Table 2 presents the independent contributions of brain volume, MCBP and education to cognitive function (i.e., main effects; Model 1) and the conditional effects when an interaction term is added (Model 2). In Model 1, brain volume, MCBP and education together accounted for 19% of the variance in MMSE, 16% of the variance in CDR, and 14% of the variance in CDR-SB ($F_s = 7.88, p_s < 0.001$). In each of these models, the independent association of MCBP and cognition was 4% or less ($p_s \leq 0.02$). In Model 2, the interaction of education and MCBP accounted for an additional 4% of the variance in MMSE, 9% of the variance in CDR, and 8% of the variance in CDR-SB ($F = 5.75, p_s \leq 0.02$), indicating the presence of moderation. The full model with the interaction term included accounted for 23%, 25% and 22% of the variance in MMSE, CDR and CDR-SB, respectively ($F_s = 9.69, p_s \leq 0.001$).

The interactions were probed to determine the years of formal education at which the effect of MCBP on cognitive function changed from being statistically significant to not significant. These values were 16.3 for MMSE, 16.2 for CDR, and 16.1 for CDR-SB. This is roughly equivalent to 16 years of formal education, i.e., 4 years of college. These results indicate that for participants with less than 16 years of education, MCBP was associated with cognitive function such that higher MCBP was associated with worse MMSE and CDR scores. In contrast, in those with at least 16 years of education, MCBP was not associated

with MMSE or CDR scores. Specifically, in the less than 16 years education group ($n = 68$), MCBP accounted for 8%, 30%, and 24% of the variance in MMSE, CDR and CDR-SB, respectively ($ps = 0.02$), whereas in the at least 16 years education group ($n = 87$), MCBP accounted for less than 2% of the variance in cognitive outcomes ($ps = 0.17$). These relationships are illustrated in Figure 1. The education groups did not differ in demographic or clinical characteristics, brain volume, MCBP, proportion of PIB+, or cognitive outcomes ($ps = 0.10$).

The moderation analyses were repeated within the PIB+ group ($n = 26$) to investigate whether education may protect cognition in the context of abnormally elevated β -amyloid. In Model 1, brain volume, MCBP and education together accounted for 27% of the variance in MMSE, 32% of the variance in CDR, and 26% of the variance in CDR-SB ($Fs = 2.28$, $ps = 0.11$). In each of these models, the variance in cognition accounted for by brain volume and MCBP together was less than 14%, as education accounted for most of the variance. In Model 2, the interaction of education and MCBP accounted for an additional 9% of the variance in MMSE, 15% of the variance in CDR, and 10% of the variance in CDR-SB ($F = 2.43$, $ps = 0.14$). In the less than 16 years education group ($n = 10$), MCBP accounted for 21%, 27%, and 17% of the variance in MMSE, CDR and CDR-SB, respectively ($n.s.$), whereas in the at least 16 years education group ($n = 16$), MCBP accounted for less than 3% of the variance in cognitive outcomes ($n.s.$). These results parallel those of the full sample analysis and suggest moderation, but the small sample size limited the ability to detect statistically significant effects.

A secondary analysis was conducted to determine whether accounting for cognitive reserve improves the prediction of cognitive impairment in PD beyond typical known clinical predictors. The moderation analyses were repeated with factors associated with the cognitive outcomes in pairwise analysis included as covariates in an initial block. This included UPDRS Motor score ($rs = 0.51$, $ps < 0.001$), age ($rs = 0.33$, $ps < 0.001$), disease duration ($rs = 0.25$, $ps < 0.002$), depression ($rs = 0.20$, $ps < 0.03$) and anti-dementia drug status ($Zs > 1.87$, $ps = 0.06$) but not gender, levodopa equivalent daily dose, or APOE4 status ($ps = 0.16$). In Model 1, the clinical covariates, brain volume, MCBP and education together accounted for 45% of the variance in MMSE, 52% of the variance in CDR, and 52% of the variance in CDR-SB ($Fs = 26.29$, $ps = 0.001$). In Model 2, the interaction of education and MCBP accounted for an additional 2% of the variance in MMSE, 6% of the variance in CDR, and 5% of the variance in CDR-SB ($F = 3.97$, $ps = 0.05$), indicating the presence of moderation. The full model with the interaction term included accounted for 47%, 55% and 53% of the variance in MMSE, CDR and CDR-SB, respectively ($Fs = 20.93$, $ps = 0.001$). In the less than 16 years education group, MCBP, accounted for 3%, 12% and 8% of the variance in MMSE, CDR and CDR-SB, respectively ($ps = 0.08$), whereas in the at least 16 years education group, MCBP was not associated with the cognitive outcomes ($ps = 0.86$).

Discussion

Educational attainment modifies the relationship between β -amyloid neuropathology and the clinical expression of cognitive impairment among individuals with PD such that those with higher education maintain better cognitive function in the presence of cortical β -amyloid

pathology. These findings provide support for the cognitive reserve theory in the context of PD and suggest that education may protect PD patients' cognition against cortical β -amyloid pathology.

MCBP was a significant but weak independent predictor of each of the three cognitive outcomes in the main effects models. However, the addition of an interaction term between education and MCBP improved the predictive power of MCBP and the overall models. It revealed that the association of cortical β -amyloid and cognition in PD is not simple but instead varies according to educational attainment. Specifically, among those with lower education, increased cortical β -amyloid is predictive of cognitive impairment, whereas among those with higher education, cortical β -amyloid is not predictive of cognitive impairment. These results illustrate that accounting for the potential influence of cognitive reserve capacity can improve the predictive value of β -amyloid for identifying cognitive decline and potentially dementia in PD. Our results are consistent with studies in AD in that education modifies the relationship between cortical β -amyloid deposition and cognition(13-16). However, the independent relationship of β -amyloid and cognition appears stronger in the context of AD, as education only attenuates this relationship in studies in AD rather than eliminates it as it did in the current PD study. These differences provide further support that the role of β -amyloid in PD may differ from that in AD(26). Cortical synucleinopathy may be the primary pathologic factor contributing to cognitive impairment in PD(3), but these and previous data suggest that abnormal cortical β -amyloid also contributes(4) or could be a marker for more severe synucleinopathy(29).

Our study addresses a significant gap in cognitive reserve research in PD. Studies of cognitive reserve in PD to-date have investigated the association between education and cognition without considering level of neuropathology(20). While the results from a number of these studies (i.e., higher education is associated with better cognition) are consistent with the cognitive reserve theory, they are limited in their interpretability because they only address two factors of a tripartite relationship. The primary hypothesized role of cognitive reserve is that it protects cognition against dementia-associated neuropathology. Therefore, quantification of neuropathology must be included in studies of cognitive reserve. The current study adds an *in vivo* measure of neuropathology, PiB PET measured fibrillar cortical β -amyloid burden, and includes moderation analysis to demonstrate that education (a proxy for cognitive reserve) influences the relationship of neuropathology and cognitive function in PD even after correct for brain volume and accounting for other relevant clinical predictors. Our findings extend the research demonstrating the protective effect of education in normal aging and AD to PD. Future work should account for other factors that may be associated with cognitive impairment and dementia-related pathology in PD (e.g., comorbidities, smoking).

The low and high education groups in this study had equivalent levels of fibrillar β -amyloid deposition, yet this neuropathology was only predictive of cognitive impairment in the low education group. These findings support the idea that cognitive reserve does not protect against the development of neuropathology but rather mitigates or delays its negative effect on, cognitive function (10, 15). Although the mechanism underlying this effect is not well understood, a leading hypothesis is that individuals with greater cognitive reserve utilize

alternate brain networks to circumvent those networks disrupted by neuropathological changes. Greater educational attainment and an active cognitive lifestyle may induce neurotrophic changes and increase the availability of these compensatory networks (18). The underlying mechanisms of cognitive reserve remain an active research topic.

Our findings have a number of clinical implications. We have shown that, similar to AD, high cognitive reserve capacity may mask or delay the cognitive consequences of dementia-associated neuropathology in PD. However, in AD there is a hypothesized threshold of neuropathological burden at which an individual's cognitive reserve capacity is surpassed and the clinical progression of dementia occurs rapidly. Those with higher purported cognitive reserve die sooner and demonstrate accelerated cognitive decline compared to those with lower cognitive reserve once the clinical manifestations of AD emerge (16). If this applies to PD, clinicians and families of highly educated patients could predict a rapid decline in function once the initial symptoms of dementia occur. Investigation of this issue in PD requires longitudinal data, and such an investigation may provide considerable value for treatment planning. In addition, if cognitive enrichment late in life can maintain or build cognitive reserve, as a number of studies suggest (12, 30), engagement in cognitively challenging activities may be an appropriate recommendation for patients looking to take a proactive role in delaying the onset of cognitive decline associated with their disease.

The generally low levels of cortical β -amyloid and low prevalence of dementia in our sample limit our analyses. The presence of significant interaction effects despite this limited variability suggests that the influence of education not only exists but might be stronger if tested, in a more diverse and representative sample. Importantly, future research should incorporate markers of neuropathology such as α -synuclein that are likely more relevant to dementia in PD than fibrillar β -amyloid measured with PiB PET. Although cortical β -amyloid burden may contribute to cognitive impairment in PD, the relatively weak association of MCBP and cognitive function in the present study indicates that it is not likely a central pathologic feature (5). However, increased, β -amyloid could reflect increased synucleinopathy, as CSF measures of β -amyloid correlate with those of α -synuclein in people with PD (29). In addition, total β -amyloid burden derived from a whole brain measure may be more informative in PD than MCBP, which is based on a set of regions determined from the AD population. The cross-sectional design limits our ability to fully evaluate the role and neural mechanisms of cognitive reserve in the development and clinical course of dementia in PD. Future longitudinal studies with measures of lifelong cognitive enrichment and a more sensitive and comprehensive cognitive battery will be important in accomplishing this goal. Despite these limitations, the current study provides novel evidence in support of the cognitive reserve theory in PD, as it is the first to demonstrate the influence of educational attainment on the relationship between neuropathology and cognitive function in this population.

Acknowledgments

We thank Johanna Hartlein, MSN (Department of Neurology, Washington University School of Medicine, St. Louis, MO), for her contribution to data collection. This work was supported by grants from NIH (NS075321, NS41509, NS058714, NS48924, K23HD071059); the Barnes Jewish Hospital Foundation (BJHF); the American Parkinson Disease Association (APDA) Advanced Research Center for Parkinson Disease at Washington

University in St. Louis; the Greater St. Louis Chapter of the APDA; the Barnes Jewish Hospital Foundation (Elliot Stein Family Fund and Parkinson Disease Research Fund). This study had no industry sponsorship.

References

1. Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. *Mov Disord*. 2005 Oct; 20(10):1255–63. [PubMed: 16041803]
2. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008 Apr 30; 23(6):837–44. [PubMed: 18307261]
3. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. *Ann Neurol*. 2005 Nov; 58(5):773–6. [PubMed: 16240351]
4. Kotzbauer PT, Cairns NJ, Campbell MC, Willis AW, Racette BA, Tabbar SD, et al. Pathologic accumulation of alpha-synuclein and Abeta in Parkinson disease patients with dementia. *Archives of neurology*. 2012 Oct; 69(10):1326–31. [PubMed: 22825369]
5. Foster ER, Campbell MC, Burack MA, Hartlein J, Flores HP, Cairns NJ, et al. Amyloid imaging of Lewy body-associated disorders. *Mov Disord*. 2010 Nov 15; 25(15):2516–23. [PubMed: 20922808]
6. Gomperts SN, Locascio JJ, Rentz D, Santarlasci A, Marquie M, Johnson KA, et al. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. *Neurology*. 2013 Jan 1; 80(1):85–91. [PubMed: 23243071]
7. Neuropathology Group. Medical Research Council Cognitive F, Aging S. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet*. 2001 Jan 20; 357(9251):169–75. [PubMed: 11213093]
8. Crystal H, Dickson D, Fuld P, Masur D, Scott R, Mehler M, et al. Clinico-pathologic studies in dementia: nondemented subjects with pathologically confirmed Alzheimer's disease. *Neurology*. 1988 Nov; 38(11):1682–7. [PubMed: 3185902]
9. Mortimer JA, Snowden DA, Markesbery WR. Head circumference, education and risk of dementia: findings from the Nun Study. *Journal of clinical and experimental neuropsychology*. 2003 Aug; 25(5):671–9. [PubMed: 12815504]
10. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002 Mar; 8(3):448–60. [PubMed: 11939702]
11. Scarmeas N, Stern Y. Cognitive reserve and lifestyle. *Journal of clinical and experimental neuropsychology*. 2003 Aug; 25(5):625–33. [PubMed: 12815500]
12. Wilson RS, Segawa E, Boyle PA, Bennett DA. Influence of late-life cognitive activity on cognitive health. *Neurology*. 2012 Apr 10; 78(15):1123–9. [PubMed: 22491864]
13. Bennett DA, Wilson RS, Schneider JA, Evans DA, Mendes de Leon CF, Arnold SE, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*. 2003 Jun 24; 60(12):1909–15. [PubMed: 12821732]
14. Roe CM, Mintun MA, D'Angelo G, Xiong C, Grant EA, Morris JC. Alzheimer disease and cognitive reserve: variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake. *Archives of neurology*. 2008 Nov; 65(11):1467–71. [PubMed: 19001165]
15. Members ECC, Brayne C, Ince PG, Keage HA, McKeith IG, Matthews FE, et al. Education, the brain and dementia: neuroprotection or compensation? *Brain*. 2010 Aug; 133(Pt 8):2210–6. [PubMed: 20826429]
16. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PloS one*. 2012; 7(6):e38268. [PubMed: 22675535]
17. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nature reviews Neuroscience*. 2006 Sep; 7(9):697–709. [PubMed: 16924259]

18. Valenzuela MJ, Breakspear M, Sachdev P. Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. *Brain research reviews*. 2007 Nov; 56(1): 198–213. [PubMed: 17870176]
19. Hindle JV, Martyr A, Clare L. Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord*. 2014 Jan; 20(1):1–7. [PubMed: 24034887]
20. Poletti M, Emre M, Bonuccelli U. Mild cognitive impairment and cognitive reserve in Parkinson's disease. *Parkinsonism Relat Disord*. 2011 Sep; 17(8):579–86. [PubMed: 21489852]
21. Cohen OS, Vakil E, Tanne D, Nitsan Z, Schwartz R, Hassin-Baer S. Educational level as a modulator of cognitive performance and neuropsychiatric features in Parkinson disease. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology*. 2007 Mar; 20(1):68–72. [PubMed: 17356347]
22. Glatt SL, Hubble JP, Lyons K, Paolo A, Troster AI, Hassanein RE, et al. Risk factors for dementia in Parkinson's disease: effect of education. *Neuroepidemiology*. 1996 Jan-Feb; 15(1):20–5. [PubMed: 8719045]
23. Muslimovic D, Post B, Speelman JD, De Haan RJ, Schmand B. Cognitive decline in Parkinson's disease: a prospective longitudinal study. *J Int Neuropsychol Soc*. 2009 May; 15(3):426–37. [PubMed: 19402929]
24. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993 Nov; 43(11):2412–4. [PubMed: 8232972]
25. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002 Jan 31; 33(3):341–55. [PubMed: 11832223]
26. Campbell MC, Markham J, Flores H, Hartlein JM, Goate AM, Cairns NJ, et al. Principal component analysis of PiB distribution in Parkinson and Alzheimer diseases. *Neurology*. 2013 Aug 6; 81(6):520–7. [PubMed: 23825179]
27. Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, et al. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology*. 2006 Aug 8; 67(3):446–52. [PubMed: 16894106]
28. Hayes, AF. PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling. 2012. [White paper]. Retrieved from <http://www.afhayes.com/public/process2012.pdf>
29. Buddhala C, Campbell MC, Perlmuter JS, Kotzbauer PT. Correlation between decreased CSF alpha-synuclein and Aβeta1-42 in Parkinson disease. *Neurobiology of aging*. 2015 Jan; 36(1):476–84. [PubMed: 25212463]
30. Valenzuela MJ, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2009 Mar; 17(3):179–87. [PubMed: 19225276]

Highlights

- We tested the cognitive reserve theory in Parkinson disease (PD).
- This is the first study of cognitive reserve in PD to measure neuropathology.
- Education moderated the relationship between β -amyloid deposition and cognition.
- Increased β -amyloid correlated with worse cognition in those with lower education.
- β -amyloid was not associated with cognition in those with higher education.

Figure 1.

Predicted relation between MCBP and (A) MMSE, (B) CDR, (C) CDR-SB for participants with < 16 years education.

For the MMSE, higher scores indicate better cognitive function, whereas for CDR and CDR-SB, higher scores indicate worse cognitive function. Standardized residuals of the outcome measures after controlling for brain volume comprise the Y-axis. The X-axis range is restricted to the bulk of the MCBP data ($M \pm 2.5 SD$). MCBP = Mean cortical binding potential; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating global score; CDR-SB = Clinical Dementia Rating sum of boxes score

Table 1

Demographic and clinical characteristics of sample (N = 155).

Variable	Value
Age	68.0 (8.5)
Male/female (n)	106 / 49
Education (years)	15.7 (2.7)
PIB +/- (n)	25 / 130
MCBP	0.16 (0.19)
MMSE ^a	26.9 (3.5)
CDR 0/0.5/1/2/3 (n)	62/68/20/3/2
CDR-SB	1.8 (2.9)
UPDRS off meds ^b	27.1 (10.9)
UPDRS on meds ^c	22.7 (10.9)
Levodopa equivalent daily dose (mg)	757 (554)
Duration of disease (yr)	5.7 (4.4)

Values are shown as mean (SD) with the exception of sex, PIB +/-, and CDR global score which are shown as numbers of participants in each category. MCBP = Mean cortical binding potential; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating global score; CDR-SB = Clinical Dementia Rating sum of boxes score; UPDRS = Unified Parkinson Disease Rating Scale, Motor. Variables with missing data are indicated with superscript letters:

^a
n = 152;

^b
n = 145;

^c
n = 139

Table 2

Multiple linear regression models examining the relation of brain volume, mean cortical binding potential (MCBP) and education to cognitive outcomes. Model 1 includes separate terms for brain volume, MCBP and education, and Model 2 adds an interaction term to determine whether education moderates the relation of MCBP and cognitive function.

Model Terms	Model 1		Model 2	
	β	<i>p</i>	β	<i>p</i>
Dependent variable: MMSE ^a				
Brain volume	0.34	< 0.001	0.31	< 0.001
MCBP	-0.19	0.014	-1.13	0.018
Education	0.24	0.002	0.19	0.021
MCBP × Education			1.10	0.018
Dependent variable: CDR				
Brain volume	-0.32	< 0.001	-0.28	< 0.001
MCBP	0.20	0.011	1.96	<0.001
Education	-0.14	0.072	-0.38	0.631
MCBP × Education			-1.78	< 0.001
Dependent variable: CDR-SB				
Brain volume	-0.30	< 0.001	-0.26	0.001
MCBP	0.19	0.020	1.85	< 0.001
Education	-0.13	0.093	-0.04	0.654
MCBP × Education			-1.68	< 0.001

MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating global score; CDR- SB = Clinical Dementia Rating sum of boxes score. Sample size for each outcome variable is indicated with superscript letters:

^a n = 152