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Aging, Brain Disease, and Reserve: Implications for Delirium

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Abstract

Cognitive and brain reserve are well studied in the context of age-associated cognitive impairment and dementia. However, there is a paucity of research that examines the role of cognitive or brain reserve in delirium. Indicators (or proxy measures) of cognitive or brain reserve (such as brain size, education, activities) pose challenges in the context of the long prodromal phase of Alzheimer's disease but are diminished in the context of delirium, which is of acute onset. This article provides a review of original articles on cognitive and brain reserve across many conditions affecting the central nervous system, with a focus on delirium. We review current definitions of reserve. We identify indicators for reserve utilized in earlier studies, and discuss these indicators in the context of delirium. We highlight future research directions to move the field ahead. Reserve may be a potentially modifiable characteristic. Studying the role of reserve in delirium can advance prevention strategies for delirium and may advance knowledge of reserve and its role in aging and neuropsychiatric disease generally.

Keywords

Reserve; Brain Reserve; Cognitive Reserve; Delirium; Dementia

Brain and cognitive reserve concepts developed from observations that some individuals demonstrate less cognitive impairment than others with comparable brain injury or neuropathology.[1-4] Higher functioning individuals were postulated to possess a reserve factor that acted to delay or ameliorate the impairments of intellect and functioning accompanying neurodegenerative conditions. Most research on reserve is based on studies in chronic progressive disorders such as Alzheimer's disease.[4, 5] Extrapolating the concept of reserve to delirium, an acute confusional state, may allow us to elucidate fundamental aspects of reserve and provide a unique opportunity to advance the field.

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Delirium (an acute decline of cognition and attention) represents a common and serious problem for older persons, particularly in the face of acute illness and hospitalization.[6] Delirium occurs in up to 56% of older adults in general hospital populations, and is associated with an in-hospital mortality of up to 33%.[6] Delirium in older persons is associated with substantial morbidity, functional decline, loss of independence, nursing home placement, and death.[6] Hospital costs of delirium are estimated to be greater than $8 billion annually, and post-hospital costs related to rehabilitation, institutionalization, and home care are greater than $100 billion annually.[7]

Clinical experience and previous studies demonstrate that delirium susceptibility varies between individuals. Delirium is typically the manifestation of a complex interrelationship between a vulnerable patient, subjected to noxious insults or precipitating factors. Previous studies have elucidated vulnerability factors for delirium including factors such as frailty, cognitive impairment, vision or hearing impairment, and comorbidity.[8, 9] Cognitive and brain reserve concepts represents important new conceptualizations to capture this vulnerability to delirium.[10] The poor outcomes of delirium cut across all causes of delirium, and persist even when controlling or stratifying by underlying causes. Thus, the outcomes may be attributable to the presence of the delirium itself, and not simply to the underlying causes. This conclusion is further supported by evidence that delirium of all causes (and its associated adverse effects) is preventable through targeted multicomponent risk factor interventions.[11-13] Thus, to maximize clinical relevance, we have considered the full scope of delirium and its multifactorial nature in this paper, and not single causes in isolation.

Objective

The purpose of this article is to review the concept of reserve in aging and brain disease and to probe its specific application to delirium. Most previous work on cognitive and brain reserve has focused on dementia and brain injury. Applying the concept to delirium requires some extrapolation, although Barnett and colleagues have previously extended the concept to neuropsychiatric disease.[14] Important questions are whether the same reserve indicators (proxy measures) identified in previous studies will apply to delirium, and how proposed working definitions of reserve need to be altered to fit application to delirium. We summarize proposed working definitions of reserve, review previous studies of reserve with emphasis on studies of delirium, and highlight key indicators of reserve. We discuss features of delirium that heighten its clinical importance for further development of the neurocognitive reserve concept.

A Working Definition of Reserve

The reserve concept, which is applicable to a broad array of clinical disorders,[15] describes variability across persons in the relationship of pathologic changes with clinical expression of disease.[4, 16] In his most recent review, Stern[17] articulates two models of reserve pertaining to neurocognitive functioning: brain and cognitive. Brain reserve refers to structural aspects of the brain, and cognitive reserve relates to how cognitive tasks are initiated and coordinated, involving access to complex cognitive networks. Stern suggests cognitive reserve is implemented via two mechanisms: neural reserve and neural compensation. Neural reserve describes the efficiency, capacity, or flexibility of brain networks or cognitive paradigms that underlie task performance in the healthy brain. Neural compensation refers to the ability to function optimally when pathology disrupts standard processing networks. Brain reserve is conceptualized as a passive process and evokes a threshold model (a critical level of brain capacity, or brain reserve capacity) for the adequate performance of cognitive tasks in the presence of pathology or depletion. Cognitive reserve is conceptualized as an active process by which pathology or depletion are met with greater efficiencies in pre-existing cognitive processes (neural reserve) or the enlistment of alternative processes (neural compensation) to achieve cognitive tasks.[17]

Current thinking is that reserve is dynamic and modifiable over the life course,[15] and as such fits within the larger concept of brain plasticity.[18] This, taken with evidence that brain structure and function are inseparable and are reciprocal causal agents,[15, 17] leads us to conclude that a clean separation between brain vs. cognitive or active vs. passive reserve is not an actual reflection of biology. Thus we will use a more general term for reserve -- neurocognitive reserve[19, 20] -- when discussing our own ideas. We use brain or cognitive reserve qualifiers when referring to published works, following the use of these concepts (or terms) in the original citation. As addressed in our discussion, more important conceptual distinctions are needed among the causes, indicators, and behavioral or clinical manifestations of reserve to inform theory development and the articulation of testable hypotheses.

Cognitive Reserve in Neuropsychiatric Illness

Recently Barnett and colleagues[14] described the potential role for cognitive reserve theory in psychiatric illness. High cognitive reserve may provide resilience to cognitive failure, and protect persons by enhancing control over aberrant thoughts. Barnett and colleagues cite evidence for this view noting that low intelligence, disrupted education, lower brain and intracranial size are associated with risk and/or long term outcomes of schizophrenia and depression.[14] Barnett and colleagues do not consider the role of cognitive reserve in delirium. However, we note that there are several studies demonstrating relationships between mental illness, cognitive impairment, dementia and delirium. Depression has been found to impair cognition in patients with dementia and may predict earlier onset of age-related cognitive impairment.[21, 22] Similarly, affective disorders and symptoms have been associated with the risk for delirium in hospitalized and post-surgical patients.[23-25]

Indicators of Cognitive and Brain Reserve

A critical first step in studying neurocognitive reserve is to identify indicators that accurately measure and quantify the concepts. If reserve is broadly defined as a discrepancy between observed and expected functional impairment associated with a given degree of neuropathology, then operationalizing reserve requires measures of both performance and neuropathology. In vivo measures of neuropathology in Alzheimer's disease, such as amyloid imaging, have only recently been identified and are not widely available.[26] Autopsy studies have been used to identify the burden of disease in dementia. However, the neuropathological basis of delirium is poorly understood, and validated measures of neuropathology do not exist. Without a measure of neuropathology, the presence and severity of disease are approximated with standardized clinical measures and diagnostic criteria, such as neuropsychological testing and functional measures. Barnett and colleagues point out that investigations of cognitive reserve in the context of neuropsychiatric disease in the absence of well-established pathological markers (e.g., as validated by tissue examination or other biomarker) using performance or severity markers as proxies for pathology is a limited approach.[14]

Many indicators of brain reserve have been proposed. Head size, intracranial volume, brain volume, synaptic density and other anthropometric measures are considered suitable indicators.[5] Proposed indicators of cognitive reserve include experiential characteristics that may boost neural connections (physical activity) or build problem solving skills (education, occupational complexity, mentally stimulating activities, intelligence).[5, 27] Less commonly, physical activity, cognitive or leisure activities, and socioeconomic status are reported. To better understand the application of cognitive and brain reserve indicators, we conducted a review of the medical literature.

Methods

Systematic Review of Indicators of Brain and Cognitive Reserve

We conducted two searches of the PubMed database, limiting to English language articles published from January, 1988 through November, 2008. For the first search, to identify indicators of cognitive and brain reserve, we used the terms “cognitive reserve”, “neural reserve” and “brain reserve”, which were combined with “education”, “occupation”, “intelligence (IQ)”, “leisure”, “physical activity”, “socioeconomic status”, “social network”, “delirium”, “dementia”, “Parkinson’s disease”, “human immunodeficiency virus (HIV)”, “cognitive decline”, traumatic brain injury”, or “risk factor”. For the second search, to examine neuroimaging in reserve, we used the terms “cognitive reserve”, “brain reserve” and “neural reserve” in combination with “imaging”, “magnetic resonance imaging (MRI)”, “single photon emission computed tomography (SPECT)”, or “positron emission tomography (PET)”. The bibliographies of all articles were hand-searched for any additional pertinent articles. For the systematic reviews, we included only original articles.

Results

Our first review yielded 67 original articles on reserve indicators, summarized in Table 1 (reference listing available on request). The conditions examined in these studies were as follows (number of articles in parentheses): Alzheimer’s disease or dementia (53), delirium (4), cognitive decline (3), human immunodeficiency virus infections (4), traumatic brain injury (2), and Parkinson’s disease (1). A wide variety of reserve indicators were considered across these 67 studies, see Table 1. For the vast majority of studies, indicators of low reserve were associated with an increased risk of dementia or cognitive decline. The major reserve indicators and their measurement are detailed below.

Educational Attainment and Measures of Socioeconomic Status—Socioeconomic status (SES) has been represented by education, occupation, income, individually or in combination.[28] Among cognitive or brain reserve indicators, educational attainment is the most widely studied. The strong inverse association of educational attainment with risk for dementia has led some investigators to claim that education may be the most important protective factor for dementia.[29] Education may increase brain reserve by promoting synaptic growth,[3] and/or may foster cognitive reserve by generating new cognitive strategies.[5]

Occupation is also an important reserve indicator. One review[30] found that “high” (contrasting managerial, technical and professional occupations with unskilled, semi-skilled, trade and clerical workers) occupational status was associated with a 50% reduction in dementia risk. It is not clear how occupation may operate in models of neurocognitive reserve. Occupation may be a reflection of underlying intelligence or academic aptitude,[31, 32] and therefore would be an outcome sharing a cause with a more fundamental neurocognitive reserve indicator. On the other hand, greater occupational complexity might enhance cognitive skills development throughout the lifetime,[33] and in this view would be a cause of neurocognitive reserve. Income has been found to predict cognitive decline independent of level of education, although the mechanism has not been speculated to conform to notions of brain or cognitive reserve.[34]

Intelligence—Several previous studies have used intelligence as a marker for reserve. Typically, literacy or vocabulary measures are used to assess pre-morbid IQ.[35] Satz argued that psychometric intelligence was a direct measure of brain reserve capacity.[4] Other investigators interpret literacy and vocabulary measures as indicators of educational quality.[36] Few lifespan studies are available that show the prospective relationship between early life intelligence and late life cognitive outcomes, but Whalley and colleagues have demonstrated that mental ability at age 11 is associated with risk for late onset dementia.[37]

Cognitive or Leisure Activities—In a previous meta-analysis, participation in mentally stimulating activities was the most robust brain reserve indicator relative to education, occupation, and premorbid IQ.[30] Summary measures of cognitive activities have been developed to capture lifetime mental activity as an indicator of cognitive reserve.[38-40] Wilson's Cognitive Activities Scale[41] measures the frequency of participation in activities across the lifespan, including activities such as reading, writing, attending concerts. Other similarly composed activity scales have been proposed (e.g., the Florida Cognitive Activities Scale[39] and the Lifetime Experiences Questionnaire[40]). These measures have been used to show that older persons with greater lifetime participation in complex mental activities showed less hippocampal atrophy,[42] diminished cognitive decline,[38] and lower risk of Alzheimer's disease.[43]

Physical Activity—At least nine previous studies use physical activity as a cognitive or brain reserve indicator or otherwise describe a protective effect for cognitive decline or dementia,[44-51] although results of clinical trials are equivocal.[52, 53] Exercise may increase brain reserve by promoting healthy cardiovascular function and diminishing cerebrovascular disease burden.[54] Exercise slows the expression of AD-like pathology in mouse models.[55] Exercise also enhances brain health and function by priming molecular memory for the plasticity molecule brain-derived neurotrophic factor.[56] Physical exercise and activity represents an neurocognitive reserve factor with public health implications, since it is potentially modifiable and produces a wide ranging health benefits.

Social Support—Epidemiological[57, 58] and clinicopathological[59] studies have suggested a potential role for social supports (e.g., network size, marital status) in dementia risk. The postulate is that cognitive processes that support the development and maintenance of social networks promote cognitive reserve.[59] Inouye found social support was related to delirium risk in a hospitalized cohort, but the effect was not independent of other predictors including cognitive level and medical comorbidity.[9]

Anthropometric Indicators—Head circumference is often used a proxy for brain size and brain reserve, and has been shown to mitigate risk for dementia in some,[60-62] but not all studies.[63] One previous study[60] demonstrated an interaction between head circumference and educational attainment in the risk for Alzheimer's disease, implying that increases in risk for AD due to small head circumference can be overcome by high education.

Neuroimaging Indicators—Neuroimaging markers can be used as both proxy measures of cognitive or brain reserve or as measures of neuropathology. For the present study, we included only those studies that examined a cognitive or brain reserve indicator (such as education) in correlation with an imaging measure, and where the imaging was used to indicate the burden of neuropathology. Imaging studies that used the imaging modality itself as a proxy measure of brain or cognitive reserve were not included. We were unable to identify neuroimaging studies examining the role of reserve in delirium.

Our systematic review yielded 25 original articles in which cognitive or brain reserve indicators were correlated with imaging findings (Table 2, references available on request). The conditions examined in these studies were (number of studies in parentheses): Alzheimer's disease (16), unspecified cognitive decline (3), mild cognitive impairment (4), frontotemporal dementia (2), and human immunodeficiency virus-related cognitive impairment (2). Cognitive or brain reserve indicators included education, intelligence (IQ), and occupational attainment, which were correlated with neuroimaging findings of increased brain pathology, including decreased brain volume, decreased cerebral blood flow, decreased metabolic activity, altered task-activation, increased amyloid uptake, and presence of white matter hyperintensities. For the majority of studies we identified, indicators of high cognitive reserve (such as education,

occupation, and IQ) were correlated with a higher degree of brain pathology by neuroimaging for the same degree of functional impairment.

Functional neuroimaging (including SPECT, PET, or fMRI) can measure resting blood flow or metabolic activity, or changes in blood flow or metabolic activity with task-related activation studies. Resting measures of blood flow or metabolic activity are important markers of neuropathology. Studies in AD patients have shown diminished cerebral blood flow in the parietotemporal regions in people with high vs. low education at comparable cognitive and functional level.[64] This pattern supports cognitive reserve theory.[17] Persons with more neurocognitive reserve will be able to perform at a given level with greater neuropathology than persons with low reserve.

A study using the brain amyloid PET ligand 11C-labelled Pittsburgh Compound B (PIB) has demonstrated that education delays expression of clinical symptoms in the presence of markers of AD pathology.[65] After controlling for dementia severity and relative to patients with low education, patients with higher education had more amyloid binding in the ventrolateral frontal cortex and reduced metabolism in the temporal and parietal cortex.

Studies on Reserve in Delirium—Brain and cognitive reserve have not been widely studied in the context of delirium. Our comprehensive review identified two previous studies that identified educational attainment as an important predictor of delirium (with a moderate to large effect size),[66, 67] but at least three failed to demonstrate a significant association.[68-70] We have examined the role of educational attainment and the risk for delirium in two large prospective cohorts.[10] Briefly, the two studies involved cohorts of hospitalized elders who were at least 70 years and free from delirium ratings at hospital admission.[71] In both cohorts, mean years of education among persons who developed delirium while hospitalized was 9 years, compared to 11 years among those who did not (P<.001), and the effect remained after control for possible confounders. The magnitude of difference was medium (d=.48 and .51, respectively). A five year difference in educational attainment was associated with a 1.6-fold decrease in the odds of delirium. Thus, education was strongly related to the risk of delirium.

In a related study[72], we evaluated the same cohorts, but focused on the role that leisure activity participation prior to hospitalization played in mediating the protective influence of educational attainment on delirium. We also explored differential effects of specific activities on the risk for delirium. Frequency of participation was assessed in 10 specific types of activities: physical exercise; yard work; hobbies; entertainment activities; reading; working at a paid or volunteer job; regularly playing games; attending religious services; visiting friends; and participating in groups. Both education and activity significantly predicted lower risk for delirium, while controlling for sociodemographic characteristics and comorbidities. In addition, activity participation fully mediated the relationship of education and risk for delirium. After exploring specific activities, participation in regular physical exercise exerted the greatest protective effect against delirium.

Discussion

This article provides a review of original articles on general neurocognitive reserve across many conditions affecting the central nervous system. We have reviewed the current definitions of reserve, including both brain and cognitive reserve and have identified indicators for reserve used in earlier studies. Neurocognitive reserve may be promoted by socioeconomic status indicators such as educational attainment, as well as by cognitive and physical activities. In delirium, educational attainment and activity participation are important predictors of delirium.

Activity level is potentially modifiable and can preserve cognitive functioning in later life, providing a target for preventive interventions.

Neurocognitive Reserve Indicators in Dementia and Delirium

Many studies use SES variables (education, occupation, income) as proxies for cognitive reserve. There are important challenges in using SES variables in aging research. Birth cohort effects, and sex and race/ethnicity differences in the average level of and quality of education[73] may be a source of bias.[74] Moreover, education may cause measurement bias in the assessment of neuropsychological performance.[75, 76] Socioeconomic status and cultural background may confound the meaning of educational attainment,[74] or contribute to psychopathology via mechanisms not consistent with cognitive reserve theory.[77, 78]

Recognizing limitations of SES indicators, some investigators have turned to measures of literacy or reading level to capture academic achievement.[79, 80] Such measures are also often used as measures of intelligence or premorbid intelligence, also often used as indicators of brain reserve.[30, 79] This strategy assumes performance on reading and literacy tests is resistant to the effects of brain pathology.[81] However, estimates of pre-morbid IQ based on literacy tests are generally accurate in persons without dementia, but less accurate among persons with AD.[82] It is reasonable to propose that accumulating neuropathology might limit vocabulary development, since AD- type neuropathological changes may be present decades prior to diagnosis (even as early as age 25[83]) and vocabulary development peaks in middle age (ages 35-45[84]). Therefore, the long preclinical phase of AD poses a challenge to studies of the existence and mechanism of neurocognitive reserve.

Problems inherent in the long preclinical phase of AD may also limit the utility of other indicators of neurocognitive reserve, such as engagement in mentally stimulating activity, and educational and occupational attainment.[5] On the other hand, delirium is not associated with a long preclinical phase. Examining indicators of neurocognitive reserve in the context of delirium may offer substantive advantages and may provide insights into the fundamental role of neurocognitive reserve in neuropsychiatric illness.

The Importance of Measures of Neuropathology

If neurocognitive reserve is conceptualized as a discrepancy between observed and expected functional impairment associated with a given degree of neuropathology, studies of neurocognitive reserve requires measures of both performance and neuropathology. Clinicopathologic autopsy studies are not uncommon in Alzheimer's disease (AD) and other dementias, and new imaging techniques offer the possibility of prospective studies of accumulating neuropathology in AD. Since he neuropathological basis of delirium is poorly understood, this is a principal prerequisite for studies of neurocognitive reserve in delirium. Serum biomarkers may be an important approach, but more research is needed in this area.[85]

A Rationale for Studying Neurocognitive Reserve in Delirium

Delirium provides many unique characteristics which make the examination of the contribution of neurocognitive reserve particularly compelling (See Table 3). To date, brain and cognitive reserve have been studied primarily in chronic, degenerative conditions with extended preclinical phases, which greatly complicate the study of reserve. Thus, studying neurocognitive reserve in delirium, an acute condition without a long prodromal phase, may provide important insights into the role of neurocognitive reserve in cognitive decline. Moreover, the fact that delirium is often due to acute and overwhelming physiological insults may overcome some of the inherent biases in diagnosis and establishing baseline status. The fact that delirium often has a catastrophic acute phase with poor prognosis (where brain reserve may play a larger role) versus a more indolent phase where recovery potential may facilitate

the examination of the mechanism of neurocognitive reserve. Finally, the preventable nature of delirium and its associated long-term adverse consequences, along with the high potential for recovery, heighten the clinical relevance of better understanding the contribution of neurocognitive reserve to its incidence and clinical course.

Conclusions

To move the concept of neurocognitive reserve forward generally, and the study of reserve in delirium specifically, the field must advance in definitions and refinements of theory, indicators, methodologic approaches, and intervention strategies. Pathophysiologic investigations, including neuroimaging and animal studies, will be critical for defining mechanisms of neurocognitive reserve in the context of delirium. Finally, intervention studies will be of fundamental clinical importance to determine whether reserve can be increased, and thus, incur direct benefits to our older population for the prevention of delirium and long-term cognitive decline. We propose a research agenda with some key research questions to explore reserve in delirium.

- Defining neurocognitive reserve in delirium:
    - What are the causes of neurocognitive reserve, and how is neurocognitive reserve manifested? This is an issue of conceptualization and measurement. For example, educational attainment may predict higher levels of neurocognitive reserve, but as currently conceptualized high educational attainment is not a consequence of higher levels of neurocognitive reserve.
    - How does neurocognitive reserve influence the occurrence, course and consequence of delirium? Does neurocognitive reserve confer resistance to delirium (lower delirium incidence), and/or promote recovery after delirium (shorter delirium duration or severity)?
    - How does neurocognitive reserve in delirium differ from its role in other acute insults such as head trauma or stroke and in more chronic insults like dementia?
- Construct validation: Can the role of neurocognitive reserve be distinguished from other fundamental causes of poor health outcomes in delirium or from other fundamental causes of neuropsychiatric disorder?
- Measurement of neurocognitive reserve: How do we measure neurocognitive reserve in delirium? How can the discrepancy between observed and expected performance be operationalized in delirium? What are the best interview, laboratory, neuroimaging indicators for indexing the degree of neuropathology in delirium?
- Contributing factors: What are the behavioral, environmental, or genetic contributors to neurocognitive reserve in delirium? How do educational level, occupation, childhood IQ, socioeconomic status, exercise, activities, health habits, etc. contribute to neurocognitive reserve in delirium? Do depression or mental illness influence neurocognitive reserve?
- Cross-cultural measures: How do we adapt measures of neurocognitive reserve in delirium across cultures, birth cohorts, or other major population sub-groups
- Pathophysiology
    - Functional neuroimaging: Can activation studies allow us to better understand the mechanisms of neurocognitive reserve in delirium (alternate pathways, neurogenesis, compensatory mechanisms)? Can we quantify neurocognitive reserve?

- Laboratory or electrophysiologic markers: Can we identify markers (e.g., cytokines, C-reactive protein, serum anticholinergic assays, cortisol levels, neurotransmitter levels, evoked potentials) that will correlate with degree of pathology in delirium?
- Neurotransmitter sensitive imaging: Using nuclear medicine studies or pharmacologic manipulation studies (such as anticholinergic or dopaminergic challenges) combined with functional neuroimaging, can we gain understanding of neurotransmitter abnormalities influencing neurocognitive in delirium?
- Animal model: Can we develop an animal model for neurocognitive reserve in delirium, such as raising animals in enriched environments and subjecting them to a delirium-inducing stimulus (e.g., drug or inflammatory challenge)?

- Neuropathological markers: Can we identify neuropathological markers for delirium, such as on brain biopsy or autopsy?
- Intervention
  - Delirium prevention: Can methods to increase neurocognitive reserve (e.g., education, activities) prevent delirium? [86] What are the most effective intervention strategies and dosages, and how late in life can these interventions begin and still make a difference?
  - Pharmacologic treatment: Do dementia-approved drugs (e.g., donepezil, memantine) prevent delirium by increasing neurocognitive reserve? Are there other pharmacologic treatments that might influence cognitive or neurocognitive reserve in delirium, such as anti-inflammatory agents, anti-platelet agents, dopamine antagonists, antioxidants?

Delirium provides a unique opportunity to better understand the concept of neurocognitive reserve. The proposed studies will allow us to better understand the role of neurocognitive reserve in cognitive functioning more generally, and importantly, offer the potential to identify effective interventions to forestall cognitive decline in late life.

Neurocognitive reserve is probably modifiable.[15] Interventions are available that may boost neurocognitive reserve. For example, mental training[87-90] and physical exercise[91] have been shown in experimental studies to improve cognition and functional outcomes. Also, public policy priorities might influence neurocognitive reserve for future cohorts of older adults. Natural experiments of State variation in compulsory schooling laws suggests a large and causal effect of greater education on memory functioning in late life.[92] Therefore, policy initiatives to mandate increased formal education are justified, and may serve to enhance the cognitive and functional health of future generations as they approach late life.

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References

1. Rothschild D, Trainor MA. Pathologic changes in senile psychoses and their psychobiologic significance. American Journal of Psychiatry 1937;93(4):757–788.

2. Blessed G, Tomlinson B, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. British Journal of Psychiatry 1968;114:797–811. [PubMed: 5662937]
3. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. Neurology 1993;43:13–20. [PubMed: 8423876]
4. Satz P. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. Neuropsychology 1993;7(3):273–295.
5. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society Mar;2002 8(3):448–460. [PubMed: 11939702]
6. Inouye SK. Delirium in older persons. New England Journal of Medicine March 16;2006 354(11): 1157–1165. [PubMed: 16540616]
7. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-Year Health Care Costs Associated With Delirium in the Elderly Population. Archives of Internal Medicine January 14;2008 168(1):27–32. [PubMed: 18195192]
8. Rockwood KJ. Out of the furrow and into the fire: Where do we go with delirium? Canadian Medical Association Journal 2002;167(7):763–764. [PubMed: 12389838]
9. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Annals of Internal Medicine Sep 15;1993 119(6):474–481. [PubMed: 8357112]
10. Jones RN, Yang FM, Zhang Y, Kiely DK, Marcantonio ER, Inouye SK. Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve. The Journals of Gerontology Series A, Biological Sciences and Medical Sciences 2006;61A(12):1307–1311.
11. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. New England Journal of Medicine Mar 4;1999 340(9):669–676. [PubMed: 10053175]
12. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. Journal of the American Geriatrics Society May;2001 49(5):516–522. [PubMed: 11380742]
13. Naughton BJ, Saltzman SND, Ramadan F, Chadha N, Priore R, Mylotte JM. A Multifactorial Intervention to Reduce Prevalence of Delirium and Shorten Hospital Length of Stay. Journal of the American Geriatrics Society 2005;53(1):18. [PubMed: 15667371]
14. Barnett JH, Salmond CH, Jones PB, Sahakian BJ. Cognitive reserve in neuropsychiatry. Psychological Medicine 2006;36(08):1053–1064. [PubMed: 16854246]
15. Sachdev PS, Valenzuela M. Brain and cognitive reserve. American Journal of Geriatric Psychiatry 2009;17(3):175. [PubMed: 19225275]
16. Studenski S, Carlson MC, Fillit H, Greenough WT, Kramer A, Rebok GW. From Bedside to Bench: Does Mental and Physical Activity Promote Cognitive Vitality in Late Life? Science of Aging Knowledge Environment June 28;2006 2006(10):pe21. [PubMed: 16807485]
17. Stern Y. Cognitive reserve. Neuropsychologia. 2009
18. Willis, S.; Schaie, K.; Martin, M. Theories of cognitive plasticity: Naturally cccurring and experimentally induced. In: Bengtson, VL.; Gans, D.; Putney, N.; Silverstein, M., editors. Handbook of theories of aging. New York: Springer Publishing Company; 2008.
19. Raiha I, Kaprio J, Koskenvuo M, Rajala T, Sourander L. Environmental differences in twin pairs discordant for Alzheimer's disease. Journal of Neurology Neurosurgery & Psychiatry 1998;65(5): 785–787.
20. Chibnall JT, Eastwood R. Postsecondary education and dementia risk in older Jesuit priests. International Psychogeriatrics 1998;10(4):359–368. [PubMed: 9924831]
21. Bassuk SS, Berkman LF, Wypij D. Depressive symptomatology and incident cognitive decline in an elderly community sample. Archives of General Psychiatry 1998;55(12):1073–1081. [PubMed: 9862549]
22. Chodosh J, Kado DM, Seeman TE, Karlamangla AS. Depressive symptoms as a predictor of cognitive decline: MacArthur studies of successful aging. American Journal of Geriatric Psychiatry 2007;15 (5):406–415. [PubMed: 17353297]

23. Ritchie J, Steiner W, Abrahamowicz M. Incidence of and risk factors for delirium among psychiatric inpatients. Psychiatric Services 1996;47(7):727. [PubMed: 8807686]
24. Schneider F, Böhner H, Habel U, et al. Risk factors for postoperative delirium in vascular surgery. General Hospital Psychiatry 2002;24(1):28–34. [PubMed: 11814531]
25. McAvay GJ, Van Ness PH, Bogardus ST Jr, et al. Depressive symptoms and the risk of incident delirium in older hospitalized adults. Journal of the American Geriatrics Society 2007;55(5):684. [PubMed: 17493187]
26. Ikonomovic MD, Klunk WE, Abrahamson EE, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain June 1;2008 131(6):1630–1645. [PubMed: 18339640]
27. Valenzuela MJ, Sachdev P. Brain reserve and cognitive decline: a non-parametric systematic review. Psychological Medicine Aug;2006 36(8):1065–1073. [PubMed: 16650343]
28. Oakes JM, Rossi PH. The measurement of SES in health research: current practice and steps toward a new approach. Social Science and Medicine Feb;2003 56(4):769–784. [PubMed: 12560010]
29. Mortimer J, Graves A. Education and other socioeconomic determinants of dementia and Alzheimer's disease. Neurology 1993;43(S4):S39–S44. [PubMed: 8389010]
30. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychological Medicine Apr;2006 36(4):441–454. [PubMed: 16207391]
31. Miech RA, Hauser RM. Socioeconomic status and health at midlife a comparison of educational attainment with occupation-based indicators. Annals of Epidemiology 2001;11(2):75–84. [PubMed: 11164123]
32. Eckland B. Genetics and sociology: A reconsideration. American Sociological Review 1967;32:173–194. [PubMed: 6041101]
33. Andel R, Vigen C, Mack WJ, Clark LJ, Gatz M. The effect of education and occupational complexity on rate of cognitive decline in Alzheimer's patients. Journal of the International Neuropsychological Society 2006;12(01):147–152. [PubMed: 16433954]
34. Lee S, Buring JE, Cook NR, Grodstein F. The relation of education and income to cognitive function among professional women. Neuroepidemiology 2006;26(2):93–101. [PubMed: 16352912]
35. Schmand B, Smit JH, Geerlings MI, Lindeboom J. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychological Medicine 1997;27 (6):1337–1344. [PubMed: 9403905]
36. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. Journal of the International Neuropsychological Society 2002;8(3):341–348. [PubMed: 11939693]
37. Whalley LJ, Starr JM, Athawes R, Hunter D, Pattie A, Deary IJ. Childhood mental ability and dementia. Neurology 2000;55(10):1455–1459. [PubMed: 11094097]
38. Wilson RS, Bennett DA, Bienias JL, Mendes de Leon CF, Morris MC, Evans DA. Cognitive activity and cognitive decline in a biracial community population. Neurology 2003;61(6):812–816. [PubMed: 14504326]
39. Schinka JA, McBride A, Vanderploeg RD, Tennyson K, Borenstein AR, Mortimer JA. Florida Cognitive Activities Scale: initial development and validation. Journal of the International Neuropsychological Society Jan;2005 11(1):108–116. [PubMed: 15686613]
40. Valenzuela MJ, Sachdev P. Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). Psychological Medicine Nov 20;2006 :1–13.
41. Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. Journal of the International Neuropsychological Society Jul;2005 11(4):400–407. [PubMed: 16209420]
42. Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. PLoS ONE 2008;3(7):e2598. [PubMed: 18612379]
43. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002;287(6):742–748. [PubMed: 11851541]
44. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA September 22;2004 292(12):1447–1453. [PubMed: 15383515]

45. Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F. Physical Activity, Including Walking, and Cognitive Function in Older Women. JAMA September 22;2004 292(12):1454–1461. [PubMed: 15383516]
46. Deary IJ, Whalley LJ, Batty GD, Starr JM. Physical fitness and lifetime cognitive change. Neurology Oct 10;2006 67(7):1195–1200. [PubMed: 17030752]
47. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Archives of Internal Medicine Jul 23;2001 161(14):1703–1708. [PubMed: 11485502]
48. Ferrucci L, Bandinelli S, Cavazzini C, et al. Neurological examination findings to predict limitations in mobility and falls in older persons without a history of neurological disease. American Journal of Medicine Jun 15;2004 116(12):807–815. [PubMed: 15178496]
49. Marquis S, Moore MM, Howieson DB, et al. Independent predictors of cognitive decline in healthy elderly persons. Archives of Neurology Apr;2002 59(4):601–606. [PubMed: 11939895]
50. Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur Studies of Successful Aging. The Journals of Gerontology Series A, Biological Sciences and Medical Sciences Apr;2002 57(4):M228–235.
51. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Annals of Internal Medicine Jan 17;2006 144(2):73–81. [PubMed: 16418406]
52. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurology Jun;2004 3(6):343–353. [PubMed: 15157849]
53. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychological Science Mar;2003 14(2):125–130. [PubMed: 12661673]
54. Shinton R, Sagar G. Lifelong exercise and stroke. BMJ 1993;307(6898):231–234. [PubMed: 8369683]
55. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. Journal of Neuroscience April 27;2005 25(17):4217–4221. [PubMed: 15858047]
56. Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. Neuroscience 2005;133(3):853–861. [PubMed: 15896913]
57. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. Annals of Internal Medicine 1999;131(3):165–173. [PubMed: 10428732]
58. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community- based longitudinal study. Lancet 2000;355(9212):1315–1319. [PubMed: 10776744]
59. Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. Lancet Neurology 2006;5(5):406–412. [PubMed: 16632311]
60. Mortimer JA, Snowdon DA, Markesbery WR. Head circumference, education and risk of dementia: Findings from the Nun Study. Journal of Clinical & Experimental Neuropsychology 2003;25(5):671. [PubMed: 12815504]
61. Schofield PW, Logroscino G, Andrews HF, Albert S, Stern Y. An association between head circumference and Alzheimer's disease in a population-based study of aging and dementia. Neurology Jul;1997 49(1):30–37. [PubMed: 9222166]
62. Borenstein Graves A, Mortimer JA, Bowen JD, et al. Head circumference and incident Alzheimer's disease: modification by apolipoprotein E. Neurology Oct 23;2001 57(8):1453–1460. [PubMed: 11673588]
63. Espinosa PS, Kryscio RJ, Mendiondo MS, et al. Alzheimer's disease and head circumference. Journal of Alzheimer's Disease 2006;9(1):77–80.
64. Hanyu H, Sato T, Shimizu S, Kanetaka H, Iwamoto T, Koizumi K. The effect of education on rCBF changes in Alzheimer's disease: a longitudinal SPECT study. European Journal of Nuclear Medicine and Molecular Imaging. Jul 12;2008

65. Kemppainen NM, Aalto S, Karrasch M, et al. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. Annals of Neurology Jan;2008 63(1):112–118. [PubMed: 18023012]
66. Galanakis P, Bickel H, Gradinger R, Von Gumppenberg S, Forstl H. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. International Journal of Geriatric Psychiatry Apr;2001 16(4):349–355. [PubMed: 11333420]
67. Pompei P, Foreman M, Rudberg MA, Inouye SK, Braund V, Cassel CK. Delirium in hospitalized older persons: outcomes and predictors. Journal of the American Geriatrics Society Aug;1994 42(8): 809–815. [PubMed: 8046190]
68. Lerner AJ, Hedera P, Koss E, Stuckey J, Friedland RP. Delirium in Alzheimer disease. Alzheimer's Disease and Associated Disorders Mar;1997 11(1):16–20.
69. McCusker J, Cole M, Dendukuri N, Belzile E, Primeau F. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. CMAJ Canadian Medical Association Journal 2001;165(5):575–583.
70. Leung JM, Sands LP, Mullen EA, Wang Y, Vaurio L. Are preoperative depressive symptoms associated with postoperative delirium in geriatric surgical patients? Journals of Gerontology Series A: Biological Sciences and Medical Sciences Dec;2005 60(12):1563–1568.
71. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Annals of Internal Medicine 1990;113(12):941–948. [PubMed: 2240918]
72. Yang FM, Inouye S, Fearing M, Kiely D, Marcantonio E, Jones R. Participation in activity and risk for incident delirium. Journal of the American Geriatrics Society 2008;56(8):1479–1484. [PubMed: 18547359]
73. Schaie KW, Willis SL, Pennak S. An historical framework for cohort differences in intelligence. Research in Human Development 2005;2(1 2):43–67. [PubMed: 16858496]
74. Jones RN. Racial bias in the assessment of cognitive functioning of older adults. Aging & Mental Health 2003;7(2):83–102. [PubMed: 12745387]
75. Jones RN, Gallo JJ. Education and sex differences in the Mini Mental State Examination: Effects of differential item functioning. The Journals of Gerontology Series B, Psychological Sciences and Social Sciences 2002;57B(6):P548–558.
76. Crane P, Gibbons L, Jolley L, et al. Differential item functioning related to education and age in the Italian version of the Mini-mental State Examination. International Psychogeriatrics Feb 15;2006 18 (3):505–515. [PubMed: 16478571]
77. Karel M-J. Aging and depression: Vulnerability and stress across adulthood. Clinical Psychology Review 1997;17(8):847–879. [PubMed: 9439871]
78. Link BG, Phelan J. Social conditions as fundamental causes of disease. Journal of Health and Social Behavior 1995;35(extra issue):80–94. [PubMed: 7560851]
79. Strauss, E.; Sherman, E.; Spreen, O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3. New York: Oxford University Press; 2006. Acheivement tests; p. 363
80. Manly JJ, Byrd D, Touradji P, Sanchez D, Stern Y. Literacy and cognitive change among ethnically diverse elders. International Journal of Psychology 2004;39(1):47–60.
81. Lezak, M. Neuropsychological assessment. 4. New York: Oxford University Press; 2004.
82. Ryan JJ, Koller WC. Comparison of NART and Barona demographic equation premorbid IQ estimates in Alzheimer's disease. Journal of Clinical Psychology 1997;53(7):713–722. [PubMed: 9356900]
83. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiology of Aging Jul-Aug;1997 18(4):351–357. [PubMed: 9330961]
84. Bowles R, Grimm K, McArdle J. A structural factor analysis of vocabulary knowledge and relations to age. Journals of Gerontology Series B: Psychological Sciences and Social Sciences 2005;60(5): 234–241.
85. Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Review article: serum biomarkers for delirium. Journals of Gerontology Series A: Biological and Medical Sciences 2006;61 (12):1281.

86. Jeffs K, Berlowitz D, Savige J, Lim W. Does an enhanced exercise and cognitive program reduce incident delirium in older hospital patients: results of a randomized controlled trial. Internal Medicine Journal 2008;38:A121.

87. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA Nov 13;2002 288(18):2271–2281. [PubMed: 12425704]

88. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA December 20;2006 296(23):2805–2814. [PubMed: 17179457]

89. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Wright E, Tennstedt SL. The effects of the ACTIVE cognitive training trial on clinically relevant declines in health-related quality of life. The Journals of Gerontology: Psychological Sciences and Social Sciences September 1;2006 61(5):S281–287.

90. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, Tennstedt SL. The ACTIVE cognitive training trial and health-related quality of life: Protection that lasts for 5 years. Journals of Gerontology Series A: Biological Sciences and Medical Sciences December 1;2006 61(12):1324–1329.

91. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Archives of Physical Medicine and Rehabilitation Oct; 2004 85(10):1694–1704. [PubMed: 15468033]

92. Glymour M, Kawachi I, Jenks C, Berkman LF. Does childhood schooling affect old age memory or mental status? Using state schooling laws as natural experiments. Journal of Epidemiology and Community Health 2008;62:532–537. [PubMed: 18477752]

TABLE 1

Review of Studies on Brain or Cognitive Reserve (N=67)*

Low Reserve Indicator	No. studies examining	Direction of association of low reserve indicator with risk of dementia or cognitive decline (No. studies)		
		Increased risk	Decreased risk	No effect on risk
Low educational attainment	35	32	2	1
Low occupational indicator (unemployed or job with low mental demand)	14	13	1	--
Low level of cognitive or leisure activities	14	13	1	--
Low level of physical activity	12	10	--	2
Low socioeconomic status	6	4	1	1
Low intelligence quotient (IQ)	4	4	--	--
Unmarried status	3	3	--	--
Poor social supports	2	2	--	--

*Includes only indicators with 2 or more published studies. Complete reference citations for articles available on request.

TABLE 2

Correlation of Cognitive Reserve Indicators With Imaging Findings (N = 25)

Imaging Finding (Indicating Increased Neuropathology)	No. of Studies	Association of Imaging Finding With Reserve Marker[a] (No. of Studies)		
		High Reserve	Low Reserve	No Association
Decreased brain volume[b]	5	3	–	2
Decreased cerebral blood flow	7	6	1	–
Decreased metabolic activity	6	6	–	–
Altered task activation	5	5	–	–
Increased PIB uptake	2	2	–	–
Presence of WMH	2	1	–	1

Notes: Complete reference citations available on request. For a given level of functioning, patients with reserve have more neuropathological findings. PIB: Pittsburgh Compound B; WMH: white matter hyperintensity.

[a] Reserve markers include education, IQ, and occupational attainment. A single study (Sole-Padulles C, Bartres-Faz D, Junqué C, et al. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's Disease. Neurobiol Aging 2009; 30:1114 – 1124) included multiple imaging modalities and contributed to both decreased brain volume and increased task activation.

[b] Decreased brain volume includes increased ventricle size, presence of atrophy, or reduced intracranial volume.

TABLE 3

Unique Characteristics of Delirium Contributing to the Study of Reserve

Delirium Characteristic	Application to Brain and Cognitive Reserve
Acute onset, without long prodromal phase	Facilitates establishing baseline status
	Avoids long preclinical phase of chronic processes such as Alzheimer disease
Catastrophic medical insult	May help to minimize biases in detection and diagnosis; less dependence on socioeconomic status
Clinical course with initial poor prognosis and later long-term recovery	May allow separate examination of brain (important early on) and cognitive (important during recovery) components
Preventable nature	Facilitates examination of specific reserve components that may contribute and be amenable to intervention
Large potential for recovery	Highlights clinical importance of identifying reserve components that contribute to recovery potential