

**How do cognitively stimulating activities affect cognition and the brain throughout life?**

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The effects of mental stimulation can extend for many years past the initial learning phase. Cognitively stimulating experiences early in life, such as extra years of education or becoming fluent in a second language, are associated with cognitive benefits years later. Those who had those earlier cognitively stimulating experiences perform better at the same level of Alzheimer's pathology than those who did not get extra education or regularly switch between languages. Consider, for example, a post-mortem sample of 2372 participants who met neuropathological criteria for an Alzheimer's diagnosis (Roe, Xiong, Miller, & Morris, 2007). Within this large cohort who suffered from Alzheimer's disease, there were no significant correlations between education and neuropathology diagnosis stage. Thus, education did not have a detectable impact on levels of brain pathology. However, clinical diagnoses before death were associated with education. On average, those who had received a diagnosis of Alzheimer's had 2-3 years less education than those who had been clinically diagnosed as not having dementia. Thus, actual levels of brain pathology were not significantly related to education, whereas late life cognitive functioning was.

The concept of 'cognitive reserve' was formulated to account for the fascinating phenomenon in which education and stimulating occupations somehow allow the aging brain to cope better even as Alzheimer's pathology accumulates (Stern et al., 1994). Over the years since it was proposed, the concept of cognitive reserve has generated a lot of interest as well as debate (Anthony & Lin, 2017; Cabeza et al., 2018; Jones et al., 2011; Medaglia, Pasqualetti, Hamilton, Thompson-Schill, & Bassett, 2017; Satz, Cole, Hardy, & Rassovsky, 2011; Stern et al., 2019; Stern et al., 2018).

*Does education create cognitive reserve or just a higher cognitive peak?*

In their paper, Lövdén et al. review existing findings to examine how education is associated with cognitive functioning across the life span. They first confirm that the association between education attainment and cognitive function holds up across all adult ages as well as across birth cohorts, cultural contexts, races and genders. They then proceed to address the question of whether this association results from education attainment reflecting peak cognitive ability achieved in the process of that education or from a relationship between education attainment and the rate of age-related decline in cognition.

This is a critical question for the concept of cognitive reserve. In general, the concept of a reserve is something that is not necessary or influential initially but can play an important role later on. If educational attainment creates reserve capacity, that should be a capacity that is not needed initially but does become useful later on. Thus, if increasing education creates cognitive reserve, this should be reflected in more than just differences in the peak cognitive ability achieved. It should change the pattern of cognitive decline seen across adulthood. This altered pattern could take multiple forms. Obviously, cognitive reserve could slow the rate of cognitive decline, as reserve capacity progressively fills in to compensate for loss in function. However, it could also lead to non-linear effects. The reserve capacity might be most useful early or late in the progression of cognitive decline and may itself fade in strength.

In general, the non-linear nature of cognitive decline (Verhaeghen & Salthouse, 1997) poses a particular challenge for examining the relationship between educational attainment and age-related decline (see Lövdén et al.'s Fig. 4 for an illustration of this). The authors make the important point that findings that more highly educated people show steeper cognitive decline after dementia diagnosis can be entirely accounted for by methodological biases. Longitudinal data across the whole adult life course would be ideal for assessing this issue appropriately, but such studies are lacking. Based on their careful review of the literature that more heavily

weights studies that have longitudinal data and use appropriate statistical approaches, Lövdén et al. conclude that the association between educational attainment and late-life cognitive decline is small and inconsistent, and that effect size estimates suggest it is at least 10 times smaller than the relationship between educational attainment and level of cognitive function. Thus, Lövdén et al.'s review suggests that 'cognitive reserve' is somewhat of a misnomer, as the benefits from education are not kept in reserve but instead exert their impact mainly by influencing the level of peak cognitive performance achieved before cognitive decline. Rates of decline from one's peak cognitive ability are similar across levels of education.

A paper published after Lövdén et al.'s literature search was completed illustrates their point in a large cohort (Wilson et al., 2019). In this study, over 2000 older adults with at least four years of annual follow-up showed a significant relationship between education level and baseline cognitive function at entry in the study, but no relationship between education and the rate of cognitive decline.

The similar rates of decline across those with different education levels not only suggests that reserve capacity plays a minimal role in rates of cognitive decline, but also contrasts with theoretical predictions that education should attenuate rates of cognitive decline because it is associated with favorable life conditions such as increased occupational status.

*What can be done after formal education ends?*

For researchers (and individuals) interested in how to optimize late-life cognition, the robust association between education attainment and cognitive functioning throughout life is yet another reason among many to push for increasing early-life educational opportunities. However, the lack of a clear link between education and rates of cognitive decline raises

questions about best approaches to protect or even enhance late-life cognition after full-time education has ended. While it is clear that education in childhood and early adulthood has lifelong benefits, does education (or similarly mentally stimulating activities) also help later in life? In particular, how can we best design effective interventions to benefit cognition in those who are already older?

Some aspects of these difficult questions about intervening during adulthood have already been tackled in previous *Psychological Science in the Public Interest* (PSPI) reviews. Hertzog et al. (2008) make the case that the potential for positive plasticity is maintained in older adult cognition. They review studies indicating that older adults' cognition can be enhanced through training (especially when the training requires executive coordination, such as complex video games, task-switching and divided-attention tasks) and that a lifestyle that is more intellectually stimulating is associated with better maintenance of cognition. In contrast with this positive outlook, a more recent PSPI review concluded that, in general (across age groups), brain-training programs clearly improve performance on the brain-training tasks themselves but beyond that show quite limited efficacy, especially when it comes to everyday cognitive performance (Simons et al., 2016).

*Why are later life interventions apparently less successful than early life education?*

Thus, these previous PSPI reviews indicate that, although there is documented potential to intervene to enhance cognition in adulthood, most of the current approaches to enhancing adult cognition – unlike the robust effects of education on peak cognition reviewed by Lövdén et al. – have yielded underwhelming results. This is likely due to multiple reasons. One, of course, is that brain training is simply not as intensive nor as engaging as full-time schooling during

childhood, adolescence and early adulthood. Another is that the potential for plasticity may decrease with age (Kühn & Lindenberger, 2016; Power & Schlaggar, 2017).

Yet another possibility suggested by emerging neuroscience research is that, while mental stimulation has many benefits for the brain, it also has metabolic costs and the cost-benefit equation may shift in aging. The benefits of education and cognitive activity have been posited to accrue in part due to the involvement of the locus coeruleus-norepinephrine system (Robertson, 2014, 2013; see also Clewett et al., 2016; Mather, 2020; Mather & Harley, 2016). Education and cognitive activity involve novelty, cognitive effort, and motivation – all of which activate the locus coeruleus, which serves as the brain's arousal hub region (Mather, 2020), and which focuses attention and working memory in the moment (Mather, Clewett, Sakaki, & Harley, 2016) while also enhancing the likelihood of synaptic changes (Inoue et al., 2013; Maity, Rah, Sonenberg, Gkogkas, & Nguyen, 2015; Palacios-Filardo & Mellor, 2019; Salgado, Kohr, & Trevino, 2012; Salgado, Treviño, & Atzori, 2016). But the synaptic activity involved in this enhanced attentional focus and that is required for synaptic change also has a metabolic cost (Holroyd, 2016; Oyarzabal & Marin-Valencia, 2019). Synaptic activity creates amyloid- $\beta$  as well as other metabolic waste (Cirrito et al., 2005). In younger adults, this metabolic waste is efficiently disposed of, but in aging the brain's waste disposal system tends to be less effective (Benveniste et al., 2019). In particular, deep sleep seems to be important – either because it enhances waste clearance or it temporarily reduces the level of synaptic activity. Older adults who have poor deep sleep tend to have greater amyloid PET amyloid binding and tau protein aggregates (Lucey et al., 2019; Mander et al., 2015) and disrupting sleep increases cerebrospinal levels of amyloid- $\beta$  and tau (Ju et al., 2017; Holth et al., 2019).

*Does education slow the pace of Alzheimer's pathology accumulation?*

Intriguingly, positron emission tomography (PET) amyloid imaging suggests education and cognitive activity may affect the dynamics of amyloid- $\beta$  in the brain. Those with more education show less PET amyloid binding than those with less education at the same age (Yasuno et al., 2015), an effect that may be specific for those with the APOE genetic risk factor for Alzheimer's disease (Vemuri et al., 2016). Likewise, those reporting higher lifetime cognitive activity showed diminished PET amyloid binding (Landau et al., 2012; Lyons et al., 2018; Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014; but see mixed effects by brain region in Arenaza-Urquijo et al., 2017; and lack of effect in Vemuri et al., 2012). However, because postmortem analyses of amyloid- $\beta$  do not tend to find a significant relationship between education and levels of amyloid- $\beta$  (Farfel et al., 2013; Roe et al., 2007; Wilson et al., 2019), further studies are needed to get a clear and consistent picture of how education affects amyloid- $\beta$ . One possibility is that the imaging studies reflect something more temporary than the postmortem studies, as a recent study suggests that amyloid PET binding can be affected by just one night's sleep deprivation (Shokri-Kojori et al., 2018), as is the case for cerebrospinal levels of amyloid- $\beta$  (Ooms et al., 2014). In particular, as in the context of cognitive ability discussed by Lövdén et al., it will be important to see whether the levels PET amyloid binding show a different rate of longitudinal change depending on education or show a consistent relationship with education level regardless of age. Nevertheless, the findings suggest a fascinating possibility: it could be that those with higher education require less brain activity to get the same cognitive task done, which in turns means that those with higher education produce less metabolic waste during their mental activity, including amyloid- $\beta$  (Jagust & Mormino, 2011; Karim et al., 2019).

## Conclusions

Education is both a life and brain altering process that has lifelong effects. Higher levels of education are associated with higher levels of cognitive ability throughout life. In contrast,

postmortem findings show little relationship between levels of Alzheimer's pathology and education attainment. Lövdén et al.'s review indicates that there is no need to invoke cognitive reserve to explain the discrepancy between brain pathology levels and cognitive function in those with higher education attainment, as a simple effect of education on peak cognition is sufficient to explain why those with more education are able to forestall diagnoses of Alzheimer's for longer. Many critical questions remain about the brain mechanisms involved. How exactly does education affect brain function through mechanisms seemingly unrelated to Alzheimer's pathology? Does education affect the efficiency of cognitive processes in the brain? Does the cost/benefit ratio involved in the brain arousal systems activated by mentally stimulating experiences shift across adulthood? As the techniques to examine brain function and structure in vivo continue to improve hopefully we will gain insight into these processes that in turn will lead to improved targeted interventions that enhance cognition throughout adulthood.

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