Neuropsychologia 51 (2013) 1124–1131

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

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

Cognitive reserve moderates the association between hippocampal volume and episodic memory in middle age

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ARTICLE INFO

Article history:
Received 20 October 2012
Received in revised form
26 February 2013
Accepted 28 February 2013
Available online 13 March 2013

Keywords:
Cognitive reserve
General cognitive ability
Episodic memory
Hippocampus
Verbal learning

ABSTRACT

Cognitive reserve is hypothesized to help people withstand greater brain pathology without manifesting clinical symptoms, and may be regarded as a preventive factor of dementia. It is unclear whether the effect of cognitive reserve is evident only among the older adults or after conversion to dementia, or if it can also be seen earlier in life before the prominent effects of cognitive aging become apparent. While finding a main effect of cognitive reserve on cognitive outcome may be consistent with the reserve hypothesis, in our view, it is unnecessary to invoke the idea of reserve if only a main effect is present. Rather, it is the interaction between a measure of reserve and a brain measure on cognitive outcome that is key for confirming that the effects of brain pathology affect people differently according to their cognitive reserve. We studied whether general cognitive ability at an average age of 20 years, as a direct measure of cognitive reserve, moderates the association between hippocampal volume and episodic memory performance in 494 middle-aged men ages 51 to 60. Whereas there was no statistically significant direct relationship between hippocampal volume and episodic memory performance in middle age, we found a statistically significant interaction such that there was a positive association between hippocampal volume and episodic memory only among people with lower general cognitive ability at age 20, i.e., lower levels of cognitive reserve. Our results provide support for the hypothesis that cognitive reserve moderates the relationship between brain structure and cognition in middle age, well before the onset of dementia.

1. Introduction

Why can some individuals with noticeable brain pathology maintain a relatively high level of cognitive performance while others with the same amount of brain damage have remarkable deficits in cognitive performance? (see e.g., Stern, 2009). This question, along with the observation that brain pathology and

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http://dx.doi.org/10.1016/j.neuropsychologia.2013.02.022

cognitive functioning do not always correlate (see e.g., Katzman et al., 1988), has led to the development of the concepts of cognitive and brain reserve. Cognitive and brain reserve may be viewed as buffers against the effects of brain pathology and protective factors against Alzheimer's disease (AD) or other forms of dementia. Reserve may also explain individual differences in cognitive functioning in the context of AD. While there is evidence for the effect of reserve in healthy older adults (Brickman et al., 2011) and in context of AD (Stern, Albert, Tang, & Tsai, 1999) and other dementia-causing conditions like vascular pathology (Zieren et al., 2013), it is not clear whether the effect of reserve is present throughout adulthood or if it becomes apparent only later in life.

According to Stern (2002, 2009), the concept of reserve can be divided into passive (structural) and active (functional) models as represented by brain reserve and cognitive reserve, respectively. The passive model refers to a threshold at which brain pathology starts to affect cognition. An example of brain reserve would be the neuroanatomical measure of overall brain size (e.g., brain or intracranial volume), the idea being that larger brains can tolerate more pathology before the threshold where cognitive deficits start to occur is reached. The active model refers to compensatory processes that are invoked in order to tolerate or circumvent brain pathology. An example of cognitive reserve would be pre-existing cognitive or compensatory abilities (e.g., higher general intelligence or ability to use different cognitive strategies); in many studies these are approximated by the proxy measure of educational level. In contrast to the passive model, there is no certain threshold of brain pathology when cognition begins to be affected. Instead, higher cognitive reserve helps the individual to compensate and thus maintain a certain level of cognitive functioning despite brain pathology.

Two individuals can have the same amount of brain reserve (e.g., overall brain size), but can still differ in how much they can tolerate brain pathology because they differ in their cognitive reserve (e.g., premorbid general cognitive ability). Because cognitive functions do not operate in isolation from brain anatomy and brain structures are plastic throughout development, the distinction between active and passive models of reserve is not clear-cut. In sum, the reserve hypothesis states that individuals with higher levels of reserve, compared to individuals with lower levels of reserve, can better maintain cognitive functioning in the presence of brain pathology.

As suggested by Christensen et al. (2007), a full model to test the reserve hypothesis should include: (1) a direct or proxy measure of reserve, (2) a measure of brain pathology, and (3) a cognitive outcome. Their review showed that most studies to date have failed to include all of these measures when testing a reserve hypothesis. Instead, many studies have tested the main effects of measures of reserve on cognitive functioning. Such studies have demonstrated, for example, that higher education is related to better cognitive performance at middle age and at old age. These kinds of studies only report the main effect of a measure of reserve on later cognitive performance. Simply showing that more highly educated people (e.g., Le Carret et al., 2003; Singh-Manoux et al., 2011) or those with higher general cognitive ability (e.g., Corral, Rodríguez, Amenedo, Sánchez, & Díaz, 2006) perform better on cognitive tests later in life does not address the question of whether people with higher levels of cognitive reserve tolerate brain pathology better than those with lower levels of reserve. Although this main effect is consistent with the reserve hypothesis, we think it is unnecessary – and therefore less parsimonious – to invoke the reserve hypothesis to account for this finding because those with more education or higher general cognitive ability will perform better on cognitive tests at any point in development, including childhood and young adulthood.

Some studies have suggested that the effect of reserve is supported by the findings that at any level of cognitive performance, people with higher reserve exhibit more brain pathology and will develop dementia later than people with lower levels of cognitive reserve. For example, by studying the Alzheimer's Disease Neuroimaging Initiative sample, Vemuri et al. (2011) found that the level of AD-related biomarkers (beta-amyloid, tau, and brain atrophy) was more pronounced at any level of cognitive functioning among people with higher cognitive reserve (based on the proxy measure of National Adult Reading Test [NART] performance) compared to those with lower cognitive reserve. This finding is important as it clearly shows that people with higher prior general cognitive ability develop dementia later and thus require more brain pathology before clinical manifestation of dementia than people with lower general cognitive ability. However, the effect of general cognitive ability was only on the intercepts, not on the slopes (i.e., individuals with higher cognitive reserve performed better at any level of pathology whereas the effect of pathology on cognition did not differ as a function of cognitive reserve).

The simplest explanation is that people who started out with higher prior cognitive ability will continue to have higher cognitive performance at any point before developing dementia. Also, they develop dementia later simply because they have farther to fall before they reach that threshold of cognitive impairment, just as an object dropped from the sixth floor will take longer to reach the ground than one dropped from the third floor. We argue that it is not necessary or particularly useful to invoke the reserve hypothesis to account for these findings. Like the objects being dropped from different heights, the outcome is virtually guaranteed. It is difficult, if not impossible, to conceive of a situation in which individuals with higher pre-existing general cognitive capacity (cognitive reserve) would not have better cognitive performance than those with lower reserve when they both have the same level of current pathology. If one shifts the scale so that two individuals with different cognitive reserve levels are equated on current cognitive performance, it is self-evident that the one with higher reserve will have greater pathology.

What is more meaningful is to test the hypothesis of a moderating effect of cognitive reserve, which means testing for the presence of a significant interaction between measures of cognitive reserve and brain pathology in prediction of cognitive performance (as suggested by Christensen et al. (2007), see also Stern (2012)). A significant interaction would suggest that the association between a brain (or biomarker of dementia or age) and the cognitive measure differs as a function of cognitive reserve. In terms of the cognitive reserve hypothesis, one would expect that greater brain atrophy would be associated more strongly with poorer cognitive performance among people with low levels of cognitive reserve compared to people with high levels of cognitive reserve. If the effects of brain atrophy on cognitive functioning were less pronounced among people with high cognitive reserve, it would suggest that individuals with high cognitive reserve can compensate more in the presence of brain atrophy, thus resulting in a weaker or zero correlation between brain atrophy and the cognitive measure.

An interaction between education and white matter pathology on cognitive functions has been reported among older adults. A significant relationship between white matter hyperintensities and cognition has been reported to be stronger in individuals with low levels of education compared to those with higher levels of education (Dufouil, Alperovitch, & Tzourio, 2003; Nebes et al., 2006). Similarly, senile plaques have been reported to be more strongly associated with poorer cognitive functioning among those with lower education levels (Bennet et al., 2003). These findings support the cognitive reserve hypothesis because the