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Review

A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease

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Abstract

The gap between symptoms and pathology in Alzheimer's disease has been explained by the hypothetical construct of "cognitive reserve"—a set of variables including education, intelligence, and mental stimulation which putatively allow the brain to adapt to—and hence mask—underlying pathologies by maintaining cognitive function despite underlying neural changes. This review proposes a hypothesis that a biological mechanism may mediate between these social/psychological processes on the one hand, and apparently reduced risk of Alzheimer's disease on the other, namely repeated activation of the noradrenergic system over a lifetime by the processes implicated in cognitive reserve. Noradrenaline's neuroprotective effects both in vivo and in vitro, and its key role in mediating the neuroprotective effects of environmental enrichment on the brain, make noradrenaline's key role in mediating cognitive reserve—by disease compensation, disease modification, or a combination of both—a viable hypothesis.

Keywords: Alzheimer's disease; Cognitive reserve; Cognition; Aging; Noradrenaline; Locus coeruleus; Environmental enrichment

1. The cognition-pathology gap in Alzheimer's disease

One of the major obstacles to developing effective treatments or preventions for Alzheimer's disease (AD) is the imperfect correlation between biological measures of pathology in the brain on the 1 hand—amyloid plaques, neurofibrillary tangles, positron-emission tomography (PET)-measured cerebral perfusion or volumetric magnetic resonance imaging for instance—and measured cognitive function and real life performance on the other (McKhann et al., 2011). In the famous "nun study" for instance (Riley et al., 2002), no less than 32% of elderly participants with Braak Stage III and IV pathology (out of a maximum of 6 stages determined postmortem) had normal memory function before death. Furthermore, while there was a modest but significant correlation of 0.57 between autopsy-determined pathology and general cognition among individuals who had some memory impairment, there was no significant relationship between pathology and global cognition in those with intact memory function, despite the existence of other types of other cognitive impairment in many of this latter group.

A common explanation for this cognition-pathology discrepancy is that cognition and memory function are maintained at relatively high levels despite the developing underlying pathology, of which the presence of amyloid plaques may be 1 important disease-specific marker; this might happen because of compensatory adjustments made by the brain which help it reorganize to maintain function despite the developing pathology (Dubois et al., 2010; McKhann et al., 2011). The development of a human amyloid marker in the form of amyloid PET scanning with Pittsburgh Compound B (PiB) (Klunk et al., 2004) appears to offer a promising advance toward better characterization of, and treatment for, such underlying amyloid pathology. Such a development was hoped to help close the cognition-pathology gap. Unfortunately this gap remains very large despite this important development.

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Roe et al. (2008) examined PiB amyloid load in relation to measures of cognitive deterioration in a sample of elderly individuals with and without diagnosed AD and did indeed find that those who were PiB positive showed very significantly lower cognitive function and significantly higher clinical dementia ratings than those who were PiB negative. There was one important caveat to this finding, however—this reassuring relationship between pathology and cognition disappeared in the group with the highest levels (post-college) of education and was significantly attenuated on most measures for those with intermediate education (some college or graduate college education). The cognition-pathology gap among the best educated in other words, widened to the extent that no correlation remained between these 2 sets of variables.

Such findings do not just apply to education as a variable, however. In a study of social networks (Bennett et al., 2006), the researchers found that while postmortem pathology and predeath cognition showed a reasonable correlation among individuals with relatively sparse social networks, the cognition-pathology correlation again disappeared—as in the case for education and cognition in Roe's PiB study—among groups with a high level of social contact and strong social networks.

Discrepancies between cognition and pathology such as these have been explained by the concept of "cognitive reserve," a concept first developed by Yaakov Stern (Stern et al., 1999). Individual differences in the efficiency, capacity, or flexibility of brain networks ("neural reserve" in Stern's terminology) or individual differences in the ability to compensate for brain pathology (Stern's "neural compensation"), may allow brains affected by Alzheimer's pathology to maintain adequate cognitive functioning (Stern, 2009).

The aim of this report is not to review comprehensively the variables and processes linked to cognitive reserve, as this has been well done elsewhere (Stern et al., 1992, 1994, 1999; Tucker and Stern, 2011; Valenzuela and Sachdev, 2006), nor does the paper attempt to elucidate the distinction between cognitive reserve and the concept of "brain reserve," which Stern and colleagues propose refers to intra-individual differences in biological substrates of the brain leading to different degrees of resilience to the effects of disease or injury. Cognitive reserve and brain reserve have been used interchangeably by other authors such as Valenzuela and Sachdev (2006), but the question posed in this report pertains to a hypothetical biological mediating mechanism by which either cognitive or brain reserve may shape the considerable pathology-cognition discrepancy commonly observed in Alzheimer's disease and other brain disorders.

The magnitude of this cognition-pathology discrepancy is considerable, estimated by Valenzuela and Sachdev in their meta-analysis of education, occupation, IQ, and mental activities components of brain reserve as a mean odds ratio of 0.54 for lowered risk of incident dementia over a median 7.1-year period (Valenzuela and Sachdev, 2006). There are 3 main theoretical interpretations of this finding.

The first is that the reserve variables and the reduced risk of AD diagnosis are correlated not due to any direct causal link, but rather because each is associated with a third common, possibly genetic, factor that causes both the high brain/cognitive reserve factor (educational and occupational attainment and IQ) and the increased resilience to the disease process. This view would hold that the observed correlation between, say, education and lowered risk of AD, is therefore more reflective of the pre-existing resilience than a direct effect of, say, education per se (Whalley et al., 2004). A Swedish study of identical twins, however, showed that those who had the minimal legal level of education for their age cohort had significantly higher levels of dementia than their identical twins who had higher levels of education, confirming that pre-existing genetic variables could not account for the cognitive reserve-symptom relationship (Gatz et al., 2007).

The second theoretical explanation for this relationship is that the apparently protective variables such as education build the brain's capacity to compensate for a disease process which in itself is unaffected by education, mental stimulation, or social interaction. Such compensatory variables could range from the increased cortical volume that has been shown to arise from intensive new learning during examination preparation in students (Draganski et al., 2006) or by learning a new skill such as juggling (Draganski et al., 2004); it could also arise from cognitive-training-related increases in white matter volume (Takeuchi et al., 2010) or from changes to critical neurotransmitter receptor densities (McNab et al., 2009). Changes to brain regions crucial for compensatory adjustments such as the prefrontal cortex may play a particular role (Erickson et al., 2007).

The third theoretical explanation is that education, mental stimulation, and social interaction directly impact the Alzheimer's disease process itself, and not only the brain's capacity to compensate for the disease (Landau et al., 2012).

Only the second and third of these theoretical positions propose a causal role for the protective effects of these cognitive reserve variables and the aim of this report is to advance a hypothesis about a possible biological route (enhanced noradrenergic signaling) which might mediate between cognitive reserve and reduced AD vulnerability in both of these theoretical cases 2 and 3 above, which I will term "compensatory" and "disease modifying" respectively. I ask in other words whether variables such as education/IQ, mental stimulation, and social engagement reduce risk of AD by improving the brain's ability to compensate for disease as outlined above and/or by directly influencing the AD disease process itself. Because it is currently not possible to measure directly brain noradrenergic function in