Cognitive Reserve: Evolution and Adaptation of an Explanatory Concept

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Brain Reserve and Cognitive Reserve

The cognitive reserve hypothesis proposes that the individual differences in cognitive performance found at similar organically defined stages of AD and during the course of normal aging are the result of differences in brain development. The more cognitive activity in leisure and work prior to illness, the longer the education and the higher the childhood IQ, the later and lesser the effects of disease, and the slower the cognitive decline in healthy aging (Scarmaes 2003; Richards, et al. 2004).

There is also evidence for the claim that cognitive reserve can explain differences in the incidence of cognitive impairment disease (Wilson, 2002) and variations in the pattern of disease progression. (Le Carret 2005) A systematic review of the literature by Valenzuela (2005) summarized about ten years of cohort studies on the relationship between presumed reserve indicators and the incidence of dementia and found a summary odds ratio of .54 with a .95 confidence interval of .49-.59 for high reserve. These were studies which included multivariate controls and a median 7.1 years of follow up.

The mechanism proposed at an early point in the elaboration of the hypothesis was that cognitive activity increased brain mass and connectivity between or within brain regions in those who had undertaken CR activities. (Katzman 1988; Scarmaes 2003) Katzman wrote,

> Ten subjects whose functional and cognitive performance was in the upper quintile of the nursing home residents, as good as or better than the performance of the upper quintile of residents without brain pathology (control subjects), showed the pathological features of mild Alzheimer's disease, with many neocortical plaques. Plaque counts were 80% of those of demented patients with Alzheimer's disease. Choline acetyltransferase and somatostatin levels were intermediate between controls and demented patients with Alzheimer's disease. The unexpected findings in these subjects were higher brain weights and greater number of neurons (> 90m2 in a cross-sectional area in cerebral cortex) as compared to age-matched nursing home control subjects. These people may have had incipient Alzheimer's disease but escaped loss of large neurons, or alternatively, started with larger brains and more large neurons and thus might be said to have had a greater reserve.

Wolf et.al. (2005) provides evidence for the brain reserve hypothesis and a good review of its limitations.

It has also been suggested that experiential effects might be preconditioned by or mediated by genetic differences such as those presumed to produce differences in standard measures of intelligence. Favorable genes provide a higher starting point and perhaps a greater effect from cognitive activities. However evidence from twin studies indicates that while the level of cognitive performance of the elderly is genetically linked in twins, change in performance in old age is not significantly so for the majority of people.(McGue and Christensen, 2002 (Danish Twins); Reynolds et al. 2002 (Swedish twins))

Some researchers distinguish cognitive reserve from brain reserve. According to Tuokko et al. (2003)

> The brain reserve capacity (BRC) model (Roth,1971; Roth, Tomlinson & Blessed, 1967; Satz, 1993) holds that there is an absolute cut-off or threshold of neural damage at which functional impairment will occur for everyone, but that there are individual differences in BRC, which results in earlier or later expression of clinical symptoms. That is, a particular amount of neural damage may result in a clinical deficit (i.e., a threshold is passed) in a person with less BRC whereas the same amount of neural damage may not manifest clinically in a person with more BRC....The cognitive reserve model, in contrast to the BRC model, posits that people differ in how effectively cognitive paradigms are used to approach a problem, rather than in how much BRC is available. The cognitive reserve model does not assume an absolute threshold of neural damage at which impairment occurs but suggests the critical threshold will differ from one person to the next depending on how effectively remaining neural tissue is used. That is, two persons with the same amount of BRC may differ in the extent to which they manifest clinical symptoms because person 1 uses more efficient cognitive strategies than person 2.

So on the BR model, people have different (innate plus acquired) brain capacities, such as memory, attention, planning-monitoring ability, and capacity for spacial and temporal orientation which underlie cognition and performance. These capacities are subject to degradation by disease but give rise to different functional effects as measured by successful task performance. Functional changes resulting from disease depend upon initial pre-disease capacities which differ between individuals. The BRC model is theorized to be a universal or general (normal) critical path model with successful performance by individuals dependent upon remaining capacity in any subset of the network but with the robustness of the network (sensitivity to damage at or between any node) as the measure of reserve capacity.

The modification proposed by Stern as cognitive reserve, CR, is to hypothesize that the reserve effect might also be dependent on the availability of more than one critical path model for any activity performance type. (A performance type is what I call a standardized task used to measure cognitive performance such as a sub set of MMSE questions.) Stern's speculation is that higher levels of IQ and education are likely

indications of such path diversity and may not be the consequence of more brain reserve capacity. By making the distinction between brain reserve and cognitive reserve, Stern and colleagues implicitly question a reductionist account of cognition and propose in its place a functionalist account which may seem better able to accommodate individual variations in cognitive performance in the face of equivalent biological challenges.

The common element in these two conceptualizations is the supposition that the disease process at the biological level of description is continuous while at the functional level it is punctuated or discontinuous with threshold effects defining the transition between normal aging and disease as well as defining disease types and stages. It is not clear whether this two stage assumption is intended as an empirical hypothesis or whether it is the consequence of the fact that investigation of cognition has proceeded along parallel lines at the biological and biochemical level and at the functional level. One implication of this bifurcation is that the effort to investigate cognitive reserve must not ignore what Tukko refers to as "ascertainment bias". People with higher levels of education or higher innate capacities will not be correctly diagnosed by functional tests that are designed for classification of people closer to the mean of pre-disease cognitive performance. Finding a lower incidence or a different typical course of disease may be explained by measurement error unless care is taken to eliminate measurement threshold effects. The suggestion then is that to track the disease process, functional testing must assess individual changes in task performance rather than changes defined by group norms and that functional disease staging and classification must also be individualized.

But such a correction to disease staging based on individualized functional norms may seem to undermine the concept of brain reserve capacity as logically tied to a mistakenly fixed model of the relationship between the functional definition of disease or disease progression and its underlying biological substrate. Brain Reserve Capacity was proposed to explain the difference between functional and biological disease markers when both biological and functional markers were taken as fixed. With an assumption of fixed markers at both levels, people picked out by high brain reserve indicators do better on cognitive tests before disease, so it is not adding much and should not surprise us discover that they do better as disease begins and progresses, at least initially. The mismatch between fixed functional markers and individualized connection between biologically defined disease progression would mean that "high reserve" people with disease would be missed at early points in the disease process because they would not have crossed the functionally defined disease threshold. Apparently lower incidence of disease would be a measurement error for high reserve people with undetected disease.

One way around this dilemma that would preserve a reductionist account of cognition and fixed functionalist disease markers would be to devise "reserve-related" corrections to standard functional measures, and then use these to normalize individual function scores. Tukko suggests this strategy. One could discount cognitive performance by years of education, for example, when assigning an individual cognition score. The problem here is that knowledge of the effect of education and other explanatory variables on the functional expression of capacities with disease underway is required. But this is what is in question

and it is what is said to be individually variable by proponents of the cognitive reserve hypothesis.

We can see the result of the two approaches in collision by comparing the conclusions of Rabbitt, et al. (2003) with those of Richards, et al. (2004) which came to opposite conclusions in answer to the question, "Do Cleaver Brains Age More Slowly?" Rabbitt found that if early IQ scores that are estimated by regression analysis using vocabulary scores as the independent variable, then adult change in IQ as measured in adulthood changes at the same rate for all IQ levels. The method assumes that the relationship between vocabulary scores (which change little) and IQ scores which change more and with more variability allows an unbiased estimate of early IQ. But this requires the reductionist assumption that the biological basis for measured IQ, a functional measure, and the biological basis for the relationship between vocabulary and IQ measures are invariant from young to old. Richards, who relied upon measured reading scores in youth and measured adult cognitive ability found that reading scores measured at age 15 were "inversely associated with rate of decline in memory, speed, and concentration in mid-life, independent of socioeconomic and health status. Ability in adulthood was also inversely associated with decline in mid-life, independent of childhood ability". The Richards result supports the non-reductionist CR assumption and points toward a compensation or protective model of reserve.

Another approach to sorting out these differences is to rely only on biological markers for describing the extent of disease in relation to changes in cognitive performance that occur during normal aging and disease. If the extent of disease and disease progression is understood in standardized biological terms (oxygen use, blood flow, brain volume, white matter hyperintensity, amyloid B and tau deposition) compared with healthy controls, then the imputed effects of cognitive reserve as measured functionally, differing between pre-disease high and low reserve people would not be measuring or describing the extent of disease but only indicating some other interesting difference in the relationship between biology and function for disease and normal states. And similarly as changes in cognition during normal aging are defined by biologically based change measures such as those provided by neuro-imaging, the reserve concept is superseded by a focus on adaptation which, when it preserves function, is described as compensation.

The pull toward biological rather than functional characterization of disease can be seen in the trend toward the identification of "pre-dementia" within the mild cognitive impairment category using brain imaging techniques. By these means, functionally identical people can be classified as pre-disease although they show no functional differences from controls. A rule of thumb to follow in matters of ascription of causation is to regard a characteristic as causally sufficient if one would support its use in a counterfactual statement. That is we would have to be willing to say of a pre-disease marker that if it had been present in anyone now healthy, that person would have developed the disease in question. (Esiri, 2001) By this standard, the search for biologically definitive signs of many cognitive disorders (sufficient conditions) has not been successful, perhaps in part as a consequence of the fact that the specification of dependent variable in functional terms is itself subject to continuing debate. (Frey. 2005)

Despite these difficulties there is considerable research aimed at linking biological markers for disease and presumed CR factors. Dufouil and colleagues (2003) found that the relationship between white matter hyperintensities and cognitive performance was modulated by education and that the effect varies across different cognitive tests. They conclude that their findings lend support to the contention that education is associated with increased cognitive reserve although they note that threshold effects of the MMSE may have affected that conclusion. Support for their general conclusion is provided by their reported data which shows a correlation between level of WMH and cognitive performance for low education subjects but no relationship for high education subjects. The result appears to hold even for cognitive tests not made suspect by ceiling effects, such as Raven Progressive Matrices test.

Scarmeas et al.(2003), continuing a line of inquiry begun by Stern a decade previously (Stern, 1993) reported an association between life activities and cerebral blood flow in a study of nine early stage AD patients as compared with sixteen healthy controls. The conclusion of this study was that IQ (as measured by reading score), education and leisure activities in the previous six months are all associated with lower blood flow for a given level of disease severity, indicating according to the authors, that these factors mediate the effect of disease and its expression as measured by clinical tests. They note that blood flow associations were found in different areas of the brain depending upon whether education, reading ability or engagement in activities was used in the analysis suggesting that "different aspects of CR mediate clinical protection in an anatomically specific way..." It is their contention that the effect of CR factors is to delay the onset of functionally described disease rather than to provide "immunity" since "non-demented individuals manifest neuropathologic changes consistent with AD at autopsy". They "assume that the pathologic changes in AD progress independently of life activities." Subsequent researchers have expended a great deal of effort to test that assumption.

At this stage (2003) in the evolution of the concept, CR is still seen by many researchers as an explanation of the mismatch between clinical presentation and the presumed definitive biological process that is thought to give rise to it. If this account is correct, findings of a truly protective effect for CR related activities such as those reported by Wilson, are being explained away. In contrast, Wilson et al. (2002) conclude that activities are protective in a study of members of religious orders, reporting a reduction of risk of 33% for each point on an activities scale. Reduction of risk remained even after non-demented but low memory participants were excluded from the analysis thereby reducing the likelihood that the results reflected undetected dementia in high activity people. In another study published that year, however, Mackinnon and colleagues (2003) reported that cognitive activity provided no protection against cognitive decline concluding this on the basis of their finding that showed decline in cognitive performance in participants who remained stable on measures of activity. The authors recognized however, that the result might reflect activity threshold effects which could not be investigated with their data.

With growing attention to the alternative conceptualization of CR as compensation

however, an alternative understanding of the implications of biological variability as described Esiri (2001) became evident.

Bennett et.al. (2005) found that education modified the association between amyloid but not tau tangles with cognitive function stating that their result shows that education not only "provides a cognitive advantage such that persons with more years of education perform better on cognitive tests and may require more pathology to reach any given level of cognitive impairment but that education is also associated with factors that somehow reduce the effect of amyloid on cognition." What is that "somehow"?

Compensation

While cognitive reserve continues to occupy the attention of many researchers, the concept of compensation has grown increasingly important as a framework for understanding and investigating diversity in cognitive change in the elderly. In 1996, Becker et al. reported a difference in the brain regions activated in AD verses control for a word recall test.

> In summary, patients early in the course of AD show normal patterns of cortical activity when performing low-level, automatic cognitive operations. When task demands increase, and additional cognitive resources are necessary, the AD patients show an abnormal activation of dorsolateral prefrontal cortex and of the parietal-temporal border.

Similarly Cabeza et.al. (1997) investigated age-related differences in neural activity during memory encoding in young and elderly normal subjects and found that " the typical asymmetrical encoding/retrieval pattern does not hold in old age." They regarded the result as consistent with a compensation process but could not rule out a non-compensatory change. In 1999, Backman and colleagues reported differences in regional activation patterns between AD patients and controls during a memory task and interpreted the differences as evidence of compensation. They observe that previous studies identified bilateral activations as compensation and they note,

> Comparing these findings with those of the current study, an intriguing pattern emerges: Specifically, young adults, normal elderly subjects, and patients with early AD may be viewed as three instances on a continuum of episodic memory ability paralleled by degree of specificity of neural processing. On this view, the observed increase in left prefrontal activity in AD may reflect a compensatory response triggered by problems in retrieving the target information.

Stern et al. (2000) addressed the issue of compensation in a study of differences between AD patients and controls. The study concluded that at least some AD patients differed from controls in the networks of brain regions used during memory tasks. The differences in a brain network which contributes to the modulation of attention were most important. They write,

> Consideration of the brain regions that participated in the network used by the

> healthy elders suggests that this network is involved in transforming the recognition task from one which requires attentional resources to a more automated task. ..Performance (i.e., SLS) across the healthy elders and the three AD patients was variable, but it was related to modulation in the expression of the same network. Individual differences in performance may represent differences in the ability to effectively recruit this network. Individuals who can recruit this normal network to a greater degree might be able to continue to do so more effectively in the face of significant brain injury, but this possibility could not be assessed in the current study....For most of the AD patients, task performance was associated with activation of a different network than that used by controls...If the term compensation is reserved for the use of a novel network that emerges in response to disease, then the alternate network does not meet this criterion. On the other hand, the role played by the alternate network differed in patients and controls in that it appeared to be mediating the ability to achieve larger SLS in the patients but not the elders. This novel use of the network may arise out of the inability to use the standard network and thus may be considered compensation.

But the overlap of regions used by healthy participants and patients led to an equivocal conclusion on the issue of whether to regard the differences as evidence of compensation. Bookeimer et.al. (2000) compared APOE4 and APOE3 subjects on a demanding memory tasks and found that the

"…greater increase in signal intensity in brain regions necessary for tasks requiring memory among the carriers of the APOE e4 allele suggests that they performed additional cognitive work to accomplish the task. Expanding the territory of neural tissue dedicated to such tasks, as well as increasing the number of neurons recruited or the firing rate within a given functional area, may augment the brain's processing capacity, operating dynamically in response to cognitive demands. In persons at risk for Alzheimer's disease, such increased brain activity may effectively serve a compensatory role, wherein subjects use additional cognitive resources to bring memory-related performance to a normal level."

Cabeza found (2002) in a comparison of hemispheric lateralization found that "low-performing older adults recruited a similar network as young adults but used it inefficiently, whereas high-performing older adults counteracted age-related neural decline through a plastic reorganization of neurocognitive networks.....One possible explanation is that additional within-hemisphere activity does not involve a network modification, whereas additional contralateral activity involves the recruitment of an alternative network. "

Grady (2003) presented evidence for compensation in AD patients. This study showed that patients with AD who used a distinct network not used by controls performed a word learning task better than those patients who did not.

Critically, activity in this network of regions was correlated with the ability of the patients to perform the tasks accurately. That is, those patients who had more activity in bilateral prefrontal areas were better able to perform tasks of semantic and episodic

memory. This is thus the first direct demonstration that recruitment of additional prefrontal areas into a cognitive network in AD patients is associated with better performance.

The transition from an emphasis on the description of reserve factors in the investigation of disease and healthy aging to a focus on compensation in healthy young and old can be seen in the work of Stern and his colleagues in 2003. (Stern et al. 2003; Stern, et.al, 2005). In a disagreement with his colleague Scarmeas' contention that CR was best understood as a confounding factor in diagnoses, Stern et.al. (2003) investigated the effect of reading and vocabulary test scores (which they took to be proxy IQ measures) on on working memory, using fMRI imaging during visual tasks adjusted to provide individualized levels of difficulty to healthy young subjects. Comparisons of low and high difficulty tasks provided evidence for the conclusion was that different regions of the brain are active in high ability subjects than are active in low ability subjects. Stern regarded this result as providing evidence for the CR hypothesis since it suggests that indicators of CR are associated with differing patterns of brain activation in a memory task. In a 2005 study Stern and colleagues used a visual memory task to investigate the regional differences in activation between young and old subjects controlling for a CR measure. Their results showed differences in effect between high and low CR categories for each age group. They found a pattern of activations that reflected a transition from easy to hard tasks (defined individually) that reversed between age groups, with the reversal correlated to CR measures.

They explain their results:

> ...we can speculate that the different relationship between CR and topographic expression in the two groups is due to some age-related physiological change in the older subjects. As a response to these changes, perhaps as a function of longer-term brain adaptation, the older subjects make use of an altered network, causing the activation of the regions captured in the covariance pattern to switch sign. This results in higher CR being associated with increased utilization of some brain areas with more positive network expression in one group, and more negative expression in the other. The age-related changes in network expression are thus most consistent with our definition of neural compensation.

In this study, there is evidently a greater effort to incorporate the work of Cabeza and others in the compensation school into a CR framework and although it is not mentioned, a tilt in the direction of the default mode interpretation of cognitive change. Notably, there is an ambiguity in the description of the changes as "neural compensation". In earlier publications Stern had distinguished between cognitive reserve (more efficient use of preserved neural paths) from brain reserve), preferring the functionalist account to the reductionalist BR model. By 2003 Stern and his colleagues had begun to take note of and investigate the compensation approach to the explanation of functional heterogeneity. At this point, Stern proposed that any change in the biological basis of functions in the presence of disease be called "compensation, while other changes ought to be referred to as "reserve". This suggestion has not been taken, as far as I can tell. In the 2005 paper, Stern and colleagues seem to have adopted a compensation paradigm and have dropped

the terminological proposal made previously. However, they had not yet taken account of the default mode hypothesis. There are no default mode references in that paper's citations. And although the compensation research provides ample support for a functionalist account of cognitive change in its many descriptions of heterogeneity in the neural basis of cognitive performance, Stern and colleagues seem to have tacked back toward a reductionalist stance.

Default Mode

A promising new avenue of research has opened up as a result of the delineation of a default mode of brain activity which provides a baseline for comparison in the study of the dynamics of the neural basis of cognition. (Raichle et.al. 2000)

A number of studies have used the default mode baseline to investigate differences in brain activity between young and old, and between AD, APOE4, and MCI and healthy controls with the result that the changes in baseline brain activity between these groups can be demonstrated. (Greicius, 2004; Rombouts, 2005; Lind et al. 2006; Liang ,2006) Since the default state is coextensive with an internal subjective focus and planning, daydreaming and episodic memory use there is an evident relationship to some of the distinctive features of normal and disease process cognitive decline. A larger scale collaborative effort has made a case for a default mode theory of cognitive decline (Buckner, etal 2005) This study integrates a number of different modes of research to arrive at the conclusion that there is a

> ...a remarkable correlation between default activity patterns in cortical regions in young adults and the topography of amyloid deposition in elderly AD patients. This correspondence raises the possibility of a relationship between activity patterns in early adulthood and later amyloid deposition. Of additional interest, the default activity pattern also correlates with posterior networks involved in memory retrieval, suggesting that memory may be affected prominently in AD because memory systems are modulated as part of default cognitive modes.

The default state theory, consists of four hypotheses:

> (1) default activity/metabolism patterns in young adults, in some unspecified manner, lead to or modify amyloid deposition; (2) cortical amyloid deposition associates with accelerated atrophy and metabolism reduction; (3) within cortical regions associated with amyloid deposition, some posterior regions are preferentially vulnerable to disruption, and other anterior regions are relatively less vulnerable; and (4) the prominence of memory impairment as an early symptom of AD is, in part, attributable to modulation of memory networks in default cognitive states.

More particularly in relation to the decades long investigation of cognitive reserve, the

default state hypothesis provides evidence for a neurological account of cognitive reserve. As stated this is that, " Default activity patterns, over many years, may augment a metabolic- or activity dependent cascade that participates in AD pathology." To make the argument explicitly, we need only recognize that the default state is the dynamic alternative to a wide variety of attention driven states which are "off" when the default mode state is "on". Thus life activities which require attention driven cognitive effort turn the default mode off. (Fox, 2005; Lawrence, 2003) And the inability to turn off default mode is associated with age related decline in cognitive ability, since the "off" state is required for the best performance of tasks demanding undivided attention. (Grady et al. 2006) Conversely, the absence of a default mode is associated with autism (Kennedy et al. 2006) which suggests that the default mode theory of amyloid deposition might be tested by an examination of the incidence of AD in autistic people.

According to the Buckner et al. theory, time in default mode results in amyloid deposition, perhaps also to metabolic stress and thereby to cognitive decline; conversely, time in "attention mode" protects against decline. There is recent evidence that synaptic activity regulates the release of amyloid B. (Cirrito 2005) Further investigation is needed to fully understand the mechanism and implications of this finding. However it does suggest that the regional deposition patterns identified in Buckner et al. (2005) can be connected more directly to the findings that associate life experiences and physiological change. The default state theory of reserve provides a bridge between the concept of reserve as the product of daily activities and its neurological and biochemical description. It is a good fit to the point of view that sees cognitive change in a context of a lifetime. (Richards 2005)

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