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Elaborating a Hypothetical Concept: Comments on the Special Series on Cognitive Reserve

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The four studies in this symposium emerged from an exciting 2009 Friday Harbor workshop that focused on using the most advanced psychometric approaches in the study of cognitive reserve (CR). The workshop participants had the pleasure of working with three outstanding data sets, all from the Rush group in Chicago, directed by David Bennett. The data sets were based on cohorts of extremely well characterized, prospectively followed elders. The autopsy rate was outstanding, as was the quality of the postmortem data. In addition, the study investigators have had a long-standing interest in issues surrounding reserve and have thoughtfully assembled a rich array of relevant data about features of the life course that might be associated with increased reserve. What made the workshop especially fun was the presence of psychometricians/biomedical statisticians who were up to the task of working with this rich data set and giving it its due.

The cognitive reserve hypothesis emerged from the observation that there is not a direct relationship between the amount of brain changes or pathology and the cognitive or functional consequences of those brain changes (Stern, 2002, 2009). Instead, there are a great deal of individual differences in people's susceptibility to pathology. The cognitive reserve hypothesis posits that these individual differences may stem from differential ability to cope with or compensate for pathology, which in turn is driven by individual differences in how tasks are processed in the brain. The epidemiologic evidence suggests that different exposures during the life course may contribute to this reserve (e.g., Scarmeas, Levy, Tang, Manly, & Stern, 2001; Stern et al., 1994). There is also more direct evidence that specific life exposures might moderate the relationship between measured brain changes and cognitive performance (Bennett et al., 2003; Stern, Alexander, Prohovnik, & Mayeux, 1992). Starting with this background, each of the studies in this series addresses some important piece of the puzzle in trying to understand how reserve may be imparted and implemented.

The study by Fyffe et al. examines the difficult issue of ethnic differences in test performance. The authors grappled with two issues. First, using differential item functioning (DIF) methodology they measured equivalence of their memory measures across whites and African Americans. Importantly, they found minimal impact of DIF, indicating that observed ethnic differences in performance, as well as the potential influence of other covariates, are not due to measurement bias. The authors then went on to investigate whether various lifetime exposures that have been associated with cognitive reserve might account for performance differences across the two groups. These variables included personal and parental education, childhood cognitive activity frequency, income at age 40, and education quality as measured by reading level. These variables were chosen because

they have been used as proxies of cognitive reserve in previous studies. The authors found that the observed memory test performance differences between the two groups were best accounted for by educational quality, as assessed with reading level. This is an interesting finding, which replicates previous observations about the power of measures of educational quality for resolving disparities in performance (e.g., Manly et al., 2000). Furthermore, the measures of reading level have been shown to be good proxies for cognitive reserve in studies looking at rate of cognitive decline (e.g., Manly, Touradji, Tang, & Stern, 2003). This study reinforces the idea that the educational experience has a strong influence on cognitive processing, and that this may be the basis for the repeated observation that educational attainment and reading level are good proxies for cognitive reserve. It should be noted that this analysis does not directly study cognitive reserve. An observed relationship between a specific life experience and task performance does not necessarily suggest that this experience will impart reserve against brain changes or pathology. Still, we would assume that variables that are associated with cognitive reserve achieve this status because they influence cognitive development in a way that is important for coping with brain damage. Therefore the fact that educational quality may account for performance differences on memory tests is of interest. An issue that remains to be addressed is the true meaning of reading test scores in these older adults. In the present study two reading tests, the National Adult Reading Test (NART) (Nelson & Windsor, 1982) and the third edition of the Wide Range Achievement Test Reading subtest (WRAT-3) (Wilkinson, 1993) are used as indicators of educational quality. It is also common to use these measures, particularly the NART as estimates of IQ or pre-morbid IQ, and they have been used in this way in studying cognitive reserve (e.g., Stern et al., 2005). Clearly prospective studies can help disambiguate this issue. Two studies clearly indicate that NART performance later in life is independently influenced by measured IQ at age 8, as well as by subsequent educational experience (Hatch, Feinstein, Link, Wadsworth, & Richards, 2007; Richards & Sacker, 2003). Therefore both interpretations are partially correct. In the context of the concept of cognitive reserve, both IQ and educational experience contribute to reserve, and these observations may help explain the power of reading measures as proxies for reserve.

The study by Dowling et al. addresses a basic building block that is needed to explore cognitive reserve: the relationship between measured brain pathology and cognition. This study is exemplary of the unique power of the Rush data sets. There are very few such large-scale cohorts with both excellent cognitive characterization and full pathologic evaluation. In addition, the statistical approach used to summarize both the cognitive and pathological variables, and their interrelationship, is state-of-the-art. As might be imagined, the observed relationships between pathological and cognitive measures were complex. Different aspects of pathology contributed to each cognitive domain, and there were regional differences as well. As the authors point out, most cognitive domains are controlled by complex systems that require the interaction of multiple brain areas. Therefore, these summary measures would not be expected to fully explicate how specific pathologic findings at specific locations might impact on cognition. Still, some of the more general observations fit with previous ideas about pathologic location and type and specific patterns of cognitive dysfunction. In summary, the neuropathological variables and brain weight contributed approximately one-third to half of the explained variance in the identified cognitive domains. Thus, a large degree of the variance is left unexplained. There are at least three possible explanations for this observation, all of which are probably partially correct. First, much more fine-grained analyses of the location of the pathologic findings might yield more explained variance. Second, the reason that some of the observed pathological findings disrupt cognitive function is unknown. For example, neuritic plaques correlate with cognitive function to some degree, but the mechanism through which they disrupt cognition is unknown. Furthermore, it is clear that some people can sustain high loads of amyloid plaque and tangle pathology without apparent cognitive deficit (Aizenstein et al., 2008; Ince,

2001), and we do not understand the reason(s) for this. Third, these pathologic measures would never be expected to fully account for cognitive function; they can only disrupt some of the networks underlying function.

The cognitive reserve hypothesis is closely related to this third idea. Three neural mechanisms have been proposed to account for individual differences in susceptibility to pathology (Stern, 2009). “Neural reserve” proposes that individual differences in task-related processing exist in individuals without pathology. For example, the neural networks underlying task processing may be more efficient or have higher capacity in some people than others. These differences may allow some to cope better with pathology than others. In contrast, the idea of “neural compensation” is that when pathology alters standard task processing networks, some people may be able to engage compensatory mechanisms better than other people. Note that both of these proposed neural mechanisms for CR invoke task-related processing, that is, the specific neural networks that may underlie processing a particular task. A third idea is that CR represents some generalized ability that is not task specific (e.g., Stern et al., 2008). This would help explain how CR might allow people to preserve function on multiple tasks in the face of pathology. The approach my group is now taking to investigating these ideas is acquiring concurrent measures of fMRI task-related activation, brain pathology, cognitive performance, and cognitive reserve.

The study by Reed et al. takes up the analyses performed by Dowling et al. and uses them as the basis for exploring life experiences that may impart reserve. A key feature of this study is the unique way that cognitive reserve is defined. Typically, cognitive reserve has been measured as some combination of the experiences that may contribute to it. Because epidemiologic data suggests that higher IQ, educational and occupational attainment, leisure activity, cognitive activity, etc., are all associated with reduced risk of developing Alzheimer's disease, these measures have been used as proxies for CR. We will return to this idea in the next study by Jones et al. Following up on a previous study by Reed et al. (2010), the current study took a different approach to defining cognitive reserve. Based on the idea that cognitive reserve accounts for the disparity between the amount of pathology and the level of cognitive performance, the authors defined cognitive reserve as the latent construct consisting of the variance in cognitive performance that is not explained by the pathology and other demographic measures. In the other study by Reed et al. (2010), a comparable latent variable correlated with reading ability (a proxy for cognitive reserve), and even more impressively, was predictive of subsequent memory decline and incident dementia. So, in the current study, the authors built on the findings of Dowling et al. and defined cognitive reserve as a latent variable that captures the variance in cognitive function that is not explained by measured pathology. They then proceed to test sets of lifetime exposures that might be predictive of more or less cognitive reserve. Determinants of reserve were socioeconomic status, education, leisure and cognitive activities both at age 40 and in late life. They found that cognitive activities throughout adulthood (at age 40 and in late life) were the strongest predictors of cognitive reserve.

While this study is notable for the insight it brings into determinants of cognitive reserve, its most unique aspect is the further development of innovative methodology for defining reserve. This approach to measuring cognitive reserve is theory based. The derived latent variable directly measures what cognitive reserve is supposed to do: account for disparity between pathology and performance, and avoids the indirect route typically used to measure reserve based on proxy variables. There are also potential disadvantages to this approach of assessing cognitive reserve. It relies on the availability of measures of pathology. Also, it assumes that we actually know what pathology determines cognitive and functional change. More important from a theoretical view, this measure of CR is a snapshot of the current status of the individual, and can only be useful at specific points in the development of a

disorder. Let us use Alzheimer's disease as an example. It works best during the phase when pathology begins to emerge. However, until pathology begins to appear, this approach can say nothing of the potential reserve against pathology that might be present. Many studies have noted that higher cognitive reserve, as assessed by proxy variables, is associated with more rapid cognitive decline once the clinical symptoms appear (e.g., Stern, Albert, Tang, & Tsai, 1999). Again, it is not clear to me how this static approach to measuring reserve can speak to this finding. Still, this approach to measuring cognitive reserve will be of great value to many researchers who have both pathologic and cognitive measures available, and it is an important contribution to studies in this area.

The final study by Jones et al. turns to the problem of modeling the determinants of cognitive reserve. As mentioned above, numerous lifetime exposures, as well as other variables, have been associated with cognitive reserve in epidemiologic studies. At this point, sophisticated psychometric techniques can be used to evaluate the unique and combined contribution of these predictors on cognitive reserve. These include path analysis and structural equation modeling. Typically, sets of variables are considered that together may form a latent variable that captures cognitive reserve. After providing a useful summary of these latent variable approaches, Jones et al. point out that most of the standard latent modeling approaches do not appropriately capture the directionality of the relationship between cognitive reserve and the variables that allow it to emerge. I am sure that these investigators will eventually suggest some new analytic approaches that will solve this nettlesome problem. One issue not raised by Jones et al. emerges from the types of analyses that are reviewed. The analyses assume that cognitive reserve is ultimately determined by sets of life experiences and brain variables. However, latent modeling approaches typically attempt to distill what is common to multiple determinants and use this commonality to define reserve. This approach may miss an important feature of how reserve develops: different experiences may contribute differentially to reserve. For example, we can show that engaging in more late life leisure activities results in a reduced risk of dementia over and above the contribution of higher educational and occupational attainment (Scarmeas et al., 2001). Therefore, leisure activity must contribute something unique that is not obtained from the other two experiences. For this reason, it will be useful for research to consider both summary variables and individual proxy variables for cognitive reserve.

These four studies capture some of the excitement of the 2009 Friday Harbor conference where the initial ideas for them germinated. Outstanding data sets were combined with state-of-the-art analytical approaches to ask unique questions about cognitive reserve. Part of the attraction of the concept of cognitive reserve is that it provides a framework for attempting to understand individual differences. These studies represent excellent “seed beds” from which to generate new research about how cognitive reserve develops and is implemented. Hopefully the cognitive reserve concept will continue to frame research toward the important goal of preserving and improving cognition and functional abilities across the life span.

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