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Commentary: Sensitive and Specific pre-clinical identification of Alzheimer's disease: A key to novel intervention development

Barton W. Palmer, Ph.D.

Professor of Psychiatry, University of California San Diego, La Jolla, CA

Early detection of preclinical Alzheimer's disease is clearly critical to development of effective interventions. By the time the clinical symptoms manifest, much of the neuropathological damage is already present. Hope for truly effective treatments rests in being able to intervene early in the pathological process, before the cascade of damage is well-underway (Cummings, Doody, & Clark, 2007).

Over the past two decades, researchers have found substantial evidence pointing to episodic memory tests as a sensitive measure to identify those in the very earliest stages of Alzheimer's disease(Bondi et al., 2008). Of note, contemporary episodic memory tests are essentially modified forms of some of the most enduring measures in existence. For example, the Rey Auditory Verbal Learning Test (RAVLT), a list learning task which remains widely used and is also the precursor to the popular California Verbal Learning Test (CLVT) was initially introduced in the early 1900s by Édouard Claparède (Boake, 2000). But there remains a need to identify high-risk people even earlier in the process of pathological change. For example, data from the well-publicized "Nun study" indicated that an index of "idea density" (number of ideas expressed per 10 words) in autobiographies written at age 18–32 predicted subsequent risk of development of cognitive impairment or dementia approximately six decades later (Riley, Snowdon, Desrosiers, & Markesbery, 2005). Such findings raise the possibility that there are subtle forms of subclinical neuropathology present decades before the emergence of mild cognitive impairment or dementia.

The need to identify people in the earliest stages of Alzheimer's disease is not one that is going to be solved by a single test, biomarker, or other index. It is likely to require a complex formulation of neurocognitive performance, identification of genetic, lifestyle, environmental, and other risk factors. Nonetheless, because neurocognitive testing remains one of the key measures that can be reliably administered in the context of routine clinical care, a part of the solution is likely to continue the search for very early cognitive markers of dementia risk. In this regard, the paper provided by Loewenstein and colleagues in this issue is of particular interest and potential value.

Rather than simply examining the standard measures from list learning tasks such as initial or delayed recall, and savings scores, the task employed by Loewenstein and colleagues focused on three process components of memory task performance, proactive semantic

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interference (PSI), retroactive interference (RI), and, importantly, ability to recover from the effects of proactive semantic interference. These authors had previously developed a novel cognitive stress paradigm, the Loewenstein Acevedo Scale for Semantic Interference and Learning (LASSI-L). This task employs controlled learning over two cued recalls trials to maximize storage of to be learned information. Then, participants are provided with a semantically similar list of targets to intentionally foster proactive semantic interference. This is followed by a repeated learning trial of the new list to evaluate examinee's ability to recover from the initial PSI effects. The authors hypothesized that maximum storage (performance on the second trial of the first presented list), combined with performance on the first cued recall for the second list (which is most vulnerable to PSI) might optimally distinguish people with MCI from cognitively normal older adults. In the study presented in the present report, the authors examined the ability of the LASSI-L to distinguish among different types of at-risk preclinical dementia groups. Subjects included 31 cognitively normal adults, 18 with subjective memory complaints but no objective evidence of cognitive impairment (SMI), 15 subjects with subjective memory complaints plus some objective evidence of mild cognitive impairment (PreMCI-Clinical), and 29 people meeting criteria for MCI. In addition to the LASSI-L, a subset of participants also received amyloid PET scans. Overall, the authors found deficits in ability to recover from PSI were significantly greater among MCI, PreMCI, and SMI subjects compared to the cognitively normal subjects. In addition deficits in recovery from PSI were associated with total amyloid load, even among those participants showing no evidence of cognitive impairment on traditional neurocognitive tests.

The findings of Loewenstein et al warrant further efforts at replication and extension. Some of the specific group sample sizes were small, particularly in regard to those receiving PET imaging. However, they are important in pointing to a potentially useful, and previously overlooked, performance marker on an episodic memory task that could be useful in detecting those at greatest risk for subsequent development of dementia, in the early pre-clinical stages of dementia. As noted above, it is in these preclinical states that interventions efforts are ultimately most likely to prove effect, but the problem in conducting such studies has been in identifying sensitive and specific markers of the high-risk individuals, i.e.., those at sufficiently high risk for developing Alzheimer's disease or other dementias such that investigations with experimental biological interventions can be ethically justified in terms of the risk:benefit ratio (Peters, Lynn Beattie, Feldman, & Illes, 2013). The paper and methods provided by Loewenstein and colleagues in this issue represent an important step toward such goals.

Acknowledgments

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