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COMMENTARY

When wrong answers lead us down the right path

Since McKhann *et al.* (1984) published their diagnostic criteria for Alzheimer's disease (AD), the methods for determining AD symptoms have moved from dementia diagnosis to prodromal (mild cognitive impairment) and most recently to subtle cognitive decline and clinically asymptomatic with AD biomarker confirmation. While significant investments have been made in imaging acquisition and biomarker methods, progressing from brain MRI to PET scans and developing higher sensitivity imaging tracers and serum markers, the primary methods for documenting clinical manifestations of AD, using neuropsychological tests to detect a cognitive impairment, have gone largely unnoticed outside of the neuropsychological professional community. The idea of using delayed recall performance on a memory task dates back to 1945, when the Wechsler Memory Scale was first published. Over time, while different list learning and story memory tasks have been developed and used, remarkably, the AD research world continues to primarily rely on the delayed recall score from memory tasks. Thus, while detecting pathological emergence of AD has evolved, the persistent reliance on the same behavioral measure for an early signal of memory impairment has meant not keeping up with the biomarker community in finding memory markers that are or might be better than those that are 75 + years old.

Within this context, there has been a small band of neuropsychologists whose work remains largely overlooked by the non-neuropsychology community. From their work, other scores on word list learning and memory measures have emerged as important for capturing early cognitive changes associated with AD, including learning trials (Grober and Kawas, 1997) and intrusion errors (Bondi *et al.*, 1994; Loewenstein *et al.*, 2004; Thomas *et al.*, 2018). The concept of neuropsychological process scores, which provides information about the type and quantity of errors as well as the approach to the task, is a key tool used in the Boston Process Approach, which was largely advanced by Kaplan (1988) and her colleagues and trainees. The goal of process scores is to provide information that will improve understanding of the underlying neural mechanism that leads to a specific outcome, behavior, or achievement, including a neuropsychological total score or cognitive diagnosis. As applied to AD, the process approach may be used to look at the pattern of incorrect or inefficient responses and errors as a potentially more sensitive measure for detecting AD and/or to better understand the underlying pathology and mechanisms. The process score profile consistent with early AD has been characterized as having slowed learning across trials of a word-list memory task (i.e. a flattened learning slope), increased susceptibility to interference, and a greater frequency of nontarget word intrusion errors, particularly on cued recall trials that pull for intrusions that are semantically related to the target words (Delis *et al.*, 1991; Loewenstein *et al.*, 2004; Salmon and Bondi, 2009).

While much of the work on process scores has used standard neuropsychological measures, there has been a push for particularly novel or difficult tasks and sensitive scores that could capture individuals in the preclinical or prodromal phase of AD and improve prognosis. The Loewenstein-Acevedo Scales of Semantic Interference and Learning (LASSI-L) exemplifies how important process variables can be relatively easily and reliably measured. Loewenstein *et al.* (2016) aptly describe the LASSI-L as a "cognitive stress test" due to it being a challenging measure designed to elicit errors related to semantic interference that would be expected in early AD. There are compelling data showing that the semantic intrusion errors from the LASSI-L are associated with AD biomarkers, early cognitive difficulties that do not yet meet criteria for mild cognitive impairment (pre-MCI) and amnestic MCI status, and progression in pre-MCI and amnestic MCI participants (Crocco *et al.*, 2021; Loewenstein *et al.*, 2016; 2018).

In this issue of *International Psychogeriatrics*, Zheng *et al.* (2021) examined semantic intrusion errors from the cued recall trials B1 and B2 of the LASSI-L, which are thought to be sensitive to proactive semantic interference (PSI) and failure to recover from proactive semantic interference (frPSI), respectively. The analyses examined age and apolipoprotein E (APOE) ϵ4 genotype and whether there was a direct relationship with semantic intrusion errors or whether there was an indirect

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effect via amyloid PET positivity and/or brain volume of AD-vulnerable regions. Results demonstrated that both amyloid positivity and lower brain volumes in AD-vulnerable regions were associated with increased semantic intrusion errors. Notably, amyloid did not exert its effect on PSI and frPSI via neurodegeneration. While age and APOE ϵ4 genotype did not have direct relationships with the semantic intrusion errors, age had an indirect effect via both amyloid positivity and brain volume while APOE ϵ4 genotype had an indirect effect via amyloid positivity only.

What is compelling about the Zheng *et al.* findings are how clearly it evidenced that analysis of incorrect intrusion responses on their task was linked to early pathological indices of AD. This is significant for both clinical researchers and practitioners because of the context of current inequities in both realms. It is now widely recognized that expensive and invasive imaging and other AD biomarker methods have inherent structural barriers of access that have, in turn, led to skewed research and clinical care. An implication of the Zheng *et al.* study is that it shows a path for how to break out of these longstanding and persistent problems.

One of the key strengths of the LASSI-L is that it is relatively inexpensive to administer compared to other more invasive measures used to identify individuals at risk for AD, including PET imaging or a lumbar puncture. Additionally, the LASSI-L has been well-studied in Spanish-speaking individuals (Cid *et al.*, 2019; Matías-Guiu *et al.*, 2017). Most of the older adult research that involves biomarkers has been conducted on predominately non-Hispanic white participants. Therefore, the fact that 53% of the sample in this study was Spanish-speaking is a relative strength. The combination of these strengths suggests that, in addition to beginning to understand some of the underlying mechanisms that may result in semantic intrusion errors, semantic intrusion errors from the LASSI-L may be useful for clinical prognostic purposes, including screening for suitability of disease-modifying drugs if/when they become available as well as sensitive outcome measures of intervention trials.

The current study pushes the field forward in regard to understanding the underlying biological mechanisms of the observed PSI and frPSI across the AD clinical spectrum, while also introducing a number of future directions. The most recent emergence of using digital tools to assess AD-related cognitive behaviors is simply a technological extension of the process concept that Zheng *et al.* have operationalized. Rather than manually scoring PSI and frPSI measures, automated algorithms analyzing digitally recorded responses would bring the work of Zheng *et al.* easily to scale and offset a limitation of this study, which is its relatively small sample size of cognitively unimpaired and pre-MCI groups. An important next study is to understand whether the pattern of relationships observed in this study varied across the clinical diagnostic stages of AD. Additionally, the sematic intrusion errors on the LASSI-L are clearly a valuable measure, but what remains unknown is whether these intrusions are diagnostically or prognostically important above and beyond the more commonly used neuropsychological scores such as total words correct during the free recall trials of the LASSI-L. As Zheng *et al.* describe, future work should also consider whether tau accumulation, assessed *in vivo* using tau PET, may be particularly important in understanding the pathologic contributions to intrusions errors given evidence that tau accumulation may be more related to cognitive functioning than amyloid (Brier *et al.*, 2016). Similarly, cerebrovascular disease, pathologies that cannot yet be reliably measured *in vivo* such as Lewy bodies and TDP-43, and combinations of pathologies remain unaccounted for and may all contribute to cognitive difficulties in older adults.

AD biomarkers have been a prominent focus of AD research for the past decade, driven by the hypothesis that cognitive symptoms emerge years after detectable changes in biomarkers (Jack *et al.*, 2010). While this assumption has been challenged by the use of more sensitive neuropsychological measures for detecting subtle cognitive changes (Jedynak *et al.*, 2012; Thomas *et al.*, 2020), the National Institute on Aging-Alzheimer's Association biological framework for AD focuses on amyloid, tau, and neurodegeneration (A/T/(N)) biomarker profiles to define AD, independent of cognitive functioning (Jack *et al.*, 2018). Recent work, however, shows that neuropsychological measures predict declines in cognition and everyday functioning above and beyond A/T/(N) biomarkers (O'Shea *et al.*, 2021). In addition to being prognostically useful, cognitive functioning should not be ignored. Cognitive difficulties and related everyday functioning difficulties are what impact people's lives, so they should continue to be emphasized as the outcomes of interest as is done by Zheng *et al.*

Zheng *et al.* begin to address the underlying mechanisms that result in semantic intrusions errors, which are known to be associated with cognitive decline and impairment. While the current analyses do not completely test the contributions of other pathologies that may cause a greater frequency of semantic intrusion errors or changes in intrusion errors, they certainly highlight the value and continued need for developing innovative cognitive assessment methods that track with

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underlying brain changes in a way that can have far greater global reach and lead to far greater parity in AD research and clinical care.

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