Digital Technologies for Cognitive Assessment to Accelerate Drug Development in Alzheimer’s Disease

C Leurent\(^1\) and MD Ehlers\(^1\)

For many neurological and psychiatric diseases, novel therapeutics have been elusive for decades. By focusing on attention interference in Alzheimer’s disease (AD), we provide a future vision on how emerging mobile, computer, and device-based cognitive tools are converting classically noisy, subjective, data-poor clinical endpoints associated with neuropsychiatric disease assessment into a richer, scalable, and objective set of measurements. Incorporation of such endpoints into clinical drug trials holds promise for more quickly and efficiently developing new medicines.

Increasingly a feature of contemporary life, multitasking comes at a cognitive price. While attention can be selectively assigned to more than one task, the simultaneous management of multiple tasks presents a challenge for the brain. The increased load in neural computation when attention is divided translates into decreased performance relative to single-task conditions. This well-described neuropsychological phenomenon is referred to as interference cost, or dual-task decrement when studied in dual-task paradigms.

A large body of evidence has linked attention impairment with early stages of AD.\(^1\) In addition to episodic memory, disrupted attentional control is among the first signs of disordered cognitive function in early AD. Among subdomains of attentional control, selective attention (i.e., search and orienting) and divided attention (i.e., multitask performance and task switching) are particularly disrupted in early stages of the disease. The neural origin of decreased attentional control observed in AD is complex, but is thought to include altered cortico-cortical tract integrity and connectivity. The inability to coordinate processing across attentional networks in turn disrupts central executive components of working memory. Such executive functions represent the ability to plan and conduct goal-oriented tasks, directly impacting activities of daily living (ADLs) such as getting dressed, cooking, or paying bills. Clinically, it is commonly reported by caregivers that patients with early AD have difficulty distributing attention, following and engaging in discussions with multiple individuals simultaneously, and planning or controlling everyday activities. A frequent clinical and experimental finding is that early AD patients perform as well as control subjects when two tasks are attempted separately, but show a disproportionate decline in performance when the tasks are performed concurrently. However, the precise stage at which AD patients exhibit dual-task decrement remains controversial.

Relative to examination of memory processes, research in attentional impairment in AD has been modest. Recently, Festa et al. reported a robust dual-task decrement in mild AD.\(^2\) The performance of 130 elderly participants, comprised of 89 mild AD patients (Clinical Dementia Rating, CDR, of 0.5 and 1) and 41 elderly controls (CDR of 0 and Mini Mental State Examination, MMSE, \(>26\)) was assessed under dual-task conditions. In this study, participants were required to simultaneously engage in a visuomotor tracking task (i.e., maintaining car position within a simulated driving environment), at subject-adjusted difficulty in combination with three different types of tasks (spatial orientation, Simon interference, and visual search). The results indicated a substantially greater interference cost in the AD group relative to healthy elderly controls in all three dual-task conditions.\(^2\) Such initial findings point to the potential utility of assessing attention interference cost to detect and monitor early AD.

Many cognitive assessments exist to characterize early memory deficits associated with AD, and it is now accepted that focused deficits accumulate over several decades before frank memory symptoms appear. The International Working Group (IWG), US National Institute on Aging, and Alzheimer’s Association have recently issued new criteria for the diagnosis of AD in order to better define clinical phenotypes and account for the role of biomarkers in the various stages of disease progression.\(^3\) The development of fluid biomarkers, positron emission tomography (PET) ligands, and volumetric magnetic resonance imaging
The authors are employees and shareholders of Pfizer, Inc.

© 2015 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals, Inc. on behalf of The American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

1. Perry, R.J. & Hodges, J.R. Attention and executive deficits in Alzheimer’s disease. A critical review. Brain 122, 383–404 (1999).
2. Festa, E.K., Heindel, W.C. & Ott, B.R. Dual-task conditions modulate the efficiency of selective attention mechanisms in Alzheimer’s disease. Neuropsychologia 48, 3252–3261 (2010).
3. Dubois, B. et al. Advancing research diagnostic criteria for Alzheimer’s disease: the IWG-2 criteria. Lancet Neurol. 13, 614–629 (2014).
4. Fiordelli, M., Diviani, N. & Schulz, P.J. Mapping mHealth research: a decade of evolution. J. Med. Internet Res. 15, e95 (2013).
5. Anguera, J.A. et al. Video game training enhances cognitive control in older adults. Nature 501, 97–101 (2013).