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Perspective

Measuring cognition and function in the preclinical stage of Alzheimer's disease

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Abstract The Alzheimer's Association's Research Roundtable met in November 2016 to explore how best to measure changes in cognition and function in the preclinical stage of Alzheimer's disease. This review will cover the tools and instruments currently available to identify populations for prevention trials, and measure subtle disease progression in the earliest stages of Alzheimer's disease, and will include discussions of suitable cognitive, behavioral, functional, composite, and biological endpoints for prevention trials. Current prevention trials are reviewed including TOMMOROW, Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease Trial, the Alzheimer's Prevention Initiative Generation Study, and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's to compare current approaches and tools that are being developed.

1. Introduction

As knowledge of Alzheimer's disease (AD) progression improves, the field has recognized that it may be possible, and perhaps necessary, to develop drugs that target early, prodromal stages of the disease and move to secondary prevention as a treatment strategy. To achieve regulatory approval for such therapeutics, appropriate clinically relevant endpoints are needed that enable detection of disease progression and response to therapy in a population that is, by definition, asymptomatic. On November 29 and 30, 2016, the Alzheimer's Association Research Roundtable convened academic, industry, and government scientists to explore cognitive, functional, and biological endpoints that will enable clinical trials to be conducted in the earliest, presymptomatic stages of AD pathophysiology and discuss the challenges that need to be overcome. A number of secondary prevention trials are already underway, providing the forum with preliminary information to guide future development.

2. Cognition across the age and disease continuum

2.1. Normal cognitive aging

Defining normal cognitive function in older adults is surprisingly complicated due to variability in how and in whom it is measured. For example, in a 2002 cross-sectional study of 345 people between the ages of 20 and 92 years, Park et al. showed that while test performance in many cognitive domains—including reasoning, working memory, and processing speed—declined over the lifespan, scores on tests of vocabulary and world knowledge increased [1]. In addition, neuroimaging has revealed that, just as with physical health, brain health declines along a continuum with age, with progressive reductions in brain volume and white matter integrity [2]. In fact, age-related declines in cognitive

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function are correlated with reductions in the volume and/or thickness of brain structures and white matter integrity, and poor cognition may serve as a proxy for the integrity of brain structure. It also is assumed to serve as a correlate for the ability to function in everyday life.

Besides measuring structural changes in the brain, it is also possible to measure brain activity using functional magnetic resonance imaging. Typically, cognitively normal adults will show increased activity, particularly in the frontal cortex, with age. Park et al. (2009) proposed the Scaffolding Theory of Aging and Cognition to account for this increased brain activity, which posits that age-related neural degradation within brain structures can be counterbalanced by "compensatory scaffolding" (i.e., the engagement of additional neural circuits, neurogenesis, and other active processes, resulting in some protection from decline in cognitive function [2]). The Dallas Lifespan Brain Aging Study was developed to test this model, and other large normative data sets, such as the Virginia Cognitive Aging Project, Health and Retirement Study, and Harvard Aging Brain Study (HABS), have provided further data to describe how cognition changes over the lifespan. In addition to documenting overall age-related declines in cognitive performance, the HABS and Dallas Lifespan Brain Aging studies have also measured the deposition of amyloid, a hallmark protein of AD, in seemingly healthy, cognitively normal adults and have shown a link between early deposition and poorer scores on tests of memory and other cognitive processes [3,4]. Amyloid deposition is associated also with the apolipoprotein E (*APOE*)-*4* gene [5] and with greater decline in cognitive function over time [6].

The methods for studying changes in cognition with age are problematic. Cross-sectional designs are used in most studies of the aging brain and may be confounded by cohort differences and sampling issues. For example, in 1963, a 20-year-old performed better on tests of psychomotor speed, executive function and language than a 20-year-old born in 1922 [7]. Hence, an age difference in cognition between a 20-year-old and an 80-year-old could be either due to decline with age or due to the fact that there was already quite a difference between the two at the age of 20 years. In addition, cohort effects on dementia incidence were recently reported from the Einstein Aging Study [8] suggesting that the adverse effects of brain aging may be diminished in younger compared with older cohorts. A related issue is that obtaining a cognitively normal representative sample of older study participants is difficult. First, older individuals carry many comorbidities that exclude large subsets of individuals from studies; second, the remarkable ability to image neuropathology such as amyloid and tau at early stages of deposition complicates what we mean by "normal cognitive aging" [9]. Another complication in lifespan studies is that middle-aged participants are difficult to recruit and often are represented by cohorts who differ in employment, education, and socioeconomic status relative to both the younger and older adult samples in a cross-sectional study. The alternative is a longitudinal cohort study (LCS) design. Often considered the gold standard for tracking cognitive performance over time, longitudinal testing may be confounded by practice effects. However, a recent analysis indicates that when practice effects are eliminated, age trends in longitudinal studies closely resemble those seen in cross-sectional studies [10].

It is important to recognize that cognition is not a unitary construct, consisting, instead, of a number of discrete domains, such as, for example, attention, memory, and language, to name a few. The accurate measurement of cognitive function requires careful sampling and an assessment of factors that could affect cognition that are unrelated to a therapeutic intervention (e.g., education, past testing, and other, myriad variables, unique to the individual). Young and old adults may rely on different cognitive operations or different sequences of operations to achieve optimal performance on an identical task. For example, young adults may rely on speed and working memory—abilities where they excel—to perform a complex task, whereas older adults may rely on their cognitive strengths—experience and vocabulary—to solve the same task [11,12].

Finally, the focus on everyday cognition (ECog) and instrumental activities of daily living (IADL) as measurements of cognitive ability has important advantages and disadvantages for measuring change. The advantage, of course, is that it more closely reflects how an individual is performing in the real world. An effect on these measurements after an intervention is therefore ecologically valid, and highly relevant to patients and caregivers. However there are also significant disadvantages—that is, people differ greatly in the types of everyday tasks they perform. For example, some are relatively simple, such as remembering to collect eggs in a farm daily at a specific time, while others are more complex, such as overseeing a bank or dispatching a fleet of trucks to transport materials across a country. Thus, a single scale of daily living activities may not be sensitive enough to measure the outcome of an intervention in very early disease stages in different individuals [13,14]. An alternative to using tests of ECog might be high-frequency assessments via cell phone or tablet computer in the context of a person's everyday environment [15]. The drawback here, however, is that many older adults have little experience with these devices and so simpler technology (a regular telephone) may be considered for those without more modern technology.

In summary, the measurement of cognition for purposes of a clinical trial is a complex issue and should be tailored to the subject population under study and the particular goals of the project. It may be advisable to include some measures that make a study comparable to others, by using instruments such as the NIH toolbox, which was designed to serve as a common currency among longitudinal and intervention studies [16,17].