ELSEVIER

Alzheimer's & Dementia 6 (2010) 145–146

Alzheimer's & Dementia

Commentary on ''Developing a national strategy to prevent dementia: Leon Thal Symposium 2009.'' Methodologic considerations for preventing Alzheimer's disease by 2020

William R. Shankle*

The Shankle Clinic for Alzheimer's Disease and Related Disorders, Irvine, CA, USA
UC Irvine Cognitive Science Department, Irvine, CA, USA
Medical Care Corporation, Irvine, CA, USA

The following position paper focuses on some methodologic considerations that will affect progress toward the goal of the Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020) initiative. In this sense, they are domain-independent, irrespective of the specific scientific knowledge that will be discovered during the course of the PAD2020 initiative. The methodologic considerations discussed here have the potential to affect the way decisions are made, the breadth of participation across eligible centers, and the way data are analyzed and interpreted.

At the Thal Symposium in November 2009, there was a consensus of opinion that a national, and possibly international, multicenter registry of subjects was needed to (1) better identify Alzheimer's disease (AD) genetic and environmental risk factors; (2) study candidate biomarkers; (3) better characterize cognitive, functional, and behavioral change in normal aging and AD; (4) detect cohorts of asymptomatic and very mildly affected AD subjects; (5) improve sample selection for research and clinical trials of asymptomatic and very mild AD; and (6) improve the methods of measuring change due to aging, disease, and treatment.

In the past, selection of a common test battery for a collaborative effort such as the PAD2020 initiative has been driven by consensus opinion. However, a consensus approach can result in suboptimal test selection as well as produce three types of bias: (1) bias due to the selected tests themselves; (2) bias due to nonparticipation by centers that prefer other tests; and (3) bias due to the loss of information or strengths contained among tests not selected for inclusion.

It would be more optimal if a variety of tests of a given ability—cognitive, functional, or behavioral—were allowed. Such an approach would benefit from potentially different strengths among the tests, would increase participation from different centers, and would allow rich sources of data that have already been collected to be mined. Such an approach requires methods that can measure the underlying neural processes common to different tests of a given ability. For example, different tests of verbal memory (eg, Auditory Verbal Learning Test, California Verbal Learning Test, Consortium to Establish a Registry for Alzheimer Disease Wordlist, and Alzheimer's Disease Assessment Scale, cognitive portion) tap into neural processes of memory encoding, temporal ordering, associability, retrieval, strength, and strategy.

Recent methodologic advances from the cognitive sciences, which combine graphical hierarchical bayesian analysis with cognitive processing models, make such measurement possible. These recently developed methods offer the following potential benefits to PAD2020:

1. They characterize tests in terms of a small number of meaningful underlying neural processes. By contrast, standard statistical methods used, such as the General Linear Model, derive parameters of a test's variables, making cross-test comparisons difficult.
2. By characterizing the common neural processes underlying different tests of a given ability:

a. These processes' relative strengths and weaknesses can be evaluated.
b. The course of each underlying process can be measured in normal aging and AD.
c. The effects of treatment on changes in these processes can be more accurately measured.

3. They can improve the correlations with AD biomarkers, disease progression, treatment effects, and other measures.

*Corresponding author. Tel.: 949-833-2383; Fax: 949-838-0153.
E-mail address: rshankle@mccare.com

1552-5260/10/$ – see front matter
doi:10.1016/j.jalz.2010.01.003

4. They would allow data already collected by different centers to be analyzed, mined, and learned from.
5. They would allow the proposed registry to accept a variety of tests of a given ability, which would permit a broader range of participation across interested centers and reduce potential sources of bias.
6. They handle a broad range of missing data patterns, which are common in research and clinical practice.
7. They simultaneously characterize both individuals and groups, which is important for clinical practice, epidemiologic research, clinical trials, and research limited to small numbers of subjects.
8. They can be applied to any distribution of the underlying data, which allows comparison across different centers, samples, and data sets.

To test the feasibility of this approach, it would be useful to apply these methods to the samples of already collected data to see whether they can (1) allow different tests of the same underlying neural processes to be compared in terms of them; (2) develop more reliable and accurate longitudinal measures of change in these neural processes; (3) better characterize the longitudinal courses of these neural processes for normal aging and AD; (4) assess changes on these underlying neural processes because of various treatments; and (5) correlate these neural process measures with available AD biomarkers.

An important implication of the proposed methodology is that the extensive and valuable sources of AD and normative research data that have already been gathered over decades can be used, mined, and learned from. There is undoubtedly much to be learned from such information, and it would take years to recapitulate such knowledge. To that end, it would be useful to collate and integrate the existing sources of such data as a part of PAD2020. Much would be learned in the process that would be useful for the task of establishing a national or international registry. The analysis of such data with the more recently developed methods discussed here would also lead to a much better understanding of the underlying neural processes that we hope to preserve through this initiative. It might otherwise take years to discover the same knowledge through the collection of new data.

Another important implication of the proposed methodology is the ability to more accurately characterize and measure the longitudinal course of a given ability in single subjects or small samples. This has real value in AD biomarker research as well as in the testing of expensive treatments such as immunotherapy, stem cell or growth factor therapy, in which studies will necessarily be limited to small samples of subjects. The development and refinement of better methods to analyze small sample clinical trials would therefore be of great value to PAD2020.

Finally, it must be recognized that public participation will be maximized when there is something they can act on soon, to the extent that the initiative can offer benefits to the public in terms of better knowledge about how to optimize AD treatment and prevention today. The mining of already collected data on such issues could advance the knowledge in these areas without the delay inherent to collecting new data.