Alzheimer disease
Can the exam predict the pathology?

Memory testing beyond the 3-word recall of brief mental status examinations is not routinely performed on patients with memory complaints. This is due to time constraints and uncertainty over how to conduct and interpret a valid learning and memory examination. Failure to evaluate memory complaints consistently with objective assessments has no doubt contributed to the impression that memory testing lacks specificity for Alzheimer disease (AD).

Memory disorders specialists who frequently diagnose AD recognize the value of a targeted memory examination. In this issue of Neurology®, Wagner et al.1 reinforce this by using memory tests that specifically probe mesiotemporal function in elderly individuals with memory deficits, demonstrating that these tests predict CSF Aβ42/tau levels. The authors found that subjects who performed poorly on tests of mesiotemporal function had low CSF Aβ42/tau ratios. Other studies have shown low CSF Aβ42/tau ratios, in turn, associate with AD.2 By establishing a neuroanatomic localization for the patient’s complaint, therefore, an appropriately applied memory examination essentially changes AD from a diagnosis of exclusion to one of inclusion. For elderly individuals with memory complaints, bilateral mesiotemporal dysfunction is usually due to AD.

The authors studied subjects with mild cognitive impairment (MCI), and analyzed data from CSF biomarker testing, the logical memory paragraph recall test from the Wechsler Memory Scale–Revised (LM), the word list learning task from the Consortium to Establish a Registry for Alzheimer’s Disease neuropsychological battery (CERAD-NP), and the Free and Cued Selective Reminding test (FCSRT).1,3 The Aβ42/tau ratio was reduced in 40% of the 185 evaluated subjects. According to new diagnostic criteria, these 40% qualified for a diagnosis of prodromal AD4 or MCI due to AD.5 All 3 memory tests correlated with a diagnosis of MCI due to AD, because poor test performance predicted a low CSF Aβ42/tau ratio. The FCSRT discriminated between the different MCI groups better than the LM and CERAD-NP.

Why did the FCSRT outperform the LM and CERAD-NP? The FCSRT uses a cued recall paradigm to assess memory.6 A card containing 4 pictures is presented to the subject. A semantic cue is provided for each picture. The card is removed and the cues are used to ensure each picture had an adequate chance to be encoded. This process is repeated with 3 more cards. Over just a few minutes the subject is exposed to 16 pictures and 16 semantic cues. After the last card, the patient counts backwards by 3s for 20 seconds; this distraction task cleanses the pictures from the subject’s prefrontal lobe–mediated working memory. The subject then states, without prompting, as many pictures as possible. This results in that trial’s “free recall” score. The previously presented semantic cues are then used to elicit the remaining pictures and generate a “cued recall” score for that trial. The sum of the free and cued items that were successfully remembered constitutes the “total recall” score. Two more trials are immediately performed and the free, cued, and total recall results from the 3 trials are summed. Approximately 15 minutes later free, cued, and total recall are probed to provide “delayed recall” scores.

The FCSRT delayed total recall score effectively predicted CSF biomarker profiles, while the FCSRT delayed free recall score was far less accurate.1 This suggests cuing paradigms interrogate functional or anatomic substrates that are minimally engaged by non-cue-based memory tests. In particular, the authors speculate that semantic cuing changes the test from one of hippocampal function to one of hippocampal plus entorhinal cortex function. This is based on evidence that argues the entorhinal cortex mediates associations between contextually related information fragments.7 In other words, semantic cuing strategically engages the entorhinal cortex, a mesiotemporal region affected in AD.8
Interestingly, the summed FCSRT total recall score from the nondelayed recall trials discriminated subjects with MCI with AD-typical CSF profiles from those with atypical profiles. This finding is relevant to the question of whether “short-term” memory becomes “long-term” memory. This difference is defined by a unit of time, but depends instead on whether information in the dorsolateral prefrontal (DLPF) “buffer” is processed by the hippocampus to enable durable retention. To use a computer analogy, the DLPF is the RAM (active memory at any given instant), while the mesiotemporal regions constitute the hard drive (or, more accurately stated, transfers RAM information to the hard drive). When mesiotemporal systems are intact, this transfer likely begins soon after the information is experienced. By acutely purging the RAM, the distraction task forces the brain to access the information from its hard drive. Failure to move information from the RAM to the hard drive is typical of AD.

Indeed, the FCSRT total recall score from the first nondelayed recall trial provided the best discrimination of all, outperforming even the summed FCSRT total recall score. The authors postulate that “ceiling” effects, which could limit test sensitivity, may have affected the latter recall trials. In any case, the study of Wagner et al. confirms prior work showing the FCSRT efficiently identifies memory deficits and further suggests ways to enhance this efficiency. In this study, a total recall score of 16 on the first recall trial strongly predicted a non-AD CSF profile, while 12 or less strongly predicted an AD-typical profile.

The case has been made that clinicians can diagnose a clinical AD syndrome, but cannot diagnose AD itself as a distinct pathologic disease state. Despite this belief, it is clear from the literature that the majority of elderly patients with an AD cognitive syndrome have AD pathology at autopsy. The argument that neurologists cannot diagnose AD pathology, therefore, is vastly overstated. While it is easy to understand why neurologists would want an AD diagnostic test that one might simply place an order for, such tests are currently under research development and not readily available at present. Specialized imaging and chemical biomarkers may one day meet this need, but in the rush to develop new AD diagnostic approaches the power of the neurologic examination should not be overlooked.

AUTHOR CONTRIBUTIONS
Dr. Swerdlow: drafting/revising the manuscript. Dr. Jicha: drafting/revising the manuscript.

DISCLOSURE
Dr. Swerdlow serves on the editorial boards of Neurology®, the Journal of Alzheimer’s Disease, Biochimica et Biophysica Acta, and Bioenergetics; has received speaker honoraria from Eisai Inc.; and has received research support from Eisai Inc., the NIH/NIA, Parkinson Foundation of the Heartland, Morgan Family Foundation, and Frank and Evangelene Thompson Alzheimer’s Therapy Development Fund. Dr. Jicha has received funding for travel or speaker honoraria from the Alzheimer Association; serves as a consultant for Pfizer and Eli Lilly and Company; and receives research support from Pfizer Inc., Elan Corporation, Janssen, Medivation, Inc., Danone, and the NIH/NIA.

REFERENCES