

ENCOUNTERING ALZHEIMER'S:

The urgent need for early identification.

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During the past months I have had close personal encounters with the ravages of Alzheimer's Disease (AD). The first instance involved the husband of one of my best friends, a renowned professor of history. He died at age 79 after a ten year history of progressive AD. The second instance involves my former editor and friend, who at age 58 has advanced to the moderate-to-severe stages of AD. In this instance, AD had an early, insidious onset and yet some of the symptoms of progressive cognitive impairment were recognizable to those who knew him well as early as a decade ago. In both cases, AD was identified at a stage when the behavioral symptoms were blatant and the prospects of meaningful pharmacological interventions

were already limited. With recent pharmacological advances, the need for early identification of progressive cognitive impairments associated with AD becomes urgent. Society at large stands to benefit, as does the patient and his or her family by improving the quality of life in the face of a currently non-stoppable, progressive pathology.

Recognizing the Early Symptoms

I recognized the behavioral symptoms in each of my friends some years before the medical community was able to make a diagnosis. In the case of the professor, some of the first symptoms were depression, paranoia and inability to deal with time, schedules and finances. After a lecture he could no longer answer questions with other than stereotypical responses.

In the case of my editor, the first symptoms I recognized occurred close to ten years ago on a shared sailing trip. My friend, an ardent and competent sailor, managed to put our boat on the rocks, literally. After that, I noticed increasing problems with task initiation, organization and completion, and that multi-tasking, which had been his strength, was no longer efficient. Because these are all symptoms of executive function disorders (EFD), several of us in the field hypothesized that we were observing a frontal-lobe dementia in progress. Unfortunately, because my friends were brilliant in so many ways, they both managed to fool content-based testing for dementia such as the *Mini-Mental State Examination* (MMSE) and others

that were administered. It was not until the families contacted me two years ago with specific questions about AD that the clinical picture became clear and I urged referral to neuropsychiatric specialists. It was then that I wished the development and clinical research of the

Alzheimer’s Quick Test: Assessment of Parietal Function (AQT)

(Wiig, Nielsen, Minthon & Warkentin, 2002) had progressed to the point where it is now.

Designing an Assessment

AQT departs from the standard content-based format for tests of cognitive function. The design focuses on obtaining objective, timed naming measures of processing speed at the perceptual and cognitive levels of performance. At the perceptual level, the test plates with 40 single-dimension visual stimuli (e.g., repeated colors or forms) probe attention to familiar visual stimuli and verbal automaticity in naming them. At the cognitive level, tests plates with 40 dual-dimension visual stimuli (e.g., repeated color-form combinations) probe executive attention, working memory, and verbal automaticity. A section of each of the color form test plates is shown in Figure 1 below.

AQT contains five different naming tasks with various stimulus combinations. The five naming tasks are Color-Form, Color-Number, Color-Letter, Color-Animal, and Color-Object Naming. All of the naming tasks are norm-referenced for the age

range from 15 to 85 years and have been tested for reliability, stability and effects of age and education. The test-retest reliability coefficients (r) for the dual-dimension naming tests are as follows: color-form .95, color-number .94, color-letter .90, color-animal .96 and color-object .88. In other words, all AQT dual-dimension naming tests are highly reliable over an interval of one- to two-weeks time. We have also studied the effects of age and education on naming times in normally aging adults with an 8th grade education or above (ages 15 to 95). Linear regression analyses consistently indicate that there is no significant effect of years of education among normally aging, literate adults.

Comparison Studies

Three of the AQT naming tasks—Color-Form, Color-Number, and Color-Letter Naming — have been the focus of comparison studies of naming times by normally aging adult speakers of English, Swedish and Spanish. One study compared color-form, and color-form naming times in 114 English and 74 Swedish normally-aging adults. There were no significant differences in naming times for any of the perceptual or cognitive speed measures ($p > .05$), and all subjects named colors, forms and color-form combinations faster than the established standard cut-offs (> 60 sec. for single colors, and forms and > 70 sec. for color-form combinations) based on the normative data.

Neuro-Imaging Research

The first AQT task, Color-Form naming, has been the focus of extensive clinical and neuro-imaging research. The team of AQT authors hypothesized that the AQT color-form combination test would probe frontal lobe executive functions such as attention and working memory. This hypothesis was based on the similarity in design between the classic *Stroop Color-Word Test* in which subjects first name colors and then read printed color words (e.g., blue). Following these baseline measures, subjects are asked to suppress attention to the printed color words and to name only the incongruent color in which most words are printed. The last task, validated with neuro-imaging is associated primarily with frontal lobe activation. Since the *Stroop* and the AQT use similar rapid naming designs, we conjectured that they might measure similar cortical functions. We were proven to be in error.

The first rCBF neuro-images explored which regions would show significantly increased blood flow during repeated color and repeated form naming over 10 minutes. For both tests, the blood flow increased significantly in both occipital lobes when compared to blood flow during open-eyed rest. Thus, the single-dimension naming tasks required primarily rapid visual processing and placed no significant demands on cortical areas known to be involved during working memory tasks. These tests were therefore interpreted as measures of perceptual speed involving visual attention and verbal automaticity. During dual-dimension color-form naming the rCBF pattern was significantly different. Thus, blood flow

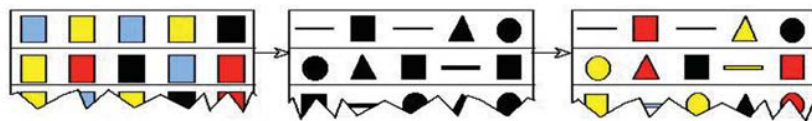


Figure 1. AQT Color-Form Naming Test, Test Plates (40 items each)

increased significantly in the temporal-parietal regions bilaterally while being significantly suppressed in the frontal regions. Obviously, color-naming was not a measure of frontal lobe executive functions, but rather of temporal-parietal lobe functions associated with visual attention, implicit working memory (or visual sketchpad memory) and verbal automaticity. In other words, we had a rapid naming test that could measure cognitive speed in small increments (seconds) and which might prove effective in detecting the progressive cognitive impairments typical of Alzheimer's.

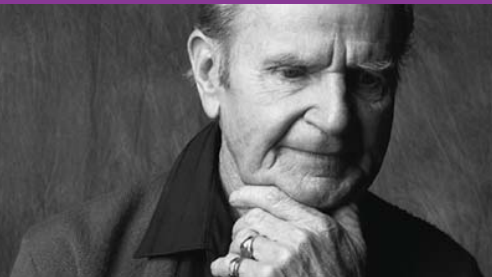
A Valid First-line Screener

These first rCBF images stimulated new directions in an already ongoing longitudinal investigation of normally aging Swedish adults and adults with mild-to-moderate AD, established according to DSM-IV and ADRDA clinical criteria. This study is compre-

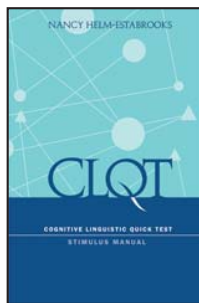
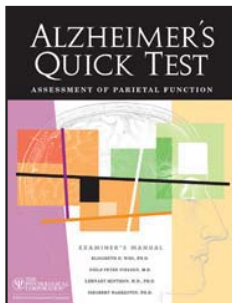
hensive and measures cognitive, behavioral, biomarker, and neurological function differences with a focus on monitoring the effects of various medications. AQT color-form naming was added to the complement of content-based cognitive tests, such as the *Mini Mental State Examination* (MMSE) and *Alzheimer's Disease Assessment Scale* (ADAS-cog.) which were already used in the study. Over the last two years of the study, this addition has paid off by providing evidence of the clinical utility of color-form naming as a first-line screener for the early identification of mild cognitive impairments (MCI) and progressive Alzheimer's pathology. During the longitudinal study, AQT was used as a behavioral measure of cognitive speed and rCBF individual and composite statistical comparison images were made during color-form naming by normally aging and AD

patients. These images are shown in Figures 2 and 3 on the next page. As seen in Figure 2, the composite statistical comparison image for 52 normally-aging adults during color-form naming and rest show significant increases in blood flow in the temporal-parietal regions and concomitant suppression of blood flow to the frontal lobe regions, thus validating the first rCBF images we obtained. Figure 3 shows the composite statistical comparison images for 32 adults with mild-to-moderate AD. These images shown significantly suppressed blood flow to the temporal-parietal regions during color-form naming with concomitant significant increases in blood flow to the superior frontal regions. This pattern is interpreted to indicate compensatory activation of cortical functions in the patients with AD. Together, the two composites (Figures 2 and 3) show

care.



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obvious and statistically significant differences in cortical flow and metabolic uptake. The differences in the cortical functions are also reflected in significant mean differences in color-naming times. Thus, the naming time mean for normally aging adults was 52.7 sec. (SD 10.5) and for adults with AD it was 90.0 sec. (SD 18.8). Furthermore, the longitudinal study has provided consistent evidence that individual rCBF patterns are “normal” up to 70 seconds total naming for color-form combinations (see Figure 2). For naming times longer than 70 seconds, the rCBF images show increasing evidence of the pathological pattern associated with AD (see Figure 3).

The Clinical Utility of AQT

The longitudinal study allowed for a comparison of the clinical utility of the AQT color-form naming test, the MMSE and the ADAS-cog in differentiating the normally aging and patients with AD. The findings of that study are summarized in Table 1.

The table first compares design and other characteristics of the three tests for cognitive impairment and ‘probable’ AD. Secondly, it shows the naming time means for each group and each test. It is evident that the specificity, sensitivity and positive and negative predictive values associated with AQT color-form naming are similar to those obtained for ADAS-cog, and better than those obtained for the MMSE. ☹

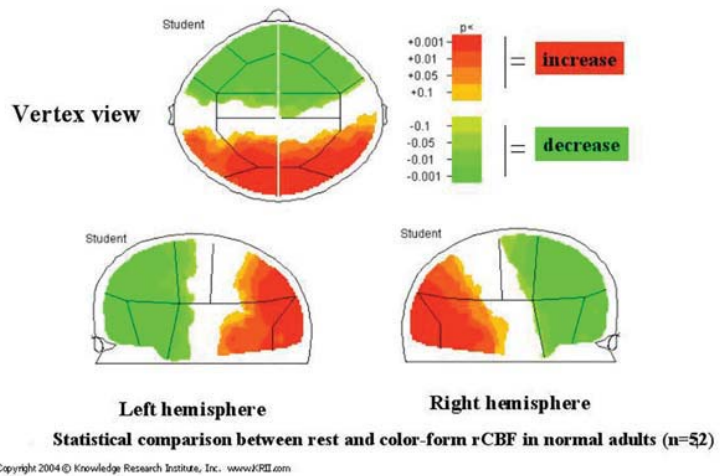


Figure 2. Cortical Areas Engaged during normal AQT Color-Form Naming.

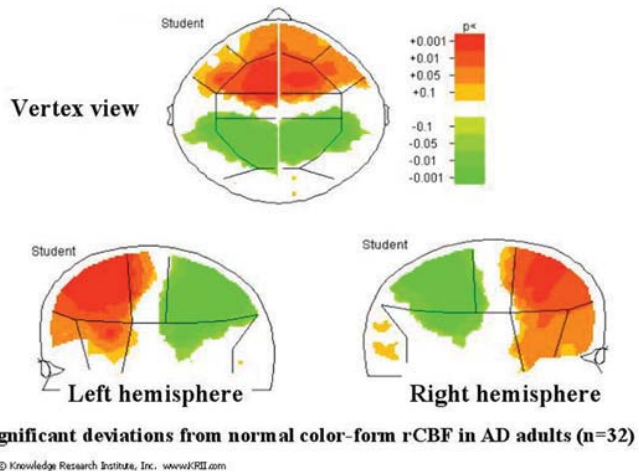


Figure 3. Alzheimer's Pathology during Color-Form Naming.

	AQT-CF	MMSE	ADAS-cog.
Normal (n = 52)	Mean = 52.7 sec. (10.5)	Mean = 28.9 (1.2)	Mean = 9.3 (4.9)
AD (n = 32)	Mean = 90.0 sec. (18.8)	Mean = 23.3 (3.8)	Mean = 30.4 (9.1)
Time	3-5 min	10 min	45-60 min
Examiner/Monitor	Nonmedical	Nonmedical	Professional
Cost	Low	Moderate	High
Conflict Factors	None (Objective)	Judgment Education Literacy Culture	Judgment Experience Age Education Literacy Culture
Predictive Values	Positive 99.9 Negative 97.8	Positive 82.6 Negative 95.4	Positive 95.3 Negative 97.3
Screening	Yes	Yes	No
Monitoring	Yes		Yes
Medication			

Mean differences significant at .01 level.

Table 1. Comparison of test characteristics and clinical utility.

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Acknowledgments

This work was funded in part by National Institutes of Health (NIDCD) under Contract # N01 DC8-2104 and Grant # R01 DC 02172- 04 to Harry Seymour, Principal Investigator, at the University of Massachusetts Amherst, with Thomas Roeper and Jill de Villiers at the University of Massachusetts and Smith College, as co-investigators. It was accomplished in conjunction with Harcourt Assessment, Inc., San Antonio, TX. The tests that are the products of this research collaboration are the *Diagnostic Evaluation of Language Variation (DELV)* assessments, the *DELV Screening Test*, *DELV Criterion-Referenced* edition, and the *DELV Norm-Referenced* edition.

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