Neurological Chronometric Assessment

Because Optimal Brain Function is Vitally Important to Quality of Life

Cenegenics® considers mental acuity and memory to be vital components of a proactive approach to the preservation of quality of life as we age. As part of our comprehensive baseline evaluation of patients considering Age Management Medicine, Cenegenics® includes a series of tests on short-term memory and cognitive (thinking) function. These abilities may erode with aging and other medical problems or treatments. Retention of thinking skills and memory is one of the critical components of a responsible program, because a longer life is of no benefit without the ability to make use of it. This is quite evident when looking at the volume and variety of information that is proliferating in the media and on the Internet. In fact, “memory” is the most common Internet search subject people use to link to our website. As more and more information and medical treatments of memory and thinking problems become available, our ability to separate the good information from the bad becomes even more daunting. Cenegenics® feels that it is important to be a source of trustworthy information for patients and to be able to screen for memory or thinking problems at the earliest detectable time. Maintaining these skills in healthy people as they age and trying to optimize the treatment and options for patients with early deficits is our goal.

Concern

Concern over mental acuity and memory loss with aging and Alzheimer’s Disease is growing geometrically as baby boomers become seniors at the estimated rate of 10,000 a week.

Unfortunately, currently available, conventional mental status exams fail to detect problems like pre Alzheimer’s states, Mild Cognitive Impairment (MCI), or other changes in cognitive function. This is especially true in people who function at mentally high levels. People whose careers demand critical thinking and reward mental proficiency and continuing education are notorious for performing beyond the measuring capabilities of conventional mental status tests. By the time these tests detect a measurable change, any underlying problem is usually much farther along. More complex testing is required to evaluate these people accurately.

Socio-economics

If cognitive decline were detected a mere 5 years earlier, the national Alzheimer’s Association estimates an annual savings of $50 billion would be achieved. This is based on an estimated 50% reduction in the need for institutionalization if conventional treatments are started early to thwart the disease’s degenerative process.

What has been needed is a mass memory-screening tool, sensitive to the earliest telltale signs of future problems.

Neurological Chronometric Assessment is just that tool and Cenegenics® now offers that service to its patients. NCA has the largest database available of general population memory and brain processing speed norms.
Graph depicts decline in brain processing speed with age (n=4500+)

Over 50,000 tests have established a substantial database of brain processing speed and efficiency norms and standard deviations, which allow for age-matched comparison of individual performances across most cognitive domains.

Imminent Need

Powerful new memory drugs are coming to the market. Some enhance the action of neurotransmitters, such as acetylcholine\(^1\), or affect certain receptors, such as NMDA\(^2\). Others act as neuroprotective agents\(^3\). Still others suppress cerebral vascular inflammation\(^4\), or enhance cranial blood flow. A few even purport to trigger a neurotrophic (regenerative) effects in the damaged areas of the brain\(^5\).

Unfortunately, many individuals experiencing short-term memory loss, Mild Cognitive Impairment (MCI), and even “early stage” Alzheimer’s Disease won’t get a timely chance to use these drugs, unless pre-disease or even earlier transitional/boundary states are detected, fully assessed, and addressed. Let Cenegenics\(^6\) make that assessment for you!

Missing Measure

It is now believed that Alzheimer’s sets foot in the medial temporal (hippocamal) area of the brain 30-40 years before “symptoms” are noticed and clinically diagnosed. Long before memory loss is so debilitating as to be labeled “dementia” and usually untreatable, there are earlier signs of a progressive slowing of working memory brain processing speed, not yet a loss in learning and memory capacity.

Early pre-disease state detection of memory loss could offer a significant advantage to treatment and even possible prevention. Cenegenics\(^6\) can now provide you with this opportunity.

Millisecond Difference

The difference between a healthy and unhealthy brain can be as little as a few hundred milliseconds (ms) in brain processing speed. The individual patient, let alone his or her friends and family, rarely notices this seemingly insignificant difference. It may start as early as age 35-40 and typically manifests as mild forgetfulness and inability to place information into short term memory, with a slowing in recalling appropriate words, names for faces, shopping items, etc. Spouses often feel that their mate is not paying adequate attention.
With this new understanding, it becomes imperative that individuals over age 40-45 start receiving regular cognitive chronometric (mental reaction time) check ups, especially to establish a benchmark so that any future deviations from baseline gives them a much-needed early warning sign and marker to follow; proper preventive and corrective therapy can then be instituted in a timely manner.

Clinical Relevance of Reaction Time Testing (Chronometrics vs. Psychometrics)

The key to treating any disease is early detection, and subsequent measurement of treatment outcome. Current “mental status” exams are inept at both, due to their inability to measure and monitor cognitive processing speed and efficiency with regard to short term or working memory.

Chronometrics differs from psychometric testing (e.g., standard IQ tests, mental status exams, etc.) in that brain processing speed and efficiency, as well as the accuracy of responses, are measured, yielding a more comprehensive view of cognitive function. It has been clinically observed that cognitive impairment, from age-associated to Mild Cognitive Impairment (MCI) to Alzheimer’s Disease (AD), typically first manifests as a slowing in brain processing speed. Unfortunately, standard screens and assessment tests fail to measure speed. Below are examples of references supporting the importance of measuring brain processing speed:

- “…..the speed of memory performance may be the first aspect of the memory system to decline as the system begins to fail.” Int’l Jnl Ger Psychiatry, Vol. 10: 199-206 (’95)
- “…..research suggests that speed of performance may reflect the efficiency of mental processes.” Nature Neuroscience 2000; 3:509-515
- “…..traditional tests for dementia were relatively ineffective for identifying its early forms. The only effective assessment…is one that measures both speed (reaction time) and accuracy.” Int Psychogeriatr, 1996;8(3):397-411
- “…..speed of information processing predicted mortality independent of age, health, sex, education & depression.” Am Jnl Epidemiology;150(9):978-86, 1999 Nov 1
- “…..speed scores identify impairments that would otherwise be missed using traditional measures. …speed scores on measures of attention & memory…identify patients with MCI”. Research & Practice In Alzheimer’s Disease, Vol. 3, 2000

A solution to the pressing need for a brief, quickly and widely distributable early detection and outcomes measurement tool is the measure of brain processing speed via cognitive chronometric monitoring. Cenegenics now offers this service to its patients.

100 Years in Development

Neurological chronometric assessment has been studied in research laboratories for almost 100 years. Over the past 50 years, with the advent of modern electronics, devices have been developed that can detect mere millisecond differences in mental processing times. These changes may be indicative of a clinically undetected stroke, MCI[8], the very early stages of Parkinson’s or Alzheimer’s Disease, ADD/ADHD, depression, and others conditions, disorders, and diseases affecting the brain/ memory and central nervous system.

In fact, the forefathers of intelligence testing (Benet, Ebbinghaus, Cattel) all postulated that it was problem-solving speed that defined raw intelligence and cognitive capacity.

A literature search will show tens of thousands of articles on physical and cognitive choice reaction time and tests of short term memory in neurologic conditions ranging from Alzheimer’s Disease, ADD/ADHD, alcohol abuse, anxiety, post-concussion syndrome, depression, and sleep disorders to stroke or schizophrenia Chronometrics has also been used for over 20 years in clinical drug trials. In fact, it was the government’s own ANAM[9] technology that found that Claritin® did not decrease alertness compared to other antihistamines, giving Schering-Plough a decided marketing advantage.
Neurological Chronometric Testing has proven to be the most sensitive and reliable practical means of quickly determining if, or how well a particular drug or nutraceutical helps the brain, or if it enhances or maintains cognitive performance. This will allow the Cenegenics® medical staff to place you on appropriate preventive or corrective therapy and to scientifically measure success.

Measure to Manage Individual Differences

With the imminent arrival of new drugs that affect different neurologic pathways or have different mechanisms of action, Cenegenics® will be faced with many more choices and decisions to make regarding appropriate drug use for our patients. For example, clinical trials reveal that less than half of Alzheimer’s Disease patients respond to today’s approved drugs (the cholinesterase inhibitors, such as Aricept (Pfizer)). As new drugs that work on different areas of the brain and via different neurotransmitter systems become available, the need for a quick and simple outcome measure becomes more and more crucial. New or multi mechanism-of-action drugs are also forthcoming for ADD/ADHD, depression, and others.

With a quick, objective testing outcome, Cenegenics® will be empowered to optimize the treatment for depression, attention disorders, dementia, stroke and other CNS disease and pre-disease states and conditions. Perhaps more importantly, detecting early signs of cognitive impairment allows for appropriate medical intervention, so the cognitive impairment never becomes clinically significant in the first place.

Assessment Technology

Neurological Chronometric Assessment allows for reaction time testing with millisecond resolution over virtually any Internet connection.

Cenegenics® currently incorporates 4 tests that measure:

- Physical (psychomotor) reflexes
- Working and short term memory
- Attention
- Executive (cognitive) functioning

“Cognitive TRW”

Performance in each cognitive category is rated against age-matched norms. To date, there have been over 10,000 individuals have been tested. This dynamic database is growing daily and offers the unique prospects for identifying MCI, pre-Alzheimer’s State, and stages of other CNS conditions based on neurocognitive decline rates.

Clinical research using reaction time testing has been conducted in a variety of conditions including the diagnosis, treatment, and monitoring of Alzheimer’s Disease, Mild Cognitive Impairment, Parkinson’s Disease, and Depression. These conditions are believed to have characteristic patterns of quantifiable differences in processing speed and efficiency across various neuro-cognitive domains. Importantly, it appears that the very early signs of impairment caused by these conditions first manifest as a slowing of processing speed - millisecond reaction time deviations from the general norm - in one or more measurable domains. The Neurological Chronometric Assessment has the largest database available of general population memory and brain processing speed norms. Cenegenics® provides the opportunity to its patients to use this new and exciting diagnostic tool to aid in the preservation of optimal brain function.
In short, this technology is an objective neurological cognitive assessment and management application that can help in:

- Early detection
- Monitoring treatment
- Establishing improvement after therapy or at least stabilization

Clinically tested.

Neurological Chronometric Assessment has been clinically tested at Stanford, Scripps and UC Irvine medical schools. Results ($n=100+$) suggest that cognitive processing speed is a uniquely sensitive and comprehensive indicator of brain function and early stages of dysfunction and impairment, specifically in memory, attention and executive function (e.g., decision-making). These tests were also found to be fully correlated with standard psychometric measures, e.g., Wechsler Memory Scale, Boston Naming Test, et al. Testing and tracking thinking and memory skills gives us objective ways to measure the benefits of Cenegenics® programs:

- Establish baseline
- Institute therapy when indicated by early signs of cognitive impairment
- Tracking response to program interventions

Designed for YOU.

With standardized testing methods we are able to quantify your memory and thinking skills compared to norms for your demographic group and to yourself over time. As annual information accumulates, we will endeavor to tailor specific supplement programs based on ongoing test results, making supplement plans more patient specific than is offered elsewhere, and more efficient. These tests use very short (1-3 minute) computerized cognitive tasks that challenge the brain’s information processing powers (efficiency and speed) across several domains, e.g., perception, sensory-motor, learning and memory, attention, and executive (cognitive) functioning.

The Millisecond Difference

What uniquely separates this technology from conventional psychometric testing is its ability to capture brain processing speed and efficiency, with millisecond resolution. Over 50 years of R&D has proven that reaction time (RT) testing provides an objective marker of brain function, cognitive performance levels, and subtle short term change. A Medline search of “reaction time and attention, Alzheimer’s, Parkinson’s, stroke, head injury, concussion, depression, anxiety, schizophrenia, epilepsy, or other conditions affecting the CNS” will reveal tens of thousands of research studies confirming the heightened sensitivity of reaction time to subtle short-term cognitive changes.

Millisecond deviations in reaction time can indicate early stages of cognitive or motor dysfunction, memory and concentration loss, or impairment that would not be diagnosed by other measures for many years. As with most disease and pre-disease conditions, the earlier they are detected the better chance for successful treatment. Cenegenics® wants to help your brain return to its optimal state and stay healthy.

Neurological Chronometric Assessment Tests at the Cenegenics® Medical Institute:

1. Delayed Memory Test
2. Working Memory Test
3. Immediate Memory and Executive Function Test
4. Psychomotor Reflex Test

Note: If this is your first time, there is a tutorial.
Matching Memory, Running Memory, and Immediate Memory. Collectively, they reflect different aspects of cognitive functioning, including working (immediate, executive) memory, and delayed memory. Scores reflect accuracy, speed, and efficiency of responses.

Psychomotor Reflex Test

The Psychomotor Reflex test measures physical reaction times. Although this is typically considered a sub-cortical (sensory-motor) process, attentional (working memory) processes are also involved. The Psychomotor Reflex test is indicated for use when a psychomotor problem may be present (e.g., head injury and stroke, Parkinson’s, other neurologic disorders). Note: If reaction time in the Memory Screen or Assessment tests is unusually slow, this quick and simple test can help determine if a psychomotor problem contributed to the out of range score.

More About the Neurological Chronometric Assessment

As mentioned above, Cenegenics® is using this first and only complete electronic outcomes management system for the objective assessment, monitoring, and enhancement (training) of cognitive functioning and memory access. Based on a scientific approach measuring the brain’s information processing speed and efficiency, Neurological Chronometric Assessment also delivers a practical cognitive assessment and monitoring tool for the management and documentation of cognitive enhancement, memory improvement, and healthy aging protocols.

In brief, this is the use of very short timed (“chronometric”) cognitive tasks that assess the brain’s information processing speed (in milliseconds) across several domains: memory, attention, and executive functioning.

This test can be used to assess following conditions that affect neuro-cognitive functioning:

1. Normal aging
2. Premature or accelerated aging
3. Age-associated and Mild Cognitive Impairment (MCI)
4. Alzheimer’s Disease (AD)
5. Depression
6. Sleep disorders
7. Anxiety/stress
8. Parkinson’s Disease
9. Closed head injury (stroke, etc.)

Brain Speed is Both a Brain Age Marker and a Longevity Predictor

A recent landmark longitudinal study of 2,380 people, age 55 to 85, revealed that the speed of processing information was a better predictor of mortality than even cardiovascular disease or diabetes. Key points in the study were:

- Information processing speed, fluid intelligence, and short term memory predicted mortality irrespective of age, sex, health, medications, or depression
- Predictive power of the three was as high as diabetes or cardiovascular disease
- Information processing speed was most successful of all “longevity markers”

The conditions listed below are of great concern to us. The sensitivity of the system allows for both early identification and monitoring of intervention for conditions such as:

- Alzheimer’s Disease
- Mild Cognitive Impairment
- Depression
- Sleep Deprivation
Additionally, if you have any of these conditions where cognitive functioning has been compromised, monitoring of intervention provides objective feedback to you and to Cenegenics®. In fact for the patient and caretaker, proof of results can act to positively reinforce treatment and/or training, thus improving outcome. Manageable conditions include:

Stanford University, Scripps Institute and UC Irvine Medical Schools Clinically Testing

The Neurological Chronometric Assessment tests correlate highly with standard psychometric measures as illustrated in the UCI study

1. Exelon (Rivastigmine Tartrate; Approved), Reminyl (galantamine; Approved), Alcar (acetylcarnitine)

2. Ampalex (CX516; Phase II) an Ampakine, and memantine (Phase III)

3. CDP-choline, Ginkgo, Vitamin E, Anthocyanins

4. Rofecoxib & naproxen (Cox-2 inhibitors)

5. Ginkgo & Vinpocetine

6. Neotrofin; AIT-082 (leteprinim potassium; Phase IIb)

There are over 30 million MSE (mental status exams rendered yearly by the medical profession). Unfortunately, few, if any, can spot the early stages of cognitive impairment. Even fewer can detect short-term changes in cognitive performance. None measure reaction time and or can be administered online with a large normative database.

MCI is considered a boundary or transitional (pre-AD) state characterized by a 1.5 SD deviation below gen’l population norms in recall but showing no signs of dementia or cognitive impairment, and displaying normal IQ.

Developed in the early 80’s to tell when military personnel suffered any cognitive impairment from nerve agents to head blows. This testing became established through use at the government’s National Rehabilitation Hospital (NRH) to evaluate head injury and track recovery. A simple measure of physical reaction times often shows a continued brain slowing years after the initial neurological insult.


DRAFT - UC Irvine Study Construct Validity

CONVENTIONAL PSYCHOMETRIC TESTS

<table>
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<th>NCAT/RT</th>
<th>MMSE</th>
<th>WMB</th>
<th>SDS</th>
<th>Boston Naming</th>
<th>WAIS Block</th>
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In a study conducted at Stanford University, by Ruth O’Hara, PhD, the Neurological Chronometric Assessment tests detected cognitive impairment (reaction time but not performance) in non-symptomatic carriers of the gene associated with Alzheimer’s Disease (APOe4 allele), whereas traditional psychometric tests failed to do so.

Individuals with the Apolipoprotein E4 allele Exhibit Significantly Slower Reaction Times on Neurological Chronometric Assessments.

Exercise, Brain Nutrients, and Pharmaceuticals

There is a growing body of research that both physical and mental exercise can increase blood flow to the brain, enhance upregulation of glucose, oxygen, and neurotransmitters. This exercise plus the appropriate brain nutrients and pharmaceuticals may aid in the stimulation of the growth of dendrites if not new neurons.

We at Cenegenics® feel the complement of tests we now have available defines the state of the art in available testing for short term memory, working memory, and neuro-cognitive function. The tests are easily administered and time efficient. We can track performance over time and recommends repeating these tests at the time of your Executive Health Annual Evaluation and more frequently if your schedule allows interim visits to the Institute.

Be assured that Cenegenics is constantly vigilant about introducing scientifically validated testing and therapeutic modalities to you so that quality of life issues can be addressed and improved. We will continue to lead the world in 21st century medicine focused on optimal health and longevity. Thank you for your continued trust and confidence.

Sincerely,

Alan Mintz, M.D.
Appendix

The following abstracts review what has been examined in the medical literature regarding our methods of neurocognitive testing.

Validation of a New Keyboard-based Reaction Time Measure
Andrew M. Johnson and Philip A. Vernon
Department of Psychology,
The University of Western Ontario

Abstract

The Neurological Chronometric Assessment technology promises to be an easy-to-use and easy-to-score measure of cognitive speed and ability. It measures responses wholly by keyboard. It is important, however, to examine this reaction time measure in conjunction with other established reaction time measures. Furthermore, its potential for use in clinical settings makes an examination of its correlations with clinical measures of cognitive speed and memory of interest. The present study discusses the psychometric characteristics of the Neurological Chronometric Assessments, and presents comparisons with a battery of previously validated reaction time measures that use an external response console and timing device. In addition to this, correlations are computed between the test subscales/subtests and the Wechsler Memory Scale, to determine whether it measures similar constructs to this well-respected memory test. Finally, the factor structure of the tests is evaluated, and a maximally weighted composite of its subscales is compared with the Raven’s Advanced Progressive Matrices – a measure that is widely considered to be one of the better measures of general intelligence ($g$). Results suggested that the Neurological Chronometric Assessments are stable across time, in both a short-term test-re-test scenario, and in a repeated practice scenario. Furthermore, the tests demonstrated significant correlations to the scales of the Wechsler Memory Scale, and to the previously validated reaction time measures. These results suggest that test batteries such as the Neurological Chronometric Assessment, may represent a potential resource for researchers and clinicians.

Reaction Time but not Performance on Cognitive Tasks Identifies Individuals At Risk for Alzheimer’s Disease: A Preliminary Report
Ruth O’Hara, Ph.D., Barbara Sommer, Ph.D., Kevin Morgan, B.A.,
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, Stanford, CA

Abstract

Objective: To compare the performance of individuals with and without the e4 allele on a battery of cognitive tests designed to detect subtle differences in cognitive performance.

Design: Performance on a computerized battery of cognitive tests (Neurological Chronometric Assessments), and standard neuropsychological tests, of 10 older adults with the e3/e4 genotype was compared to that of 17 older adults with the e3/e3 genotype.

Setting: Aging Clinical Research Center, Stanford University.

Participants: 27 community-dwelling older adults were recruited from a pool of 120 individuals who already had participated four to five years earlier in a memory training study and a five-year, follow-up study. These individuals were originally recruited through newspaper advertisements and contacts with local senior centers. The 27 subjects who agreed to participate in this investigation were between 62 and 85 years of age.
**Measurements:** Subjects were administered a computerized battery of cognitive tasks, the Neurological Chronometric Assessment Technology tests, which measure verbal and spatial memory, working memory, attention, speed-of-processing, and visuo-spatial abilities. Additionally, subjects were administered a subset of neuropsychological tests which had been administered at baseline and at the five-year follow-up testing. APOE genotype had been determined at the previous follow-up.

**Results:** Demographically, there were no differences between the e3/e4 and e3/e3 subjects. The two groups did not differ significantly on any of the neuropsychological measures. With respect to performance on the Neurological Chronometric Assessment battery of tasks, the two groups did not differ in terms of their physical reflex reaction time. Additionally, with respect to accuracy, the two groups did not differ significantly except on the measure of immediate memory, with the e3/e4 group exhibiting higher numbers of errors. However, the subjects positive for the e4 allele were significantly slower in performing all of the Neurological Chronometric Assessment memory tasks.

**Conclusion:** Reaction time performance on the memory tests of the Neurological Chronometric Assessment battery was able to differentiate the performance of subjects positive for the e4 allele from those without the e4 allele. This study suggests that reaction time performance on the Neurological Chronometric Assessment test battery may be able to detect subtle cognitive deficits in older adults. Implications of the use of such measures for the identification of early cognitive decline in older adults are discussed.

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**Cognitive changes with Ginkgo Biloba and Vinpocetine in Normal Adults:**

**Systematic assessment of perception, attention, and memory**

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**Abstract**

A computerized response time cognitive test battery was used to assess the effects of Ginkgo biloba (Chronometric Assessment) assessed perceptual, attention, and short-term memory and Vinpocetine [1] (GB and V) in a double-blind placebo controlled study of 24 normal adults. Ten cognitive tasks (Neurological functioning. Response time (RT) and error rate (ER) were obtained, and performance variability was minimized by requiring task practice and two trial blocks through all ten tasks for each condition. Subjects were given either placebo or GB and V capsules to consume for 14 days, after which they performed all ten tasks twice. They then received the other capsule condition and returned 14 days later and completed the final test session in the same manner. RT and ER decreased for all tests after the first practice session and then stabilized for the placebo and GB and V conditions. “Working memory capacity” demonstrated a statistically significant 50-millisecond RT decrease difference between the placebo and GB and V capsules with no ER effects. The results indicate that Ginkgo biloba and Vinpocetine speeds short-term working memory processing in normal adults.
Early Detection of Dementia in the Elderly

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University of California, Irvine

Abstract

The early detection of cognitive impairments is essential as the aged population increases. The computerized test battery of the Neurological Chronometric Assessment was used to assess 26 volunteers, 47 years of age or older for perceptual ability, memory and response speed. Results were compared to standardized tests for memory, language, visual-spatial, frontal lobe and global cognitive function. In general, the number of errors and variability on the Neurological Chronometric Assessment increased with reaction time. Age alone was not a significant factor. The highest correlations were between the Neurological Chronometric Assessment tests and Logical Memory, which is sensitive to age-related cognitive change and dementia. High correlations were observed between Neurological Chronometric Assessment perceptual/spatial tasks with WAIS III Block Design and Similarities, and may be sensitive to parietal and frontal lobe function. Memory and spatial ability are closely associated with hippocampal function, a structure often compromised early in dementia such as Alzheimer’s Disease. This study provides an estimate of the utility for the Neurological Chronometric Assessment to detect early cognitive changes in excess of normal age-related changes or associated with the onset of dementia.

[1] Compound also includes Vitamins B1, 3,5 & 6, folic acid, DMAE, and tyrosine.