

INHANCE STUDY: FREQUENTLY ASKED QUESTIONS

1. What was this study about?

The INHANCE (Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise) trial is an NIH-funded imaging study organized to determine if a special type of computerized brain exercises can upregulate the brain's production of the brain chemical acetylcholine.

2. What is acetylcholine and why is it important?

Acetylcholine is a very important brain chemical, which is both a neurotransmitter (signaling between neurons and cells) and a neuromodulator (altering the activity of other neurons and cells). It is sometimes called the “pay attention” chemical, because it is produced in the moment when the brain needs to attend. For example, when you study hard and well, you produce acetylcholine – you could think of it as the brain's way of saying “this is important, pay attention.” Acetylcholine plays a crucial role in attention, problem-solving, learning and memory. It also is considered a brightening neuromodulator that has a positive impact on mood. It also plays a role in managing the autonomic nervous system, muscle contraction, and the immune system. It also makes the brain more “plastic” – more capable of physical change and reorganization.

As with other brain chemicals, the brain system that produces acetylcholine (the cholinergic system) is known to typically peak in a person's 20s and then to slowly and progressively downregulate. At first, the downregulation is not perceptible, but it grows with each passing decade, and it becomes more noticeable with normal aging and with certain diseases and injuries.

Acetylcholine production is known to downregulate in relatively healthy older adults by about 2.5% each decade. The downregulation is significantly larger in people with pre-dementia conditions, such as Mild Cognitive Impairment (MCI), and acetylcholine levels plummet with Alzheimer's disease.

For decades, the most prescribed medication for Alzheimer's disease has been cholinesterase inhibitors (such as Aricept®), which artificially flood the brain with acetylcholine—typically, with a short-term benefit and then a sharp decline — rather than fixing its downregulated production.

Downregulation of acetylcholine is associated with cognitive aging, pre-dementia, and Alzheimer's disease, and it also is associated with many mood disorders, (depression, anxiety, and fatigue), as well as with schizophrenia.

3. How was the study run?

Researchers conducted a double-blind, randomized controlled trial at The Neuro at McGill University, one of the few places in North America that has the technology for this type of neuroimaging. The researchers recruited community-dwelling, healthy older adults near McGill in Quebec Canada and arrived at an intent-to-treat (ITT) sample size of 92 largely healthy older adults. The study population included 46 participants in each of the intervention — doing BrainHQ exercises (sometimes called the “speeded” arm) -- and in the active control — doing casual but attentionally demanding online games (sometimes called the “non-speeded” arm).

The ITT population was 72 years on average, educated, and non-depressed.

The researchers' "speeded" versus "non-speeded" short-hand designations of the intervention and control groups reflect that the intervention exercises progressively challenge users to recognize information, presented at greater and greater speed as they get answers correct, while the control activity (attentionally-demanding games based on games like solitaire and match-3 type games (like Candy Crush or Bejeweled), which demand attention but allowed users to respond to stimuli that did not progressively get faster in response to correct answers.

The exercises used by the intervention group were originally designed for the commercially available BrainHQ brain training app. The dozens of exercises in BrainHQ are based on principles from the science of neuroplasticity and have been conceived, tested, and validated by an international team involving hundreds of brain scientists. BrainHQ exercises have been the subject of [more than 300 published peer-reviewed journal articles](#) across varied populations, abilities, and health conditions.

Each participant was asked to do 30 minutes of daily brain training activity (the BrainHQ exercise intervention or the causal games active control) for 10 weeks, for a total of 35 hours of training.

Before and after the 10-week training period, each participant was measured on a number of outcome measures. Cognitive control was assessed using 3 computerized subtests (Flanker, Set-Shifting, and Anti-Saccades) from a validated neuropsychological battery, NIH EXAMINER. Participants also completed 2 train-to-task cognitive assessments (the Double Decision assessment and the Freeze Frame assessment modeled directly on the 2 intervention exercises). Behavioral measures sensitive to acetylcholine function were also collected, including heart rate variability and pupillometry.

All cognitive and behavioral assessments were conducted at baseline, posttest, and at a 3-month no-contact follow-up.

4. Which BrainHQ exercises were used by the intervention group?

BrainHQ includes dozens of brain exercises that have been validated in studies. For this study, the researchers chose two exercises, Double Decision and Freeze Frame, for their role in dementia risk reduction and posited abilities to successfully drive gains in the production of acetylcholine.

5. Which exercises were used by the active control group?

The active control included spin-offs of two casual games — one based on the card game solitaire (Double Klondike Solitaire) and one based on match-3 games (Bricks Breaking Hex).

6. What were the findings?

The researchers reported that upon completion of the 10-week intervention, they observed a 2.3% upregulation in the production of acetylcholine in the intervention group in the anterior cingulate cortex – a brain region crucially in working memory, decision-making, and attention - and no significant change in the control group. The researchers noted that this increase roughly offsets the average 2.5% decline for older adults each decade noted in the literature.

There was also a significant increase in cholinergic binding of 4.7% in the hippocampus and 5.3% in the para hippocampal gyrus, which are regions known to be particularly vulnerable to age-related declines in

cholinergic function, and a general pattern of improved acetylcholine function across virtually every brain region measured.

The cholinergic system has major projections from the basal forebrain to brain structures involved in memory, and these findings suggest enhancement in memory-related processes that help explain the biochemical benefit on memory performance of this type of BrainHQ training reported in previous studies.

7. What are the implications of this study?

This is the first confirmation in humans that the brain's chemical system that produces acetylcholine (the "cholinergic system") is plastic (capable of change based on how the brain is used). Prior demonstrations of the plasticity of the cholinergic system have only previously been shown in other mammals.

By demonstrating the cholinergic system is plastic, the researchers have demonstrated a novel pathway for addressing the downregulation of acetylcholine associated with normal aging as well as the deeper downregulation associated with pre-dementia (such as mild cognitive impairment), and the severe decline associated with Alzheimer's and other diseases.

In this study, the researchers reported that after 10 weeks of training with BrainHQ for 30 minutes per day (for a total of 35 hours) the participants in the intervention group had a 2.3 percent increase in the production of acetylcholine in resting state compared to no significant increase in the active control group. The researchers noted that this upregulation in the production of acetylcholine nearly offset the average downregulation experienced each decade by healthy older adults. No drug or other type of intervention has been shown to upregulate acetylcholine production.

This study offers a biochemical explanation of prior findings from other studies showing that BrainHQ exercises reduce dementia [risk](#) and [incidence](#), improve performance [across dozens of studies in people with mild cognitive impairment](#), and improves many standard measures of cognitive function ([attention](#), [speed](#), [memory](#), [executive function](#)) and of gerontological life function ([maintaining independence](#), [driving safety](#), [fall risk](#), [general health](#), [healthcare costs](#)) across [scores of studies of largely healthy older adults](#). The finding of an improvement in acetylcholine production (sufficient to offset about a decade of decline) is also consistent with a [prior study](#) of BrainHQ, indicating that there was an average of about 10 years improvement in attention and memory among largely healthy older adults, using a standard age-stratified assessment.

8. What might this news mean for members of your audience?

- The effects of cognitive aging are largely preventable and now have been shown to be bio-chemically reversible.
- Because of their design based on principles of brain plasticity, BrainHQ exercises, uniquely, have been shown across scores of published studies of older adults to improve cognitive performance across many standard measures of cognition, to improve quality of life across many standard gerontological measures, and to improve performance at real world daily activities.
- The specifics of what you do with your brain matters – the **BrainHQ brain training** exercises improved acetylcholine function, but ordinary "cognitively stimulating" **computer games** did not.

- The pathway demonstrated in this study to upregulate brain chemical production has promise for a host of other conditions that involve downregulation or other deficits in brain chemistry (including, for example, other conditions related to deficits in acetylcholine (such as Alzheimer's, Huntington's Parkinson's, Mild Cognitive Impairment, myasthenia gravis, LEMS, depression, anxiety, and schizophrenia); conditions related to deficits in dopamine, (such as Parkinson's, depression, schizophrenia, bipolar, restless legs syndrome, and ADHD); conditions related to deficits in noradrenaline and norepinephrine (such as anxiety, stress, fatigue, depression, hypertension, ADHD, and sleep disorders).

9. What is some of the history of this research?

Dr. Michael Merzenich ("Mike"), now age 85, is the co-founder and chief scientist of Posit Science, which makes BrainHQ. For more than 60 years he has been a pioneer pushing the frontiers of brain plasticity research, with an ever-growing cohort of co-investigators, supporters, and successors of his research, now numbering in the tens of thousands, or more. In short, Mike pioneered the field of brain plasticity – and created a scientific movement that is now the dominant way to understand how the brain works.

He is a renowned neuroscientist for his work in brain plasticity, has been awarded the Kavli Prize in Neuroscience (the highest honor in the field), and has been honored by each of our National Academies (having been elected to both the National Academy of Science and the National Academy of Medicine, and having been awarded the Russ Prize in Bio-Engineering by the National Academy of Engineering). However, he may be best known to the general public for a series of specials on public television (and an Australian TV series broadcast in the US on the Discovery channel) about the power of brain plasticity.

When Mike was a young neuroscientist (and for a long time thereafter), brain scientists were taught that the brain started as a blank slate, and as you came into the world the brain was "plastic" — capable of chemical, physical, and functional change, based on your experiences — during childhood. However, by the time you reached early adulthood, the brain became set and was no longer plastic. This was in the early days of building computers, and brain scientists thought the brain was like a mechanical "thinking machine," where, in childhood, you built out your operating system, and, then, when you reached adulthood, you could still push new information through your brain, but you could not change the operating system, and as you got older, just like an old machine, it was destined to wear out. This seemed to fit with the apparent age-related normal cognitive decline and with dementia as a disease of aging. Everyone "knew" that plasticity ended with childhood. And, it turned out, everyone was wrong.

Early in his career, Mike ran experiments that conflicted with this orthodoxy of childhood-only brain plasticity, and Mike showed that plasticity is lifelong. This became a pattern in his professional life. He became the Wayne Gretzky of brain science for decades — accurately predicting where the puck was going long before others could see it. His breakthrough findings repeatedly were critiqued and questioned and the subject of debate and controversy — only for the whole field to eventually move in his direction, as study after study confirmed his breakthroughs.

Publishing those early studies showing that — maybe — plasticity did not end with reaching adulthood, nearly got Mike drummed out of the profession. A recipient of the Nobel Prize in Medicine, who had discovered childhood plasticity, was asked at a conference about those early studies. The Nobel Laureate declared to the conference that he would re-run Merzenich's studies and prove him wrong. The next year

at the same annual conference, as a scientist of integrity, that Nobel Laureate declared that he had re-run those experiments and that “Merzenich was right.” Others who sparred with Mike about theories and finding over the years have not all been as gallant. This controversy (over whether plasticity was lifelong or ended at adulthood) has been reported on rather dramatically in a couple books ([The Brain that Changes Itself](#) and [The Mind and the Brain](#)).

Mike was recruited at this time to help develop the cochlear implant (to restore hearing to people with cochlear deafness). The cochlea is small organ in each ear that turns sound waves into electric pulses which the brain interprets as sounds and speech. The natural cochlea has thousands of connections into the brain, and while it was not considered impossible to build an electronic cochlear implant to turn sound waves into electric pulses, many thought build a practical implant was impossible because it would require surgeons to make thousands of connections into the brain. Mike’s contribution as a co-inventor of the cochlear implant was to identify a handful of connection points and then rely on the brain’s plasticity to “eventually” enable people to hear and converse. Mike himself was surprised that “eventually” turned out to be within a matter of days, not weeks or months. That was probably the first time humans made an invention to harness brain plasticity.

Mike wanted to do more, and he realized he could do it without drilling holes in the head, if he did it with the holes humans already had — their eyes and ears. He thought that the PC that Steve Jobs had invented would allow him to build auditory and visual exercises, based on the principles of plasticity, that could progressively drive brain performance and health in a positive direction. His first demonstration project was in children with language learning impairments, which resulted in the public company Scientific Learning (now owned by Carnegie Learning).

Then, Mike started what became the BrainHQ brain training app, with a prediction that cognitive aging could not just be prevented, it could be reversed, and with theories about dementia and other health conditions that were far from proven, but in retrospect were highly prescient.

Based on animal research from his labs and the labs of colleagues that few “experts” had read, Mike insisted that BrainHQ exercises needed to be designed to be progressively challenging and attentionally demanding (to pump acetylcholine), laden with rewards (to pump dopamine), and filled with novelty (to pump noradrenaline and norepinephrine). These brain chemicals would make the brain more plastic, would (when released during the progressively challenging exercises) rewire the brain to operate more effectively, would improve mood, and would help address a wide variety of brain insults and injuries.

Having been shown to be ahead of the puck on hundreds of things across more than 300 studies of BrainHQ, it’s a real capstone to Mike’s career to have been proven right about the plasticity of brain chemical production and to provide a bio-chemical model that not only explains so many of the prior results, but will radically improve our abilities to upregulate brain chemistry. One additional outcome of this study, covered in a separate paper, is the first digital 3-minute estimator of acetylcholine levels, affirming Mike’s prescience that, in the near future, you’ll be able to measure and improve your brain health continuously with an app on your phone.

And, as always with Mike’s work, there are more studies underway, and new results coming.