Brain Training and Dementia—Media FAQ

The News

Q: What are the new scientific results? What makes this big news?
A: Researchers have published peer-reviewed results from a ten-year study of cognitive training, and have shown that a specific type of brain training can reduce the risk of dementia. This is the first time any intervention — pharmacological or behavioral — has been shown to cause a reduction in the risk of dementia in a peer-reviewed randomized controlled trial. That's a pretty big deal.

Q: How big a problem is dementia?
A: More than 5 million Americans are living with dementia, with a new person developing dementia every 66 seconds. In 2016, the costs of dementia will be over $236 billion. [source: Alzheimer's Association]

Q: What specifically did the study show? What was the primary finding?
A: The primary finding of the study was the study arm who used one specific cognitive training program, called "speed of processing training" in the study, showed a statistically significant 29% reduction in the risk of dementia, at any given point in time (also known as their "hazard ratio"). The other cognitive training programs, in memory and reasoning, showed no significant effect. The risk reduction of speed training was even larger for people who did more of the training.

Additional findings are discussed below in "OTHER FINDINGS."

The Study Design

Q: How was the study conducted?
A: These newly published results come from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, a large multi-site randomized controlled trial organized and funded by the National Institutes of Health. ACTIVE followed 2802 community-dwelling and generally healthy participants, with an average age of 74, at the beginning of the study, for 10 years. They were randomly assigned into one of three cognitive training groups (speed, memory, or reasoning training), or to a control group. A comprehensive set of cognitive assessments was done before training, after training, and 1, 2, 3, 5, and 10 years after training.

Q: What cognitive training programs were used in ACTIVE?
A: ACTIVE evaluated three different cognitive training programs:

- In memory training, participants were taught mnemonic strategies for remembering word lists and sequences of items, text material, and main ideas and details of stories. For example, participants were instructed how to organize word lists into meaningful categories and to form visual images and mental associations to recall words and texts.
- In reasoning training, participants focused on the ability to solve problems that follow a serial pattern, like identifying the pattern in a letter or number series or understanding the pattern in an everyday activity such as prescription drug dosing or travel schedules.
- In speed training, participants performed brain-plasticity-based, intensive, adaptive, computerized training that was designed to improve the speed and accuracy of visual information processing, while expanding the visual area over which a person could pay attention and make rapid decisions.

Q: How much training did people in the ACTIVE study do?
A: Everyone assigned to a cognitive training program group was asked to do 10 hours of training. People trained in a group setting, twice per week for about an hour at a time, over the course of five weeks. About half of the people in each cognitive training group were assigned to do booster training, where they did an additional 4 sessions of training at the end of the first year, and another 4 hours of training at the end of the third year, for a total of up to 18 hours for the booster group.

Q: Who were the scientists who organized the ACTIVE study?
A: ACTIVE was organized and funded by the National Institutes of Health (specifically, The National Institute on Aging and the National Institute for Nursing Research). Six principal investigators originally designed, executed, and analyzed the study:

- Dr. Karlene Ball (University of Alabama), Director of the UAB Edward R. Roybal Center for Research on Applied Gerontology
- Dr. George Rebok (Johns Hopkins University), Professor & Core Faculty, Center on Aging and Health
- Dr. Sherry Willis (Pennsylvania State University, University of Washington), Professor of Human Development
- Dr. Michael Marsiske (University of Florida), Associate Professor of Clinical & Health Psychology
- Dr. Fred Unverzagt (Indiana University), Professor of Clinical Psychology in Clinical Psychiatry
- Dr. John Morris (Hebrew Senior Life), Alfred A. and Gilda Slifka Chair in Social Gerontological Research

More than 40 other researchers contributed to the ACTIVE Study.

Q: Who wrote this paper?
A: Six of the researchers are co-authors on the new paper:

- Dr. Jerri D. Edwards (University of South Florida) Professor of the College of Medicine
- Dr. Huiping Xu (Indiana University) Assistant Professor, Department of Biostatistics
- Dr. Daniel O. Clark (Indiana University) Associate Professor of Medicine
- Dr. Lin T. Guey (Moderna Therapeutics) Director, Rare Diseases
- Dr. Lesley A. Ross (Pennsylvania State University) Associate Professor, Health and Human Development
- Dr. Frederick W. Unverzagt (Indiana University) Professor of Clinical Psychology in Clinical Psychiatry

Q: Where are these results being published?
A: The results on dementia incidence are being published in an article entitled "Speed of Processing Training is Associated with Lower Risk of Dementia" in the journal *Aging and Dementia: Translational Research and Clinical Interventions*, which is a peer-reviewed journal of the Alzheimer's Association.

Other Findings

Q: Given that the ACTIVE Study looked at cognitive aging over a 10-year period, what other results has the ACTIVE study shown?
A: Previous results from the ACTIVE study have been published in dozens of articles in peer-reviewed, journals including the Journal of the American Medical Association and the Journal of the American Geriatrics Society (among many others). Results have shown that all three types of cognitive training can improve cognitive function and protect against declines in instrumental activities of daily living—the skills required for a person to live independently in their own home. Speed training has uniquely been shown to improve everyday speed (activities like looking up a phone number, or reading a medication label), protect against declines in health-related quality of life and depressive symptoms, reduce predicted medical expenditures, improve locus of control, and reduce the incidence of at-fault car crashes.

Q: This sounds familiar – have these dementia results been announced before?
A: The ACTIVE Study announced dementia results at the five-year mark. At that time, they saw a trend toward protection from speed training, but the results were not yet significant. On average, ACTIVE participants were only aged 79 at that point, and the incidence of dementia was not all that high. Five years later, the average age had increased to 84, and the incidence of dementia had risen, allowing a more powerful statistical analysis.

In addition, preliminary findings with respect to these 10-year dementia results from the ACTIVE Study were announced at the Alzheimer's Association International Conference in 2016. Those results were "preliminary" and had not been peer-reviewed or published. The newly published results confirm the basic preliminary findings and significantly extend them.

Q: If these results flow from what was seen in prior studies and are expected, what makes their publication news?
A: This is the first publication in a peer-reviewed scientific journal of a specific activity that can protect against the onset of dementia. A scientist who deeply understood the previous studies — showing that speed training improved cognitive function and real-world function — might have predicted speed training would protect against the onset of dementia. However, the proof is always in the doing, and given the enormous number of failures in clinical trials in dementia, it is crucial to directly demonstrate that something works.

Major scientific breakthroughs generally advance fairly slowly in a step-by-step manner. If you think about our ability to "send a man to the moon" that was a decades-long process, in which we orbited the moon and returned to earth before we ever had someone set foot on the moon. That made it pretty certain we could land someone on the moon and bring that person back to earth before that actually happened. Nonetheless, that first step was itself major news. In some ways, this is similar.

Also, for lay people, especially those aware of FTC actions against certain brain game companies (with little or no peer-reviewed research backing their products), this may come as a big surprise.

Q: How is dementia defined in the study?
A: One significant new finding in the published study is that speed training has a significant impact on dementia risk whether "dementia" is defined broadly or narrowly.

Dementia is defined as a decline in cognitive function that leads to significant difficulties with everyday activities. There is no specific diagnostic test for dementia — there's no blood test (like there is for an infectious disease) and dementia can't be detected with brain scans (like can be done for a stroke). After dementia is diagnosed, a detailed discussion with a trained physician can help identify what subtype of dementia a person may have — Alzheimer's dementia, which is characterized by deficits in memory, or Lewy Body dementia, which is characterized by visual hallucinations, or other dementias. Because of stigma and lack of effective treatments, dementia often goes undiagnosed in the community.

The ACTIVE study was originally designed to measure cognitive function and everyday activities, but was not originally designed to examine dementia, because not many participants were anticipated to go on to dementia within five years — the original duration of the study. At the five-year review, the researchers concluded that all three types of cognitive training improved their targeted cognitive function and helped people maintain their everyday activities. Based on that data, researchers decided it was appropriate to evaluate the effects of the cognitive training programs on dementia as well, because the diagnosis of dementia is based on cognitive function and everyday activities. They set up criteria for measuring dementia in the study population, choosing a broad definition of dementia given that dementia is often under-reported in real-world settings.

The broad criteria included those participants whose personal physician had diagnosed them with Alzheimer's disease, and those who fell (over the course of the study, and remained) below widely-accepted cut-points for dementia on standard measures used in the study. The broad criteria also included people who were institutionalized (because dementia is the primary reason for institutionalization of elderly) and those whose families refused further participations (as dementia is often a reason for such refusal).

These broad criteria were used for the initial 5-year follow-up analysis, which showed positive trends but no statistically significant protection, because dementia was rare after only five years following the start of the study. These criteria were then used as "a priori" criteria in the 10-year follow-up analysis — meaning the researchers did not change the criteria to help or hurt their chances of finding an effect of the training. The preliminary findings announced at AAIC 2016 used the broad criteria and found a of a 33% reduction in risk.

This analysis is included in the final report. In addition, to be conservative, the researchers now highlight a new finding using narrower criteria for dementia. The narrower criteria limit dementia only to those participants whose personal physician had diagnosed them with Alzheimer's disease and those who fell (and remained) below widely-accepted cut-points for dementia on standard measures used in the study. With the narrower definition, the researchers still find substantially similar results – a 29% risk reduction in the speed of training group. Results in the other training groups (reasoning and memory) were not significant.

Showing that speed training protects against the onset of dementia using several definitions of dementia strengthens the result, by showing that the effect is not unique to only a specific set of dementia criteria.

Q: How do we know whether those who trained more actually got more benefit and weren't just inclined to train more because they were already in better cognitive shape?
A: In the original study design, only participants who completed at least eight of the ten initial sessions of training were eligible to be randomized into booster sessions. About half of those participants were randomized into another four hours of training at the end of each of month 11 and month 35. In the preliminary findings (based on the broader definition of dementia), the researchers announced that the participants who got more training had a 48% lower risk of dementia as compared to the control group.

There were concerns that the better performance by those who did more speed of processing training might be due to the fact that these participants were randomized from those who had better completion records in the first phase of training, and, therefore, might already be in better cognitive condition. To unpack this result, in the published study, the researchers compare the dementia incidence rates of those who did the most training (13-18 sessions) across all three training arms, as well as against the control.

They found the incident rate of dementia for those who completed the most sessions in speed training (at 5.9 percent) was 45 percent lower than the control (at 10.8 percent); 42 percent

lower than the incidence rate for those who did the most memory training (at 10.1 percent); and 39 percent lower than the incidence rate for those who did the most reasoning training (at 9.7 percent).

Q: Should this intervention be widely adopted? How does a 29% risk reduction compare to what we see from other health interventions that have become widely adopted?
A: Another finding in the newly published study is that the speed training intervention is actually more effective at reducing a health risk than some commonly prescribed drugs.

The published study creates context for the size of the risk reduction found from speed training, by comparing it to the effectiveness of taking blood pressure medicine in reducing the risk for major cardiovascular events (e.g, heart failure and stroke). They find the risk reduction of speed training for dementia is 2-4 times greater than the risk reduction of hypertension medicine for major cardiovascular events. This suggests that medical providers should pay attention to plasticity-based brain training as a new type of therapeutic that can deliver significant clinical benefits.

Q: How important is the social aspect of attending a class which was a part of the speed of processing training in this study?
A: All three training groups were assigned to on-site small classes that met twice a week for 10 weeks. Those who participated in booster training, also completed four additional classroom sessions in each of month 11 and month 35. This leads some to wonder how important the social activity was in the intervention. However, all three groups attended classes, but only one — speed training — had a significant reduction in dementia. This suggests that the social aspects of the classes are not themselves the cause of the effect.

Furthermore, a follow-on study to ACTIVE, funded by the NIH, was run to answer this and other questions. That 681-person study, the IHAMS Study, divided those engaged in speed training into three groups: one group took part in on-site small classes, a second group got started on-site and then completed subsequent sessions at home, and the third group initiated and did all training on their own at home. The IHAMS researchers found no significant difference among the three groups. Many subsequent studies have used speed training with participants training at home on their own computers, further indicating that it is the brain training that is responsible for the cognitive gains from speed training, not the social aspect of group training.

What About Other Approaches to Address Dementia?

Q: What about physical exercise, or the Mediterranean diet? I've heard those are good for the brain.
A**:** Physical exercise, particularly aerobic exercise, has been shown in randomized controlled trials to improve certain aspects of cognitive function, particularly executive function. However, no randomized controlled trial has yet evaluated whether these effects reduce the risk of dementia.

Diet and nutrition studies typically track what people report eating, and establish correlations between eating patterns and cognitive outcomes. Numerous large studies have now shown correlations between better diets (e.g., a Mediterranean diet) and better cognitive outcomes. However, without a randomized controlled trial, it's not possible to rigorously determine that eating the healthy diet leads to the better cognitive outcome, because it's possible that the kind of person who eats a healthy diet is already predisposed to have better brain health. So, while the evidence for the positive effects of physical exercise and a healthy diet are good, neither have yet been shown in a "gold standard" randomized controlled trial to reduce the risk of dementia.

Q: What about medications, like cholinesterase inhibitors?
A: Cholinesterase inhibitors (like Aricept, Reminyl, or Exelon) have been shown to slow the rate of decline of people who already have Alzheimer's disease. However, in a number of large-scale randomized controlled trials, they have failed to protect healthy people from going on to develop Alzheimer's disease.

Q: What about other cognitively stimulating activities, like crossword puzzles?
A: Crossword puzzles (and sudoku, and the like) are a great way to spend an afternoon. But no randomized controlled trials have ever shown that doing crossword puzzles improves cognitive function. Studies which track what kinds of sctivities people report they engage in have shown a correlation between engaging in cognitively stimulating activities and reduced risk of dementia. However, those studies have not been able to untangle cause and effect—perhaps people who aren't experiencing the earliest subtle signs of dementia are more likely to engage in cognitively stimulating activities. In fact, in recent years, researchers have been using crossword puzzles and similar brain games as an active control activity in studies of plasticity-based speed training, because, while widely believed to have benefit, they do not show significant benefit in randomized controlled trials.

The Science

Q: How can this unique type of brain training reduce the risk of dementia?
A: Neuroscientists now recognize that the brain is "plastic"—or capable of change—at any age. This ability to change—what scientists refer to as "brain plasticity"—is fundamental to how the brain perceives, thinks, remembers, and makes decisions. By building certain kinds of specific brain-training exercises based on the principles of brain plasticity, scientists can drive specific changes in the structure, function, and chemistry of the brain. Because dementia is a form of brain change itself, researchers have hypothesized that correctly-designed types of brain training could slow, halt or perhaps reverse the brain changes that lead to dementia.

Q: What changes in the brain as a result of plasticity-based brain training?
A: There are literally thousands of scientific papers in the field of brain plasticity documenting brain changes in human and animal models as a result of training programs. Researchers have

now specifically studied plasticity-based brain training (very similar to the speed training in the ACTIVE Study) in human and animal models of aging, and have shown that plasticity-based brain training drives changes at the molecular, cellular, and systems level of the brain.

At the molecular level, brain training has been shown to improve markers of neuro-modulatory chemical synthesis and neural wiring integrity. At the cellular level, speed training has been shown to revivify the number of interneurons that coordinate coherent global brain activity. And at the systems level, this type of training improves the speed and accuracy of neural information processing.

Brain plasticity research continues to reveal that the brain is an interactive organ where small positive or negative changes have wide-ranging effect across the entire organ. Small improvements or decrements in the basic building blocks of cognition — namely speed and accuracy — have an impact on not only higher cognitive function, but on virtually everything a person does.

In addition, by performing progressively challenging exercises that are attentionally demanding, filled with novelty, and laden with rewards, the brain's neuro-modulatory system — which gates learning and brain change—is heavily engaged in a manner that up-regulates a brain's natural production of acetylcholine, norepinephrine and dopamine. Key neuromodulators are down-regulated in advanced aging and are also down-regulated across various cognitive disorders and diseases. The up-regulation of neuromodulator facilitates the structural changes of plasticity and the overall health of the brain as a biological organ.

Q: How can just 10 to 18 hours of brain training completed in the first year or in the first three years of training show such significant effects 10 years later?
A: Plasticity-based brain training drives a very specific type of change in the brain, called "perceptual learning" (also called "implicit memory" or "non-declarative learning"). This kind of learning is like learning to ride a bicycle — it drives significant brain change that can last a very long time. A child can learn to ride a bike in 10 hours — a learning activity that requires a tremendous amount of brain rewiring across the visual, motor, and balance systems. And once the child has learned how to ride a bike, they will retain that brain-based skill for decades. Plasticity-based brain training (such as the speed training used in the ACTIVE study) appears to work in the same way, driving a long-lasting, important brain change in the course of 10-18 hours of learning. Visual processing speed is a fundamental cognitive skill, which most of us employ nearly every second of every waking day. Normal aging typically results in a slowing of processing speed in each decade after our early 20's. In addition, most cognitive diseases and disorders also involve a deficit in processing speed. Making a split-second improvement in such a fundamental skill has been shown to have widespread effects.

Q: What about the argument that brain training only improves your ability at the task trained?
A: A lot of brain games, at best, only improve performance at the task trained. Speed training - and plasticity-based brain training in general - is very different. People who did speed training

showed both an immediate and sustained (10-year) improvement in speed of processing compared to the control and to the other training arms. Importantly, in prior results published by the ACTIVE study, speed training also showed improvement in measures not directly tied to the task trained, including better performance in measures of depressive symptoms, confidence, health-related quality of life, the ability to live independently, the ability to quickly accomplish everyday tasks, and the ability to drive safely. In other studies, other similarly-constructed plasticity-based brain training exercises have shown better performance at standard measures of processing speed, attention, memory and executive function, as well as in additional real-world activities such as balance, gait, hearing, and everyday cognition.

Q: What about the idea that brain training cannot generalize?
A: In a sense, it all depends on what you mean by "generalization." The field of psychology has century-old theories about how the mind learns, which hold that learning one task will not generalize to another. Some believe this quite literally — for example, that learning to memorize a poem will not help you in learning to memorize the next poem. Others concede what most of us observe in daily life — that learning a skill often translates to related skills. For example, learning Latin may help in learning Italian. Psychologists refer to this as "near transfer." On the other hand, few of us would believe that learning Latin will substantially help you learn to ride a bicycle. That would be what psychologists call "far transfer."

True plasticity-based brain training exercises are quite unlike the cognitive training that came before them. Traditional cognitive training emphasizes compensatory strategies to make up for cognitive deficits, and that approach fails where the strategy has not been (or could not be) applied. For example, it's likely to be hard to come up with a mnemonic device to remember all the salient details of what your doctor tells you about your diagnosis, treatment, and prospects in a short doctor visit.

As discussed above, plasticity-based brain training starts with progressively challenging and improving the basic building blocks of cognition: processing speed and attention. By improving sensory speed and accuracy, it improves your ability to capture, accurately store, retrieve and manipulate information. As shown in studies, this leads to improvements in higher cognitive ability, such as memory, planning, decision-making and reasoning. It also drives the chemical and structural "plastic" changes to brains cells and systems that make the functional improvement possible.

Because timing and attention underlie all brain function, we see widespread transfers. Whether these are "near transfers" or "far transfers" is a question of how relevant you think the task trained is to the task improved. The brain clearly views speed and accuracy as highly relevant to many tasks that we perform, but it may not seem that way to everyone. For example, some may not think (at first) that improving brain speed should improve real world measures, such as depressive symptoms, confidence, health-related quality of life, the ability to live independently, the ability to quickly accomplish everyday tasks, the ability to drive safely, balance, gait, etc. However, if you ask what activities would be degraded by impaired speed of processing and attention, it is hard to name ones that would not.

While academicians will continue to debate the issues of near and far transfer, we can say, based on numerous studies, that speed of processing training generalizes to an ever-growing list of real world activities.

The Cognitive Training Program

Q: Who invented the speed of processing training used in the study?
A: The "speed training" used in the ACTIVE Study was originally developed by Dr. Karlene Ball and Dr. Daniel Roenker. In their original studies of the basic science of visual attention, they developed a computerized assessment tool to measure the "Useful Field of View" — the visual area over which information can be extracted at a brief glance without eye or head movements. In initial studies, they showed that this assessment was highly predictive of auto crashes in older adults. They also showed that the fundamental skill could be trained with an adaptive computerized program they called "speed training." Through a number of NIH-funded studies, Drs. Ball and Roenker (and their colleagues) showed that speed training generalized to improvements in a variety of real-world measures, including on-road driving safety and timed instrumental activities of daily living. These results led to the inclusion of speed training in the ACTIVE study.

Q: Where is speed training available now?
A: The inventors of speed training, Dr. Karlene Ball and Dr. Daniel Roenker, initially commercialized the product through a small business called Visual Awareness Inc. In 2007, as Posit Science began to build visual brain-training exercises, researchers from Posit Science met with Drs. Ball and Roenker to discuss collaborative opportunities. Those discussions led to the acquisition of exclusive rights to the speed training program by Posit Science. Researchers and developers at Posit Science then worked closely with Drs. Ball and Roenker to port speed training from the original MS-DOS platform to modern computing platforms and to make it more engaging. The updated version of speed training was then directly compared with the original version in a head-to-head clinical trial, and shown to drive equivalent improvements.

Q: Is speed training available to the public?
A: Yes. The speed training exercise used in the ACTIVE study has been updated, and is now available as an exercise called Double Decision. Double Decision is one of the exercises in BrainHQ, an online cognitive training program from Posit Science. The exercise is patented, and is not available on any other website or program. To access Double Decision (and 28 other exercises), people can subscribe to BrainHQ at www.BrainHQ.com. Subscriptions are US$8-14 per month, depending on length of subscription. BrainHQ subscriptions are also available without charge to the end user through many public libraries and military libraries, senior centers, retirement communities, and adult education programs. BrainHQ is also available as a free iPhone, iPad, or Android app or at www.BrainHQ.com, with limited daily access to exercises, which can be upgraded to general access with a subscription.

Q: What about other brain games? Do these results show that brain games, in general, can reduce the risk of dementia?
A: Absolutely not. In fact, the study shows the opposite. Three types of brain training designed by thought leaders in cognition and aging were tested – only one showed significant results in reducing dementia risk. The other two training programs have shown other benefits in studies of older adults, and that makes them quite different than most brain games and apps that are commercially available. The ACTIVE study shows that speed training, in particular, reduces the risk of dementia, and that other forms of cognitive training do not.

The first (and thus far only) systematic review of commercially-available brain games and apps targeting older adults was conducted by experts from five Alzheimer's research institutes and published earlier this year in the journal Neuropsychological Review. It found that 11 of the 18 apps reviewed had no studies showing any benefit. Of the other seven apps, it found only one program, BrainHQ, had multiple high-quality studies. There are more than 140 peer-reviewed papers on the benefits of exercises and assessments in BrainHQ.

There are many brain training programs now commercially available. Over the past two years, the FTC has been very actively enforcing existing consumer protection laws to stop brain game companies from making false advertisements and claims of efficacy.

Any brain game or brain-training program that wants to state that it reduces the risk of dementia must go through a clinical trial like ACTIVE — which took more than 10 years to complete and cost over $30 million — to establish a basis for that claim, as well as regulatory processes.

What's Next?

Q. What does the future look like for plasticity-based brain training?
A. No one knows. But these new results, as well as scores of other studies in clinical populations suggest that the right kind of brain training may emerge as a new type of therapeutic – especially in the area of previously intractable cognitive disorders.

Posit Science is currently in discussions with regulators about the most efficient path to bring such products to market. Posit Science is committed to making brain training ubiquitous and inexpensive or free for end users.