Hi Henry, and thank you for doing this AMA.

I saw the Edwards et al. paper earlier this month, and I have to admit I found it a bit implausible. Maybe you can help to dispel some of my doubts!

From the paper:

**Study design:** Up to 10 training sessions were delivered [to healthy, older adults] over 6 weeks with up to four sessions of booster training delivered at 11 months and a second set of up to four booster
sessions at 35 months. Outcome assessments were taken immediately after intervention and at intervals over 10 years.

Just from the start, I am a bit skeptical. Is there any precedence for something like this? It seems a lot to ask of any training program for it to be played a handful of times and then meaningfully impact dementia a decade later. Is there any precedence for something like this? To be honest, it seems a bit wild.

Results: A total of 260 cases of dementia were identified during the follow-up. Speed training resulted in reduced risk of dementia (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.50–0.998, P = .049) compared to control, but memory and reasoning training did not (HR 0.79, 95% CI 0.57–1.11, P = .177 and HR 0.79, 95% CI 0.56–1.10, P = .163, respectively).

So the speed training barely hit the P = 0.05 cutoff (and with the multiple tests being performed, I am surprised the cutoff was not more stringent).

What type of analysis was this - intent to treat or per protocol? It looks like the attrition rate in this trial was pretty large, and I am trying to understand how this may impact the results. Just looking at the results in Table 3, it looks like if just one more patient had presented with dementia then the result would have missed the P = 0.05 cutoff. Further it looks like the paper gives at least three definitions of dementia - psychometric criterion, the MMSE criterion, and the reported diagnosis of dementia criterion. To be clear, which definition was used for these results? How robust was the result for each of the different definitions?

Also, looking at the trial design, it seems the pre-specified endpoints don't match the results reported in the paper. It looks like the paper (please correct me if I am wrong) measures dementia with the mini-mental state examination. But the trial design specified different tools to measure changes in cognition and I don't see the results being reported for these measures in the main text.

The paper reports the hazard ratio for dementia at 10 years. I didn't see any additional data looking at the longitudinal impact over time. Is there a Kaplan-Meier curve showing the dementia free survival in patients across the different arms? A figure like that (for the ITT and PP populations) - although not pre-specified - would go a long way toward allaying my concerns. I just have a hard time imaging how the curves would separate though based on the data being reported.

Thanks!

SirT6

Great set of thoughtful questions!

Precedence: Most cognitive training studies are run with between 10 and 40 hours of training (and some, a bit more than that). How could 10-18 hours of cognitive training drive neurological changes that lead to a reduced incidence of dementia? I offer a few lines of thought:

(1) Neurological: Animal models of cognitive training show that speed training programs (adapted for rats, of course) and training periods lead to improvements in the overall neurological health of the brain, de Villars Sidani 2010 and Zhou 2015. A pilot study in people with MCI Lin 2016 showed preservation of the DMN compared to decline in controls. A reasonable interpretation of these neurological results is that the cognitive training contributes to brain/cognitive reserve, and in humans this manifests as a reduced risk of dementia.

(2) Behavioral: Previous results in ACTIVE and other RCTs have showed that 10-18 hours of speed training transfers to real-world measures of cognitive speed Edwards 2002, as well as slowing decline in IADLs Rebok 2014, health-related quality of life Wolinsky 2006, and depressive symptoms Wolinsky 2009. If we conceptualize dementia as a decline in cognitive function accompanied by a decline in everyday function, then an intervention that improves/maintains each of those components could
plausibly lower the risk of going on to dementia.

(3) Another way to think about it is this: my daughter learned to ride a bike recently. In about 10 hours of intensive practice, she drove significant brain plasticity across her sensory, cognitive, and motor systems, giving her an ability she did not have before. If she stopped riding her bike for several years, those brain changes would endure sufficiently such that (with some proficiency decline) she’d still be able to ride a bike. Speed training likely works the same way - through long-lasting non-declarative memory changes.

Analytic approach, p-value: The main analysis in the Edwards paper was an intent-to-treat analysis, meaning that all participants who met enrollment criteria were analyzed. A survival analysis takes into account the final resolution of all participants, including those who dropped out or were otherwise lost to follow-up. As you point out, the p-value is 0.049 - just under the threshold for significance. This is mainly driven by the statistical power, which in turn is driven by the number of observed cases of dementia in the population. When these results were originally presented at the Alzheimer’s Association International Conference in 2016, with a slightly broader definition of dementia yielded more observed cases, the p-value was 0.012. I think the investigators were happy to see the result was still significant with the tighter definition of dementia used in the published paper.

Multiple comparisons: There’s a lot of debate among statisticians about how to handle statistical corrections with multi-arm trials. Of course, if a research team has a two-arm trial (intervention vs control) and 20 outcome measures with no a priori primary outcome measure, multiple comparison correction is a good idea (and writing a better data analysis plan!). On the other hand, comparing each of three interventions to a single control with an a priori data analysis plan doesn’t create the same kind of false positive rate (assuming the question is not does any cognitive training work). Here’s a nice review (http://dx.doi.org/10.1016/S0140-6736(05)66461-6) of this exact issue.

Dementia Criteria: The paper defined dementia in the methods section (2.3) as any one of (1) significant decline neuropsychologically assessed cognitive function coupled with decline in IADL performance, (2) falling and staying below 22 on the MMSE, or (3) participant or family members states that the participant has received a diagnosis of Alzheimer’s from their doctor. Hope that clarifies your question.

KM Curve, Hazard Ratio: As you probably know, the hazard ratio incorporates all information over the observation window, and it’s a bit tricky to estimate any actual time-varying underlying effect. That being said, a KM curve would be a handy visual aid. That curve was presented at the AAIC 2016 meeting, and it looks like you might expect - the group separation becomes larger over time as more cases are observed. I can ask the ACTIVE study team to update that figure with the final analysis methods. Thanks!

I have heard some talk that video games are good for preventing dementia. How true is that?

Is dementia more genetic or behavioral?

lightninhopkins

(1) No one knows for sure if video games are good for preventing dementia because no one has run a randomized controlled trial of video games using dementia as an outcome measure.

That being said, as a scientist, I think it’s quite likely that different kinds of video games will have very different properties. For example, collaborators of ours have used computerized crossword puzzles as a control group Wolinsky 2013, and found that speed training was superior to that kind of game on measures of cognitive function. Other studies have shown some beneficial effects of action video games Green, 2003, but a specifically designed brain training program like speed training shows
greater cognitive benefits Belchior 2013.

(2) It’s both (sorry for the lame answer). There are absolutely specific genes that elevate risk for dementia, like ApoE4 or presenelin. Most of the identified genes increase risk, but do not mean a person is guaranteed to get dementia. And many people get dementia without genetic risk factors. That means that the environment (if I may rephrase your question) is crucial. What happens to our brains (e.g., head injury), what we do with our brains (e.g., live cognitively stimulating lives), where we live (e.g., exposure to environmental risks) all contribute to our individual risk of going on to dementia.

You’re stuck with your genetics, so the most important thing you can do is modify your lifestyle risks - don’t smoke, maintain an appropriate weight and blood pressure, eat a healthy diet (the Mediterranean diet or similar), and do things that improve your cognitive function, with a focus on processing speed.

My mom has presented some symptoms of dementia, she basically forgets stuff that happened minutes ago or asks the same question over and over, it’s not all the time she’s perfectly lucid 98% of the time. What are the most basic two or three things we can do to help her sooner rather than later on slowing the progression as much as possible?

Thanks!

SifuPepe

I’m sorry to hear about your Mom, and thanks for sharing your story. My grandfather went on to dementia when I was very young, and I remember the challenges that created for my family. I’m glad to hear your Mom has you looking out for her.

The first thing is to get a proper diagnosis. It’s possible your Mom has another health problem that is showing up like dementia, and that could be treated (like medications that are interacting badly).

The Alzheimer’s Association has a great set of resources for caregivers like you - they can answer questions, direct you to doctors, and help you understand what to expect and how to look after your Mom. You can find all of that here.

If she’s in the earliest stages of cognitive decline like this, in your personal life with her, I would suggest you help her develop/maintain a set of varied cognitively stimulating activities. Depending on her interests and her level of function, you might go for walks in new areas and talk about what you see and hear, play games together, sing/play/listen to music together. Of course, in my line of work, if she’s capable of using a computer or tablet, I’d also suggest she do speed training and related cognitive training on BrainHQ. You can message me if you’d like help with that.

I came across an interesting book called The End of Alzheimer’s by Dr. Dale Bredesen. He published several case studies reporting a reversal of cognitive decline with the optimization of nutrition, sleep, stress, physical exercise and brain training in patients with MCI or dementia Bredesen, 2014, Bredesen et al., 2016. You might take a look and decide if this could be helpful for your Mom.

Why did you decide to focus on dementia (as opposed to other neurological conditions)? Would it be easy to apply and test this brain training regime with other conditions such as Alzheimer’s, for example? Are there certain conditions where you think it would not be effective or helpful?

Thanks! Dementia runs on both sides of my family. So I’m fairly curious about this for selfish reasons! :)

kiri-kin-tha

The ACTIVE study researchers who published the recent study were originally focused on cognitive
enhancement - could cognitive training improve cognitive function and generalize to real-life improvements. As they saw that cognitive training improved those measures (published in a series of previous papers), they decided to ask a natural next question - did cognitive training also protect against the onset of dementia (the current results). In this way, the dementia analysis was a natural outgrowth of the existing results showing benefits to cognition and real-world function.

Other researchers have used our cognitive training exercises (including speed training) in a number of other neurological and psychiatric conditions. Just over the past year, there have been studies in multiple sclerosis Charvet 2017, chemobrain Bray 2016, and bipolar disorder Lewandowski 2017 for example. You can find our shared database of clinical trials in brain training here. Just note that this database includes the trial literature on brain training more generally, which means that if you only want clinical trials using BrainHQ exercises, then just check that the ‘Posit Science’ tab is highlighted in yellow on the left-hand side. The other tabs available will allow you the filter the database by the condition or outcomes or training programs you’re interested in reading about.

As a scientist, it’s my viewpoint that cognitive training exercises based on the principles of brain plasticity that improve the underlying speed and accuracy of neural information processing will likely have broad brain health benefits in a number of neurological and psychiatric conditions. I think that there are a variety of different ways that a brain can be driven into a poor information processing state (like brain injury, genetic factors, acquired diseases, and aging); however once in that state, regardless of the cause, improving speed and accuracy will help. Of course, in each clinical condition it’s essential to do a proper clinical trial to see if that’s the case!

My own interest in this field comes from my work as a neuroscientist - I did my PhD at UCSF in the lab of Dr. Michael Merzenich, where we studied brain plasticity. As that research (from many scientists) made it clear that intensive brain training programs could rewire the brain, it eventually became obvious that it was imperative to take this basic science and make it an applied science.

OK, some questions.
1) My reading of the paper finds one group's results that stick out. The people who received speed training AND chose to do an extra 8 hours, or so, had a much lower dementia conversion rate than the other subgroups. In fact, were it not for this subgroup, the entire paper would have very little to report. However, they were 1 in a thousand different from other groups (5.9% conversion vs ~10% average) in 220 subjects. Yes - that is 13 out of 220 instead of 22...but the p value is through the roof.

1a) I am hoping you can comment on the potential for selection bias to be present in this group (they self-selected to perform more training).

1b) Why the specificity? The speed training (extra hours) group shows the effect, but the reasoning and memory do not?

1c) Can you comment on the return on investment in time? These subjects spent something like 15-18 hours performing one computer game. How do you envision this could possibly translate into a reduced dementia conversion over the following 10 years? Is this some type of keystone to the causes of dementia? If it is reproducible, what possible mechanisms are being harnessed?

2) Any followups being planned (or underway) by the authors or other colleagues of BrainHQ?

3) A horse may weigh 1000 pounds, a duck about 2. Would you rather fight 500 duck-sized horses or one horse-sized duck?

JohnShaft

(1) Yes, the sub-group analysis supports the idea that the additional booster training - at the end of the first and third year - is important to the protective effects. That makes intuitive sense to me, because
some amount of ongoing training seems likely to be required to drive a long-lasting effect.

(1a) The booster group didn't self-select to perform more training. The way the protocol worked is that participants were randomized into the four groups, and each treatment group was asked to do 10 one-hour training sessions. At the end of the initial treatment period, participants who had completed at least 8 sessions were then further randomized into booster/non-booster groups. So a person may have been eligible for booster and perhaps even wanted to do booster, but randomized into non-booster and so did not perform booster sessions.

I think it's unlikely that the small number of people not eligible for booster randomization (because they did not complete 8 initial hours) contributed to the dementia risk reduction results, because that occurred in all three treatment arms, and the booster arms for memory and reasoning did not show a dementia risk reduction, which they should have if high-dementia risk early-stage dropouts contributed to the effect.

(1b) Speed training operates through procedural learning, whereas memory and reasoning training operate through declarative learning (strategy learning). These types of learning are known to operate on distinct brain systems. It's like the difference between learning how to ride a bike (procedural) and learning the capitals of Europe (declarative). Furthermore, I think that speed of processing is key to much of cognitive function (at the behavioral level) and brain health (at the biological level).

(1c) Well, one view of the return on investment in time was that this was the most valuable 15-18 hours of time these study participants ever spent, in that it significantly reduced their risk of dementia :-) That's a good ROI.

One way to think about the results is at the behavioral level: speed training improved cognitive performance and reduced the risk of functional decline as measured by instrumental activities of daily living, health-related quality of life, and depressive symptoms. So naturally, it reduced the incidence of dementia.

Another way to think about the results is through the concept of cognitive reserve: we already know that certain groups of people, as a result of their life experience, show lower incidence of dementia - people with high education levels, for example. These results are conceptualized as defining a "cognitive reserve" where cognitive engagement and education contribute to the reserve. So one way to think about speed training is that it contributes to cognitive reserve - more immediately and more quickly than a lifetime of education, but perhaps in the same way.

And finally, you can think about the results at the neurological health level. Animal models of cognitive training show that speed training programs (adapted for rats, of course) and training periods lead to improvements in the overall neurological health of the brain, de Villlars Sidani 2010 and Zhou 2015. A pilot study in people with MCI Lin 2016 showed preservation of the DMN compared to decline in controls. A reasonable interpretation of these neurological results is that the cognitive training contributes to directly to the health of the brain as a biological organ, and in humans this manifests as a reduced risk of dementia.

(2) There are quite a few studies of BrainHQ in progress - our internal database of research collaborators show more than 100 studies in progress. Specifically with regard to dementia prevention, for example, there are active trials in mild cognitive impairment going on. Dr. Edwards is specifically planning a follow-up to the current ACTIVE student results (cross your fingers for a favorable grant review, and ongoing funding of NIH research by Congress).

(3) 500 duck-sized horses are likely to exhibit emergent distributive cognitive network properties, which could make them exceedingly tricky; so I would in principle choose the horse-sized duck. Now a horse-sized crow might be an entirely different issue, as crows are extremely smart, so thanks for sticking with the traditional duck.
If I search around on reddit enough someone must have Kobayashi Maru’d this, so I’d actually start there.

Hi, thanks for this AMA. In your opinion how much does the overuse of technology to do everyday cognitive tasks effect future generations ability to develop dementia. Do you see a potential rise in dementia cases in society due to this?

**Wagamaga**

It’s a very interesting question. There’s a viewpoint that as we outsource cognitive function to our devices (and AIs), that we increase our risk for cognitive decline and dementia because we aren’t using our brain as much. A countervailing viewpoint is that we free our brain from cognitive drudgery and can engage in more cognitive stimulating activity, which could enhance our cognitive function and lower our risk of dementia.

I think the answer will be both (sorry!). By way of analogy, if we look a food abundance in the developed world, we see that it has positive consequences - we have come close (not close enough, but still close) to eliminating hunger and diseases of nutritional deprivation; but at the same time, we have negative consequences - like type II diabetes.

Technology that offloads cognitive function may have similar results on our brain function - people who use it well will have longer, enriched, and cognitively stimulating lives; and people who don’t may end up cognitively worse off.

Dr. Mahncke,

Thanks for doing this AMA. I have a few (related) questions:

1) Cognitive training has been the target of more than a little bit of criticism over the last years, possibly related to exaggerated claims of efficacy. How would you characterize the degree of improvement in cognitive function that is possible through cognitive training, *among the average high-functioning younger-middle aged adult*?

2) "Far Transfer" has been the gold standard. On its face, far transfer of a working memory task to, say, inhibitory or attentional functions, is very cool. I don’t mean to detract from any of the far transfer findings, however, isn’t far transfer a misnomer? Any challenging working memory task requires engagement of inhibitory and attentional function. Isn't it all really just near transfer, but the best training paradigms are those that engage the most integrated systems/functions during training, to facilitate the greatest degree of near transfer?

3) Although I am personally unimpressed by claims of cognitive training effects in healthy community-residing adults, I believe it has phenomenal potential among certain populations, including children, aging adults, and across a wide spectrum of disordered behavior (e.g., ADHD, addiction) and neurological insults (e.g., TBI). In your opinion, in which areas/samples/fields is the most exciting, promising, cognitive training research going on?

4) For the researchers reading this, particularly those less-than-knowledgeable about the methodology involved in cognitive training experiments, what are the critical factors? For instance, I think most CT researchers would agree that providing sufficiently challenging tasks/activities, usually through adaptive-difficulty methods is a critical factor. What else?

5) Are you hiring neuroscientists who can't bear to write another grant? Kidding! (mostly. but not. help.)

Seriously, it's very cool that you're doing this. I'm sure you've heard this before but among scientists
who take issue with some commercialized cognitive training, I have frequently heard BrainHQ cited as an exception to their concerns. Good on you guys!

TestPilotBeta

(1) We think that higher cognitive function in midlife is related to dementia risk in later life (here’s an example study. So it seems likely to me that improving cognitive function in midlife is a good investment in your future, just like improving physical function (through exercise) and (for that matter) saving for your retirement.

Our internal analyses of people doing BrainHQ exercises have shown - to my surprise - that the magnitude of within-task improvement is about equal for younger people and older people, suggesting that cognitive training is beneficial for both groups.

When I thought about it more, that made sense to me. If we think about physical exercise, younger people and older people can both improve their physical fitness, and no one would recommend waiting until you’re 65 to start a physical exercise program.

Doing cognitive training clinical trials in younger people can be challenging. Many of the standard neuropsychological measures exhibit ceiling effects in younger people, and since healthy younger people do not typically have functional impairment it’s not obvious what measures of real-world functional or cognitive transfer would be appropriate.

Dr. Fred Wolinsky at the University of Iowa did a very nice study explicitly comparing people aged 50-64 to those 65 and older, and saw equivalent cognitive gains in both groups.

(2) That’s a great point because I agree with it completely :-). I think that the focus on far transfer is at best a semantic issue and at worst an active impediment to scientific progress. People conflate far transfer with real-world function in a confusing and unhelpful way.

It’s absolutely important to show that cognitive training causes real-world results - improvements in directly observed function, patient self-report of cognitive function, health related quality of life, instrumental activities of daily living, depressive symptoms - all of which were shown in ACTIVE and other studies to be improved by speed training and related plasticity-based brain training exercises.

But it just doesn’t matter from a clinical perspective if speed training improves an unrelated cognitive ability. Critics of ACTIVE have said that because speed training did not improve reasoning abilities (for example), then speed training does not meet the bar for efficacy. But that ignores all of the broad measures of transfer mentioned above.

In my view, all transfer is near transfer, and as scientists we would be well served to view the pattern of improvements on outcome measures - neuropsychological measures of cognition, real-world measures, patient/informant report - as assessments of neural overlap. It may be surprising to find that speed training lowers driving crash risk Ball 2010, but rather than thinking of that as far transfer, we should think of that as a real-world outcome measure and teaching us that the neural pathways improved by speed training are directly (“nearly”) related to those used by driving.

(3) Outside of cognitive improvement in healthy populations and dementia risk reduction, I think the most interesting areas of cognitive training research are around.

(a) Mechanisms of action: how does cognitive training change brain structure and function to achieve its results? Dr. Yankee Lin has done a very nice study Lin 2016 in people with Mild Cognitive Impairment showing that speed training helps stabilize decline in measures of functional connectivity in the brain. I’d like to see more brain imaging research like this, particularly focused on these kinds of measures and also measures of neural health like white matter integrity and neuromodulatory function.

(b) Field trials: how can we put cognitive training to work across systems of care? We worked with the
American Automobile Association (AAA) to offer speed training (called Drivesharp there) to their older insured drivers, based on ACTIVE study data showing reduced car crashes Ball 2010 and together showed that people completing 10 hours of training reduced their crash related claims by ~25%. I'm very interested in extending work from academic randomized controlled trials into real-world evaluations like this, so we can move science from pure research to practice that benefits ordinary people.

(4) I think that brain training exercises focused on speed and accuracy, that are adaptive, with stimuli designed to generalize to real-world sensory environments, that appropriate engage neuromodulatory systems have a high likelihood of showing cognitive and real-world benefits.

Speed and accuracy are fundamental to virtually all cognitive and real-world function. Cognitive slowing is a core symptom of virtually every brain based disorder, including normal aging, and targeting core neural information processing in this way is essential. I don’t believe that cognitive activity with no speed/accuracy component (e.g., crossword puzzles) is likely to be broadly beneficial.

Any cognitive training exercise needs to rapidly adapt to an individual's day-to-day and moment-to-moment performance. Exercises that are too hard or too easy do not drive neural change.

When we design the stimuli for cognitive training exercises, we work to efficiently span the natural statistics of real-world stimuli. For example, in auditory exercises, we consider the characteristics of human speech (the most important auditory stimulus for cognitive function), and for visual exercises, we consider naturalistic issues like clutter, contrast, and pop-out; all with the goal of driving generalization of neural performance improvements instead of stimulus specific improvements.

Finally, exercises should consider how attention, reward, and novelty are delivered with the goal of engaging cholinergic, noradrenergic, and dopaminergic systems, the health of all of which contributes to overall brain and cognitive function.

That’s the secret sauce, please use this information to benefit humanity.

(5) DM me and let’s stay in touch.

As a musician - does music training improve brain function? Does learning how to play music have mental health benefits, for younger and/or older people?

Thanks!

Phyrexian_Possum

There is a lot of evidence that music training changes brain structure and function. For example, the brain devotes more resources to regions of the brain that control the fingers of the left hand in string players than in non-musicians Elbert 1995, probably because of the intense careful finger movements in the left hand required to play a string instrument. Professional keyboard players show differences in the thickness of their grey matter compared to amateur musicians or non-musicians Gaser 2003.

Research suggests that musicians have better cognitive function than non-musicians, particularly with cognitive function that depends on auditory function - like verbal memory (memory for speech). There are always questions about where the music training causes the improved cognitive function, or if kids with better cognitive function choose/are more successful at pursuing music. Here’s a nice review arguing that the music training itself causes the cognitive function improvement. And playing a musical instrument is associated with reduced dementia risk in a twin study Ballbag 2014.

In my view, the core aspects of music training - intense procedural learning through practice, focused attention, the need for quick and accurate sensory and motor performance - are all the core
components of a good brain training exercise.

My own Mom inherited a harpsichord and after retirement became a dedicated player, with weekly lessons and practice. I think her practice and the associated focus on speed, accuracy, and attention all have contributed to her cognitive vitality. It's also really nice to visit and hear all the wonderful harpsichord music :-)

Are there any brain training exercises you could suggest for those with ADHD?

Breaking_the_BAD

See my answer here

Can this help with children/adults with ADHD?

meowkatswithak

My colleague Dr. Jyoti Mishra who was a postdoc here a Posit Science and is now on the faculty at UCSD conducted a study with children with ADHD using a novel set of cognitive training exercises focused on attention enhancement and distractor suppression. She showed that these exercises improved the study’s primary outcome measure, the ADHD rating scale, compared to a video game active control; and also improved measures of cognitive function (a response inhibition measure and Stroop interference).

These exercises are still under development and testing, and aren’t yet available as part of BrainHQ. For a person broadly interested in improving attention, I would suggest the exercises in the brain speed and attention suites in BrainHQ.