The basic and applied science of brain training

Posit Science

March 2021

brainHQ
from Posit Science

Contents

- Overview of Posit Science and BrainHQ
- Core efficacy data in normal aging
- Data in clinical indications

Introduction to BrainHQ

Please watch Maria Shriver discuss BrainHQ on the Today Show:

https://vimeo.com/328521490/dd26121ea2

BrainHQ overview

BrainHQ is an online brain-training system that represents the culmination of 50 years of research in neurological science and brain plasticity.

It was designed by an international team of neuroscientists, led by Michael Merzenich—a UCSF professor, member of the National Academy of Sciences, inventor of the cochlear implant, and Kavli Prize laureate.

BrainHQ uses a neurobiologically informed therapeutic approach, leveraging the brain's ability to actively re-wire itself to improve the speed and accuracy of information processing, strengthen neuromodulatory function, and improve cognitive and functional performance.

The science makes us unique in this field

Basic Science

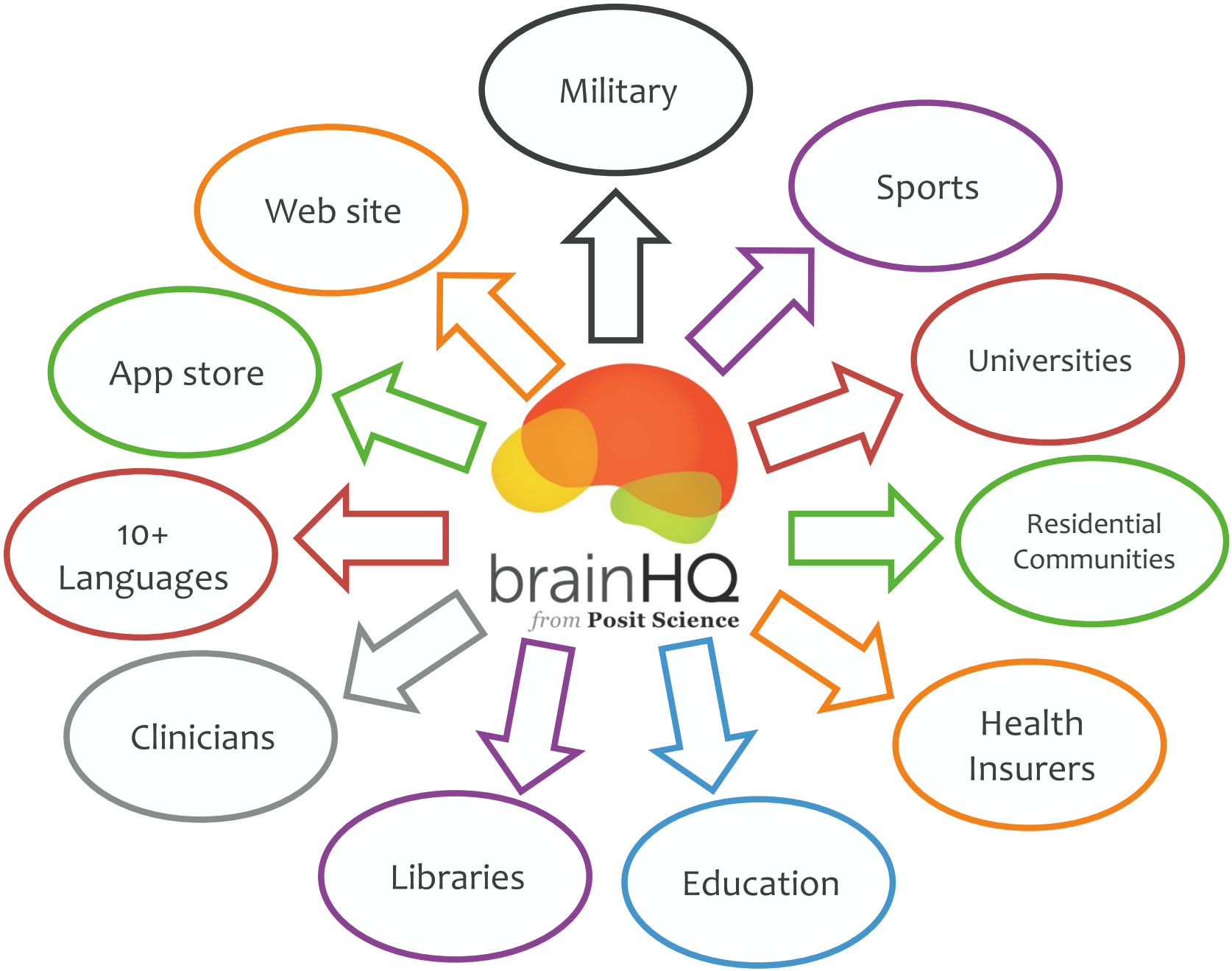
- Dr. Michael Merzenich, UCSF

- National Academy of Sciences, Institute of Medicine
- Co-Inventor of the cochlear implant
- World leader in brain plasticity science
- 10 PhD FTEs

Clinical Evidence

- 233 publications from RCTs
  - 72 in healthy aging
  - 161 across 20 clinical indications
  - All with BrainHQ exercises
  - Most from independent academic investigators with grant-funded studies
- 380+ ongoing RCTs (from planning through analysis)
- Neurocognitive, functional, self-report, and brain imaging measures
- Exercises are protected by 14 US and 11 non-US patents on brain training
- No other company or group with this evidence base

Broad Reach Makes BrainHQ Unique



External validation makes us unique

- Independent researchers Shah et al (2017) published the first systematic review behind commercially available brain-training programs in healthy aging.
- Identified 18 products
  - 11 companies had no clinical trials or empirical evidence at all
  - Only BrainHQ was identified as having multiple high-quality RCTs
- BrainHQ has a firm commitment to validation before commercialization.

"Multiple peer-reviewed articles evaluating Posit Science programs have fulfilled the gold standard for clinical trials…"

Latest Statement by NIH makes us unique

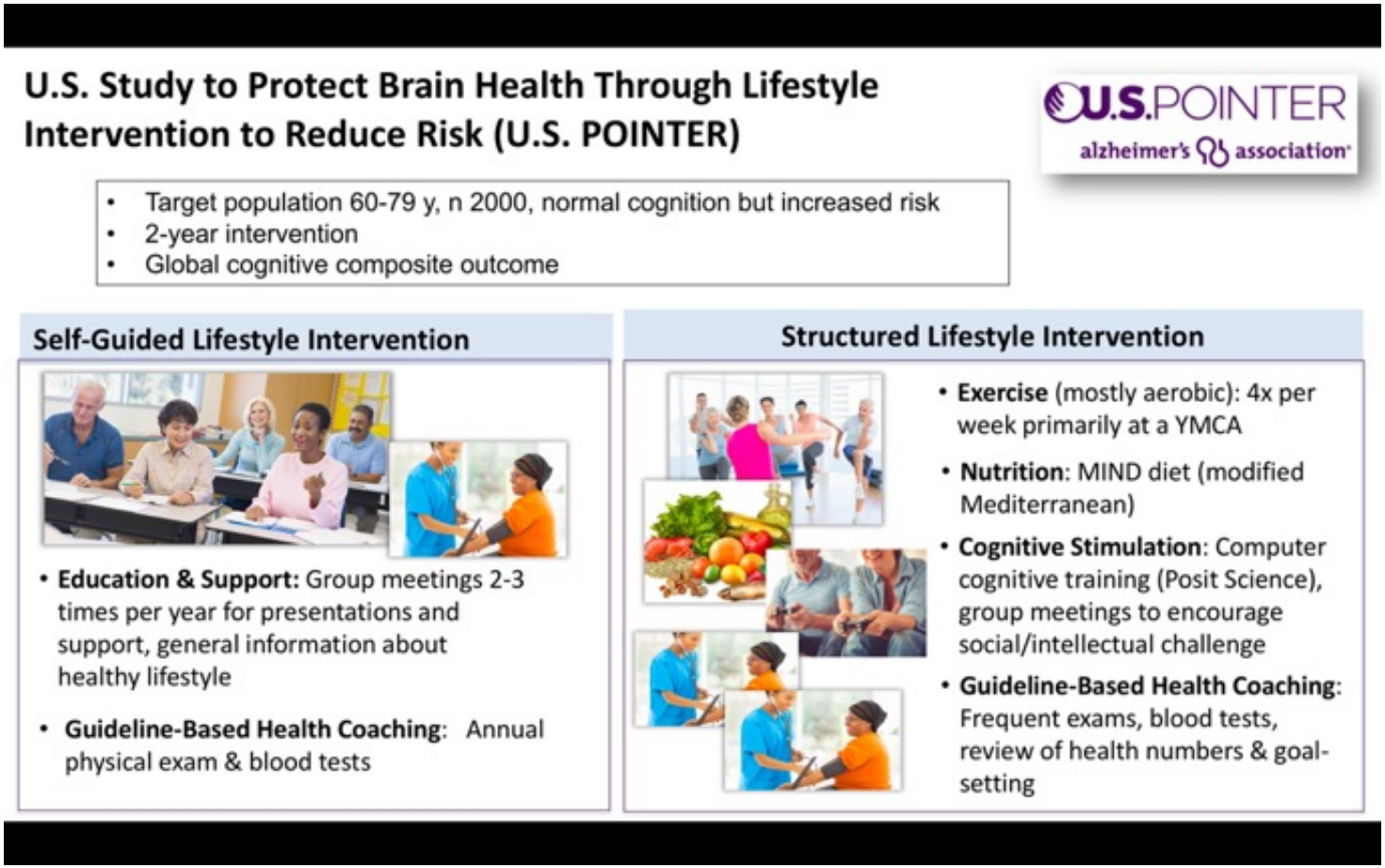
"Posit Science training drives improvements that are significantly better than other types of cognitive exercise."

NIH NIA website

Commercial reach makes us unique

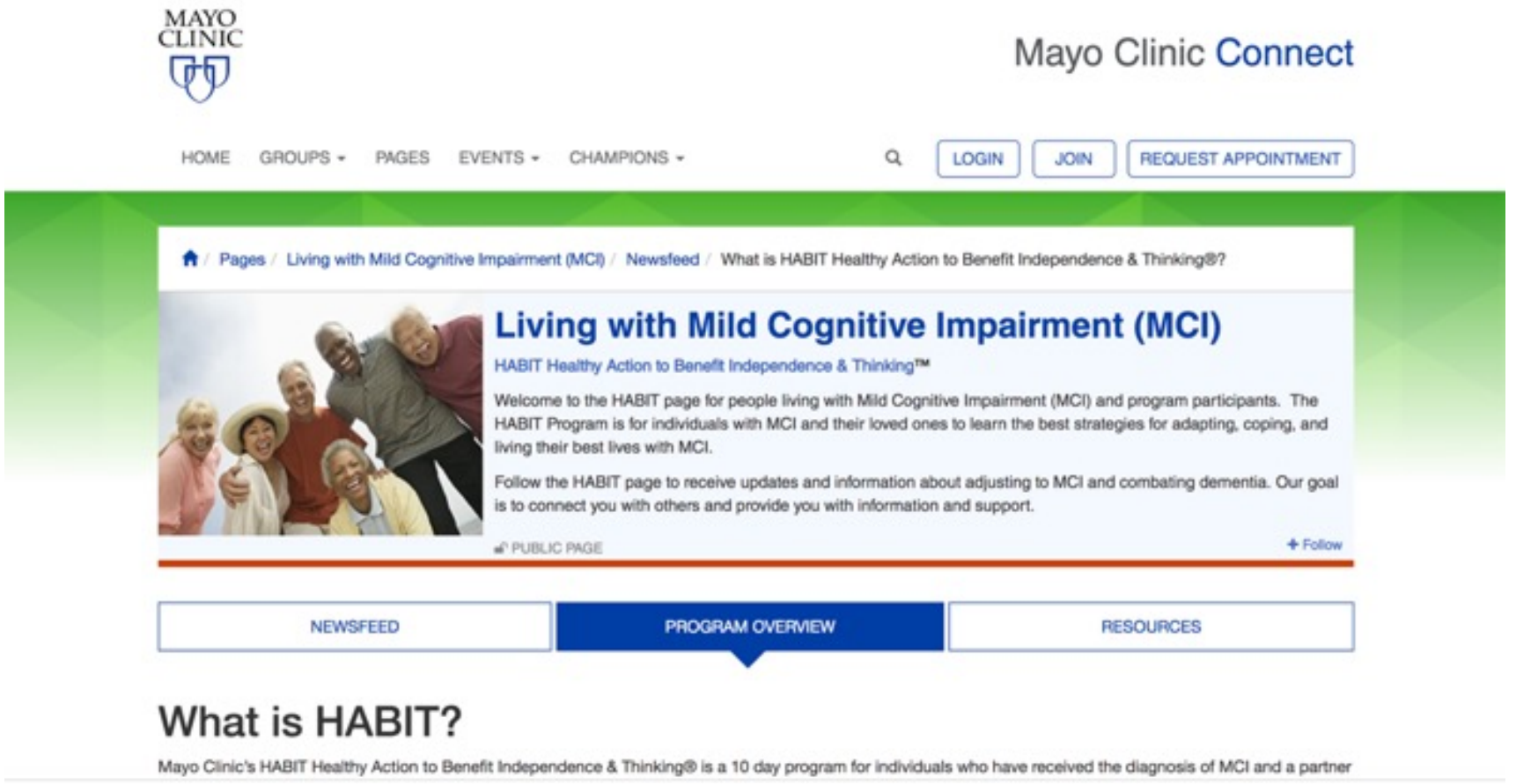
- BrainHQ is available on popular web browsers, iOS and Android tablets and smartphones
- In English and across 10 languages
- To millions:
  - BrainHQ is available to millions of Medicare Advantage members through multiple health insurance plans
  - BrainHQ is available to library members across the country
  - BrainHQ is available to all military personnel through DEMCO
  - BrainHQ is available to clinician groups, mental health facilities, senior centers, retirement communities, rehab centers, hospitals, and adult education centers.

Selection by the Alzheimer's Association for a large behavioral trial (US POINTER) makes us unique



ALSO: Selected for the Latin America, Australia, Ireland, Netherlands, and Japan versions of the FINGER studies and by lead investigators of all three large dementia trials recently funded by NIH

Selection by the Mayo Clinic for its HABIT brain wellness program makes us unique



ALSO: Selected as brain training component of

- **Cleveland Clinic Brain Wellness program**
- **UCLA/Buck Institute MEND Protocol**
- **Dr. Dale Bredesen's RECODE Protocol**

Brain plasticity – a new approach to improving memory and cognitive function

"Brain Plasticity"

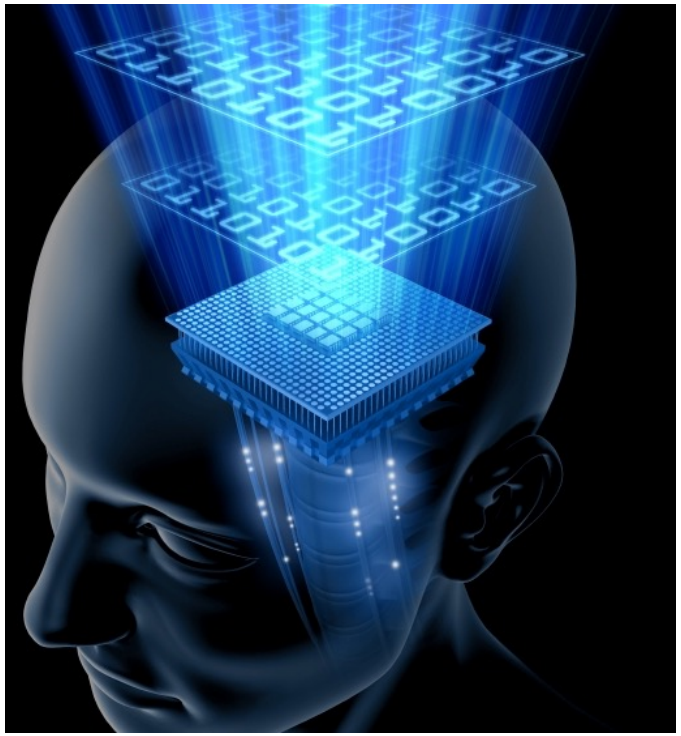
The brain's ability to adaptively reorganize itself throughout life

Brain Plasticity is the biological correlate of learning and memory, and includes:

- Structural changes
- Functional changes
- Chemical changes

Scientists' understanding of how the brain works has undergone an enormous change

The old view:
The brain is "hard-wired"



The new view:
The brain is "soft-wired"

Merzenich 2013 ("Soft-Wired")

Training produces brain-wide restoration in animals

Our studies began by comparing the brains of older versus younger animals. With simple forms of training, the negative changes attributable to aging were restored. What's rejuvenated?

1. PHYSICAL BRAIN

1. Myelination (insulation on brain 'wires')
2. Dendritic and axonal arbor branching
3. Inhibitory neuron numbers, morphologies
4. 'Mini-column' size, neuronal constituencies, boundaries
5. Representational orderliness

2. BRAIN CHEMISTRY

1. Trophic factor (BDNF, EGF) expression
2. Receptors & subunit constituencies
3. Modulatory neurotransmitter expression
4. Neurotransmitter transporters

3. BRAIN DEFENSE

1. Blood-brain barrier integrity
2. Microglia-based immune response
3. Norepinephrine expression

4. NUTRITIVE SUPPORT

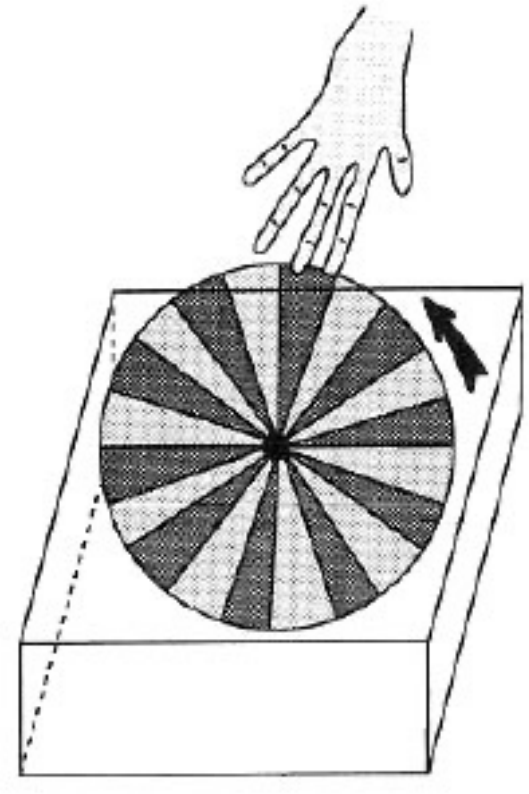
1. Astroglial cell branching, endfeet
2. Reactive hyperemia
3. Small-vessel elaboration

5. BRAIN FUNCTION

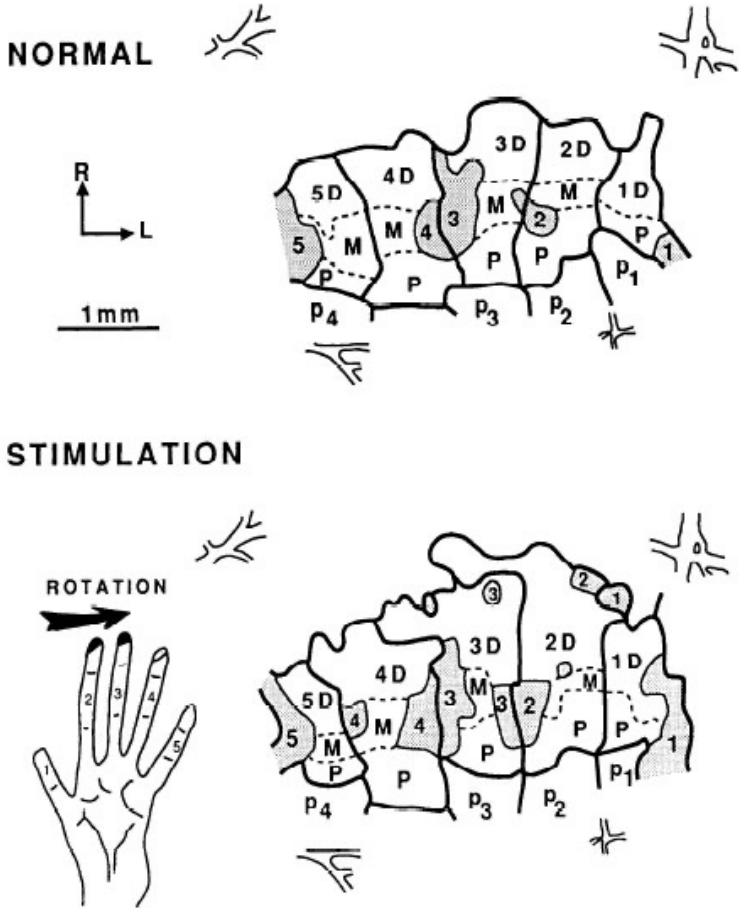
1. Processing speed, sequential processing
2. Response power, reliability
3. Complex-feature representation
4. System connectivity feed-forward power

de Villers-Sidani et al, 2010, PNAS 107:13900; Zhou et al, 2011, J Neurosci 31:5625;de Villers-Sidani & Merzenich,Prog Brain Res 191:119; Mishra, et al, 2014 Neuron; Lin, Zhou et al, 2016, PNAS

Training changes cortical maps



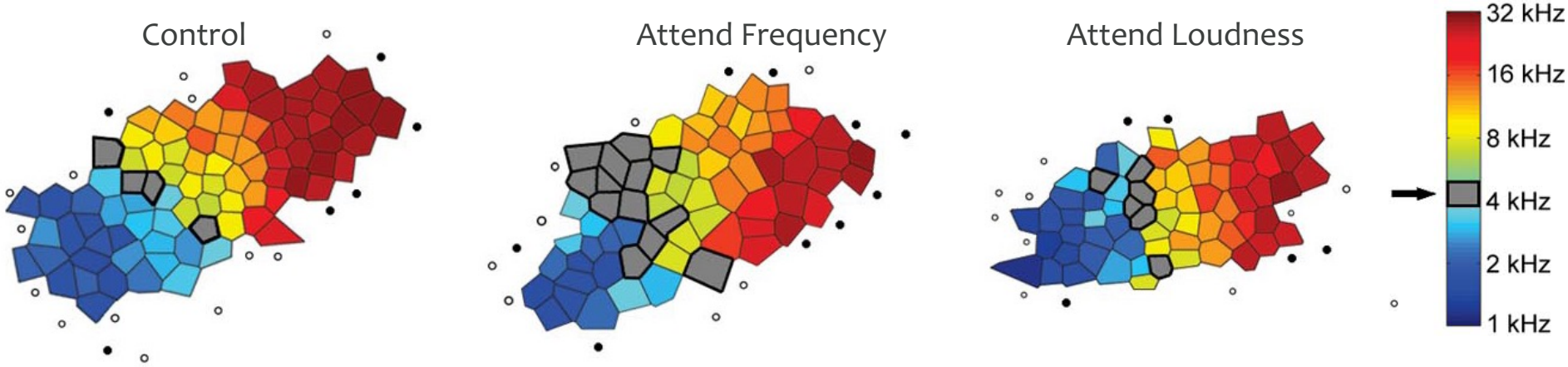
Monkeys trained to apply the tips of their second and third fingers to a rotating disc…



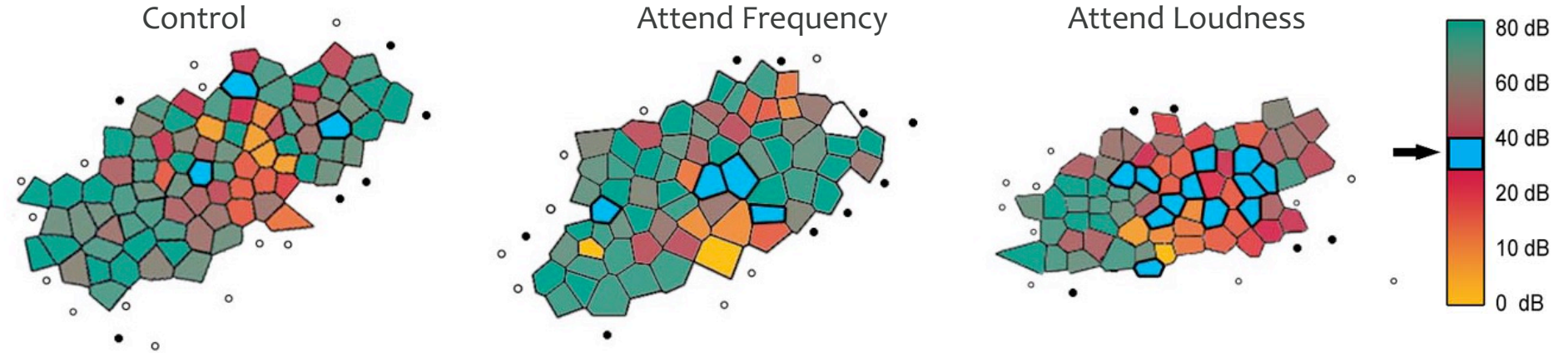
… show substantially enlarged cortical representations of those digits tips

Specific changes in brain function can be driven by specific task demands

Only rats attending to frequency changes in an auditory stimulus stream with frequency and loudness variation show expansion of the representation of the target frequency…

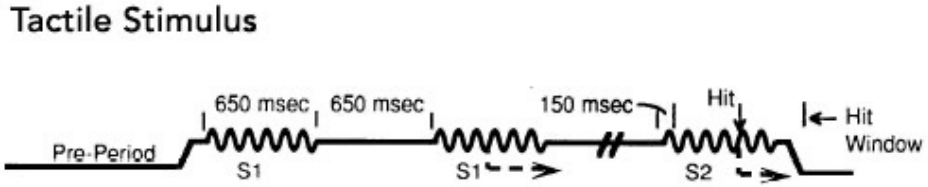


…while only rats attending to loudness changes in show expansion of the representation of the target loudness

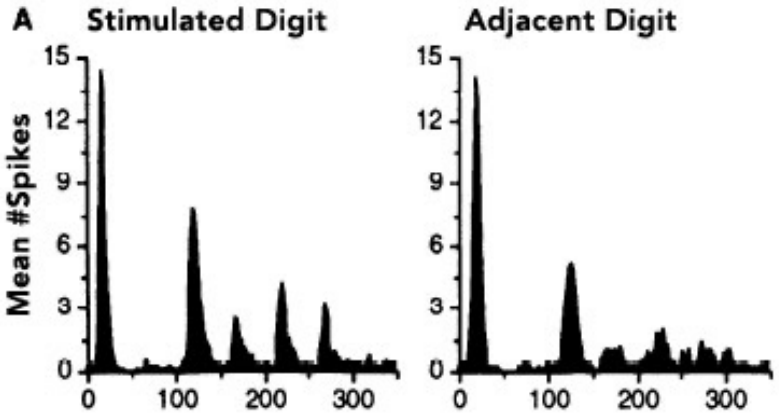


Polley 2006 (J Neurosci)

Changes in information processing



Monkeys trained to discriminate flutter vibration frequency…

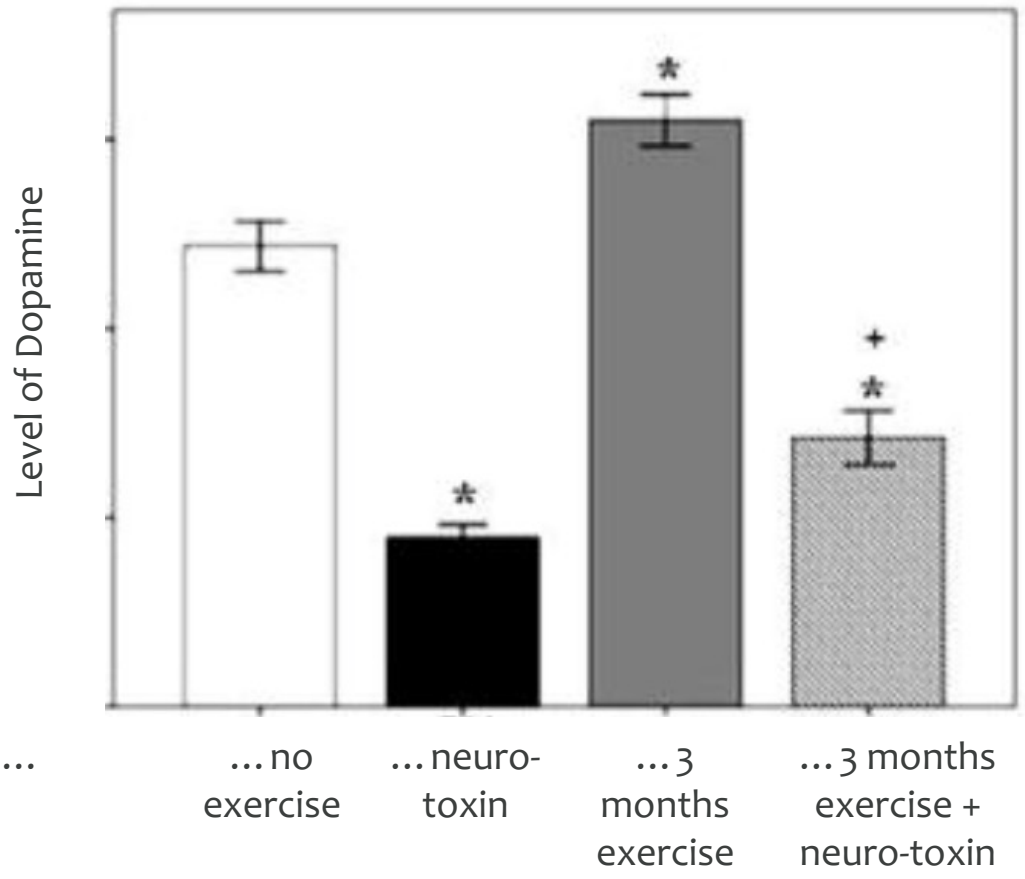


… show increased stimulus representational fidelity on the trained digit

Recanzone 1992 (J Neurophysiol)

Brain plasticity can change neuromodulatory function as well

Rats who exercise intensively (with associated environmental richness and social contact) show higher levels of dopamine, and show protection against damage to dopaminergic systems



Gerecke 2010 (Brain Res)

Brain training improves brain health in older animal models

young

old

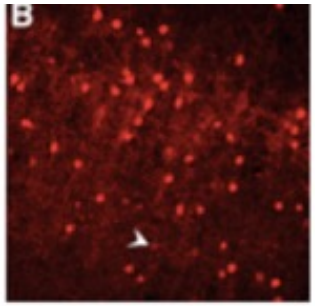
old, trained

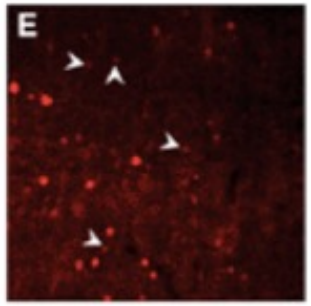
Neural Precision

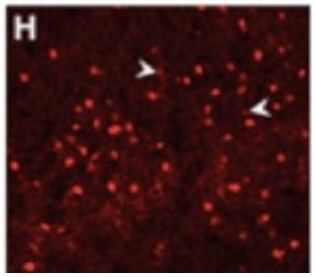
Bandwidth maps, higher/ redder is less precise

Neural Coordination

Parvalbumin positive inhibitory interneurons

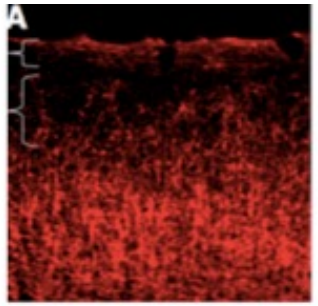


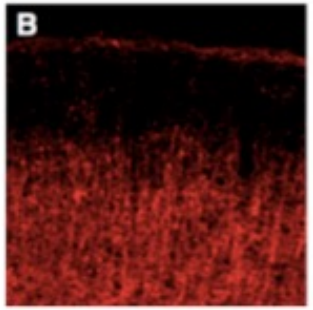


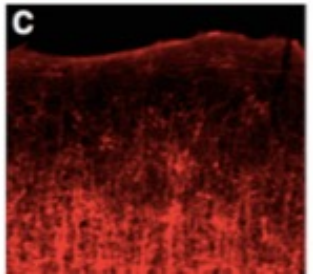


Neural Wiring

Myelin basic protein positive oligodendrocytes







De Villars-Sidani 2010 (PNAS)

What is the mechanism of action?

- Intensive training of perceptual speed & accuracy re-refines noisy cortical information processing through brain plasticity...
- …which allows improved brain activation (response strength, response coherence) in response to sensory stimulation…
- …which drives stronger engagement of cognitive systems

All of which drive structural, chemical, and functional changes and the molecular, cellular, and systems level leading to a healthier and more resilient brain

These observations lead to a set of principles governing the design of efficacious brain training

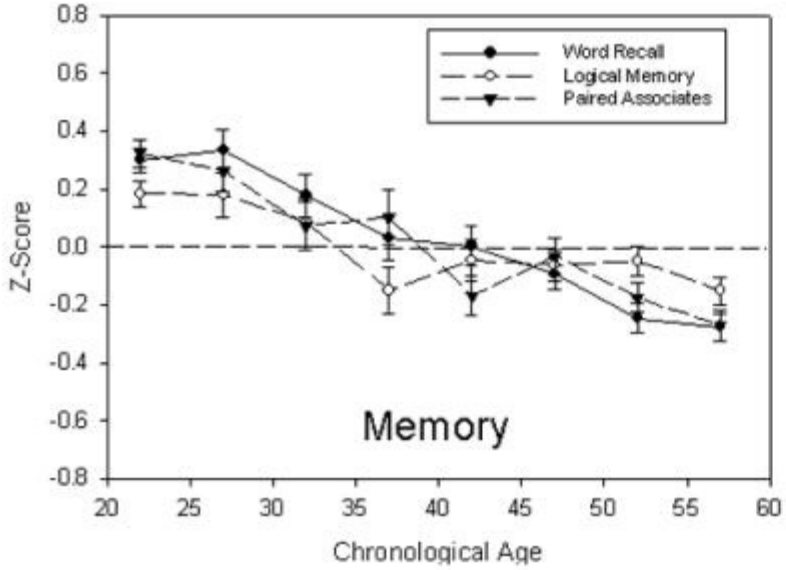
Speed	Employ increasingly brief stimuli and increasingly rapid sequences
Accuracy	Employ increasingly challenging discriminations
Adaptivity	Constantly adapt to individual user's performance – maintain challenge with a high level of success (70-90%)
Generalizability	Begin training with emphasized stimuli to strongly drive brain plasticity Complete training with statistically naturalistic stimuli to drive real-world generalization Efficiently span relevant real-world stimuli
Engagement	Frequently and repetitively engage attention (cholinergic), reward (dopaminergic), and novelty (noradrenegic) systems

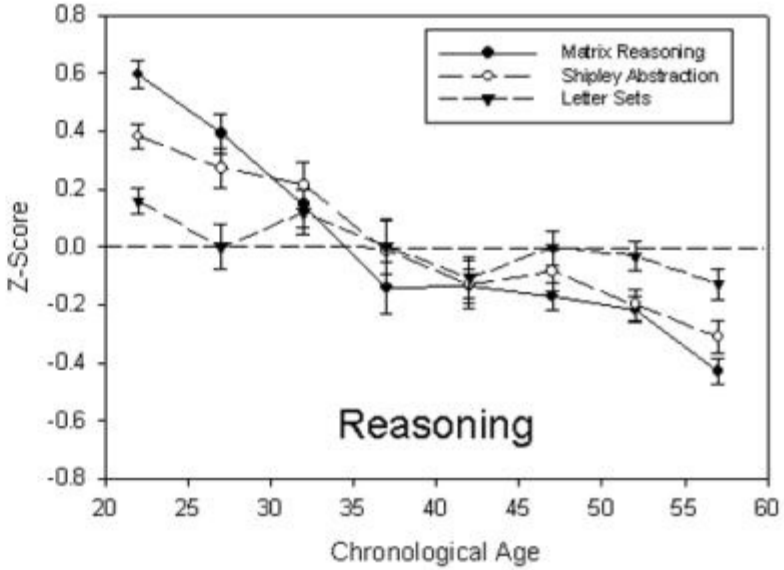
What can we do with this technology?

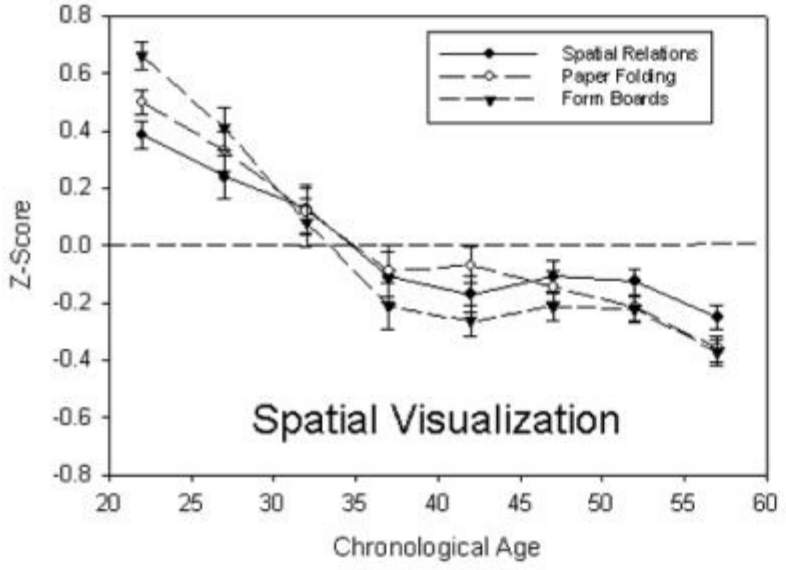
- Re-refine cortical maps
- Improve speed and accuracy of information processing
- Strengthen neuromodulatory function
- Improve brain health

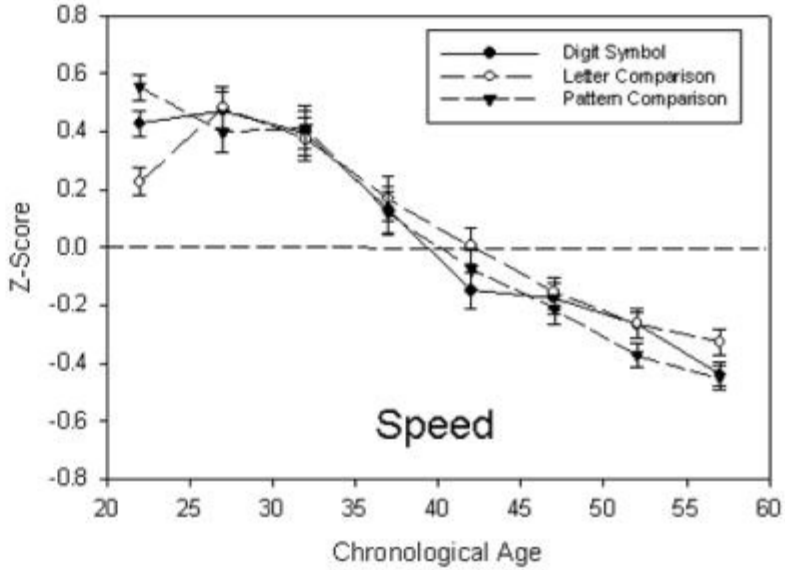
This could be helpful for many people

Cognitive function peaks in our 20s, then declines









Salthouse 2010, Neurobiol. Aging

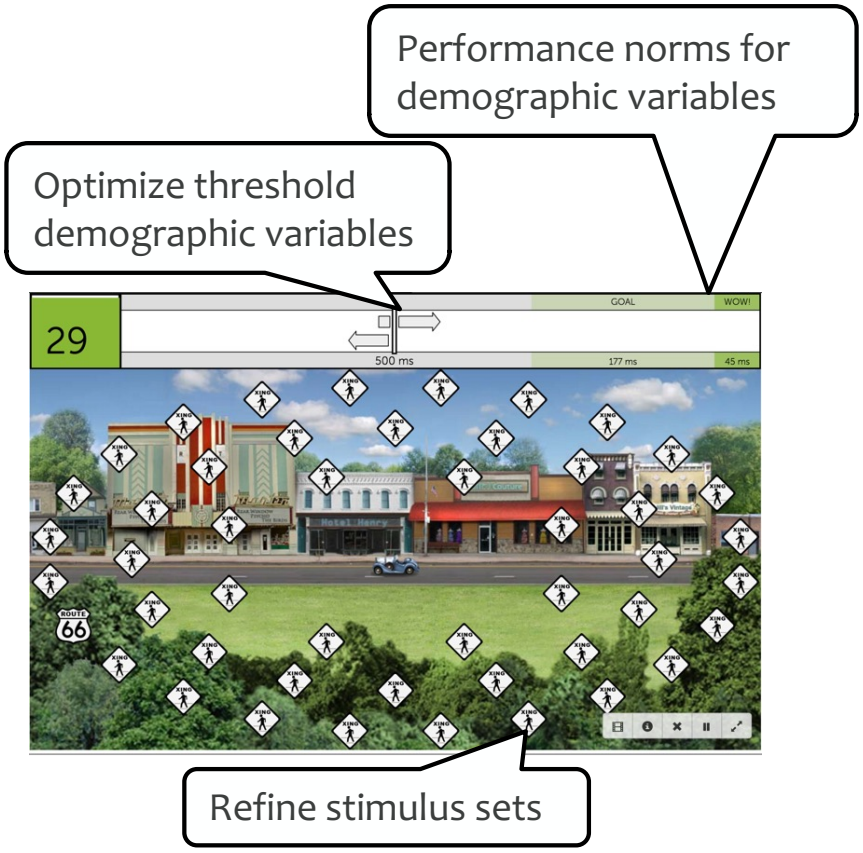
A plasticity-based brain training program for people

Built on AWS, HIPAA and SOC-2 compliant, available on web, iOS, Android

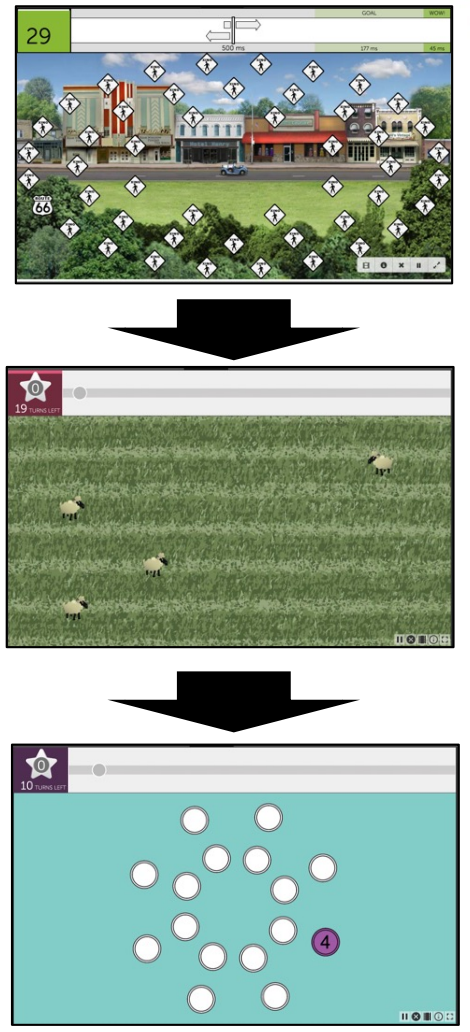
Principles of brain plasticity guide the exercises…

- Speed
- Accuracy
- Adaptivity
- Generalization
- Engagement

…exercises are normed and refined on an increasingly large user population…



…adaptive algorithms sequence exercises and stimulus sets



Using BrainHQ in a clinical context

- Exercises can be grouped in a specific course designed for a specific clinical condition
- Users can be configured to permit access only to a specific course, to ensure they perform the precise exercises designed for their clinical condition; and do not have access to other exercises or individually selected exercises
- Clinicians can remotely supervise usage, progress, and performance of patients through a secure web-based group portal
- Security policies, procedures, and technical implementations for HIPAA compliance, and support our recent SOC-2 certification

Training restored *neurological integrity* and *behavioral performance*

...and generalized to everyday life.

Contents

- Overview of Posit Science and BrainHQ
- Core efficacy data in normal aging
- Data in clinical indications

Strong evidence for BrainHQ in aging

Brain Function

- Change in N1 EEG measure related to visual stimulus processing (Berry 2010)
- Change in P3b and N2pc EEG measures related to attention (O'Brien 2013)
- Change in fMRI measures of attention processing (Scalf 2007, Lin 2020)
- Change in DTI measures of white matter integrity (Strenziok 2014)
- Change in functional connectivity measures (Lin 2017, Lin 2020, Chen 2020)

Cognitive Function

- Improvement in memory measures (Smith 2009)
- Improvement in processing speed measures (Ball 2002, Anderson 2013)
- Improvement on attention measures (Van Vleet 2016)
- Improvement in executive function measures (Wolinsky 2013, Lin 2020)
- Improvement on a global outcome (mMMSE) (Gooding 2015)

Dozens of Studies Show Transfer

Not just getting better at the trained tasks

A total of 33 RCTs show that BrainHQ generalizes to everyday life, including:

- **48%** decrease in at-fault motor vehicle collisions (Ball et al., 2010)
- Slower decline in instrumental activities of daily living over 10 years (Rebok et al., 2014, Ball et al., 2002, Edwards et al., 2002, Ball et al., 2007, Edwards et al., 2005)
- Improved skill acquisition (Van Vleet., 2016)
- **68%** greater likelihood of improved locus of control 5 years post training (Wolinsky et al., 2010)
- **38%** reduction in the risk of global decline in health-related quality of life 2 years post training and a **26%** reduction at 5 years with an associated **0.8%** predicted reduction in the 5-year mortality rate (Wolinsky et al., 2006, Wolinsky et al., 2006)
- **38%** reduction in the onset of age-related depression (Wolinsky et al., 2009)
- **30%** reduction in depressive symptoms (Wolinsky et al., 2009)
- **$243** decease in health care payer-related costs one year post training and $143 two years post (Wolinsky et al., 2009)
- Improved hearing in noisy situations (Anderson, 2013)
- A dose-dependent decreased incidence of dementia of **29-48%** a decade after an intensive training epoch of 10-18 hours, respectively (Edwards et al., 2017).
- Better workplace safety, cognitive efficiency, and decision making in the workplace (Hamilton et al., 2019, Walters et al., 2019, Miller et al., 2019)

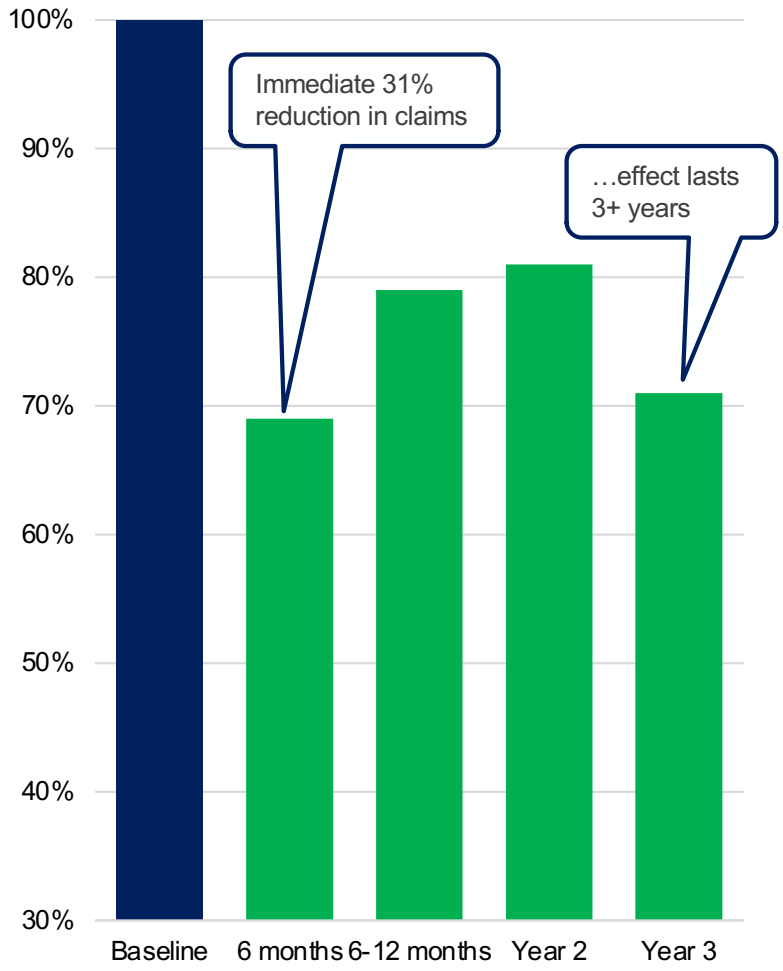
Field study demonstrating real-world performance

Completed in 2011 with >7000 drivers

- Insurer X offered BrainHQ at no cost to adults
- Drivers receive up to 10% insurance discount for completing
- Insurer used direct mail, email, magazine content to raise awareness of offer to members
- Insurer collected real-world crash-related claims data
- BrainHQ collected individual performance and completion data

Real-World Results

Crash-Related Claims
(Normalized to Baseline Incidence)



Main goals of the IMPACT study

Improvement in ***M***emory with ***A***daptive ***P***lasticity-based ***C***ognitive ***T***raining

- Replicate results from pilot studies with a multi-site randomized controlled trial conducted by independent academic investigators
- Appropriate statistical power to demonstrate between group significance
- Assess multiple objective standardized measures of memory and quantitative participant-reported outcome (PRO) measures
- Two-arm RCT of BrainHQ vs active control (DVD-based educational instruction)

Strengths of the IMPACT study design

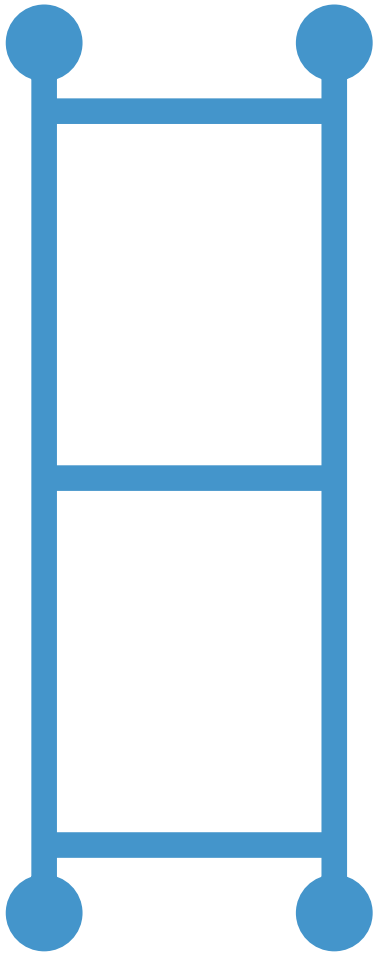
- **Independent Investigators:** Study principal investigators (Glenn Smith, Mayo Clinic; Elizabeth Zelinski, USC) and data review committee (Kristine Yaffe, UCSF; Ron Ruff, Stanford; Rob Kennison; CSU LA) independent from Posit Science
- **Multi-Site:** Results not specific/peculiar to a single site, results from different sites can be compared for consistency
- **Randomized:** Participants recruited, then complete baseline assessment, then randomized into intervention and active control groups – ensuring that between group differences are the result of the intervention
- **Active Control:** Control group engages in equivalent number of hours of cognitive stimulation – ensuring that between group differences can be attributed to the specific properties of the intervention
- **Double-Blind:** People conducting assessments do not know which group participants were assigned to (minimizing bias); participants do not know that which group is hypothesized to be more effective (minimizing placebo effects) because the consent form describes the study as comparing two different forms of cognitive stimulation
- ***A Priori* Statistical Analysis Plan:** Primary outcome measure and time point defined in advance – preserving statistical power and preventing p-hacking
- **Intent-to-Treat Analysis:** Linear mixed models used to account for missing data due to drop-outs – ensuring that results are not affected by characteristics of participants not completing study

IMPACT used a set of assessments designed to evaluate generalization of benefits

Assessments Very Unlike Training

Generalization

Assessments Very Similar to Training



Assessments

Participant-Reported Outcome
- CSRQ-25

Neuropsychological
- RBANS (primary outcome measure)
- RAVLT
- RBMT
- WMS-III digits backwards, letter-number sequencing

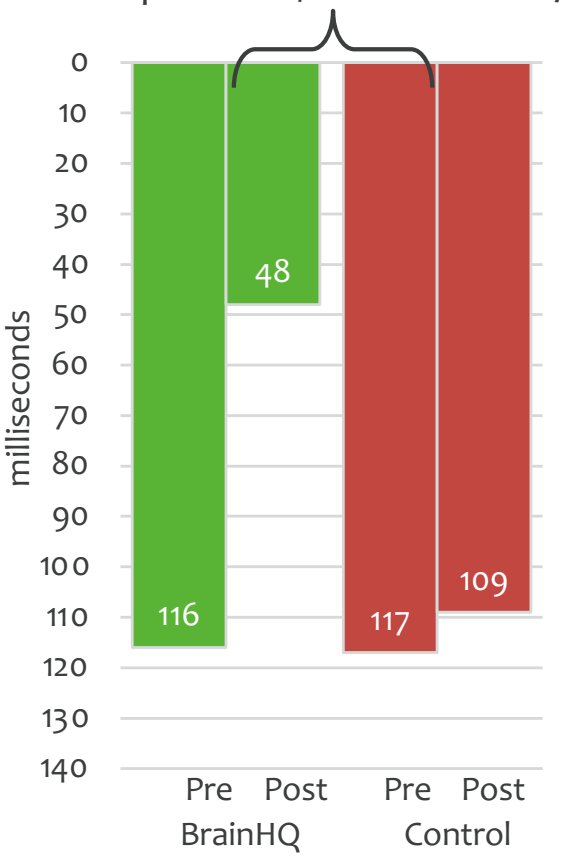
Exercise-Based
- Processing speed

BrainHQ improvements occur across multiple levels of generalization

Processing Speed

High or Low
(lower is better)

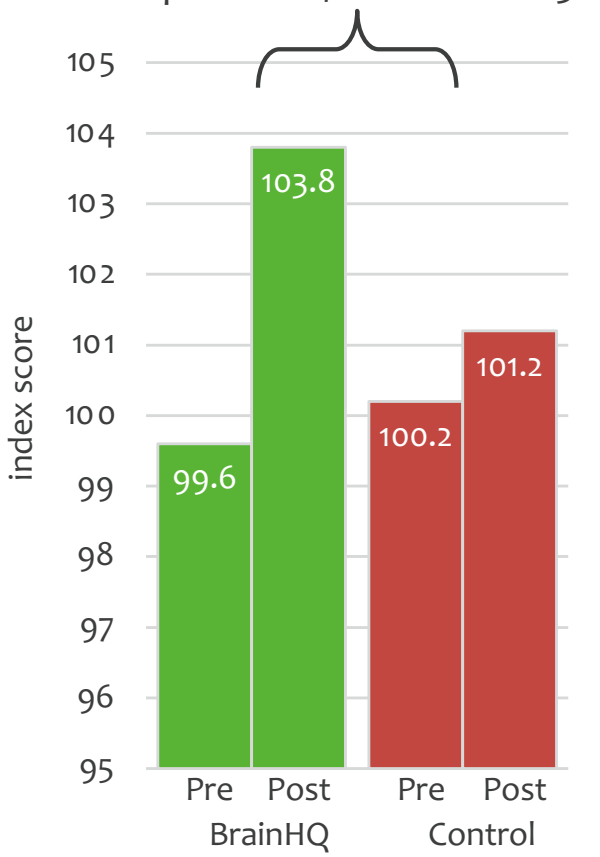
p < 0.001 / effect size 0.87



Overall Memory

RAVLT, RBMT, Digits Backwards, LNS
(higher is better)

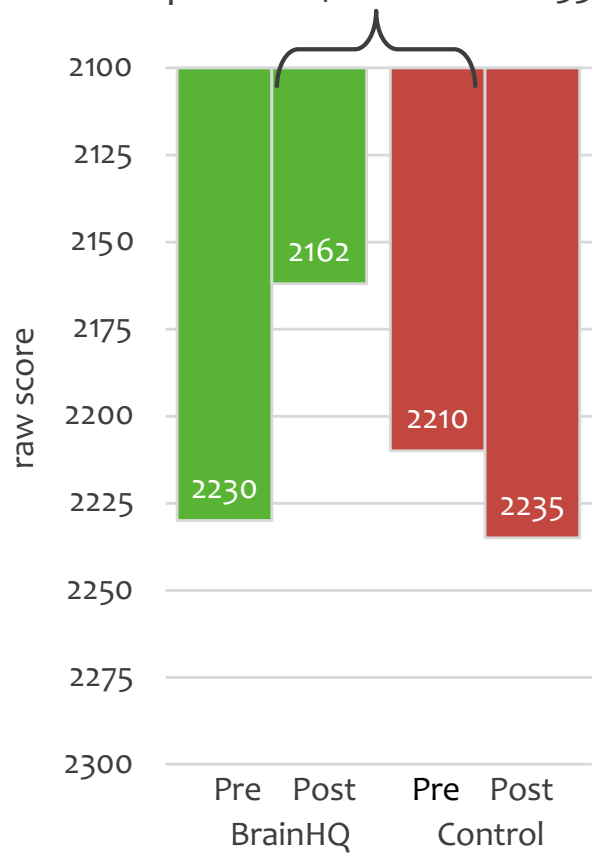
p = 0.002 / effect size 0.30



Everyday Cognition

CSRQ-25 (PRO)
(lower is better)

p = 0.001 / effect size 0.33



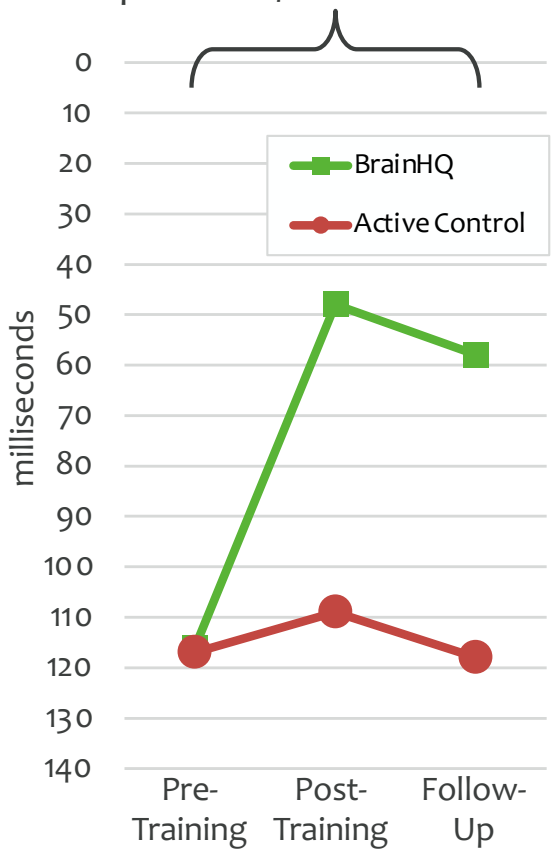
Smith 2009 (JAGS)

Benefits persist after training is complete, but begin to wear off

Processing Speed

High or Low
(lower is better)

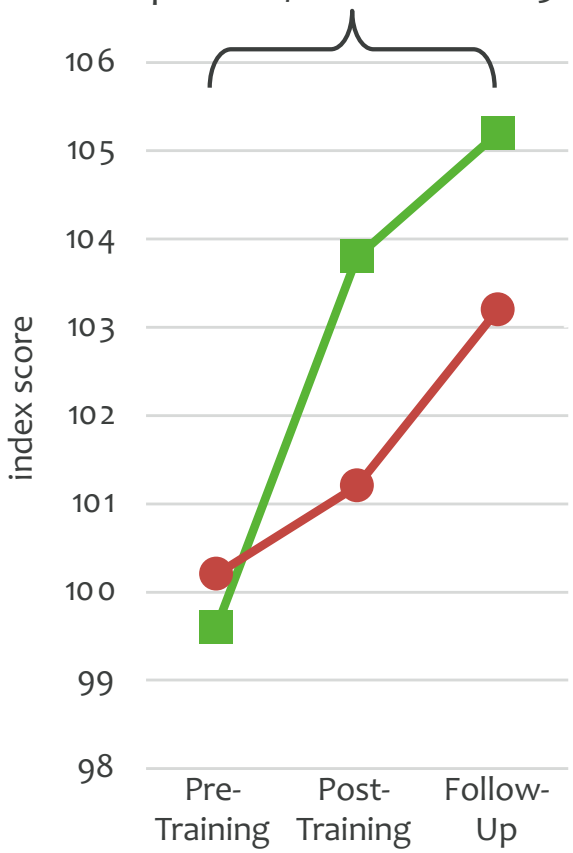
p < 0.001 / effect size 0.80



Overall Memory

RAVLT, RBMT, Digits Backwards, LNS
(higher is better)

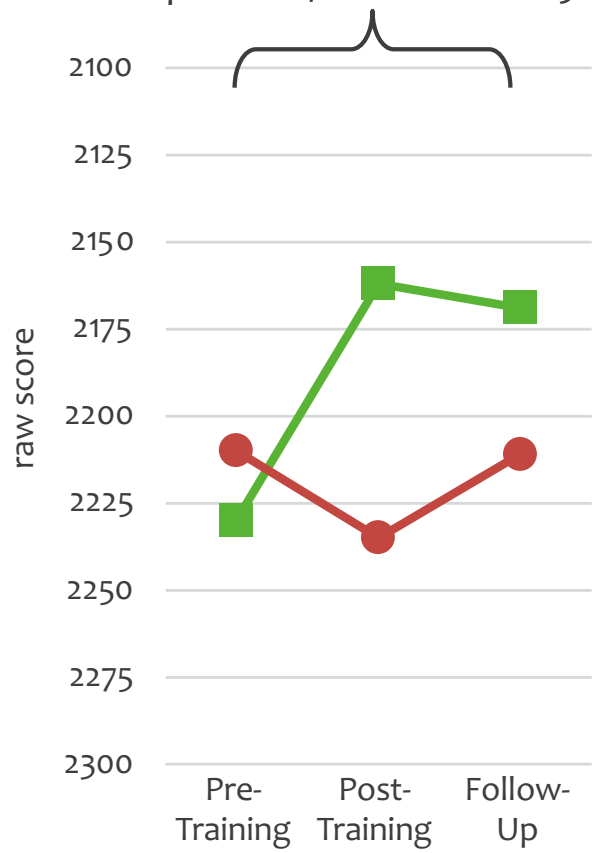
p = 0.01 / effect size 0.25



Everyday Cognition

CSRQ-25 (PRO)
(lower is better)

p = 0.06 / effect size 0.19



Main goals of the ACTIVE study

Advanced ***C***ognitive ***T***raining for the ***I***ndependent and ***V***ital ***E***lderly

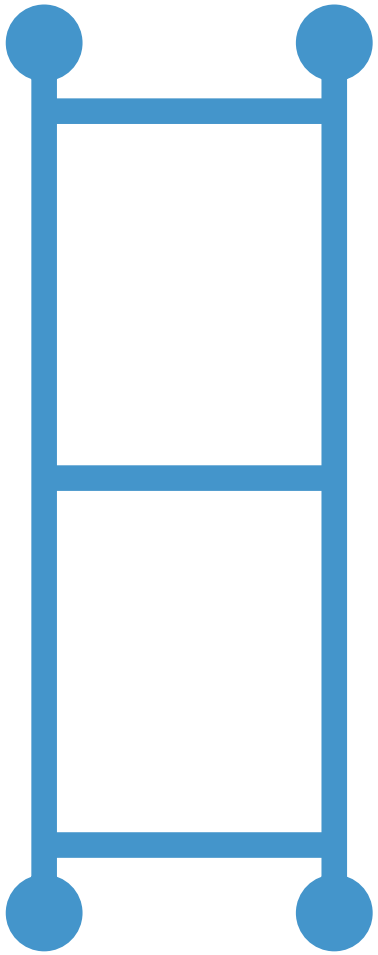
- Replicate results from pilot studies of three cognitive training programs with a large-scale multi-site study
  - Speed training (computerized, now BrainHQ)
  - Memory training (strategy-based, instructional)
  - Reasoning training (strategy-based, instructional)
- Four-arm RCT with three treatment arms vs treatment-as-usual control group
- Assess benefits in trained domains and generalization to functional and real-world measures
- Measure persistence of gains after completion of training
- Organized and funded by NIH

ACTIVE used a set of assessments designed to evaluate generalization of benefits

Assessments Very Unlike Training

Generalization

Assessments Very Similar to Training



Assessments

Real-World
- SF-36 Health-Related Quality of Life
- On-Road Car Crashes

Functional
- MDS-Home Care Instrumental Activities of Daily Life
- Timed Instrumental Activities of Daily Life

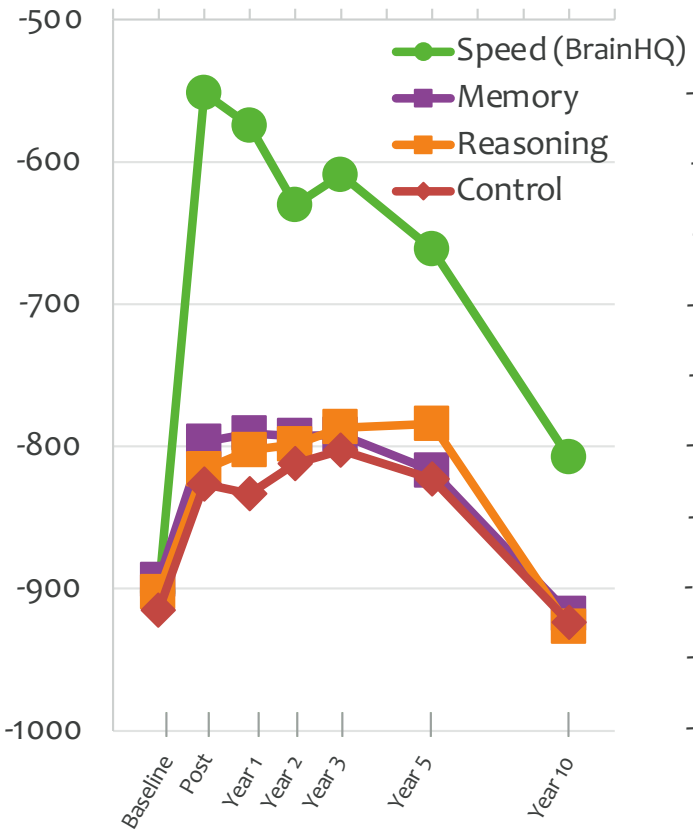
Exercise-Based
- Processing speed, Memory, Reasoning

Ten-year results from the ACTIVE study have shown functional and real-world benefits

ACTIVE Study: 2,832 healthy older participants, NIH-funded, multi-site RCT, 10 year longitudinal trial
Compared BrainHQ speed training vs memory training vs reasoning training vs control

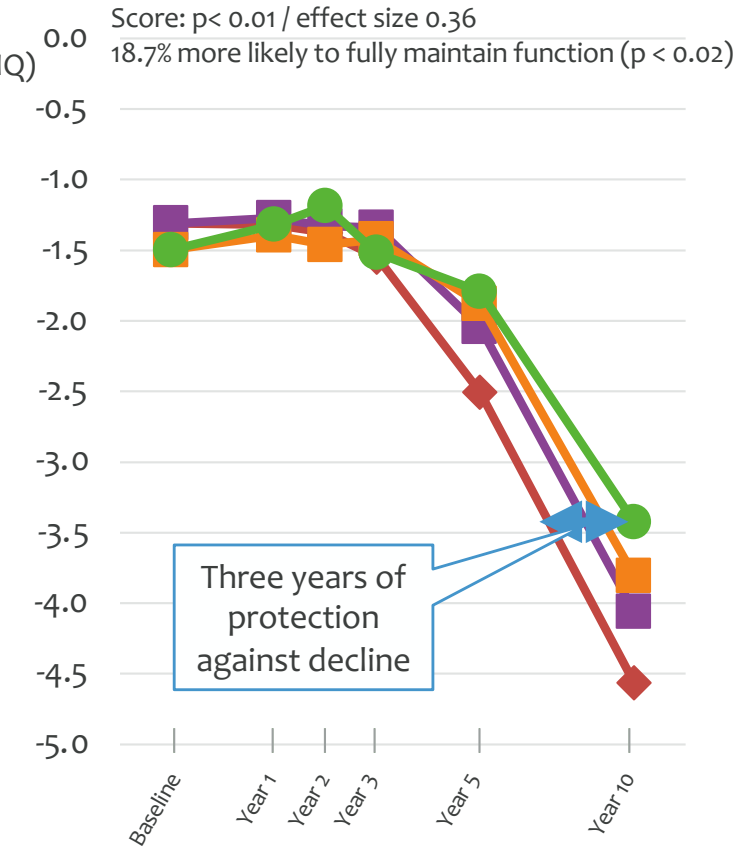
Trained Measure

Visual Speed
Useful Field of View (milliseconds)



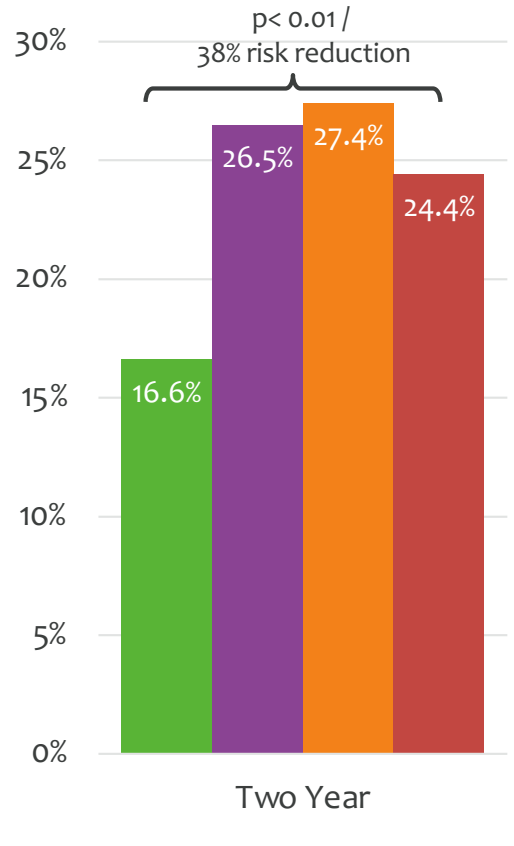
Functional Measure

Instrumental Activities of Daily Living
MDS-Home Cate (inverted raw score)



Real-World Measure

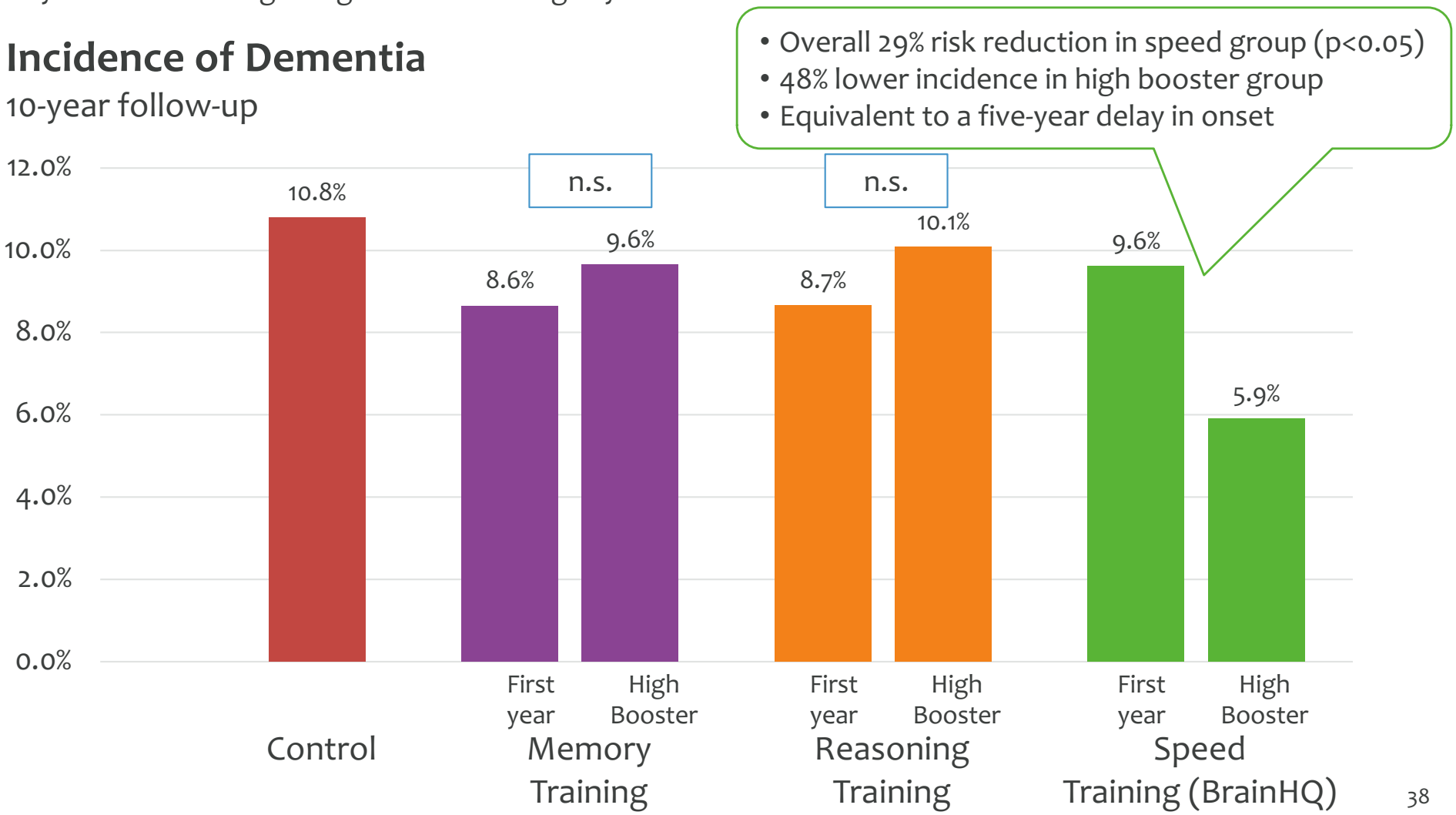
Health Related Quality of Life
SF-36 (risk of serious decline)



Ball 2002 (JAMA); Willis 2006 (JAMA); Rebok 2014 (JAGS); Wolinsky 2006 (J Gerontol)

Time-to-dementia analysis from ACTIVE shows protection against the onset of dementia

ACTIVE Study: 2,832 healthy older participants, NIH-funded, multi-site RCT, 10 year longitudinal trial
Compared BrainHQ speed training vs memory training vs reasoning training vs control; each group trains in first year with subset getting booster training in year three



Edwards 2017 (Alz & Dem: Trans Res and Clin Int)

BrainHQ is an effective cognitive training program

In 2016, the ***Institute of Medicine*** recommended five requirements for a cognitive training program:

IoM Criteria

Results from Randomized Controlled Trials

Near Transfer	Training improves directly trained skills
Far Transfer	Training improves standardized untrained measures of speed, attention, and memory; participant reported outcomes; and real-world skills
Benefit Persistence	Benefits continue to be evident three months to ten years after completion of training – but clearly wear off
Active Control	Training is statistically superior to cognitive stimulation active control
Independent Investigators	Multiple studies conducted by independent academic investigators

Recent meta-analyses show efficacy in healthy aging

Shao 2015 (N=12 studies) "Computer-Based Cognitive Programs for Improvement of Memory, Processing Speed and Executive Function during Age-Related Cognitive Decline: A Meta-Analysis"	"CCP should be recommended as a complementary and alternative therapy for age-related cognitive decline, especially in memory performance and processing speed."
Lampit 2014 (N=52 studies) "Computerized Cognitive Training in Cognitively Healthy Older Adults: A Systematic Review and Meta-Analysis of Effect Modifiers"	"CCT is modestly effective at improving cognitive performance in healthy older adults, but efficacy varies across cognitive domains and is largely determined by design choices."
Mewborn 2017 (N=97, CCT and non-CCT) "Cognitive Interventions for Cognitively Healthy, Mildly Impaired, and Mixed Samples of Older Adults: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials"	"Overall, results indicated that cognitive interventions produce a small, but significant, improvement in the cognitive functioning of older adults . Effects were larger for directly trained outcomes but were also significant for non-trained outcomes (i.e., transfer effects)."
Edwards 2018 (N=17, speed training only) "Systematic review and meta-analyses of useful field of view cognitive training"	"Training transfers to real-world tasks, including those that are vital to older adults' maintained independence, with significant, lasting effects."

Cognitive training is supported by meta-analyses and clinical guidelines in healthy aging, MCI & dementia

Meta-analyses support cognitive training in healthy aging, MCI and dementia

- Basak 2020 (215 studies in healthy aging and MCI) shows significant benefits in healthy aging (near transfer g=0.38, far transfer g=0.22) and MCI (near g=0.27, far g=0.18)
- Mewborn 2017 (97 studies in healthy aging and MCI) shows significant benefits (near transfer g=0.44, far transfer 0.15)
- Lampit 2014 (52 studies in healthy aging) shows significant benefits (near transfer g=0.22)
- Bahar-Fuchs 2019 (33 studies in overt dementia shows significant benefits (near transfer g=0.84)
- Hill 2017 (17 studies in overt dementia) shows significant benefits (near transfer g=0.26)

Emerging guidelines recommend cognitive training

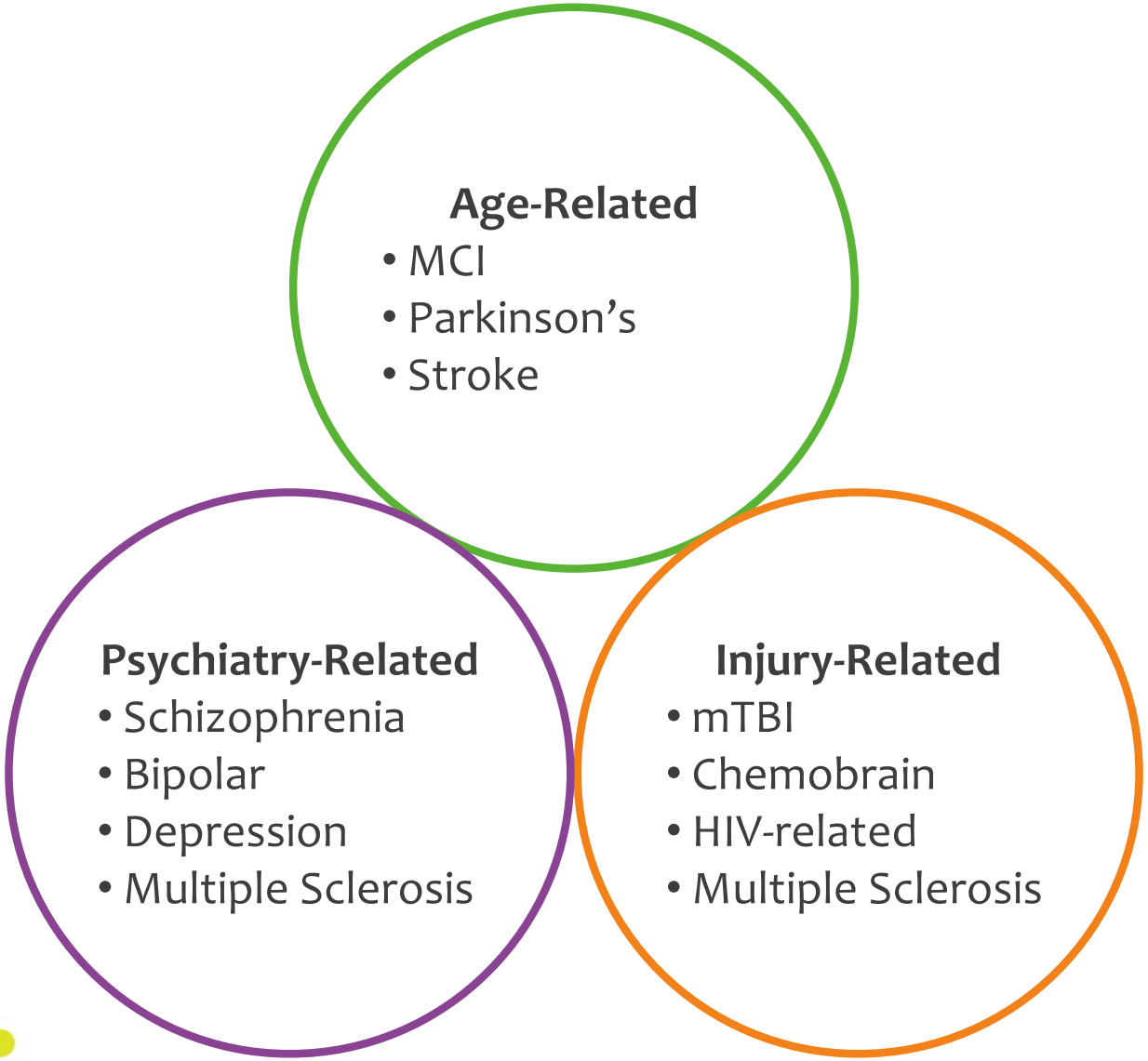
- Alzheimer's Association 2015: "The evidence has now reached a point that it can no longer remain simply an exercise in academic discussion."
- NASEM 2017: "the evidence is strong enough to suggest the public should at least have access to these results to help inform their decisions about how they can invest their time and resources to maintain brain health with aging."
- AAN 2018: "Clinicians may recommend cognitive training"
- WHO 2019: "Cognitive training may be offered to older adults with normal cognition and with mild cognitive impairment to reduce the risk of cognitive decline and/or dementia."

Contents

- Overview of Posit Science and BrainHQ
- Core efficacy data in normal aging
- Initial data in clinical indications

Applications of brain training to clinical indications are being evaluated

Examples of conditions with published clinical trial data with BrainHQ



Cognitive training is supported by meta-analyses and draft clinical guidelines in schizophrenia

Meta-analyses support cognitive training in SZ

- McGurk 2007 (26 studies) shows significant benefits in cognitive performance (g=0.41), psychosocial functioning (g=0.36) and symptomology (g=0.28)
- Prikken 2019 (24 studies) shows significant benefits in attention (g=0.31), working memory (g=0.38), positive symptoms (g=0.31), and depressive symptoms (g=0.37)
- Kurtz 2012 (19 studies) shows significant benefits on facial affect recognition (identification, g = 0.71 and discrimination, g = 1.01), theory of mind (g=0.46), total symptoms (g=0.68), and observer-rated community and institutional function (g=0.78)

Emerging guidelines recommend cognitive training in SZ in the U.S.

- APA 2019 draft guidelines: "APA suggests (2C) that patients with schizophrenia receive cognitive remediation"
- Cognitive remediation is already included in several notable CPGs outside of the US, including Australia/New Zealand, Scotland, and Canada.

Overview in schizophrenia (SZ)

- **The Need**: Cognitive impairment is prevalent. Performance is typically 1 SD below the mean of age-matched controls across speed of processing, attention, working memory, verbal and visual learning, reasoning and social cognition (Dickinson 2007; Fioravanti 2005).

- **The Evidence Base**: There are 66 published RCTs using BrainHQ in patients with SZ. BrainHQ has been applied in clinically-at-risk SZ populations, first episode SZ, chronic SZ, in-patient SZ, and schizoaffective disorder. Endpoints often include MATRICS MCBB, PANSS, PSP, and UPSA.

- **The Training**: BrainHQ's Focus on Auditory Processing

- **The Findings**: Participants training on BrainHQ demonstrated improvements in neurocognition, symptomology, social functioning, and quality of life. Training also improved the structural and chemical integrity of the brain. Effect sizes generally ranged between 0.4-0.8.

Two studies in schizophrenia study – trial design

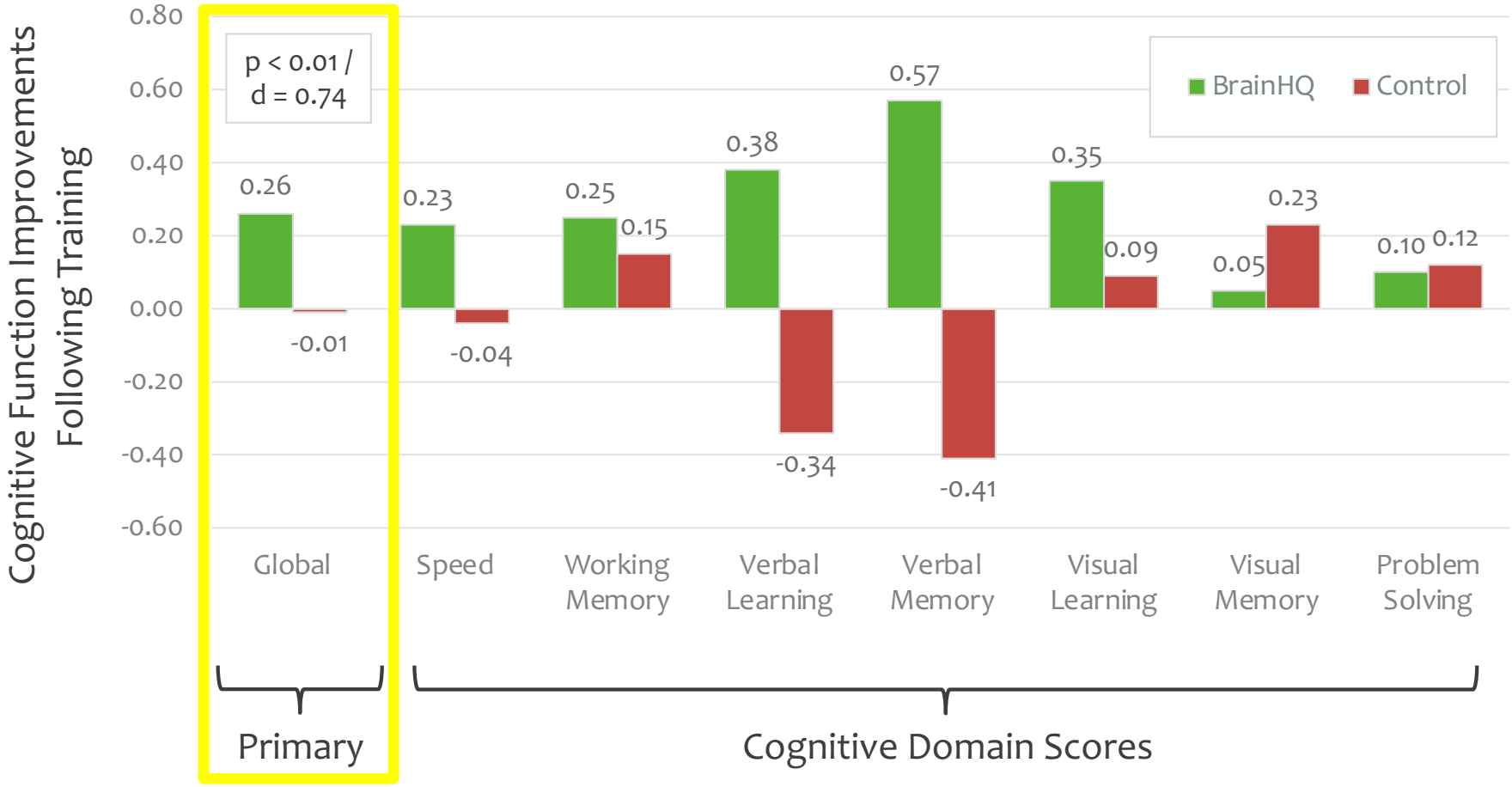
- NIH funded, led by independent academic investigator – Dr. Sophia Vinogradov (UCSF, UMN)
- Two-arm RCT, BrainHQ vs active control (video games)
- Target 40 hours of training for intervention and active control (1 hr per day, 5 days per week, ~8 weeks)
- Outcome measures at baseline and post-training, analysis focused on change score from baseline to post-training

A first chronic schizophrenia study shows improvements in cognition

N = 87 chronic schizophrenia, mean age ~42 years

Two-arm RCT: BrainHQ vs computer games; 40 hrs in-clinic training)

MCCB domain z-score change from baseline to post-training



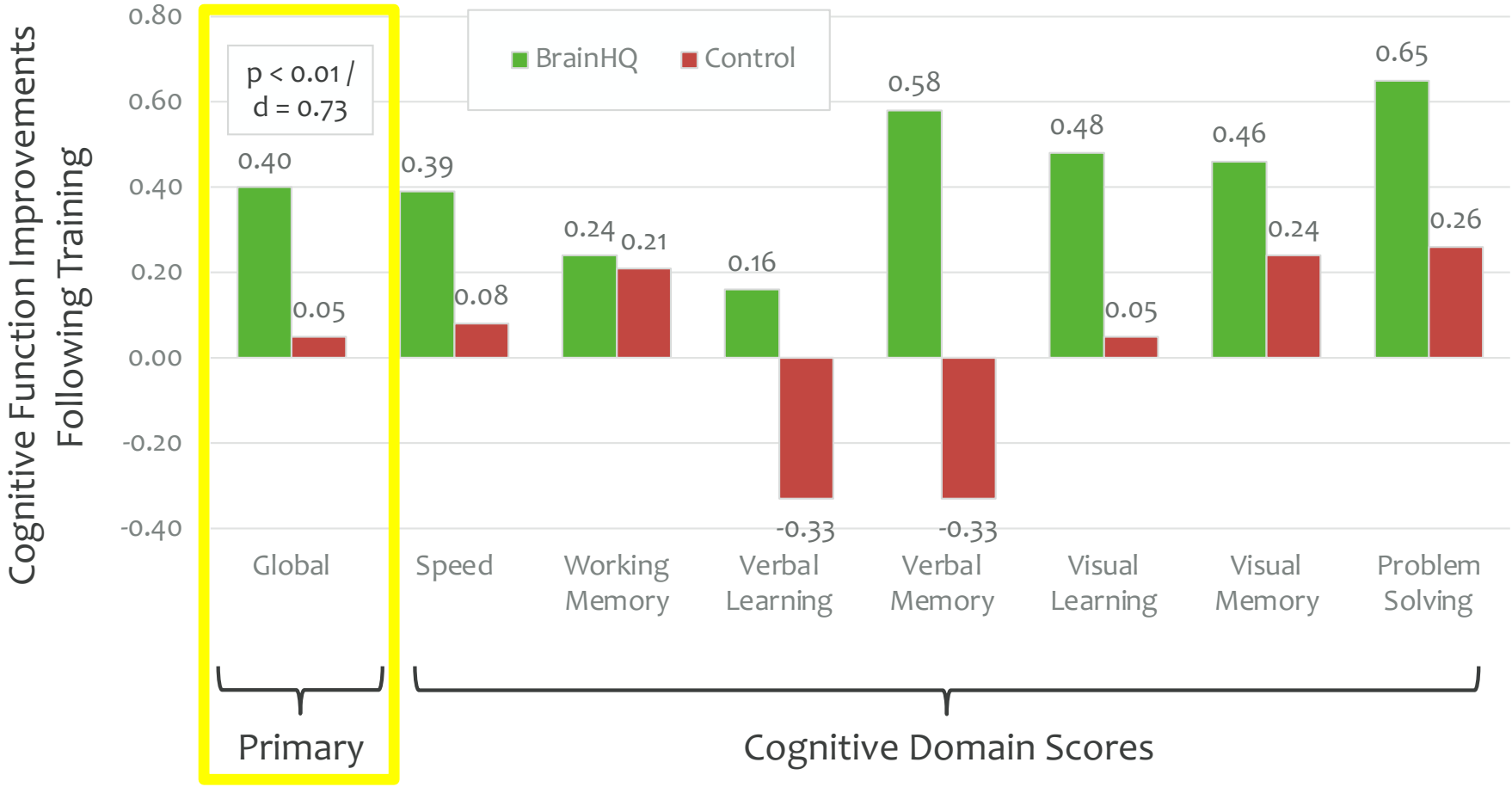
Fisher 2016 (Sz Res: Cog)

A first recent-onset schizophrenia study shows improvements in cognition

N = 86 recent onset schizophrenia (< 5 years), mean age ~21 years

Two-arm multi-site RCT: BrainHQ vs computer games; 40 hrs in-home training)

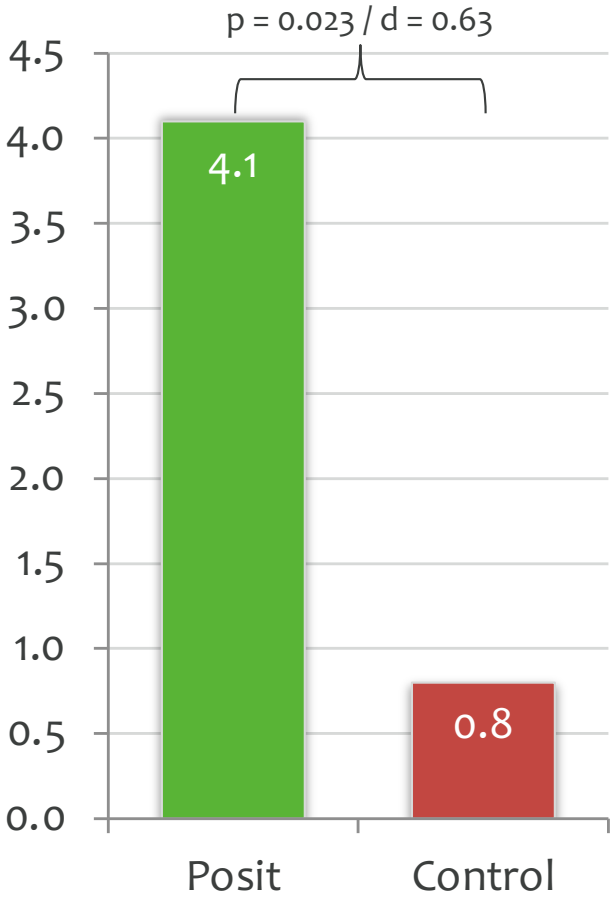
MCCB domain z-score change from baseline to post-training



Multiple SZ studies show strong results

CRIS Study (UCSF)

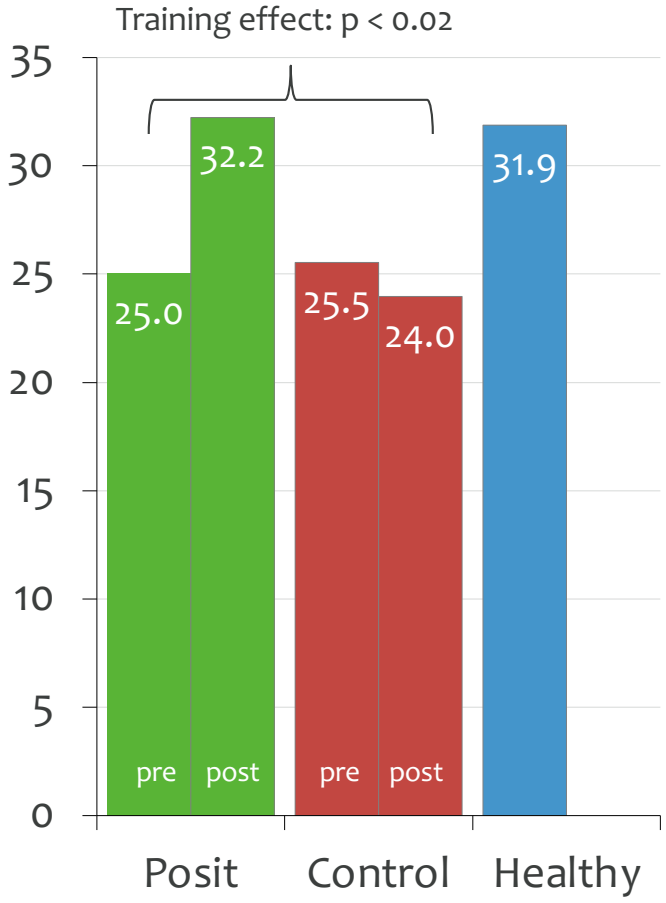
RCT vs computer games; N = 55
Change in **MATRICS** Score Points
(from baseline)



Fisher 2009 (American Journal of Psychiatry)

Neurotrophic Factors

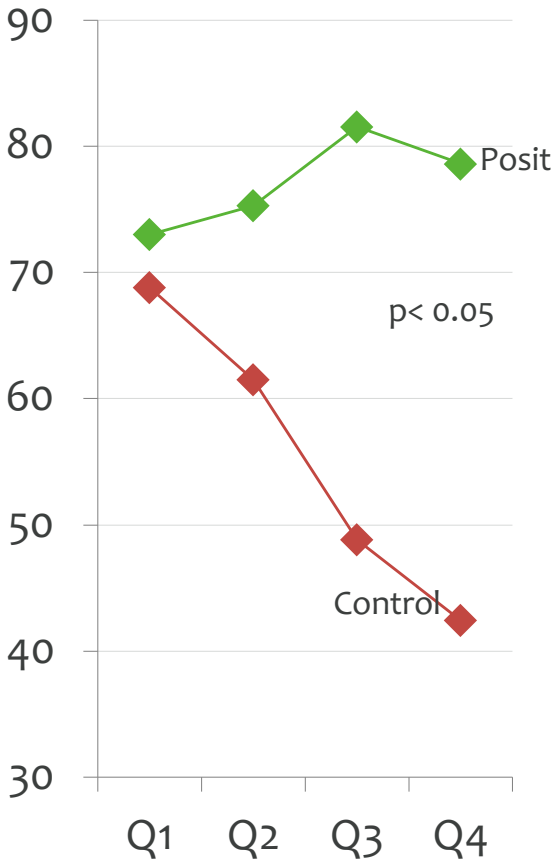
Serum levels of Brain-Derived
Neurotrophic Factor, ng/ml



Vinogradov 2009 (Biological Psychiatry)

Employment

Total hours worked, year
after intervention



Bell 2008 (Schizophrenia Research)

Responder analyses suggest the following populations benefit most

Population	Population Showing Larger Benefits
Early auditory processing	More impaired EAP (assessment with tone matching)
Mismatch negativity	Less abnormal MMN (assessed with EEG)
Serum anticholinergicity	Lower anticholinergic burden (assessed by serum)
Age	Younger age (assessed by DoB)
Cognitive function	Better speed, attention, memory (assessed by MATRICS MCCB)
Duration of illness	Fewer than 5 years from onset (from medical records)
Clinical stability	More stable participants (assessed by clinician evaluation)
Intrinsic motivation	Higher intrinsic motivation (assessed by QLS scale)

Overview in multiple sclerosis (MS)

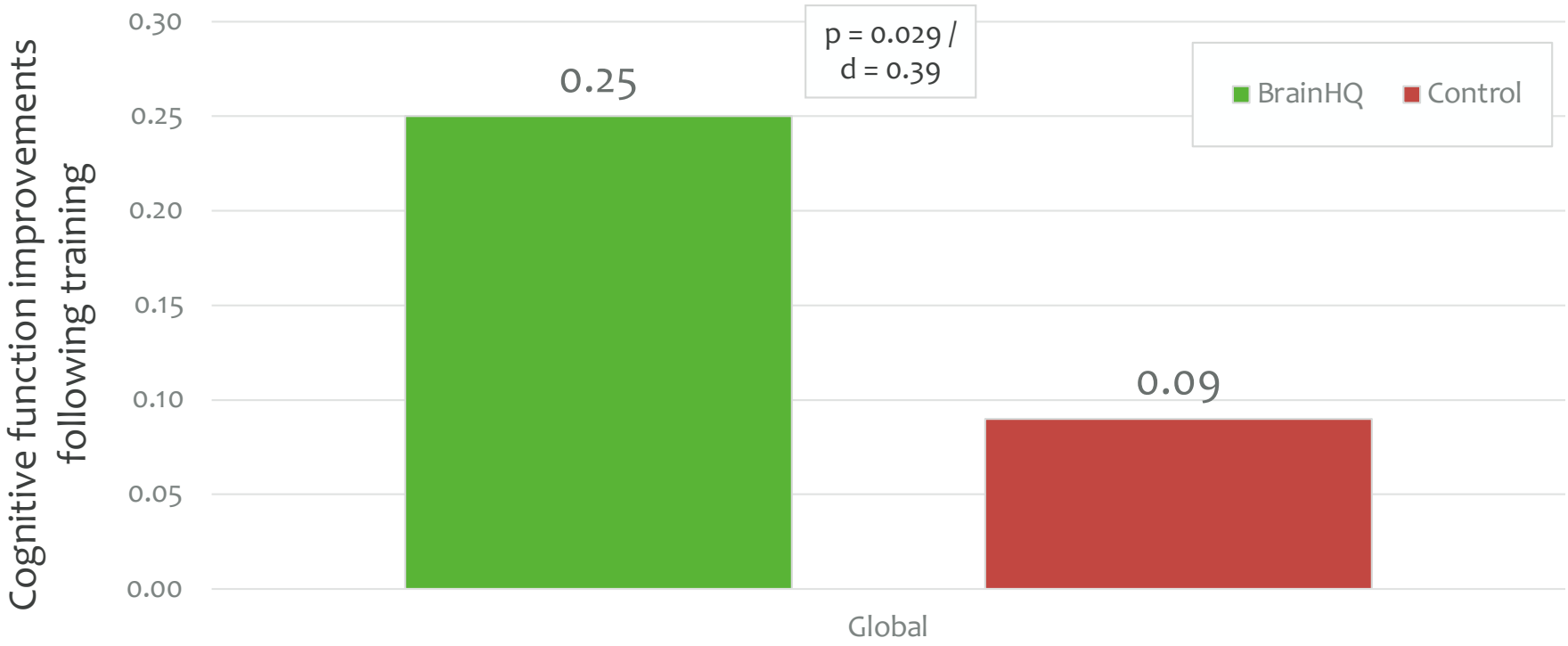
- **The Need:** Approximately 40–65% of patients with multiple sclerosis experience cognitive deficits, with processing speed and working memory often being the most affected (Hancock 2015) as well as attention and visuomotor coordination tasks (Basenes 2014).
- **The Evidence Base:** There are 9 published RCTs using BrainHQ in patients with multiple sclerosis.
- **The Training:** BrainHQ's Focus on Auditory Processing and Focus on Visual Processing, among several additions from the 29 available exercises.
- **The Findings:** Large improvements on various cognitive subdomains ranging between 0.38-0.74. Recent responder analyses show that patients with relapsing-remitting MS improve most.

A first MS study – trial design

- Funded by the National MS Society, led by independent academic investigator – Drs. Leigh Charvet and Lauren Krupp (NYU)
- Two-arm RCT, BrainHQ vs active control (video games)
- Target 60 hours of in-home remotely supervised training for intervention and active control (1 hr per day, 5 days per week, ~8 weeks)
- Outcome measures at baseline and post-training; analysis focused on magnitude of the between groups difference in change scores from baseline to post-training

A first MS study shows improvement in cognition

N = 135 multiple sclerosis
Two-arm RCT: BrainHQ vs computer games; avg of 37 hrs in-clinic training delivered
z-score change from baseline to post-training



Overview in bipolar disorder (BD)

- **The Need**: Dramatic fluctuations in mood impair cognitive and functional abilities that persist during periods of remission. The most affected cognitive domains are attention, verbal learning and memory, executive function and social cognition (Sole 2017).
- **The Evidence Base**: There is 1 published RCT using BrainHQ in patients with BD.
- **The Training**: BrainHQ's Focus on Auditory Processing and Focus on Visual Processing, among several additions from the 29 available exercises.
- **The Findings**: Large improvements were found on the MCCB composite at post-test (d = 0.80) and at follow-up (d = 0.83).

A first bipolar study – trial design

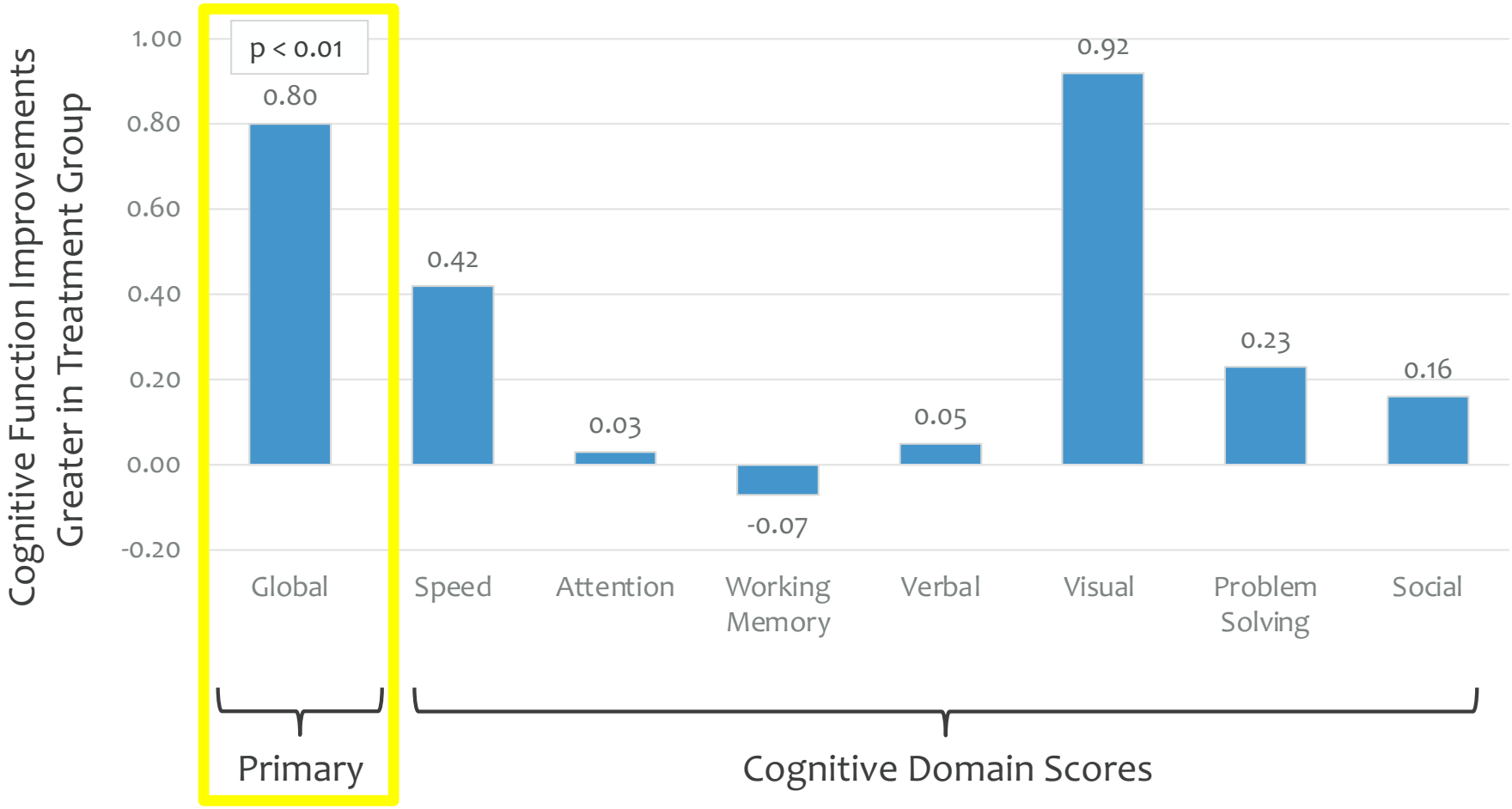
- NIH funded, led by independent academic investigator – Dr. Eve Lewandowski (Harvard)
- Two-arm RCT, BrainHQ vs active control (video games)
- Target 70 hours of training for intervention and active control (1 hr per day, 3 days per week, 24 weeks)
- Outcome measures at baseline and post-training; analysis focused on magnitude of the between groups difference in change scores from baseline to post-training

A first bipolar study shows persistent improvements in cognition

N = 75 bipolar

Two-arm RCT: BrainHQ vs computer games; avg of ~43 hours of training delivered

Cohen's d effect size (change in treatment group minus change in control group)



Also: gains shown to persist 6 months after training

Overview in chemobrain

- **The Need:** Approximately 70% of patients with cancer undergoing chemotherapy report cognitive deficits, which have been confirmed in meta-analyses showing the deficits in speed of processing, memory, and executive function (Ball 2002; Jansen 2005).
- **The Evidence Base:** There are 4 published RCTs using BrainHQ in patients with chemobrain.
- **The Training:** BrainHQ's Focus on Visual Processing
- **The Findings:** Cognitive improvements found across multiple different cancers with effect sizes ranging between 0.18-0.82. Enduring gains were found at follow-up +6 month benchmarks.

A first chemobrain study – trial design

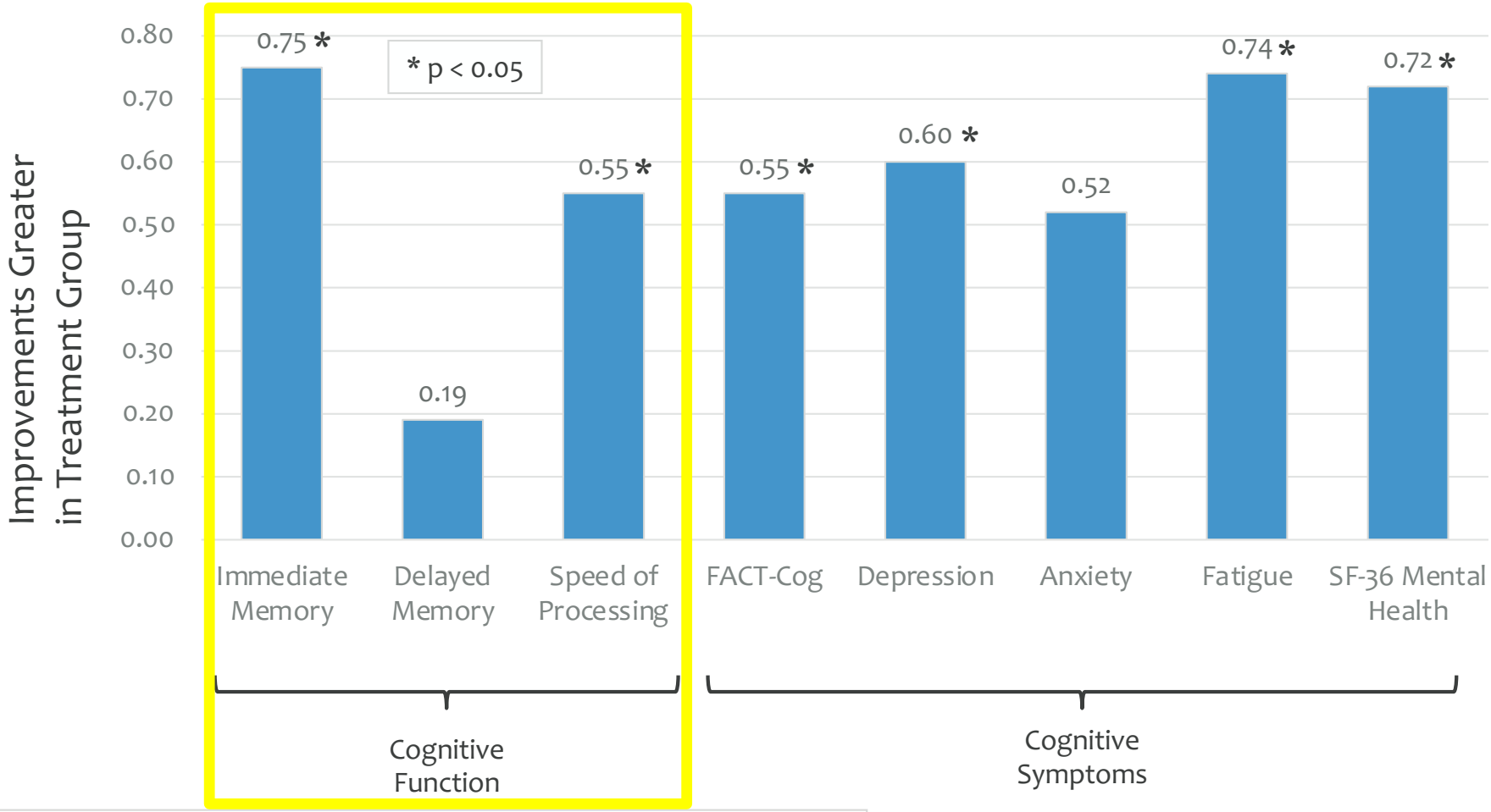
- Funded by the Robert Wood Johnson Foundation, led by independent academic investigator Dr. Diane Von Ah (Indiana University/Purdue University of Indiana)
- Three-arm RCT with two independent intervention arms (BrainHQ, classroom memory training) each vs treatment-as-usual control
- Target 10 hours of in-clinic training (1 hr per session, 10 sessions over ~7 weeks)
- Outcome measures at baseline and post-training; analysis focused on magnitude of the between groups difference in change scores from baseline to post-training

A first chemobrain study shows improvement in cognition

N = 82 breast cancer survivors (data shown for BrainHQ vs control)

BrainHQ speed training vs memory training vs waitlist control; 10 hrs in-clinic training

Cohen's d effect size (change in treatment group minus change in control group)



Also: gains shown to persist 2 months after training

Von ah 2012 (Breast Cancer Res Treat)

Overview of mild cognitive impairment (MCI)

- **The Need:** Existing treatments for Alzheimer's disease are minimally effective at slowing cognitive and functional decline. Despite enormous investments of government and private research, no new treatment has emerged since 2003.
- **The Evidence Base:** There are 18 publications in mild cognitive impairment
- **The Training:** BrainHQ's Focus on Visual Processing were the most frequently used training program.
- **The Findings:** Participants training on BrainHQ demonstrated improvements in cognition, function, neuroimaging, and physiological measures such as heart rate variability. Effect sizes generally ranged between 0.16-1.4.

Summary of core MCI studies using BrainHQ

Over a dozen publications in MCI have shown cognitive and functional benefits using BrainHQ. For example:

- ***Barnes 2009:*** 47 participants with MCI, BrainHQ vs active control, effect size 0.33 in RBANS total score, 0.85 on spatial span, and 0.16-0.53 on learning & memory measures.
  - ***Rosen 2011:*** Sub-analysis of 12 participants showed higher left hippocampal activation that was positively associated with memory scores on the RBANS, effect size 1.14
- ***Gooding 2015:*** 74 participants with MCI, BrainHQ vs active control, effect size 0.81 on modified MMSE, 0.80 on verbal memory, 0.69 on verbal learning
- ***Lin 2016:*** 21 participants with MCI, BrainHQ vs active control, effect size effect size 1.28 on NIH EXAMINER working memory
- ***Valdes 2017:*** sub-analysis of 49 participants with MCI from the SKILL trial, BrainHQ vs active control, effect size 0.39 on TIADLS
- ***Lin 2020:*** 84 participants with MCI, BrainHQ vs active control, effect size effect size 0.51 on UFOV speed & attention

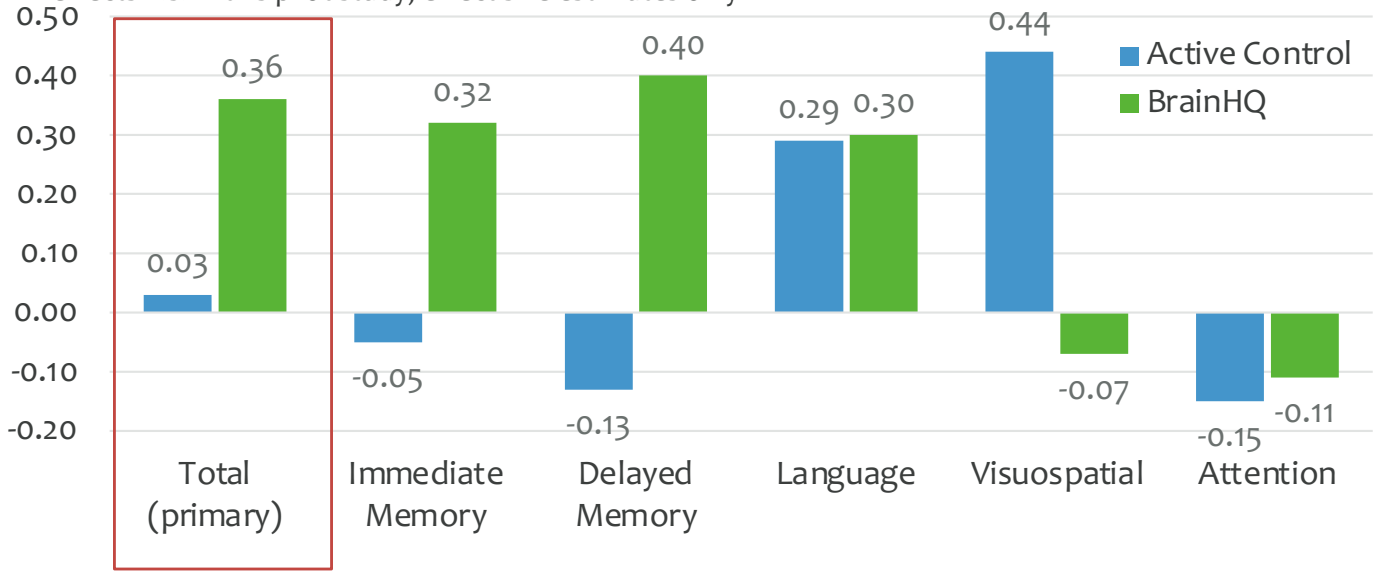
BrainHQ improves overall cognitive function in MCI, with strong effects on memory

40hrs training/6 weeks, BrainHQ auditory exercises, active control adult learning

Barnes 2009:
Behavior
(N = 47, MCI)

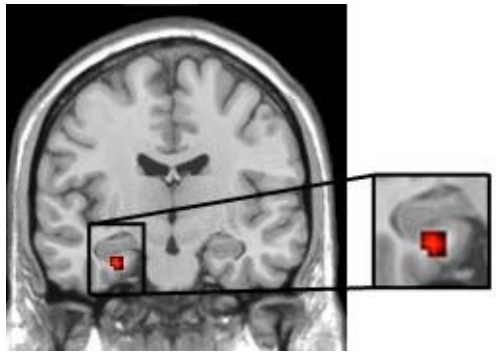
RBANS change scores (standardized effect sizes)

All effects n.s. in this pilot study, effect size estimates only



Rosen 2011:
fMRI
(N = 12, MCI)
Subset of Barnes 2009

Significant group x time interaction for fMRI activation during memory task

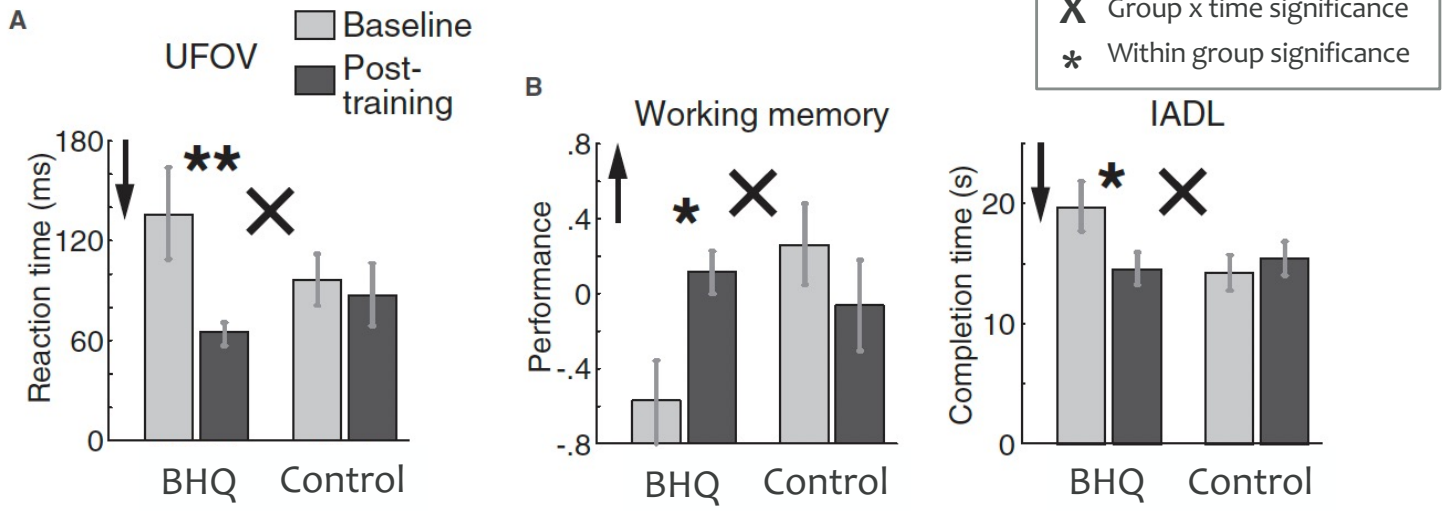


Barns 2009 Alzheimer Dis Assoc Disord, Rosen 2011 JAD

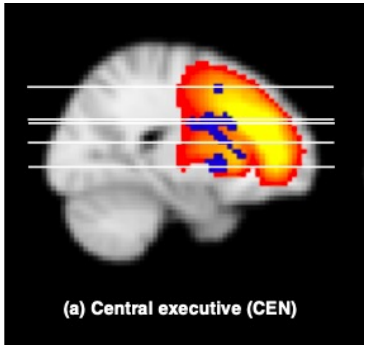
BrainHQ Improves Cognitive/Functional Performance and Brain Connectivity in MCI

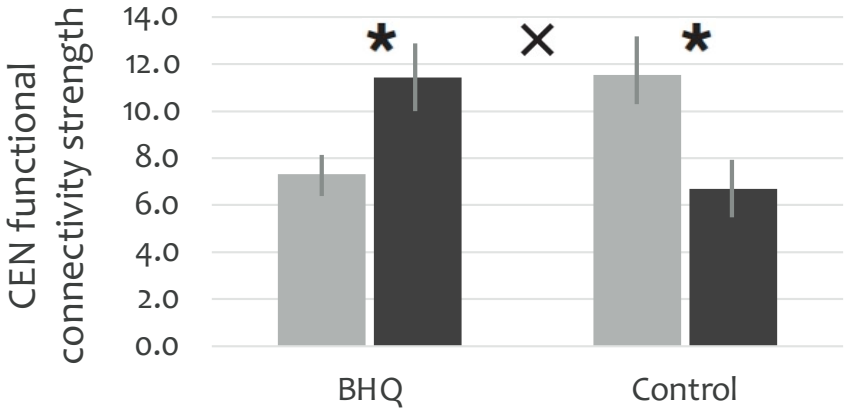
24hrs training/6 weeks, BrainHQ visual exercises, active control computer games

Lin 2016:
Behavior
(N = 21, MCI)



Lin 2020:
fMRI
(N = 84, MCI)





Lin 2016 JAGS, Lin 2020 NeuroImage

Responder analysis in MCI suggests everyone benefits

All subtypes of psychometrically-defined MCI showed significant improvements in cognitive function following BrainHQ training (Valdes 2012).

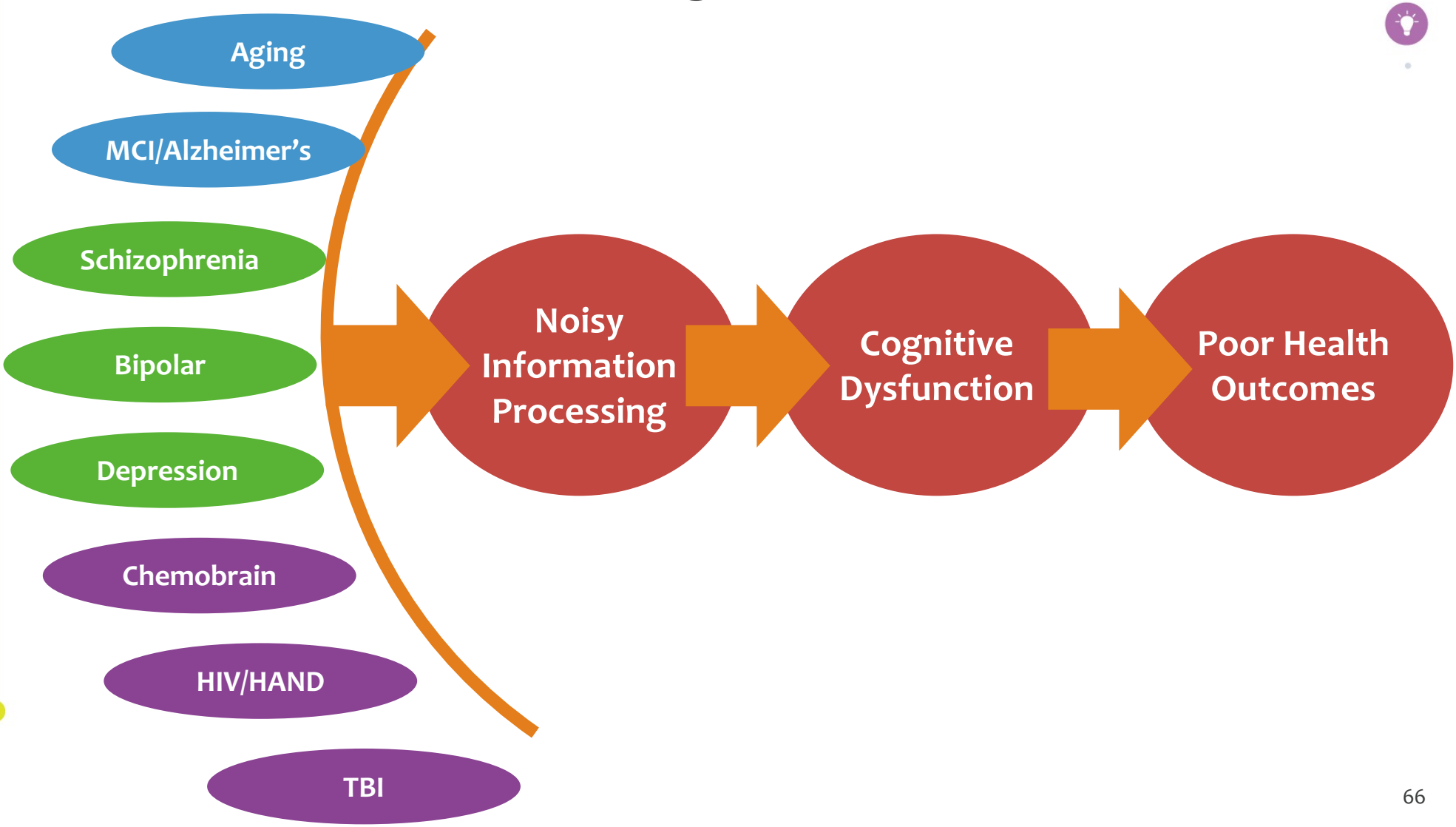
- Amnesic
- Single-domain non-amnesic
- Multi-domain

Training gains are impartial to indication

Conditions with published clinical trial data with BrainHQ:

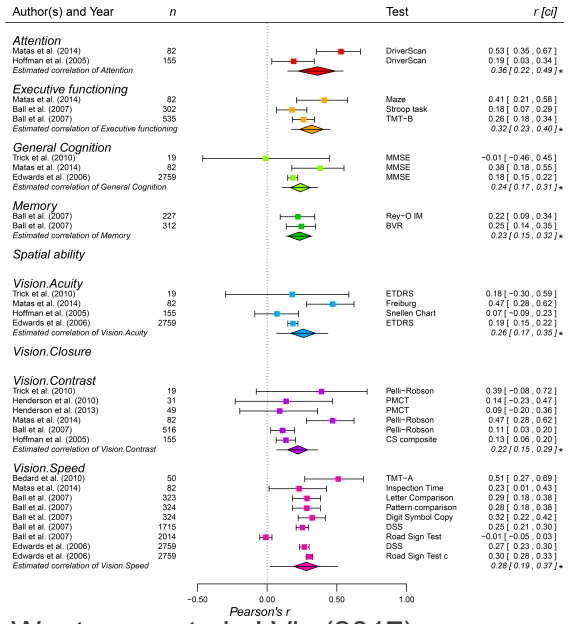
1. Neurological losses associated with normal and "pathological" aging (mild cognitive impairment, Parkinson's).
2. Brain changes underlying psychiatric illnesses (schizophrenia, bipolar, depression, substance abuse, body dysmorphia).
3. Impairments secondary to physical disease (diabetes, kidney disease, heart failure, genetic conditions, stroke, multiple sclerosis)
4. Neurological losses associated with brain poisoning (chemobrain), infection (HIV), and life events (TBI, tinnitus)
5. Childhood impairments that frustrate success in school and in life (ADHD, conduct disorder)

Many neurological and psychiatric conditions may have a common endpoint in noisy processing driven by poor processing speed and attention



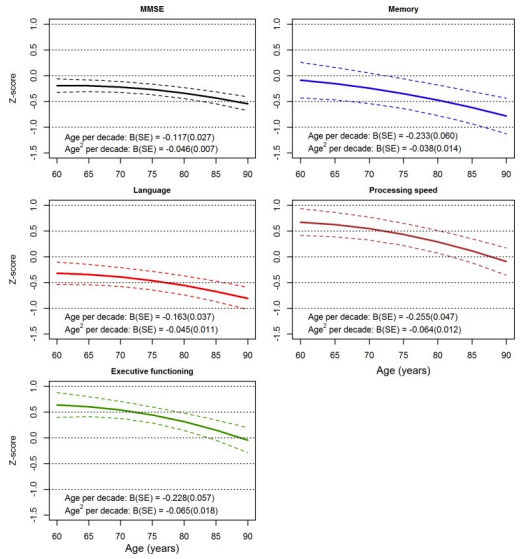
BrainHQ focuses on the most valuable forms of training: processing speed & attention (PS/A)

PS/A underpins all cognitive domains across adulthood



Woutersen et al. J Vis (2017)

Decline in PS/A is substantial in aging, including APOE4+ carriers



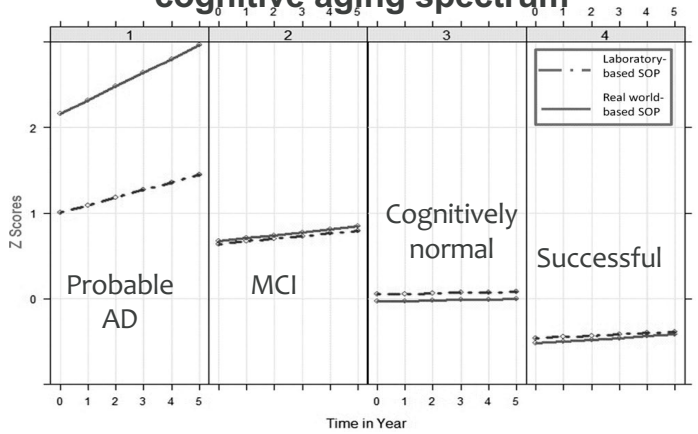
Lipnicki et al., Plos Med (2017)

Meta-analysis of cognitive training effect in cognitively healthy older adults

		Overall
	All studies	0.22**
CCT type	Multidomain	0.18**
	Attention	0.34*
	Speed of Processing	0.25**
	Video Game	0.42*
	Working Memory	0.17

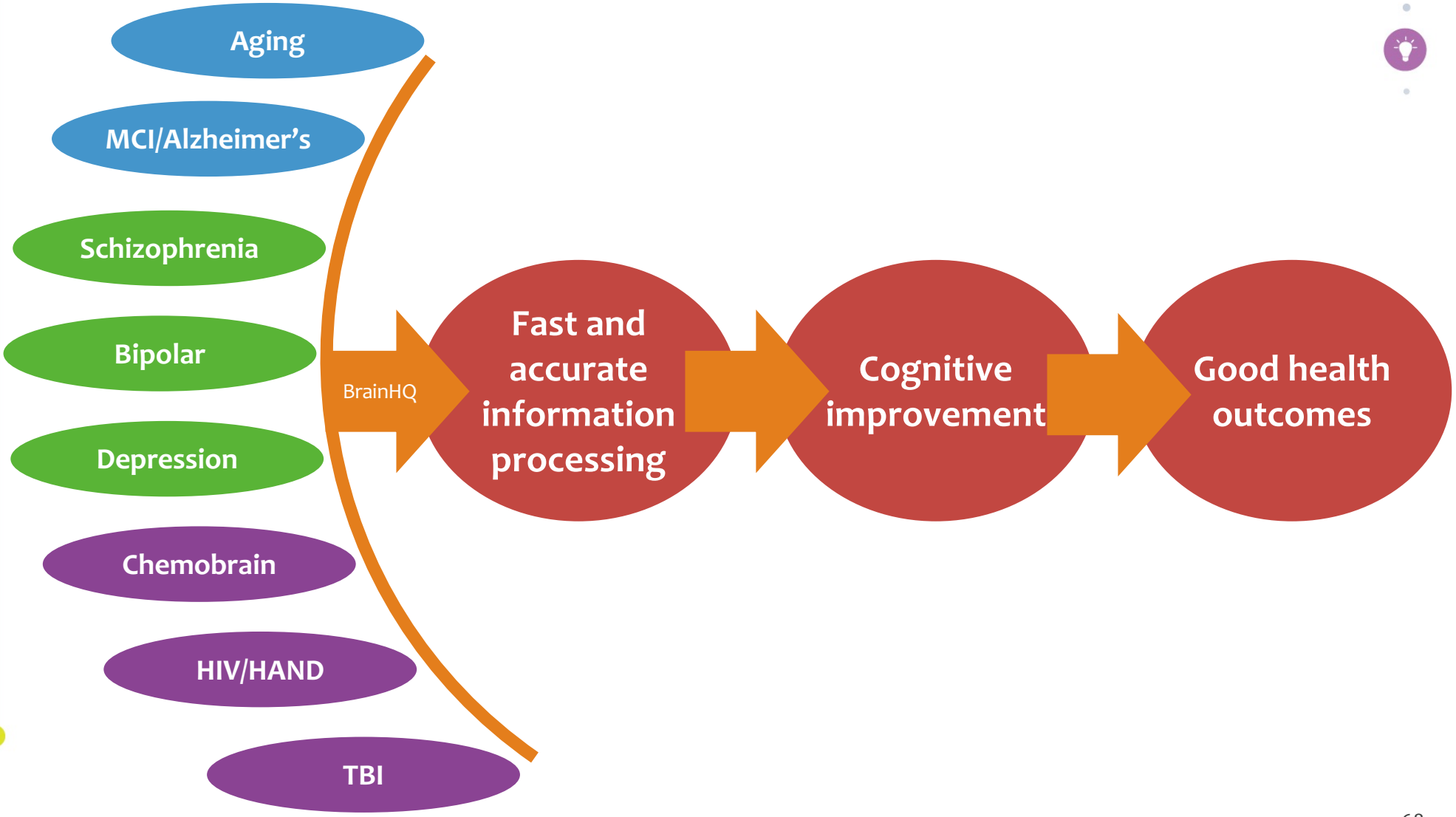
Lampit, et al., Plos Med (2014)

PS/A trajectories differ across the cognitive aging spectrum



Lin, et al. J Gerontol B Psychol Sci Soc Sci, (2013)

Many neurological and psychiatric conditions may have a common treatment in BrainHQ



The Opportunity For Digital Therapeutics

- A software-based cognitive training program that improves cognition in specific neurological and psychiatric conditions
- Cleared by the FDA as a software-based medical device
- Proven effective in a pivotal trial
- Fundamentally safe, with no risk of side-effects or drug interactions
- Prescribed by physicians, reimbursed by payors
- As a stand-alone, or in combination with pharmaceuticals

A new way forward for a field that demands new solutions

Public health impact

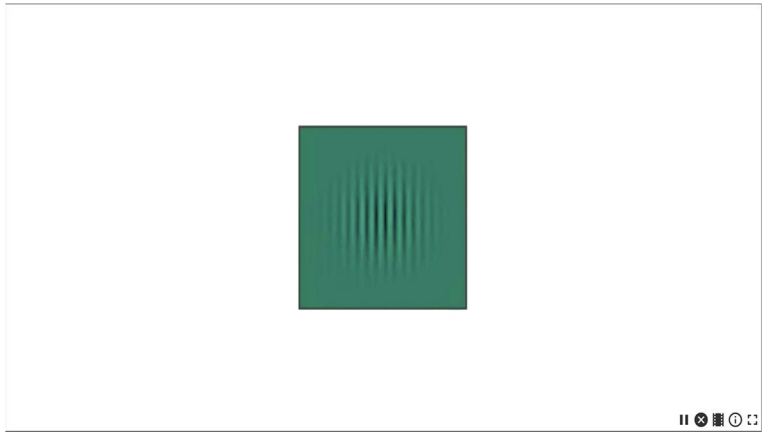
- **Cost-Effective**: priced like consumer software, not like a pharmaceutical agent
- **Safe**: no significant adverse events associated with use, no interactions with existing medications
- **Scalable**: available on web, iOS, and Android; in 10 languages; through health plans, clinicians, and senior communities
- **Accessible**: available at home to people with personal devices and internet connections, and at community centers/libraries for people in need

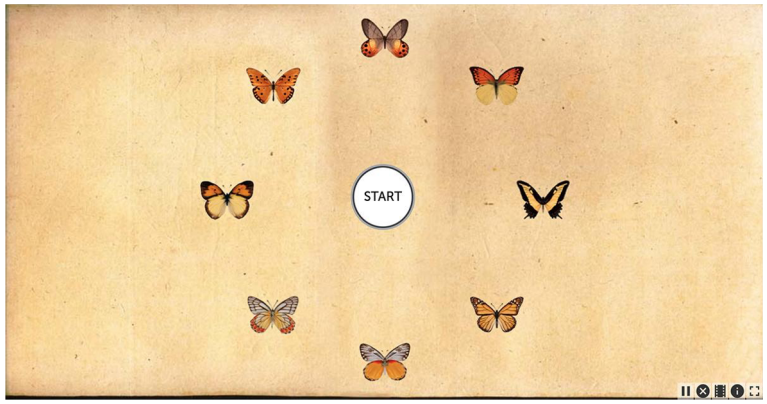
Potential for significant benefit at the population health level

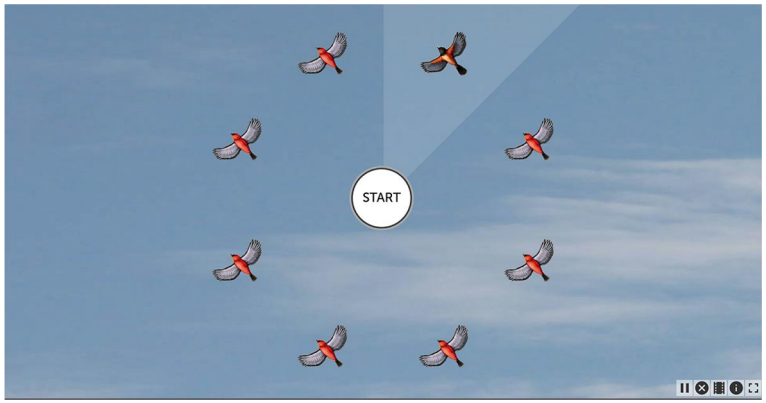

brainHQ
from Posit Science
Think Faster
Focus Better
Remember More
www.brainhq.com

EXTRA SLIDES

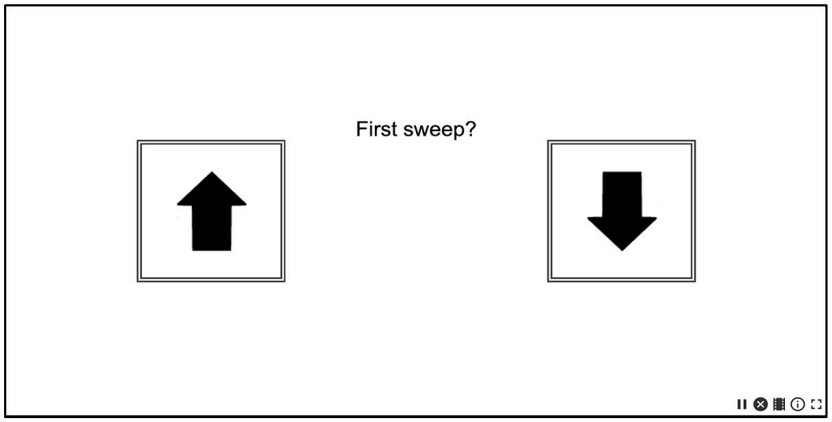
Focus on Visual Processing

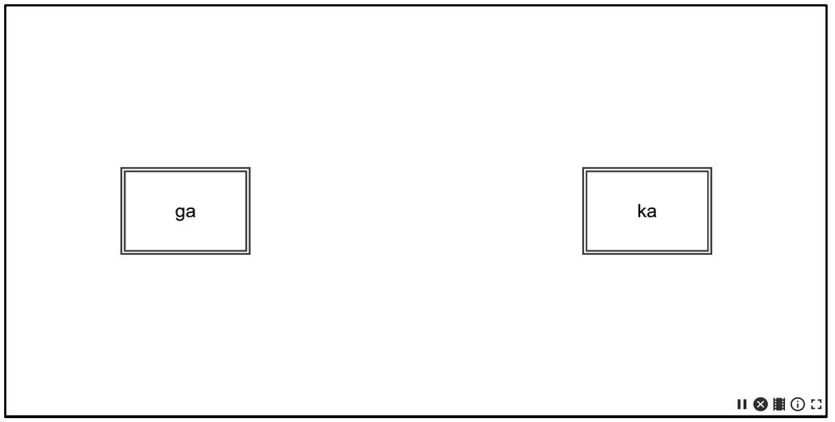


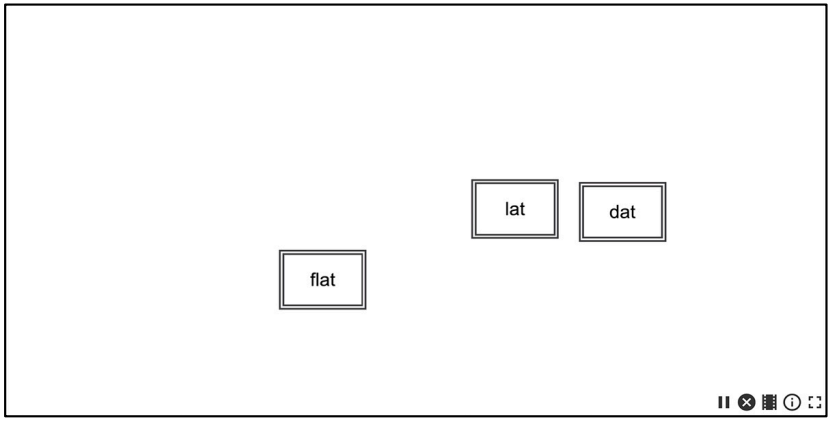


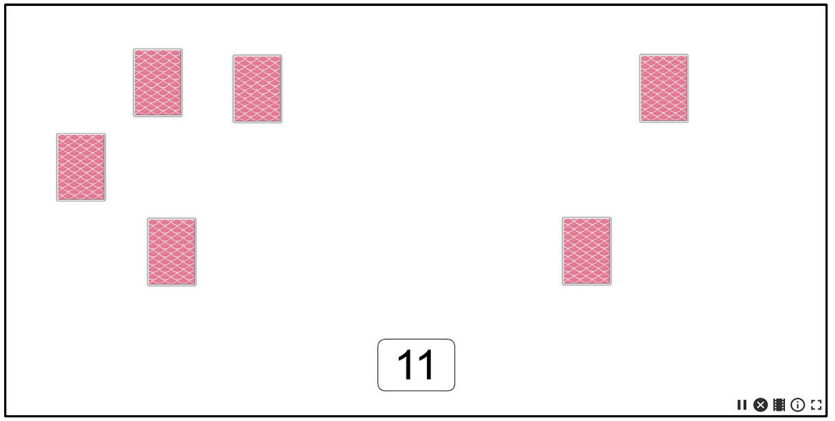


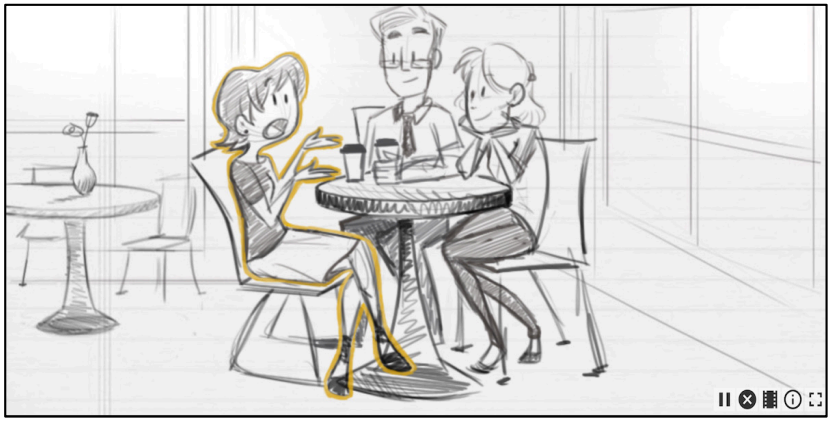
Focus on Auditory Processing



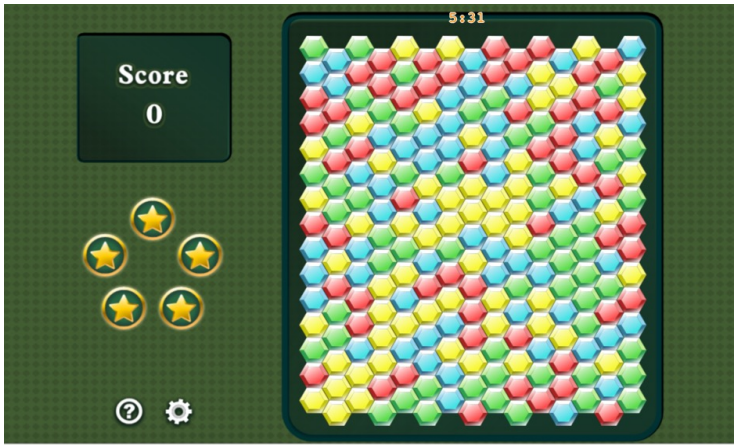


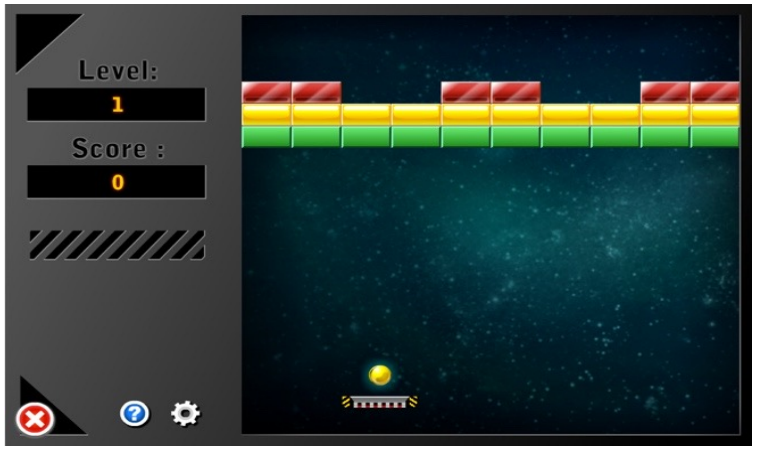


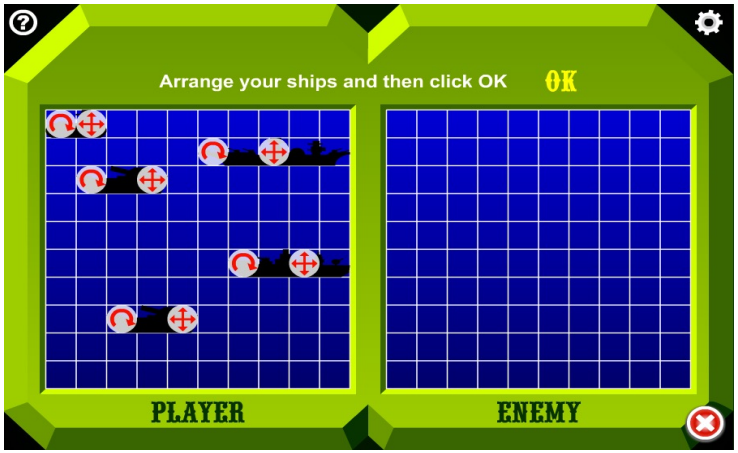


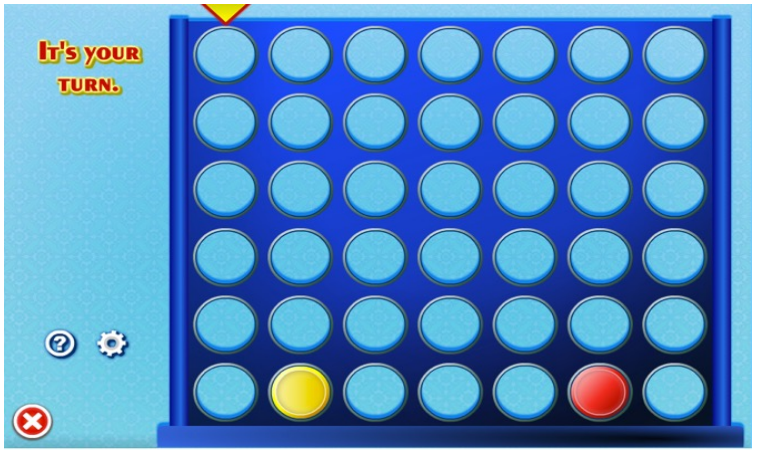


Active Control Games



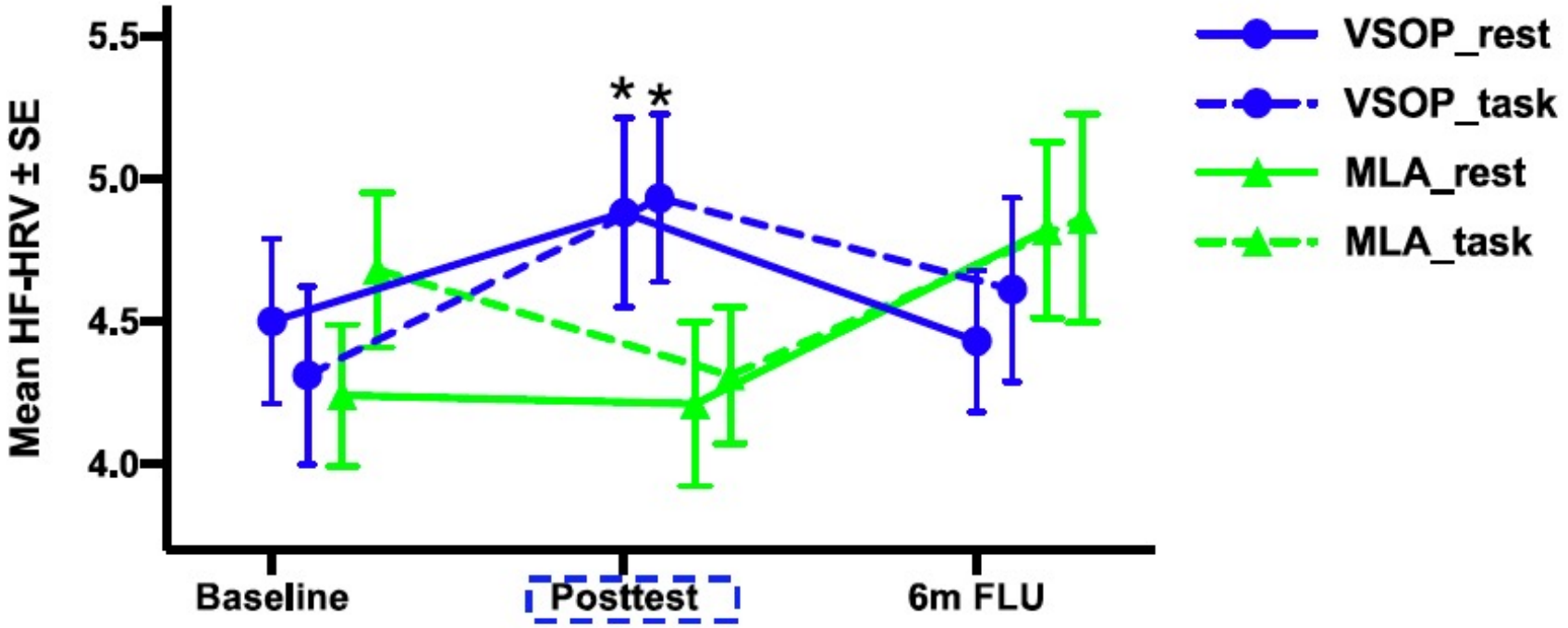






Training may temporarily change HRV.

BrainHQ temporarily altered physiological processes such as by improving heart rate variability (Lin 2020, Lin 2017, Gary 2019)



Lin 2020, NeuroImage