Assessing Then Improving Organic Brain Health and Functional Ability. A Neuroscience Perspective

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1.0 PLASTICITY 101.

The predominant historical scientific perspective from the late 19th Century into the middle of the 20th Century was that the brain was 'plastic' throughout life, physically revising its machinery as you acquire or improve any skill or ability. Beginning in the 1950's, scientists conducted compelling studies that appeared to contradict those long-held beliefs. Elegant experiments conducted in the visual brain revealed that large scale remodeling occurred after the loss of one eye in infancy, but this capacity for dramatic re-wiring and functional re-adjustment appeared to be limited to the earliest epoch in post-natal life—translatable in the human brain to the first year or two after birth (see Merzenich, 2013, Merzenich et al, 2014, and Lambert K et al, 2019, for review).[1]

In the same era, other scientists manipulated the great 'trunk lines' delivering information to the brain from the body senses or cochlea or retina or manipulated the major trunkline connections in the forebrain itself and repeatedly showed that those pathways could be 'plastically' re-routed in the brain after these manipulations. To cite one of many examples, when scientists eliminated all inputs from the inner ear or from the retina, the deaf or blind infant animal's hearing or visual brain was rapidly occupied and dominated by inputs from other senses. For example, the hearing brain in a deaf animal became a visual brain area. In what was correctly interpreted as an astounding example of brain plasticity, animals manipulated in infancy could be shown to be capable of operating visually with a brain that could now *only* use this normally-hearing brain area for its visual operations. Again, remodeling of brains following such manipulations appeared to be at least largely limited to the earliest epoch of post-natal life.

In a third demonstration of what appeared to be infants-only neuroplasticity, scientists began to study elemental aspects of connectional remodeling ("synaptic plasticity") *in vitro*, that is, in brain tissues kept 'alive' in a dish, or by recording from single nerve cells (neurons) in living brains, artificially manipulating the inputs delivered to these nerve cells (neurons) to study resultant connectional (plastic; synaptic) remodeling—their 're-wiring'. In these studies, it was generally easy to induce changes in a very young animal or in excised brain tissues studies where the kept-alive tissues were *from* a very young animal, but that capacity for plastic change was usually NOT expressed in excised tissues taken from older animals, or in intact older brains.

These studies (one of which directly led to the award of a Nobel Prize) were collectively a kind of 'perfect storm' for strongly supporting the conclusion that the brain 'grew up' in infancy to become 'hard-wired', with that now-mature, now-permanent wiring unalterable for the duration of the brain's life. The conclusion that plasticity was limited to the first year or two of post-natal life hardened in the mainstream scientific, medical and educational communities.

Nothing could be further from the truth.

[1] Also see https://www.Soft-Wired.com

2.0 PLASTICITY IS AN ELEMENTAL LIFE-LONG FORCE IN OUR BRAINS

In parallel with these studies in mainstream medical neuroscience, scientists studying 'learning' mechanisms in the brain from a psychological perspective—"physiological psychologists"—were conducting studies that challenged this predominant perspective. Their primary focus was on a form of 'learning' originating with the great historic Russian scientist Ivan Pavlov, in which our brains learn to associate a 'stimulus' (for example, the ringing of a bell) with a 'reward' (for example, a small piece of meat for a hungry dog) or punishment (for example, a mild shock to the dog's paws). In this example, a dog demonstrably learns that the bell immediately preceding the meat or foot-shock predicts their occurrence for the animal. Changes in the brain *must* underlie their now-reliable prediction, so obviously manifested by the dogs' behavioral responses to bell ringing. The emergence of associations between a stimulus and an important outcome can, of course, be generated in an animal (human) at any age.

More contemporary investigators in the 2nd half of the 20th Century went farther to show that the brain *was* demonstrably remodeled in ways that almost certainly accounted for this 'Pavlovian conditioning'. By that physical change, the brain exaggerated the representation of the 'now-very-important' reward or punishment, enlarged a specific representation of the now-exaggerated responses to the association of stimulus and reward, and directly linked ('associated') one to the other (see Merzenich M, 2013 and https://www.Soft-Wired.com for review).

Mainstream neuroscience began to fully appreciate these important studies when *they* began to more directly show how their seemingly clear-cut parallel studies had been misinterpreted. Operating from the mainstream of medical neuroscience, my colleagues and I recorded dramatic remodeling in adult brains following manipulations of inputs from the body senses. In parallel with other investigators, we also repeated showed that when we behaviorally trained an animal in skill acquisition or improvement, the neurological machinery in the brain was physically refined and specialized for the specific demands of 'representations' of sensory information central in the task, and specifically refined and specialized to support the special behavioral responding in the task, in ways that directly accounted for the behaviorally advances documented by quantified improvements in performance. In those studies, we repeatedly showed how the elemental machinery of the brain was physically and functionally advanced from a primitive to a specialized, from a sluggish to a fast, and from an unreliable and error-ridden to a nearly flawless level of information processing, all through progressive brain remodeling.

Physical brain remodeling—plasticity—*equates* with behavioral/functional change. It is operational in our brains from before birth, out to the last day of our life.

2.0.1 THE BOTTOM LINE: In the 1980's and 1990's, the leading edge of mainstream neuroscience 'came on board' with the physiological psychologists. The brain IS plastic on a large scale, across the entire span of our lives. Its plasticity underlies the development and the refinement of ALL the skills and abilities that define our operational personhoods. Its plasticity creates the 'self' through a massive schedule—trillions of moments—of association of our sensations and feelings and actions and thoughts with their source—our self. That operational self, that operational personhood, is continuously subject to neuroplastic remodeling.

Why were earlier observations so grandly misinterpreted? First, the visual cortex IS privileged and exceptional, and does hard-wire an integrated, balanced representation of the two eyes in the brain—necessarily integrated in that balanced way to support the representation of stereoscopic vision, dependent on fine comparisons of inputs from our two eyes. This balance is sustained in the older brain in an exceptional way. While the visual cortex is plastic in every other respect, this unique facet of the visual brain is not.

Second, as the brain organizes its connectivity on the basis of growing response coordination, the scale of plastic remodeling advances from crude, large-scale remodeling to more refined, more localized remodeling. On that local (micro) scale, plasticity continues apace; in a human lifetime, your operational personhood has been created by *quadrillion*s of moments of change in brain wiring strengths and connections, still involving hundreds of thousands or millions of daily synaptic-change moments. Cruder earlier studies did not record these micro-changes, even while they were occurring on a massive scale.

Third, the brain grows up in ways that enables it to *take control* of plasticity change processes. In the infant brain, plasticity is NOT strongly modulated as a function of behavioral state or outcome. As the brain advances in early infancy, it develops its modulatory control (plasticity-controlling) machinery that later *only* 'permits' rewiring changes when the brain interprets that change (by several different sets of criteria) to advantage it. Those conditions were NOT met in *in vitro* or isolated and artificially limited *in vivo* studies using older-animal models, where the now-controlling neuromodulatory machinery now *required* their consideration.

3.0 PLASTICITY PROCESSES ARE FUNDAMENTALLY BI-DIRECTIONAL (REVERSIBLE)

Those physiological psychologist forerunners also demonstrated, from Pavlov onward, that changing underlying stimulus: punishment/reward associations were *reversible*. In that Pavloviaan ('classical conditioning') model, a learned association could be 'extinguished' by simply withdrawing the presentation of the formally-predicted reward or punishment after repeated stimulus presentations. In that context, the animal 'learned' to ignore it, i.e., not to expect that earlier-predicted reward or punishment. In the brain, the exaggerated representations and associations of the stimulus and the rewards/punishments and the conditioned responses that had resulting from 'learning' the association (prediction) faded back to the starting line, in a reversible passage to 'extinction'.

As we studied changes in the brain associated with skill acquisition, we repeatedly showed that we could improve neurological processes in ways that empowered OR degraded them, driving the brain operationally forward OR backward, at will. Put in simple terms, we could refine OR degrade the accuracy with which an animal's cerebral cortex could make refined or complex distinctions. We could accelerate OR decelerate sampling rates and advance OR regress a rich variety of underlying neurological processes. We could destroy a monkey's ability to control the manipulation of objects in its hand, turning that hand into a useful claw by engaging it in a few weeks of training. OR we could refine its hand control to grow and elaborate its manual powers OR advance its haptic abilities so that it could far more accurately identify things held in its hand to an extraordinary performance level. It is important to understand that this was easy to achieve in our experiments because, with research support from many other neuroscientists, we had defined the elementary *rules* that govern neuroplasticity. *Advances or degradation or improvement were achieved by merely following those rules.* Note to reader: NEUROSCIENTISTS HAVE DEFINED THE RULES THAT GOVERN 'ADULT' NEUROPLASTICITY. Within the limits of those rules, we can change your (anyone's) neurology, at will.

We later addressed this issue of the reversibility of plasticity in another way by comparing the physical and functional status of a brain that was healthy with the physical and functional status of a brain that was 'struggling'. In one comparison, we quantified the status of 15-20 (later, more than 40) physical and chemical and functional indices of neurological structure, chemistry and function in struggling near-end-of-life animals with the same indices recorded in the brains in thriving young adult animals (de Villers-Sidani E et al, 2010). In another series of studies, we compared a similarly broad array of physical and chemical and functional indices of organic brain health and neurological performance in animals that had struggled across an epoch of neurological challenges in early life (stress, rearing in noise and chaos, environmental toxins et al) with their brains compared again with the brains of thriving animals that had the advantages of a 'normal' childhood (Zhou X et al, 2007, 2009; 2011; Zhu X et al., 2014).

What differed in thriving vs struggling (old vs young, or environmentally challenged childhood vs normal childhood) brains? The answer? EVERYTHING that we (and other scientists had) measured (in the same general context). Included on that list:

- The brain's PHYSICAL/STRUCTURAL machinery (dendrite and axonal and glial cell elaboration; myelination)
- Its CHEMISTRY (synaptic receptor subunits; neuromodulators regulating plasticity; growth factors)
- Its DEFENSES (its intrinsic immune response; the integrity of the 'blood-brain barrier' protecting the brain against viruses and other infectious agents)
- Its NUTRITIONAL SUPPORT (astrocytic processes controlling nutrient supply; reactive hyperemia, i.e., on-demand blood flow; brain cell metabolism)
- Its INFORMATION PROCESSING MACHINERY (response specificity, stimulus representation, processing speed at every level, association/prediction)
- Its CONNECTION STRENGTHS in brain systems supporting attention, memory, 'self'-genesis, executive control, emotion control, social cognition, et alia.

We asked: "How many of these physical, chemical and functional indices were stronger—more physically elaborated/intact, more chemically advanced, more reliable, faster, more refined,—in the **struggling** animal?

The answer: None of them. BY EVERY MEASURE, struggling brains were physically, chemically and functionally degraded and under-performing, compared to normal (thriving) brains.

The next question we asked led to a definitive study: "How many of these degraded physical and functional and chemical weaknesses could be improved—reversed and 'brought up to speed'—by appropriately *training* the struggling animal."

The answer: ALL OF THEM (de Villers-Sidani E et al, 2010; Mishra J et al, 2014; Zhou X et al, 2007; 2009; 2015; Zhu X et al, 2014)

For the near-end-of-life animal, **ALL** physical, chemical and functional indices of physical status and performance and health were sharply improved, to approach and often equal the status recorded in that young, healthy, prime-of-life brain. For the developmentally challenged brain, as a consequence of simple forms of training primarily addressing weaknesses in brain accuracy and speed and the control of processes underlying attention, ALL measured indices of organic brain health and neurological functional status approached the values recorded in a brain that had had the benefits of an enriched younger life.

We (and others) have asked: "What underlies these differences? Why is the average old or environmentally challenged brain so different in its physicality, its chemistry, its health, its functionality, as indexed by these >40 measures? What underlies its regression in aging, or its failure to advance given a high-stress early life. Guided by our understanding of the rules governing adult neuroplasticity, we engaged healthy, thriving prime-of-life brains and 'drove their health and functionality into the ditch' (for example, see Zhou et al., 2011). By that training, we elevated the level of noise (meaningless 'chatter') in the neurological processes in the brain. In real life, there are a hundred ways in which that can occur. Continuous stress, heavy alcohol exposure, concussive and other 'soft' and direct brain injury, anxiety or depression, a long list of other mental and physical illnesses, genetic weaknesses, ADHD, and a host of common environmental poisons and medications are on this list. In our animal models we initially used the simplest of tactics to amplify 'brain noise'. In the listening brain, we simply exposed the animal to moderately loud continuous acoustic noise for all of its waking hours over several successive weeks of life. As a consequence, BY ALL MEASURES, the animal's listening brain system matched the status of that recorded in a 'near-end-of-life brain', or of an untreated brain that had survived a stress-loaded childhood.

We can only account for these 40+ physical and chemical and functional things changing TOGETHER by processes that involve complexly *coupled* gene regulation. There appears to be a kind of 'master switch' in the brain. Throw that switch in a positive, health-ward, functionally advancing direction and EVERYTHING advances. Throw it in a negative health-degrading, functionally retreating direction and EVERYTHING degrades.

We understand how to control the switch.

We've hypothesized that the evolutionary value of this bi-directionality is simple: Beyond the earliest epoch of childhood, brain plasticity is controlled by brain-adjudged outcomes. If behavioral success (again, from the brain's own neuromodulatory perspective) is too-often NOT achieved, or if the brain is consistently NOT responding to novel information, there is a gene regulation change that results in a progressive relaxation of the brains temporal operational characteristics. In a sense, in the more difficult signal-to-noise conditions that apply for a struggling brain, it *must* take longer to 'get the answer right'. The brain's goal in this bi-directional process is to always operate at a reasonable performance level, even while stress or concussion or chemical poisoning or blood-brain barrier leakage or a multitude of other phenomic (environmental/brain health) factors increase meaningless 'chatter' in the highly excitable tissues of the brain. Reversible plasticity assures that we humans always mostly 'get the answer right' for those operations that are most crucial for our survival, even while that may be achieved in brains with large scale differences in organic brain health and refined operational capabilities.

Finally, we asked: Even in the thriving young prime-of-life animal, the brain is plastic. If we trained the THRIVING animal, would that confer a protective advantage for the animal in its 'old age'? Would it grow what psychologists have called 'cognitive reserve' in the brain?

The answer is "Yes". Normal animals trained in the prime of life retain high functionality into normal old age, while their untrained brothers and sisters decline at the normal down-hill rate as the months go by (Cheng Y et al, 2017). And they live longer.

4.0 IN ITS BROADLY-COORDINATED EXERCISE-DRIVEN REMODELING, BRAIN FITNESS IS AKIN TO PHYSICAL FITNESS

Almost every aspect of physical health related to movement control is advantaged by the right forms of physical exercise that advances the operation of motor control in speed, precision, and power. Positive changes are not limited to muscle tissue; they extend to every vascular and pulmonary and intrinsic metabolic and immunological and alimentary and waste-removal process that directly or indirectly *supports* movement. So, too, in the brain. Why, then, have we not broadly adopted 'brain gym' or natural 'outside' neurological exercises that reliably grow and sustain organic brain health and function? Why is there no routine 'brain exam' deployed to assay and help manage our organic brain health, to assure that we are safer, more reliable, more controlled, and more powerful, and 'smarter' in our neurological operations?

Why, indeed?

Paradoxically, the brain is the only organ that can directly respond to a myriad of direct enquiries about its operational and physical and behavioral status. A massive neuroscience literature has recorded how the status of the physical and function brain relates to simple psychophysically-measured performance abilities. Why don't we more routinely deploy these highly scalable strategies to 'ask' our medical clients or the members of our work forces about the health, safety and performance capabilities of their brain?

Again, why, indeed?

5.0 DOCUMENTING THE HEALTH AND THE FUNDAMENTAL AND SPECIAL PERFORMANCE CHARACTERISTICS OF THE BRAIN.

We've designed a series of more than 40 assessment tools designed to measure neurological performance capabilities in the great systems of the human forebrain, evaluating operational neurological capabilities in those systems at different levels. Each tool has been deployed in many thousands of individuals in the normal population, and in thousands of individuals with a rapidly growing number of neurological and psychiatric clinical indications. To cite a simple example, how long does a 'normal' individual have to be exposed to a visual representation of a familiar object to identify it? Or, from the obverse perspective, how many visual objects could they identify, operating as rapidly in object recognition as they can, within a fixed period of time? At one end of the human continuum, high performers can reliably identify a visual presentation of a familiar object in about 1/30th of a second—and identify many objects over the period of a minute. A lower-performing normal individual may require a stimulus presentation time that is >10x longer, and may struggle to identify more than 1 or 2 or 3 stimuli in a minute.

From this single measurement, we know a lot about those different individual brains. It informs us about the state of myelination (the insulation on the 'wiring') in the engaged brain system because well-insulated 'wires' (axons) are faster. It informs us about the time constants of synaptic processes in the system. It informs us about the strengths of connectivity from the bottom to the top of the visual reception/recognition system because fast systems are strongly connected level to level, while slow systems are not. It informs us about the selectivity of operation of the representational machinery, at every system level.

From other historic human experiments, we know that a brain that is fast at operations like this one is better at almost any elementary visually-limited ability (for example, see Salthouse TA, 1996a,b; 2000). We've known for more than 40 years that visually fast brains are 'smarter' when their intelligence is visually interrogated (Jensen AR, 1980). Fast brains that operate with high accuracy have better memories and stronger reasoning powers.

As we have earlier described, the status of processing speed (with sustained accuracy) in a brain system is strongly correlated with everything else we have been able to measure (again, more than 40 indices) to document the status of that system in physical, chemical and functional terms. A more accurate and faster brain will be organically healthier—at least in the great brain system under examination. A slower brain is correspondingly less healthy.

6.0 TRANSLATING THIS SCIENCE TO IMPROVE ORGANIC BRAIN HEALTH, AND TO IMPROVE THE OPERATIONAL POWERS OF THE BRAIN

It's fortunate, then, that in humans as in animals, it is relatively easy to accelerate neurological processes even while we grow performance accuracy via progressive training on a computer or pad or smartphone. That training can be localized to the different major operational systems in our brains, strengthening their operations at every system level. When we began to understand these possibilities, we turned our research focus to developing strategies for delivering individuated forms of training to restore and strengthen underperforming brains in human populations. Those training programs[2] delivered on internet-connected computers (later also on pads and smartphones) are:

[2] For a program description, see https://BrainHQ.com

- *Adaptive and progressive*, designed to rapidly adjust to (customize), then advance the performance abilities of any 'Brain Gym' (*BrainHQ*) program user.
- *Optimized* with an understanding of the 'rules' governing plasticity to assure that the trainee will reliably and rapidly improve their neurological performance abilities.
- *Targeted*, to recover/advance important neurological performance abilities in different operational modes, at different brain system levels.
- *Extensive*, to achieve 'rejuvenation' or 'recovery' or 'renormalization' or to achieve more advanced or superior operational capabilities in the neurological machinery that accounts for a rich variety of important skills and abilities related to organic brain performance and brain power.
- *Continuously validating outcomes*, by driving the trainee to—and thereby quantifying—performance functional limits in the task, in every training cycle. (This strategy also embodies the most effective way to drive plastic changes with optimal efficiency.)
- *Proven to work*, as has been validated in more than 200 peer-reviewed reports summarizing the outcomes of randomized control trials (RCTs).[3]
  - *Training is effective in struggling, normal and high-performance subject populations.* A majority of these training outcomes trials were conducted in variously struggling human populations. Others were conducted in the normal population, or in high-performance workers or athletes. *ALL were advanced in neurological and behavioral ability as a result of progressive computerized training*.
  - *Training remodels the physicochemical brain, in the predicted ways.* A majority of these studies cross-confirmed neurological recovery and improvement by documenting positive neurological changes using EEG, MRI, fMRI, MEG, PET or blood chemistry measures. In many of these studies, these direct neurologically documented improvements were correlated with recorded behavioral changes.
  - Training on our BrainHQ programs in the 'Brain Gym' GENERALIZED to untrained operations in everyday life—or in high performers, to specialized neurological performance abilities. Changing the fundamental operational machinery of the brain is different, in this respect, from directly practicing those complex skills and abilities that apply for a high-achieving brain, because the now-healthier, now-functionally-empowered brain trained in these ways that advance brain health and fundamental neurological operations deploys that now-more-advanced machinery in the achievement of every task that uses that more advanced machinery. As in well-designed physical fitness programs, advancing brain fitness empowers almost every physical challenge undertaken from that point forward. So, too, in your brain.
- *Clinically monitored (optionally) via the internet*, through a internet portal designed to help a clinician or program monitor or medical specialist or program administrator:
  - Record and assure training program usage and compliance.
  - Coach the trainee (if necessary).
  - Evaluate and document individual and training group outcomes.
- *Scalable.* Computerized assessment and computerized training provide a powerful AND inexpensive AND efficient way to advance neurological health and human performance abilities.

[3] For a complete list of—and URLs to access—those studies: https://www.brainhq.com/world-class-science/information-researchers/ More than 400 additional studies are now underway. Also see Basak C, 2020, for a review that also includes related brain science-based training programs.

7.0 PRACTICAL APPLICATIONS

We have applied these these new tools to calibrate then advance the neurological abilities of normal human populations (all ages), workplace specialists, high-performance professionals, and individuals with a diagnosis of—or who are at high risk for onset to—a long and growing list of neurological and psychiatric clinical indications. Examples include:

7.0.1 Brain science-based assessments…

- …for the general public. Working with the Seattle-based Institute for Systems Biology, we are deploying an assessment strategy designed to be provided to the general public in a public health/medical clinic context, to broadly assess (then respond to) their neurological weaknesses or distortions. Once those neurological weaknesses or distortions are defined, we deploy intensive progressive computer-delivered training strategies designed to reduce the risks of progression to future psychiatric or neuropathological clinical indications.
- …for military recruits. An enlightened neuroscience- and psychological science-informed team in the Italian Army is now routinely using a subset of these assessments to evaluate aspects of attention, processing speed and executive control in candidate soldiers.
- …for special forces trainees. Again, in a program led by a ground-breaking Italian Army training command team, and in a second effort now underway in American forces, BrainHQ assessments are being applied to define the strengths and weaknesses of candidate troops, setting up subsequent training designed to overcome neurological/operational weaknesses and to rapidly further grow neurobehavioral competencies.
- …for adolescent children. A sister company (Stronger Brain Corporation) an Australian Foundation (Stronger Brains Foundation) and a British non-profit child health mentoring company (Evolve) are deploying another relatively broadly configured assessment battery delivered over three school class days designed to define, in substantial detail, the organic brain health, neurological performance abilities and risks for progression to mental illness, in a large adolescent student and young adult population. Again, assessments lead to specific individuated training programs designed to address assessment-revealed neurological deficits and distortions. The goal of this "Stronger Brains Program) is to improve student performance and academic completion rates and behavior, and to reduce the incidences of mental illness, oppositional behaviors and criminal offending, addictions, ADHD, PTSD, et alia.

It is important to note that in all of these applications of brain science-inspired assessments, we have constructed training program modules that specifically target assessment-documented weaknesses, with performance recovery/improvements documented by the repeated use of these highly efficient and scalable assessment tools.

7.0.2 Training designed to improve the neurological status of psychiatric and neurological patient populations, and to reduce the probability of a progression to a psychatric or neuropathological diagnosis in aan at-risk individual, Once the neurological weaknesses and distortions or ability level are defined by computerized assessment, we direct our attention toward neurological improvement, often by initially broadly advancing organic brain health and overall neurological performance status, then zeroing in on specific deficits that apply for that specific class of individuals in training. A few examples:

- Training to improve attentiveness and distractor suppression (ADHD). Benefits achieved in a 30-hour-long training BrainHQ regime were equivalent to those achieved with use of stimulant drugs (Ritalin or Adderall), with the exception that several months after computerized training, benefits of treatment are sustained, while sustaining benefits from pharmaceutical treatment require continuous medication, with progressively elevated dosing (see Mishra J et al, 2013; 2016; Stevens C et al, 2010; Van Vleet T et al, 2016). In adolescent child studies, we are now routinely integrating that BrainHQ training program suite with brief daily epochs of computer-monitored meditation, also shown to drive positive neurological changes in ADHD-impacted individuals.

- Training to up-regulate modulatory control processes in ways that accelerate learning rate. With about 10 hours of training in the right form, the processes that control plasticity have been shown to be significantly upregulated, and in parallel, we record a highly significant increase in learning rate (see Van Vleet T, 2016). In contradistinction to pharmaceutical strategies, changes appear to be sustained without further training. In practice, we periodically assess the underlying processes with the goal of re-engaging them, if training benefits fade.

- Training to strengthen the modulatory control machinery that critically enables and supports cortical plasticity processes. With these forms of training, studies in animal models and in human trials have directly documented strong impacts on the locus coeruleus's production and distribution of noradrenaline (Van Vleet et al., 2018), the basal nucleus of Meynert's production and release of acetylcholine,[4] the dorsal raphe's production and release of serotonin (Zhou et al., 2015), and the production and release of brain derived neurotrophin (e.g., Fisher M et al,2016). In extensve application of neuroscience-based training tools, we associate the elevation of the production and release of these and other neuromodulators with improvements in learning rates in neurologically struggling training groups.

- Training to improve mental health in diagnosed psychiatric patients. Many studies have documented functional and neurological gains resulting from computerized training in patients with schizophrenia, major depressive disorder, bipolar disorder and anxiety disorders.[5] To cite a handful of many examples:

  - In patients with a major depressive disorder, a well-designed RCT engaged treatment-resistant patients in about 30 hours of progressive computerized training, comparing outcomes with best-practices pharmaceutical treatments. Behavioral improvements were equivalent, with two exceptions (Morimoto SS et al, 2014; also see Routledge KM et al, 2021). First, brain plasticity-based (BrainHQ) training significantly advanced executive control. No such benefit was recorded in antidepressant-treated patients. Second, benefits from brain plasticity-based training were sustained with no continuing engagement after program completion. Pharmaceutically treated patients will presumably have to continue drug treatment into the indefinite future—and will require some level of continuous monitoring and probable drug treatment to the end of life.

    Note that our now-recommended course of treatment in a patient population like this one is to evaluate neurological status at the end of a first round of intervention —then customize a brain-training-Round 2, as needed, to achieve still-stronger and still-more-complete neurological restoration. In contradistinction with single-chemical pharmaceutics, brain plasticity-based training can drive a progressively elaborated set of neurological changes on a true path to neurological normalcy.

    - In patients diagnosed with schizophrenia, recent seminal studies indicate that the combination of speech reception-focused and visual recognition-focused training integrated with social cue recognition training could substantially and broadly improve the neurology and behavioral and quality of life status of patients with schizophrenia (see Vinogradov S et al, 2012; Scoriel L et al, 2020; Nahum M et al, 2021) in a way that impacts their behavioral operations to a level that has never been recorded before, via any alternative strategy.

- Training to <u>prevent</u> a progression to mental or neurological illness in at-risk individuals.

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[4] https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2018.06.689

[5] See Depression, Schizophrenia and Bipolar Disorder RCT reports listed with URLS at: https://www.brainhq.com/world-class-science/information-researchers/

- *Depressive and anxiety disorders*. Even a brief period of training (10-18 hours of progressive training on a computer) reduces the risks of progression to a diagnosed mood disorder in a high-risk older-age population—and if a diagnosed depressive disorder arises in an attention- and speed-trained individual, it is expressed in a milder clinical form (Wolinsky FD et al, 2009a,b; 2015).

- *Training designed to improve the prodromal expressions expected to lead to a later schizophrenia diagnosis* is a focus of studies that are now underway. At this point in our collaborative family's research, they have confirmed that at least most prodromal weaknesses indexing the risks for progression to schizophrenia onset appear to be at least partially reversible via intensive computerized training.[6] It remains to be seen whether or not this neurological strengthening shall reliably delay or prevent future diagnosis-level 'disease' expression.

- In a training study conducted in youth employment setting in juveniles and young adults, mental stability and suicidal ideation was assessed at program onset, then again at training program completion. Most of the >200 young trainees who were identified as at high risk for a progression to mental illness at program onset fell within the middle of the 'normal' by these same measures after program completion.[7] EEG measures further documented positive neurological changes that at least partially accounted for these neurobehavioral improvements.

- *Training to delay or prevent a progression to a neuropathological disorder*. Our primary focus up to this time has been on delaying or preventing a progression to dementia/Alzheimer's. This research is relevant to military personnel because they (like police) have an amplified job-related risk of an earlier progression to dementia—and have shorter lifespans—because of the brain-noise-elevating, 'soft brain damaging' impacts of their higher-stress lives. We have supported studies conducted in both the general population, and in high-risk patient groups. For example:

  - *In a series of studies conducted in 'mildly cognitively impaired' individuals*, at high risk for a conversion to Alzheimer's or other dementias within 1-3 years, scientists recorded large-scale neurological *BrainHQ*-driven neurological gains paralleling functional and behavioral recoveries (for example, Styliadis V et ala, 2015; Klados MA et al, 2016; Feng L et al, 2016, 2017; 2020). A reversal of the progressive demyelination, reductions in brain area volumes, and of a progressive loss of brain system connectivities resulted from this neuroplasticity-based intervention.

  - *In an important study conducted in the general aging population*, only 10-18 hours of computerized training *at a single attention- and speed-targeted exercise* (in subjects that were initially 75 years of age on average) resulted in a highly significant reduction in the likelihood of their progression to dementia over the subsequent post-training decade (Edwards JD, 2017). That included patients who were diagnosed with MCI—expected to rapidly advance to an Alzheimer's diagnosis—prior to this training. In parallel, the brain speed of these trainees at a +10 year post-training benchmark was still faster than when they initiated training, a decade earlier; and they were adjudged to *still* be cognitively advantaged over non-trained controls (Rebok G et al, 2014). We now recommend, of course, that the initial training dose for the average citizen be a little more serious, and that ongoing periodic assessments and as-required 'booster' training be a part of managing brain health in older—indeed, in every citizen.

For military personnel, it now appears likely that training in the right forms can also increase neurological resilience in ways that red uces the likelihood of a work-related genesis of a PTSD, of a concussive injury, or of extended epochs of fear or stress.

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[6] See https://www.brainhq.com/world-class-science/information-researchers/#1612824163359-6da56a7f-6fb4 for a list of the >60 reports describing brain plasticity-based training's impacts on the neurological and behavioral expressions of schizophrenia

[7] See https://drive.google.com/file/d/1-Bx6eEg1KwsEAEyR0x_Xru6FK5ZnpPZH/view?ts=61491cb3 for the full government report on these important trial outcomes.

7.0.3 Training to improve on-the-job performance

An extensive series of studies have documented the benefits of training on workplace performance. Here, we focus on studies conducted in workers that have performance demands that most directly relate to personnel in military service. For example:

- *Law enforcement personnel* have significantly benefited from computerized brain plasticity-informed training.
  - *With 20 hours of computerized training focused on fast visual reception and recognition and on social cue recognition*, 300 members of a large metropolitan police force had a 50% reduction (over the period of the post-training year compared to their performance in the year before training) in their resorting to violence in policing; a 50% reduction in citizen complaints about their policing; and only 1/4th as many driver-caused traffic accidents.
  - *With 20 hours of BrainHQ training focused on improving attention control and executive control, and on fast visual reception, recognition and controlled responding*, trained police had highly significant improvements in decision accuracy in simulations of 'shoot/don't shoot' scenarios AND strong improvements in fast-decision-context shooting accuracy (Hamilton JA et al, 2019).
- *Special ops forces* in Italy and America are initiating training regimes expected to advance their operational skills, guided by brain science-based assessments designed to reveal neurological limitations/weakness, and to track training-driven progress.
- *Trained high risk ('high line') workers* in the American electrical service industry had a sharp reduction in accident rate attributable to brain training. Benefits of training were fully sustained out to a post-three-year training benchmark (that is, more than 33 months after training was completed)—with a greater than 50% reduction in the incidence of serious work-related accidents still sustained across the 2nd and 3rd post-training year (re comparisons with accident incidences in the years immediately preceding training; see Miller SL et al, 2019).
- *Trained equipment operators/drivers* have significantly lower driver-caused accident rates. Drivers who are >60 years of age (i.e, on average, expressed age-related decline in brain health and operational ability)(had a reduction of accident rates following 10-12 hours of computerized training of about 30-50% (for example, Ball KJ et al, 2010). Large scale performance differences were also recorded in driver simulation-based studies (Roenker DL et al, 2003).
- *When engineers and other technical specialists were trained in a high-tech research and development facility*, their work productivity sharply improved (Walters J et ala, 2019). EEG studies documented strong improvements in attention, memory and executive control systems that paralleled those gains.
- Many high-performing athletes and other specialists have improved their abilities using B*rainHQ* training. Examples include:
  - One of the greatest all-time American football players Tom Brady, still playing at a high performance level at age 44, specifically credits *BrainHQ*'s computerized brain training as a key aspect of his sustained athletic competence (Brady T, 2017).
  - Using a form of brain training in which a football player responds by interaction with a large two-dimensional response board, the Italian company Microgate has trained a large and growing number of premier-level players—again repeatedly documenting the values of integrating brain fitness training with physical skills training.

7.0.4 Training to rescue the risks and the neurological consequences of work-relted 'soft' and direct brain injury.

- *Brain training has been effectively applied to accelerate neurological recovery after concussive injury—*

and to reduce the probability of, and severity of future concussions, by using training strategies that are known to strengthen the integrity of the blood-brain barrier (which is compromised in concussion).

- *Training to address functional losses attributable to TBIs*. Substantial positive impacts were recorded in a DARPA-sponsored RCT (Mahncke H et al, 2021).
- *Training to overcome 'soft brain damage' resulting from chronic stress.* Many studies have shown that the negative neurological consequences of chronic stress are broadly reversible.
- *Training to upgrade performance in older personnel.*

8.0 HOW SHOULD *YOU* DEPLOY THESE NEW TOOLS TO IMPROVE THE PERFORMANCE CAPABILITIES OF YOUR ARMED FORCES?

There are a number of obvious ways by which this new science could be exploited to improve the health and performance capabilities of military personnel. Specifically:

8.0.1 Assessment of recruits.

The Italian Army has used a brief form of a computerized *BrainHQ* assessment battery as one of their screening tools for evaluating the prospective performance capabilities of incoming personnel. This simple toolset indexes processing speed and attention control—which is highly informative about the organic brain health and neurological capabilities of young trainees.

8.0.2 Addressing neurological performance issues in entry-level personnel.

Our militaries are routinely accepting young men and women into service who shall fail in training and fail to complete their service obligations. Neurological abilities could easily be routinely calibrated via self-administered computerized testing *and at least the most elemental of neurological weaknesses addressed* in incoming recruits. The first round of this brain-strengthening training could be potentially achieved before the candidate formally initiates service, with their compliance and performance gains documented by military-based monitors in the Training Command, or by contract monitors. Alternatively, customized brain training could be integrated directly into basic training schedules.

8.0.3 Train military specialists to improve their special occupational competencies.

That brain training should be localized to address the specific neurological competencies that impact the job performance of special ops personnel, heavy equipment operators, accident-prone specialists, high-stress-loaded professionals, fast and accurate combat responders, marksmen, technical specialists, et alia. They are ALL subject to brain training driven improvements that can make substantial differences in their health, operational safety, performance, and attitude.

8.0.4 Evaluate neurological status with a sensitivity to risks of progression to mental illness, oppositional behaviors, et alia.

More than 30% of older juveniles and young adults are at high risk for these force-destructive outcomes at a young age. Many young men and women carrying these burdens show up at your recruitment centers and are enlisted into your armed forces. Minimizing the incidences of these life- and performance-degrading outcomes across their terms of military service, achieved by identifying and addressing underlying neurological weaknesses, should be a high priority for your Training Command teams.

8.0.5 Assess the neurological status of every standing member of your military.

Brain health issues apply for EVERYONE in military service. Beyond a focus on recruits and specialist training you should prepare the ground for ultimately assessing the neurological performance abilities of ALL of your standing personnel. You should also be prepared to back up that round of assessments by providing brain training assets to address operational weaknesses, individual by individual. That is achievable because of the low cost in money, time and individual and supporting efforts required to implement force-revitalization on this scale. An annual, briefer, computerized 'brain check' for all military personnel would subsequently assure that you are identifying *emergen*t brain health and neurological performance deterioration that is impacting the operational capabilities of your armed forces.

8.0.6 Train individuals in ways that help assure that they can make a successful transition from military service back to general civilian life.

Insofar as possible, make certain that they do NOT return to that civilian life with military service-damaged brains that now unfairly foretells a progression to dementia at a younger age, and a shorter lifespan. And make certain that you have not substantial added to neurological burdens that foretell a civilian future with a personality disorder, mental illness or addiction.

8.0.7 Finally, review your training procedures, asking yourselves: Do aspects of our training plausibly drive brain plasticity in a NEGATIVE neuroplastic direction? Could THAT be a major reason why military retirees are at that higher risk of an early progression to older-age dementia? Could that be part of the reason why they have shorter lifespans? Could any aspect of your training approach actually DEGRADE neurological performance abilities? The intelligent deployment of brain science-inspired computerized assessments would help you quickly definitively answer these important questions.

9.0 CONCLUSIONS.

This science, and these new strategies for assessing and improving human performance abilities, could be transformation for your military personnel and for mission fulfillment. From this scientist's perspective, it is important that you take this science seriously *and exploit it* on the path for sharply improving both the health and the performance abilities of our mutually protecting armed forces.

REFERENCES CITED

[1] Ball KJ, Edwards JD, Ross LA, McGwin G Jr (2010) Cognitive training decreases motor vehicle collision involvement of older drivers. J Amer Geratrics Soc 58:2107. https://doi.org/10.1111/j.1532-5415.2010.03138.x.

[2] Basak C, Qin S, O'Connell MA (2020) Differential effects of cognitive training modules in health aging and mild cognitive impairment: AA comprehensive meta-analysis of randomized controlled trials. Psychol Aging 35:220.

[3] Brady T (2017) The TB12 Method: How to Achieve aa Lifetime of Sustained Peak Performance.

[4] Cheng Y, Jia G, Zhang Y, Hao H, Shan Y, Yu L, Sun X, Zheng Q, Kraus N, Merzenich MM, Zhou X (2017) Positive impacts of early auditory training on cortical processing at an older age. Proc Natl Acad Sci 114:6364. doi: 10.1073/pnas.1707086114.

[5] Stevens C, Fanning J, Coch D, Sanders L, Neville H (2008) Neural mechanisms of selective auditory attention are enhanced by computerized training: electrophysiological evidence from language-impaired and typically developing children. Brain Res 1205:55. doi: 10.1016/j.brainres.2007.10.108.

[6] de Villers-Sidani E, Alghoul L, Zhou X, Simpson KL, Lin CS, Merzenich MM (2010) Recovery of functional and structural age-related changes in the rat primary cortex with operant training. PNAS 107:13900. Doi: 10.1073/pnas.1007885107

[7] Edwards JD, Huiping Xu, Clark DO, Guey LT, Ross LA, Unerzagt FW (2017) Speed of processing training results in lower risk of dementia. Alz & Dementia Trans Res & Clin Intervent 3:603. https://www.sciencedirect.com/science/article/pii/S2352873717300598

[8] Hamilton JA, Joseph A, Lambert G, Suss J, Biggs AT (2019) Can cognitive training improve shoot/don't shoot performance? Evidence from live fire exercises. Amer J Psychol 132:179.

[9] Jensen AR (1980) Chronometric analysis of intelligence. J Social Biol Struct 3:103.

[10] Klados MA, Styliadis C, Frantzidis CA, Paraskevolpoulos E, Bamidis PD (2016)

[11] Beta band functional connectivity is reorganized in mild cognitive impairment after combined computerized physical and cognitive training. Front Neurosci10:1.https://doi.org/10.3389/fnins.2016.00055.

[12] Lin, Feng, Kathi L. Heffner, Ping Ren, Madalina E. Tivarus, Judith Brasch, Ding-Geng Chen, Mark Mapstone, Anton P. Porsteinsson, and Duje Tadin. "Cognitive and Neural Effects of Vision-Based Speed-of-Processing Training in Older Adults with Amnestic Mild Cognitive Impairment: A Pilot Study." *Journal of the American Geriatrics Society* 64, no. 6 (June 2016): 1293–98. https://doi.org/10.1111/jgs.14132.

[13] Feng L, Heffner KL, Ren P, Tadin D (2017) A role of the parasympathetic nervous system in cognitive training. Curr Alzheimer Res 14:789. https://www.ingentaconnect.com/contentone/ben/car/2017/00000014/00000007/art00011

[14] Feng L, Quanjing YT, Anthony M, Zhang Z, Tadin D, Heffner KL (2020) Processing speed aand attention training modifies autonomic flexibility: A mechanistic intervention study. Neuroimage 116730. https://pubmed.ncbi.nlm.nih.gov/32165263/.

[15] Fisher M, Mellon SH, Wolkowitz O, Vinogradov S (2016) Neuroscience-informed auditory training in schizophrenia: A final report on the effects on cognition and serum brain-derived neurotrophic factor. Schizophr Res Cogn 3:1 doi 10.1016/j.scog.2015.10.006

[16] Lambert K, Eisch AJ, Galea LAM, Kempermann G, Merzenich MM (2019) Optimizing brain performance. Identifying mechanisms of adaptive neurobiological plasticity. Neurosci Biobehav Rev 105:60. doi: 10.1016/j.neubiorev.2019.06.033

[17] Mahncke HW, DeGutis J, Levin H, Newsome MR, Bell MD, Grills C, French LM, Sullivan KW, Kim S-J, Rose A, Stasio C, Merzenich MM (2021) A randomized clinical trial of plasticity-based cognitive training in mild traumatic brain injury. Brain 144:1994. doi: 10.1093/brain/awab202

[18] Merzenich M (2013) *Soft-Wired. How the New Science of Brain Plasticity Can Change Your Life.* Parnassus Publishing, San Francisco. [Chapter by chapter annotation at https://www.Soft-Wired.com]

[19] Merzenich MM, Van Vleet TM, Nahum M (2014) Principles of brain plasticity-based therapeutics. Front Hum Neurosci 8:385. doi: 10.3389.fnhum.2014.00385

[20] Mishra J, Merzenich MM, Sagar R (2013) Accessible online neuroplasticity-targeted training for children with ADHD. Child Adolesc Psychiatry Ment Health 7. doi: 10.1186.1753-2000-7-38.

[21] Mishra J, de Villers-Sidani E, Merzenich M, Gazzaley A (2014) Adaptive training diminishes distractibility in aging across species. Neuron 84:1091. doi:10.1016/j.neuron.2014.10.034.L

[22] Miller SL, Chelian S, McBurnett W, Tsou W, Kruse AA (2019) An investigation of computer-based brain training on the cognitive and EEG performance of employees. *41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)::* 51821. https://doi.org/10.1109/EMBC.2019.8856758.

[23] Morimoto SS, Wexler BE, Liu J, Hu W, Seirup J, Alexopoulos GS (2014) Neuroplasticity-based computerized cognitive remediation for treatment-resistant geriatric depression. Nature Comm 5:1. https://doi.org/doi:10.1038/ncomms5579

[24] Nahum M, Lee H, Fisher M, Green MF, Hooker CI, Ventura J, Jordan JT, et al. (2021) Online social cognition training in schizophrenia: A double-blind randomized controlled multi-site clinical trial. *Schizophrenia Bull* 47:108. https://doi.org/10.1093/schbul/sbaa085.

[25] Rebok GW, Ball GW, Guey LT, Jones RN, Kim H-Y, King JW, Marsiske M, et al. (2014) Ten-year effects of the Advanced Cognitive Training for Independent and Vital Elderly Cognitive Training Trial on cognition and everyday functioning in older adults. J Amer Geriatrics Soc 62:16. https://doi.org/10.1111/jgs.12607

[26] Roenker DL, Cissel GM, Ball KK, Wadley VG, Edwards JD (2003) Speed-of-processing and driver simulation training result in improved driving performance. *Human Factors* 45: 218 https://pubmed.ncbi.nlm.nih.gov/14529195/

[27] Salthouse TA (1996) The processing-speed theory oof adult age differences in cognition. Psychol Rev 103:403. doi: 10.1037/0033-295x.103.3.403.

[28] Salthouse TA (2000) Aging and measures of processing speed. Biol Psychol 54:35. doi: 10.1016/s0301-0511(00)00052-1.

[29] Salthouse TA (1996) General and specific speed mediation of adult age differences in memory. J Gerontol B 52:30. doi: 10.1093/geronb/51b.1.p30.

[30] Scoriels L, Genaaro LT, Mororo L, Keffeer S, Guimaraes AL, Ribeiro P, Tannos FM (2020) Auditory versus visual neuroscience-informed cognitive training in schizophrenia: Effects on cognition, symptoms and wuality of life. Schizophrenia Res 222:319. https://doi.org/10.1016/j.schres.2020.05.017.

[31] Styliadis V, Panagiotis K, Paraskevopoulos R, Andreas A. Ioannides SS, and Panagiotis D. Bamidis PF (2015) Neuroplastic effects of combined computerized physical and cognitive training in elderly individuals at risk for dementia: An Eloreta controlled study on resting states. *Neural Plasticity* e172192. https://doi.org/10.1155/2015/172192.

[32] Van Vleet TM, DeGutis M, Merzenich MM, Simpson GV, Zomet A, Dabit S (2016) Targeting alertness to improve cognition in older adults: A preliminary report of benefits in executive function and skill acquisition. Cortex 82:100. https://doi.org/10.1016/j.cortex.2016.05.015.

[33] Van Vleet T, Voss M, Dabit S, Mitko Aa, DeGutis J (2018) Randomized control trial of computer-based trainng targeting alertness in oler adults: th ALERT trial protocol. BMC Psychol 622. Doi: 10.1186/s40359-018-0233-4.

[34] Walters J, Sheft SE, Stellmack MA, Abele A (2019) Improving attentiveness: Effect of cognitive

training on sustained attention measures. *Professional Safety* 64: 31. https://www.onepetro.org/journal-paper/ASSE-19-04-31.

[35] Routledge KM, Williams LM, Harris AWF, Schofield PR, Gatt JM (2021) The impact of online brain training exercises on experiences of depression, anxiety and emotional wellbeing in twin sample. J Psychiat Res 134:138. https://doi.org/10.1016/j.jpsychires.2020.12.054.

[36] Vingradov S, Fishe M, de Villers-Sidani (2012) Cognitive tainng for impaird neural systees in neuropsychiatric illness. Neuropsychopharm 37:43. doi: 10.1038/npp.2011.251.

[37] Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Dotson MM (2015) The effect of cognitive speed of processing training on the development of additional IADL difficulties and reduction of depressive syptoms results from the IHAMS Randomized Control Trial. J Aging Heaalth 24:334. https://doi.org/10.1177/0898264314550715.

[38] Wolinsky FD, Mahncke HW, Vander Weg MW, Martin W, Unvezagt FW, Ball KK, Jones RN, Tennstedt SL (2009) The ACTIVE cognitive training interventions and the onset of and recovy from suspected clinical depression. J Gerontology Series B 64:577. https://doi.org/10.1093/geronb/gbp061.

[39] Wolinsky FD, Vander Weg MW, Matin R, Unvezagt FW, Baall KK, Jones N, Tennstedt SL (2009) The effect of speed-of-processing training on depressive symptoms in ACTIVE. J Gerontol. Series A. 64:468. https://doi.org/10.1093/gerona/gln044.

[40] Zhou X, Merzenich MM (2007) Intensive training in adults refines A1 representations degraded in an early postnatal critical period. PNAS 104:15935-40. doi: 10.1073/pnas.0707348104.

[41] Zhou X, Merzenich MM (2009) Developmentally degraded cortical temporal processing restored by training. Nat Neurosci12:26. doi: 10.1038/nn.2239

[42] Zhou X, Panizzutti R, de Villers-Sidani E, Madeira C, Merzenich MM. (2011) Natural restoration of critical period plasticity in the juvenile and adult primary auditory cortex. J Neurosci 31:5625

[43] Zhou X, Lu JY, Darling RD, Simpson KL, Zhu X, Wang F, Yu L, Sun X, Merzenich MM, Lin RC (2015) Behavioral training reverses global cortical network dysfunction induced by perinatal antidepressant exposure. Proc Natl Acad Sci 112:2233. doi: 10.1073/pnas.1416582111.

[44] Zhu X, Liu X, Wei F, Wang F, Merzenich MM, Schreiner CE, Sun X, Zhou X (2014) Perceptual training restores impaired cortical temporal processing due to lead exposure. Cereb Cortex 26: 334. doi: 10.1093/cercor/bhu258