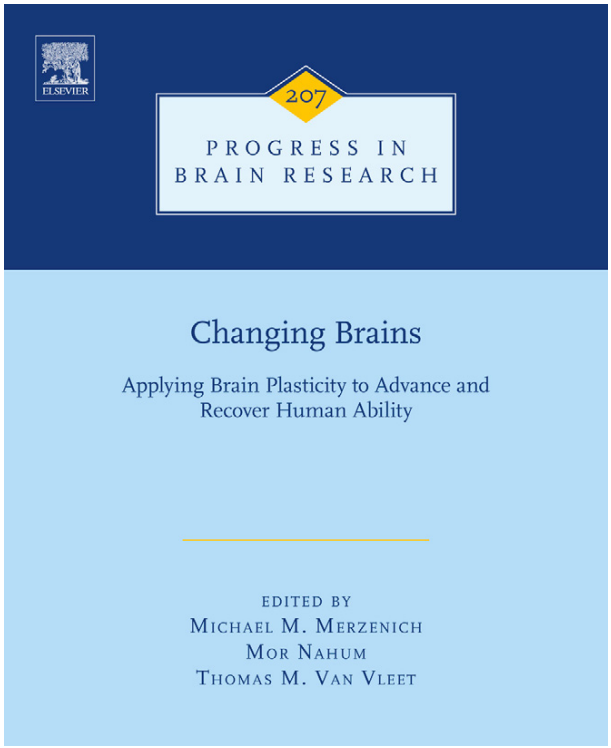

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CHAPTER

Principles of Neuroplasticity-Based Rehabilitation

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Abstract

The purpose of this review is to summarize how our perspective about the neuroscience of brain plasticity, informed by perceptual, experimental, and cognitive psychology, has led to the designs of a new class of therapeutic tools developed to drive functionally distorted and damaged brains in corrective directions. How does neuroplasticity science inform us about optimal therapeutic program designs? How do we apply that science, using modern technology, to drive neurological changes that address both the neurobehavioral distortions and the resulting behavioral deficits that are expressed in specific neurological and psychiatric disorders? By what strategies can we achieve the strongest and most complete rehabilitative corrections? These are questions that we have extensively explored in our efforts to establish new medical applications of neuroplasticity-based therapeutics. Here, we summarize the state of this rapidly emerging area of translational neuroscience, beginning with an explanation of the scientific premises and strategies, then describing their implementation in therapeutic software to address two human illnesses: the treatment of social cognition deficits in chronic schizophrenia and in autism; and the amelioration of age-related functional decline using strategies designed to delay the onset of—and potentially prevent—Alzheimer's Disease and related causes of dementia in aging.

Keywords

brain plasticity, social cognition, Alzheimer's Disease prevention, cognitive training, therapeutic programs, BrainHQ

1 INTRODUCTION

We begin the chapter with a description of our approach to creating brain plasticity-based therapeutic tools to treat neurological and psychiatric impairment attributable to "disease" and brain injury by outlining the principles derived from

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the science of neuroplasticity. In Part 2 we build on these principles to describe how we design training programs to target-specific deficits to address different clinical indications. Part 3 briefly summarizes our strategies for evaluating a training program's usability and efficacy, and the goals established for outcome trials. Finally, in Part 4 we provide two examples of therapeutic tools: a more narrowly focused treatment for overcoming social cognition deficits in schizophrenia and autism; and a broader program created to help overcome neurobehavioral decline in aging, and to increase an individual's resilience against the possible onset of Alzheimer's Disease (AD).

2 PART 1: PRINCIPLES OF BRAIN PLASTICITY; PREMISES FOR THERAPEUTIC TOOL DEVELOPMENT

Before we describe specific design strategies for our development of brain plasticity-based therapeutic tools, it is important to review our neuroscience-informed perspective about the neurological origins of behavior, and about the plasticity processes that underlie controlled rehabilitative changes in neurobehavioral ability.

2.1 Our Behaviors are the Products of Brain *Systems*

A large body of science has now shown that our expressive behaviors are a product of complex, multilevel recurrent networks (Edelman, 1987; for further discussion and review, see Merzenich, 2013). In these networks, information is represented with greatest resolution in detail in place, feature, and time at the lowest network (system) levels. At successively higher levels, there is an integration of representation to progressively more complex objects, relationships and actions, as they apply in the "real world." At the "top" of brain systems, those most-completely-integrated neurological representations generate enduring neural activity that is selective for their representation. That enduring, reverberant activity, providing the neurological basis of working memory, can be sustained in the human brain for tens of seconds to minutes of time (see Badderley, 2012; Compte et al, 2003; Goldman Rakic, 1995; Merzenich, 2013). Representational information is continuously fed backward from this highest (and from all other) levels. It is important to understand that in these recursive recurrent networks, the operational levels contributing to the representation of any aspect of input or action in brain systems are inseparable; in other words, *all explicit behaviors are a product of the system.* Therefore, when evident behaviors are distorted or impaired, as they are in the many ways that define the fundamental deficits and nuances of different neurological and psychiatric clinical indications, we necessarily target neurological renormalization at all system levels when designing therapeutic training programs.

It should be noted that cognitive therapists and other rehabilitation specialists have usually focused exclusively on training explicit, obviously impaired behavioral

abilities. If an individual has an evident failure in memory, for example, the therapist most often engages the patient to practice remembering, or to develop compensatory strategies to help them work around their memory loss. By contrast, from a more neurological perspective, we focus on improving the many deficits *across the various system levels* that contribute to the degradation of the neurological representation of information that the patient is struggling to record. Going back to the memory failure example, the focus of neuroplasticity-informed training would be on the clarity, in neurological terms, with which they represent that information, the suppression of distractors that disrupt remembering, the baseline levels of attention that support all epochs of remembering (among others), all aimed at improving the different operations of the relevant brain network before reexercising explicit memory abilities themselves.

2.2 Feedback Connections: Plasticity is Being Controlled "From the Top"

Recent neuroscience studies have also shown that through recursive reentrant feedback, the representation of information "at the top" of our forebrain processing systems *selectively* enables plastic changes contributing to the progressive behavioral success of brain systems. At highest system levels, behavioral targets are held, as described, via sustained target-specific activities, in working memory. That sustained persistently reverberant activity is projected backward down to "lower" system levels, where it positively enables plasticity for any fed-forward activity that can potentially contribute to a progressively improving resultant. Scientists often call the opening of this window that controls, through this top-down biasing, what the brain can change *to*, a "selective attention" process. In fact, "working memory" and "selective attention" can be considered as two descriptors of the same persistent reverberant activity-based representation/feedback process (see Fuster, 2008). The neurological processes that bias networks that are feeding these highest system levels to enable system plasticity are now understood, at a first level. Biasing is achieved, neurologically, by disinhibition processes in cortical networks controlled by convergent modulation "from the top" on the one hand (the working memory/selective attention process), and from a cholinergic subcortical input source engaged under conditions of focused attention, the basal nucleus of Meynert (see Froemke et al., 2007; Sarter et al., 2001, 2006; Weinberger, 2004; Chapter 3), on the other hand.

Ahissar and Hochstein (Ahissar et al., 2009; Hochstein and Ahissar, 2002) have described this feedback plasticity-enabling biasing, in psychological science terms, as the "Reverse Hierarchy Theory" (RHT). According to RHT's perspective, the brain holds a model of a behavioral event or training goal in working memory; that model, fed back to lower system levels, selectively amplifies activities (through disinhibition) that the brain can change *to*, as it progressively sharpens and refines, through learning, the resultant - its working memory-sustained models.

Given this new understanding of the neurological processes underlying top-down control of plasticity, we construct our training tasks with highly salient training targets held in working memory (Mahncke et al., 2006; Merzenich, 2013; Merzenich et al., 1998).

2.3 Feed-Forward Connections: Local Response Coordination, a Primary Product of Plastic Change, is the Principal Determinant of Feed-Forward (and Feedback) Power

Plasticity is primarily expressed by a change in connectional strength at the synapse level, achieved both by increasing the powers and the numbers of synapses specifically supporting a progressively improving behavior. Processes that control plasticity strengthen all synapses that are activated together at each brief moment in time that have contributed to just-past behavioral success. The great principal postulated by the Canadian psychologist Donald Hebb (1949) applies: "What fires together wires together."

Through Hebbian network plasticity, the extensively cross-wired neurons in the cerebral cortex also strengthen their connections with their nearest neighbors. When the brain is engaged behaviorally, inputs that are activated nearly simultaneous in time *strengthen together*, increasing their cooperativity to generate more salient (i.e., more powerful and more reliable) responses. That plasticity-driven growth in local "teamwork" is a critical aspect of the improvement in selective, specialized processing of information supporting any learning-based advance in behavior (see Merzenich, 2013; Merzenich and deCharms, 1996; Merzenich and Jenkins, 1993).

A growing neuronal response coordination is *the* primary determinant of the feed-forward power of any plastically strengthening cortical process. Cortical neurons at all "higher" system levels are integrators operating with very short time constants. *Their* plasticity processes are also coincident-input dependent. The greater the coordination of neurons in the lower levels of the network that feeds them, the greater *their* selective powers and selectivity, and the greater the power of that input to drive plastic remodeling at higher system levels. Moreover, at the "top" of our great brain systems, coordination of activity is a primary determinant of the power with which cortical networks can sustain the reverberant activities that are selective for behavioral targets or goals (i.e., working memory) (see Wang et al., 2004). The strengths of these key plasticity-gating processes at the top are critically dependent upon the strengths of the coordinated inputs that feed them.

Given this relatively recent neurological understanding of the basis of plastically increasing selectivity and reliability on the path to improving neurobehavioral performance in learning, we routinely emphasize stimulus features in tasking in ways known to drive more strongly correlated local responses within cortical networks. We also specifically apply training tools designed to grow the powers of coordinated actions in simple and serial behaviors. Our goal is to rapidly increase the *coordinated* representations of the *details* of all task-relevant stimuli and actions in ways that broadly generalize to all behaviors arising from targeted brain systems.

2.4 Progressive Changes Achieved Through Small Learning Steps Enable Ultimately-Large-Scale Change; Substantial Repetition and Overlap in Training are Requisites for Achieving Optimal Change Rates

In the post-critical-period brain, the capacity for change, at any system level, is limited by the spreads of inputs that are fed to that system level (see Chapter 1). At any moment in time, in any given cortical area, neurons are most-strongly engaged—dominated in their responses—by a limited subset of specific, most-effective inputs that represent a small minority of the total input repertoire anatomically projecting to that cortical locus. Under the control of "top-down biasing," in attended learning, normally ineffective inputs are disinhibited. By that change, the cortex can *now change* the connection strengths of those inputs, so that these alternative, formerly *sub-rosa* inputs can now come to dominate this cortical zone. That change in neuronal dominance is the essence of brain plasticity. By its nature, this process imposes limits on the magnitudes of the steps over which learning-driven change can be achieved. Those learning steps must necessarily be within the limits of anatomically available input sources; if they are, plasticity that strengthens behaviorally important inputs and that weakens noncontributing inputs is achieved. Notably, changes are only possible if physical (i.e., anatomical) sources of input can support them.

In practice, in brain systems, because inputs change through the elaboration of horizontal inputs when changes in inputs that are predominant change, large-magnitude changes can be commonly achieved if a system is engaged to change in a series of small steps (Mahncke et al., 2006; Merzenich et al., 1998; also see Knudsen, 2002). It might be noted that this principle was earlier discovered in empirical studies in experimental psychology that showed that learning-driven changes could be achieved for small parametric steps in perceptual learning - ultimately achieving large-scale changes - but was frustrated when the learning step was too great, that is, did not "overlap" with the already-mastered ability (Sutton, 1998).

We have extensively studied the parametric dimensions of progressive stepwise change, and have studied the dose–response (repetitive stimulus-trial) conditions required for progressively driving enduring change (Merzenich, 2013; Merzenich et al., 1998). Our training strategies are informed by these studies, in an attempt to optimize achievable rates and magnitudes of learning-driven change.

2.5 Plastic Changes Link Representations of Serial Events in Complex Behaviors

Studies have shown that the brain plastically also strengthens connections between the predicted (serial) events in any learned behavior (Zhou et al., 2010; see Merzenich, 2013). The processes underlying this successive-signal/successive-action signaling are a key target for strengthening, in the recovery of almost any complex, real-world neurobehavioral ability.

We extend training to directly exercise the representation of predicted (syntactically important) serial events in all therapeutic training regimes.

2.6 Plasticity is Controlled by Neuromodulatory Processes

In the adult brain, plasticity is regulated as a function of behavioral state. One set of processes mediated by the release of *acetylcholine* from the subcortical nucleus basalis engages excitatory and inhibitory processes to enable plastic change. As noted earlier, the nucleus basalis is engaged by any significant neural activity generated in a closely attended behavior (Sarter et al., 2001, 2006). Once engaged, as is described by Froemke et al., (2013; see Chapter 3; also see Kilgard and Merzenich, 1998; Wright et al., 2010; Chapter 11), a plasticity-enabling epoch is open for several following minutes.

A second set of processes, mediated by the modulatory neurotransmitter *noradrenaline* (norepinephrine), amplify the activity generated by any unexpected event or by any closely attended input. These effects are rapidly attenuated if that input is nonvariant (Aston-Jones and Cohen, 2005; Sara, 2009; Sara and Bouret, 2012). Importantly, if repeatedly engaged under the right conditions (see Chapter 13), the actions of the primary midbrain source of noradrenaline are *enduringly* upregulated, to increase the baseline level of excitability (arousal) in the cortex, thereby positively amplifying plastic change.

A third set of processes mediated by the modulatory neurotransmitter *dopamine* selectively controls plasticity for input that has occurred just before that rewarding stimuli, or via engagement by the same modulatory control machinery after any event that the brain itself judges to have been positively achieved.

Operating collectively, these (and several other neuromodulatory) enabling processes could be thought of as "on–off switches" controlling plasticity in the post-critical-period brain. Each adds its own nuance to cortical plasticity processes (Merzenich, 2001). Acetylcholine is released when the brain is engaged by unexpected (novel) stimuli, and when attention is focused on a task at hand. As noted earlier, top-down biasing selectively determines the neurological machinery that is enabled to change, through disinhibition driven by this more general cholinergic input. As is elegantly documented in the studies of Robert Froemke and colleagues (see Chapter 3; see also Chapter 9), the disinhibition, again, results in increase in the local power of excitatory inputs in that window of attention/working memory. In effect, these processes open up a window defining *which* new inputs can come, through plasticity, to dominate. Noradrenaline is also released when the brain is engaged by unexpected stimuli, and under conditions of focused attention. It broadly amplifies cortical activities in ways that promote plastic change. Dopamine release is induced by hedonic rewards associated with behavioral success, and by processes in the brain that expressed goal or target achievement (Bao et al., 2001, 2002; Schultz, 2007). It selectively enables positive change for inputs that contribute to that

immediate-past success, *and* broadly weakens competitive activities that are uncorrelated with that success.

Plasticity-related studies (supplemented by a long history of empirical studies from experimental psychology) have now defined the optimal conditions for evoking these crucial neuromodulatory activities. In the training programs we develop, we consistently apply these "rules" to optimize neuromodulation resulting in most enduring change.

2.7 The Neuromodulatory Machinery of the Brain is Also Plastic

Studies conducted initially in animal models have shown that the processes in the brain that control fast learning can themselves be upregulated by specific forms of training. Training in particular forms has been shown to recover the power of acetylcholine-based processes that enable plasticity. In one variation of the studies demonstrating the plasticity of neuromodulatory control systems, we used a pharmaceutical strategy to grossly dysregulate plasticity in infant animals (Zhou et al., in review). As a result, they grew into adulthood with grossly impaired modulatory control processes. Through relatively simple forms of training, nearly-normal processes controlling the production and release of dopamine, noradrenaline, serotonin, and acetylcholine were restored in now-adult animals.

With such training in humans, this key contributor to the powerful disinhibition that underlies learning under conditions of focused attention is restored to high-normal levels (see Chapter 13). The second contributor, working memory/selective attention, can also be significantly improved or restored by specific forms of intensive training (see Berry et al., 2010; Smith et al., 2008; Wolinsky et al., 2013; see Chapter 7). These and other forms of exercises also reinvigorate dopamine and acetylcholine signaling in learning. With their upregulation through training, their positive modulation of change is significantly increased; learning rates and asymptotic achievement levels in learning are both elevated, when these strategies are applied in human models.

Learning rates are also impacted by the processes in the brain that suppress external and internal noise (distractors). When these processes are weak, as is usually the case in the impaired brain, a trainee responds with more false-positive responses when they are challenged in learning. Lower learning rates and goal achievement ceilings are the result. We recently developed learning strategies that resulted in a recovery of this key distractor-suppression faculty (Mishra and Gazzaley, 2012; Mishra et al., in review; see also Chapter 14).

We incorporate strategies for renormalizing the learning-control machinery of the brain in the therapeutic training program that we apply. Targets include the neuromodulatory processes mediated through acetylcholine, dopamine, noradrenaline, and serotonin; the strengthening of working memory and selective attention processes contributing so critically to learning; and the suppression of neurological noise (internal and externally generated "distractors"; noncorrelated process "noise") that interferes with learning and memory.

2.8 Plasticity Processes are Bidirectional

By its nature, plasticity engages fundamentally reversible neurological change processes. We have conducted a number of studies in which we demonstrated that neuroplasticity follows Hebbian principles: the representations of inputs and actions are competitively sorted on the basis of the temporal distributions of inputs (Merzenich and DeCharms, 1996; Merzenich and Jenkins, 1993). Following these principles, it is just as easy to degrade the brain's processing abilities as it is to strengthen or refine it. In the designs of therapeutic training regimes, the Hebbian "rule" must be considered to assure that training-driven changes are always in the positive, strengthening, recovering, renormalizing direction.

We have recently conducted a number of studies in animals, richly confirmed by plasticity-based training studies in humans, which show that plasticity processes are very broadly reversible. For example, we documented many aspects of the function, anatomy, and chemistry in the brains of aged versus young adult animals, showing that every measure differed markedly (de Villers-Sidani and Merzenich, 2011; de Villers-Sidani et al., 2010; Mishra et al., in review). In the aged rats' auditory cortices, time and space constants were longer and greater; response selectivity was poorer; reliability of sound feature representation was poorer; response correlation was weaker; the neuron populations representing sensory inputs were more weakly coupled, operating with far weaker cooperativity; inhibitory processes controlling "top-down" modulation were dramatically weaker; local and long range (with other cortical areas; to the frontal cortex, dorsal thalamus) connections were poorly myelinated; level-to-level (system) coordination expressed in gamma and theta frequency ranges was less sharply localized and more ephemeral; representational topographies were degraded; trophic factors contributing to physical brain remodeling were only weakly expressed; the normal strong adaptation to repeated identical stimuli and the responses to unexpected stimuli against a continuous or repeated background were sharply reduced; the strong suppression of nonattended distractors was reduced; receptor subunits for inhibitory and excitatory processes were altered in a degrading direction; and the modulatory control processes controlling plasticity itself were all more weakly operating in very old versus prime-of-life animals (see Fig. 1 for a summary). After finding these striking differences between aged and young rats' brains, we then asked which of these operational characteristics of the brain can be "rejuvenated" by appropriate behavioral training. Somewhat to our surprise, with training limited in these aged rats to approximately 1 h/day for about 1 month, the answer was: *all of them* (de Villers-Sidani and Merzenich, 2011; de Villers-Sidani et al., 2010; Mishra et al., in review). In fact, most were driven to the functional and physical state that applied for rats studied in the prime-of-life.

Interestingly, the fundamental reversibility of plasticity processes works in the other direction as well, as is demonstrated in studies in which we increased levels of noncorrelated noise (chatter) in the processing machinery of the brain in young, vigorous adults. That manipulation resulted in highly accelerated brain "aging," as

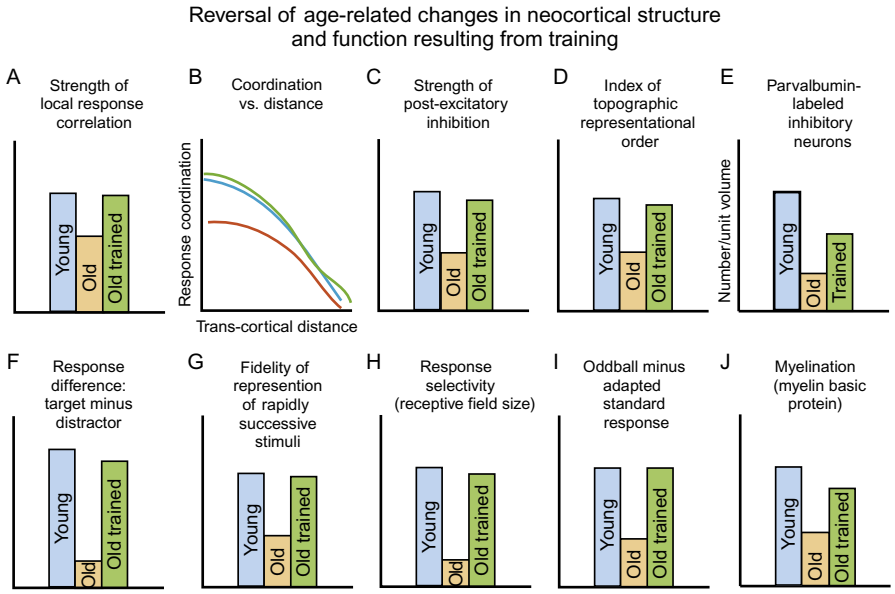

FIGURE 1

Ten of the more than 40 specific measures of neocortical structure, chemistry, and function shown to differ in the aged versus the young Norway rat brain (A–J). As with these examples, *all* indices manifested a degraded physical and functional status of the cerebral cortex in the aged versus the young adult animal; and *all* indices were substantially or completely reversed in aged rats by training them (a) to respond to variant stimuli against a repeated background of standard stimuli, with a staircase adaptation of variant-to-standard disparities, or (b) to respond to a target presented in a background of "distractors," with the disparities between distractors and targets again adapted in a staircase progression. Note that many of these same measures (all that were measured) were seen to very rapidly change to the aged-rat status in healthy normal young adult rats by applying strategies that increased cortical process noise (uncorrelated neuronal "chatter") over a 3-week-long young adult epoch (Zhou et al., 2011).

Illustration adapted from de Villers-Sidani et al. (2010); and Mishra et al. (in review).

indexed by degrading changes in the functional and physical characteristics of the machinery of the brain as noted above (Zhou et al., 2011).

Because these reversible change processes can drive neurological changes in an advancing or degrading direction, driving the processing and physical characteristics of the brain backward to simulate aging is also equivalent to driving the animal *backward* in age: The physical and functional properties of the brain near the end of life closely corresponds to those same characteristics in the brain near the beginning of life. That conclusion is supported by documenting the operational and physical characteristics of the machinery of the brain in very old and very young animals: they

closely match one another. It is also manifested by the fact that accelerated changes leading to "premature aging," carried forward far enough, similarly result in the reopening of the "critical period" (Zhou et al., 2011; and see Chapter 1).

Because chronic neurological or psychiatric illness and brain injury invariably leads to "negative plasticity" attributable to an increase in background "chatter" (noise that is not correlated with the behavior in play), the fundamental reversal of these functional characteristics of the neurological machinery of the brain is a target of every training program that we have developed, on the path to renormalizing neurological processing and the physical brains of individuals with various clinical indications.

2.9 Our Overall Goal is to Restore - Insofar as Possible - Normal *Neurological* Function

Neurorehabilitation strategies addressing many human problems have been based on the premise that the distorted or damaged brain is irreparable in adults. Empirically based rehabilitation strategies have focused on "getting the most out of" the brain, substantially through finding alternative ways to work around lost or failing abilities. By contrast, our goal is to engage the resources of the brain itself to restore its weakened or lost abilities to their natural, healthy state. The brain is everywhere plastic, throughout our lifetimes. When the brain is intact, we believe that large-scale restoration "in place" necessary for overcoming almost any distortion or limitation is usually achievable. To the extent to which that is true, the medical outcome is no longer palliative; it is, by definition, curative.

3 PART 2: DESIGNING PROGRAMS TARGETING SPECIFIC CLINICAL INDICATIONS

With these premises for designing neuroplasticity-based therapeutic training programs in mind, we now turn to describe how, guided by this perspective, we attempt to address the neurological weaknesses and distortions that describe specific clinical indications in neurological or psychiatric patient populations. In general:

3.1 Our Starting Point is an Understanding of the Nature and Origins of the Neurological Expressions of the Specific Targeted Disorder

Our training programs are specifically designed to target the major aspects of the patients' neurology. We assume that plasticity-driven changes, if appropriately implemented, will significantly renormalize brain systems in ways that can be expected to reestablish generalized neurobehavioral recovery. Two examples of the development of specific programs on this basis are described in Part 4 below: (a) training to establish more competent social cognition and social control

in psychotic and autistic patients and (b) achieving functional rejuvenation and resilience training in aging. For other examples of therapeutic programs that are based on this approach, see Chapters 7, 12, and 13.

3.2 Common Features Implemented in Our Therapeutic Programs

All training modules are designed to be *continuously adaptive*, following "staircase" procedures (Levitt, 1971) or other training progressions assuring success in training on about 75% of exercise trials. By that strategy, every trainee quickly establishes a challenge level in training that matches their capabilities, adjusting automatically to continuously sustain that difficulty level as their abilities advance. This is important since studies have shown that learning does not occur if the task is too easy or too difficult (see Engineer et al., 2012). Training can usually be sustained in rewarded manner at this level with high enthusiasm. Importantly, training controlled near the edge of the trainee's abilities results in *sustained close attention* in tasking - an important state condition for most efficiently driving plastic remodeling. We also commonly apply behavioral "observing responses" initiating task cycles, to further assure close attention to the demands of the training challenge.

In implementing these staircase progressions, training always advances through a series of *small challenge steps*, constructed to assure neurologically supportable improvements. In most of our training programs, we also introduce carefully *staged progressions in task difficulty*. In any given module, those advances in difficulty are implemented as a series of progressively more challenging subtasks arrayed across two training dimensions - for example, speed of stimulus presentation might vary across one dimension, while task complexity or cognitive load varies across a second. Following that design, the trainee might begin the training module with a subtask that can be achieved (for example) with relatively slow reception, decision, and action-control processes, solving a task problem presented in an elementary form. At the highest training level, the brain must operate at high speed in reception, decision-making, and responding, at a task problem now presented in a very challenging form. Tasks are also designed with the *practice repetition* that assures that training results in the induction of stable, enduring neurological changes.

Performance feedback is also a routine feature of every training program. Applied trial by trial at an approximately time-optimized way, positive feedback is more strongly emphasized in training than performance error. This feedback is designed to directly exercise the reward machinery of the brain to upregulate its actions contributing to the control of learning and memory. Surprises (unexpected stimuli delivered under conditions of close attention and controlled expectation) are also systematically introduced into training exercises because they strongly, directly engage and train cholinergic, adrenergic, dopaminergic, and serotonergic neurons in subcortical neuromodulatory control nuclei (see Mahncke et al., 2006; Merzenich, 2013, for review).

Every task is also designed to provide efficient, repeated *measures of performance abilities*. Adaptive task formats result in the rapid establishment of a

performance benchmark (i.e., threshold) in each brain training cycle. That benchmark has two values for the trainee. First, it documents the trainee's abilities at that task, compared to those of all others who have completed the same task for the first time. That performance data can be related specifically to the average ability of others in their (or in other) demographic(s) - for example, to an individual of the same gender and age in the normal distribution, or to the distribution of all other patients also in treatment for the same clinical indication. Second, these benchmark "scores" provide a standard that the patient is challenged to improve upon, through repetitive tries. Their goal is to ratchet up training achievements cycle by cycle in training - documenting, with each try, the growth of their abilities again referenced to those neurological capabilities in the grand trainee population.

Finally, *we continuously document training gains* for the patient as a part of training task implementation, and across the course of training, in ways designed to contribute to trainee motivation. For addressing clinical indications using tools that are prescribed and monitored in use by rehabilitation professionals, patient compliance and outcomes data can be provided to those clinicians via an established social network link. This professional monitoring is designed to help promote patient compliance, inform the clinician about trainee progress, provide them with insights into how their other treatments might contribute to more-complete positive recoveries, and provide a continuous line of communication between patients and the professionals responsible for their treatment and care.

3.3 There are Common Training Targets in Almost all Therapeutic Programs

Some aspects of the functionality of an impaired brain are improvable, and are therefore general targets of our therapeutic training programs (see Mahncke et al., 2006; Merzenich et al., 1998). These common deficits arise because a compromised brain changes its operational characteristics (speed of operations; resolution of perceptual detail) in predictable ways to sustain control of behavior under more-challenging conditions, and because the machinery controlling learning itself is almost always compromised in a chronic disorder, illness, or brain-injury scenario (see Merzenich, 2013). In our initial training in therapeutic applications, we usually record weaker-than-normal operations of these aspects of brain function at training outset. One common early goal in training is to recover these basic operational characteristics of the processing machinery in the brain in ways that will help enable learning success and recovery, at all due speed. These common targets include: (a) processing speed, (b) processing accuracy, (c) processes controlling phasic and sustained attention, (d) neuromodulatory control of learning and the subcortical systems that support it, (e) working memory, and (f) noise/distractor suppression.

3.4 Therapeutic Programs Should be "Localized" to Address Neurological Distortions Specific to the Targeted Clinical Condition

While all programs are constructed on the same platform with training modules following the same basic designs, it is necessary to adapt them in detail so that they can be effectively applied to each specific target population. Each clinical indication manifests condition-specific neurological impairments and distortions that must be separately addressed in training. Moreover, patients for any given clinical condition are on a journey of recovery that specifically applies for that neurological or psychiatric profile, and our interactions and "conversation" about their journey must be adapted with an acknowledgment of its specific nature. As an aspect of creating therapeutic training programs that apply to specific clinical conditions, we also try to embed education and training in domains that are outside of our Internet/computer- and pad-delivered training. Some examples of this extension of training to "real life" are illustrated in the clinical tool examples described in Part 4 below.

3.5 Therapeutic Programs Must Also be "Localized" in Ways That Assure Effective Application to Specific Patient-Population Demographics

Training programs should be "localized" to the site (country, subculture, language, computer/pad/smartphone access) and the population of use. The tools that might apply for a child or young adult or older adult might need to be sharply differentiated, both with respect to (a) stimulus sets, training targets, and goals, and (b) the feedback, reward, and "gaming" aspects of training. Some of those changes relate to training content; others relate to "playability" required to assure that trainees in the targeted subpopulation "take their medicine." For example, if the goal was to recover individuals suffering from a conduct disorder, the tasking required for improving social cognition and social control (and related perceptual and cognitive processing weaknesses) would be very different if applied in a misbehaving 5-year old, in an incarcerated 30-year old, in an addicted 50-year old parolee, or in a socially disturbed senior. In each case, the challenge, entertainment, and goal achievement values of the training program would necessarily be radically different - *localized to each demographic* - to achieve wide acceptance of use.

3.6 Embedded Assessments Continuously Document Gains Achieved Through Training

As noted earlier, every task we apply therapeutically is adaptive, using an algorithm that quickly advances to quantitatively measure ability for that task. Each time the trainee reinitiates that specific task, their goal is to advance above their earlier "highest score." In practice, trainees almost always advance their abilities try by try. For an individual completing a serial, many-part training program addressing a major

psychiatric or neurological impairment, we may derive hundreds or thousands of these measures of performance ability across the course of rehabilitative training - thereby richly documenting performance and neurological improvements across training spectra, throughout the rehabilitation epoch.

Because all of these measures apply for improvements of the many subtasks that we are directly training the subject on, it is also important to determine whether training benefits extend to other, nonpracticed but related abilities (near transfer) - and even more importantly, to untrained abilities that impact everyday quality of life (far transfer). To assess these near and far-transfer outcomes for training, we can embed similar tasks that have no direct equivalent in training (assessing near transfer), or that document gains in important measures of real-life abilities that are outside of our direct training repertoire (evaluating the extents of far transfer). As is argued compellingly by Jacoby and Ahissar in Chapter 5, the establishment of real-life benefits is a key goal of any therapeutic training program. Many programs applied as "cognitive therapy" fail to achieve it, in large part because while they may result in "training-to-the-task" benefits, they fail to recover implicit abilities underlying the general expressive deficits arising from their impaired or dysfunctional brain systems.

3.7 Delivery Platform Enables Self-Administration of Training and, if Necessary, Supports Clinical Monitoring and Support

One practical goal of our research has been to produce Internet delivery platform that can enable the rapid delivery of programs with all of the assets described above, efficiently localized to any clinical condition or demographic. That platform is now in hand. An online clinician portal, which allows for secure and easy user enrollment, tracking and monitoring, is also available for use.

4 PART 3: EVALUATING PROGRAM PLAYABILITY AND EFFICACY

Once a program has been created in its initial form, we progress in an iterative "agile" development process in which feedback from outcomes and playability reports is used to further refine program designs. Some of that feedback comes from standard use measures embedded in modern Internet-delivered software production tools and formats. Other feedback comes from compliance and training progression data derived, as described, from every training subtask and module. We also commonly collect group and individual user responses and invite feedback comments on reward structures and "meta-game" designs. Our initial goals are (a) to assure that the demands of the program are willingly (ideally, enthusiastically) achieved by targeted clinical trainees; and (b) to measure the extents to which a program effectively drives positive changes in therapeutically targeted brain systems and behaviors. In this latter case, these preliminary outcomes determinations are usually designed to provide an initial estimate of dose–response relationships, and of program versions and

population sizes required to achieve statistically secure evaluation of program effectiveness in a larger, random-assignment, controlled outcomes trial.

Once playability and usability have been established, a goal is to measure program efficacy on the path to validating medical claims via an FDA-quality (real-world, randomized, appropriately controlled) outcomes trial. Here, the objective is to create a medical deliverable: A program for which outcomes are assured, to an FDA-medical device standard of proof.

5 PART 4: EXAMPLES OF PRACTICAL THERAPEUTIC TOOLS CONSTRUCTED FOLLOWING THESE PRINCIPLES

We have now translated this science to create about 20 different program versions targeting specific psychiatric and neurological clinical indications. Three are described in other chapters in this volume. Paula Tallal has described neuroscience-based programs designed to improve aural language and reading abilities in school-age children (Chapter 7). Tom Van Vleet and Joe DeGutis describe a training approach that has been shown to ameliorate visual reception and related losses at the heart of hemispatial neglect syndrome following brain damage or stroke (Chapter 13). Bruno Biagianti and Sophia Vinogradov describe the state of development of training tools designed to renormalize the neurological abilities of chronic and first-onset schizophrenia patients (Chapter 12). It is useful to describe how we have constructed specific training programs, to understand how we have applied brain plasticity science to address the deficits of a particular clinical indications. The first is a social cognition training program which targets social cognition deficits in schizophrenia; the second is an Alzheimer's Disease prevention program designed for healthy aging adults.

5.1 Targeting Developmental and Adult-Acquired Impairments in Social Cognition

5.1.1 Neurological Basis of Therapeutic Program Design

Social cognition (SC) is defined as the mental operations underlying social interactions: the perception, processing, and interpretation of social information, and the generation of responses to this information (Augoustinos et al., 2006; Brothers, 1990a,b; Fiske and Taylor, 2008; Kunda, 1999). SC is considered to span five distinct domains (Adolphs, 1999, 2009): emotion perception (the recognition of facial and vocal affect), social cue perception (the ability to detect and comprehend cues in a social context; Augoustinos et al., 2006; Fiske and Taylor, 2008; Kunda, 1999), theory of mind (the mental capacity to infer one's own and others' mental states), attributional style (attribution of causes of events to the self, to others, or to factors in the environment), and empathy (the ability to share, understand, and appropriately react to the emotional states of others; Shamay-Tsoory et al., 2005). Abilities in these

domains, normally acquired early in life, enable the social behaviors that underlie our function as part of a society.

However, in schizophrenia, in addition to the various positive and negative symptoms associated with the illness, as well as persistent cognitive deficits (see Green, 2006), patients exhibit deficits in all five domains of SC (e.g., Addington and Addington, 1998; Brune et al., 2007; Edwards et al., 2002; Frith and Corcoran, 1996; Harrington et al., 2005; Mandal et al., 1998; Williams et al., 2003; see recent reviews in Billeke and Aboitiz, 2013; Kohler et al., 2010; Hellewell and Whittaker, 1998). These deficits are considered core in schizophrenia, as they persist throughout the course of the illness (Green et al., 2012), are expressed very early in the course of the illness (Edwards et al., 2001; Green et al., 2012; Pinkham et al., 2007), and are even recorded in prodromal patients (Pinkham et al., 2007) and in unaffected relatives of schizophrenia patients. Moreover, SC deficits are closely linked to functional ability in schizophrenia (Pinkham et al., 2003; Penn et al., 2008) and affect daily living factors including occupational status, community functioning, independent living skills, relapse rate, and quality of life (Addington et al., 2006; Bell et al., 2009; Couture et al., 2006; Fett et al., 2010; Horan et al., 2012; Sergi et al., 2007; Vauth et al., 2004). In addition, SC deficits have been found to mediate the relationship between neurocognition and functional outcomes in schizophrenia (Couture et al., 2006), as well as predict conversion to psychosis in young individuals at risk for psychosis (Vauth et al., 2004). In fact, the degree of SC impairment is a stronger predictor of the level of everyday functional ability than are cognitive abilities or the severity of positive symptoms (Horan et al., 2012).

These behavioral deficits have been recently shown to be rooted in anatomical and functional abnormalities within the complex brain network known as "the social brain" (Adolphs, 1999, 2009; Botvinick et al., 2005; Lamm et al., 2007; Wicker et al., 2003). Significant anatomical and functional abnormalities have been localized to the superior temporal sulcus (STS; Straube et al., 2013), anterior insula (Sheng et al., 2013), amygdala (Gur et al., 2002; Schneider et al., 1998), medial prefrontal cortex (mPFC; Russell et al., 2000), and to the cingulate cortex (Pinkham et al., 2008a,b), all are known to be critically involved in perception and processing of social information.

Collectively, these behavioral and neurological abnormalities make SC an important target for neuroplasticity-based intervention in schizophrenia. As the goal of any effective treatment is to improve life outcomes for patients, the direct link between SC and functional outcome in schizophrenia makes renormalization of SC function a clear target. The fact that SC deficits are resistant to pharmacological treatments including second-generation antipsychotic medications (Green, 2007) or to cognitive training *per se* (see Sacks et al., 2013 and Chapter 12 for summary of cognitive training in schizophrenia) further stresses the importance of targeted SC training for schizophrenia. Indeed, several studies have recently shown some promising effects of social skills and SC training in chronic patients (see recent reviews in Bartholomeusz and Allott, 2012; Choi et al., 2009; Kurtz and Richardson, 2012).

5.1.2 Plasticity-Based Strategies for Treating Social Cognition in Schizophrenia

We have recently completed the development and feasibility testing of an online SC training program (*SocialVille*), which implements the neuroplasticity principles described in this chapter. In particular, the SocialVille exercises target processing speed and accuracy of information representation in the social brain areas that underlie SC and social function (see Nahum et al., 2013a,b), the same areas that have been shown to abnormally operate in schizophrenia patients.

The SocialVille program suite is Web-based and browser playable; this allows training to be completed from any Internet-connected computer or laptop, using a unique password-protected login. The 23 exercises currently included in the SocialVille suite collectively target the SC domains listed above, emphasizing speed of processing, working memory, and attention to social cues. All SocialVille exercises use adaptive algorithms (e.g. up-down, Levitt, 1971) which allow maintaining about 75–80% success throughout training. The exercises are designed so that a "block" of trials takes between 5 and 10 min to complete in a given training session. Feedback is provided for every trial, used both to provide reinforcement and learning-through-correction. In the course of training, the tasks become more challenging by either adding more options to the response array, more stimulus types, increased similarity between stimuli, and more complex social situations. For example, in "Find that Feeling" exercise, the user is required to find the face that shows emotion which matches that of the target face. In a single training session, the duration of presentation of the target face becomes shorter (i.e., more challenging) as the user succeeds, and longer if the user makes mistakes. In the course of training, across several sessions, several parameters gradually change to make the task more challenging. These include the number of foils in the response array, the depth of emotion, the number of emotions in the set, the angle of presentation of the face, etc. To allow for this large variability in the course of training, we have produced a large number of stimuli for the SocialVille program suite. This stimulus set includes clips featuring 15 types of emotions from 100 actors; a set of neutral faces from various angles; a set of 900 gaze shifts; a large database of sentences spoken in various emotional prosodies; and a set of social stories, scenarios, and vignettes. We use these social stimuli repeatedly in the course of training, across basic perception tasks, working memory tasks, social attention tasks, and the like.

5.1.3 Specific SocialVille Delivery Strategies

The exercises described above are delivered in the context of the SocialVille "city" setting (Fig. 2). This is used to provide a unified context for the various exercises, which can increase motivation, compliance, and interest. The exercises are embedded within a colorful city setting, and each exercise corresponds to a specific map location in the city. On a given training session, upon login, the user can explore the various open locations of the SocialVille city (e.g., the bank, the theater, the park, the museum) and complete them in any order. The user gains points, awards, and

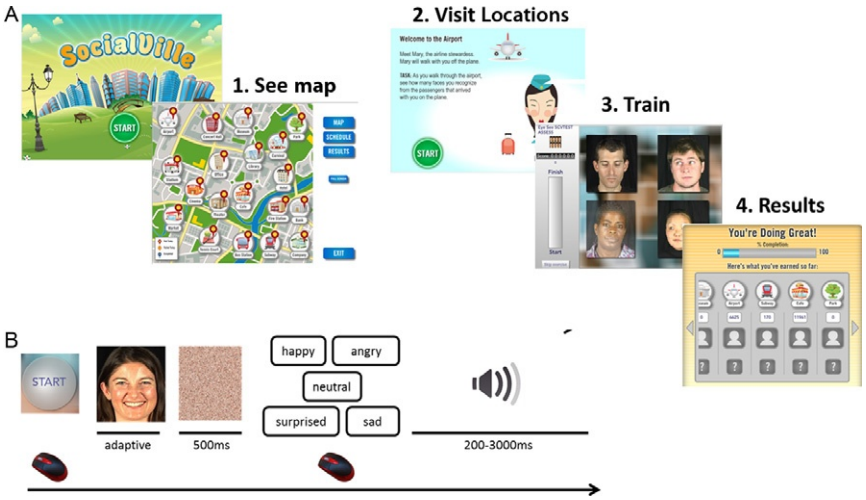

FIGURE 2

The SocialVille social cognition training program. (A) Upon entering the training (through a Web browser), the user is prompted with the SocialVille "city" map, which shows the open locations that should be visited today (1). Upon entering a location on the map, an introductory screen is shown, explaining the task (2). Then, the exercise starts, comprised of several (20–70) trials (3); feedback is given following every trial. A "Results" screen is also accessible, showing the points earned from each location, and the bonus awards and friends earned (4). (B) An example of the SocialVille "name that feeling" exercise (café location on the map). On every trial, an image of a person showing emotion is presented on the screen for a short period of time. The picture is followed by a mask for 500 ms, which is then followed by a response array with emotion names. The user should select the correct emotion by clicking on it. A feedback is given after every trial. The presentation time of the target is adaptively set based on the user's responses. A block of this task contains 70 trials, which allow calculating the threshold for about 75% correct in the task. The number of response options in the array, and the number of emotions vary throughout training.

game friends upon completion of game milestones. These meta-game awards and progress can be reviewed in a separate "Results" screen.

Embedded assessments are included for each of the SocialVille exercises, which allow measuring progress on this particular exercise in the course of training. Assessments are completed by the user at the beginning, half-way through, and at the end of training for each exercise, to allow tracking user progress in the course of training. Data from each training exercise is transferred to a secure clinician Web portal, which allows the treating clinician to track progress and compliance, derive performance thresholds, and enroll new users to training.

We have thus far successfully completed a feasibility study of SocialVille use in 17 early schizophrenia patients (Nahum et al., submitted). We further initially

tested the program in several other clinical populations that show similar SC deficits. These include children and adolescents with autistic spectrum disorders or Asperger's Syndrome, and healthy older adults. The program is now being localized to be applicable to these populations.

5.2 BrainHQ; Targeting Age-Related Impairments and Increasing Resilience Designed to Delay the Onset of Senile Dementia

5.2.1 Neurological Basis of Therapeutic Program Design

Functional neurological losses associated with normal aging are "the universal brain disease." A massive body of evidence describes age-related decline and its neurological bases (see Merzenich, 2013, for review). Those negative functional changes marking - to a highly variable extent - every older life, are the primary targets of the progressive training programs that we have created at BrainHQ. Those physical and functional changes progress to emergent and visible neuropathology in the brains of about half of individuals in sampled American and European populations by their mid-60s (Jagust, 2013). In an estimated 5.4 million Americans, that progressive pathology has resulted in the formal diagnosis of AD. This large population, surviving for an average of 4.7 years after diagnosis, is rapidly rising in world populations (CDC/NIMH, 2013). Our first goal in developing therapeutic tools for application in adult populations is to broadly strengthen - and at an older age, rejuvenate - their brains, restoring "more youthful" perceptual, cognitive, action control, and social control abilities. A second goal is to increase resilience in the brains of older (and younger at-risk) individuals against that destructive progression to AD.

We began our consideration of tool development, again, with an analysis of patterns of progressive loss and neurological impairment recorded in normally aging individuals - and, to meet our second goal, by reviewing how these changes relate to the onset of AD pathology. AD is a "neurodegenerative disease" marked by the pathological formation of beta-amyloid within neurons and in extracellular tissues, by the formation of amyloid crystals that, with soluble forms of amyloid, poison and render dysfunctional brain cells in the immediate areas in which they form, and by the formation of microfibrillary "tangles" within nerve cells that directly destroy their functionality and ultimately result in cell death (see Merzenich, 2013; Reitz et al., 2011). The earliest physical signs of pathology are subcortical, in the limbic system areas that modulate plasticity processes in the forebrain: the locus coeruleus (norepinephrine), ventral tegmental area and substantia nigra (dopamine), basal nucleus of Meynert (acetylcholine), and the dorsal raphe nucleus (serotonin) (see Braak et al., 2011; Grudzien et al., 2007; Zarow et al., 2003). Because the functional integrity of these subcortical nuclei is dependent on active behaviorally driven feedback connections from the forebrain, their deterioration is greatly contributed to by a progressive disconnection of highest brain levels - the "default network" (Buckner et al., 2008) - controlling "highest" brain functions, recorded as a consequence of

aging in numerous human studies (Hahn et al., 2013; Heister et al., 2011; Kenny et al., 2012; Lo et al., 2011; Weiner et al., 2013). Blood flow and glucose metabolism studies have repeatedly documented progressive, negative changes in this meso- and neocortical machinery in parallel with losses in cognitive and action-control abilities in normal aging. Importantly, the degree of this "functional disconnection" resulting in default system inactivity is strongly, directly correlated with the emergence of pathological markers of AD.

In our own studies, we have shown that "noise" (neuronal "chatter") grows progressively in the brain as we age (see de Villers-Sidani et al., 2010; Mishra et al., in review; Zhou et al., 2011). That growing noise results in natural plastic changes in the way that the brain represents, by its neural activities, the details of what you see or hear or feel or smell. Because those striking changes in brain speed, accuracy, and reliability ultimately degrade the quality of information "fed forward" in our forebrain systems to the default-network level of our brain's operation, these "highest levels" of brain systems are the first to be functionally disconnected in age-related decline (see de Villers-Sidani and Merzenich, 2011; Merzenich, 2013, for review). The emergence of AD pathology adds to this progressive, highest level deactivation because the pathology amplifies an individual's "brain noise" and weakens feedback to lower brain system levels, including the modulatory machinery that enables plasticity itself.

What underlies the poisonous production and release of amyloid and amyloid-body formation in the first place? What engenders the destructive proliferation of microtubules in nerve cells? We know that they are both contributed to by compromised immune processes. The altered blood perfusion attributable to changes in neuronal activity is an almost-certain contributor to connectional diselaboration, accumulated cellular debris, and immunological compromise. A recovery of more normal perfusion resulting from more normal levels of default system engagement could be expected to result in immune system strengthening. Moreover, the increased brain activity expressed through a functional recovery of the default system should result in its parallel metabolic recovery. We also know that there is a substantial downregulation of brain-produced noradrenaline in most aged individuals (Mufson et al., 2002; Zarow et al., 2003; and see Heneka et al., 2006), and that the physical (metabolic, neuronal population, noradrenaline production, transporters) status of its primary brain source, the mid-brain locus coeruleus, is directly correlated with cognitive performance abilities and with risks of AD onset in elder populations. Noradrenaline is a key regulator of the subpopulation of microglial cells that scavenge infectious agents and debris in brain tissues. Damage to the neurons supplying it results in a rapid increase in amyloid production and release (Heneka et al., 2006; Jardanhazi-Kurtz et al., 2009). Increasing circulating levels of noradrenaline in older brains results in a faster clearance of cellular debris following focal lesions and increases the scavenging of soluble amyloid itself (Heneka et al., 2010). A key design goal in creation of our therapeutic treatment strategy is to reinvigorate this machinery in the older brain.

The inactivation of the default network in aging results in a diselaboration of synaptic connections and ultimately in cell death. Both of these negative changes provide rich sources of prions and other amyloid-attracting brain matter debris. Moreover, the emergent AD pathology leads to more death and destruction, which exacerbates the problems in sustaining functional integrity by impaired immune system machinery. We expect the broad recovery of immune system function contributed by revascularization and noradrenaline system revitalization to result in a more efficient scavenging of debris argued to contribute to pathology genesis, neuropil reduction, and cell death.

Finally, changes in synaptic processes related to neuronal activity levels in AD models have been argued to lead to a cascade of changes that result in intracellular amyloid accumulation that plausibly set neuropathological processes (e.g. tau accumulation; cell death) in motion (Bredesen et al., 2010; Koffie et al., 2011). These changes arise, again, in forebrain structures that are functionally decoupled. We hypothesize that the strong reengagement and reactivation of this machinery will change the course of these destructive intracellular processes that contribute so strongly to neuropil reduction, microfibrillary tangle formation, and neuron death.

In summary, we hypothesize that the destructive changes that presage AD can be delayed by forms of training that broadly recover forebrain system functionality, and enduringly grow and sustain the levels of engagement of the brain's default-network and noradrenaline-producing machinery. BrainHQ was created to achieve these important therapeutic brain health objectives.

5.2.2 Plasticity-Based Strategies for Ameliorating Functional Losses Associated with Normal Aging, and for Growing Resilience Against Possible AD Onset

We have created a program called "BrainHQ" (by Posit Science), designed to rejuvenate brain systems known to be progressively functionally impacted by normal aging (http://brainhq.com). Because losses ultimately impact all brain systems, training is necessarily extensive in scope. The BrainHQ training tools focus on driving changes in (1) modulatory system function and control; (2) attention control; (3) aural speech and language; (4) visual perception; (5) memory, syntax, and other dimensions of cognition; (6) executive control; (7) social cognition; and (8) spatial and temporal scene reconstruction and navigation.

To achieve these broad objectives, trainees are engaged in game-like exercises targeting different levels of processing in brain systems accounting for these different domains of behavior. As described above for the SC training suite (SocialVille), exercises begin by training subjects in ways that improve the speed, accuracy, and reliability of the processing of features of inputs or actions that ultimately underlie explicit neurobehavioral abilities. To cite a specific example, listening training focuses on making progressively finer acoustic distinctions of features important for high-accuracy, high-speed aural speech reception, initially exaggerating those features to facilitate neuroplastic change. It then advances to improve accurate, high-speed reception under sparse coding conditions at the phonemic, syllabic, word, and

connected-speech levels. In parallel, other exercises are designed to upregulate attention, broadly suppress interfering distractors, strengthen the modulatory control machinery controlling learning rates, and improve working memory - all major contributors to recovering the high-speed, high-accuracy, high-coherence operations of this (or any other) great brain system. With its recovered powers, the ability of this system to effectively engage "highest" (default-network) brain levels is sustained or, if necessary, recovered - in an organic, comprehensive way that we believe should grow resilience against AD onset. In BrainHQ, we provide several hundred hours of brain exercises that, over the course of time, provide the basis for broad, generalized improvements and protections for the adult brain.

5.2.3 Specific BrainHQ Delivery Strategies

Exercises on BrainHQ are designed to be playable on an Internet browser on any connected computer; modified forms of all exercises are playable on Internet-connected iPads. At BrainHQ, a trainee can choose any program module(s) for that day's/week's exercise, or can follow recommended schedules provided in BrainHQ "courses." Work on those courses may be completed independently, or by design, can be monitored via a "clinician portal" by a supervising medical professional. All exercises are constructed following earlier-described principles. In general, the trainee has a series of brief (10–20) subtasks to complete each training day; they begin each task by "setting a benchmark" at that specific challenge, then must immediately improve on their performance on this progressive exercise before other subtasks are "unlocked." In this game-like setting, those now-unlocked boxes represent the next level of challenge in the specific task domain(s) that they are working on. The trainee is guided back to the same tasks over a series of successive days, mastering progressively more-challenging task forms as they advance in training. Every time a trainee completes a subtask (box), their abilities are defined relative to every other individual who has ever engaged in this exercise for the first time. This measured performance ability on that task provides a crucial reference for documenting training-driven improvements. The trainee can easily access displays provided at the Website that track their progress in any subtask, task, or broad cognitive domain, and can evaluate their current abilities compared to others in their demographic(s). A BrainHQ user can be expected to quickly derive many of these personalized performance measures to generate an increasingly in-depth reconstruction of their broader, detailed neurobehavioral status - and can track, in detail, changes in that status attributable to their efforts spent in training (Fig. 3).

The Alzheimer's Prevention Course (*TAP*) was created at BrainHQ to provide a more regulated program specifically designed to assure that the kind of broad training designed to recover functionality in ways believed to be neurologically protective are assured. Thus, for example, special emphasis is paid to (a) revitalizing the locus coeruleus, to strengthen noradrenaline signaling of immune response activity in the brain; and (b) assuring that we effectively restore more normal engagement

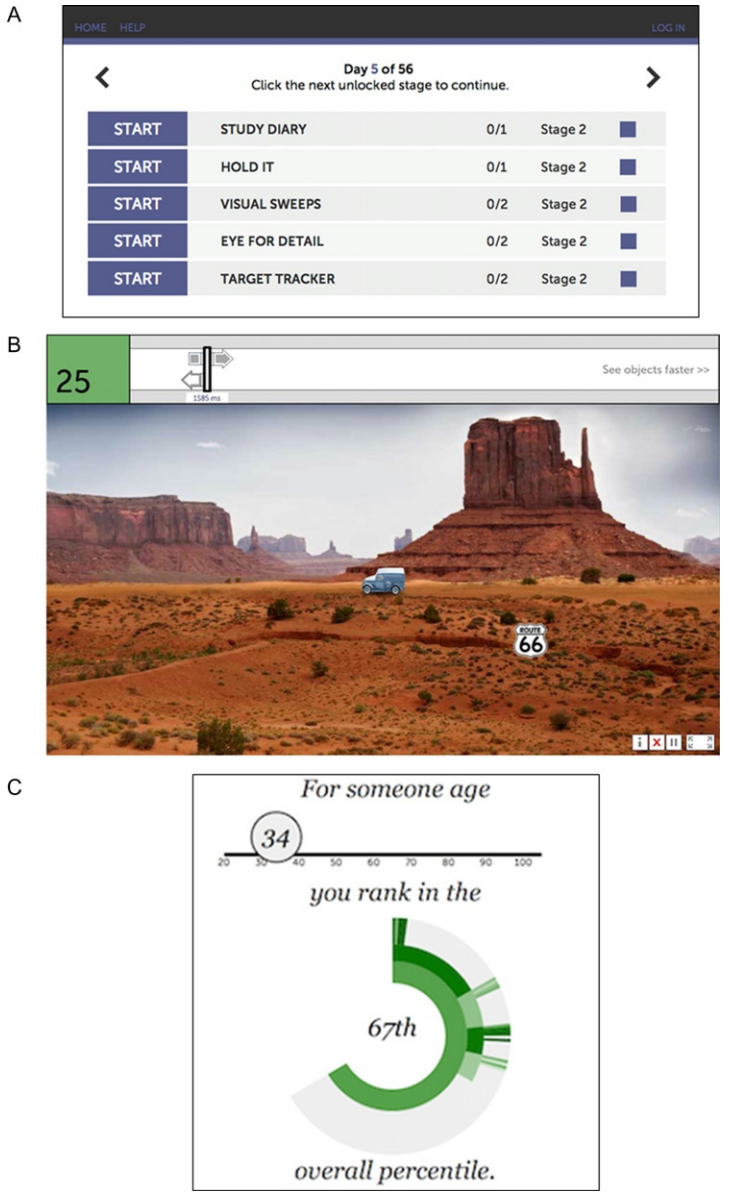

FIGURE 3

The BrainHQ training program for AD prevention. (A) The exerice view. For each exercise, the level ("stage") that the user is in is presented. The user can complete and unlock more and more levels and can go back and redo levels that were unlocked. (B) An example of a BrainHQ training exercise (Useful Field of View, UFOV). In this exercise, participants must identify a visual stimulus presented in the center of gaze, while simultaneously locating a target in the peripheral vision. The game is adaptive as the task gets difficult with successful brain training. In this example, the duration of visual stimulus presentation decreases. (C) Feedback is given on their relative performance compared to their age cohort.

(connectivity) of the default network, where AD pathology rises with particular initial virulence. In this course, trainees initially complete extensive survey information documenting their neurological status, and self-assess their quality of life. They then complete 12 program-delivered assessments that are specifically designed to evaluate default-network functionality before - and at periodic benchmarks after - training. We also collect daily information about lifestyle and other probable contributors to their improving brain health. Those queries also provide self-reports of trainees about their neurological and physical status that are very important for documenting far-transfer training impacts, and for documenting how other changes in lifestyle contribute to recovered brain health. After approximately 50-training-hour epochs, self-reports related to brain and physical health and quality of life and the 12 special automated assessment measures are repeated, to determine the improvements in neurobehavioral status and the resilience values of this training course.

In its present form, TAP delivers more than a hundred hours of brain training designed to be used in 30-min daily training sessions completed over a period of 40–50 weeks. Our goal is to extend training in program participants out into the future, potential to the end of their lives.

5.2.4 Evidence That This Training is Effective

Nearly 40 controlled outcomes studies have evaluated the effectiveness of use of different programs delivered at BrainHQ; most of these validated programs are incorporated in the AD-resilience training provided by TAP. To briefly summarize: (1) Training targeting the aural speech/language system have been shown to substantially improve all measured listening, memory, and related cognitive abilities, with broad generalization demonstrated by quality of life/everyday life assessments (Mahncke et al., 2006; Smith et al., 2008; Zelinski et al., 2011; Stevens et al., 2008). Many additional studies demonstrating the behavioral and neurological values of this form of training are documented in studies in children and young adults, described by Tallal in Chapter 7. In studies conducted in individuals of all ages, recoveries in perceptual abilities in listening repeatedly document improved speed of processing, accuracy, and attention control in processing abilities. (2) Training targeting visual perception and related cognition abilities result in sharp improvements in visual processing (e.g., Ball et al., 2007; Berry et al., 2010; Wolinsky et al., 2013). Improvements in speed and accuracy of processing and improvements in spatial vision (saccade sampling rates; multitasking; local and global reconstructions; scene reconstruction; useful field of view) were, again, repeatedly recorded in these studies. These aural languages and visual training studies also extensively document improvements in attention, working memory and immediate and delayed recall, and in associative memory/syntactic abilities. (3) Training targeting social cognition and social control have been described for other neurological populations, and the behavioral and physiological evidence supporting their use has been summarized earlier. (4) Studies document benefits of training for executive control and temporal and spatial navigation processes in training (e.g., see Ball et al., 2007; Merzenich, 2013; Smith et al., 2008). With working memory and

with the highest levels of operation in SC, these explicit behaviors normally directly engage frontal, posterior parietal, anterior and posterior cingulate, medial ventral and hippocampal zones that undergo disconnection as a preamble to AD onset. (5) Broad far-transfer effects are recorded - for example, to everyday quality of life (Ball et al., 2007; Smith et al., 2008), to sustained confident independence (Edwards et al., 2009; Wolinsky et al., 2010a), to resilience impacts against the onset of depression (Wolinsky et al., 2009), to measures documenting improved brain health (Wolinsky et al., 2006, 2010b), and to sustained (Edwards et al., 2009) and safer automobile driving (Ball et al., 2010) - among other indices (Wolinsky et al., 2006, 2007, 2009, 2010a,b; Ball et al., 2010; Edwards et al., 2009). (6) Positive improvements have been shown to endure for many months to years following training completion (e.g., Wolinsky et al., 2006, 2009, 2013; Zelinski et al., 2011).

Does this form of training delay AD onset? Does it block, and can it reverse neuropathology progressions? Answering that question is the current goal of a large controlled Internet-delivered trial, led by Dr. Hyunkyu Lee that is now underway. A growing body of evidence provides increasingly compelling evidence that this is, indeed, the case. By training thousands of individuals at risk for AD onset at BrainHQ, we should be able to answer this question, with finality, in the immediate future.

6 CONCLUSIONS

Neuroplasticity-based training strategies are emerging as a new class of therapeutic tools providing a new level of organic treatment of neurological and psychiatric illness. Because they can broadly address neurological impairments and disease-driven neurological distortions, they hold promise of driving more complete and more enduring changes in the brains of patients with many brain-related clinical indications. Training programs constructed on these bases are relatively inexpensive to produce and validate, and can be delivered to patients in need of help at low cost via the Internet. Confirmation of use, compliance, and training benefits are routinely recorded, with the supervising clinician "in the loop," as an integral part of program use. Patient use and outcomes are *measured* by assessments embedded directly in these programs. We strongly believe these new therapeutic tools shall be a large part of the picture of improved medical treatments of developmental and acquired-adult neurological and psychiatric impairments and disease over the coming decade.

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