

Cognitive Training for Impaired Neural Systems in Neuropsychiatric Illness

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Neuropsychiatric illnesses are associated with dysfunction in distributed prefrontal neural systems that underlie perception, cognition, social interactions, emotion regulation, and motivation. The high degree of learning-dependent plasticity in these networks—combined with the availability of advanced computerized technology—suggests that we should be able to engineer very specific training programs that drive meaningful and enduring improvements in impaired neural systems relevant to neuropsychiatric illness. However, cognitive training approaches for mental and addictive disorders must take into account possible inherent limitations in the underlying brain ‘learning machinery’ due to pathophysiology, must grapple with the presence of complex overlearned maladaptive patterns of neural functioning, and must find a way to ally with developmental and psychosocial factors that influence response to illness and to treatment. In this review, we briefly examine the current state of knowledge from studies of cognitive remediation in psychiatry and we highlight open questions. We then present a systems neuroscience rationale for successful cognitive training for neuropsychiatric illnesses, one that emphasizes the distributed nature of neural assemblies that support cognitive and affective processing, as well as their plasticity. It is based on the notion that, during successful learning, the brain represents the relevant perceptual and cognitive/affective inputs and action outputs with disproportionately larger and more coordinated populations of neurons that are distributed (and that are interacting) across multiple levels of processing and throughout multiple brain regions. This approach allows us to address limitations found in earlier research and to introduce important principles for the design and evaluation of the next generation of cognitive training for impaired neural systems. We summarize work to date using such neuroscience-informed methods and indicate some of the exciting future directions of this field.

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INTRODUCTION

It is now axiomatic that neuropsychiatric illnesses—the mental and addictive disorders—are associated with dysfunction in distributed prefrontal, fronto-limbic, and fronto-striatal neural systems that underlie perception, cognition, social interactions, emotion regulation, and motivation (For definition of key terms used in this review, please see Appendix) (Bush, 2010; Eisenberg and Berman, 2010; Hartley and Phelps, 2010; Koob and Volkow, 2010; Price and Drevets, 2010). The prefrontal cortical association

areas are uncommitted at birth, programmed to be shaped over the lifetime by the individual’s unique perceptual, cognitive, and affective experiences. This high degree of learning-dependent brain plasticity—combined with the availability of advanced computerized technology that allows us to deliver well-defined and constrained learning events to the brain—suggests that we should be able to engineer very specific training programs that drive meaningful and enduring improvements in impaired neural systems relevant to behavioral disorders.

If successful, this form of computerized cognitive neurotherapeutics should result in healthier, more adaptive real-world behaviors—and indeed, a whole field of research in this area has opened up over the past few years. (We will use the term ‘cognitive training’ and ‘cognitive neurotherapeutics’ interchangeably, with the understanding that the focus of treatment may be on perceptual, cognitive, or

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socio-affective functions. ‘Training’ is likely the better term, since the treatment method involves harnessing and promoting intact physiological mechanisms of neuroplasticity that support adaptive behaviors.) For example, Klingberg *et al* (2005) investigated intensive computerized working memory training in children with attention deficit disorder (ADD), and found improvements in response inhibition and reasoning as well as a decrease in parent-rated symptoms. In healthy subjects, training was associated with activation changes in frontal and parietal cortex, consistent with plasticity in a working memory network (Klingberg, 2010). Vinogradov’s group examined intensive computerized auditory training in adults with persistent schizophrenia and showed that participants significantly improved their verbal memory performance as well as early magnetoencephalographic (MEG) responses in auditory and prefrontal cortex; cognitive gains were positively associated with quality of life 6 months later (Adcock *et al*, 2009; Fisher *et al*, 2009, 2010; Dale *et al*, 2010). In a large-scale trial of older adults, subjects who received computerized training in perceptual speed of processing showed significantly improved cognition, lower rates of depression, and lower medical expenditures at 1 year, plus greater self-rated health outcomes at 5 years, compared with those who received therapist coaching in reasoning and memory (Wolinsky *et al*, 2009a,b, 2010); electroencephalography (EEG) revealed training-induced modifications in early visual processing that were associated with improvement in working memory (Berry *et al*, 2010). This ensemble of findings from across the lifespan indicates that individuals with impaired cognition from a number of etiologies can respond to targeted computerized neurocognitive training; that training can change functional activation patterns in the brain; that it can generalize to meaningful improvement in real-world behaviors; and that improvements can endure.

This notion of harnessing brain plasticity mechanisms for therapeutic interventions is not a new one (for a comprehensive recent review, see Cramer *et al*, 2011); it has been investigated in stroke and in traumatic brain injury (TBI) for some years and at an implicit level has served as the underpinning of neurorehabilitation approaches for the past century. Yet, neuropsychiatric illnesses have features that set them apart from other neurological disorders (Table 1):

- First, neuropsychiatric illnesses are associated with multiple genes of small effect and have a strong neurodevelopmental component; some (or perhaps many) of the contributing genes affect plasticity-related mechanisms in the brain (Grande *et al*, 2010; Balu and Coyle, 2011). This suggests that the neuropsychiatrically impaired brain may—in some instances—be programmed at the outset to be an ‘impaired learner.’
- Second, given their neurodevelopmental component, mental and addictive disorders generally have a gradual onset and often show high rates of comorbidity. In addition, illness course tends to be chronic or relapsing,

with slow recovery and with each episode of illness increasing the likelihood of future episodes, through what has been termed a process of sensitization (Patten, 2008; Robinson and Berridge, 2008). This pattern suggests that the physiological experience of illness expression drives key neural systems in the direction of ever-more dysfunctional configurations. In other words, the neuropsychiatrically impaired brain is also an ‘overlearner’ of maladaptive associations, having spent many years practicing dysfunctional perceptions, cognitions, emotions, and actions. Reverberations throughout interacting systems—for example, between prefrontal and limbic networks—further amplifies such dysfunction over time and perpetuates illness-related behaviors, given the role that prefrontal cortex plays in social cognition, self-referential processing, cognitive appraisal, emotion regulation, motivated behavior, and impulse control.

- Third, unlike neurologic disorders, neuropsychiatric illnesses have clinical trajectories that are heavily influenced by the social environment. Social/emotional learning and attachments, interpersonal experiences, psychological trauma, internal representations of self and others, and socio-cultural influences all influence the expression and course of illness (Grossman *et al*, 2003; Leonardo and Hen, 2008). This indicates that the neuropsychiatrically impaired brain—like all human brains—is a ‘networked learner’ and that cognitive interventions must capitalize on the various ways that social-emotional contexts can influence motivation, treatment adherence, and treatment response over the course of development (Meltzoff *et al*, 2009).

Taken together, these features indicate that cognitive training for mental and addictive disorders has several unique challenges: it must take into account possible inherent limitations in the underlying brain ‘learning machinery’ due to pathophysiology; it must grapple with the presence of complex overlearned maladaptive patterns of neural functioning; and it must find a way to ally with psychosocial and developmental factors that influence response to illness and to treatment (Table 1). The kinds of behavioral interventions that can work well for a healthy brain may not yield the desired outcomes when applied to a developmentally- and plasticity-impaired brain.

In this review, we will take a systems neuroscience-informed approach to these challenges. We will argue that cognitive training for neuropsychiatric disorders must be explicitly designed to induce specific and substantial distributed changes in cortical and subcortical representations and processing efficiency, and we will present suggestions on how to accomplish this goal. At the same time, we will keep in mind that any useful treatment tool built on these principles must also be delivered in a developmentally appropriate and scalable context that is engaging, rewarding, and motivating for the learner.

TABLE 1 Brief Summary of Key Features of Neuropsychiatric Illnesses that Pose a Particular Challenge to the Design of Cognitive Training, and Suggested Approaches to These Challenges

Features of neuropsychiatric illnesses	Challenges for cognitive training	Systems neuroscience approach to these challenges	Rationale
Associated with multiple genes that affect plasticity; brain may be an 'impaired learner'	There may be limitations in underlying 'learning machinery' due to pathophysiology	Address limitations in perceptual and pre-attentive processing	Perceptual and pre-attentive processing affect higher-order functions, and <i>vice versa</i>
Illness expression drives neural systems toward dysfunctional 'configurations'; brain may be an 'overlearner'	There are complex 'overlearned' maladaptive patterns of neural functioning	Deliver constrained and intensive training at threshold (thousands of precisely defined training events)	Large-scale and enduring changes in cortical representations occur during the slow phase of learning
		Harness intact implicit learning mechanisms and repetitive practice to drive improvements	Improvement in implicit learning systems may help to 're-tune' impaired working memory and explicit memory functions
		Re-normalize ability of prefrontal cortex to make adaptive predictions and normalize neuromodulatory function through careful attention to learning schedule and timing of rewards	Improvement in the brain's ability to make accurate (appropriately rewarded) input/output matches refines the detection of salience Prefrontal cortex integrates reward representation and initiates motivated behavior
Heavily influenced by social-emotional experiences and developmental context; brain is a 'networked learner'	Psychosocial and developmental factors, as well as beliefs and self-representations, influence response to illness and to treatment	Embed training exercises in developmentally appropriate contexts that foster adaptive beliefs and expectations and that are socially motivating, engaging, non-stigmatizing	Robust plastic changes occur when a learner is attentive and motivated

We will:

- briefly review the current state of knowledge on cognitive remediation in neuropsychiatric illness, including methodological issues and other emerging questions in the field;
- use findings from systems neuroscience both to answer some of the emerging questions and to think about how principles of learning-induced neuroplasticity can inform the design of cognitive neurotherapeutics;
- present suggestions on how to translate these principles into successful computerized training methods for the impaired brain;
- provide our thoughts about emerging research and future directions for this exciting new field.

CURRENT STATE OF KNOWLEDGE

Cognitive remediation as a specific form of intervention first emerged in the late 1960s, when Wagner performed a remarkably sophisticated experiment with schizophrenia inpatients—using a slide projector, levers, bells, and buzzers—to compare the effects of four 1/2-h contingent-reinforcement training sessions in attention and abstraction (Wagner, 1968). He observed that basic cognitive capacities were present but reduced in patients, and that patients definitely responded to training; he also noted that the experimenter was a positive social reinforcer who clearly 'enhanced the motivational condition of the subjects.' By

the mid-1980s, Spaulding *et al* (1986) were suggesting that 'persons with schizophrenia show deficits in ... attention, perception, and cognition' and that 'remediation of these deficits by direct training may facilitate the effectiveness of ... therapy'.

Since that time, essentially all of the research on cognitive remediation in neuropsychiatric illness has taken place in schizophrenia and has examined a wide variety of rehabilitation approaches, from computer-based drill-and-practice training in attention to the use of educational software to therapist-guided strategy coaching in pencil and paper problem-solving tasks. A large majority of the studies have been based on a neuropsychological model of brain function, which tends to emphasize: (1) The notion of 'separable domains'—the idea that cognitive functions are 'separate' and can be assessed and trained independently of one another—for example, that attention, memory, and executive control are discrete functions; and (2) The concept of 'rehabilitation' or 'remediation'—the idea that brains with cognitive impairments need to develop work-around approaches to compensate for functions that are unalterably damaged. McGurk *et al* (2007) performed a meta-analysis of 26 studies of cognitive remediation in schizophrenia and found a mean effect size of 0.41 for cognitive improvement and 0.36 for functional outcome. There was no significant heterogeneity in effect sizes across various cognitive domains based on either the type of method or hours of training, with the exception of verbal learning and memory. In this one domain, a larger effect

size was associated with more hours of remediation (0.57) compared with fewer hours (0.29) and with computerized drill-and-practice (0.48) compared with drill-and-practice plus strategy coaching (0.23) (we will return to this finding later). Wykes *et al* (2011) recently performed a meta-analysis of 40 studies undertaken from 1973 to June 2009, rating the trial methodology of each study using the Clinical Trials Assessment Measure (assessing sample characteristics, allocation to treatment, comparison treatments, etc.) (Table 2). As in the study by McGurk *et al* (2007), many different forms of remediation were represented, had been studied in various combinations with other therapies or psychosocial rehabilitation, and were compared with a large assortment of 'control conditions'. A mean global cognition effect size of 0.45 was found, with heterogeneity of effect sizes in global cognition, speed of processing, and reasoning and problem solving; however, the meta-analysis did not find that type of remediation, participant characteristics, or trial quality could account for this heterogeneity in cognitive outcomes (Table 2). In an exploratory analysis, functional outcomes were significantly better in the four studies where cognitive remediation was combined with some other form of rehabilitation and when it included strategy coaching (Table 3).

As one carefully examines the studies performed thus far in schizophrenia, perplexing questions emerge (we note that similar questions have emerged in the field of TBI and cognitive remediation (Rohling *et al*, 2009). Why—across a wide range of approaches—do average effect sizes for the most part remain stuck against a glass ceiling in the low-to-medium range? Why do identical approaches used in different studies (Penades *et al*, 2006; Wykes *et al*, 2007) yield such different outcomes? Why do more hours of remediation result in stronger effects for verbal learning and memory in the McGurk meta-analysis (McGurk *et al*, 2007)? What unexamined variables account for the heterogeneity of effects in the Wykes meta-analysis (eg, treatment 'dose,' treatment intensity) (Wykes *et al*, 2011)? Why—in the absence of adjunctive psychosocial interventions—do patients show little significant change in real-world functioning (Table 3)? Why do benefits show a tendency to fade over time once the patient is no longer actively engaged in treatment? Recalling Wagner's observations, what are the possible confounding effects when the intervention is delivered with positive social reinforcers that greatly enhance motivation, such as the enriched psychosocial context of a rehabilitation environment and meaningful social interactions with a therapist?

The short answer to these questions is that it is difficult to draw any definitive conclusions from the prior literature since a large and extremely disparate range of (combinations of) interventions delivered across a wide range of treatment durations and intensities using a multitude of study designs and analytic approaches applied to small samples of patients all appear to induce modest positive effects that do not generalize widely or robustly outside of the trained task in the absence of additional psychosocial therapy. Moreover, a number of the interventions

have included therapist contact or other positive social reinforcement not provided in the control condition. Wykes *et al* (2011) infer that the various forms of cognitive remediation have 'few salient differences' and instead 'lie along a dimension of learning support'; they suggest that the critical elements that result in the best outcomes are the explicit teaching of strategies and the use of 'transfer techniques'—though their exploratory analysis indicates that this is true only when cognitive remediation occurs concomitantly with a rehabilitation environment, which was the case in only four studies, which for the most part were unblinded and/or did not control for confounds in terms of the amount of psychosocial incentives between treatment and control conditions. Thus, there is only one definite conclusion we can draw at the present time from the meta-analytic work in schizophrenia: that non-specific cognitive stimulation based on any number of approaches is moderately beneficial, and patients who receive such stimulation while getting one-to-one involvement/coaching from a therapist in a rehabilitation environment show better functional outcomes. This unsurprising conclusion—combined with a widely held view that serious mental illness is characterized by immutable neurodevelopmentally based impairments—is perhaps the source of what has been a fair amount of skepticism in the field about the ultimate usefulness of cognitive remediation as a targeted therapeutic treatment for neuropsychiatric illnesses.

We argue here that, moving forward, if a cognitive intervention is to be successful, it must have a well-articulated theoretical rationale and clearly understood, specific mechanisms of action that are grounded in the neuroscience of learning and cognition; it must induce a specific, robust, and enduring change in a well-defined set of cognitive/socio-affective functions and neurological outcome measures when studied under rigorously controlled conditions; and it must generalize beyond the trained task and result in meaningful behavioral improvements that affect real-world functioning. We also propose that the neuropsychological model of remediation requires updating and that a number of innovative and perhaps counter-intuitive training approaches are necessary for achieving robust and widespread gains in cognition in the impaired brain. Advances in systems neuroscience provide a useful theoretical framework for addressing these issues, and point the way for the development of the next generation of cognitive training techniques.

KEY PROCESSES MUST BE ADDRESSED AS THE FIELD MOVES FORWARD

The past 15 years of experimental neuroscience have unequivocally demonstrated two fundamental principles regarding brain function. The first principle is that the brain performs its computational work *via* distributed neural systems that are continuously making predictions about incoming data and that are interacting in a probabilistic

TABLE 2 Summary of 12 Studies of Cognitive Remediation in Schizophrenia that Received the Highest Clinical Trials Assessment Scores (from lowest to highest) from Wykes *et al* (2011). This table illustrates the wide range of treatment approaches, study designs, and outcomes in the field

Study	Remediation approach and number of subjects	Hours per week and # of weeks of remediation	Control condition	Effect size for global cognition
Bellucci <i>et al</i> (2002)	Computerized educational software (Captain's Log) (N = 17)+positive reinforcement from a therapist+day treatment	1 h/week 8 weeks	Treatment as usual (day treatment) (N = 17)	0.46
Hermanutz and Gestrich (1991)	Computerized attention training (N = 10) Note: all subjects were inpatients	~2 h/week 3–4 weeks	1. Integrated psychological therapy (IPT) focusing on cognitive, communication, and social training (N = 10) 2. Treatment as usual (N = 10)	0.46
Sartory <i>et al</i> (2005)	Computerized training of attention, working memory, problem solving (Cogpack) (N = 21) Note: all subjects were inpatients	5 h/week 3 weeks	Treatment as usual (N = 21)	0.58
Kurtz <i>et al</i> (2007)	Computerized training of attention and working memory (CogRehab and Progressive Attention Training)+day treatment (N = 23)	1.9 h/week 52 weeks	Computer skills training (eg, Microsoft Office)+day treatment (N = 19)	0.36
McGurk <i>et al</i> (2005)	Computerized training of attention, working memory, problem solving (Cogpack)+therapist coaching+supported employment+day treatment (N = 23)	2 h/week 12 weeks	Supported employment only (N = 21)	0.44
Penades <i>et al</i> (2006)	Individualized therapist coaching for errorless learning in executive functions (Delahunty) (N = 20)	2–3 h/week 16 weeks	1. Cognitive behavioral therapy (CBT) (N = 20) 2. Treatment as usual (N = 20)	1.02
Wykes <i>et al</i> (1999)	Individualized therapist coaching for errorless learning in executive functions (Delahunty) (N = 17) Note: subjects were inpatients and outpatients	3–4 h/week 8–10 weeks	Occupational therapy (N = 16)	0.20
Fisher <i>et al</i> (2009)	Computerized training in low-level auditory processing and auditory/verbal working memory (Posit Science) (N = 29)	5 h/week 10 weeks	Computer games (N = 26)	0.86
Wölwer <i>et al</i> (2005)	Computerized <i>emotion recognition training</i> and desk work with a therapist, including errorless learning techniques (N = 28)	1.5 h/week 6 weeks	1. Computerized <i>cognitive training</i> and desk work with a therapist, including errorless learning techniques (N = 24) 2. Treatment as usual (N = 25)	–0.24 (Cognitive training group made greater Cog gains relative to emotion group)
Spaulding <i>et al</i> (1999)	Therapist coaching in cognitive techniques (IPT cognitive component) (N = 49) Note: all subjects were inpatients	2.6 h/week 26 weeks	Supportive group therapy (N = 42)	0.22
Dickinson <i>et al</i> (2010)	Computerized educational software targeting a broad range of cognitive domains+one-on-one coaching (N = 34)	3 h/week 15 weeks	Computer games+one-on-one sessions (N = 27)	0.06
Wykes <i>et al</i> (2007)	Therapist coaching for individualized errorless learning in executive functions (Delahunty) (N = 43)	3–4 h/week 12 weeks	Treatment as usual (N = 42)	0.06

Notes: Most studies used small subject samples. Five studies included other interventions (day treatment, coaching) in addition to the cognitive training method under study (we except the Delahunty method here, as coaching is part of the training method). Seven studies, due to their nature and design, do not permit for subject blinding or blinding of study personnel. Five studies included socially reinforcing interventions in the treatment group, such as active therapist coaching and motivational enhancement, which were not provided in the control condition. Two of the three studies with the largest effect sizes (Sartory *et al*, 2005; Penades *et al*, 2006; Fisher *et al*, 2009) also had the highest treatment intensity (5 h/week). The third study (Penades *et al*, 2006) used 2–3 h/week of the Delahunty program and found the largest effect size of all 12 studies. However, Wykes *et al* (2007) and Wykes *et al* (1999) also used the Delahunty program and found small to no effect sizes (0.2 and 0.06). The two studies using Cogpack (Sartory *et al*, 2005; McGurk *et al*, 2005) show similar effect sizes. Sartory *et al* (2005) show a slightly larger effect and used 5 h/week of training compared with 2 h/week in McGurk *et al* (2005).

TABLE 3 Summary of Findings on Follow-Up and on Functional Outcome from 12 Studies of Cognitive Remediation in Schizophrenia that Received the Highest Clinical Trials Assessment Scores (Wykes *et al*, 2011). Only a few studies have examined functional outcome and durability of effects, with mixed results

Authors	Follow-up	Effect on symptoms and functioning
Bellucci <i>et al</i> (2002)	None reported	Cognitive remediation subjects showed improvement in SANS-negative symptoms at post-training
Hermanutz and Gestrich (1991)	None reported	Both the attention training and IPT groups showed improvement in symptoms at post-training
Sartory <i>et al</i> (2005)	None reported	Symptom and functional outcome measures were not reported
Kurtz <i>et al</i> (2007)	None reported	Symptom and functional outcome measures were not reported
McGurk <i>et al</i> (2005)	Work outcomes at 1 year	Cognitive remediation subjects showed improvement in depression and PANSS autistic preoccupation at post-training. At 1 year, cognitive training subjects were more likely to work, worked more jobs, worked more hours, and earned more wages
Penades <i>et al</i> (2006)	6 months	Cognitive remediation subjects showed improvement in cognition and PANSS Cognitive Subscale and Life Skills Profile at follow-up. The CBT group showed improvement on the PANSS Depression Subscale at follow-up
Wykes <i>et al</i> (1999)	None reported	Neither group showed changes in symptoms or social functioning
Fisher <i>et al</i> (2009)	6 months	Cognitive training subjects showed no overall change in PANSS symptoms or Quality of Life Scale at post-training or at follow-up. However, cognitive gains post-training were positively correlated with improved QLS scores at 6 months
Wölwer <i>et al</i> (2005)	None reported	The affect recognition group showed gains in affect recognition at post-training
Spaulding <i>et al</i> (1999)	None reported	Cognitive remediation subjects showed improvement in social competence. A differential effect on symptoms was equivocal
Dickinson <i>et al</i> (2010)	3 months	Cognitive training subjects showed no improvement on neuropsychological or functional outcome measures at post or follow-up
Wykes <i>et al</i> (2007)	6 months	Cognitive remediation subjects showed improvement in working memory at post-training and at follow-up, but no significant change on other cognitive measures. Cognitive training subjects also showed improvement in PANSS symptoms and self-esteem at post, but not at follow-up

manner through variations in their oscillatory patterns (Buzsaki, 2006). The second principle is that inputs from the senses, the environment, and other brains calibrate and modify neural connections; that is, the brain changes with the introduction of new experiences and with the training of new perceptual, cognitive, socio-emotive, or motor skills (Figure 1, adapted from Buzsaki, 2006). Put another way, during successful learning, the brain selectively promotes neural activity patterns—cortical representations—that represent meaningful stimuli and behaviors at both lower and higher levels of processing, particularly those associated with reward (Figure 2, adapted from Jenkins *et al*, 1990; see Cruikshank and Weinberger, 1996 and Buonanno and Merzenich, 1998 for reviews). In addition, the past 10 years of clinical neuroscience have unequivocally demonstrated that major mental illnesses are characterized by a range of impairments in neural system functioning, including perceptual and pre-attentive processing; higher-order cognitive operations such as attention, working memory, and inhibitory control; and the processing of socio-affective stimuli (see Table 4; although most of this work has been done in schizophrenia, there has been a recent surge of findings in other disorders as well). We propose that any meaningful treatment approach to the complex problems of neuropsychiatric illness must be grounded in these three fundamental principles.

In contrast to earlier neuropsychological models of cognition, this is a systems neuroscience conceptualization, one that emphasizes the distributed nature of neural

systems or neural assemblies that support cognitive and affective processing, as well as their plasticity. It is based on the notion that the brain can adapt throughout the lifespan to salient experiences by representing the relevant sensory and cognitive/affective inputs and action outputs with disproportionately larger and more coordinated populations of neurons that are distributed (and that are interacting) throughout multiple brain regions. It also implies that the impaired brain is capable of adaptive plastic change despite its underlying neuropathology, but that the magnitude of global improvement driven by any remediation method will be limited by the weakest link in the interacting neural systems. This neuroplasticity-based systems model allows us to address some of the limitations found in earlier remediation research and to propose three important considerations for the design of successful cognitive training for impaired neural systems.

Cognitive Training must Address Limitations in Perceptual/Pre-Attentive Processing

The first consideration is that neuropsychiatrically impaired brains often have limitations or alterations in their sensory and pre-attentive perceptual processing capacities. Though these have been particularly well studied in schizophrenia (Butler *et al*, 2007; Javitt, 2009; Dias *et al*, 2011), they are also present in bipolar disorder, in depression, in PTSD, in alcoholism, in cocaine addiction, in ADD, in autism, and in the aging brain (Table 4). In order for prefrontal

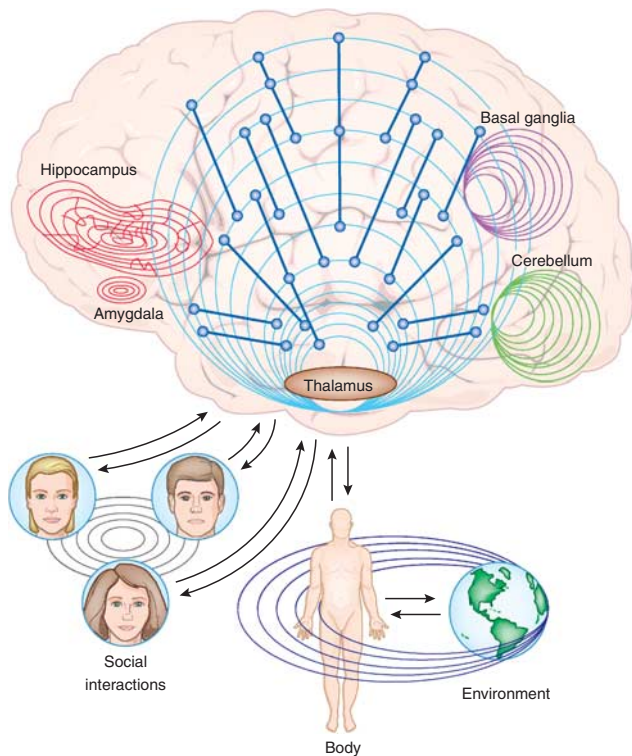


Figure 1. The brain is organized in a hierarchy of neural assemblies that consist of multiple parallel loops. Intermediate- and long-range connections link the various loops in the cerebral cortex, and link cortical assemblies to subcortical structures. Sensory information passes through the thalamus to sensory cortex, and is in turn modulated by prefrontal influences. Modification of connections is determined by input from the senses, the environment, and interactions with other brains. Adapted from Buzsaki (2006).

'higher-level' cortical operations to engage in efficient decision-making and adaptive learning, the brain must be able to continuously make accurate predictions about the near future (Liang *et al*, 2002; Mukai *et al*, 2007; Cao *et al*, 2008; Miller *et al*, 2008; Friedman-Hill *et al*, 2010; Nahum *et al*, 2010; Roelfsema *et al*, 2010; Rutman *et al*, 2010; Zanto *et al*, 2011). These predictions rely on rapidly and correctly comparing high-fidelity 'lower-level' perceptions of our current internal and external environments with past experiences (Figures 3 and 4). Thus, any process that leads to significant distortions in sensory and early perceptual representations in the brain can affect its ability to make accurate and relevant predictions and comparisons, to assign appropriate salience to incoming data, and to respond in an adaptive manner to environmental demands. For example, deficits in automatic auditory information processing in otherwise healthy individuals are associated with poor working memory and delayed verbal memory performance (Light *et al*, 2007); impaired sensory prediction is related to measures of delusional ideation in a psychiatrically normal sample (Teufel *et al*, 2010); and hearing loss in mid-adulthood significantly increases the risk of later developing dementia (Lin *et al*, 2011). The idea here is that throughout our lives, the establishment and maintenance of

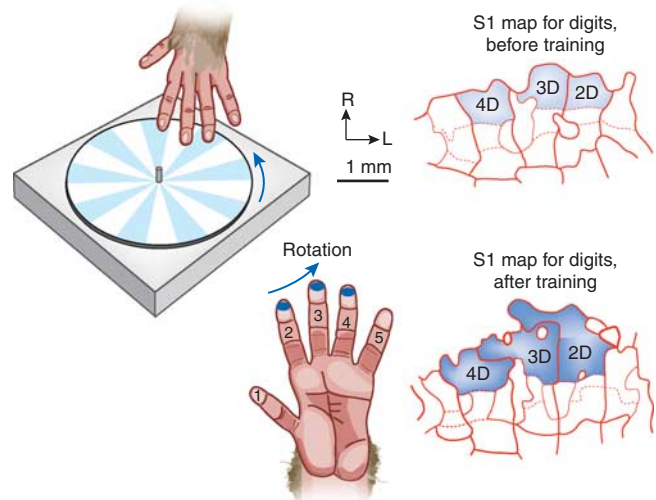


Figure 2. During successful learning, the brain enhances the neural representations of behaviorally relevant stimuli and actions. Monkeys trained to apply the tips of their second and third fingers to a rotating disc show substantially enlarged cortical representations of those digits' tips after training (Jenkins *et al*, 1990).

new skills are highly dependent on the quality of perceptual processing, for our senses are our sole source of information about the external world (Merzenich and DeCharms, 1996). When the quality of perceptual representations is degraded or abnormally biased, cognitive and socio-affective consequences appear (Figure 4). Perceptual representations may be affected by 'primary' deficits in the earliest phases of sensory inputs (peripheral sense organs, thalamus, sensory cortex), or they may be altered 'secondary' to deficits in prefrontal modulation of attentional resources that affect the appropriate processing of incoming information.

How might this consideration be translated into a cognitive training technique? As a simple example, people with major depression show a decreased latency in their P1 response to negative vs positive target stimuli (Yang *et al*, 2011), indicating a very early pre-attentive negativity bias in emotion perception. Such a bias toward the processing of negative emotional stimuli will then feed forward and induce prefrontal association areas to preferentially attend to and assign salience to negative stimuli, as well as generate abnormal/maladaptive responses in amygdala and associated limbic system regions (Victor *et al*, 2010). This in turn perpetuates a brain that is biased toward selective enhancement of very early perceptual processing of all potentially negative emotional information encountered in its environment, a brain that is responding to a world continuously perceived and experienced as distressing (Kilgard, 2002). Successful treatment can certainly occur when the individual learns to challenge the conscious cognitions and biased interpretations related to these perceptions, as happens during cognitive behavioral therapy—though even remitted symptom-free patients still show abnormal pre-attentive ERP responses to emotional stimuli, perhaps indicating risk of relapse (Shestyuk and Deldin, 2010). An alternative (or complementary) approach might be to train the brain to pay

TABLE 4 Neuropsychiatric Illnesses Are Characterized by a Range of Impairments in Neural System Functioning that have an Impact on Clinical Outcome. Although most of the work in this area has been done in schizophrenia, findings are rapidly emerging in a number of other disorders as well. Several recent representative findings from key clinical disorders are highlighted here for illustrative purposes

Disorder	Observed deficits in perceptual processing/pre-attentive processing	Observed deficits in higher-order cognitions	Impact on clinical/functional outcome
Schizophrenia	↓ Sensory (P1, N1) and pre-attentive (N2, CNV) visual ERP components (Dias <i>et al</i> , 2011) Sensory processing deficits predict impaired cognitive ERP generation (Dias <i>et al</i> , 2011)	↓ Attention, working memory, processing speed, cognitive control, learning and memory, receptive and expressive language, visual perceptual/constructional performance, fine-motor skills, and social cognition (Kalkstein <i>et al</i> , 2010)	↓ Working memory and verbal memory predict ↓ functional outcome (Hofer <i>et al</i> , 2011) ↓ Auditory MMN related to ↓ social cognition and ↓ occupational outcome (Wynn <i>et al</i> , 2010)
Bipolar disorder	↓ P50, N100, and P200 auditory sensory gating (Lijffijt <i>et al</i> , 2009) ↓ visual P1 (Yeap <i>et al</i> , 2009) ↑ P1 and ↓ N170 to happy vs sad faces (Degabriele <i>et al</i> , 2011)	↓ Processing speed, cognitive control, learning and memory (Antila <i>et al</i> , 2009; Bora <i>et al</i> , 2010; Martinez-Aran <i>et al</i> , 2004)	↓ Processing speed and verbal learning predict poorer social and work outcomes (Burdick <i>et al</i> , 2010) ↓ Verbal memory associated with unemployment status (Dickerson <i>et al</i> , 2004)
Major depression	EEG α asymmetry (Gordon <i>et al</i> , 2010) ↓ Visual MMN responses (Chang <i>et al</i> , 2011) ↓ P1 latency to negative vs positive target stimuli (very early onset of negativity bias in emotion perception) (Yang <i>et al</i> , 2011) Abnormal amygdala responses to sad faces presented below consciousness (Victor <i>et al</i> , 2010) Mood-independent abnormalities in P2 response to emotional self-referent information (Shestyuk and Deldin, 2010)	Mood-dependent abnormalities in effortful processing of emotional self-referent information (Shestyuk and Deldin, 2010) ↓ Processing speed, cognitive control, learning and memory (Bora <i>et al</i> , 2010) ↓ Cognition at age 20 predicts higher risk for depression at midlife (Franz <i>et al</i> , 2011)	Enduring cognitive impairment in MDD has a significant effect on employment (Baune <i>et al</i> , 2010) ↓ Poor episodic memory predict depressive symptoms and future MDD diagnosis (Airaksinen <i>et al</i> , 2007; Simons <i>et al</i> , 2009)
Attention deficit disorder	↓ Cortical reactivity to unpredictable sensory events (Dockstader <i>et al</i> , 2009) ↓ Auditory N2 (Anjana <i>et al</i> , 2010; Barry <i>et al</i> , 2009) ↓ Auditory N1, N2, and visual N2 to attended target stimuli (Satterfield <i>et al</i> , 1994)	↓ Response inhibition, working memory, executive planning, and attentional set shifting (Chamberlain <i>et al</i> , 2011) ↓ Attention, inhibitory control, and error processing (Shen <i>et al</i> , 2011)	Working memory problems are related to social-functioning impairments (Kofler <i>et al</i> , 2011) Poorer functional outcomes seen in young adults 13 years later (Oie <i>et al</i> , 2011)
Post-traumatic stress disorder	↓ Auditory MMNi (Menning <i>et al</i> , 2008) ↓ N2 latency on auditory oddball task (Veltmeyer <i>et al</i> , 2005)	↓ Response inhibition ↓ Attentional control (Aupperle <i>et al</i> , 2011; Leskin and White, 2007) ↓ Inhibitory control ↑ Sensory processing (Falconer <i>et al</i> , 2008) ↓ Sustained attention ↓ Verbal memory retention/retrieval (Veltmeyer <i>et al</i> , 2005)	Impairments in response inhibition and attention regulation may predate trauma exposure, serve as risk factors for the development of PTSD, and relate to the severity of symptoms (Aupperle <i>et al</i> , 2011) High/persistent symptoms predict functional impairment (Thomas <i>et al</i> , 2010; Westphal <i>et al</i> , 2011) Pre-trauma neurocognitive functioning moderates the effects of trauma exposure on PTSD symptoms (Marx <i>et al</i> , 2009)
Addictions	↓ P50 sensory gating in abstinent alcoholics (Marco <i>et al</i> , 2005) ↓ P50 sensory gating in abstinent cocaine users (Boutros <i>et al</i> , 2002)	↓ P3 in adolescent alcohol abuse (Koskinen <i>et al</i> , 2011) ↓ Attention, memory, and processing speed in substance-abusing adolescents ↓ Visuospatial ability in high-risk adolescents with+family history of alcoholism (Thoma <i>et al</i> , 2011) ↓ Delay discounting in drug use and gambling (Reynolds, 2006)	Lower executive functioning in recently abstinent alcoholics predicts poorer occupational outcome 18 months later (Moriyama <i>et al</i> , 2002) Impaired performance on decision-making tasks predicts relapse in drug abuse 3 months later in opiate-dependent patients (Passetti <i>et al</i> , 2008)
Autism	↓ P1 response to faces (Batty <i>et al</i> , 2011) Early sensory processing abnormalities in vision, smell/taste, and touch (Leekam <i>et al</i> , 2007)	Abnormalities in social orientation at 20 months old (Swettenham <i>et al</i> , 1998) Impairments in skilled motor, complex memory, complex language, and reasoning domains (Minshew <i>et al</i> , 1997)	Cognitive capacity predicts adaptive behavior, beyond autism symptom severity (Kanne <i>et al</i> , 2010) Cognitive and language scores at age 2 predict outcome status (Turner <i>et al</i> , 2006)
Aging brain and risk for dementia	↓ Auditory MMN in older adults (Cooper <i>et al</i> , 2006) ↓ Suppression of irrelevant stimuli early in visual processing in elderly (Gazzaley <i>et al</i> , 2008)	Neuropsychological test performance predicts the transition from healthy cognitive aging to MCI (Cherbuin <i>et al</i> , 2010)	Poor cognitive test performance in older adults predicts risk for dementia (Barnes <i>et al</i> , 2009) Decline in executive functioning predicts self-neglect in elderly (Dong <i>et al</i> , 2010)

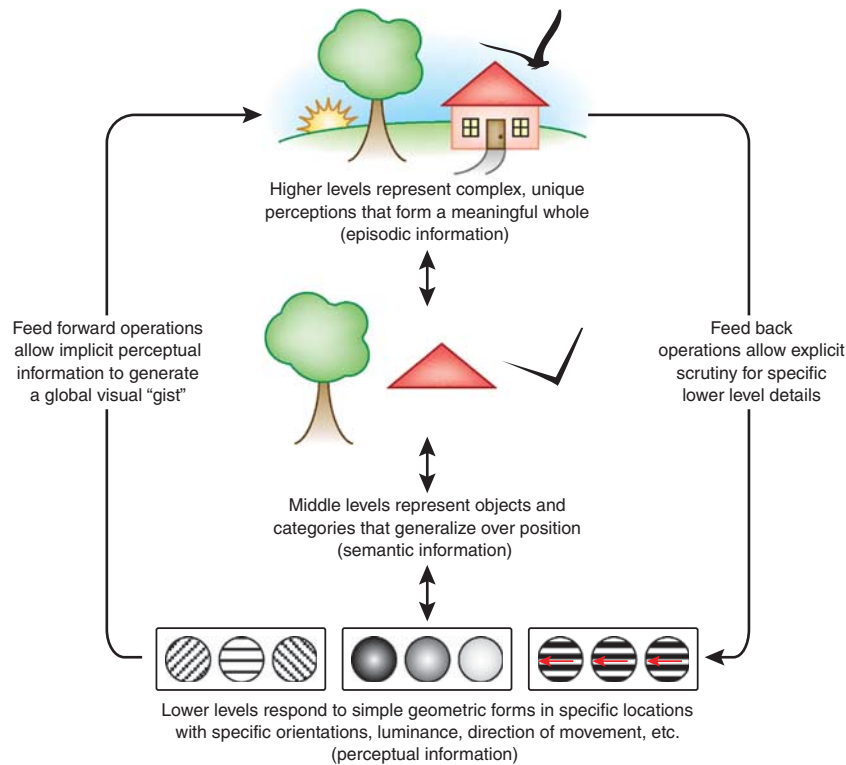


Figure 3. Prefrontal cortical areas interact bidirectionally with lower levels of sensory and perceptual operations, with multiple feed-back and feed-forward effects. A schematic representation is presented for the visual system. Adapted and modified from Ahissar *et al* (2009).

less selective attention to negatively biased perceptual information, for example, through the kind of computerized tonic and phasic alertness training that has been successfully used to address abnormal attention bias in hemi-neglect patients (Degutis and Van Vleet, 2010). Indeed, such an approach has been successfully piloted in highly anxious children who show abnormal attention bias toward threatening stimuli (Bar-Haim *et al*, 2011) and is under study in major depression (Thomas Van Vleet, personal communication).

We emphasize that the interaction between higher and lower levels of processing is complex and bidirectional, for prefrontal cortical areas continuously and strongly influence multiple aspects of sensory and perceptual operations, with powerful feed-back and feed-forward effects (Figure 3; see also Liang *et al*, 2002; Mukai *et al*, 2007; Cao *et al*, 2008; Miller *et al*, 2008; Friedman-Hill *et al*, 2010; Nahum *et al*, 2010; Roelfsema *et al*, 2010; Rutman *et al*, 2010; Zanto *et al*, 2011). Gazzaley (2010), for instance, has shown that prefrontal modulation of early perceptual processing (100–200 ms after stimulus onset) impacts subsequent working memory performance—but that task practice, perceptual training, and aging effects in the brain, can all affect this relationship. Regardless of etiology or of the original location or directionality of the primary ‘lesion,’ the evidence indicates that degraded or biased processing of lower-level perceptual information will reverberate throughout distributed neural systems, and will affect higher-level prefrontal efficiency and function, including working memory and long-term memory encoding, as well

as limbic and subcortical activation patterns. We postulate that attempts to remediate or improve higher-level functions in neuropsychiatric illnesses may hit a bottleneck if underlying perceptual processing limitations are not addressed. For instance, in order to perform a basic social cognition task successfully, such as identifying the emotion on a face, the brain must rapidly and accurately perform a visual scan of informative facial features (eyes, mouth, midfacial region), and then process that visual data in an efficient and accurate manner, creating stable and detailed cortical representations of the relevant sensory inputs. If these basic processes are degraded or ‘noisy’ in their earliest representations, as is the case in schizophrenia and autism (Wong *et al*, 2008; Butler *et al*, 2009; Hileman *et al*, 2011), the brain will have difficulty performing appropriate and adaptive complex multimodal operations, predictions, comparisons, or decisions on the visual data (Figure 5). This can lead not only to failures in encoding relevant signals from the environment, but also to high errors or ‘false alarms’ about irrelevant signals (see pre-clinical data on the higher-level effects of degraded auditory processing from the aged rat brain in de Villiers-Sidani *et al* (2010). High ‘false alarms’—or the processing of task-irrelevant stimuli—in turn leads to overload on working memory systems (Zanto and Gazzaley, 2009).

High rates of task-irrelevant interference occurring at the pre-attentive level not only affect working memory, they also disrupt the brain’s ability to assign appropriate salience to incoming information, and lead to abnormalities in

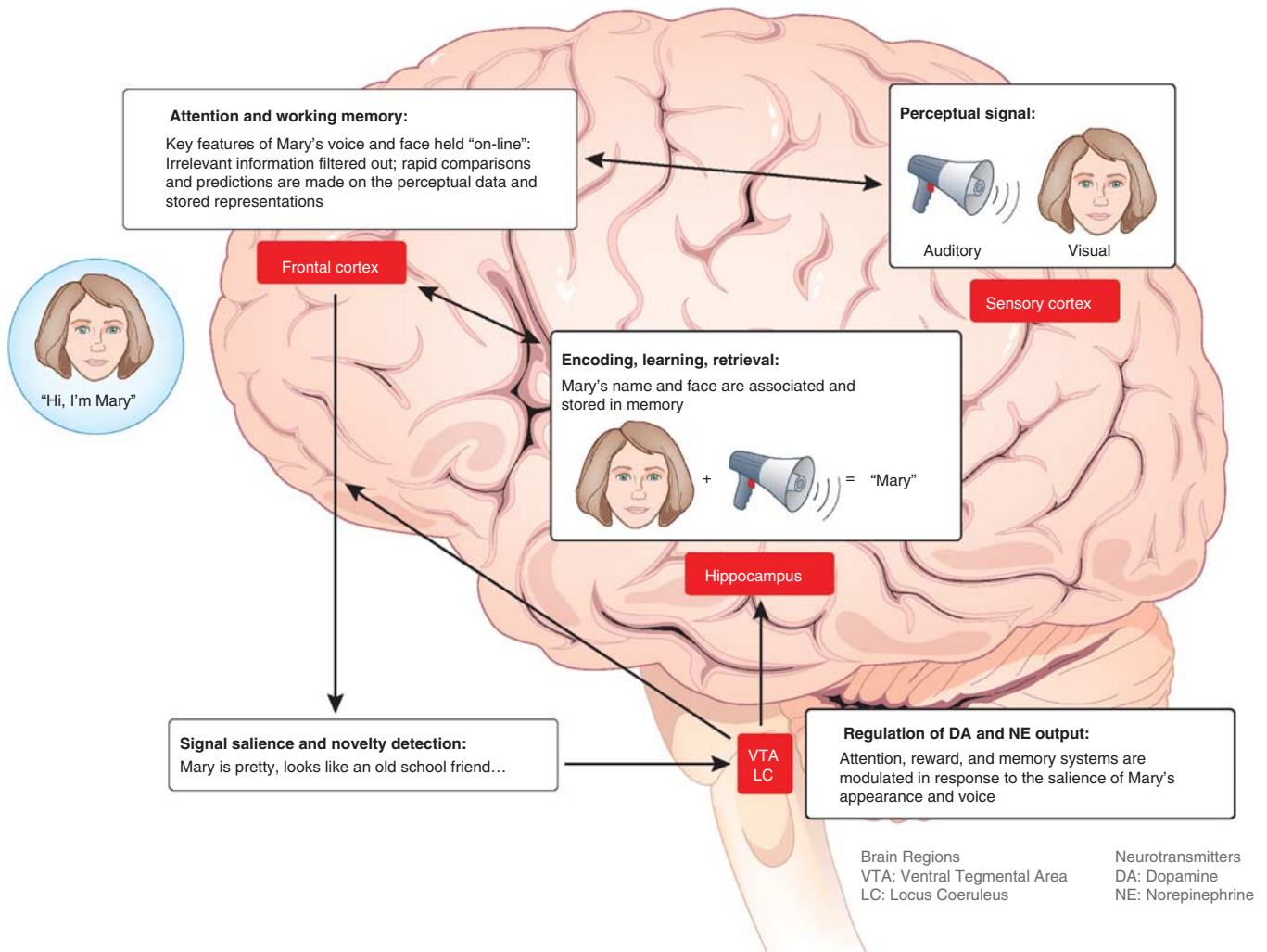


Figure 4. In order for prefrontal cortical operations to engage in efficient decision-making and adaptive behavior, the brain must be able to continuously make accurate predictions about the near future. These predictions rely on rapidly and accurately comparing high-fidelity perceptions of our current internal and external environments with past experiences.

neuromodulation (for discussion of prediction errors, learning, and neuromodulatory functions in the healthy brain, see Schultz and Dickinson, 2000; Nomoto *et al*, 2010; see also Axmacher *et al*, 2010; for discussion in the context of schizophrenia see Keefe *et al*, 2011). Relevant or novel stimuli are 'missed' and fail to generate the appropriate input/output mismatch that leads to attentional salience and representations in working memory. Irrelevant stimuli capture attentional resources, are incorrectly coded as salient or novel, enter into working memory, and increase activity in subcortical noradrenergic and dopaminergic systems. This creates an unstable state in the brain, leading to further inappropriate learning (see Mercado *et al*, 2001; Kilgard, 2002). As an example, the abnormal early processing of visual data from faces found in autism and schizophrenia appears to be a strong contributor to the poor social cognitive abilities in these disorders; poor social cognitive abilities combined with affective arousal and inappropriate attribution of salience found in schizophrenia in turn increases the risk for paranoia, further perpetuating

a state of maladaptive memory formation (Dalton *et al*, 2005; Akiyama *et al*, 2008; Heinz and Schlagenhaut, 2010; Kirchner *et al*, 2011).

The point we are making here is that any remediation approach that does not address impairments or biases in early perceptual processing can lead to modest improvements in behavior, especially if the remediation is provided in an enriched therapeutic environment (as has been shown in the meta-analytic studies of schizophrenia), but it is unlikely that these gains will be robust, will generalize to broad new learning patterns, or will be associated with widespread and enduring improvements in the efficiency of distributed neural systems. For instance, we would predict that any attempt to train a person with schizophrenia or with autism to have better social skills—through group therapy, therapist coaching, or a virtual reality platform—will hit a plateau if the lower-level face-processing deficits are not addressed. Training that also improves the perception of and appropriate salience of facial features—along with their representation and manipulation

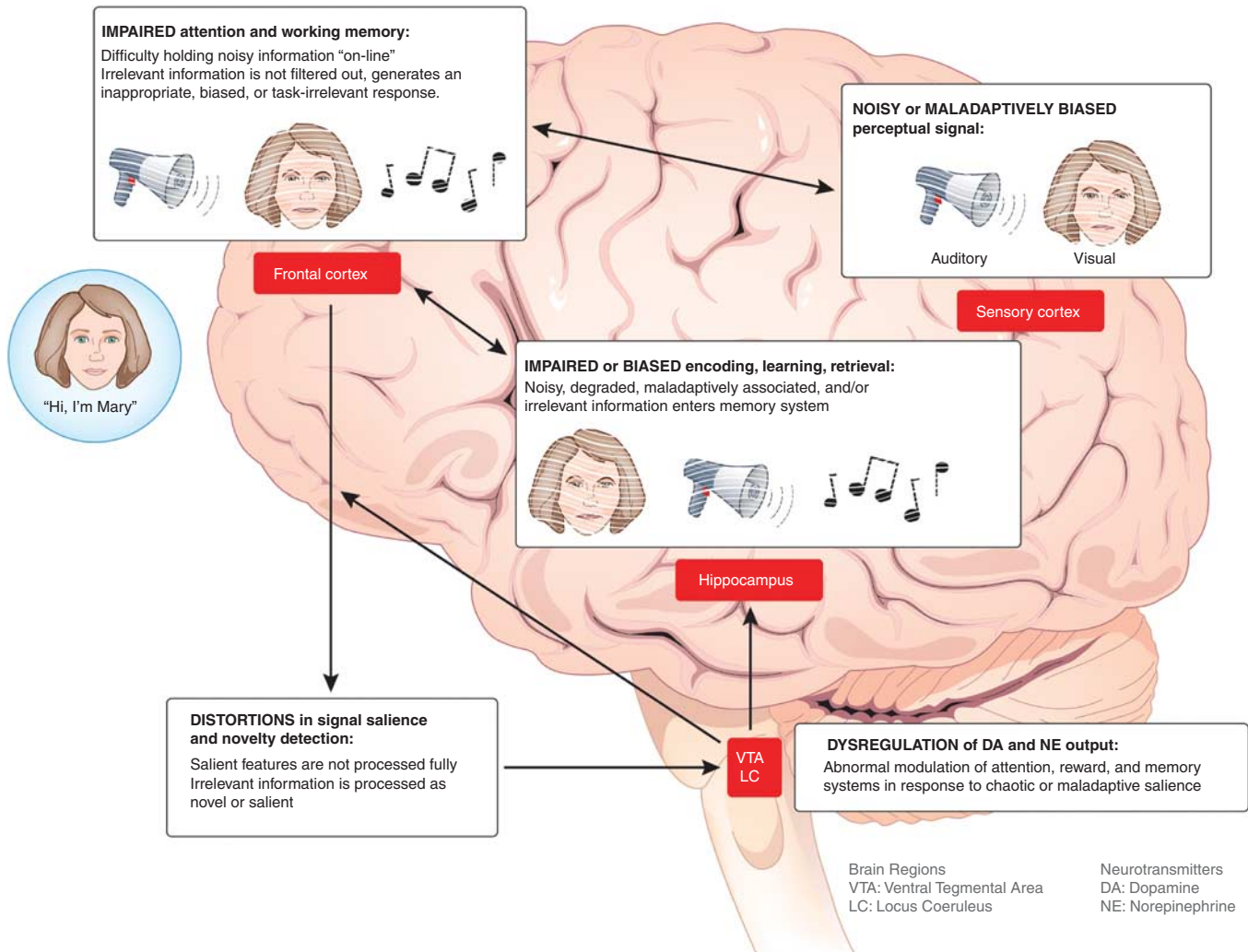


Figure 5. If lower-level perceptual and/or attentional processes are degraded or abnormally biased, the brain will have difficulty adaptively performing other more complex multimodal operations, predictions, or decisions on the data.

in working memory—will, we propose, greatly enhance the success of social skills interventions in these disorders. Indeed, this has been recently shown to be the case both in schizophrenia (Roberts and Penn, 2009) and in autism (Hopkins *et al*, 2011). We note that this approach is ‘restorative’ in nature—the idea is not to develop compensatory or work-around strategies for impaired perceptual processes (be they basic and ‘primary’ in nature, or secondary to attentional biases), but rather to drive the impaired neural systems in the direction of more normal functioning through carefully engineered training strategies.

Constrained and Intensive Training Is Necessary to Induce Robust Plastic Changes in Cortex

The second consideration we propose is that, in order for a brain to undergo significant plastic changes, it must practice a well-defined skill at a sufficient level of difficulty for a sufficient amount of time; this may be especially true for an impaired brain. Skill learning is characterized by two general phases. The first phase involves rapid

improvements in performance that are observed within a single training session and/or after initial training (Figure 6a). The second slower phase involves moderate gains in performance that progress across multiple training sessions (Kleim *et al*, 1996, 1998; Nudo *et al*, 1996; Karni *et al*, 1998). Each phase is supported by unique neural responses. For example, in motor skill learning, the initial fast phase is associated with activation of cerebellum and then fronto-striatal regions, whereas the later phase engages motor cortex (Ungerleider *et al*, 2002). Kleim *et al* (2004) have shown in rats that synaptogenesis and reorganization of motor maps within the cortex only occurs during the second, slower phase (see also Maviel *et al*, 2004 for similar findings concerning spatial memory in mice). Large-scale learning-dependent neural plasticity is temporally dissociated from learning-induced improvements in behavior; major plastic changes in neural representations occur only after sufficiently intense training of a specific skill.

Prior cognitive remediation methods—and indeed many behavioral interventions in neuropsychiatric illness—have

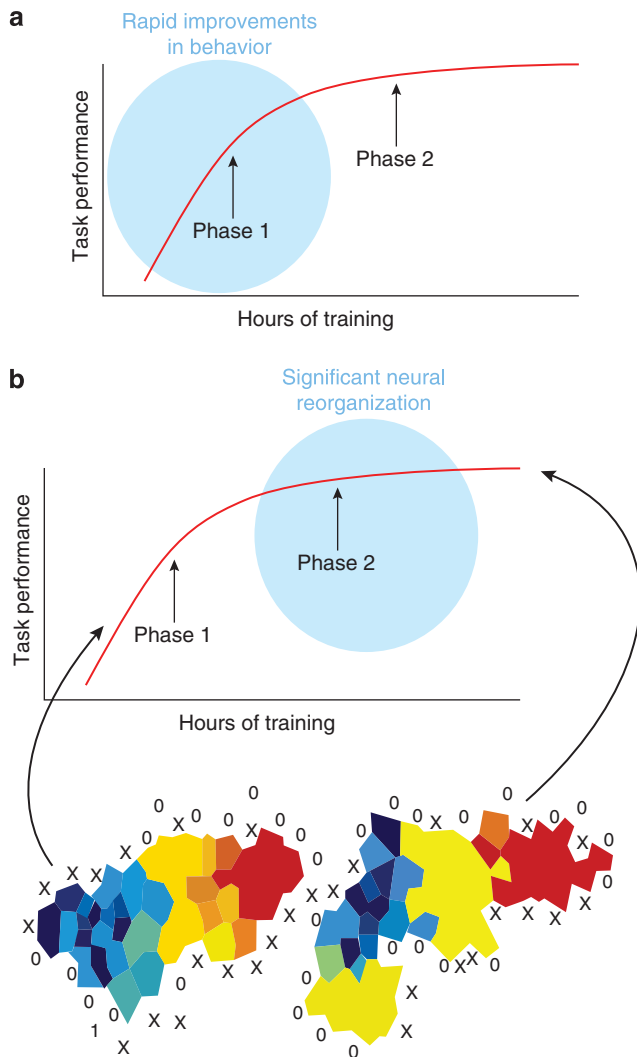


Figure 6. (a) The first phase of skill learning involves rapid improvements in performance. (b) The second phase of learning is characterized by massive reorganization of task-specific representations in the brain.

tended to focus mainly on the first phase of learning, and often ask patients to train simultaneously across a diffuse set of skills. This phase can be thought of as a non-specific task-induced increase in performance efficiency, where rapid behavioral gains occur, probably due to the creation of a general task schema relying heavily on prefrontal processes (see Ahissar and Hochstein, 2004). This phase engages an early set of less-persistent plasticity mechanisms that involve changes in the efficacy of existing synapses (Riout-Pedotti *et al*, 1998), increases in neuronal excitability (Aou *et al*, 1992), changes in neural activity that reflect the encoding of novel task-relevant patterns (Riout-Pedotti *et al*, 1998; Laubach *et al*, 2000), or transient changes in task-specific cortical representations that occur, but do not persist, outside of the training session (eg, changes in movement representations after a single training session can last for several minutes before reverting to the pre-training state (Classen *et al*, 1998). This might explain the gains seen in any number of previous forms of cognitive

remediation in schizophrenia: improvement in task performance occurs due to the activation of early plasticity mechanisms and/or from non-specific frontally mediated processes related to the creation of a more efficient task schema. This also likely explains the non-specific general effects seen when comparing multiple different cognitive remediation approaches in schizophrenia (McGurk *et al*, 2007; Wykes *et al*, 2011).

These processes are quite distinct from those in the second phase of learning. During this phase, behavioral gains are more modest and are approaching an asymptote, and yet experimental data indicate that the cortex is showing first, significant synaptogenesis, and next, massive reorganization of task-specific representations (Figure 6b). For example, Kleim *et al* (2004) have shown that during training in rats on a skilled reaching task, significant increases in synapse number within the motor cortex are not detectable until well after significant skill acquisition has occurred. Although trained animals exhibit a significant increase in reaching accuracy after only 3 days of training, the number of synapses per neuron within motor cortex does not significantly differ from untrained animals until after 7 days of training, while the distal forelimb representations in motor cortex are not significantly larger until after 10 days of training. In a human study, Karni *et al* (1995) used fMRI to show the reorganization of motor cortex in healthy adults while they performed motor tasks requiring rapid sequences of finger movements. Behavioral performance, indicated by the speed at which the trained sequence could be performed, reached an asymptote after 3 weeks of training. It was only at week 4 of training that the motor cortex, activated by the practiced sequence, became significantly enlarged compared with the unpracticed sequence. Additionally, this reorganization of motor cortex that occurred during the slow phase of learning persisted for several months, suggesting that it is related to the actual retention of the new motor skill.

In sum, the basic science indicates that, in order to (efficiently) move the learner well into the second phase of learning where significant and enduring cortical reorganization occurs, learning trials must be well defined or constrained, must be adaptive to the level of the given individual (must continuously adjust so that learning is occurring with a high level of success and at asymptote), and must be given for a sufficient number of trials. This indicates that the ability to develop many thousands of precisely defined learning events with precisely engineered timing, difficulty level, and reward schedules is an important feature of effective cognitive training methods.

Indeed, we would argue that cognitive training of insufficient intensity or duration—where the learner is not involved in precisely defined learning trials at threshold of performance for a sufficient number of trials—will not drive distributed enduring adaptive changes in a specific set of neural representations of interest, particularly in a neuropsychiatrically impaired brain. This may explain why many different remediation methods (usually of relatively

low intensity and/or short duration and/or that train diffusely) applied in many different clinical contexts have yielded some behavioral improvement, but without convincing evidence of strong and lasting benefits. In the 26 schizophrenia studies in the McGurk *et al* (2007) meta-analysis, the median treatment intensity was 2 h/week and the median treatment duration was 7 weeks. The recent study by Owen *et al* (2010) in which roughly 30 min a week of 'brain training exercises' given for 6 weeks in over 10 000 individuals in Britain failed to drive significant improvement in cognition, may likely be an example of underdosing; it is equivalent to saying that a leisurely stroll around the block twice a week for several weeks in healthy individuals fails to significantly improve aerobic capacity, proving that exercise does not improve physical fitness. The need for sufficiently intensive training of sufficiently long duration may be especially important in neuropsychiatric illness characterized by impaired neuromolecular mechanisms combined with many years of maladaptive learning events.

Cognitive Training Must Focus on Implicit Learning Mechanisms

The third consideration we propose is that the neuropsychiatrically impaired brain is often a 'poor learner of new behaviors' either through etiologic factors and/or the self-perpetuating nature of ever-more dysfunctional neural configurations related to disease expression. Thus, explicit instruction, insight, and strategy coaching often do not help the individual to change maladaptive patterns of behavior. The success of these kinds of approaches relies heavily on declarative/explicit learning and memory, and on intact motivation/reward systems, two domains that are demonstrably impaired in a number of neuropsychiatric illnesses (Ragland *et al*, 1996; Heckers *et al*, 1998; Kurtz *et al*, 2001; Arts *et al*, 2008; Bora *et al*, 2009; Hermens *et al*, 2010; Torralva *et al*, 2010). We suggest that impairments in the brain systems subserving explicit learning provide an inherent limitation to the utility of stand-alone instruction, strategy coaching, and other declarative memory-based therapeutic methods. (We will address the issue of motivation and reward at the conclusion of the review.) It is interesting to point out that, in the McGurk *et al* (2007) meta-analysis described earlier, a larger effect size in verbal learning/verbal memory was significantly associated with more hours of remediation *vs* fewer hours, and with drill-and-practice *vs* drill-and-practice that had been combined with strategy coaching. Two ideas emerge from this meta-analytic finding.

The first idea is that many hours of drill-and-practice can be successful in an impaired brain—suggesting that the effects of implicit learning and repetitive practice are still (relatively) intact even when explicit learning is broken. Indeed, although there are some inconsistent findings, the overall pattern is that behavioral responses to implicit learning and to repetitive practice of a well-defined task

can be harnessed successfully in most major neuropsychiatric illnesses, including schizophrenia, Alzheimer's dementia, depression, and autism (Klimkowitz-Mrowiec *et al*, 2008; Nemeth *et al*, 2010). Similar to the point we made earlier about constrained and intensive training, this indicates that cognitive training should harness implicit learning mechanisms and employ repetitive, adaptive practice of critical cognitive and affective processing skills.

The second idea is that the addition of explicit instruction—the attempt to use declarative memory along with implicit learning—actually results in less behavioral improvement for the patient. This counterintuitive notion will require further investigation as the field moves forward. At present, our understanding of the detailed relationship between implicit and explicit learning mechanisms is still relatively unsophisticated, but a great deal of evidence suggests that—at least in the young, healthy brain—there is anatomic and behavioral dissociation as well as competition between these two systems (Poldrack and Packard, 2003; Voss and Gonsalves, 2010). However, the anatomic differentiation that seems so apparent in the healthy brain may not represent the picture in the impaired brain. Dennis and Cabeza (2010) recently showed that young subjects recruited the striatum for implicit learning and the medial temporal lobe for explicit learning, while—surprisingly—older adults recruited the medial temporal lobe during implicit learning. In fact, older adults showed no preferential regions of recruitment for either task, suggesting that, in the aging brain, there may be de-differentiation across memory systems. Patients with schizophrenia also show abnormal brain activation patterns during implicit learning, despite normal behavioral performance, as do patients with major depression (Zedkova *et al*, 2006; Naismith *et al*, 2010). It appears that in certain neuropsychiatric conditions, the neural instantiations of implicit and explicit learning may not show normal patterns of differentiation; the picture is of a brain that is inefficient in its various learning and memory operations. Due to these inefficiencies, training that occurs simultaneously or diffusely across perceptual or cognitive modalities may be ineffective or even counterproductive (see also Ahissar *et al*, 2009). Vinogradov's group have found evidence of possible competitive interference in verbal learning/memory in schizophrenia subjects assigned to a control computer games condition; these subjects showed *worse* performance on a list-learning task after 50 h of visually demanding computer games (Fisher *et al*, 2009). It appears as if intensive visual perceptual processing over a 10-week period interferes with explicit learning of verbal material in individuals who have impaired verbal memory systems. This finding, if replicated, will have important implications for the design and sequencing of training exercises for the impaired brain.

Indeed, in keeping with these data and with the basic neuroscience principles we underscored at the start of this section, recent models of human learning and memory

emphasize the predictive and interactive nature of multiple memory systems (Henson and Gagnepain, 2010; Fell and Axmacher, 2011). In these models, the various memory systems differ primarily in their representational content and computational principles. For example, explicit/declarative memory binds items to their context and is available to consciousness, while implicit perceptual learning, which is not available to consciousness, enhances the representation of recurring features in the environment that define items of interest. Henson and Gagnepain (2010) propose that encoding and retrieval arise from recurrent interactions among the multiple systems: 'lower' representations of perceptual and semantic features feed forward to 'higher' representations of current items and their episodic context, while 'higher' representations generate predictions that are in turn fed back to lower levels (see also Takashima *et al*, 2006).

Put another way, interactions among the different memory systems are continuously occurring based on perceptual and semantic information that is being fed forward as well as expectancies and predictions that are being fed backwards (Figure 3)—given that the brain's machinery is continuously generating predictions about patterns in its environment and then using perceptual data for comparison and detection of either matches or mismatches (Buzsaki, 2006; Henson and Gagnepain, 2010). According to this model, training that improves the brain's ability to extract relevant perceptual and semantic data with high precision and feed it forward, and that also increases the brain's efficiency at making implicit rapid and accurate predictions/decisions about incoming data, should result in enhanced working memory and declarative memory function. Indeed, as Takashima *et al* (2006) concluded from an MEG study of the encoding of complex scenes, working memory processes associated with deep perceptual and semantic processing appear to act in tandem with top-down modulation of contextually constrained visual perception to promote successful declarative memory formation. This notion of continuously interacting memory systems is also consistent with the role of oscillatory phase synchronization between different brain regions in supporting interactions between working memory and long-term memory storage (Fell and Axmacher, 2011; see also Khader *et al*, 2010). We propose that these emerging ideas suggest that 'tuning up' perceptual and semantic processing and working memory capacity through implicit learning and/or repetitive practice may be the optimal approach to fixing broken explicit learning and memory systems in neuropsychiatrically impaired brains. Vinogradov *et al* have shown that intensive computerized auditory training in schizophrenia (implicit learning) improves performance on verbal delayed recognition tasks (explicit learning), with 'normalization' of brain activation patterns during a meta-cognitive verbal memory task (Subramaniam *et al*, in press), while Klingberg *et al* (2005) have shown a similar pattern of generalized behavioral and neural improvement after intensive visual working memory training in ADD.

IMPORTANT MODEL FEATURES OF LEARNING-DEPENDENT NEUROPLASTICITY

In the previous section, we selectively reviewed the emerging basic science of learning, and we argued that three somewhat counterintuitive considerations may be key to the design of cognitive neurotherapeutics for mental and addictive disorders: the need to target limitations or distortions in perceptual processing, the need to provide well defined and sufficiently intensive training at threshold, and the need to harness implicit learning mechanisms—both to improve critical cognitive/socio-affective skills, and to make the brain a more efficient 'learner.' Though we have elucidated each of these considerations as if they are independent from one another, they are in fact deeply interrelated, and they derive from pre-clinical findings of how neural systems change in response to experience. In this section, we briefly examine several features of learning-dependent neuroplasticity in auditory cortex as a model system for understanding critical neuroplasticity mechanisms. We then translate these features into specific principles that help to inform the design of human therapeutic tools.

Brain Plasticity Mechanisms Continuously Shape Neural Circuits and Behavior

The mechanisms that support plastic reorganization in the brain and its consequences on perception and behavior have been most extensively studied in animal models that focus on primary sensory cortical areas. We will highlight a few specific experiments from the auditory system, which is arguably one of the most studied systems with relevance to neuropsychiatric illness and has been extensively studied in humans and animal models using comparable neurophysiology techniques such as EEG (Arlinger *et al*, 2009; Javitt, 2009; Hitoglu *et al*, 2010; Witton, 2010).

Developing cortical circuits in primary auditory cortex (A1) are extremely sensitive to the presence or absence of clear sensory input patterns in the environment. Exposing infant rats to pulsed tones of a particular frequency 24 h/day during the second week of life (the sensitive period of plasticity in the rat auditory system) increases by threefold the number of A1 neurons tuned to that frequency (Zhang *et al*, 2001; de Villers-Sidani *et al*, 2007). Such distortion in A1 frequency coding persists into the adult life and profoundly shapes—or interferes with—perceptual discrimination in behavioral tasks (Han *et al*, 2007). Conversely, if the same animals are kept in an auditory environment devoid of sensory input patterns (because of the presence of moderate intensity auditory noise for example), functional maturation of the cortex is suspended and auditory cortical neurons, including inhibitory interneurons, remain very immature in their responses properties (Chang and Merzenich, 2003; de Villers-Sidani *et al*, 2008). These experiments indicate the intimate relationship linking

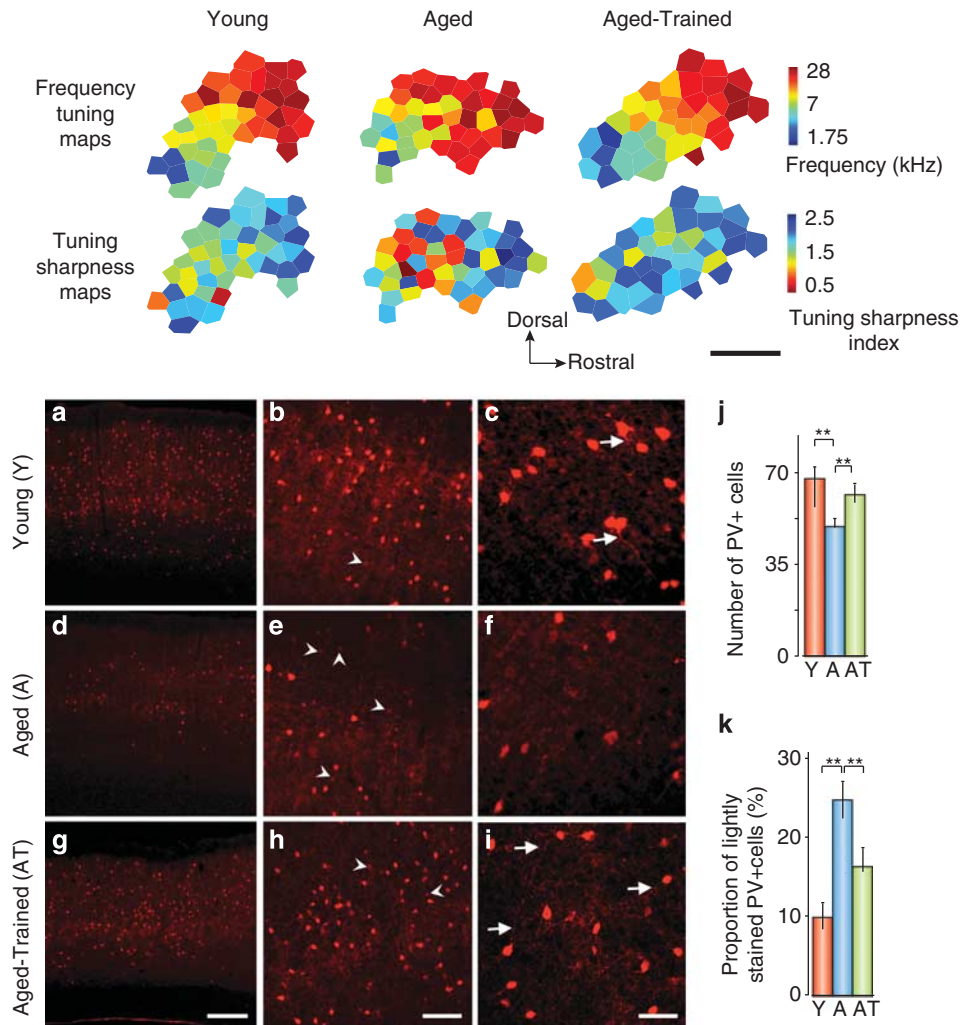


Figure 7. Targeted auditory training improves functional and structural impairments in the aged brain. (Above) In the aged rat brain, the normally smooth gradient of frequency tuning in the primary auditory cortex (A1) is disorganized and neurons lose their frequency tuning selectivity. Forty sessions of intensive training on a deviant tone detection paradigm completely reverses these impairments. The polygons shown above represent the location of neurons recorded in a typical rat A1 during cortical mapping experiments. On the top row, the color represents the neurons' frequency tuning (blue for low frequency, red for high), while in the bottom row, the color represents the sharpness of tuning. (Below) Low power photomicrographs demonstrate the loss of parvalbumin (PV) immunoreactivity in the aged A1. PV is contained in a specific class of interneurons involved in salient stimulus detection and noise suppression in the cortex. The same auditory training task described above significantly increased the number of cells staining for PV in the cortex (a, d, g, j), decreased the number of cell staining only lightly for PV (b, e, h, k) and increased dendritic PV immunoreactivity (c, f, i). Error bars are SEM. Scale bar in g (apply for a and d): 200 μ m; in h (apply for b and e): 100 μ m; in i (apply for c and f): 50 μ m. $**P < 0.01$. Adapted from de Villers-Sidani *et al* (2010).

environmental inputs during critical periods of development, cortical maturation, cortical mapping, and adult perceptual behavior; they suggest that aberrant, self-perpetuating cognitive, affective, and behavioral patterns may be set in motion early in life in genetically and constitutionally vulnerable individuals and amplified by dysfunctional environmental inputs. Thus, as we have noted earlier, while multiple genes of small effect contribute to the risk for mental and addictive disorders, extremely powerful developmental brain plasticity mechanisms probably also make a significant contribution to the clinical expression of these disorders.

Experience-dependent plasticity is not limited to early development, but significant differences do exist between

adult plasticity and that of the developing brain. For example, while short passive exposures to discrete stimuli such as those described above have no measurable impact on adult cortical maps (Zhang *et al*, 2001; de Villers-Sidani *et al*, 2007), very prolonged and dramatic distortions in sensory inputs can influence the frequency representation in A1, as seen after a permanent lesion of a portion of the cochlea (Irvine and Rajan, 1997). In such instances, A1 progressively reorganizes to maximize the area of cortex responsive to the remaining active sensory inputs. Furthermore, prolonged noise exposure can revert A1 to a very immature and plastic state (Zhou *et al*, 2011). So in effect, cortical circuits constantly triggered by patterned inputs are consolidated, while those engaged in chaotic

or undifferentiated activity remain ‘detuned’ and relatively more plastic. This observation has potentially interesting clinical implications. First, several common neuropsychiatric conditions—including autism, schizophrenia, and aging—have been associated with poorly integrated, dyscoordinated, or inefficient brain activity (Caspary *et al*, 2008; Oblak *et al*, 2009; Gonzalez-Burgos *et al*, 2010). This raises the possibility that sources of noise within the brain itself are directly contributing to the emergence of cognitive deficits. Second, the notion that ‘noisy’ or degraded representational systems might be maintained in immature but relatively more plastic states could represent an interesting opportunity for the elaboration of highly specific training strategies aimed at improving processing in systems having the most plastic potential first.

Cognitive Training Remodels Neural Circuits and Depends Heavily on Neuromodulatory Activity

In the mature cortex, the most effective method of achieving directed plastic reorganization of cortical circuits is by using attention-demanding intensive behavioral training strategies (Mahncke *et al*, 2006a; Seitz and Dinse, 2007). Reinforcement-based operant conditioning refines cortical mapping and processing in A1 in the adult rat (Bao *et al*, 2004), and induces changes in protein expression, inhibitory circuitry, and supporting glia (Klintsova *et al*, 2004; Bengtsson *et al*, 2005; Tokarski *et al*, 2007). Training can also induce adaptive reorganization in the auditory cortex of aged rats which, at baseline, show evidence of abnormal or degraded cortical maps due to age-related cognitive decline (Dinse, 2006; de Villers-Sidani *et al*, 2010) (Figure 7).

Training-directed brain plasticity depends heavily on the activity of neuromodulator systems involved in the regulation of arousal, attention, and reward mechanisms (Buonomano and Merzenich, 1998; Weinberger, 2003; Blake *et al*, 2006; Roelfsema *et al*, 2010). For example, passive pairing of an acoustic tone with electrical stimulation of cholinergic (nucleus basalis) or noradrenergic (locus ceruleus) nuclei massively increase the area of cortex tuned to the frequency of the tone (Kilgard and Merzenich, 1998; Bao *et al*, 2001; Froemke *et al*, 2007; Edeline *et al*, 2010). Interestingly, the precise timing of the electrical stimulation relative to the stimulus can reverse the direction of the plasticity. Bao *et al* (2001) showed that stimulation of the ventral tegmental area (VTA) *after* the occurrence of a 4-kHz tone but *before* a 9-kHz tone more than triples the area of A1 tuned to 4 kHz and selectively reduces A1 tuning to 9 kHz (Figure 8). Given that VTA activity is tightly linked to behavioral salience of inputs and to reward (Arias-Carrion *et al*, 2010), this finding suggests that the precise timing and nature of the delivery of rewards is important in developing effective training strategies (Rutkowski and Weinberger, 2005). This may be especially true in the impaired brain, where the response to rewarded events is

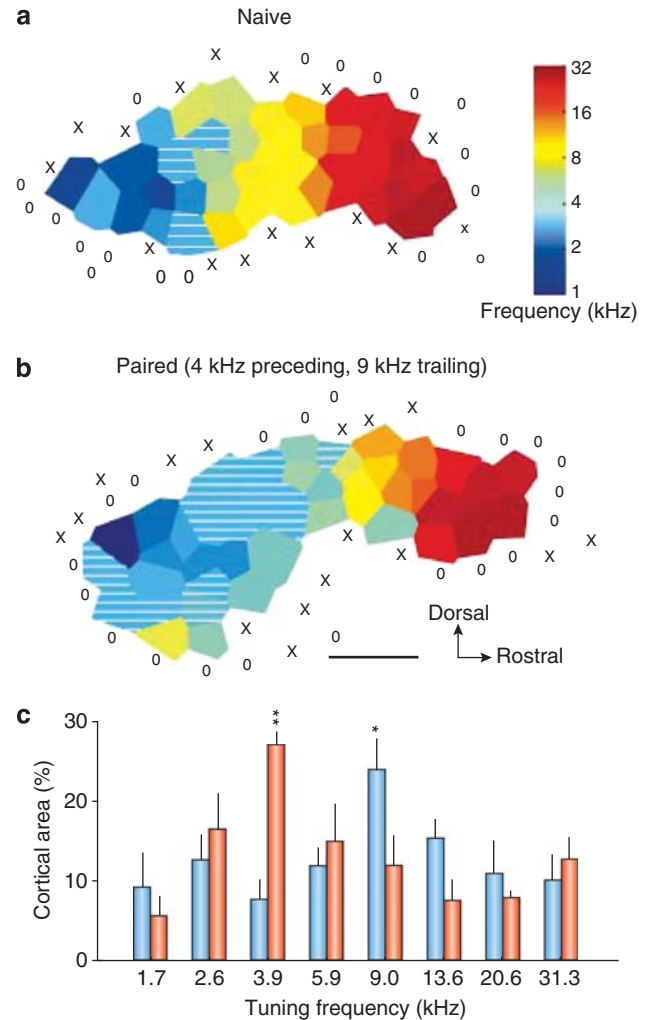


Figure 8. Pairing auditory tones with VTA stimulation affects plastic changes in A1. In A1, frequency tuning follows a tonotopic gradient where neurons tuned to low frequencies are found at one extremity of the map and neurons tuned to high frequencies are located at the other (a). Here, a sequence of two tones was presented along with stimulation of the VTA, which releases dopamine in the cortex. The first 4 kHz tone preceded the VTA stimulation by 500 ms; the second 9 kHz tone followed the VTA stimulation 500 ms later. This simple paradigm resulted in an ~300% increase in the A1 area tuned to 4 kHz and a 50% decrease in A1 tuning to 9 kHz (b, c). These findings suggest that the timing of a reward provided in the context of perceptual training has to be carefully considered in order to maximize cortical plasticity responses * $P < 0.05$, ** $P < 0.0005$. Adapted from Bao *et al* (2001).

weakened or biased; for example, in schizophrenia (Morris *et al*, 2008; Koch *et al*, 2010).

In an elegant macaque study, Blake *et al* (2006) showed that a cognitive stimulus-reward association, or the ability to clearly identify a particular stimulus as a to-be-rewarded target *vs* an unrewarded non-target, is necessary to drive the stimulus-specific plastic changes observed in reinforcement-based learning. In this experiment, the monkeys had to identify a pre-determined target sound presented along with distractors. The animal, kept thirsty, signaled his response by slightly moving his head. If the answer was correct, a fluid reward was delivered through a tube. Since

auditory cortical responses were continuously monitored, the authors noted that significant plastic changes in sound coding in A1 only occurred when the animal appeared to ‘know’ what the answer was (ie, the animal began to lick immediately after a correct answer, but before the fluid reward was delivered). In other words, for training to drive significant cortical reorganization, the animal in training must be able to reliably predict that its answer is going to be correct. Guessing a correct answer, even in the presence of a reward, will not be effective to drive plastic changes. Again, this finding highlights the necessity of being able to carefully control both the performance level and the reward schedule of training—learning events must be constructed such that the animal is able to predict with a high degree of accuracy when it has made a correct response. The key is to ‘re-calibrate’ the brain’s ability to successfully predict meaningful associations.

In a paired-tone task, Zhou *et al* (2010) observed that once the initial stimulus in the target sequence was presented, neurons in the primary auditory cortex changed dynamically, specifically to exaggerate further the representation of the ‘predicted’ second stimulus in the target sequence. When the second stimulus occurred within the target sequence, more strongly excited, more coordinated, and more selectively responding neurons represented this over a larger cortical area (Figure 9). This study showed that cortical areas are not static, but instead can be biased moment by moment in time as a function of a prediction state. In a related study performed in rats, Polley *et al* (2006) demonstrated that ‘top-down’ prefrontal influences are involved in this phenomenon and therefore participate in the gating of training-specific plasticity in sensory cortex. These results are consistent with emerging work in humans.

To follow-up on the Zhou *et al* (2010) experiment, Panizzutti *et al* (under review) looked for structures in the frontal cortex that could be involved in the enhanced response to the predicted second tone. Rats were trained to recognize a target sequence of two pure tones among non-target two-tone sequences, as in the previous study. Unit and local field potential responses were recorded from the auditory and ventral orbital frontal cortices simultaneously, during presentation of the target and non-target stimuli. Panizzutti *et al* (under review) found marked θ and γ band oscillation in the ventral orbital cortex during the silence inter-tone interval when the animal was expecting the second tone in the target sequence but not in the non-target condition. These findings again highlight the distributed and dynamic nature of neural changes involved in learning and emphasize the feed-forward and feed-back networks involved in predictions about sensory events.

Three Guiding Principles Emerge from the Neuroscience

Taken in aggregate, these findings from basic systems neuroscience provide us with three guiding principles for the application of cognitive training to neuropsychiatrically

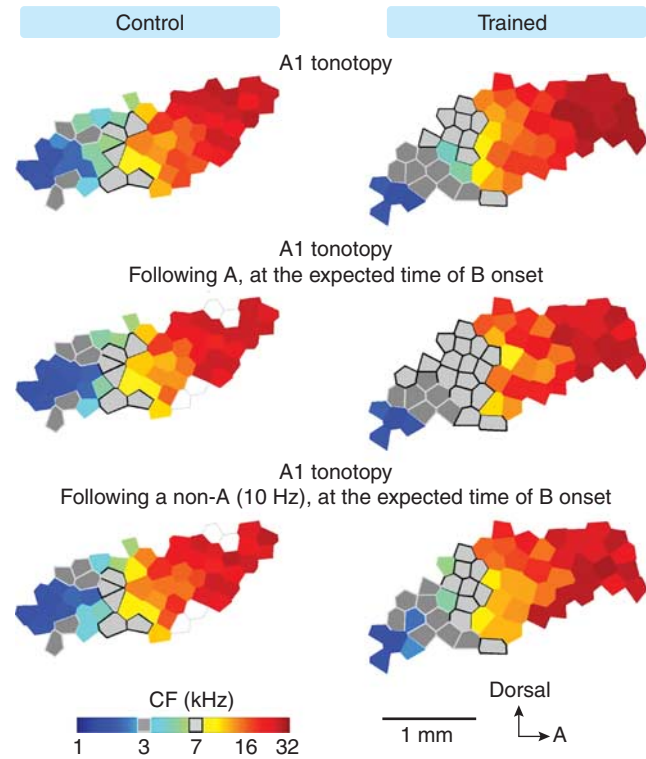


Figure 9. Moment-to-moment top-down biasing of frequency tuning in A1 occurs after training on a sound sequence. The color of each polygon indicates the frequency tuning of neurons recorded in the A1 of control rats and rats trained to respond to the occurrence of a 7-kHz tone presented only after the occurrence of a 3-kHz tone. (Top row) Training resulted in a slight increase in the representation of each tone presented in isolation. (Middle row) When measured right after the presentation of a 3-kHz tone, the area of A1 tuned to 7kHz is more than doubled compared with when a different tone is used first in the sequence (bottom row). Dark or light-gray polygons indicate recording sites tuned to 3 or 7 kHz \pm 0.25 octaves, respectively. A, anterior; D, dorsal. Adapted from Zhou *et al* (2010).

impaired brains. We articulate each principle here, and provide a relevant example from current clinical research.

- (1) The fundamental neural mechanisms that support learning-induced plasticity are in place throughout life and can be harnessed in the impaired brain. The adult brain is not a fixed and rigid system; most often, it has difficulty learning new behaviors due to competitive interference from prior learning successes. Adults have difficulty learning a new language because their primary language is stored in widely distributed, powerful, massively practiced cortical representations that compete with the formation of new language-based neural responses (Merzenich *et al*, 1991; Merzenich and DeCharms, 1996). This principle helps us to understand the catastrophic and enduring reorganization of cortical representations in neuropsychiatric patients who have experienced multiple episodes of maladaptive high-salience ‘learning events’ (see Figure 10 for a basic science example of this phenomenon, adapted from

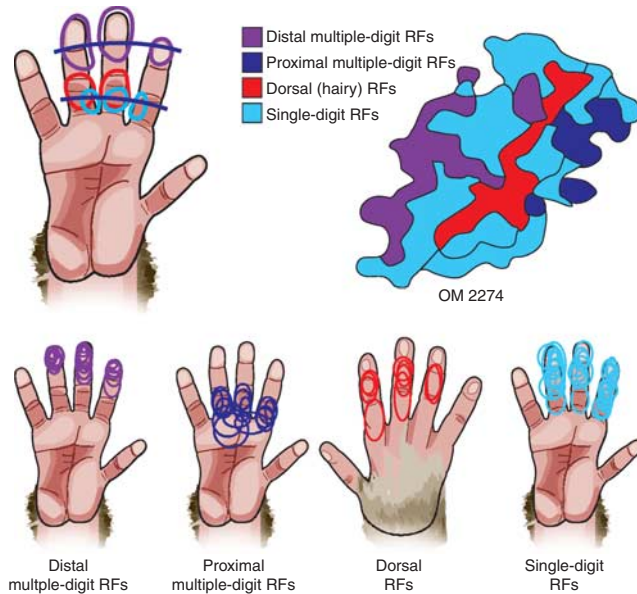


Figure 10. Cortical reorganization can occur in maladaptive directions: monkeys trained to detect a bar contacting the second, third, and fourth finger simultaneously show a degraded and undifferentiated representation of those digits in somatosensory cortex (Wang *et al*, 1995); this degraded map leads to focal hand dystonia. Similar principles of maladaptive reorganization of somatosensory cortex underlie the development of phantom limb pain (Yang *et al*, 1994).

Wang *et al*, 1995). Though we do not yet fully understand how illness-related changes in neuroplasticity mechanisms affect the capacity of the impaired brain to respond to training, evidence from persistently ill schizophrenia patients indicates that even in this disabling condition, the brain is capable of significant behavioral and neural activation improvements after appropriate training (Haut *et al*, 2010; Subramaniam *et al*, in press).

- (2) Training-induced enhancements in lower-level perceptual representations have a beneficial effect on higher-level cognitive operations. For example, as a monkey learns to perform a sensory-guided hand movement (eg, to retrieve a small object from a hidden cubby), areas that represent the relevant tactile, proprioceptive, and kinesthetic inputs in sensory cortex, and areas that represent motor planning and output zones of the frontal cortex, all develop more tightly coordinated oscillatory activity to reflect the newly trained hand movements. These practice-driven, coordinated neural networks feed forward and deliver a proportionately more salient and more coherent signal to downstream cortical and subcortical areas involved in prediction, association, encoding, and action control (Merzenich and DeCharms, 1996). Indeed, evidence from older adults shows that successful perceptual training induces more efficient and reliable prefrontal cortical operations, allowing for improved working memory performance (Berry *et al*, 2010; Gazzaley, 2010). Vinogradov *et al* have shown increases both in the amplitude of the M100 response in A1 and in very early γ band oscillatory power in lateral prefrontal cortex after

intensive auditory training in schizophrenia, concomitant with improved behavioral performance (Dale *et al*, 2010; Brown *et al*, under review).

- (3) Learning-induced plasticity is critically dependent on the behavioral state of the animal, and is profoundly influenced by neuromodulatory neurotransmitters. Cholinergic, dopaminergic, and noradrenergic neuromodulation are fundamental components of learning-induced plasticity in cortical systems (Kilgard and Merzenich, 1998; Bao *et al*, 2001; Roelfsema *et al*, 2010). Long-term plastic changes are induced when a behavior is closely attended and rewarded (ie, when the animal is ‘motivated’ to perform the behavior), but not when equivalent schedules of input or action events occur without the animal attending to them. In humans, inducing activation of midbrain regions containing dopamine neurons that project to hippocampus before learning (*via* monetary incentives) improves memory for events that follow the activation (Adcock *et al*, 2006). This principle indicates that training must be delivered in such a manner that the learner attends to every trial, and that trials must be delivered with both a sufficiently high reward schedule and a sufficiently challenging difficulty level so that the learner maintains motivation while improving performance. The abnormal neuromodulatory function seen in addictions, schizophrenia, ADD, major depression, and post-traumatic stress disorder (to name a few) likely has a direct effect on cortical plastic responses during learning, as do the medications commonly prescribed for these illnesses. In patients with schizophrenia, for example, higher levels of medication-induced anticholinergic burden adversely affect the response to cognitive training (Vinogradov *et al*, 2009).

NEUROPLASTICITY-BASED COGNITIVE TRAINING IN NEUROPSYCHIATRIC ILLNESSES

The neuroscience principles discussed above can be translated into specific therapeutic approaches for human disorders whose goal is to harness mechanisms of neuroplasticity and to drive meaningful neural representational change through implicit learning. The goal is to create a brain that is a more efficient learner with more finely tuned and accurate cognitive and affective processing and a better ability to engage in adaptive real-world behaviors. In this section, we delineate some of the key ‘active ingredients’ for a neuroscience-informed approach to cognitive training, and we highlight promising findings using this approach in several clinical populations.

Features of Neuroscience-Informed Cognitive Training Methods

Based on the findings we reviewed earlier, the critical active ingredients for a neuroscience-informed approach to

cognitive training in an impaired brain would include the following features:

- (1) Initial use of training to improve impaired perceptual processes and drive adaptive plastic changes in distributed brain systems of interest, followed by use of stimuli and tasks that support generalization to real-world environments. In other words, there must be precise engineering of stimuli and tasks in order to improve the speed and accuracy of relevant information processing throughout the targeted neural system(s), including lower and higher levels of processing. As extensively reviewed in Ahissar *et al* (2009), the past 15 years of research into human perceptual learning has unequivocally demonstrated that the specific features of a training protocol have a significant impact on the degree of improvement in a given task as well as the amount of generalization to untrained tasks. To summarize briefly, training that focuses in a blocked manner on a specific lower-level perceptual process (such as visual contrast discrimination) will induce profound improvements in performance, will show a high degree of specificity, and will only transfer if contrast discrimination is relevant to the new task. Training that focuses on a higher-level process, such as scene recognition, especially if delivered in an interleaved or ‘mixed stimuli’ manner, will show only moderate improvements in performance, will generalize to untrained similar tasks, but will be limited by the lower-level information available to the higher levels of operation. Any practice-induced improvements in higher-level discrimination between similar stimuli will be the result of a gradually gained access to more informative, lower-level populations (Ahissar and Hochstein, 2004)—either through a successful ‘back-tracking search’ from higher-level operations (Figure 11a) and/or through massive training of all of the relevant lower-level inputs (Figure 11b). Thus, sensory stimuli used during an initial period of cognitive training for an impaired brain should be exaggerated or emphasized relative to naturalistic stimuli in order to make initial levels of the task easier—in other words, in order to improve the access of potentially impaired higher-level operations to appropriate informative lower-level neural representations (see Lee and Park, 2006; Javitt *et al*, 2007 for two studies showing that working memory performance can be enhanced in schizophrenia by increasing the sensory salience of the cue). The initial phases of lower-level and mid-level training should focus on the range of processes that contribute to the higher-level operation(s) of interest (Figure 11b). For instance, a social cognition training program might focus initially on blocked exercises designed to improve contrast sensitivity, visual selective attention, visuospatial working memory, and eye-gaze detection, in order to train the learner to generate and maintain strong and

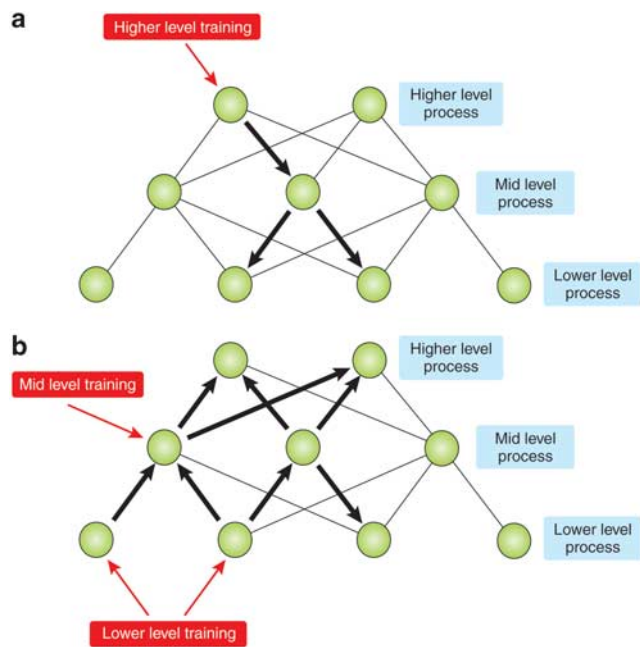


Figure 11. Learning across a distributed neural system can be conceptualized as occurring across hierarchical ‘levels.’ For illustrative purposes only, three levels are shown schematically, ranging from lower-level perceptual representations, to explicit higher-order perceptions and operations, to global high-level ecologically meaningful cognitions and contexts. Mid-level and higher-level representations are influenced by the quality of lower-level perceptual processing, just as pre-attentive perceptual processing is biased or influenced by higher-level predictions and expectancies. (a) During an initial learning phase, higher-level neural representations are strengthened, as the prefrontal cortex orients toward the task at hand, and very few plastic changes occur at lower levels. With sufficient intensive practice, in a healthy brain, plastic changes can propagate backwards from these higher-level representations, resulting in strengthened accuracy and fidelity of processing at lower-levels of the system (eg, the wine expert who is able to taste and identify a very wide range of flavors). In an impaired brain, distortions or limitations at any level will create bottlenecks for learning-induced widespread adaptive changes. (b) If training of sufficient intensity and duration progresses on specific sets of informative lower-level and middle-level stimuli and tasks, plastic changes will feed forward to improve the representational fidelity of information at higher levels, and learning will be partially transferred to higher-level contexts that use the trained lower-level features. Adapted and modified from Ahissar *et al* (2009).

accurate lower-level cortical representations of visually informative facial details. As training progresses, performance improves, and the learner becomes more ‘expert’ at processing visual information from the human face, the learner might be provided with higher-level exercises that focus on recognizing facial emotion, identifying changes in facial expression, and interpreting social interactions. In other words, stimuli and tasks are modified to have gradually increasing degrees of spatiotemporal detail, higher degrees of naturalistic appearance, and greater ecological validity, to ensure that training generalizes to real-world situations.

- (2) Highly intensive training schedules of carefully controlled and constrained learning events along with individualized adaptation of task difficulty to drive

learning and preserve reward schedules. The relevant 'skills' (or sets of skills, or component processes) must be identified, isolated, then practiced through hundreds if not thousands of trials on an intensive (ie, quasi-daily) schedule (Roelfsema *et al*, 2010). Difficulty level must begin at a level where the impaired brain is able to perform with success; it then must be parametrically modified (more complex stimuli, shorter stimulus presentation, higher working memory load, etc.) in an appropriate manner to drive the learner to higher and higher levels of performance over multiple trials. Individualized adaptation of task difficulty ensures that learning trials progress under carefully controlled conditions tailored to the unique capacities of each learner; simultaneously, this maintains a high trial-by-trial reward schedule, improving the brain's ability to engage in successful predictions. As an example, children with anxiety show an attention bias toward threat-related cues. Exercises could be designed to disengage attention from threat cues (eg, angry faces) and focus it on other targets; the goal would be increasingly accurate disengagement at speed from threat stimuli being presented for shorter durations. This in turn would allow prefrontal cortical regions to reduce their expectancy bias toward social threat in the environment, reducing the child's anxiety level (see Bar-Haim *et al*, 2011). Well-designed training is thus based on: first, precisely defining the specific set of skills to be trained so that the desired generalization will occur, and second, delivering the training with sufficient intensity and duration. For example, Nishi and Kewley-Port found that training Japanese speakers on the entire set of English vowels subsequently generalized across context to other words and speakers, whereas training on a subset of vowels did not (Deiber *et al*, 2007). Burk and Humes gave subjects either short (5 h) or long (15 h) training on the identification of words in noise, and found that the long but not the short training generalized from isolated words to fluent speech (Molinuevo *et al*, 2011).

- (3) Frequent and repetitive engagement of selective attention and reward systems in the brain, and consideration of the psychopharmacologic state of the learner. In order to maximize enduring plastic changes in cortex, the learner must attend to each trial or learning event on a trial-by-trial basis and a very high proportion of the learning trials must be rewarded immediately (rather than at the end of a block of trials or on a trial-and-error basis) (Buonomano and Merzenich, 1998; Beitel *et al*, 2003; Blake *et al*, 2006; Roelfsema *et al*, 2010). The immediate and repeated release of neuromodulators engaged by a dense schedule of successfully predicted learning events is required to drive enduring brain plasticity. In addition, the goal must be to develop training—or a context for the training—that is entertaining, engaging, and motivating for the learner. Finally, though very little research has been done in this

area, there is no doubt that medications with effects on dopaminergic, noradrenergic, serotonergic, and cholinergic modulation will influence plasticity mechanisms in ways that we will need to account for as we design more sophisticated training protocols (Vinogradov *et al*, 2009).

Neuroscience-Informed Cognitive Training: Current Findings

Neuroscience-informed cognitive training based on the three features listed above was first investigated using a computerized auditory processing training program for individuals with language-based learning disabilities (LLD) over 10 years ago (FastForward, Scientific Learning). Two laboratory studies as well as a field study of 500 LLD children who underwent 40 h of training demonstrated significant improvement in language-related cognition and verbal memory in subjects who performed the training but not in control groups (Tallal *et al*, 1996). MEG studies demonstrated that early cortical representations of auditory inputs were enhanced after training as compared with baseline (Hayes *et al*, 2003), while functional MRI revealed that the abnormal response patterns during key language tasks seen in both child and adult LLD patients was restored to more normal patterns with training (Temple *et al*, 2003).

More recent work with neuroscience-informed cognitive training is summarized in Table 5. Mahncke *et al* (2006a) investigated a training program designed similarly to the LLD studies, but constructed specifically for aging adults, with the goal of intensively training low-level auditory processing and auditory/verbal working memory in order to partially reverse normal age-related losses in verbal memory. Training (40–50 h) focused heavily on auditory perceptual processes and auditory/verbal working memory, with a small amount of training in ecologically meaningful whole-language tasks. Significant improvements were found in the active training group in measures directly related to the training (eg, auditory processing speed) as well as untrained measures of verbal memory, indicating generalization of the training effects, while no such improvements were seen in either active control or no-contact control groups. Memory enhancement was sustained after a 3-month no-contact follow-up (Mahncke *et al*, 2006b). In a multisite RCT of 487 older adults with this same software training for 40 h, similar improvements were found with an effect size of 0.3 for verbal memory and 0.87 for processing speed in an intent-to-treat analysis (Smith *et al*, 2009). These two independently conducted, tightly controlled studies using a well-defined neuroscience-informed cognitive training protocol demonstrate clinically significant effect sizes, durability of effects, and indicate that the verbal memory decline of aging may be partially reversible in response to intensive training of lower-level auditory processing and auditory/verbal working memory operations.

TABLE 5 Summary of Key Features of Recent Studies of Neuroscience-Informed Cognitive Training

Study, clinical focus, cognitive target, and training approach	Study design	Strengths of study	Unique features and/or limitations	Outcomes/effect sizes
Mahncke <i>et al</i> (2006b) <i>Cognitive decline of normal aging</i> Target: age-related declines in verbal memory functions Approach: intensive training of lower-level auditory processes and auditory/verbal working memory to improve episodic memory	RCT N = 182 3 groups: 40–50 h (8–10 weeks) of computerized auditory training ^a vs watching educational DVD's on computers vs no-contact control	Rigorous control condition; double-blind study; follow-up assessment showed that gains in working memory were durable at 3 month follow-up; generalization occurred to untrained tasks	Older adults (60–87) Per protocol analysis	Global auditory memory = 0.25 Excluding subjects who showed pre-training ceiling effects, global auditory memory = 0.61
Smith <i>et al</i> (2009) <i>Cognitive decline of normal aging</i> Target and approach: same as above	Multisite RTC N = 487 2 groups: 40 h (8 weeks) of computerized auditory training ^a vs general cognitive stimulation program	Rigorous control condition; double-blind study; generalization to untrained tasks; intent-to-treat analysis; large sample size	Older adults, unrepresentative sample (high-functioning subjects, primarily Caucasian and well educated)	Auditory memory/attention = 0.23 Memory = 0.30 Processing speed = 0.87
Wolinsky <i>et al</i> (2009a, b, 2010) Edwards <i>et al</i> (2009) <i>Cognitive decline in at-risk older adults</i> Target: visual attention and speed of processing Approach: intensive training of lower-level visual speed of processing to improve everyday speed, instrumental ADLs, and driving habits	Multisite RCT N = 2802 5-year follow-up N = 1804 4 groups: 10 h (6 weeks)—and up to 4 h of booster sessions—of computerized visual speed of processing training ^b vs therapist-guided coaching for memory vs therapist-guided coaching for reasoning vs no contact group	Testers blind to experimental condition; generalization to important real-world outcome measures; propensity score weighing used to adjust for attrition bias; results reported for 1-, 2-, 3-, and 5-year follow-up	Older adults (65 and older) at risk for loss of functional independence; per protocol analysis	Speed of processing at post-training = 1.46 Speed of processing at 2-year follow-up = 0.87 Participants who completed speed of processing training were 40% less likely to stop driving in the next 3 years compared with other participants Speed of processing group was 30% less likely to experience clinically important increases in depressive symptoms at 1 and 5 years post-training
Fisher <i>et al</i> (2009, 2010) <i>Schizophrenia</i> Target: impaired auditory processing and verbal memory functions Approach: intensive training of lower-level auditory processes and auditory/verbal working memory to improve episodic memory and global cognition	RCT N = 55 2 groups: 50 h (10 weeks) of computerized auditory training ^a vs 50 h of computer games	Rigorous control condition; double-blind study; use of MATRICS outcome measures; generalization to untrained tasks; 6-month follow-up showed a positive association between training-induced cognitive gains and improved quality of life	Chronic schizophrenia, small and unrepresentative sample (stable higher-functioning outpatients); per protocol analysis	Verbal learning and memory = 0.86 Global cognition = 0.86
Keefe <i>et al</i> (in press) <i>Schizophrenia</i> Target and approach: same as above	Multisite RCT Feasibility study N = 47 2 groups: 40 h (8–12 weeks) of computerized auditory training ^a +weekly group adapted from NEAR vs 40 h of computer games+weekly healthy lifestyles groups	Rigorous control condition; double-blind; use of MCCB; generalization to untrained tasks	Small sample; intent-to-treat analysis; use of MCCB <i>T</i> -scores (different composite scores from Fisher <i>et al</i> study)	At 20 h: Verbal learning = 0.69 Global cognition = 0.28 At 40 h Verbal learning = 0.39 Global cognition = 0.18
Klingberg <i>et al</i> (2005) <i>Attention deficit disorder</i> Target: working memory dysfunction Approach: intensive training of visual, visuospatial, and auditory working memory capacity	Multisite RCT N = 53 2 groups: 17 h (25 40-min sessions over 5 weeks) of computerized working memory training ^c with trial-by-trial adjustment in difficulty level vs same training set at the easiest initial level	Rigorous control condition; double-blind study; generalization to untrained tasks; follow-up showed gains in working memory durable at 3 months	Children with ADHD (age 7–12); small unrepresentative sample (excluded subjects whose education and SES level made it unlikely to follow procedures); used one-tailed tests; per protocol analysis	Working memory at post-training = 0.93 Working memory at 3 months follow-up = 0.92

TABLE 5 Continued

Study, clinical focus, cognitive target, and training approach	Study design	Strengths of study	Unique features and/or limitations	Outcomes/effect sizes
Rabiner <i>et al</i> (2010) <i>Attention deficit disorder</i> Target: auditory and visual sustained attention Approach: twice per week training of attention to promote attention in the classroom and improve academic performance	RCT N = 77 3 groups: 28 h (14 weeks) of computerized attention training (CAT) ^d vs computer-assisted training (CAI) vs waitlist	Test administrators were blind, but the majority of teachers became unblind; generalization to untrained tasks; follow-up at 1-year showed that computerized intervention may have long-term benefits for those with higher rates of ADHD symptoms; intent-to-treat analysis	First graders with ADHD; unrepresentative sample (primarily minority students from lower SES families with below average cognitive abilities); group and individual rewards for passing exercises; study is relatively underpowered	Control subjects improved by 16% on ratings of inattention, while 44% of CAT students and 56% of CAI students showed improvement. Estimate of effect sizes (none reported): Control vs CAT = 0.63 Control vs CAI = 0.87
Bickel <i>et al</i> (2011) <i>Methamphetamine users</i> Target: auditory and visual working memory and verbal memory Approach: training of working memory and verbal memory to improve delay discounting	RCT N = 27 2 groups: 6–15 sessions of computerized working memory/verbal memory training ^e vs same training with answers provided	Rigorous control condition (subjects in both conditions were exposed to the same stimuli with modified task demands); double-blind; generalization to an untrained task, intent-to-treat analysis; all subjects completed all assessments	Adults treated for stimulant abuse; small predominantly male sample; participants paid for participation; no significant differences between groups on change in verbal cognitive measures Number of sessions was contingent on individual performance, completed over ~25 days (length of each session not specified)	Delayed discounting task = 0.54
Hopkins <i>et al</i> (2011) <i>Autism</i> Target: social skills Approach: training of lower-level social cognition (eye gaze, recognizing facial expressions, and recognizing faces)	RCT N = 49 2 groups: 2–5 h (10–25 min, twice a week over 6 weeks) of computerized social cognition skills training ^f vs computerized art software	Rigorous control condition; raters of social behaviors were blind to training condition and parents were blind to group assignment; effects of computer training generalized to naturalistic environment; low and high function autism represented in sample; intent-to-treat analysis; all subjects completed all assessments)	Children with ASD; small predominantly male sample; gains not uniform across sample, suggesting a prerequisite level of functioning; the specialized school used as recruitment site may limit generalizability	Social skills rating system Composite = 1.01 for low-functioning autism and 0.29 for high-functioning autism Social skills observation total = 0.81 for low-functioning autism and 1.34 for high-functioning autism
Bar-Haim <i>et al</i> (2011) Children with severe, persistent anxiety Target: attention-bias to threat-related stimuli Approach: modification of allocation of attention to socially threatening stimuli	RCT N = 34 2 groups: 4 h (four 1-h sessions over 14 days) of computerized attention bias modification vs control (cue-target contingencies not designed to modify attention)	Rigorous control condition; double-blind study; short follow-up showed effects were maintained for 4–6 days; some generalization to similar stimuli	10-year-old children with persistent documented anxiety; small predominantly female sample; per protocol analysis; no formal diagnosis, stress vulnerability was not measured at the beginning of the study; training was very brief and completed in two sessions	No effect size reported

^aBrain Fitness Program, auditory module, Positscience.
^bUseful field of view training, now part of Brain Fitness Program, visual module, Positscience.
^cRoboMemo, Cogmed Cognitive Medical Systems AB.
^dCaptain's Log, 10 of the exercises targeting auditory and visual sustained attention, Braintrain.
^ePSSCogRehab, four of the exercises targeting working memory and verbal memory.
^fFaceSay, Symbionica, LLC.

The ACTIVE multisite RCT of 2802 older adults compared 10 h of computerized visual speed of processing training ('Useful Field of View') vs 10 h of therapist-guided training in a group format in reasoning or in memory techniques. The initial cognitive outcomes showed an effect size of 1.46. More impressively, in independently conducted analyses of long-term follow-up data, there were fewer medical expenditures, less depression, a delay in driving cessation, and better self-rated health in those who received the perceptual speed of processing training compared with those who received direct instruction training (Edwards *et al*, 2009; Wolinsky *et al*, 2009a,b, 2010). These studies indicate that intensive perceptual training in older adults shows a gradual generalization to improved real-world functioning over a 5-year period, but that therapist-guided strategy coaching for problem solving or memory does not. We hypothesize that the feed-forward effects of improved perceptual abilities drove enduring adaptive plastic changes in distributed higher-level operations in these at risk older adults, as per Figure 11b.

Vinogradov's group performed interim analyses on a double-blind RCT of 50 h (10 weeks) of neuroplasticity-based cognitive training for auditory/verbal learning deficits as a stand-alone treatment in 55 middle-aged adults with persistent schizophrenia. They applied 50 h of a research version of the software described above in the Mahncke *et al* study and compared it with 50 h of commercial computer games, examining behavioral outcomes as well as changes in serum biomarkers, MEG indices of early neural processing, and fMRI patterns of activation during untrained memory tasks (Adcock *et al*, 2009; Fisher *et al*, 2009, 2010; Dale *et al*, 2010; Hinckley *et al*, under review; Subramaniam *et al*, in press). Schizophrenia participants showed significant improvement in verbal learning and memory and in general cognition in response to training (effect sizes of 0.86 in a per protocol analysis); cognitive improvements were associated with improved quality of life at 6 months; subjects exposed to training showed significant increases in serum BDNF levels, while computer games control subjects did not; medication-induced serum anticholinergic activity was negatively correlated with the cognitive response to training; training increased resting-state α band functional connectivity in cortex; and also increased BOLD activation patterns in medial prefrontal cortex during an untrained memory task and restored the association between level of activation and task performance. More compellingly, training-induced increases in prefrontal activation were associated with improved ratings of social functioning 6 months later. Keefe *et al* (in press) performed a double-blind multisite feasibility study using 40 h (over 8–12 weeks) of the same software in 47 subjects with schizophrenia and found an effect size of 0.69 in verbal learning after 20 h of training, and 0.39 after 40 h of training. (Differences in study methods with the Fisher *et al* report include fewer hours of training delivered over a longer time period, the addition of a therapist coaching 'bridging group' component, an intent-to-treat analysis on all enrolled

participants vs a per protocol analysis on all study completers; and differences in definition of cognitive outcome variables: *z*-scores from MATRICS-derived measures vs *T*-scores from MCCB-defined domains.) Despite some differences in design and magnitude of cognitive change, these two tightly controlled double-blind studies using a well-defined cognitive training protocol based on the neuroscience principles described earlier demonstrate that patients with schizophrenia who have been ill for 20 years can still mount a positive response to intensive training, with improvements in verbal learning and memory. The Fisher *et al* follow-up study suggests that subjects who respond to training show generalization to real-world quality of life improvements 6 months later (Fisher *et al*, 2010). Haut *et al* performed an RCT with 21 schizophrenia patients who received 25 h of intensive computerized training in attention and working memory (CogPack Marker Software) plus training in verbal and picture *N*-back tasks (training followed some but not all of the neuroscience-informed elements described above); participants were compared with subjects receiving group-based social skills training. An effect size of 0.89 in verbal working memory and 1.4 in picture working memory was found, as well as increased fMRI activation in dorsolateral prefrontal cortex, anterior cingulate and frontopolar cortex (with correlations between improved performance and increased activation in a subset of regions) (Haut *et al*, 2010). Together with the data from Vinogradov's laboratory, these findings indicate that (1) after intensive training, individuals with schizophrenia can show significant plasticity in distributed cortical systems, with activation patterns appearing more similar to those of healthy individuals than they did at baseline and (2) training-induced increases in cortical activation are correlated with improvements in behavioral performance. These findings should help to address some of the therapeutic nihilism that has characterized the field of schizophrenia treatment research.

Klingberg *et al* (2005) performed a multicenter double-blind RCT of 17 h of intensive computerized visuospatial working memory training based explicitly on the neuroscience principles described earlier. Fifty-three children with ADD trained for 40 min a day over a 5-week period (20 days), and 42 were evaluated at follow-up 3 months later. A significant improvement from baseline to post-intervention on an untrained visual working memory task was found in the treatment group compared with the comparison group in a per protocol analysis (effect size of 0.93 at post-intervention, and 0.92 at 3 months follow-up). Significant treatment effects were also observed on measures of response inhibition, complex reasoning, and verbal working memory, indicating generalization of training. Significant decreases in parent-rated symptoms of inattention and hyperactivity/impulsivity were seen at post-intervention and at 3 months follow-up. Klingberg (2010) also performed imaging studies in healthy subjects that demonstrate changes in frontoparietal activation patterns as an effect of training, a possible basis for generalization of training

between different working memory tasks. He found that after 5 weeks of training, the increase in working memory capacity for each subject was positively correlated with changes in cortical D1 receptors, suggesting that training was associated with an increase in endogenous dopamine release and that training may improve capacity partly by tuning dopaminergic transmission (as would be predicted by the basic science). Rabiner *et al* (2010) have examined the positive behavioral effects of 28 h of computerized attention training in children with ADD based in part on the principles described earlier, while Hoekzema *et al* (2010) have demonstrated behavioral gains plus enhanced activity in frontal and cerebellar networks after a 10-day trial of cognitive training in unmedicated children with ADD. Taken together, these data indicate that working memory impairments in ADD respond to intensive training, and that the most robust and sustained effects to date are seen from the Klingberg *et al* group, who explicitly designed their training based on harnessing neuroplasticity mechanisms in the brain.

Three other recent interesting studies deserve mention as they have been based at least in part on the neuroscience principles described earlier. Bickel *et al* (2011) performed a trial with 27 adults receiving treatment for stimulant use, with the aim of targeting delay discounting in substance-abusing adults. His hypothesis was that an improvement in working memory function would improve impairments in delay discounting, and that this could have implications for real-world addictive behavior. Participants were randomly assigned to receive computerized working memory training (PSS Cog Rehab) or a 'sham' control training experience (no learning progression) using a yoked experimental design. The training that each subject received was not specified (in terms of session content or duration) but appears to have had some of all three of the features described earlier (simplified stimuli, intensive training, frequent and repetitive engagement of attention and reward systems); training was given for 9–44 days (an average of 25 days). Rates of discounting of delayed rewards were significantly reduced by about 50% among those who received working memory training but were unchanged in those who received the control condition. This study supports the notion that neuroscience-informed training can be used to target the impairments that underlie impulse dyscontrol and executive dysfunction in people with addictions. Hopkins *et al* (2011) performed a well-controlled RCT of 5 h of computerized training in eye-gaze detection and facial emotion recognition in 49 children with autism and saw improvements in the trained domains, as well as improved social interactions in a natural environment, indicating that improvements in relatively low-level and mid-level processing of facial features and emotions can show real-world generalization of effects. Bar-Haim *et al* (2011) performed a randomized placebo-controlled trial of computerized training for threat-related attention biases in 34 highly anxious 10-year old children (four 1-h sessions on 4 different days over a 2-week period). They found that training facilitated attention

disengagement from threat cues and reduced state anxiety during a stressor task, suggesting that it could be beneficial for reducing stress vulnerability in anxious children. These latter two studies in children show that repetitive training (implicit learning) that focuses on relatively lower-level impairments can result in clinically meaningful generalized improvements in real-world behavior and affect. Taken together, this emerging body of work underscores the extremely high clinical potential of carefully constructed cognitive training that is based on an understanding of systems neuroscience. Indeed, active research is underway in TBI, PTSD, bipolar illness, substance abuse, and anxiety disorders.

FUTURE RESEARCH DIRECTIONS

While the emerging data are very promising, much important work remains to be done. Our understanding of how to deliver 'neural systems' training with optimal efficiency and efficacy to individuals with impaired neuro-cognition is in its infancy. We are at the place that physical fitness training was 100 years ago—we know that it is good to run and lift weights, but we do not yet grasp the nuances of how to tailor a maximally efficient training program that targets an individual person's unique strengths and weaknesses. In this section, we present some of the exciting and challenging areas for future research in this area.

We Must Improve Our Understanding of the Neural Mechanisms that Underlie Successful Training

Perhaps the most basic challenge is for cognitive neuroscience to develop a more sophisticated understanding of pre-attentive processing and implicit learning mechanisms in health and disease and their relationship to higher-order cognitive operations in humans such as working memory, declarative memory, cognitive control, emotion regulation, delay discounting, and problem solving; we must also investigate the ways in which this relationship can be exploited in order to design the most efficient and successful forms of training possible.

Another key challenge is to more fully understand the specific training methods that promote maximal gains in the impaired brain—the exact intensity and duration of training, to what degree there must be a focus on perceptual and pre-attentive processing, whether and how competitive interference occurs during training, and the training modalities that promote generalization across cortical sectors and across behaviors. Dose–response curves must be generated for specific sets of exercises that target specific neural system impairments in specific clinical populations. Studies must be designed to control for common confounds: some of these include participant selection bias; effects of uncontrolled exposure to social reinforcers or psychosocial therapies; lack of 'blinds' for participants and personnel performing assessment procedures; inconsistent

definitions of outcome variables and analytic approaches. Method development must be coincident with investigation of the brain's responses to training, during both early and late phases of learning as well as weeks or months after cessation of training. Future studies must employ well-defined neurological outcome measures based on EEG, MEG, and fMRI methods (eg, as championed by the CNTRICS initiative (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia; Carter *et al*, 2011))—preferably with a sophisticated analysis of the precise timing and changes in neural oscillatory patterns that support successful learning, as well as the changes in functional connectivity that occur as a result of treatment and that are related to improvements in real-world behavior.

We Must Improve Our Development of Training Content

In addition to these improvements in our understanding of optimal neuroplasticity-based cognitive training methods, our field must move forward to develop improved training content that is based on experimental evidence of the neural system dysfunctions that are relevant to neuropsychiatric disorders. Our field awaits the development and evaluation of carefully designed cognitive exercises that adaptively train cognitive control, delay discounting, emotion regulation, source memory, self-referential processing, and social cognition, to name just a few. Ideally, randomized controlled trials will be conducted to identify the necessary and sufficient domains of training, and the optimal sequence of training (critical sets and ordering of exercises) for specific profiles of dysfunction and will examine their generalization to real-world demands in order to develop the most efficient treatment approaches possible. We emphasize that exercises will need to be developed to target neural system dysfunction in critical cognitive/affective processing domains, rather than to target specific diagnoses. Any given set of exercises might be useful across multiple disorders—social cognition training, for example, would be important in schizophrenia and autism, while training in delay discounting would be important in addictions and impulse control disorders.

Additionally, evidence from basic neuroscience (Berridge, 2004; Barch, 2005; Huitt and Cain, 2005; Adcock *et al*, 2006) indicates that motivation, rewards, and learning are intimately linked, and this association can be exploited for therapeutic purposes in well-designed exercises. For example, the Klingberg *et al* (2005) and Bickel *et al* (2011) control groups did the exact same exercises as the active training group, but with no progression in difficulty and thus no rewards—and they showed no cognitive improvements. Adcock and colleagues have recently shown that motivation to obtain reward in humans is instantiated by a transfer of information from the DLPFC to the nucleus accumbens and VTA (Ballard *et al*, 2011); dopaminergic neuromodulation *via* activation of these reward pathways is critical for

increasing the salience of stimuli or actions (incentives) that promote learning (Berridge and Robinson, 2003). Training that drives prefrontal cortex to create strong and predictable associations between successful learning events and rewards will not only lead to stronger learning, but may also improve the functioning of the distributed neural system related to incentive salience and motivation. Similarly, disturbances in working memory are related to impaired motivation, presumably because they impede the ability to represent goal or reward information (Berridge, 2004); thus, training that focuses on working memory (perhaps especially on affective working memory) and reward representation could have beneficial effects on motivated behavior. Indeed, the Bickel *et al* (2011) study represents a first foray into this area. Future research must determine to what extent these various cognitive training approaches translate into meaningful improvements in patients' motivated behavior in the real world.

We Must Improve Our Understanding of the Factors that Influence the Response to Training

Our field must learn to characterize the relationship between an individual patient's characteristics at baseline—including genetic factors, developmental stage, possible neurophysiologic biosignatures, and neurocognitive profile—and their ability to make and retain benefits from neuroplasticity-based cognitive training (Bell *et al*, 2003; Fiszdon *et al*, 2005; Bosia *et al*, 2007). For instance, a small study found that schizophrenia patients with the catechol-O-methyl transferase Met (COMT) allele made greater gains in cognitive flexibility after computerized cognitive training than patients without the Met allele, while Vinogradov *et al* have preliminary data indicating that polymorphisms in the COMT gene may be associated with cognitive gains after training (Bosia *et al*, 2007; Panizzutti *et al*, under review). This group has also found that baseline α band resting-state functional disconnectivity in key cortical regions in schizophrenia predicted the response to cognitive training (Hinckley *et al*, under review), while Klingberg *et al* have found that lower activation patterns in DLPFC are associated with greater cognitive improvement after training in ADD patients (personal communication). In healthy subjects, it has been shown that an individual's intrinsic neural dynamics affects their rate of learning and the nature of their learning-induced neural response patterns (Vernon *et al*, 2003; Mukai *et al*, 2007; Hickok *et al*, 2011). A better understanding of the relationship between an individual's underlying genetics, neurobiology, and developmental stage and their ability to benefit from cognitive training will permit an evidence-based adaptation of programs to a broader range of clinical needs.

We must also examine the ways that commonly prescribed medications with anticholinergic and antidopaminergic effects—as well as those with noradrenergic and serotonergic effects—can influence the response to plasticity-based cognitive training. As noted earlier, Vinogradov *et al* (2009)

have shown that the amount of serum anticholinergic activity assessed in patients with schizophrenia *via* radioreceptor assay (due to their medications) is inversely correlated with the overall improvement in cognition seen in these patients after 50 h of neuroplasticity-based auditory training. It is naive to believe that the standard current psychopharmacologic armamentarium is without impact on the brain's ability to engage in successful learning (see also the implications of Klingberg, 2010) findings on dopamine receptor changes during successful training).

Similarly, as our field eagerly turns to the promise of cognitive-enhancing medications, we must be prepared to explore the most advantageous ways in which these agents can—and probably should—be combined with training in order to optimize cognitive gains in patients (Keefe *et al*, 2010). Again, it is probably naive to assume that administering such agents in a behavioral vacuum to patients will, absent any engagement of the brain in new and adaptive learning events, result in significant functional gains. Indeed, some agents may be of no value when given alone, but may substantially facilitate the effects of cognitive training.

Medications are not the only possible adjuvants to enhance the brain's response to cognitive training. The use of transcranial magnetic stimulation (TMS) and direct current stimulation (tDCS), in combination with sensory stimulation, have both shown to be inducers of cortical plasticity (Celnik *et al*, 2009; Khedr *et al*, 2010). Anecdotal reports suggest that these methods may improve working memory (Jo *et al*, 2009), attention (Kang *et al*, 2009), and aphasia (Monti *et al*, 2008) in stroke patients. Pascual-Leone's group showed that when a night with sleep follows rTMS to M1, the capacity to induce subsequent plasticity in M1 is enhanced (Cohen *et al*, 2010). Exercise is another potent, safe, and valuable 'neurotrophic agent' that could be combined in innovative ways with cognitive training regimens to maximize a patient's response to treatment (see Pajonk *et al*, 2010).

We Must Translate Cognitive Training into Meaningful Interventions that Change People's Lives

No cognitive training program, however precisely engineered, can substitute for meaningful and developmentally appropriate psychosocial rehabilitation for people with serious neuropsychiatric illness. Evidence from the educational field, including electrophysiologic data, indicate that beliefs can influence learning success through top-down biasing of attention and conceptual processing toward goal-congruent information (Mangels *et al*, 2006). Vinogradov *et al* have early results indicating that schizophrenia participants who believe that intelligence is malleable show better cognitive outcomes after computerized training than those who believe it is a fixed entity, even though they were blind to group assignment and even after controlling for baseline cognition and number of hours of training (unpublished data). We predict that beliefs, expectations, and self-representations will turn out to have powerful

neurobiologic influences on the brain's ability to make use of cognitive training and will be another therapeutic leverage point that can be purposefully harnessed to maximize treatment response. Indeed, prior research has already shown, at least in schizophrenia, that integration of cognitive remediation with other psychosocial treatments provides significant synergistic benefits (McGurk *et al*, 2007; Wykes *et al*, 2011). As a corollary, we predict that cognitive neurotherapeutic approaches that explicitly and continuously demonstrate to patients their ongoing cognitive improvements will challenge their assumptions about the chronic, fixed nature of their impairments. Future work can explore whether this approach helps patients to develop more adaptive internalized beliefs about their capacity for change, and whether it increases motivation and engagement with the larger therapeutic learning environment (Meltzoff *et al*, 2009).

Finally, and perhaps most ambitiously, we believe that the greatest gains will occur when neuroplasticity-based restorative cognitive training is implemented in conjunction with early detection and intervention in young people who are in the very earliest phases of clinical expression of a neuropsychiatric illness. In schizophrenia, for example, neuropsychological data indicate unequivocally that cognitive deficits are found in prodromal and 'first-episode' individuals; these deficits appear to worsen as the individual progresses into the illness and predict functioning several years later (Brewer *et al*, 2005; Keefe *et al*, 2006). Vinogradov *et al* (unpublished data) have demonstrated that neuroplasticity-based cognitive training can be successfully delivered to young early psychosis individuals at home *via* laptop, with significant improvements in cognition. These young patients have not yet experienced the repeated psychotic episodes that induce catastrophic cortical reorganization and that impede psychosocial development, and have not yet been subjected to years of anticholinergic and antidopaminergic medication. Successful cognitive training may thus result in enduring gains in these individuals and may go a long way to significantly improving their clinical outcomes. It is certainly conceivable that well-designed and thoughtfully applied training for impaired neural system functioning, when applied early, could normalize some of the aberrant neurodevelopmental trajectories that characterize mental and addictive disorders, and could pre-empt the full-blown expression of a chronic and deteriorating illness. Much the way we vigorously treat amblyopia in very young children by 'forcing' the lazy eye to work, we can envision a day when we 'force' impaired distributed neural systems to become strengthened through appropriate training.

CONCLUSION

Though we have focused this review on the impaired brain, it is obvious that many of the principles we have outlined are applicable to improving the cognitive processing

capacities of healthy brains as well. As such, carefully designed cognitive training exercises will undoubtedly promote neuroresilience in healthy individuals, much the way that physical fitness training promotes cardiovascular and immune system resilience. Neuroresilience may encompass not only improved ‘resistance’ to the cognitive effects of aging (as already shown in the ACTIVE study), and to various processes associated with the dementias, but also to physical and psychological stressors, such as sleep deprivation, emotional trauma, cognitive or affective loading, and changing social demands.

It is not surprising—in fact, it is inevitable—that the science behind our understanding of how to develop effective training is occurring in parallel with the development of extremely sophisticated entertainment software that is already engaging millions—perhaps hundreds of millions—of brains of all ages in learning experiences with cognitive and affective impact. These advances in entertainment software indicate that cognitive training can be developed that will generate the same interest, engagement, perceived value, and social acceptability as web-based games. Indeed, novel collaborative efforts are already underway to join technological expertise from the entertainment software industry with neuroscience efforts aimed at improving performance in neural systems. The likely outcomes will be browser-based treatment tools available on a scale never before imagined for any other therapeutic intervention—‘neural network treatments’ that not only engage inherent brain reward mechanisms through their entertainment value, but that also allow the learner to ‘neurally network’ with other learners and participate in a socially rewarding and developmentally appropriate therapeutic activity that is free of stigma.

We began this review by pointing out that successful cognitive training for neuropsychiatric illnesses will need to induce specific and substantial distributed changes in cortical and subcortical representations and will need to be delivered in a scalable and developmentally appropriate manner that is engaging and motivating. The science we have reviewed here describes key steps to accomplish the former goal. We will be limited only by our creativity and imagination in accomplishing the latter.

FUTURE RESEARCH ISSUES

Improve Our Understanding of Fundamental Mechanisms in Order to Design the most Efficient and Successful Forms of Training

- Develop a more sophisticated understanding—in health and disease—of the interaction between implicit learning mechanisms and higher-order cognitive operations in humans such as working memory, declarative memory, and cognitive control.

- Investigate the specific training methods that promote maximal gains in the impaired brain—the exact intensity and duration of training, to what degree there must be a focus on perceptual processing, and the training modalities that promote generalization.
- Examine the brain’s responses to training, both within early and later phases of learning—preferably with a sophisticated analysis of the precise timing and neural oscillatory patterns that support successful learning, as well as the changes in functional connectivity that occur as a result of treatment and that are related to improvements in real-world behavior.

Improve Our Development of Training Content

- Develop and test cognitive training exercises using an evidence-based approach to known neural system dysfunctions relevant to neuropsychiatric disorders.
- Explore the neural systems linking motivation and cognition in order to exploit this association for therapeutic purposes; determine the appropriate methods of enhancing reward representation during training and explore transfer to real-world functioning.

Improve Our Understanding of the Factors that Influence the Response to Training

- Characterize the relationship between an individual patient’s status at baseline—including genetic factors, developmental stage, possible neurophysiologic biosignatures, and neurocognitive profile—and their ability to make and retain benefits from neuroplasticity-based cognitive training.
- Examine the ways that commonly prescribed medications with anticholinergic, antidopaminergic, noradrenergic, and serotonergic effects can influence plasticity-based neurocognitive improvement.
- Explore the most advantageous ways in which cognitive-enhancing agents can—and probably should—be combined with training in order to optimize cognitive gains in patients.
- Study other adjuvants to enhance the brain’s response to cognitive training, such as TMS, tDCS, and exercise.

Translate Cognitive Training into Meaningful Interventions that Change People’s Lives

- Discover the manner in which cognitive training can best be combined with meaningful and developmentally appropriate psychosocial rehabilitation for people with serious neuropsychiatric illness. Explicitly foster beliefs, expectations, and representations that enhance the response to training.

- Implement neuroplasticity-based cognitive training in conjunction with early detection and intervention in young people who are in the very earliest phases of clinical expression of a neuropsychiatric illness; focus on pre-empting the full-blown expression of a chronic and deteriorating illness.
- Investigate novel and creative ways in which cognitive training can be combined with entertainment software to create scalable web-based treatment tools; ideally such 'neural network treatment tools' will not only engage inherent brain reward mechanisms through their entertainment value, but will also allow the learner to 'neurally network' with other learners and participate in a socially rewarding and developmentally appropriate therapeutic activity that is free of stigma.

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DISCLOSURE

Dr Vinogradov is a paid consultant to Brain Plasticity Inc., a company with a commercial interest in cognitive training software.

SUMMARY POINTS

- Neuropsychiatric illnesses are associated with dysfunction in distributed prefrontal neural systems that underlie perception, cognition, social interactions, emotion regulation, and motivation. The high degree of learning-dependent brain plasticity in these networks suggests that we should be able to engineer very specific training programs that drive meaningful and enduring improvements in their operations.
- Neuropsychiatric illnesses have features that set them apart from other neurological disorders, including possible inherent limitations in the underlying brain 'learning machinery' due to pathophysiology. They are also characterized by the presence of complex overlearned maladaptive patterns of neural functioning. Cognitive training must therefore be designed to induce specific and substantial distributed changes in cortical and subcortical representations and processing efficiency. It must also be delivered in a scalable manner that is engaging and motivating for the learner.
- We propose that several considerations from basic and clinical neuroscience should inform the design of the next generation of cognitive training approaches for the impaired brain: (1) training must address any significant limitations in perceptual and pre-attentive processing due

to the critical interactions that link prefrontal predictive operations with perceptual processes and working memory; (2) constrained and intensive training must be employed in order to induce robust and enduring plastic changes in cortex; and (3) training must harness implicit learning mechanisms in order to 're-tune' degraded working memory and long-term memory functions.

- These considerations are supported by a wealth of data from the past two decades of basic research in systems neuroscience. These data demonstrate that (1) the fundamental neural mechanisms supporting learning-induced plasticity are in place throughout life; (2) learning-induced enhancements in lower-level processing can drive improvements in higher-order cognitive operations; that is, successful skill learning induces large-scale distributed changes in cortical representations; and (3) learning-induced plasticity is profoundly influenced by behavioral state and neuromodulatory neurotransmitters.

- These basic science principles can be translated into key elements for the design of cognitive training exercises for the impaired human brain. Such elements include (1) use of stimuli and exercises that drive plasticity in both lower and higher levels of processing in impaired neural systems; that is, precise engineering of stimuli and tasks to improve the speed and accuracy of information processing targeting the impaired neural system(s) of interest; (2) highly intensive training schedules of carefully controlled and constrained learning events, as well as individualized adaptation of task difficulty to drive learning and to preserve reward schedules; and (3) frequent and repetitive engagement of attention and reward systems in the brain, and attention to the psychopharmacologic status of the learner.

- Early research using computerized cognitive training based on these principles is very promising. Data from trials in the elderly, in adults with schizophrenia, and in children with attention deficit disorder, demonstrate robust effect sizes, generalization to untrained tasks, durability of effects, evidence of plasticity in both frontal and sensory systems, and a relationship with improved functioning. Studies are underway using this approach in autism, anxiety disorders, PTSD, bipolar illness, and traumatic brain injury. New collaborations between clinical neuroscientists and experts in entertainment software suggest an emerging era of highly engaging 'neural network training' that can potentially occur on a massive scale.

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APPENDIX

DEFINITION OF KEY TERMS

Neural Systems: Groups of neuronal assemblies that interact with each other and the environment to drive a physiological system (eg, visual perception).

Neural Networks: Groups of neurons that are chemically or functionally associated to perform a specific set of

computations. Sometimes used interchangeably with Neural Systems.

Cortical Representations: Neuronal ensembles in cortex that are devoted to representing behaviorally important stimuli.

Neuroplasticity/Brain Plasticity: The ability of the human brain to change as a result of experience.

Neural Inputs: The integration of spatial and temporal electrical and chemical information a neuron receives (or a group of neurons receive); input information may be related to sensory data (from the external world) or cognitive data (from the internal world).

Neural Outputs: The electrical and chemical information a neuron transmits (or a group of neurons transmits). Output information may result in motor or cognitive actions.

Sensory Processing/Perceptual Processing: The processing of information received through our sense organs from the environment.

Perceptual Learning: The process that generates long-lasting improvement in the performance of perceptual tasks (ie, evaluating, organizing, and responding to information received from sense organs).

Pre-attentive processing: Early or lower-level operations on sensory data that precede conscious awareness or focused attention. These occur very rapidly in low-level sensory systems, typically within 200 ms or less after stimulus onset, and are often assessed using event-related potentials. Both stimulus salience and expectancy can influence pre-attentive processes.

Working Memory: The short-term temporary storage and manipulation of the information necessary for higher-order cognitive tasks.

Implicit Learning and Memory: The encoding and learning of complex information without conscious awareness of what has been learned.