Cognitive Training in Mental Disorders: Update and Future Directions

Matcheri S. Keshavan, M.D.

Sophia Vinogradov, M.D.

Judith Rumsey, Ph.D.

Joel Sherrill, Ph.D.

Ann Wagner, Ph.D.

Objective: This article reviews the conceptual basis, definitions, and evolution of cognitive training approaches for the treatment of mental disorders.

Method: The authors review the current state of the knowledge on cognitive training in psychiatric illnesses, and its neural and behavioral targets, and summarize the factors that appear to relate to a successful response, including learner characteristics that influence clinical outcome. They also discuss methodological issues relevant to the development and testing of cognitive training approaches, with the goal of creating maximally efficient and effective approaches to training. Finally, they identify gaps in existing knowledge and outline key research directions for the future.

Results: While much of the early research has been conducted in schizophrenia, cognitive training has more recently been applied to a widening range of neuropsychiatric illnesses, including attention deficit hyperactivity disorder, mood disorders, and substance use disorders. Cognitive training harnesses the inherent neuroplastic capacities of the brain, targeting neural system function across psychiatric disorders, thus improving the cognitive processes that play a role in emotion regulation, clinical symptoms, and adaptive community functioning.

Conclusions: Cognitive training offers considerable promise, especially given the limited efficacy of pharmacological interventions in ameliorating cognitive deficits. However, more research is needed to understand the mechanisms underlying cognitive training, predictors of response, generalization and real-world applicability, and approaches to dissemination in practice settings.

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Introduction

On April 9 and 10, 2012, the National Institute of Mental Health convened a group of experts in cognitive training to review the current state of evidence for the efficacy of current and emerging cognitive training approaches for mental disorders, to identify challenges as well as research gaps, and to learn of efforts to adopt cognitive training interventions in clinical practice. Cognitive training methods that harness neuroplasticity mechanisms for cognitive enhancement in impaired neural systems show promise as evidence-based interventions in psychiatry. The meeting participants expressed optimism that one day in the not-too-distant future we will be able to identify the key neural system impairments unique to individual patients and prescribe personalized cognitive training programs in order to enhance cognition, improve community functioning, and optimize well-being.

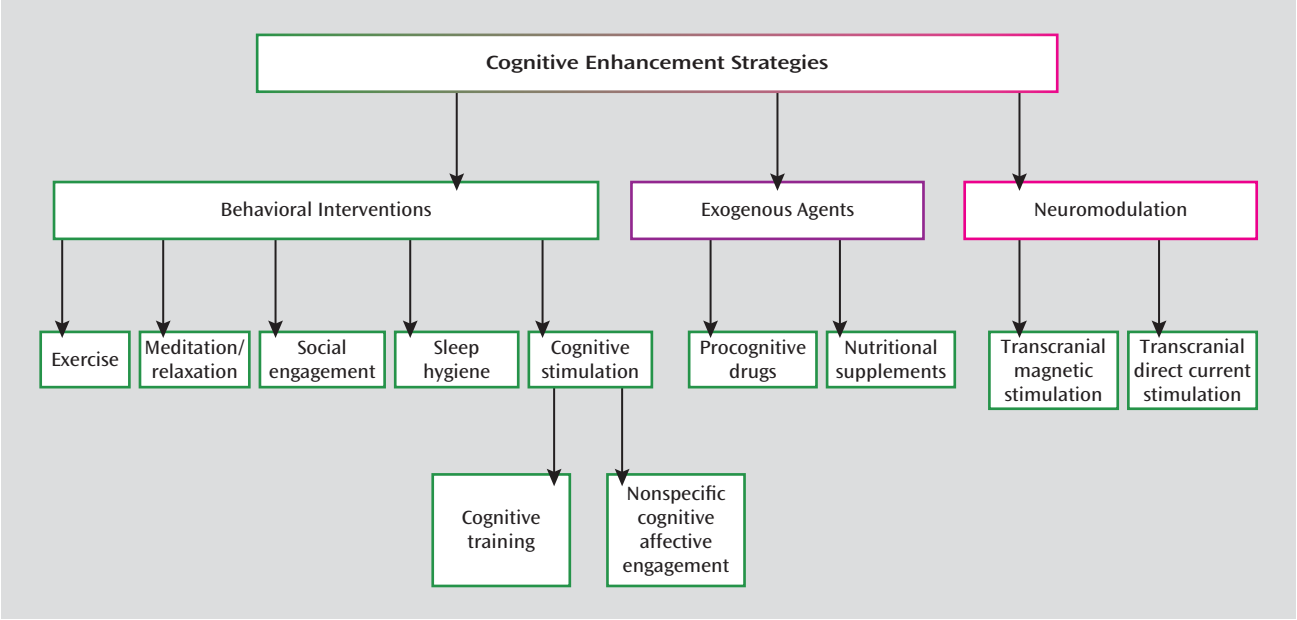
Cognitive training is one of a range of behavioral interventions for cognitive enhancement (Figure 1) that also includes exercise, mindfulness-based meditation practice, and other approaches (including the more nonspecific cognitive and socio-affective engagement that can occur in psychotherapy). Cognitive training in psychiatry uses diverse approaches (paper and pencil, computer-administered exercises, or guided behavioral exercises) to enhance cognitive function and optimize well-being in mental disorders.

How is Cognitive Training Defined?

The terms cognitive training, cognitive remediation, and cognitive rehabilitation are used both interchangeably and inconsistently in the literature and in clinical practice. We herein broadly define cognitive training as an intervention that uses specifically designed and behaviorally constrained cognitive or socio-affective learning events, delivered in a scalable and reproducible manner, to potentially improve neural system operations. The eventual goal of cognitive training is to target known neural mechanisms of behavioral impairment to affect clinical change.

This article is featured in this month's AJP Audio, is an article that provides Clinical Guidance (p. 522), and is discussed in an Editorial by Dr. Harvey (p. 482)

FIGURE 1. Taxonomy of Approaches to Cognitive Enhancements in Mental Illness[a]



[a] Cognitive training is one of many potential interventions to enhance cognitive functioning.

Cognitive training aims to drive learning and adaptive neuroplastic changes in an individual's neural representational systems through specifically defined, neuroscience-based, and controlled learning events. Specifically defined and controlled learning events that are delivered in cognitive training differ from the relatively unconstrained, uncontrolled, and unpredictable approaches to learning, e.g., those associated with cognitive-behavioral therapy or with the use of a psychoeducational video tutorial. We also distinguish cognitive training from the broad and nonspecific (although therapeutically important) forms of cognitive and socio-affective stimulation that occur, for example, from participating in a 12-step program or by joining a community organization such as a church group. Cognitive training as defined above is typically embedded in a larger therapeutic context that makes use of therapist and participant expectancy, the instillation of hope, and other psychosocial ingredients. These factors are themselves all potent agents of neurobehavioral change. Indeed, cognitive training, like many successful treatment programs (such as group therapies, vocational rehabilitation, and psychosocial skills training) explicitly harnesses multiple nonspecific and contextual therapeutic factors in order to maximize overall functional gains for participants.

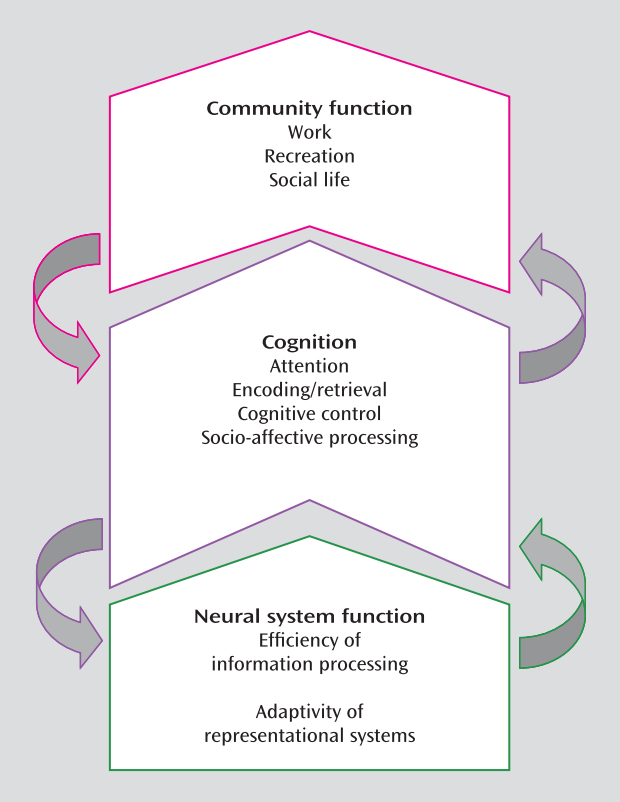
Another term that is applied in the field is cognitive remediation, which the Cognitive Remediation Expert Working Group has defined as "a behavioral training-based intervention that aims to improve cognitive processes with the general aim of durability and generalization to community functioning" in Wykes et al. (1). In our article, we emphasize the term "training" as opposed to "remediation," since the former carries less stigma and implies the improvement or restoration of physiological mechanisms in individuals at all levels of functioning, while the latter implies the correction of a fault or deficiency and may also include the development of compensatory or "work-around" skills.

Mental Illness, Neuroplasticity, and Cognitive Training

Clinical interest in "brain remediation" dates back to World War I (2) when methods were developed to treat war-related brain injuries in soldiers. However, emerging basic and clinical research has motivated a theory-driven design of cognitive training approaches, with an emphasis on harnessing the brain's inherent capacities for change in order to promote or restore adaptive cognitive and socio-affective processes. How might this principle be applied in mental illnesses? First, mental illnesses can be broadly viewed as resulting from inefficient, maladaptive, or biased distributed neural representations underlying critical cognitive and emotional processes that are necessary for successful community functioning (Figure 2). Second, experimental neuroscience has unequivocally revealed that the brain changes with the introduction of new experiences and with the training of new perceptual, cognitive, or motor skills—a process termed neuroplasticity.

Neuroplasticity occurs in at least two (not mutually exclusive) developmental contexts (Figure 3). Very early in development, experience and its resulting neuronal activity can shape neuronal response properties irrespective of an organism's attention to a stimulus. This process of experience-expectant neuroplasticity (3) shapes neural representations to reflect statistical regularities in inputs

FIGURE 2. Translational Hierarchy of Outcomes With Cognitive Therapy[a]



[a] Carefully targeted improvements in neural system function in mental illness should translate into better community functioning via their effects on cognition.

(e.g., from one eye versus another [4]) and in the environment (5). Such plasticity is often conceptualized to occur within a finite window, a so-called critical period. Maladaptive experiences or insults to the developing brain during these critical periods can have lasting behavioral consequences.

A qualitatively different process, experience-dependent neuroplasticity, occurs throughout development. Also termed "learning," this process involves changes in neuronal activity that represents meaningful stimuli and behaviors, particularly those associated with reward; such activity in turn effects lasting neural representations (6–12). Maladaptive or distorted learning about behaviorally important events or stimuli (particularly during the extended critical period for socio-affective development), followed by enduring alterations in neural representations, can serve as a model for how psychiatric symptoms first emerge precipitously or insidiously, and then stabilize and become chronic.

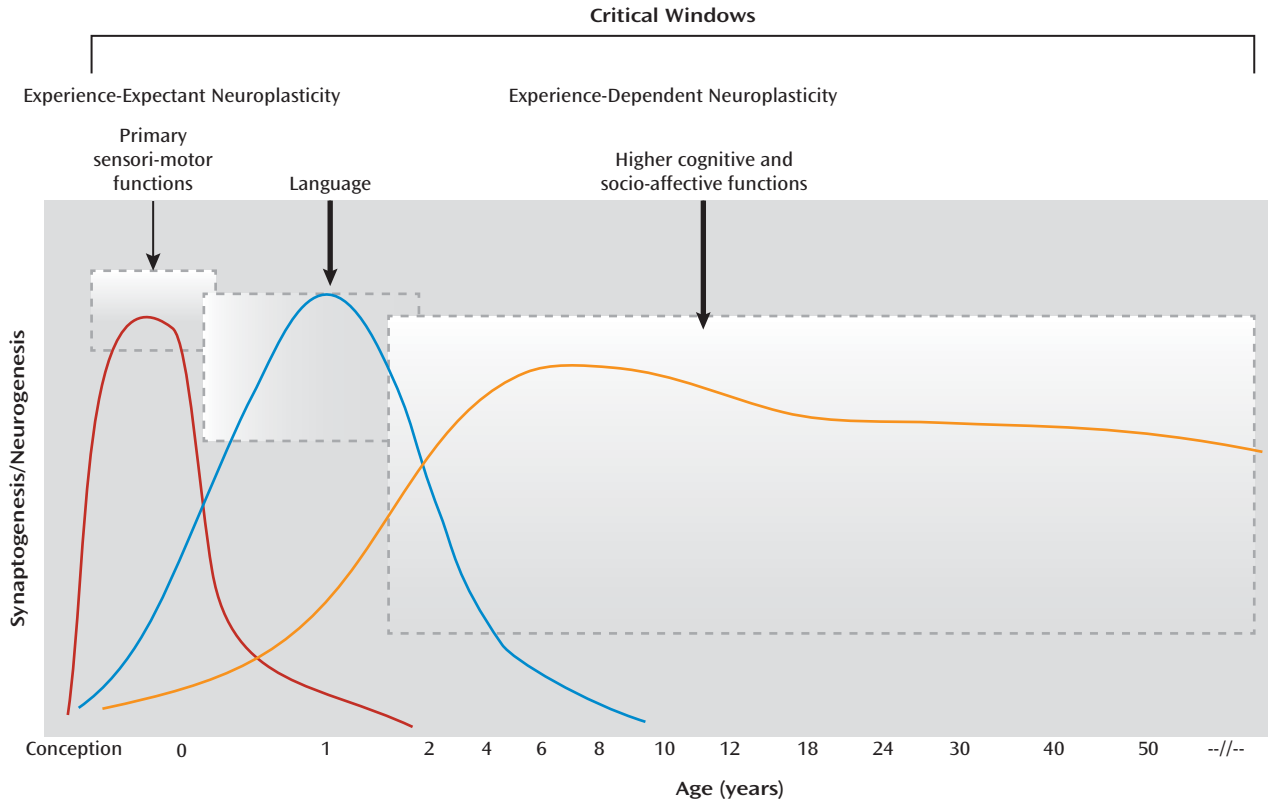
Neuroplastic processes related to learning can be intentionally harnessed for therapeutic purposes across a wide range of disorders. Cognitive training focuses on identifying the impaired representational systems underlying critical cognitions and then training such processes via implicit or explicit learning mechanisms in order to improve the speed and accuracy of task-relevant information processing and distributed neural responses, thereby improving community functioning. Growing knowledge of the specific processing anomalies, developmental features, and distributed neural circuits that characterize various psychiatric illnesses will inform the next generation of cognitive training approaches, including their content and timing. This development will require a constant iterative process that bridges cognitive, affective, and developmental neuroscience with clinical treatment development.

Neural Targets for Cognitive Training in Mental Illness

Cognitive or socio-affective deficits are found in all major neuropsychiatric disorders, often predate the symptoms, and may determine functional outcomes (13–15). Such disturbances may reflect aberrant neural representations involving affect regulation, motivation, incentive salience, self and other, and social perception (15). Emerging evidence shows that targeted intensive cognitive training can induce more normal and efficient neural system operations and can potentially harness inherent plasticity processes (16). Improving neural functioning at the macrocircuit level may de facto affect cellular and synaptic-level functioning at the microcircuit level, including the neurotransmitter and neurotrophin systems (17).

Relevant distributed neural system targets are being identified for such intensive cognitive training approaches in mental illness. Successful cognitive training can harness "bottom-up" or "feed-forward" processes (such as perception and preattentive perceptual biasing) and "top-down" or "feed-back" processes (e.g., attention, cognitive control, and metacognitive appraisal), as will be discussed later. In schizophrenia, for example, these targets range from impairments in sensory encoding to inefficient prefrontal operations that affect working memory, episodic memory, and social cognition (16). As observed in major depression, impairments in executive function and processing speed related to aberrant activity in prefrontal and limbic system networks are associated with affect dysregulation (18–20) and abnormal biasing of attention to negative cognitions (21). Thus, disorders are characterized by both distinct and cross-cutting patterns of neural dysfunction, offering unique combinations of cognitive and socio-affective targets for training. However, the ultimate goal is to identify target processes in which training will induce the widest range of generalized clinical and behavioral improvement. For example, inefficiencies or biases in prefrontal predictive and cognitive control operations may represent a fundamental or common denominator underlying a range of mental illnesses, resulting in disorder-specific or cross-diagnostic impairments or biases in perception, affect, and cognition (22). Such

FIGURE 3. Critical Windows of Neuroplasticity During Human Life[a]



[a] Cognitive training makes use of experience-dependent plasticity that is present throughout the human lifespan.

processes may represent promising cognitive training targets, not only as a treatment, but potentially as a preventive or preemptive intervention. However, challenges to this approach include the fact that no current assessment or intervention approaches address single neural system targets, nor is this likely to ever be the case; changes in one brain system (e.g., attention) inevitably affect other systems (such as working memory).

Current State of Knowledge

Cognitive training approaches have been applied across various mental illnesses and have used a variety of methods and study designs, making it currently difficult to integrate findings, draw definitive conclusions, or suggest best practices. Study outcomes have also revealed varying efficacy in targeted cognitive domains, while others have demonstrated generalization or transfer to untrained domains and to functional outcome; only a few studies have examined issues of durability beyond the end of treatment. We briefly review the current state of knowledge, beginning with the areas with the strongest evidence base.

Schizophrenia. Several cognitive training approaches have been studied in schizophrenia, ranging from repetitive practice to therapist-guided strategy coaching. These approaches have targeted a wide range of cognitive processes, including perception, working memory, attention, and social cognition, or combinations of these functions. A meta-analysis of 40 studies conducted between 1973 and 2009 (1) found modest efficacy, with a mean effect size on cognition of 0.45; some cognitive training benefits appear durable after the end of treatment (23, 24). Functional outcomes were significantly better in studies where cognitive remediation was combined with other forms of rehabilitation and when it included strategy coaching. Age, pretreatment cognitive function, motivation, clinician expertise, therapeutic alliance, and measures of "brain reserve" may in certain cases be predictors of a positive treatment response (25–28). Initial neuroimaging findings suggest that cognitive training response is associated with structural and functional changes in key prefrontal brain regions (16, 26, 27, 29, 30). Overall, the evidence thus far supports the neurobiological rationale and the efficacy of cognitive training in schizophrenia, but replication of positive results is needed; many questions remain with regard to therapeutic mechanisms, key therapeutic ingredients, and approaches to dissemination in routine clinical settings.

Attention deficit hyperactivity disorder (ADHD). Cognitive training, focused on executive functioning and working memory, may benefit individuals with ADHD (31–33). Klingberg et al. (34) demonstrated that cognitive training improved working memory as well as nontrained functions of response inhibition and reasoning; parent-rated

inattention and hyperactivity/impulsivity symptoms also decreased after cognitive training, and the positive effects were maintained at 3 months. Such improvements appear to be related to increased activity in the frontoparietal and striatal regions mediating working memory functions in ADHD (35). In an open-label study of preschool-age children with ADHD and their parents, who participated in group sessions, Halperin et al. (36) used motor activities and games designed to enhance inhibitory control, working memory, attention, visuospatial abilities, planning, and motor skills. Parental involvement facilitated the implementation of this play-based intervention at home. Both parent and teacher ratings indicated significant improvement in ADHD symptoms. Similarly, an open trial of metacognitive executive function training for ADHD resulted in improved attention, working memory, and cognitive flexibility (37). Cognitive training targets for ADHD may need to be broadened to include self-control or delay aversion (38). Taken together, cognitive training appears effective in the treatment of ADHD, but well-powered and well-controlled randomized trials with precisely defined targets and outcome measures, as well as longitudinal follow-up to examine durability, are needed.

Anxiety disorders. Anxiety disorders are characterized by implicit attentional biases to threat-related stimuli (39). This has led investigators to develop attention bias modification strategies, where response targets are repetitively presented at the location of neutral stimuli, rather than threat stimuli, with the goal of inducing an implicit bias away from threat in order to reduce overall anxiety levels. Two meta-analyses of attention bias modification training in adults with anxiety disorders (40, 41) revealed moderate to large effect sizes (0.8–1.4) for changes in attentional bias, and an effect size of 0.61 for clinical symptoms, comparable to what is seen with cognitive-behavioral therapy and selective serotonin reuptake inhibitors. Reductions in anxiety symptoms were also observed in a large randomized controlled trial of children with anxiety disorders (42). Critical next steps include determining the components of successful training (stimuli, optimal task design, and training duration) and the neural mechanisms that support behavioral change, demonstrating the robustness and durability of the effects of attention bias modification on subjective experiences and real-world functioning, and developing approaches to dissemination in routine clinical settings.

Mood disorders. Emerging research indicates that major depressive disorder and bipolar disorder are both associated with persistent cognitive impairment in domains such as processing speed and executive functioning. In addition to these impairments in "cold" cognition (43–47), depression is associated with attentional bias to negative emotional stimuli, even at a level below awareness (40–43). Emerging evidence suggests (18) that cognitive training can be effective in mood disorders. Deckersbach et al. (48) found that a 14-session remediation program targeting residual depressive symptoms and cognitive functioning was associated with decreased ratings of depression and improved executive functioning scores that were related to better work functioning. A meta-analysis (49) found an effect size of 0.32 for cognitive training in studies with patients with affective or schizoaffective disorders. Attentional bias training in depression seems to potentially reduce relapse risk in depression (50). Further studies need to examine specificity, durability, mechanisms, and generalization of cognitive training effects in mood disorders.

Substance use disorders. Substance use disorders are associated with a range of cognitive impairments, particularly in attention, working memory, response inhibition, and delay discounting (i.e., preference for immediate versus delayed rewards), which predict poor outcome and adherence to treatment. Although the nature, course, and significance of these deficits are unclear at present, cognitive training is under active investigation in this field. For instance, cognitive training on computerized working memory tasks has been shown to reduce impulsivity and delay discounting among stimulant users (51). Cognitive bias modification (brief training to automatically avoid alcohol cues) has also shown promise in treating alcohol addiction patients during a 1-year follow-up (52). While promising, the field is in its early stages and many questions still need to be addressed. For example, it remains unclear whether cognitive training approaches might work generally for individuals with substance use disorders, or whether they need to be reserved for those with demonstrable cognitive impairments (53). In addition, the cognitive targets that will result in the highest yield clinical outcomes are as of yet unknown.

Autism spectrum disorders (ASDs). There is an emerging trend toward the use of social cognition training in ASDs, although the field is in its infancy (54). Eack et al. (55) observed significant improvement (effect size >1) in cognition, social cognition, and overall functioning in a preliminary study of individuals with ASDs treated with cognitive enhancement therapy, which combines computerized neurocognitive and social-cognitive remediation with social skills group therapy. Another approach has focused on computerized methods that promote a holistic approach to face processing, which is known to be abnormal in ASDs (56). Overall, cognitive training research in children and adults with ASDs is currently very limited and needs to capitalize on emerging findings of neurocognitive and neural system impairments in these illnesses.

Other disorders. Cognitive training applications in other brain disorders will be briefly mentioned here, but the details are beyond the scope of this review. Cognitive training directed at enhancing phonological awareness and auditory processing, related to impaired left parieto-temporal cortex engagement, is effective in the treatment

of dyslexia (57). Several studies have examined the effects of cognitive training interventions in mild cognitive impairments in older adults and have found promising but inconclusive results; it is unclear if cognitive training interventions affect the conversion rates from mild cognitive impairment to dementia (58). There is also evidence for the benefits of cognitive training in traumatic brain injury and stroke (59); however, overall the current evidence on the efficacy and utility of cognitive training approaches in stroke and other acquired brain disease remains insufficient (60).

Predictors and Moderators of Response to Cognitive Training

Learner Characteristics

Age and neurodevelopmental effects. Few studies have systematically examined the effects of age or neurodevelopmental stage on the response to cognitive training. "Sensitive periods," when specific neural systems are undergoing rapid change, may provide windows of opportunity during which cognitive training could have a particularly potent effect. Early adolescence, characterized by a heightened sensitivity to reward and the rapid development of cognitive control systems, may be one such period.

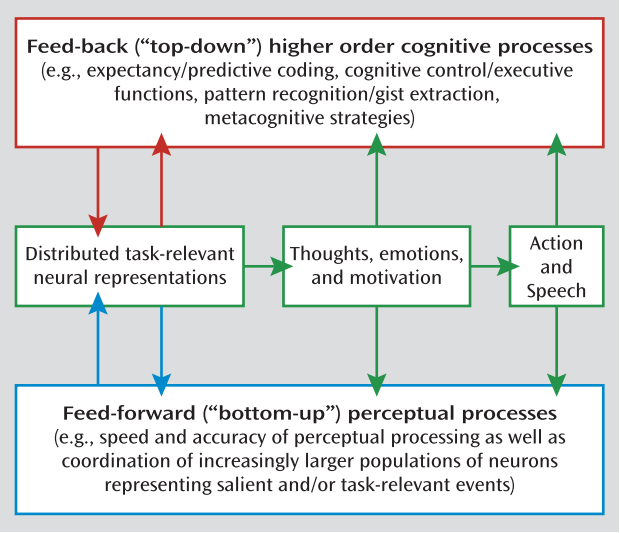
Cognitive training delivered as a preventive or preemptive intervention may diminish the cascading effects of psychopathology, at both the neural and environmental levels; such an intervention could potentially be used to prevent increasing deterioration in role functioning as well as the development of comorbidities. Such potential effects have been shown with early (childhood) interventions in anxiety (42), ADHD (61), and depression (62). This view is being tested in animal models as well; a study (63) showed that "adolescent" cognitive training in juvenile rats prevented adult cognitive control impairment in rats with neonatal ventral hippocampus lesions, an established neurodevelopmental model of schizophrenia. Clearly, once effective cognitive training approaches have been developed, they will prove highly useful if delivered preemptively across a broad range of psychopathologies.

Genotype. Given that genetic factors regulate plasticity and cognition, genotype will likely moderate response to cognitive training in people with mental illnesses. Genetic variability related to the catechol O-methyltransferase (COMT) gene (Val158Met polymorphism), a gene regulating prefrontal dopamine levels, has been investigated as one such factor. Bosia et al. (64) reported a greater response to cognitive training in schizophrenia patients who were COMT Met carriers, although no such relationship was observed by Greenwood et al. (65). However, using an intensive computerized cognitive training paradigm in schizophrenia patients, Panizzutti et al. (66) showed an association between eight single nucleotide polymorphisms at the 3′ end of the COMT gene and global cognition improvement (66). Brain-derived neurotrophic factor (BDNF) polymorphisms have been associated with greater gains in response to cognitive training in older adults (67). Genetic factors may interact with one another; in healthy adults, the interaction of BDNF with COMT polymorphisms demonstrates a clear role in human cortical plasticity, and genotype-related differences in neurophysiology translate into behavioral differences (68). Given the large sample sizes needed from well-defined clinical trials to determine the relationship of genotype to behavioral outcome, it will be many years before we have definitive answers on the role of specific genes and gene interactions in cognitive training response.

Cognitive function and brain reserve. Baseline cognitive function may be a moderator of outcome with cognitive training (69, 70). Keshavan et al. (28) demonstrated that pretreatment neurobiological reserve, operationalized as whole-brain surface area and gray matter volume, significantly moderated the effects of cognitive enhancement therapy (computerized cognitive training plus group-based social skills practice) in early-course schizophrenia. Greater reserve predicted a more rapid social-cognitive response to cognitive enhancement therapy in the first year of treatment, while individuals with less reserve responded at a slower rate. The lower gray matter volume at baseline may itself reflect an underlying pathophysiological process with an adverse impact on plasticity or previous environmental insults and stressors that have affected neural substrates. The ability to improve basic auditory processing speed during cognitive training in schizophrenia may be related to the overall cognitive gains made by individuals (71), suggesting that an inherent psychophysical learning capacity influences the response to training. Baseline cognitive and neuroplastic potential may thus predict treatment response; lower reserve may require adjunctive physical exercise interventions, pharmacological enhancement (72), or neuromodulation (73), as discussed below.

Motivation and emotional state. Factors linked to motivation, self-efficacy, and emotional state clearly play an important role in treatment response to cognitive training. For example, in healthy individuals motivational state exerts both local and global neural effects on cognitive control operations, while a positive mood enhances prefrontal activation and facilitates creative problem solving (74). Intrinsic motivation can best be fostered by providing a personalized context that links cognitive training to goals of everyday life and by promoting autonomy so that aspects of the training can be tailored to the learning style and goals of each participant (75). In addition, internalized beliefs influence cortical responses to feedback during learning (76) and are likely to moderate response to cognitive training. Finally, interindividual variations in reward sensitivity predict rates of learning, and will need to be the focus of future studies (77).

FIGURE 4. Schematic Representation of the Interaction Between Feed-Back and Feed-Forward Information Processing Operations



Features of Training

Training approaches. The field is barely at the threshold of understanding the key "active ingredients" for the development of training methods that maximize cognitive and functional gains in patients with mental illness. As discussed earlier, cognitive training involves varying combinations of top-down or feed-back approaches (training of higher-order metacognitive skills, executive functioning, or strategic techniques) and bottom-up or feed-forward approaches (training of perceptual and attentional skills) (Figure 4). Neurocognitive operations rely on both feed-forward and feed-back operations in the brain, as these processes may not be as distinct as was once thought; their synergistic interactions may be especially critical in impaired brains (e.g., impaired perception can influence higher-order cognition, as degraded bottom-up sensory representations may lead to increased competition for attentional resources) (78). Thus, the field may benefit from describing cognitive training methods in terms of their relative emphasis on these levels of operations as well as their emphasis on implicit versus explicit learning methods (15). "Bridge" groups (19) are an example of a top-down approach that is often combined with computerized cognitive training in order to help patients apply newly acquired cognitive skills to real-world situations and promote socialization. As the field moves forward in developing targeted cognitive training methods, the key challenges will be to identify and engineer precisely defined learning trials relevant to the neural system impairments of interest, and to elucidate their behavioral and neural effects in both healthy and impaired brains.

Intensity and progression of training. Several principles for achieving robust and specific integration of neural representations have been proposed and supported (15). A desired skill has to be practiced through repetitive trials on an intensive and frequent schedule. Close engagement of attention and reward systems is needed; with a high proportion of the learning trials being attended to, performed correctly, and immediately rewarded. Individualized adaptation of task difficulty helps to drive learning, so that accurate performance on initial "easy" trials is gradually led toward accurate performance on systematically more difficult trials (scaffolding), while maintaining a high trial-by-trial reward schedule. Learning tasks should drive progressively refined and detailed neural representations of task-relevant stimuli. Finally, learning approaches need to support generalization of improved function to real-world environments (such as through the use of bridging groups) (19). Learning-driven improvements in cognitive and socio-affective operations must generalize to untrained stimuli, tasks, and, most importantly, to cognitively demanding real-world situations.

Adjunctive Cognitive-Enhancing Interventions

Physical exercise. Physical exercise has important benefits for patients with mental disorders (79). In addition to its important metabolic effects, aerobic exercise has been associated with increased neurogenesis, angiogenesis, and the production of neurotrophic factors such as BDNF involved in neuroprotection and synaptic plasticity (80). One study (81) reported increased hippocampal volume in schizophrenia patients and healthy individuals following 3 months of aerobic exercise (cycling) with no change in a control condition (table football). Schizophrenia patients, but not healthy comparison subjects, exhibited a corresponding increase in hippocampal N-acetylaspartate, a marker of neuronal integrity. Physical exercise may also promote neurocognitive function and development in ADHD (82). Combining cognitive training with physical exercise programs may particularly help psychiatric patients who have been sedentary. However, the field needs a more precise understanding of the effects of specific types of exercise on cognition in mental illness and its potential interactive effects with cognitive training.

Pharmacological agents. In schizophrenia, the field now agrees that procognitive agents need to be developed and tested in combination with cognitive training in order to obtain maximal behavioral effects (83); these issues also apply to other psychiatric disorders. Examples of procognitive agents include the glycine agonist D-serine, the GlyT1 inhibitor sarcosine, ampakines (84), metabotropic mGlu2/3 agonists, the GABAergic agent MK-0777 (85), modafinil (which has complex effects on multiple neurotransmitter systems), and *d*-amphetamine (86, 87). Given these various mechanisms of action, drugs with different molecular targets may potentiate cognitive training effects in diverse clinical populations. For example, cholinergic enhancement with donepezil has been found to improve perceptual learning in healthy individuals (88), but its

effects in clinical groups are unknown. Dopaminergic and cholinergic agents may potentially enhance reward-related learning and thereby augment cognitive enhancement (89). A great deal of preclinical and clinical work lies ahead.

Brain neuromodulation. Neuromodulation approaches, such as transcranial magnetic stimulation, transcranial direct current stimulation, and vagal nerve stimulation, can potentially enhance cognition by modulating neuronal excitability (90). The effects of brain stimulation may be determined by the initial neural activation state (91); thus, manipulating neural activation states may allow one to selectively enhance activity in a given neural circuit. Andrews et al. (92) demonstrated that in healthy individuals, transcranial direct current stimulation applied while performing an n-back working memory task resulted in better performance, compared with sham transcranial direct current stimulation and stimulation applied while at rest. Ditye et al. (93) reported that anodal transcranial direct current stimulation combined with cognitive training was able to improve performance on the stop signal task. Animal research indicates that pairing vagal nerve stimulation with specific learning events increases the cortical representations of those events (94). Systematic studies of specific neuromodulatory interventions combined with cognitive training are needed in various clinical populations. It is unclear whether adjunctive neuromodulation will be most useful in illnesses characterized by widespread neural deficits and cortical inefficiency (e.g., schizophrenia) or as a "learning accelerator" in illnesses characterized by more circumscribed representational impairments (e.g., ADHD or anxiety disorders).

Trial Design Issues

Several critical methodological issues must be addressed as the field moves forward in the development and testing of cognitive training approaches for psychiatric illness (Table 1) (95).

First, the etiological and phenotypic heterogeneity of mental disorders makes it unlikely that particular domain-specific neurocognitive deficits will be universal to all individuals within a diagnostic category. Different cognitive phenotypes may have a similar clinical presentation; not all individuals will demonstrate specific cognitive deficits of interest, and specific cognitive deficits may cut across disorders and healthy states (96). This raises the question of how to operationally define caseness in selecting individuals for intervention studies. Thus, if the entry criteria consider only diagnostic criteria without addressing baseline neurocognitive heterogeneity, individuals for whom the proposed cognitive training intervention is not relevant could inadvertently be included in the sample.

Second, if we are to develop prescriptive, personalized intervention strategies, we must design cognitive training studies that include dense multimodal baseline assessments of participants so that we can determine both predictors of treatment response and factors associated with successful target engagement. In this manner, the feasibility of assessing putative moderators, as suggested by theory and research, could be explored in pilot studies. These putative moderators could then be examined in formal moderator analyses in subsequent studies with larger samples. Robust moderators thus identified could then be used as tailoring variables for more prescriptive treatment assignment. For example, neurobiological measures derived from imaging, electrophysiology, or transcranial magnetic stimulation (97) may be used to assess neural reserve or neuroplastic capacity. Genotype, reward sensitivity, motivational state, and internalized beliefs may also be important baseline predictive factors.

Third, understanding the mechanisms driving behavioral change requires us to define the treatment target of the cognitive training intervention under study and to demonstrate target engagement. Accordingly, preliminary proof of concept studies would seek to demonstrate that the intervention results in predicted changes in the hypothesized proximal target (e.g., a specific brain circuit or a psychological process, such as working memory or attention bias). Larger studies would then formally interrogate mediational pathways and examine whether changes in the presumed target mediate or translate into clinical benefit.

We must also control for nonspecific factors such as concomitant therapies that can influence behavioral outcomes unrelated to cognitive training. In schizophrenia (1), meta-analyses suggest that adjunctive psychosocial rehabilitation enhances cognitive training's impact on functional outcomes, but the specificity of this effect is unclear. Future studies need to quantify extra-protocol interventions and assess outcomes to identify synergistic benefits and develop optimized interventions.

A final but highly important consideration involves the dissemination of cognitive training into practice. Many factors contribute to delays in the research-to-practice translation (98), including fundamental differences between efficacy studies and the usual care context. This research-to-practice gap has prompted calls to rethink the intervention development and testing process. For example, a deployment-focused model of intervention development and testing (99) emphasizes incorporating information from different stakeholder perspectives (e.g., patients, consumers, family members, providers, administrators, insurers, and payers) much earlier in the intervention testing process. Careful consideration of patient characteristics (e.g., common comorbidities), candidate interventions (e.g., scalability, complexity, patient burden, and costs), potential providers (e.g., current competencies and training needs) and settings (e.g., capacity, competing demands, supervision infrastructure, and reimbursement

TABLE 1. Points for Consideration in the Design, Conduct, and Review of Cognitive Training Intervention Research

Item	Description
Participant characterization	Are potential predictors/moderators (e.g., baseline cognitive function, psychopathology, and neural reserve) assessed?
	Are inclusion/exclusion criteria (e.g., presence of targeted cognitive capacity/deficits) justified?
Intervention targets	Are cognitive targets (deficits/capacities) linked to clinical status and functioning?
	Do the cognitive training interventions match the perceptual/cognitive/affective processes that characterize the disorder and/or neural circuits implicated?
	Is the hypothesized therapeutic mechanism supported by research and theory?
Outcome assessment	Are potential predictors/moderators (e.g., medications, therapist engagement) of outcomes considered?
	Do assessments provide for the elucidation of intervention mechanisms (e.g., temporal precedence between putative mediators/mechanisms and target outcomes)?
	Are retention/completion rates assessed and reported?
	Are cognitive/functional outcomes distinguishable from practice effects?
	Are valid measures of proximal (e.g., performance on training tasks, neurocognitive measures) and more distal outcomes (clinical status, functioning, adverse effects, durability, generalization of cognitive and affective outcomes distinct from training tasks) included?
	Does the plan include measures at multiple levels of analysis (e.g., genes, molecules, cells, circuits, physiology, behavior, and self-report) as appropriate (64).
Concomitant treatments	Is cognitive training intended as a monotherapy or as an adjunctive treatment? Are concomitant treatments considered in the assessment and analysis plan?
	How might the proposed concomitant therapies potentiate (e.g., promoting plasticity; generalization of skills) or interfere with (e.g., medication side effects) cognitive training effects?
	Are concomitant treatments held constant across treatment conditions and/or quantified and considered in analyses?
Comparison condition	Is the comparison condition justified in terms of the research question and stage of intervention development/testing?
	Does the comparison condition control for attention, expectations, and potential practice effects associated with training/assessment protocols, as appropriate?
Scalability/potential for dissemination	Are all relevant stakeholders considered (i.e., patients/families [e.g., acceptability], clinicians [availability of an appropriately trained workforce], and policymakers [competing demands, therapist time/involvement, and other costs])?
	What are the implementation strategies (e.g., delivery within existing services, such as employment training; use of Internet or other facilitative technology for conducting assessments and delivering the intervention; provisions to facilitate motivation/engagement)?
Design considerations	Are randomization procedures clearly detailed and justified?
	Are intervention protocols standardized and manualized?
	Are there plans to monitor fidelity and operationalize the delivery of the experimental and comparison conditions?
	Are statistical approaches state of the art and appropriately matched to the research question and data structure?

structure) will also likely facilitate the development of more practice-ready, scalable, cost-efficient interventions.

Conclusions and Future Directions

Current evidence indicates that cognitive training interventions can result in significant, albeit modest, improvements in specific cognitive functions (e.g., memory, attention, and problem solving) across a range of mental illnesses. In parallel, the mechanisms underlying neuroplasticity as well as neural circuitry alterations in psychiatric disorders are increasingly well understood. These developments are promising, especially given the limited efficacy of pharmacological interventions in improving cognitive and socioaffective processing. However, the durability and effects of cognitive training (as currently studied) on symptoms and everyday functioning vary across clinical populations and need further study.

The field is in its infancy, and rigorously designed, adequately powered, randomized controlled trials are needed that investigate variability of treatment response, in addition to testing efficacy, and determine mediators and moderators of cognitive training effects. Future studies must also incorporate measures of the hypothesized mechanisms of action and of target engagement, as well as determine the time course and time scale of exposure needed for enduring changes in neurocognition and functioning. The synergistic effects of combining cognitive training with other interventions are another highly promising area of inquiry (e.g., cognitive training plus physical exercise in ADHD or cognitive training plus group social skills training for schizophrenia and autism).

Cognitive training's promise as a safe, preventive, and early intervention for individuals at younger ages and at earlier stages of illness highlights the need to design engaging and developmentally appropriate methods, which may or may not be computer based. Even more compelling is the prospect of early prodromal detection and intervention for impaired neural systems in order to preempt the onset of full-blown illness. There may even be the possibility of primary prevention of mental disorders if neural biomarkers of vulnerability can be found and improved through cognitive training, although ethical issues related to labeling individuals without overt symptoms will need to be addressed. Finally, our field must develop models to disseminate efficacious cognitive training approaches into community settings, and to emphasize deployment-focused models of intervention development.

Received Aug. 13, 2013; revision received Nov. 22, 2013; accepted Dec. 19, 2013 (doi: 10.1176/appi.ajp.2013.13081075). From the Department of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston; the Department of Psychiatry, University of California, San Francisco; San Francisco VA Medical Centers, San Francisco; the Clinical Neuroscience Research Branch, Division of Adult Translational Research and Treatment Development, NIMH, Bethesda, Md.; the Treatment and Preventive Intervention Research Branch, Division of Services and Intervention Research, NIMH, Bethesda; and the Neurobehavioral Mechanisms of Mental Disorders Branch, Division of Developmental Translational Research, NIMH, Bethesda. Address correspondence to Dr. Keshavan (mkeshava@bidmc.harvard.edu).

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Clinical Guidance: Psychological Interventions for Psychosis

Cognitive-behavioral therapy is superior to other psychological treatments for reducing positive symptoms, and social skills training is more efficacious for negative symptoms, according to a meta-analysis by Turner et al. (CME, p. 523). Befriending is less helpful in ameliorating symptoms than other interventions. In his editorial, Strauss (p. 479) underscores the need to consider the diversity of treatment options in relation to the even greater diversity of patients with severe mental illness. Cognitive training focuses on neural systems rather than symptoms, and Keshavan et al. report that it can benefit patients with schizophrenia and may improve functioning when combined with other forms of rehabilitation and coaching. The editorial by Harvey (p. 482) notes that training in a global cognitive process, such as planning, exercises multiple basic skills, such as sustained attention.