Brief report

Cognitive training in schizophrenia: a neuroscience-based approach

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Meta-analytic data from over a decade of research in cognitive remediation, when combined with recent findings from basic and clinical neuroscience, have resulted in a new understanding of the critical elements that can contribute to successful cognitive training approaches for schizophrenia. Some of these elements include: the use of computerized repetitive practice methods, high dosing schedules, a focus on sensory processing, and carefully constrained and individually adapted learning trials. In a preliminary randomized controlled trial of cognitive training exercises based on these principles, we demonstrated significant improvements in working memory, verbal learning and memory, and global cognition in patients with schizophrenia. These cognitive improvements were accompanied by neurobiological findings suggestive of learning-induced cortical plasticity. Future directions for research and essential remaining questions are discussed.

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Over the past several years, our field has recognized the urgent need to develop treatments for the cognitive dysfunction of schizophrenia, as it represents a critical determinant of functional outcome.[1] The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), Treatment Units for Research on Neurocognition and Schizophrenia (TURNS), and Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiatives have focused on psychopharmacologic interventions; however, pharmacotherapy trials of potential cognitive-enhancing agents have so far not demonstrated significant benefits. At the same time, there has been growing interest in evidence-based behavioral treatments, such as social skills training and cognitive remediation for schizophrenia (for review see refs 2,3-8). Nearly 30 randomized controlled trials (RCTs), using a wide range of remediation methods, have firmly established that schizophrenia patients can improve their performance on trained tasks, as well as show some generalization of improvement to untrained functions.[2,9] In fact, many experts now believe that optimal treatment benefit for patients will be achieved when cognitive-enhancing medications are combined with some form of behavioral cognitive enrichment or cognitive remediation.[10]

In this brief overview, we will describe several key issues for cognitive training in schizophrenia, based on a perspective that is directly translated from current experimental neuroscience. We use the term "cognitive training" rather than "cognitive remediation," since this approach is analogous to physical fitness training, where specific behaviors are used to harness intact physiologic mechanisms in order to restore or enhance performance.

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We will: (i) highlight relevant findings from previous cognitive remediation studies in schizophrenia; (ii) delineate key factors for the design of a neuroscience-based approach to cognitive training in schizophrenia; (iii) summarize recent results from our laboratory; and (iv) indicate what we see as the next directions for the development of neuroscience-informed approaches to cognitive training in psychiatric illness.

Three key findings from previous research

Previous studies of traditional approaches to cognitive remediation in schizophrenia have been confounded by various methodological issues (see refs 11,12): small subject samples, "open-label" conditions, treatment-as-usual control groups, unblinded assessments, and unspecified plans for statistical analysis. Studies that avoided these issues have tended to find only small to moderate effect sizes.[11,13-15] Nonetheless, the following findings point to some interesting next steps for the field:

- With the exception of verbal learning and memory, the meta-analysis by McGurk et al found no significant heterogeneity in effect sizes on various MATRICS-defined cognitive domains based on either the number of hours of training or the method employed.[2] This indicates that for the majority of cognitive domains, neither the training method, nor the amount of training (several hours to over 100 hours) has been a key moderating variable. Thus, although previous cognitive remediation approaches have provided modest non-specific cognitive benefits, further refinement of the intervention and the use of rigorous study designs are critical next steps for the field.
- Meta-analyses have also shown that in verbal memory, larger effect sizes are obtained when computerized training is given in a drill-and-practice approach for a large number of hours.[2,12] This suggests that computerized cognitive remediation given in a sufficiently large "dose" may be a highly important approach in schizophrenia.
- Significant synergy occurs when cognitive remediation is combined with a psychosocial intervention, such as vocational rehabilitation or social skills training.[2-4,12,16-18] This indicates that appropriate cognitive training can prepare the individual with schizophrenia to benefit from ecologically meaningful learning events, and underscores the fact that optimal treatment in schizophrenia will necessitate multimodal approaches.

How do we use new knowledge from basic and clinical neuroscience to design a cognitive training intervention?

Over the past decade, clinical neuroscience research has unequivocally demonstrated that declarative memory (those processes involved in recollection of facts and events) is impaired in schizophrenia[19,20]; thus, in keeping with the meta-analysis findings discussed above, it seems clear that strategy coaching and other direct instruction methods are likely to be of only limited benefit for patients. Further, the sensory processing deficits of schizophrenia, which demonstrate a strong association with higher-order cognitive dysfunction, may confer a bottleneck in the response to behavioral interventions.[21] A neuroscience-guided approach to cognitive training in schizophrenia should therefore take into account the following factors:

- The use of both implicit learning, through which skills and abilities are acquired indirectly and without direct awareness, and repetitive practice, may be crucial for maximizing patients' response to cognitive training.[22-28] In addition, attention to sensory processing deficits may be necessary in order to drive an optimal response to cognitive treatments.[21]
- Basic experimental work with motor skill learning and motor cortex remapping indicates that significant cortical synaptogenesis and reorganization of task-specific representations occurs after an animal reaches the "flat" portion of the learning curve, where performance gains are asymptotic.[29] Congruent with the meta-analysis findings described earlier, this suggests that "dosing" and "intensity" of training is important: in order to drive maximally enduring and neurologically reliable cognitive gains, subjects must perform large numbers of learning trials and must train at threshold (ie, training must be individually adapted to the capacities of each learner).
- During learning, the brain selectively promotes both "bottom-up" and "top-down" neural activity patterns that represent meaningful stimuli and behaviors; successful learning is most efficiently driven by exercises which target all of the specific component "skills" of a given cognitive process. For example, intensive computerized frequency-sweep discrimination exercises markedly improve the ability of language-impaired children to recognize and respond to speech stimuli.[30] For patients with schizophrenia, intensive training in a

wide range of basic cognitive operations is likely to be necessary to improve higher-order functions (eg, it may be necessary to train the representational fidelity of early sensory data; vigilance; working memory; etc. before achieving significant gains in executive functions).

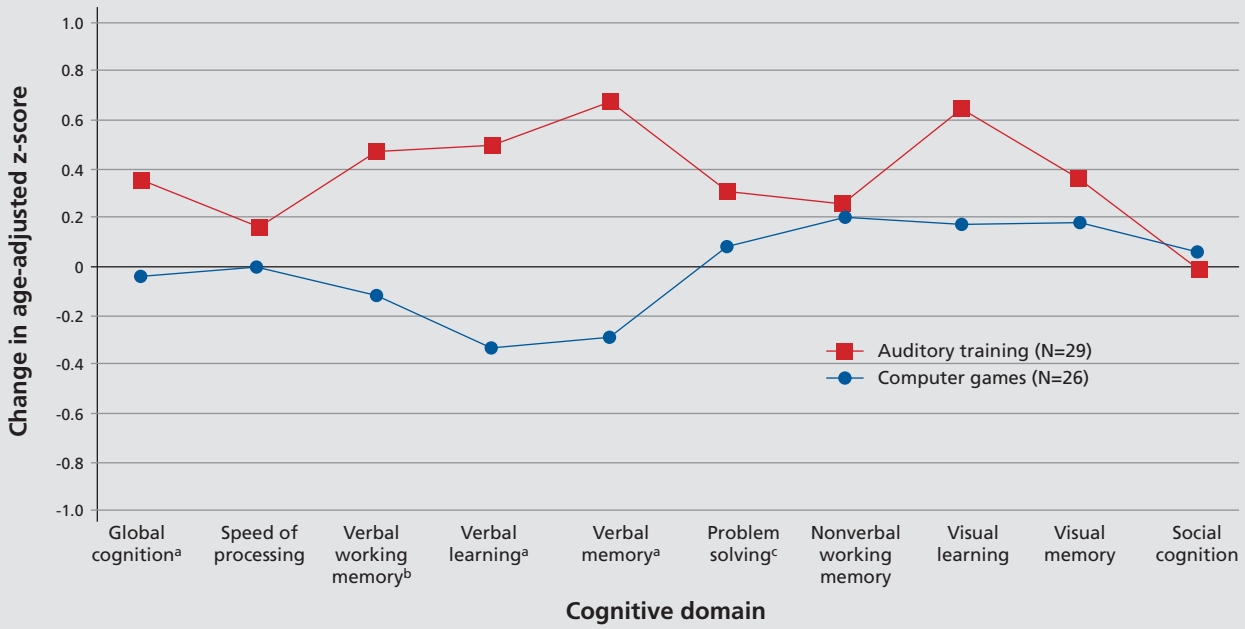
- Learning-based plasticity is profoundly influenced by neuromodulatory neurotransmitters[31-33]; therefore, learning trials must be designed that are closely attended by the subject and that involve a heavy reward schedule. Moreover, some of the medications currently used in schizophrenia may adversely affect the response to cognitive training strategies.

Current findings from our laboratory

We have been investigating the efficacy of a set of neuroscience-based cognitive training exercises designed with the considerations described above (software developed by Posit Science, Inc). Subjects were randomly assigned to either 50 hours (1 hour per day, 5 days per week) of a computer games control condition, or to 50 hours of computerized training that places implicit, increasing demands on auditory perception and accurate aural speech reception. Frequency discrimination and phoneme recognition exercises targeted aspects of early auditory processing deficits of schizophrenia, which have been shown to affect higher-order cognitions such as verbal memory, reading ability, and social-emotional recognition.[34-37] This psychophysical training was embedded within increasingly complex auditory and verbal working memory/verbal learning exercises that progress from simple frequency discrimination to phoneme identification and then recall of verbal instructions and narrative details.

Cognitive improvement after 50 hours of training

Compared with age- and education-matched subjects in the computer games control condition, we found that



[a] Significant difference between groups ($P<0.01$, repeated-measures ANOVA)
[b] Significant difference between groups ($P<0.05$, repeated-measures ANOVA)
[c] Nonsignificant difference between groups ($P=0.10$, repeated-measures ANOVA)

Figure 1. Change in cognitive performance in patients with schizophrenia after 50 hours of computerized auditory training or 50 hours of computer games.[38]

subjects who underwent targeted cognitive training showed significant increases in Working Memory, Verbal Learning and Memory, and Global Cognition *(Figure 1, Table I)*.[38] These data suggest that an intensive dose of computerized cognitive training focused on auditory and verbal processing results in improved verbal learning and memory in adults with schizophrenia.

Duration of cognitive improvement 6 months after training

Cognitive training subjects showed significantly greater improvement in verbal learning and memory measures from baseline to a 6-month follow-up assessment, indicating the durability of the cognitive training effects beyond the immediate post-training period.[39] Furthermore, improved cognition was significantly associated with improvements in quality of life at 6 months.

Neurobiologic findings associated with cognitive training

- Serum anticholinergic activity (SAA), reflecting medication-induced anticholinergic burden, showed a significant negative correlation with cognitive improvement after training. Consistent with basic science research, this suggests that the anticholinergic burden reduces the efficacy of cognitive training in driving cognitive improvement.[40]
- Subjects in the cognitive training condition showed a significant increase in serum brain-derived neurotrophic factor (BDNF) levels compared with the computer games control group.[40] This suggests that BDNF may be a peripheral biomarker for the effects of intensive cognitive training, and provides an indication of neurobiological response induced by the training.
- Magnetoencephalography studies of a syllable discrimination task showed a "normalization" of physiological response patterns in auditory cortex within the cognitive training group but not the computer games control group—indicating that adaptive plastic changes in auditory processing systems can be induced in schizophrenia patients in response to a behavioral training intervention.[21]

Outcome measures	F and *P* values[a]	AT effect size
Global cognition	**12.82 (<0.01)**	0.86
Speed of processing	0.61 (0.44)	0.21
Verbal working	**4.46 (0.04)**	0.58
Verbal learning	**9.97 (<0.01)**	0.86
Verbal memory	**8.60 (<0.01)**	0.89
Problem-solving	2.82 (0.10)	0.55
Nonverbal working memory	0.04 (0.85)	0.05
Visual learning	1.64 (0.21)	0.35
Visual memory	0.28 (0.60)	0.15
Social cognition	0.03 (0.86)	-0.05

Table I. Scores on cognitive domains before and after intervention for patients with schizophrenia who received computerized auditory training and patients who played computer games.[38]
[a] Repeated-measures ANOVA for condition-by-time interaction

Conclusions

Although these early data using a neuroscience-informed approach to cognitive training in schizophrenia are promising, they require replication with larger, more representative samples across multiple treatment sites. In addition, they raise many crucial questions for future studies:

- What are the necessary and sufficient ingredients essential for successful cognitive training in schizophrenia? What are the optimal methods, cognitive domains, and sequence of training?
- What is the minimum amount of cognitive training that results in meaningful cognitive improvement in patients? At what minimal frequency can training be delivered?
- What is the relationship between individual patient profiles at baseline (eg, genotype, biomarkers, neurocognitive profile) and their ability to realize and retain benefits from cognitive training (see, for example, refs 41-43)?
- What is the influence of commonly prescribed anticholinergic and antidopaminergic medications on cognitive training outcomes? How can novel cognitive-enhancing medications be combined with training?
- How can we maximize the synergistic benefits of combining cognitive training with psychosocial rehabilitation treatments?
- Can targeted cognitive training be used to remit pre-existing cognitive deficits and to promote recovery of function in young individuals who are in the very earliest phases of schizophrenia?

If the promising initial findings we describe here are replicated, we will enter an exciting time for the field of schiz-

ophrenia treatment, one which will require active collaborations between basic and clinical neuroscientists with expertise in neuroplasticity; researchers who perform clinical trials as well as experts in psychosocial remediation; clinical and research psychopharmacologists, and designers of computer games. We will enter a time of paradigm shift, and we will have the privilege of developing novel beneficial treatments for our patients. ❑

Entrenamiento cognitivo en la esquizofrenia: una aproximación basada en las neurociencias

La combinación de datos provenientes de estudios de meta-análisis, realizados desde hace más de una década de investigación en manejo cognitivo, con hallazgos recientes de las neurociencias básicas y clínicas ha permitido una nueva comprensión de los elementos críticos que pueden contribuir para que las aproximaciones de entrenamiento cognitivo en la esquizofrenia resulten exitosas. Algunos de estos elementos incluyen: el empleo de métodos computarizados de prácticas repetitivas, los horarios exigentes, un foco en el procesamiento sensorial, y ensayos de aprendizaje circunscritos cuidadosamente y adaptados individualmente. En un ensayo preliminar -randomizado y controlado- de ejercicios de entrenamiento cognitivo basado en estos principios se demostró una mejoría significativa en la memoria de trabajo, el aprendizaje verbal y la memoria, y aspectos cognitivos globales en pacientes con esquizofrenia. Estos progresos cognitivos se acompañaron de hallazgos neurobiológicos sugerentes de plasticidad cortical inducida por el aprendizaje. Se discuten futuras líneas de investigación y algunas preguntas esenciales que persisten.

Entraînement cognitif dans la schizophrénie : une approche basée sur les neurosciences

Des données métaanalytiques issues de 10 ans de recherche en remédiation cognitive, associées aux résultats récents des neurosciences cliniques et fondamentales ont permis une nouvelle approche des éléments essentiels contribuant au succès d'exercices cognitifs pour la schizophrénie. Ces éléments comprennent : l'utilisation d'exercices répétés sur ordinateur, des emplois du temps chargés, une attention particulière sur les processus de traitement sensoriels et un apprentissage soigneusement limité et personnalisé. Nous avons montré, dans une étude contrôlée randomisée préliminaire comportant des exercices d'entraînement cognitif basés sur ces principes, des améliorations significatives de la mémoire verbale, de la mémoire de travail et de la mémoire, ainsi que de la cognition globale des patients schizophrènes. Ces améliorations cognitives étaient accompagnées de résultats neurobiologiques évocateurs d'une plasticité corticale induite par l'apprentissage. Dans cet article, des orientations futures pour la recherche et les principales questions en suspens sont discutées.

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