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REVIEW ARTICLE

Integrating psychopharmacology and cognitive remediation to treat cognitive dysfunction in the psychotic disorders

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Cognitive deficits are a prominent and enduring aspect of schizophrenia, which pose a significant barrier to achieving functional goals. The most promising intervention for treating cognitive impairment is cognitive remediation (CR), a behaviorally based therapy associated with medium effect sizes for cognitive and functional outcomes. However, there is a sizeable group of nonresponders whose CR outcomes become limited when the therapeutic approach fails to address individual differences in baseline cognition, motivation variables, and the extent to which CR offers opportunities for generalization. This speaks to a need to develop cognitive interventions that are both personalized and scalable. Emerging data suggest that specific pharmacological agents have the potential to enhance and accelerate behaviorally based CR effects. This article will review the rationale and preliminary evidence to support combining CR and pharmacotherapy. We will review crucial aspects of cognitive interventions that offer the most promise for improving not only cognitive outcomes, but also for enhancing improvement in real-world functioning. Finally, we will address methodological issues to be considered for future research on combined pharmacological and CR interventions.

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Introduction

Cognitive impairment is a core symptom of schizophrenia that is evident in the prodrome and at first episode of psychosis, and is persistent but stable throughout the course of illness.[1,2] Cognitive functioning predicts the ability to live independently and maintain employment,[3] and thus continues to be an abundant and critical area of continued research. Over the last 20 years, impaired cognition has increasingly been the focus of intervention. The most promising of these interventions is cognitive remediation (CR).

CR is a behaviorally based training intervention that was founded on evidence for neuroplasticity and the ability of people with schizophrenia to learn new skills. It uses repeated exposure to cognitive exercises, which is thought to strengthen and/or repair neuroanatomical connections underlying neuropsychological abilities, leading to improved cognitive performance. Scientific principles of learning have been employed in the design of CR methodologies to restore those cognitive skills that have been adversely affected by illness processes. Targeted neurocognitive skills most commonly include attention, executive function, working memory, verbal learning and memory, and processing speed.[4,5] CR for social cognition may target one or more domains of social cognition, including facial affect recognition, social perception, Theory of Mind, and attributional style.[6] Empirical evidence for this therapeutic mechanism in people with schizophrenia is supported by data that have shown changes in neural activity following CR[7,8] and a decelerated loss or an increase in gray matter volume associated with improved cognition.[9] Thus, even despite pre-existing neurophysical limitations, CR has the potential to improve cognitive functioning and enable the use of adaptive cognitive skills in real-world contexts.[10,11]

Given that cognitive deficits in the schizophrenia population are heterogeneous, broad approaches are warranted such that multiple domains of cognitive impairment are targeted and transfer of cognitive gains to real-world functioning can occur. Typically, CR entails some exposure to drill-and-practice exercises, which often use computerized cognitive training programs, as well as a therapist who guides the choice of activities and may teach strategies for approaching the tasks. Restorative approaches targeting basic neuro- and social-cognitive skills may be paired with real-world cognitive challenges (eg, listening and summarizing a news story, interpreting and responding to affective cues in a social scenario) and/or metacognitive exercises to contextualize cognitive

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processes, aid abstraction, and generate strategies for completing cognitive tasks.[12–14] Recent meta-analyses of CR for the cognitive symptoms of schizophrenia have collectively studied over 2700 patients.[4–6] Effect sizes indicate a moderate effect on global neurocognition and daily functioning with evidence of persistence of moderate effect, on average, 8 months after neurocognitive training.[4,5] Kurtz and Richardson's[6] meta-analysis of 19 studies and 692 subjects found moderate to large effect sizes for social cognition training (affect perception and Theory of Mind) for improving overall psychiatric symptoms and daily functioning.

An ongoing challenge faced by the field of CR research is to augment CR outcomes while also maintaining the scalability of CR so that it is both clinically effective and cost effective when provided in a community context. To this end, a burgeoning area of investigation is the prescription of pharmacotherapy to augment CR outcomes[15] (for a review of pharmacological treatment of cognitive symptoms of schizophrenia, see Opler in this issue). While medication trials have yet to reliably support pharmacotherapy as a standalone intervention for the treatment of cognitive deficits in schizophrenia, there is good reason to hypothesize that a combination behavioral and pharmacological approach may prove more effective than either medication or CR alone.

Rationale for Combining CR and Pharmacotherapy

The rationale for combining pharmacotherapy with CR is based on our understanding of cognition and neuroplasticity. First, cognitive functions can be conceptualized as existing on a hierarchy, ranging from those that are relatively circumscribed and basic to cognitive skills that are complex and multidimensional. Auditory working memory is, for example, a more circumscribed skill than problem solving, which requires working memory, planning, goal setting, prioritization, and reasoning. In a hierarchical approach, cognitive treatment proceeds by targeting more basic discrete cognitive skills, then moving toward more complex skills. This assumes that the basic skills must be tuned before more complex skills can work efficiently. At present, cognitive training exercises are used to enhance the more basic cognitive skills, but pharmacotherapy holds promise as a more efficient treatment. If pharmacotherapy improves the cognitive skills that form the foundation of the hierarchy, CR can then focus on training the more complex skills, in essence promoting generalization of cognitive benefit by teaching patients how to use the pharmacologically enhanced skills to perform the multidimensional cognitive tasks.

Second, what we know about the mechanisms underlying neuroplasticity suggests that cognitive abilities and their underlying substrates are malleable (ie, can be improved) to the extent that they are exercised.[16,17] There is promise for pharmacological agents to offer short-term cognitive benefits and, importantly, to modulate long-term neuroplastic changes in the brain.[18–21] However, the impact on functioning is likely to be minimal unless cognitive skills are actively engaged. If a person with schizophrenia receives medication that enhances attention and working memory, but remains homebound and socially isolated, he or she will not be exposed to situations in which those cognitive skills are used. Conceivably, by pairing neuropharmacological and behavioral methods, neurochemically enhanced cognitive skills may be exercised in novel, increasingly complex environments, thereby providing opportunities to reinforce learning and promote generalization. Preliminary evidence from studies supports the synergistic effect of integrating pharmacotherapy to enhance CR outcomes.

Review of Randomized Controlled Trials (RCTs)

There are 4 published randomized controlled trials involving combined pharmacotherapy and psychosocial/behavioral treatment.

D'Souza *et al.*[22] reported a partial double-blind, placebo-controlled trial evaluating the feasibility, safety, tolerability, and efficacy of 12 weeks of D-serine (30 mg/kg), a *N*-methyl-D-aspartate (NMDA) receptor agonist, combined with CR in the treatment of cognitive deficits in schizophrenia subjects. Schizophrenia subjects (N = 104) at 2 academic sites in India (N = 82) and in the U.S. (N = 22) were randomized to D-serine + CR, D-serine + behavioral control, placebo + CR, or placebo + behavioral control groups. CR required 5 hours per week on computer-based cognitive exercises from Psychological Software Services' CogRehab. The behavioral control condition was of equal duration and involved non-interactive viewing of TV programs. Completion rates were 84% and 100% in the Indian and U.S. samples, respectively. The pharmacological and behavioral interventions were well-tolerated. At post-treatment, there was no significant change in cognition as measured by the Global Cognitive Index in any of the four arms, and no significant main or interactive effects. CR alone was effective at improving performance on Digit Span Forward, a measure of attention, but none of the other 10 individual cognitive test scores. D-Serine did not increase the effects of CR on individual cognitive test performance. A comparison between post-treatment and follow-up performance showed a trend level association between D-serine and higher scores on the Global Cognitive Index. There were no significant effects for D-serine, CR, or D-serine–CR interaction

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over time on functional outcome measures. This is the first study to demonstrate the feasibility, safety, and tolerability of combination pharmacotherapy and CR. Although the cognitive findings were limited, the authors recommend additional research using higher doses of D-serine, which may be combined with more personalized CR strategies whose efficacy is supported by multisite studies.

Gottlieb *et al*.[23] tested the hypothesis that a dose of D-cycloserine could potentiate memory consolidation and learning of cognitive-behavioral techniques aimed at reducing delusion symptom severity. Although not a CR trial per se, because cognitive behavioral therapy (CBT) focuses on higher lever cognition (eg, thoughts, beliefs), this study similarly examines the combined impact of skills-based training and pharmacotherapy on learning. In a double-blind placebo-controlled, single-dose crossover trial, adult outpatients (N = 21) with schizophrenia or schizoaffective disorder were randomized to receive a single-dose of D-cycloserine (DCS; 50 mg) or placebo in a counterbalanced order on 2 consecutive weeks prior to training in the generation of alternative beliefs to target delusions. Using assessments of symptom change from baseline to 7 days following the first study drug administration, and 7 days following the second study drug administration, the authors found no significant DCS effect on delusional distress or severity. However, there was an unexpected order effect, whereby subjects who received DCS first had significantly reduced delusional severity, distress, and belief conviction compared to subjects who received placebo first. Noting research with animal models in which DCS enhances learning only when accompanying the first exposure to training, the authors speculated that DCS should be administered immediately prior to an initial skills training session to exploit the facilitation of "new learning." Subsequent sessions of skills training may reinforce learning thereafter, even if unaccompanied by DCS.

Goff *et al*.[24] tested whether DCS combined with CR improved practiced auditory discrimination tasks, unpracticed cognitive tasks [MATRICS Consensus Cognitive Battery (MCCB) composite score], and negative symptoms Scale for the Assessment of Negative Symptoms (SANS) score in 36 stable medicated adults with schizophrenia. All subjects were exposed to a CR program consisting of POSIT Brain Fitness administered 3–5 times weekly, and were randomly assigned to once weekly treatment with DCS (50 mg) or placebo for 8 weeks. Of the 32 subjects who completed the trial, DCS was associated with more negative symptom improvement in those with baseline SANS >20, and performance on the trained auditory task improved more in the DCS than placebo group. Only the placebo group improved on the untrained cognitive tasks (MCCB). The evidence for some enhanced learning indicates that there may be merit in trying DCS in combination with other CR approaches.

Marder[25] reported a trial designed to evaluate whether treating patients with intranasal oxytocin (OXY) improves response to social cognition training by increasing the salience of social information. In this randomized trial, 30 patients received 12 sessions of social cognition training over 6 weeks; 40 IU of intranasal OXY or placebo was administered to patients on the days they received the training. OXY was well tolerated. Social cognition was measured at baseline, 7 weeks post-training, and 1 month later. Composite and basic component social cognition scores were not differentially affected, but empathy, a higher-level component of social cognition that was also the focus of some of the social cognition training, did show significantly greater improvement in the OXY condition. This study provides some preliminary evidence that while social cognition training alone effectively targets more basic social cognitive skills, OXY may facilitate the impact of the training on empathetic accuracy, which is a complex social cognitive skill.

A Case Example

Authors AM and LAO have been using a combination of oxytocin and social cognition training to treat a 26-year-old woman with developmental disabilities, who was diagnosed with schizophrenia at age 18. When she started outpatient treatment with LAO at age 20, she was in a highly dysfunctional state marked by screaming outbursts, throwing objects, and running from rooms in response to hallucinations and delusions that dictated her social interactions. Unable to take clozapine due to a chronically low white blood cell count (less than 3000), she was treated for 4 years with risperidone and supportive psychotherapy, which diminished the intensity and frequency of hallucinations, resulting in fewer outbursts. The persistence of functional impairment led to a referral to AM for psychosocial skills training when she was 24 years old. At intake to the Lieber Recovery Clinic (http://www.lieberclinic.com), the rating of her functioning using the Multnomah Community Ability Scale (MCAS),[26] a 17-item measure completed by the clinical team leader, was at the 55th percentile (total score 58) for women her age with severe and persistent mental illness. After 4 months of travel training, CBT for psychosis, cognitive remediation, and social cognition training, there was increased motivation and engagement in her environment, more independent functioning, and further diminution of outbursts. Her MCAS rating increased to the 75th percentile (total score 64). Due to the persistence of social anxiety and

paranoid beliefs about social interactions, oxytocin oral tablets (30 IU) were added to her medication regimen. Six months after starting combination treatment with oxytocin and social cognition training (1 hour of weekly group and 4 hours of weekly community-based social cognition coaching[27]), her MCAS score improved to above the 90th percentile (total score 69). She continues to be able to manage college courses, tolerate all the therapies well, and be highly engaged in treatment. There has been marked improvement in negative and disorganization symptom severity, and some further diminution of positive symptoms, which she manages with increasing success using CBT techniques. This case exemplifies, even in the absence of total symptom remission, the benefit of a sustained duration of combined treatment, and is the first known report of combined oxytocin and social cognition training with a female.

Methodological Considerations

Combined intervention trials raise questions about the relative efficacy of CR and pharmacological treatment alone, compared to the combination of treatments and to placebo. In order to participate in this new area of research, there are multiple design variables to consider, including study design, subject characteristics, choice of outcome variable(s), timing of post-intervention assessments, choice and duration of medication, CR and control interventions, and feasibility for large-scale clinical trials.

Study design

A 4-cell design allows randomization of subjects to the following groups: CR + medication, CR + placebo, medication + CR control condition, and placebo + CR control condition. A large total sample size is necessary to achieve adequate power to detect treatment differences in a 4-cell design. Some researchers have instead chosen 2-cell designs to focus on the benefit of adding drug/placebo to subjects receiving a given behavioral intervention, or of adding CR/control to subjects receiving a given drug. A 2-cell design may be carried out more feasibly, although the questions that such studies can answer will be more constrained.

Subject characteristics

For CR trials, it is recommended that subjects demonstrate an IQ greater than 75, and are not currently abusing substances or using concurrent medications with known negative impact on cognition. There are no current recommendations pertaining to inclusion/exclusion based on age[4,28]; however, this may be an artifact of the limited age range in the meta-analytic studies.

Choice of outcome

The primary endpoint is typically change in cognitive performance on measures independent from the training tasks, such as the MATRICS Consensus Cognitive Battery (MCCB)[29,30] or Brief Assessment of Cognition in Schizophrenia (BACS).[31] Measures of social cognition may also be considered. Much of the emphasis on the treatment of cognition in schizophrenia stems from the notion that improving cognition may lead to improvements in the functional outcomes that cognitive abilities predict. Because functioning in patients with schizophrenia is determined by multiple factors that are independent of the individual or the intervention (eg, availability of social resources), it is prudent to consider intermediate indicators of functional capacity and distal measures of functional competency. Functional capacity measures assess skill performance in a controlled setting in reference to functionally relevant domains such as social skill, medication management, finance management, self-care, and independent living.[32–35]

Functional competency is a distal measure of outcome and refers to the attainment of a sustained level of functioning in a real-world setting. Rating behaviors in real-world settings can be challenging in a clinical trial, given the practical challenges of direct observation or self-report. There is potential to examine intermediate personal goal attainment, which may reflect adaptive skill acquisition en route to vocational, educational, social, or independent living end-goal attainment. This is particularly relevant if CR is paired with other meaningful skills-based interventions, such as supported employment or social skills training. In addition to functional outcomes, the impact of the intervention may also be gauged via ratings of psychiatric symptoms, motivation, session attendance, or medication adherence.

Choice of CR intervention

The choice of CR approach needs to take into consideration whether positive cognitive and functional outcomes have been demonstrated, whether there are replication studies from independent laboratories, and the success of approaches in multisite trials. Eclectic CR approaches that utilize therapists who give strategy instruction during CR and lead verbal discussion groups have been successfully used in multisite trials to enhance both cognition and functional outcome.[36,37]

Research data indicate that a variety of additional person-related and environmental factors can limit the extent to which cognitive abilities transfer to everyday life. Performance anxiety, self-competency beliefs, intrinsic motivation, and an autonomy supportive

environment have all been identified as factors that are significantly associated with improvement in functional performance.[38] While pharmacotherapy may enhance the capacity for a given cognitive skill, a CR approach that addresses these factors may facilitate the translation from capacity to competency in real-life situations. Thus pairing pharmacotherapy with a model of CR that addresses the psychological factors associated with learning may assure the greatest amount of neuroplasticity and clinical benefit.

Choice of control comparator

The researcher's choice of control condition should be informed by elements of the active intervention, including the type of cognitive activity, degree of interpersonal contact, and necessity of maintaining subject blindness. Generic computer-based activities are a suitable control condition when CR is computer-based, as computer exposure, level of therapist interaction, and degree and type of mental stimulation can be controlled. Alternatively, remediation tasks that do not increase in difficulty can be used, as they limit the potential remediation value, although potentially at cost to subjects' task engagement. Both options are suitable for maintaining subject blindness, since the modality is kept constant.

Feasibility

The large sample sizes required to examine interaction effects, and also the extended timeline and personnel to accommodate the CR component, add to protocol complexity. Furthermore, the degree of intervention complexity will impact the extent and feasibility of therapist training required to maintain fidelity across sites in a multisite clinical trial. Interventions that include clinician-mediated CR benefit from in-person training sessions, clinician's training manuals, and supervision. Fidelity monitoring thereafter is an important component of controlled trials, which requires additional personnel, training, and supervision for the duration of the study.

Attrition in CR studies is, on average, less than 10%, and 90% of studies do not provide payment for CR sessions.[4] When medication is added to CR, the study timeline and complexity of the rating requirements increase significantly, as does attrition. This might lead some investigators to start paying subjects to attend CR—a practice that might in fact diminish cognitive outcomes[38] and certainly limit scalability, since community clinics do not pay subjects to attend treatment programs. Given that there is no evidence that monetary compensation for CR sessions enhances retention, pegging payment to the assessment visits obviates the potential negative impact on motivation and learning, as well as scalability, while keeping compensation consistent with the obligations required.

Conclusion

The combination of medication and cognitive remediation has the potential to facilitate the 2-step process of enhancing basic neurocognitive functioning and facilitating generalization to promote functional change. There is considerable promise in this burgeoning area of research to find pharmacological agents that enhance the immediate and long-term effects of cognitive remediation training.

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