Keynote Lecture: Cognitive Remediation in Schizophrenia

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Summary. The symptomatic, neurocognitive and functional phenomena of schizophrenia are in constant interaction and flux as determined by the activity of the brain, psychotropic drugs, environmental antecedents and consequences, and behavioral repertoires. Neurocognitive functioning has been hypothesized to be "rate limiting" in the learning capacity of individuals with schizophrenia for acquiring and utilizing knowledge and skills for success in everyday life. Interventions to favorably affect neurocognition can be staged from several levels or sources, including medication and direct training, or through more general therapies that may have indirect salutary benefits on brain function. Atypical antipsychotic drugs, such as risperidone and olanzapine, have been documented to enhance neurocognition in schizophrenia; however, whether or not such enhancements result in improved psychosocial functioning may depend upon the concomitant impact and demands of the therapeutic milieu. Direct training of the brain can normalize neurocognition in schizophrenia, but these effects have not been shown to have broad clinical value. Newer methods of cognitive remediation, such as errorless learning, may have more durable and generalizable effects on psychosocial functioning, but their focus will have to be on compensating cognitive deficits that are directly linked to instrumental role activities. Social skills training and a systematic therapeutic environment that reinforces adaptive behavior may also yield both improved neurocognition and higher levels of instrumental role functioning.

Key words. Cognitive remediations, Schizophrenia, Rehabilitation, Train the brain, Skills training

The clinical priorities for psychiatrists and other mental health professionals must be the social and role functioning of persons with disabling mental disorders, as well as on their material and subjective quality of life. Symptoms and cognitive impairments and abnormalities in brain function or structure are only important to the extent that they intrude upon a person's functional capacity and satisfaction in daily living. Con-

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sequently, interventions that are efficacious in ameliorating or removing symptoms and cognitive impairments must be ultimately evaluated in terms of their success in improving independent living skills, social competence, and everyday pleasures. Before homing in on cognitive remediation, the focal point of this presentation, I will provide an introductory context for this approach to clinical intervention.

Despite advances in neuroscientific understanding of schizophrenia during the past "decade of the brain," we are not much further along in our knowledge of the biological underpinnings of this most disabling of the mental disorders. Although hypotheses have been paraded with much fanfare regarding genetic and neurodevelopmental abnormalities that supposedly underlie schizophrenia, the mechanisms that translate these putative predispositions into the onset or relapse of the symptoms and disabilities of the disorder are not known. Examination of the distributions of neurocognitive functioning and structural and functional abnormalities of the brain in persons with the categorical diagnosis of schizophrenia immediately reveals the great overlap with distributions of the same variables among normal samples. Statistical significance in differences between persons with schizophrenia and various normal or psychopathological contrast groups has not yielded the qualitative differences that would be desirable when trying to identify etiological mechanisms. Whether one reviews the research on ventricle-to-brain ratios or the size of the hippocampus, thalamus, prefrontal cortex blood flow visualized by functional magnetic resonance imaging (fMRI), hypofrontality assessed by positron emission tomography (PET), or other neurocircuits, the biological basis of schizophrenia has proven as elusive as the "schizophrenogenic mother."

Moreover, if neurocognitive abnormalities, as genetic markers, are as enduring as they have been posited to be [1,2], how can we explain the recovery from schizophrenia that has been well documented [3–6]? If neurocognitive abnormalities are supposed to be "rate limiting" for psychosocial functioning and endure throughout periods of symptom exacerbation or remission, how are we to explain the gifted intellectual contributions of Dr. William Minor, the "madman" who was as responsible as anyone for the first edition of the Oxford Dictionary of the English Language [7], even as he languished in a British asylum for lunatics?

Determinants of Social and Role Functioning

As shown in Fig. 1, factors within the individual and the environment interact in two directions to determine the social and role functioning and quality of life of persons with schizophrenia. Whereas genetic endowment, premorbid social adjustment, negative symptoms, medication side effects, and cognitive impairments—as attributes of the individual—combine with favorable or adverse environmental variables, such as a supportive and rewarding family climate or stressful life events, to influence social and role functioning, so does functioning in a reciprocal fashion affect these individual and environmental factors.

For example, research conducted at our UCLA Center for Research on Treatment and Rehabilitation of Psychosis has shown that the negative symptoms and subclinical psychopathology of an individual with schizophrenia can provoke emotionally intrusive and critical responses in family members, which, in turn, have an

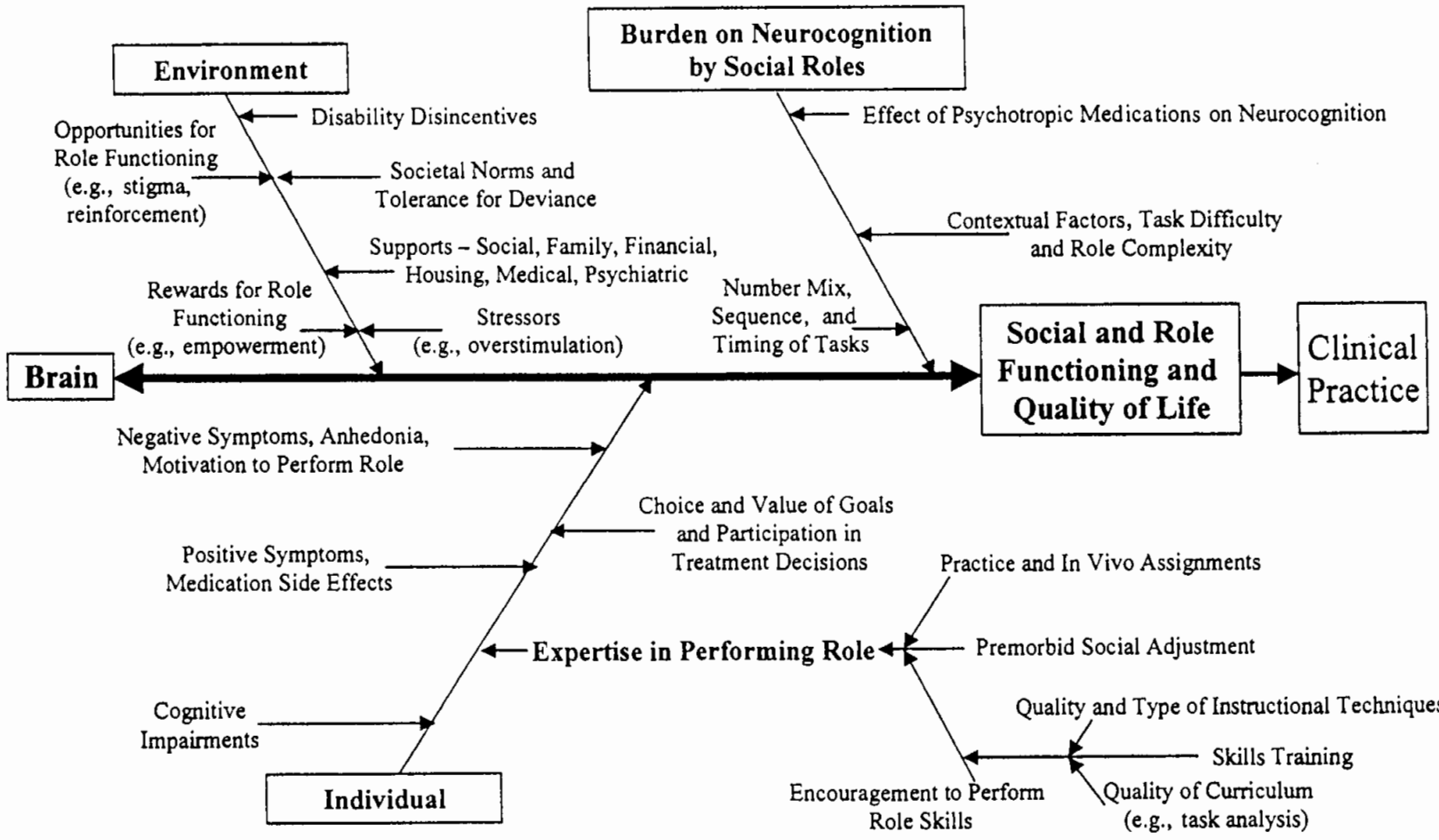

FIG. 1. Factors that influence social and role functioning and quality of life in schizophrenia. The variables or factors that operate from the individual, environmental, and central nervous system levels interact among one another. Thus, environmental factors affect the individual and the brain; the factors within the individual affect the environment and are affected by the functioning of the brain; and the brain is affected by the environment and behaviors of the individual

escalating effect on the individual's symptomatology. If the family interaction continues under these stressful conditions, relapse or exacerbation of psychosis may ensue and the emotional burden on the family may increase [8]. Similarly, imperceptiveness of an individual with schizophrenia to the emotional states of peers may lead the person to awkward or provocative conversational initiatives that may result in rejection or even hostility from peers. As a consequence, the individual may suffer overarousal that even further imperils the accuracy of social perception and decision-making.

As can be seen from Fig. 1, cognitive deficits are but one domain that influences social and role functioning—a multivariate, pluralistic, reciprocal, and probabilistic framework is needed to understand the determinants of an individual's functioning and quality of life. In fact, cognitive dysfunction may not be the most important determinant of social functioning at any one given time and place for an individual with schizophrenia. For instance, among young persons with recent onset of schizophrenia who were treated with risperidone and case management services in an outpatient clinic, high expressed emotion within the family predicted educational and vocational functioning after one year somewhat better than cognitive deficits; furthermore, high expressed emotion also predicted symptomatic relapse, which was not the case with cognitive deficits [9].

Given our genetic endowments and learning histories, we and our patients with schizophrenia share the attributes of dynamic, living organisms in an ever-changing world. We move freely and experience a multitude of antecedents and consequences in our environments that shape our behavior. Our behavior—including cognitions, affects, work, friendships, family relations, recreational activities, and imagery—is always having an impact on our environments, and, reciprocally, our environments are constantly influencing our behavior. The corollary of this science of human behavior [10,11] is that treatment and rehabilitation of persons with schizophrenia, if they aim to achieve durable and substantial improvement, remission of symptoms, and recovery of social functioning, must be multimodal, comprehensive, linked to the phase of the disorder, continuous, coordinated, collaborative, and consumer-oriented [12].

Strategies to Improve Social and Role Functioning

As highlighted in the Practice Guideline for Treatment of Schizophrenia by the American Psychiatric Association [13], treatment and rehabilitation must be keyed to the phase of the individual's disorder. As shown in Fig. 2, during the acute phase of the illness, when symptoms are at their peak, pharmacotherapy is given priority, because it has the greatest efficacy on symptoms. However, interventions that reduce socioenvironmental stressors—such as hospitalization with predictable, low-demand, secure, and stable scheduling of activities and interactions—are also indicated for the acute phase. When symptoms begin to subside in the stable phase of the disorder, treaters give priority to titration of antipsychotic medication to optimal therapeutic effects while minimizing side effects. During both of these phases, it is essential for the psychiatrist and treatment team to engage the family or other natural caregivers in psychoeducational and supportive sessions and to begin educating the patient

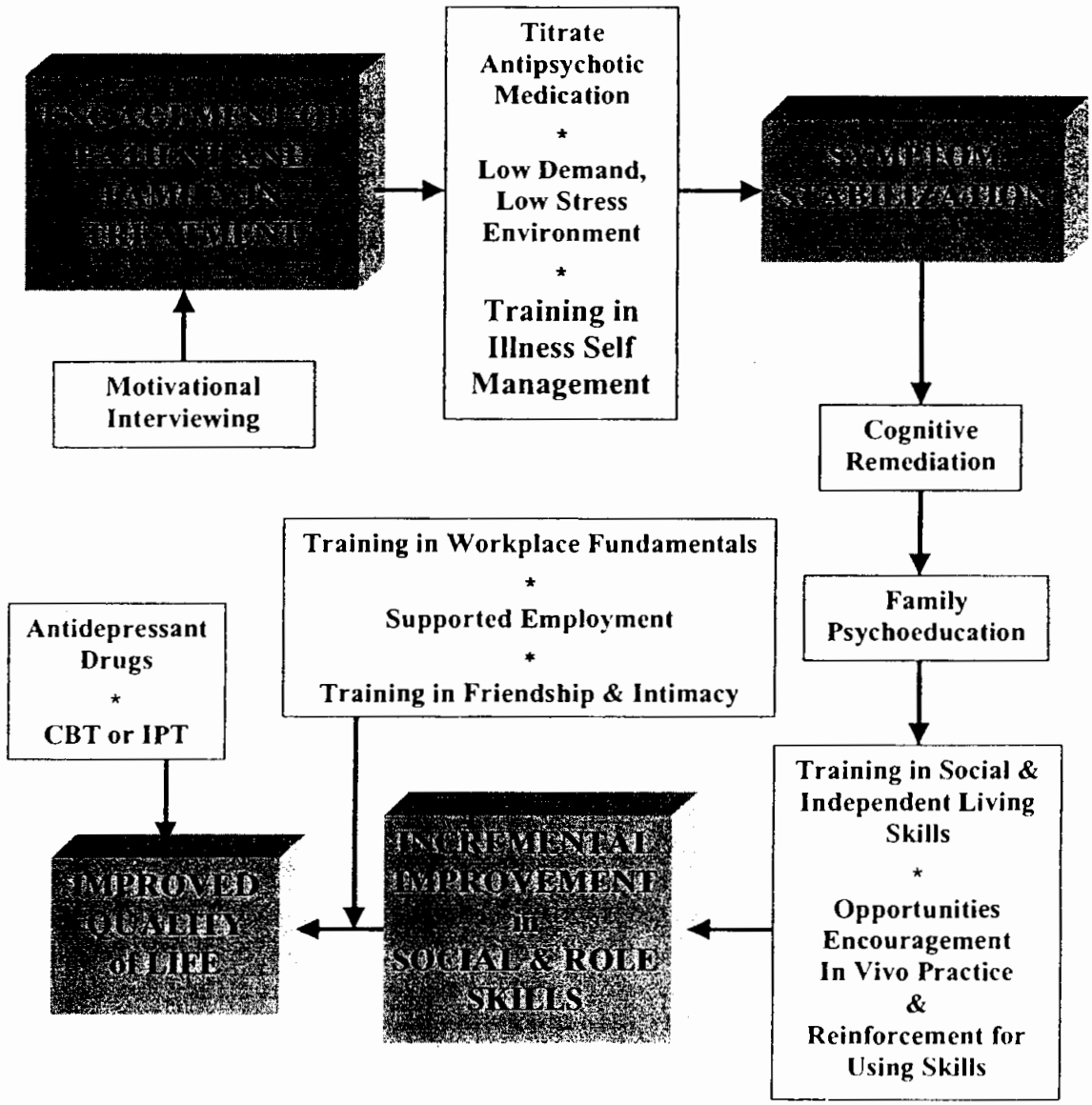

FIG. 2. Phasic progress for clinical improvement in schizophrenia. Treatment and rehabilitation of schizophrenia should be linked to the phase of the disorder. Treatments that are appropriate for the acute phase of the disorder are customarily changed to be suitable for the stabilizing and stable phases of the disorder. *CBT*, cognitive behavioral therapy; *IPT*, interpersonal therapy

regarding the purposes, benefits, side effects, and self-administration of medication. With stabilization of psychotic symptoms, the next goals are to help the patient and family develop an "emergency plan" to thwart relapses and promote the capacity for the patient to connect with and sustain long-term aftercare services in the community.

Regaining social and vocational functioning usually lags behind symptomatic improvement; thus, it is usually advisable to delay active efforts in these domains until the individual has been in the stable phase of the disorder for at least six months. With symptoms in abeyance and the person's social network providing encouragement and positive reinforcement for incremental improvements in daily self-care and instrumental role skills, social functioning gradually improves. However, it is only after con-

siderable time has passed with a successful resumption of involvement in social, educational, and vocational activities that one can expect any improvements in quality of life. The latter is also sensitive to the mood states of the individual; hence, a supportive therapeutic relationship balanced by attainment of realistic yet personally selected goals is an efficient means of bolstering morale and protecting the individual from post-psychotic depression. It is during the stable phase of the disorder that interventions to overcome cognitive deficits can be strategically made.

What are the various strategies for cognitive remediation? There are two direct strategies and one indirect approach. The direct strategies are neurocognitive pharmacotherapy and precision teaching or training of cognitive functions. The indirect strategy aims to compensate for the cognitive deficits that are present, either through use of social skills training or social support that can provide substitutes for deficits in memory, learning, problem-solving, or perception.

Neurocognitive Pharmacotherapy

There is increasing evidence that atypical antipsychotic drugs, especially risperidone and olanzapine, have greater salutary effects on a range of neurocognitive functions than conventional or typical antipsychotic agents. This overall conclusion must be tempered, however, by the fact that most of the extant studies have been sponsored by pharmaceutical companies and, thus, must be replicated by independent investigators supported by governmental or foundation grants. A recently published meta-analysis [14] and a thorough review of the literature [15] have documented the spectrum of benefits of the atypical antipsychotics on specific cognitive mechanisms.

It appears that clozapine improves attention and verbal fluency; that risperidone improves working memory, executive functioning, attention, reaction time, and motor and verbal learning; and that olanzapine improves verbal learning and memory, verbal fluency, and executive function. The significantly greater effects of these atypical drugs remain even after the reduced use of anticholinergic agents (e.g., benztropine) has been partialed out statistically. Although the improvements found with these psychoactive agents have been statistically significant when compared with baseline functioning or with the effects of typical agents such as haloperidol, residual cognitive impairments in patients, even after optimal doses of pharmacotherapy, point to the need for better drugs or supplementary behavioral interventions for further remediation.

It is encouraging, however, that the direct effects on cognitive remediation produced by clozapine, olanzapine and risperidone have been found even with patients who were previously treatment refractory and who had been institutionalized for many years [16]. A number of caveats regarding methodology for research on neurocognitive pharmacotherapy are apt when interpreting the significance of findings that are reported in the scientific literature. These include the needs to register the baseline medication and symptomatic status of the patients, conduct studies with random assignment and double-blind conditions, evaluate the changes in neurocognition after varying periods of treatment, use appropriate dosing strategies and levels with adequate sample size, use appropriately selected and standardized neurocognitive test batteries, and prevent confounding from concurrent changes in symptoms,

adjunctive medications, medication side effects, and psychosocial or behavioral treatments

Little is known about the neuropharmacology of cognitive functions in human beings; hence, the use of medications to remediate deficits in neurocognition will remain an empirical enterprise, devoid of theory-driven and hypothesis-testing efforts, for the foreseeable future. As we open the opaque curtain on the functioning of the brain, it is very likely that "designer drugs" will be forthcoming from the laboratories of academia and the pharmaceutical industry that will revolutionize the cognitive remediation of schizophrenia. Until then, there are many new atypical antipsychotic drugs in the pipeline and other drugs that are reasonable candidates to study for their effects on cognition: selegiline, donepezil, modafinil, methylphenidate, dextro-amphetamine, pemoline, and combinations of psychoactive medications. Moreover, little research has been done on the long-term cognitive benefits that may accrue from electroconvulsive therapy or from transcranial magnetic stimulation, even though some evidence exists for better outcomes for persons with schizophrenia who do not respond to any of the available drugs but who do respond to initial and maintenance electroconvulsive therapy [17,18].

Direct Training of Cognitive Functions

One might view effective direct modes of cognitive remediation, using either drugs or behavioral training, as building a higher platform for individuals with schizophrenia to mount as a point of departure for broader and more comprehensive psychosocial and vocational rehabilitation [19]. One of the first efforts to directly train a cognitive function was undertaken about 100 years ago by Carl Jung, who gave frequent assignments to a schizophrenic patient to read and memorize passages from the Bible. Jung tested her recall of the passages and reported that this "treatment kept alert the patient's attention, appeared to improve her functioning and reduce her hallucinations." [19a] Research on cognitive remediation can be divided into two main training strategies: improvements aimed at focused neurocognitive functions, with training taking place under highly controlled laboratory conditions; and more clinically ambitious training of a hierarchy of cognitive and sociobehavioral deficits. The latter strategy has been pursued mainly by Brenner and his associates, with only ambiguous and indecisive effects on both the neurocognitive and clinical outcomes targeted for intervention [20–22]. The laboratory studies of direct training of sustained attention, executive function, and other neurocognitive domains, while in some cases showing changes that approximated normalization of the functions, have not been associated with demonstrable improvements in psychosocial functioning, and it is possible that the training effects reflect nonspecific enhancement of motivation to perform the tasks rather than specific improvements in the cognitive functions per se [23].

Computer-assisted training of performance on cognitive tasks has yielded improvements in the tasks, and on more general problem-solving exercises, with patients reporting satisfaction with the exercises [23a,23b]. Educational techniques such as contingent reinforcement for task engagement were used to facilitate learning. An example of computer-aided cognitive remediation is shown in Fig. 3.

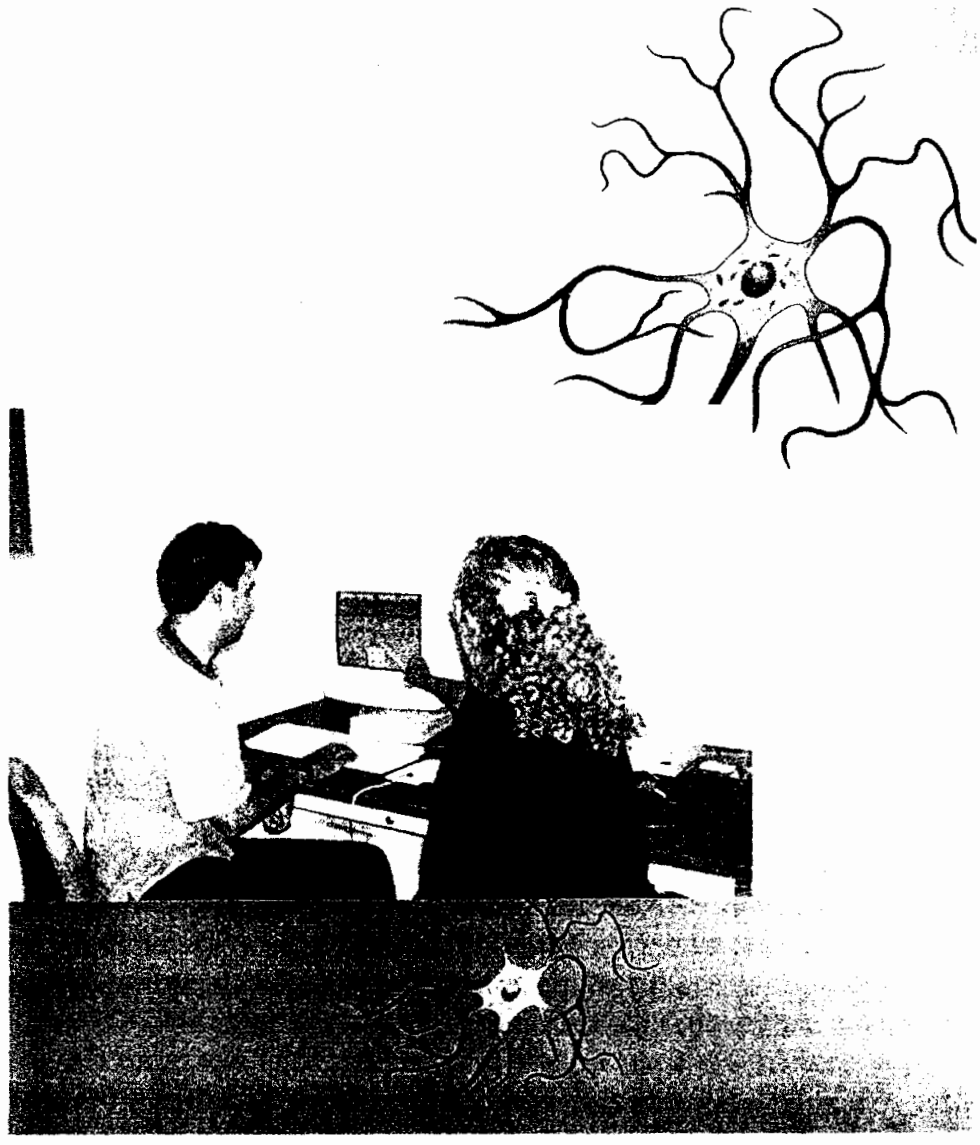

FIG. 3. Recent advances in cognitive remediation include computer-assisted training of neurocognitive functions and abilities

Cognitive Remediation of Social Perception

A study conducted by our group attempted to bridge the gap between the laboratory and the clinic [24] by targeting for remediation an interrelated set of cognitive functions related to social perception that were considered broad enough to have clinical significance. For example, one of the targeted cognitions was accuracy in perceiving the emotions of others, which required learning how to filter relevant from irrelevant stimuli. A second function targeted for remediation was learning how to recall memories of past events that might aid the individual in understanding the cues, context, norms, and rules for appropriate behavior in social situations. Another function included in the training was accuracy in understanding the meaning of facial expres-

sions through a serial analytic process, which we felt might improve patients' ability to rapidly recognize the emotions of others during social interactions.

In our analysis of the impact of training, we evaluated the effects of training on perception and examined whether generalization occurred, as measured by pre-post assessments of attention, memory, and executive functioning. Since positive psychotic symptoms and neurocognition have little or no association with each other, we did not expect to find improvements in psychopathology.

Hospitalized patients who had been stabilized for approximately three months and who were able to demonstrate compliance with instructions for participating in role play tests were invited to participate in the cognitive remediation study. Most were taking atypical antipsychotic medications, had graduated from high school, and showed deficits in self-care and social skills. Forty-two patients were randomly assigned to either 22 sessions of cognitive remediation (20 minutes each, twice weekly for approximately three months) or similar amounts of leisure activities supervised by the same staff who conducted the cognitive remediation. The two groups did not differ on any clinical or demographic variables, including baseline neurocognitive performance, duration of illness, severity of symptoms, or medication dosage in haloperidol equivalents. Patients were maintained on their initial type and dose of medication throughout the duration of the study.

The results showed a beneficial effect of training on measures of perception, but not on attention, memory, or executive functioning. The improvements noted in perception were substantial (increases of 2.5–3.5 standard deviations), with the patients who received training approximating the performance of normal samples at the time of post-testing. The training effects that we discerned may be explained by several possible mechanisms, which at this point must remain speculative: similarity between the training materials and the pre-post materials used to test for emotion perception; use of inductive reasoning and compensatory procedures in the training; or use of homework between sessions and role play exercises in the training.

At this point in the early development of direct training of cognitive functions in schizophrenia, it will be important to identify those neurocognitions which are most closely linked to various types of psychosocial activities and use those cognitions as targets for intervention; [24a] to design and test environmental supports that will enable individuals with schizophrenia to compensate for deficits that are not malleable; to determine if training social and independent living skills at the molar level (e.g., as in the UCLA modules for skills training) will translate into improvements in neurocognition at the molecular level; and to develop new and more powerful methods of precision teaching that will have greater efficacy and generalized impact on neurocognition as well as on broader social functioning. Two examples of the last-named strategy are exemplified by the use of two innovative approaches to teaching now being studied at our UCLA Center for Research on Treatment and Rehabilitation of Psychosis: errorless learning methods, and shaping of sustained attention for rehabilitation readiness.

Errorless Learning of Neurocognitive Functions and Work Skills

Building on previous work that documented the relatively normal capacity of individuals with schizophrenia in procedural learning and memory, errorless learning procedures were adapted for teaching patients to perform the Wisconsin Card-Sorting

Task, a test of dorsolateral prefrontal lobe functioning. The procedure required a task analysis of the card-sorting test, followed by hierarchical arrangement of its constituent components according to level of complexity. The training procedure enabled individuals to succeed at low levels of task complexity and to use these successful learning experiences as building blocks for sequential and incremental completion of more complex tasks. Training consisted of guided instruction, modeling (which incorporates procedural learning principles), and reinforcement to minimize the commission of errors. Once the trainee demonstrated initial mastery of a given level of task complexity, the degree of trainer involvement was gradually faded out. The results showed effective and durable performance of the card-sorting task with improvements bringing the trainees to the level of normal controls [25].

The errorless learning paradigm has been applied to teaching individuals with schizophrenia to perform well on entry-level job tasks in a simulated work environment, with the aim of facilitating employability and sustained employment in the competitive job market. Patients were randomly assigned to either errorless learning or standard, trial-and-error learning conditions. Training was conducted in small groups during the course of a single session lasting approximately 45 minutes for each of two tasks—sorting index cards using various rules and assembling a toilet tank flush mechanism. These tasks had previously been validated by employers and vocational rehabilitation counselors as representative of entry-level jobs available in the community [26]. The results from the first 30 subjects (out of a total of 100) support the effectiveness of errorless learning for these job tasks. Performance was very high for the subjects trained using errorless learning, with accuracy of more than 98% for each task. Three month follow-ups revealed no appreciable drop in performance by the subjects who were exposed to errorless learning. Errorless learning appeared to have compensated for the subjects' neurocognitive deficits, since measures of neurocognition showed a stronger relationship to performance for subjects given standard training than for those involved in errorless learning.

Shaping Sustained Attention for Conversation Skills

Because individuals who are relatively unresponsive to even the new atypical antipsychotic drugs are often thought-disordered, highly distractible, and less able to benefit from verbally mediated treatments, we have initiated a multisite demonstration study at our UCLA Research Center to use behavioral shaping procedures to extend the sustained attention of such individuals as they participate in a conversation skills training module. Investigators at sites in New York, Missouri, Nebraska, and California are utilizing a common protocol aimed at increasing the attentional capacity of thought-disordered and disorganized schizophrenic patients by using "shaping tokens." As each patient meets or exceeds a previously determined threshold of eye contact and appropriate responsiveness to the instructions of the conversation skills trainer, he or she receives both a shaping token and positive social reinforcement (e.g., praise). A cotherapist is responsible for monitoring the attention span of each participant in the group and for dispensing the shaping tokens on a contingent basis, initially every few minutes. Later, after sustained attention has been demonstrated by the patient for increasingly longer periods, the shaping tokens and associated praise are given more sparsely. At the end of the sessions, the patients can trade in their accumulated tokens for special treats and privileges.

The findings thus far have been very encouraging, with the vast majority of these very regressed and institutionalized patients making significant progress in their attention spans—from less than a minute at baseline to an average of 45 minutes after three months [27]. These individuals were then able to participate constructively in a Basic Conversation Skills module [28], without intensive supervision. Similar favorable results from modeling and shaping procedures have been seen in studies of thought disorder, on-task behavior, completion of academic assignments in a remedial education classroom, and appropriate verbal behavior [29–31]. Thus, it appears that shaping procedures, combined with modeling and social reinforcement, can enhance the participation level of patients who had previously been written off as treatment failures unable to benefit from psychosocial rehabilitation. Whether the improvements are specifically a result of improvements in the target neurocognitive and linguistic behaviors or whether the therapeutic effects are mediated through more general enhancement of the motivation and alertness of patients, the point remains that previously refractory patients can now be brought into the mainstream of comprehensive and standard treatment and rehabilitation services.

Compensatory Strategies for Overcoming Cognitive Impairments

In compensatory strategies that seek to overcome cognitive deficits, more indirect interventions are employed to enable individuals with schizophrenia to cope with their cognitive impairments or to function despite being hampered by neurocognitive deficits. These include social skills training, cognitive adaptive training, social learning programs (token economy), and supported employment.

Social Skills Training

In social skills training, the basic learning principles that are helpful for human beings to acquire knowledge and skills are organized and structured so that even patients with cognitive deficits can have their deficits overridden or compensated for, with the result that learning can occur [32]. For example, if a patient has severe memory problems and has difficulty sustaining attention to questions or videotaped models, the trainer can repeat the sequence once or twice or more, or have other group members with more efficient memories to serve as models until the individual responds correctly. Then, drills can be offered that give an individual with problems in memory retention an opportunity to practice what has been presented so that it is overlearned. There is evidence that social skills training can compensate for patients' learning disabilities, enabling individuals with a wide variety of psychiatric symptoms to acquire social and independent living skills [33]. Although evidence has accumulated that there are significant predictive relationships between verbal learning, verbal memory, and executive functions with laboratory analogues of skills training, these analogues are simple questions and answers and do not realistically mirror the actual clinical use of skills training procedures [23].

One of the reasons that social skills training is effective with schizophrenic persons comes from the fact that learning social skills, in large measure, depends upon procedural or implicit learning. This type of learning and memory is unimpaired in schizophrenia and is not significantly different than that in normal persons [34]. Procedural learning does not require conscious awareness or the processing of complex verbal or abstract information; rather, it takes place automatically or effortlessly outside the person's awareness, much like when people learn a new dance step or how to ride a bicycle [35]. Implicit learning is similar to imitative learning which utilizes neural circuitry in the pre-motor cortex and Broca's area. These brain regions have not been shown to be reduced in size or activity in schizophrenia, accounting for the efficacy of social skills training in schizophrenia. Thus, the cognitive skills practiced and utilized in social skills training are based on neural circuits that have been "spared" from impairment in schizophrenia.

The modules in the UCLA Social and Independent Living Skills Program capitalize on the intact neural systems underlying implicit and procedural learning. These modules include Medication Management, Symptom Management, Basic Conversation Skills, Friendship and Intimacy, Recreation for Leisure, Community Re-Entry, and Substance Abuse Management [28]. Each module comprises seven recurring learning activities which are used to teach the skills in each topical area and which are designed to overcome or compensate for cognitive impairments. The learning activities that enable the modules to exert prepotency over all but the most severe cognitive and symptomatic impairments include motivational interviewing and induction of therapeutic but realistic expectations; video models with Socratic questions and answers; role play exercises with coaching and video feedback of "self-as-model"; problem-solving exercises related to gathering resources for using the skills and overcoming unexpectedly encountered obstacles en route to using the skills; and in vivo and homework exercises to promote generalization. The ability of the modules and other modes of skills training to compensate for cognitive impairments is reflected by the international dissemination of the modules [36], their translation into 16 different languages [37], and their demonstrated effectiveness in a range of naturalistic settings. Although further systematic study is required, preliminary data from a controlled study of social skills training at our Research Center at UCLA, Keio University, and Fukushima Medical College [see chapter by Mizuno and Kashima, this volume; S. Niwa, unpublished paper] revealed that improvements occurred in selected neurocognitive functions as a result of the skills training. This suggests that "top-down" cognitive remediation may be a possibility which is congruent with basic neuroscience studies of the plasticity of the brain.

Cognitive Adaptive Training

Cognitive Adaptive Training (CAT) consists of a battery of neurocognitive and behavioral assessments paired with manual-driven interventions that are designed to compensate for the specific deficits in executive functions, attention, and memory that were detected during the assessment phase. CAT interventions include such environmental supports as posted signs, checklists, signaling devices (e.g., beepers), specially labeled containers for organizing belongings, and palm-held computers or other scheduling tools. These compensatory methods are established in the patients' homes

and maintained and updated during weekly home visits by a therapist. Empirical evaluations of CAT found that the interventions improved adaptive functioning and quality of life, as well as reducing relapse rates by approximately 45% in comparison to control conditions [38].

A case vignette illustrates how CAT can be helpful to patients who are pursuing vocational goals. A 41-year-old university graduate, who had formerly worked in jobs that required business acumen, had been unemployed since the onset of his schizophrenia 12 years previously. His neurocognitive testing revealed unimpaired intelligence but significant impairments in organization, planning, sustained attention, and working memory. His assets included normal or above-normal verbal fluency, language abilities, psychomotor speed, visual-motor sequencing, concept formation, and cognitive flexibility (e.g., normal performance on the Wisconsin Card Sorting Test). With the help of a palm-held computer, which he was taught to use, and daily to weekly telephone reminders, prompts, and reinforcement, he was able to obtain and sustain a job as a clerk in an upscale bookstore, which he enjoyed because it brought him into contact with fellow college graduates and enabled him to use his language and vocabulary skills. In Fig. 4 is shown a spectrum of electronic communication devices that can promote continuity and coordination of mental health services, adherence to treatment, and application of social and independent living skills into everyday life.

Other Compensatory Programs

Two other compensatory programs that can enable patients with schizophrenia to overcome or accommodate to their cognitive deficits and symptoms while achieving their personal goals with higher levels of psychosocial functioning are supported employment and social learning programs (token economy). Supported employment is characterized by a "place, then train" ideology of rehabilitation, which has been documented to enable individuals with severe and persisting mental illness to obtain ordinary jobs in the competitive marketplace much more frequently than the old-fashioned, transitional, or sheltered employment programs that featured a "train, then place" philosophy [39].

Jobs are found for patients, or patients find their own, with the help of the vocational specialist, who continues to provide follow-along emotional and professional support to the individual indefinitely while the individual continues to work. If a job is lost, the debacle is viewed as a learning experience, and the vocational specialist and patient persevere in finding another job. Other attributes of supported employment include integrating the activities of the vocational specialist or job coach within the services of a comprehensive psychiatric treatment team; frequent consultation between the employment specialist and the other members of the treatment team, especially with the psychiatrist, who must often make judgments regarding adjustments in the patient's type and dose of medication and provide crisis intervention; a positive and informed expression of desire to work by the patient prior to beginning a job search; and matching the person with the job, using the person's preferences, interests, assets, and deficits to optimize compatibility.

When a structured, manual-driven approach to supported employment is used with high fidelity by staff members, evidence to date suggests that upwards of 40% of persons with schizophrenia can obtain competitive employment. Because of fears of

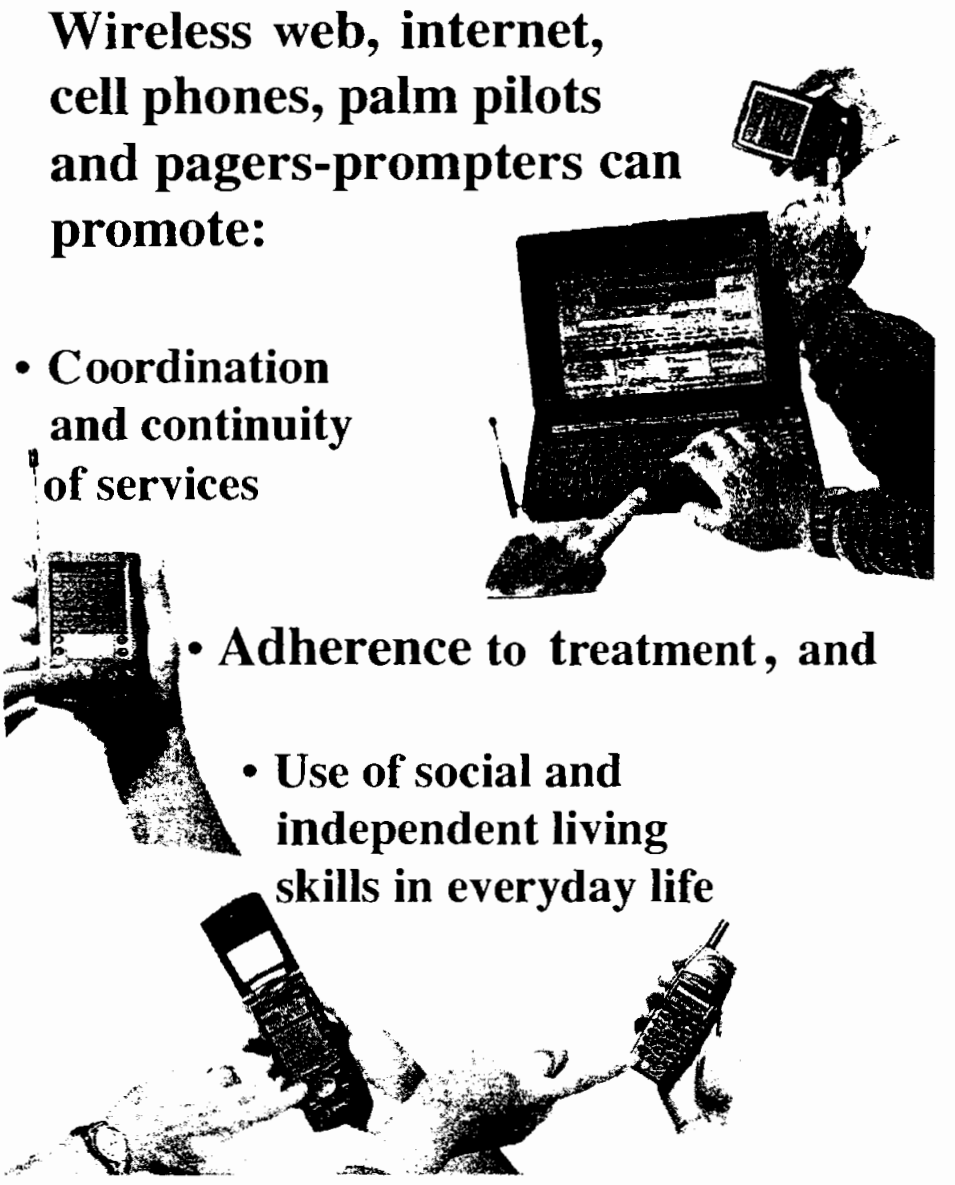

FIG. 4. Electronic communication devices useful in mental health services

jeopardizing their Social Security benefits, most of these individuals choose part-time jobs not exceeding 10–20 hours per week [40]. It is likely that the supportive role of the employment specialist and the "wrap-around" and well-coordinated services of the psychiatric team permit the schizophrenic patient to compensate for cognitive deficits in obtaining and maintaining work. Unfortunately, follow-up studies have found that fewer than 50% of those participating in supported employment who do get to work are still working at that job six months later. Inadequate job tenure may derive from deficits in work or social skills, neurocognitive impairments, loss of interest or motivation, or exacerbations of psychosis.

The Workplace Fundamentals Module was designed to improve the job tenure and satisfaction of persons with mental disabilities. As shown in Table 1, this module consists of four major skill areas, the first of which aims to establish motivation for working and the subsequent ones to improve job performance. An evaluation of this

TABLE 1. Skill areas of the Workplace Fundamentals Module

Why work? Identifying the benefits and demands of working
Getting comfortable on the job: What is this job and this workplace?
Anticipating stressors on the job: What problems may occur?
Coping with stressors on the job: How am I going to solve this problem?

The Workplace Fundamentals Module has four major skill areas which focus on establishing motivation for the individual's decision to work, followed by preparing participants to anticipate and cope with stressors at the workplace. The primary coping technique taught in the Workplace Fundamentals Module is social problem-solving

module documented a doubling of the knowledge and skills among patients participating in a group, accompanied by almost 20% more hours in competitive work during the 3 months of training [40a].

Round-the-clock social learning or token economy programs have been among the best-replicated and validated psychosocial interventions for schizophrenia [41]. These programs create an ongoing "learning environment" for patients with schizophrenia where the involvement of participants in educational programs aimed at improving self-care, personal hygiene, social relations, academic skills, and adaptive behavior is supported by a motivational climate wherein tangible, material, and social reinforcers are delivered contingent upon appropriate behavior by the patients [42–44].

One study carried out at the longest-lived token economy, the Camarillo-UCLA Clinical Research Unit of the UCLA Center for Research on Treatment and Rehabilitation of Psychosis, showed the prepotent effectiveness of the social learning procedures in overcoming neurocognitive deficits in patients with treatment-refractory forms of schizophrenia. Patients were randomly assigned to receive risperidone or haloperidol in a double-blind evaluation of the effects of these two antipsychotic drugs on a spectrum of neurocognitive functions. Whereas risperidone had significantly greater effects on a wide range of neurocognitions (including verbal fluency, verbal learning, working memory, and emotion perception), these advantages were not translated into better ward functioning for the risperidone-treated patients compared to those who received haloperidol. Presumably because the token economy was such a powerful motivational force, patients under both drug conditions showed similar improvement in activities of daily living and aggressive and destructive behavior. Similar prepotency of psychosocial intervention was reported for supported employment programs that observed the differential effects of atypical antipsychotics on cognition.

Conclusions

We should not heed the skeptical, cynical, and disbelieving views of colleagues who would turn away from the challenge of developing techniques for directly modifying neurocognition in schizophrenia. Challenges abound in science and medicine that deter the faint of heart. Advances cannot and should not be blocked by dissenters and

Philistines who publish their nay-saying in the guise of sound, critical expertise. Practical applications in science and medicine have always had to await the development of scientific breakthroughs and new technology to bring about further advances in practice.

Our knowledge of the brain, its structure and functions, is in its infancy. One only need to ponder the extraordinary complexity inherent in the brain to appreciate the discoveries that are still beyond the horizon; the brain has 100 billion neurons, each of which has 200,000 synapses. Each synapse probably has a minimum of 200 different neurotransmitters affecting its excitation and inhibition, but we only know something about 25 of these chemical messengers at present. Each neurotransmitter very likely articulates with 50 different receptors, and each connection of neurotransmitter with receptor opens a flood of secondary and tertiary changes in the cell membrane, transporter systems, protein and enzymatic synthesis or inhibition and further chemical changes that we may not fully appreciate at present. With the plasticity of the brain reflected by well over 200 billion neural circuits, why can't we be optimistic of gaining greater mastery over cognitive impairments in schizophrenia in the future?

Without the scientific discoveries of Michael Faraday, Alessandro Volta, and Humphrey Davy, the development of the electric light bulb and the movie camera by Thomas Edison would not have been possible. Without the basic anatomical work of Thomas Harvey and the discovery of ether and nitrous oxide as anesthetics, modern surgery would not have been possible. Without the basic theoretical and experimental work of von Neumann, Aiken, Mauchly, and Eckart, the omnipresent computer would not be available to us. Without the pioneering research of Pavlov and Skinner, behavior therapy would not be in widespread use; and without the serendipitous discovery of chlorpromazine by the French physicians Henri Laborit, Jean Delay, and Pierre Deniker 50 years ago, we would still be treating persons with schizophrenia by anachronistic custodial and constraining methods in locked wards of large asylums.

Plasticity of the Brain: Procedural or Implicit Learning and Memory

In addition to the infusion of new training techniques that can be drawn from the field of applied behavior analysis (e.g., errorless learning, antecedent control) and precision teaching (e.g., academic learning time, automatic learning, flexible learning environments), we can look forward to new opportunities for cognitive remediation from the basic knowledge that is emerging from the view of the brain as possessing plasticity and redundancy in its own capacities for managing information and for compensating for damaged neural circuits, cells, and regions.

There is increasing evidence that persons with schizophrenia have well-preserved procedural (implicit) capacities for learning and memory that lie outside of conscious awareness and are most likely dependent upon the functioning of the sensory (parietal) neocortex [45], but not the medial temporal structures that may be impaired in schizophrenia. Acquisition of new information via procedural mechanisms appears to activate the parietal, motor, and prefrontal areas, whereas consolidation and memory appear to be mediated by the cerebellar, parietal, and premotor areas, which are not viewed as impaired in schizophrenia [46]. This would suggest that training techniques that utilize implicit procedures—such as errorless learning and probabilistic classifi-

cation learning—may permit individuals with schizophrenia to improve their neurocognition, through training of compensatory systems that can replace or substitute for impairments in attention, working memory, emotion perception, or executive functions. Developments in educational technology and cognitive neuroscience may soon magnify the therapeutic impact of clinical neurocognition.

New developments in brain plasticity underscore an optimistic view of the future for cognitive remediation of schizophrenia. Reprogramming the brain has been achieved with constraint-induced movement therapy for stroke survivors with hemiplegia or hemiparesis. By involving patients full time in a regimen of planned immobilization of their nonaffected limb, patients were required to feed themselves and carry out a spectrum of exercises and self-care functions with their disabled limb. After a month, not only did the post-stroke patients regain approximately 65% of the use of their disabled limbs, but neuroimaging found that the area of the brain impaired by the stroke had doubled in size. If this type of reprogramming is feasible in the brains of individuals with cerebrovascular accidents, there is good reason to design similar treatment strategies for persons with schizophrenia; for example, in developing constraint-induced therapy for working memory and verbal learning.

Two other studies of the surprising capacity of the brain for functional abilities suggests that procedural or implicit learning and memory may be mobilized for more utilitarian purposes than heretofore in the treatment of schizophrenia. In one of these studies, post-stroke individuals who were unable to articulate or give rationales for observed interpersonal interaction showed an uncanny ability to discern dissimulation when observing videotapes of notorious public figures (e.g., President Nixon lying about his involvement in the Watergate fiasco or President Clinton lying about his involvement with Monica Lewinsky). That implicit learning and memory may also be utilized in remediating emotion perception is suggested by studies that have shown how quickly and unconsciously people can make accurate and reliable "snap" judgments of applicants who are going through job interviews or teachers who are instructing their students in class. Rapid judgments based on viewing 15 seconds of videotape excerpts, where the raters were not able to articulate the reasons for their judgments, were astoundingly sound and consistent with ratings made from entire job interviews or experiences of students at the end of an entire semester with their teachers. The advent of virtual reality methods, based on computer technology, has already led to therapeutic applications for anxiety disorders and behavioral medicine in pain and circulatory management. Given the key role of emotion perception in mediating social and vocational functioning in schizophrenia, virtual reality techniques may have therapeutic potential in improving schizophrenics' perception of emotion through brain mechanisms of implicit learning and memory [47].

Brain Plasticity: Well-Preserved Brain Regions and Neuronal Growth

As noted above, an area of the brain that is well preserved in schizophrenia and that may account for the efficacy of social skills training is the premotor cortex, which is activated during fMRI experiments when subjects are asked to imitate hand gestures demonstrated by a model. In other words, the same regions of the brain that send commands to our muscles when we act also seem able to recognize the same action

when performed by others. Providing a bridge from thought and action to the crucial role of imitation in our social behavior, both the premotor cortex and Broca's language area may reveal the neuroanatomy that mediates communication and social skills.

The plasticity of the brain invokes the prospects for new and more effective methods of cognitive remediation. Several recent findings utilizing neuroimaging provide more detailed insights into the scope of neuroplasticity. In a landmark study that demonstrated the normalization of abnormalities in the brain of patients with severe psychopathology, both pharmacotherapy and behavior therapy brought about normal glucose metabolism in the right caudate nucleus among patients with obsessive-compulsive disorder. The normalization of metabolism, viewed by PET scans, was seen only in those patients who responded therapeutically to the two types of intervention [48]. As psychiatric treatment and rehabilitation increases the number of individuals with schizophrenia who recover symptomatically and functionally from their disorders, pre- vs. postneuroimaging studies of temporo-frontal-thalamic regions of the brain (which have been found to be abnormal in size and function in schizophrenia) will become research priorities. Such studies will push back the frontier of the clinical significance of neuroplasticity in schizophrenia.

A plethora of experimental findings have documented the influence of experience, environment, and behavior on brain structure. Just as stimulus deprivation leads to anatomic as well as functional loss, enriched stimulation from the environment produces increased density of neurons and processes in the brain. Engaging subjects in learning tasks leads to synaptogenesis. Remapping of the brain has been found with as little as 15 min of practice on a given task [49], and educational interventions have been shown to increase cognitive capacity [50].

Several processes affecting brain structure, such as myelination, arborization of dendrites and axons, synaptogenesis, formation of new neurotransmitter receptor sites, and neuronal cell structure persist throughout the life span, especially during childhood and adolescence [51]. The corpus collosum increases in size from age 3 to 9 years. Because this structure integrates the activity of the left and right cerebral hemispheres, the increased size may reflect increased ability to perform higher-level cognitive abilities. Longitudinal studies of children and adolescents have charted the growth spurts in the brain between the ages of 3 and 15 years that coincide with important leaps in learning ability. During this age interval, rapid growth is seen in the frontal circuits responsible for focusing attention, maintaining alertness, planning actions, organizing new skills, and learning new behaviors. During adolescence, higher growth rates are seen in the parietal lobe and premotor cortex, areas associated with language skills, mathematical thinking, and understanding of spatial relationships.

Other investigators have found brain growth through age 21, primarily related to additional neuronal columns and progenitor neural cells in the ventricles of older adults. The concept of "reserve brain capacity" suggests that intellectual experience throughout life can have a salutary effect on neural structure and function, even engendering resilience of the brain and protecting the person from the ravages of brain injury or disease. For example, at the older end of the age spectrum, nuns whose language was grammatically and conceptually more complex earlier in life were significantly less likely to develop Alzheimer's disease than nuns with more mundane

language capacities. As neuropharmacologists make further progress in the isolation and development of nerve growth factors, we may look forward to a day when the so-called rate-limiting psychosocial adaptations linked to impairments in neurocognition of persons with schizophrenia will only remain as a bad memory.

Even adequate amounts of sleep can have salubrious effects on the brain, and sleep is certainly a modifiable element in the everyday life of a person with schizophrenia. Researchers have shown that when people learn a new skill, their performance does not improve until after they have had more than six and preferably eight hours of sleep. Even new factual information may be encoded more reliably when sufficient sleep has been had. During both deep, slow-wave sleep and dreaming or rapid eye movement (REM) sleep cycles, physical and chemical reactions occur that apparently strengthens memory traces.

The evidence from experimental psychology and neuroscience is that the human brain is not fully formed at birth; rather, the growth of synapses, neurotransmitter receptors, and even neurons is strongly influenced by experience. The frontal lobes, where planning, initiative, learning, emotion, and reasoning are integrated, do not fully develop until adolescence and young adulthood. Every behavioral action, emotional response, personality trait, and neurocognitive function involves both nature and nurture. The timeless and tiresome questions "Is it nature or nurture?" or "Is cognitive remediation possible?" should be replaced by "What forms of pharmacological and behavioral interventions facilitate the most desirable and functional qualities in human nature, schizophrenia, and neurocognition?" As the interrelationships of social and neurochemical influences become more widely recognized and studied, the identification, design, and empirical validation of new interventions for cognitive remediation will mature into an organized scientific effort that will push back the frontier of our ignorance of interactions among brain, behavior, and environment.

Future Directions

Cognitive remediation, like charity, begins at home. This means that our own cognitions and attitudes must change in many ways if we are to effectively offer cognitive remediation to our patients with schizophrenia. What are the attitudes that mental health professionals must adopt for themselves?

- A realistic optimism, based on recent outcome studies, that symptomatic remission and functional recovery is possible in upwards of 50% of persons with schizophrenia. We must surrender outdated stereotypes and beliefs about the deteriorating course of schizophrenia.
- Willingness to provide comprehensive (including cognitive remediation), continuous, coordinated, and consumer-oriented treatment and rehabilitation that involves the patient and family in the treatment enterprise. We must discard former styles of treatment that were patronizing and paternalistic.
- Providing treatment and rehabilitation in the natural environment, using mobile outreach and personal telecommunication technology that has the potential for stretching our limited time and personnel to prompt, reinforce, and monitor progress in our clientele. This approach, grounded in the lives of our patients and

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their own personal goals, will also enhance the generalization of skills and cognitive remediation to patients' everyday life.
- Encouraging our patients to manage their own illnesses, by taking more responsibility for learning how to reliably use their medications, identify their warning signs of relapse, and implement relapse prevention plans. The corollary of patients' becoming partners with us in treatment, rather than passive receptacles for our services, is our responsibility to design and validate evidence-based methods for teaching illness- or disease-management skills to patients.
- Helping to erase stigma by discussing openly with patients, relatives, and the general public the names, nature, and treatment of the disorders which we treat. We must avoid euphemisms and stop closeting our own mental disorders. If we cannot speak openly about our own recovery from mood, anxiety, and other disorders, how can we expect the public and media to speak openly about schizophrenia? If we do not become part of the solution to stigma by taking every opportunity to speak directly and candidly about serious mental disorders, then we are part of the problem.

The future is bright with hope for consumers, carers, and clinicians. The twenty-first century will see the control of schizophrenia as a scourge of mankind around the world, just as infectious diseases were controlled or eliminated in the twentieth century.

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