Should Schizophrenia Be Treated as a Neurocognitive Disorder?

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Abstract

The search is on for meaningful psychopharmacological and cognitive/behavioral interventions for neurocognitive deficits in schizophrenia. Findings in this area are emerging rapidly, and in the absence of integrating frameworks, they are destined to emerge chaotically. Clear guidelines for testing neurocognitive interventions and interpreting results are critical at this early stage. In this article, we present three models of increasing complexity that attempt to elucidate the role of neurocognitive deficits in schizophrenia in relation to treatment and outcome. Through discussion of the models, we will consider methodological issues and interpretive challenges facing this line of investigation, including direct versus indirect neurocognitive effects of antipsychotic medications, selection of particular neurocognitive constructs for intervention, the importance of construct validity in interpreting cognitive/behavioral studies, and the expected durability of treatment effects. With a growing confidence that some neurocognitive deficits in schizophrenia can be modified, questions that seemed irrelevant only a few years ago are now fundamental. The field will need to reconsider what constitutes a successful intervention, what the relevant outcomes are, and how to define treatment efficacy.

Keywords: Neurocognition, cognition, antipsychotic medication, cognitive remediation, functional outcome.


Although the presentation of schizophrenia has changed minimally over time, our perceptions of the disorder have changed dramatically, particularly over the past two decades. During the 1980s, schizophrenia went from being viewed as mainly a progressively deteriorating disorder to one of neurodevelopmental origin, partly because it was discovered that very early events can influence risk for the disorder. Also during the 1980s, the predominant view of the phenomenology of schizophrenia broadened beyond a narrow focus on psychotic symptoms to include negative symptoms as well. In the 1990s, another change in our perception of schizophrenia occurred, which may be even more fundamental. With this change, we have expanded the phenomenology of schizophrenia even further, beyond symptoms altogether, to include a strong emphasis on neurocognitive aspects of schizophrenia.

The study of the neurocognition of schizophrenia is not new; key deficits in attention, perception, and cognition were noted by very early descriptive psychopathologists (Bleuler 1950; Kraepelin 1913/1971), and experimental psychopathologists have worked to identify the core abnormalities for several decades (Shakow 1962; Chapman and Chapman 1973; Goldstein 1978; Nuechterlein and Dawson 1984; Braff 1993). But neurocognitive studies of schizophrenia are now viewed as having direct implications for treatment. Interest in the topic has extended far beyond a rather small and dedicated group of experimentalists. Practitioners now believe that schizophrenia can legitimately be viewed, in essence, as a disorder of neurocognition.

Articles in this theme issue represent the state of the art in pharmacological and cognitive/behavioral treatments for neurocognitive deficits in schizophrenia. Findings in this area are emerging rapidly and in the absence of integrating frameworks are destined to emerge chaotically. In this article, we present three models of increasing complexity that are designed to serve an organizing function. Through discussion of the models, we will address methodological challenges inherent in research on neurocognitive interventions, drawing from the articles in this theme issue to illustrate points. Let's start with the simplest model.
Simple Model

Figure 1 depicts a simple model based entirely on three conclusions that can be drawn from the literature. First, conventional neuroleptics are generally effective for psychotic symptoms, but their effects on neurocognition are relatively weak (Cassens et al. 1990; Strauss 1993). Conventional neuroleptics sometimes have short-term detrimental effects on tests of psychomotor speed, and some studies have shown longer-term benefits for vigilance and early visual processing. However, the modal finding across studies and neurocognitive constructs is that of no significant effect.

Second, the cross-sectional relationships between neurocognition and psychotic symptoms are usually minimal, particularly for hallucinations and delusions. The relationships are weak for most neurocognitive constructs, even when they are statistically significant (Comblatt et al. 1985; Green and Walker 1985; Nuechterlein et al. 1986; Green et al. 1992; Strauss 1993). In cross-sectional studies, it is unusual to find relationships between psychotic symptoms and neurocognitive measures in which more than 10 percent of the variance can be explained (Goldberg et al. 1993). Nevertheless, it is possible that some very specific neurocognitive processes underlie particular positive symptoms. For example, several rather comprehensive theoretical models have proposed testable links between particular types of psychotic symptoms and neurocognitive deficits (Frith and Done 1988; Hemsley 1994).

In addition, some studies have linked formal thought disorder (sometimes considered to be on a disorganized symptom dimension instead of a positive symptom dimension) to performance on a highly specific laboratory measure of neurocognition and psychotic symptoms are usually minimal, whereas the relationships between psychotic symptoms and functional outcome are weak or questionable. In a review of the literature (Green 1996), mostly from 1990 to 1995, certain neurocognitive constructs such as verbal memory and vigilance emerged as reliable correlates and predictors of several outcome areas in chronic schizophrenia, including community functioning, social problem solving, and psychosocial skill acquisition. Within these same studies, the relationships between psychotic symptoms and functional outcome were much weaker than those for neurocognitive variables. Data from Bellack et al. (1999, this issue), as well as several recent studies published subsequent to this review, lend support for these conclusions (Dickerson et al. 1996; Brekke et al. 1997; Harvey et al. 1997; Velligan et al. 1997).

A problematic mismatch is immediately apparent in the simple model. Conventional neuroleptics have an impact on symptoms but, in general, not on most areas of neurocognition. However, functional outcome appears to be more closely related to neurocognitive abilities than to symptoms. When viewed within this model, common treatment experiences that previously seemed paradoxical no longer are. A treatment team should not be puzzled when it successfully eliminates psychotic symptoms of a patient only to find that the patient is unable to resume social functioning. Likewise, parents should not be surprised to discover that their son or daughter with schizophrenia is able to return to work despite rather prominent auditory hallucinations. These situations would be expected when viewed within the simple model in figure 1.

Figure 1. Pathways from conventional antipsychotic treatment to functional outcome

![Diagram](https://academic.oup.com/schizophreniabulletin/article-abstract/25/2/309/1919077)

Note—This simple model represents a possible mismatch: the aspect of illness most influenced by conventional antipsychotic medications (psychotic symptoms) is not the aspect most associated with functional outcome.

Which Neurocognitive Deficits to Target. If neurocognitive deficits are more closely related to functional outcome, then should neurocognitive deficits themselves become a target of treatment? Improvement in neurocognition suggests but does not logically guarantee improved outcome, because we do not yet understand the causal pathways. Most of the articles in this theme issue consider...
the prerequisite question of whether it is possible to alter neurocognition in schizophrenia, and the results are generally encouraging. Assuming we can improve neurocognitive deficits, we are faced with a difficult decision: With such a wide array of deficits to choose from, which ones do we select for intervention efforts? The need for selection is particularly pronounced for cognitive/behavioral interventions that focus on one neurocognitive deficit (and maybe one cognitive construct) at a time. However, pharmacological intervention studies are not immune to this problem, because it is highly likely that certain agents will influence some neurocognitive constructs more than others (Meltzer and McGurk 1999, this issue). One way to approach this question of construct selection is first to determine which deficits are associated with outcome areas of interest. For example, if the goal is to improve skill acquisition, constructs that have reliable associations with this outcome area, such as verbal memory and vigilance, may be excellent candidates for interventions.

An alternative approach would be to target deficits for which the neural substrates are known. This approach might be particularly attractive for pharmacological intervention studies, especially to the degree that certain neurocognitive deficits may be linked to specific neurotransmitter systems in particular brain regions (Robbins and Everitt 1995; Keefe et al. 1999). Working memory, for example, has substantial current appeal as a target for intervention, partially because of our understanding of its neural circuitry and neurotransmitter mediation (Fuster 1989; Goldman-Rakic 1991).

More Complex Model

While the simple model in figure 1 has the advantage of parsimony, it is woefully incomplete. A more complex model, depicted in figure 2, has three additional components: new antipsychotic agents, anticholinergic agents, and negative symptoms. Three types of arrows have been added to convey the presumed strengths of the associations. While not based on a formal path analysis, the model is intentionally presented in the style of a path diagram. The neurocognition component is placed in an oval for emphasis, not to indicate that it is a separate type of variable.

Whereas the impact of conventional antipsychotic medications on neurocognition has been unimpressive, early indications are that the story for newer antipsychotic medications is quite different.
medications is more encouraging (Hagger et al. 1993; Green et al. 1997; Jeste et al. 1998). Because this field of investigation is still young, the arrow in the model from new antipsychotic medications to neurocognition indicates a potential, instead of a known, effect. Three articles in this issue consider the role of new antipsychotic agents for treatment of neurocognitive deficits (Keefe et al. 1999; Kern et al. 1999, this issue; Meltzer and McGurk 1999, this issue). These articles contribute to an emerging opinion that the new medications are better than the old ones for neurocognition. If this is so, we need to consider whether the beneficial effects of these medications are direct or indirect.

Direct versus Indirect Psychopharmacological Effects. A direct effect would involve an action of a particular medication on a particular neurocognitive construct. An indirect effect would mean that some aspect of treatment other than a direct action of the agent itself is responsible for a change in neurocognition. A possible mechanism for an indirect effect is represented in figure 2. Consider the situation in which a new antipsychotic agent is compared with a conventional one. Conventional antipsychotic medications involve a much greater coadministration of anticholinergic medications (e.g., benztropine mesylate) than do novel medications. Medications with strong anticholinergic properties are known to have a negative effect on certain aspects of neurocognition, particularly memory (Spohn and Strauss 1989). Thus, it is unclear whether a differential treatment effect is the result of something good (from the new medication) or the absence of something bad (from the anticholinergic agent).

Although anticholinergic agents have a reputation for disrupting neurocognition (Spohn and Strauss 1989), we
know surprisingly little about the degree and scope of the detrimental effect. Data indicate a negative effect on aspects of secondary verbal memory that may rely on rehearsal strategies. In contrast, other aspects of memory, such as immediate or working memory, are less affected (Drachman and Leavitt 1974; Sweeney et al. 1991), and the effects on other neurocognitive abilities, such as perception, are relatively unknown. Hence, we do not know if anticholinergic agents are the neurocognitive culprits we often believe them to be. Nonetheless, these medications still represent the source of a possible indirect effect.

One way to control for this possibility is demonstrated in the article by Kern et al. (1999, this issue), in which anticholinergic medication was entered as a covariate into the statistical model. This made it possible to demonstrate that the neurocognitive effects of the antipsychotic agent were significant, over and above any effect of the anticholinergic medication. The tentative conclusion is that new antipsychotic medication may actually be good for neurocognition, instead of merely not bad.

How does one address and interpret the role of symptom changes and neurocognition? One variable in the article by Kern et al. (1999, this issue), recall consistency, showed a significant differential response to risperidone compared with haloperidol. This beneficial effect remained significant when anticholinergic medication was entered into the model. However, the effect weakened slightly and became a trend when changes in psychotic and negative symptoms were entered. Do we conclude that the neurocognitive effect of the medication is an indirect effect of changes in clinical state? Not necessarily. It depends on how we view the interrelationships between symptoms and neurocognition. If neurocognitive changes contributed to the symptom changes, statistical adjustment for the presumed “effect” of symptom changes would lead to the entirely incorrect interpretation that the medication’s impact on neurocognition is accounted for by its impact on symptoms. Meehl (1971) describes similar interpretive errors that can arise when effects of a variable X are used as covariates to examine the relationships between Y and X. To disentangle such relationships, careful examination of temporal sequence and of the intervention’s impact on neurocognition in relatively asymptomatic patients will likely be needed.

Alternative Causal Pathways for Negative Symptoms. The addition of a component for negative symptoms, separate from psychotic symptoms, creates new pathways and new challenges. One question is the degree of overlap between neurocognitive deficits and negative symptoms. Relationships tend to be stronger between neurocognitive deficits and negative symptoms (Nuechterlein et al. 1986; Censits et al. 1997) or between neurocognitive deficits and the more narrowly defined deficit syndrome (Buchanan et al. 1997) than they are between neurocognitive deficits and psychotic symptoms. However, since the percent of variance explained is still relatively small (10%–15%), we believe that negative symptoms and neurocognitive deficits can be placed on different pathways.

Also, neurocognitive deficits appear to start earlier than negative symptoms (Cornblatt et al. 1992). We have conservatively used a double-headed arrow between neurocognition and negative symptoms in figure 2 to indicate shared variance without making any assumptions about causality, but it is entirely possible that the critical pathway runs from neurocognitive deficits to negative symptoms. In support of that view, Nuechterlein et al. (1986) used longitudinal data to conclude that vigilance and perceptual span deficits act as vulnerability factors for development of negative symptoms rather than as secondary effects of negative symptoms.

A single-headed arrow indicates a moderate relationship between negative symptoms and functional outcome, but the nature of this relationship is not yet clear. First, the assessment of negative symptoms sometimes overlaps with the assessment of social functioning, so it is not always clear if relationships are due to associations between separate constructs or to redundancy of assessment. Assuming the constructs are moderately associated, the relationships between negative symptoms and functional outcome can have two quite different interpretations. It might be that negative symptoms have a direct, causal impact on functional outcome, an interpretation that is obvious, intuitive, and quite possibly wrong. Instead, the moderate relationship may be explained by (1) the shared variance between negative symptoms and neurocognition and (2) the strong associations between neurocognition and functional outcome. In other words, the causal pathways from negative symptoms to functional outcome may be due to a common neurocognitive intersection. Indeed, two recent studies based on statistical models (Harvey et al. 1997; Velligan et al. 1997) have arrived at exactly this conclusion.

Complex Model

The second model is also incomplete, so we introduce three new components in a third and final model: cognitive/behavioral interventions, adjunctive pharmacology, and social cognition (see figure 3). To distinguish the neurocognitive oval from the box on social cognition, the oval was relabeled as “basic” neurocognition. This model also depicts some of the subcomponents of the complex,
multifactorial domains of neurocognition and functional outcome.

Three articles in this theme issue address cognitive/behavioral interventions for neurocognitive deficits (Bellack et al. 1999, this issue; Spaulding et al. 1999, this issue; Wykes et al. 1999, this issue). One key interpretive challenge for many cognitive/behavioral studies is construct validity.

Construct Validity. To understand construct validity, one needs to distinguish between a construct (or latent variable) and an indicator (Loehlin 1987; Nunnally 1978). In the study of neurocognition, we are inevitably interested in constructs that cannot be directly observed. Instead we measure performance on an indicator that presumably reflects a particular construct. For example, performance on a continuous performance test is an indicator; vigilance is the underlying construct. The neurocognitive function, vigilance, has numerous performance and psychophysiological indicators (Davies and Parasuraman 1982; Nuechterlein 1991).

This distinction between the construct and the indicator creates difficulties in the context of remediation studies. Consider a training method for performance on the continuous performance test: if subjects’ performance on one task improves following training, it is difficult to know if the intervention affected the underlying construct (vigilance) or some aspect of the task unrelated to vigilance (perhaps skill in initiating a button press). One way to test for construct validity is to use multiple indicators of the same construct. When it comes to training schizophrenia patients on a continuous performance task, the results have been mixed (Benedict et al. 1994; Medalia et al. 1998). Training on one task can bring about clear improvement, but the benefits do not always extend to another measure of the same construct. This situation could arise if training improved the underlying construct but the second test was not a good indicator of that construct. However, it is also possible that the training brought about improvement at the level of the indicator, but not at the level of the construct.

Construct validity is somewhat less of a concern for pharmacological studies than it is for cognitive/behavioral interventions that focus training on particular tasks. Certainly, there is still the inherent separation of the construct from the measure, but with pharmacological interventions, there is no training task. If a drug improves performance on a test of verbal working memory in a controlled trial, it is often reasonable to conclude that the drug helped verbal working memory. But without different indicators of verbal working memory, it remains possible that the improvement is due to a pharmacological effect on an isolated component of the verbal working memory task (e.g., oral fluency) rather than on functions that are considered to be more central to the construct.

The complex model includes two other components that represent largely unexplored territory. One is adjunctive pharmacology; the other includes hypothesized mediators between neurocognition and functional outcome.

Adjunctive Psychopharmacology. The use of adjunctive pharmacology for neurocognitive deficits has only recently received serious consideration (Davidson and Keefe 1995). Some of this emerging interest in adjunctive medications undoubtedly stems from recent developments in the pharmacological treatment of cognitive decline in dementia. The medications for dementia act on the cholinergic system, which is related to memory functioning. It is not yet known whether this system is also critical to the pathophysiology of schizophrenia. Perhaps more relevant to schizophrenia is the glutamate system. It has been suggested that hypofunction of the N-methyl-D-aspartate subtype of glutamate receptor may be a key disease mechanism for schizophrenia (Olney and Farber 1995). This receptor is modulated by glycine, which has led to interest in using glycineric agents to treat schizophrenia. Preliminary data on a small sample of patients showed improvement in choice reaction time when d-cycloserine, a partial glycine agonist, was added to conventional antipsychotic medications (Goff et al. 1995). If adjunctive agents are found to improve neurocognition, schizophrenia patients may start receiving one medication for each major domain of illness: symptoms and neurocognitive deficits.

Social Cognition as Mediator. Between basic neurocognition and functional outcome are a cluster of mediating variables labeled as social cognition. In the model, components of social cognition include emotion perception, social schema, insight into illness, and coping/attributitional strategies. Our intention is to distinguish these variables, which have substantial social or emotional components, from basic neurocognition, although the precise boundaries between basic and social cognition are not clear-cut.

One key aspect of social cognition is the ability to perceive emotion in others. Perception of emotion in schizophrenia is associated with basic neurocognition (Schneider et al. 1995; Bryson et al. 1997), suggesting that intact basic neurocognition is necessary for accurate perception of emotion. It is reasonable to expect that a reduced ability to perceive emotion in others would result in misinterpretation and compromised social interactions. Indeed, perception of emotion appears to be closely
related to social competence in schizophrenia inpatients (Mueser et al. 1996; Penn et al. 1996).

In this model, we have also included insight and coping in the “social cognition” box even though they are not generally considered to be prototypic features of social cognition. A subsequent model may place them in a separate box for “attributional” or “metacognitive” constructs. The relationship between insight and neurocognition is not at all clear. Most studies have reported that insight is related to better neurocognitive performance, particularly on measures of executive functioning (Silverstein and Zerwic 1985; Young et al. 1993; Lysaker and Bell 1994). However, other studies have not found such relationships (Cuesta and Peralta 1994; Dickerson et al. 1997). Disparity in these findings may stem from differences in the definition and measurement of insight.

By placing social cognition between basic neurocognition and functional outcome, this model may help to illuminate an issue that has preoccupied investigators: whether deficits in social cognition are general rather than specific (reviewed in Penn et al. 1997). For example, several studies have evaluated whether emotion perception deficits in schizophrenia are specific to emotional stimuli or whether they are part of general perception deficits. While this question remains scientifically interesting, the distinction between a specific emotion perception deficit and a general nonemotion perception deficit is not entirely relevant to the complex model. In this model, basic and social cognition are closely related but not identical components. Basic neurocognition is a prerequisite for social cognition, and social cognition, in turn, is a prerequisite for social functioning.

Overarching Questions

The models described here help to isolate components that serve as intersections between treatment and outcome. Stepping back from the components, several broad questions emerge. The questions are rather basic, which is understandable given their recency. Pondering interpretations and implications of neurocognitive interventions will be pointless until there is some agreement that intervention in this domain works. Now that there is growing confidence that at least some neurocognitive deficits in schizophrenia can be modified, we are forced to confront seemingly simple definitional matters. Only a few years ago these questions seemed irrelevant; now they seem fundamental.

What Constitutes a Successful Intervention? Some neurocognitive deficits in schizophrenia are rather stable over time (Nuechterlein et al. 1992, 1994; Cornblatt et al. 1997), and it would be unreasonable to expect long-standing deficits to improve permanently with a short-lived treatment. So, how long should an effect last for an intervention to be considered successful? The answer seems to depend on whether the intervention is psychopharmacological or cognitive/behavioral. If a medication improves neurocognition while it is administered but not after it is stopped, it is usually considered a success. If a cognitive/behavioral intervention improves neurocognitive performance while the training is administered but not after the intervention is stopped, it is usually considered a failure. As Wykes et al. point out (1999, this issue), this double standard complicates notions of what constitutes successful treatment. Whether an intervention is a success depends on both implicit and explicit goals. The goal of psychopharmacological interventions is to treat; the goal of cognitive/behavioral interventions is to retrain. The complementarity of these two related but separate goals provides a rationale for combining the approaches. To the extent that psychopharmacological treatments are successful, they are likely to open the door for effective retraining.

It is possible that the dichotomy is not absolute between the treating and retraining approaches to neurocognitive deficits in schizophrenia. Behavioral studies make it clear that learned skills can deteriorate over time and that booster sessions are often called for. For psychopharmacological treatments, it is entirely possible that a short-term treatment could deregulate a dysregulated neurochemical system and not require ongoing administration, or at least not at the same dosage. Hence, the effects of retraining are not necessarily durable, and the effects of medications are not necessarily transient.

What Are the Relevant Outcomes? When a reasonable intervention for a neurocognitive deficit is achieved, the question shifts to the selection of a relevant outcome. Specifically, what benefits do we expect to see? Frequently, the goal of clinically based cognitive intervention programs is symptomatic improvement. Although this seems like a reasonable goal, it presents an interpretive challenge. The model in figure 3 shows no direct mechanism for an effect on psychotic symptoms. Instead, neurocognitive interventions might be more beneficial for nonpsychotic symptoms such as blunted affect and hostility. This, in fact, may be the case (Brenner et al. 1990).

However, it is likely that neurocognitive interventions will have their greatest impact outside the domain of symptoms. The rather strong relationships between neurocognitive deficits and functional outcome indicates that we might expect to see an effect here. One notion is that these deficits act as “neurocognitive rate limiting factors”
and restrict the functional adaptation of the patient (Green 1996). Following intervention for neurocognitive deficits, this limitation is eased, allowing for more complete skill acquisition and functioning. If new learning is required to achieve the functional gains, we should expect a time lag between any improvement in neurocognitive functioning and measurable improvement in outcome.

The Delta Question. A key question, which we refer to as the “delta” question, is whether changes in neurocognition translate into changes in functional outcome. Given the associations between neurocognition and functional outcome, it is reasonable to expect that changes in the two domains would be associated. However, most studies have examined whether level of neurocognitive performance is associated with functional outcome, not whether changes in neurocognitive functioning are directly linked to changes in functional outcome.

Some data bearing on this point suggest that changes in the two domains may be linked. For example, Buchanan et al. (1994) found that changes in memory over 1 year were correlated with changes in quality of life in schizophrenia patients. Wykes et al. (1999, this issue) report that change in cognitive flexibility was related to improvement in social functioning in a relatively short treatment trial (8 weeks). Spaulding et al. (1999, this issue) report that improvement in card sorting was associated with improved social competence, and that improvement in verbal memory was associated with increased psychosocial skill acquisition over the course of a 6-month intervention study. These studies provide very preliminary, but encouraging, support for the hypothesis that changes in the neurocognitive domain will result in changes in functional outcome.

It may be even more informative to phrase the delta question in quantitative terms: How much of a change in neurocognition is needed to bring about a meaningful change in an outcome area? In this way, the question can be answered with cost/benefit considerations in mind. Knowing the amount of neurocognitive improvement required to make a clinically meaningful improvement in daily functioning for a given domain would enable us to better evaluate the practical utility of neurocognitive gains that may be possible through psychopharmacological or cognitive/behavioral intervention. Clearly, a key challenge facing this entire area of investigation will be to understand the process through which short-term performance gains can be converted into long-term functional benefits.

How to Define Efficacy. Several articles in this theme issue strongly suggest that the new generation of antipsychotic agents acts on more than one domain of illness. If so, then we are confronted with the problem of how to define efficacy. Traditionally, efficacy has been defined in terms of reduction of psychotic symptoms, but more recently, the reduction of negative symptoms has been added to the definition. However, if the new medications act on multiple domains of illness, then symptom reduction is simply too narrow a definition of efficacy (Green et al. 1997). Even our language betrays us; the very term “antipsychotic” may prove to be too narrow for the new generation of medications.

To the extent that new medications and innovative cognitive/behavioral interventions act in the neurocognitive domain, it may be more accurate to describe an intermediate goal of treatment as impairment reduction. And if psychopharmacological and cognitive/behavioral neurocognitive interventions translate into functional gains for patients, then even impairment reduction may be too narrow. In this case it may be more accurate to describe the eventual goal of treatment as disability reduction. The articles in this theme issue can be viewed as concerted efforts toward these goals of impairment and disability reduction.

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