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Antipsychotic Treatment in Schizophrenia: The Role of Computerized Neuropsychological Assessment

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Abstract: The present study analyzes the role of neurocognitive assessment instruments in the detection of the contribution of antipsychotic treatment to cognitive functioning. Recently, a panel of experts suggested six main domains (working memory; attention/vigilance; verbal/visual learning and memory; reasoning and problem solving; speed of processing) implicated in schizophrenia-related cognitive deficits, which serve as a theoretical base for creation of real-time computerized neurocognitive batteries. The high sensitivity of computerized neuropsychological testing is based on their ability to adopt the reaction time (RT) paradigm for the assessment of brain function in a real-time regime. This testing is highly relevant for the monitoring of the cognitive effects of antipsychotics. Computerized assessment assists in the identification of state- and trait-related cognitive impairments. The optimal real-time computerized neurocognitive battery should composite balance between broad and narrow coverage of cognitive domains relevant to the beneficial effects of antipsychotics and will enable better planning of treatment and rehabilitation programs.

Introduction

Schizophrenia affects cognition, emotion and behavior. Neuropsychological assessment enables a better understanding of antipsychotic effectiveness and brain processes which underlie cognitive functioning in schizophrenia.

Neurocognitive deficits in schizophrenia patients can apparently explain up to 61% of the variance of functional outcome and are important predictors of social reintegration (1) and independent living activity (2). Impaired social functioning in patients with schizophrenia has been associated with increased health-care costs. Since social and occupational disability may generate the largest indirect costs of the illness, treatment of cognitive deficits has an enormous impact on the cost and disability associated with schizophrenia (3, 4).

In addition, cognitive functioning is closely related to insight (5) and may influence compliance with medication (6). However, the gap between cognitive science and clinical practice limits the implementation of cognitive assessment in the routine evaluation of patients with schizophrenia. The pharmaceutical industry has initiated numerous large scale, multisite studies on the impact of novel antipsychotics on cognitive deficits in schizophrenia patients.

The aim of the present study is to analyze the role of neurocognitive instruments in the identification of the specific contribution of antipsychotic treatment to alterations in cognitive functioning, pertinent for everyday clinical practice.

Real-Life Cognitive Evaluation Versus Neuropsychological Test Analysis

The best way to assess patients' functioning in the "real-world" is through direct observation in naturalistic settings. This assessment method seems to be "ideal," but it is not cost-effective. In contrast, neuropsychological measures measure functioning in artificial, laboratory conditions, designed to reflect real-world behavior. Therefore, appropriate and objective assessment batteries focused on cognitive changes in schizophrenia should be developed (2, 7).

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The primary aim of cognitive neuropsychologists is to develop a standardized assessment which is able to detect and to quantify patients' performance. These techniques have many advantages: they do not rely on observation of patients' behavior, are less dependent on patients' insight and can objectify the magnitude of the functioning impairments.

Cognitive Changes During Antipsychotic Treatment

The ability of antipsychotics to alleviate cognitive impairments is a main focus of modern psychopharmacology (8). A recent meta-analysis of data from 34 studies published between 1957 and 2002 showed that conventional antipsychotics have mild benefits for performance (9). Significant effects were obtained in attention, automatic processing, language, and perceptual processing, with negative effects on motor function in conjunction with extrapyramidal side effects (EPS) and memory (related to anticholinergic activity or the use of anticholinergics to reduce the EPS). Conventional antipsychotic-induced changes in cognitive function appear to correlate inversely with dosage (10, 11). However, cognitive deficits which appear in the course of psychotic illness are only marginally corrected by conventional antipsychotics, even when medication is administered at lower doses (12).

Several meta-analyses revealed that novel antipsychotics are more effective than conventional neuroleptics in producing cognitive improvement (13–18). It remains unclear whether putative cognitive benefits represent a direct cognitive enhancement or are indirect effects mediated through decreased EPS or as a result of anticholinergic adjunctive treatment (10). In contrast, high doses of the atypicals clozapine, risperidone and olanzapine did not show aversive effects on neurocognition which may indicate that atypicals are better tolerated with respect to neurocognitive functioning (13). However, some comparisons of patients treated with conventional and atypical antipsychotics showed inconsistent findings across studies, indicating that the available research is preliminary, and significant questions remain unanswered (19, 20). For example, results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed that the only conventional drug studied, perphenazine, yielded the greatest effects on cognition after 18 months of treatment, but that the magnitude of improvement was extremely small (21).

Enthusiasm for the results of the majority of antipsychotic trials must be tempered, since rigorous attempts to rule out or control for possible confounding variables (such as learning associated with repeated testing, lack of cooperation and motivation, symptom reduction, and inclusion of outliers were not properly conducted (22).

Cognitive improvement is part of a general treatment response associated with improved functional outcomes (21). This raises the question of whether the observed improvements represent a true cognitive enhancement per se or simply more effective utilization of cognitive resources due to effective resolution of acute psychotic disturbances. Usually, the results of neuropsychological evaluation reflect a "final common pathway" of several distinct pathological brain processes. There is a fairly consistent relationship between primary (deficit) symptoms and neuropsychological measures of disturbed frontal and parietal lobe functions, and it is possible that this relationship may emerge from a common neural substrate (23, 24). In contrast, the improvement of secondary negative symptoms (alleviation of psychomotor slowness, associated with affective symptoms, improvement of bradyphrenia and bradykinesia) and motivation can lead to improvement of cognitive performance.

Thus, antipsychotic treatment may have some beneficial impact on state-related cognitive deficits via normalization of brain and cognitive abilities that are disturbed during psychosis (reduction of "secondary" cognitive impairments).

Implementation of a Standard Cognitive Assessment

The choice of tests for a neurocognitive battery is often controversial. As a result, the assessment of neurocognitive deficits in schizophrenia presents a major challenge to the clinician and researcher, and efforts are being made to develop a reliable and valid cognitive battery for use in pharmacological clinical trials. Such a battery is expected to collect data based on cognitive enhancing effects of different

antipsychotics. Therefore, it is important that batteries of tests for the drug trials are approved by expert consensus.

In order to standardize an assessment approach and stimulate the development of drugs to treat cognitive deficits of schizophrenia, in order to clarify requirements for regulatory approval and facilitate the development of appropriate methods for collecting neuropsychological data, the U.S. National Institute of Mental Health has established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiative (25).

The MATRICS Neurocognition Committee concluded that six unique factors had been replicated in multiple studies of schizophrenia patients and were appropriate for the consensus cognitive battery for clinical trials: 1) Working memory; 2) Attention/vigilance; 3) Verbal learning and memory; 4) Visual learning and memory; 5) Reasoning and problem solving; 6) Speed of processing (26). Once the final battery of paper and pencil tests (with the exception of the Continuous Performance Test) was selected, it was expected to become a standard instrument for clinical trials of cognitive enhancing agents in schizophrenia.

For the CATIE study the panel of experts ultimately chose a combination of the computerized neuropsychological assessment and traditional paper and pencil tests (22). In the CATIE study computerized tests were only 3 from 11 of full battery (22), in MATRICS battery 1 from 11 (25), and in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) 1 from 17 (27)

Real-Time Versus Paper-and-Pencil Cognitive Assessments of Treatment Outcome in Schizophrenia

The wide use of neuropsychological paper-and-pencil tests in clinical practice is limited by the requirement that test administration and interpretation be undertaken by trained personnel, and by the practice of administering tests on a one-to-one basis. This process is time consuming, expensive, and beyond the means of most psychiatric clinical facilities. These practical limitations have led to the development of a variety of computerized cognitive batteries, which provide a relatively inexpensive alternative to paper and pencil assessment. The American Psychological Association has recognized the value of computerized psychological testing and in 1987 published guidelines to assist in the development and interpretation of computerized cognitive tests (28). The major benefits of computerized assessment were identified as: 1) the ability of the interactive computer-based environment to capture and engage the interest of the examinee; 2) the flexibility of software, which can help to reduce the examinee's frustration and negative self-evaluation, and provide 3) greater sense of mastery and control for the examinee; 4) the availability of automated data collection and storage which can free the clinician from test administration and scoring, allowing more focus on interpretation; 5) greater ability to measure aspects of performance not possible through traditional means (e.g., latency, strength, and variability in response patterns) and human observation (e.g., milliseconds, millimeters); 6) the significant increase of efficiency by eliminating extensive setup and/or preparation time that would normally be required with the presentation of complex tests (28). 7) Sensitivity: Recent studies using paper-and-pencil assessment estimate that the majority of schizophrenia patients performed between 0.46 and 1.41 standard deviation below the mean of the general population (29), while using the reaction time (RT) values these patients showed impaired performance at a level 3.5 standard deviation (30, 31). Moreover, it has been shown that while cognitive deficits measured by paper-and-pencil test were stable over time, the slowing of RT progressed with time (32, 33). 8) The ability of computerized testing to recruit memory and attentional resources in real-time manner, which, in turn, activates the higher levels of cognitive processes. As a result, motivation-related fluctuations in cognitive performance can be better detected by ongoing real-time computerized recording of behavioral responses as compared to paper-and-pencil method. 9) The test is time effective, the test battery to be completed within 1–2 hours. Using traditional pencil-and-paper equivalents would take many hours to administer, thus the computerized neuropsychological tasks reduce the effects of fatigue which can often occur in the traditional tests.

A further benefit of computerized testing lies in computerized output reports. One reason for the popularity of computer testing is that it automates test administration, scoring and, in some cases, even interpretation of tests. The output from computerized neuropsychological testing is either: "yes, cognitive function has changed during treatment"; or "no, cognitive function has not changed or even worsened." This is reflected in the reports provided by the currently available computerized batteries. Such computerized interpretation of reports does not require neuropsychological expertise. Automatic interpretation of cognitive testing increased accessibility and usage of computerized tests as well as immediate on-line availability of the reports detailing the patients' cognitive function and the assessment of the impact of the pharmacological treatment on the cognitive function. A further correlation between the changes in cognitive and clinical/symptomatic status can be calculated.

Despite the extensive benefits of computerized testing there have also been criticisms that have needed to be addressed:

1) Failure to meet established testing standards. Some software addresses this issue by providing reliability and validity data within the computerized tests, but many programs do not.
2) Another probable pitfall is related to computer interface and computer illiteracy of patients in using a keyboard or mouse. In such cases, visual and auditory instructions and training feedback increase the patients' understanding. More recent methods of computerized testing, including immediate data transfer and availability of on-line feedback on test scores (34) might reduce this limitation.
3) Reduced face-to-face interaction between the clinician and examinee. Therefore, the notes describing the behavior of the patient during the tests' procedure should be taken into consideration within the results analysis. The computerized assessment does not replace the clinical interview, which is essential for the appropriate interpretation of the computerized results.
4) Some probable computer-related inaccurate timing and spatial measurement procedures. For example, the temporal accuracy of the procedures is within ±5 msec for visual stimuli and ±1 msec for auditory stimuli. The spatial accuracy of the touch screen is recalibrated before each use and is within ±3 mm.
5) The computerized tests may be more susceptible than non-computerized tests to fail to provide meaningful results. The reasons for missing data were largely attributed to invalid scores and computer test malfunction rather than patient uncooperativeness, and a greater percentage of patients may not complete one of the computerized tests compared to the non-computerized tests (7).
6) The sensitivity of the different real-time tasks to the changes appearing during antipsychotic treatment is also variable. For example, some studies have reported that antipsychotic treatment may lead to improvement in CPT performance in schizophrenia patients, but other studies have failed to show this effect (35, 36). This inconsistency may be partly explained by the fact that some versions of the computerized CPT require different perceptual and working memory loads and may have different sensitivity to treatment-related changes. Different neural circuits are recruited during simple as opposed to complex target detection. Thus, different cognitive functions exhibit different levels of sensitivity to antipsychotic effects (37).

Reaction Time (RT) as a Paradigm for Computerized Neurocognitive Assessment

The RT tasks reflect speed of information processing at the basic cognitive level, and may represent an unbiased reflection of fundamental neurobiological systems necessary for higher levels of processing. Moreover, RT reflects an individual's "environmental responsivity," which may be a critical factor in the prediction of clinical and functional outcomes. For example, it was shown that acute schizophrenia patients with faster RT at admission tended to show greater clinical improvement at follow up compared to schizophrenia patients with slower RT (11).

The focus on RT has been resumed recently

(mostly, following the development and accessibility of computerized approach to real-time neurocognitive assessment), due to the recognition of the importance of efficient speed of information processing for optimal cognitive functioning. A recent meta-analysis of RT studies indicated that generalized slowing of information processing accounted for 87% of the variance in RT (38).

Computerized assessment assists in the separation of two different aspects of cognitive impairments. First, trait-related RT deficit is present in patients before the onset of illness and persists during psychotic episodes and remissions (39). Second, state-related RT deficits are secondary to specific clinical symptoms of schizophrenia (40) and improve following successful antipsychotic treatment. Real-time neurocognitive assessment is more sensitive to state-related cognitive impairments. For example, the slowing of RT was linearly positively correlated with number of psychotic episodes (11, 40). Hence, real-time neurocognitive performance may reflect alterations due to treatment or exacerbation of the disorder during relapse periods.

Future Directions and Conclusions

There is a need to investigate further the value of computerized cognitive examinations in the monitoring of time course and response to treatment in schizophrenia patients. Several computerized cognitive batteries have been developed, but they have not been validated against traditional tests. Moreover, the comparison of different batteries during treatment period within the same patient is limited. Head to head comparisons of sensitivity and specificity of different computerized cognitive batteries are scarce (41). Constructional and ecological validity of different computerized cognitive batteries are not investigated in antipsychotic trials. The value and usefulness of neuropsychological batteries, consisting of different tasks with myriad variables, which spanned different neurobehavioral constructs and have different sensitivity to cognitive changes among schizophrenia patients during treatment, merits further investigation (34, 42–44).

There is a need to create an "optimal" real-time, fully-computerized neurocognitive battery based on the principles suggested by the MATRICS Consensus panel (23, 25). It was noted that if the cognitive battery is too long and perceived by patients as burdensome, the chance of a patient dropping out of evaluation prematurely increases, while an assessment battery containing too few tests has an alternative risk of missing important findings. It is important to emphasize that the "optimal" battery should composite balance between broad and narrow coverage. Such an approach can enable the preservation and the development of the achievements obtained in the paper-and-pencil method within the real-time computerized neuropsychological examination, and may be useful in psychopharmacological trials.

Therefore, it seems reasonable to adopt the recent recommendations of the MATRICS Consensus panel with the experience accumulated since 1874, using the RT paradigm (39) in existing and in constructing real-time computerized neurocognitive batteries. Intelligent selection of an appropriate real-time computer-based neurocognitive battery will hopefully help psychiatrists in the assessment of the impact of antipsychotics on the cognitive profile in the individual patient and will enable better planning of treatment and rehabilitation programs.

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Correction

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The following line was missing at the bottom of Table 3, page 108:
GHQ scores were recalculated using 1-37 as the range of the 12-GHQ values