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Schizophrenia Research 72 (2004) 29–39

SCHIZOPHRENIA RESEARCH

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Identification of separable cognitive factors in schizophrenia

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Received 3 September 2004; accepted 3 September 2004

Abstract

One of the primary goals in the NIMH initiative to encourage development of new interventions for cognitive deficits in schizophrenia, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), has been to develop a reliable and valid consensus cognitive battery for use in clinical trials. Absence of such a battery has hampered standardized evaluation of new treatments and, in the case of pharmacological agents, has been an obstacle to FDA approval of medications targeting cognitive deficits in schizophrenia. A fundamental step in developing such a battery was to identify the major separable cognitive impairments in schizophrenia. As part of this effort, we evaluated the empirical evidence for cognitive performance dimensions in schizophrenia, emphasizing factor analytic studies. We concluded that seven separable cognitive factors were replicable across studies and represent fundamental dimensions of cognitive deficit in schizophrenia: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Verbal Comprehension. An eighth domain, Social Cognition, was added due to recent increased interest in this area and other evidence of its relevance for clinical trials aiming to evaluate the impact of potential cognitive enhancers on cognitive performance and functional outcome. Verbal Comprehension was not considered appropriate for a cognitive battery intended to be sensitive to cognitive change, due to its resistance to change. The remaining seven domains were recommended for inclusion in the MATRICS-NIMH consensus cognitive battery and will serve as the basic structure for that

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0920-9964/$ - see front matter
doi:10.1016/j.schres.2004.09.007

battery. These separable cognitive dimensions also have broader relevance to future research aimed at understanding the nature and structure of core cognitive deficits in schizophrenia.

Keywords: Cognition; Schizophrenia; Factor analysis; Neuropsychology; Psychopharmacology

1. Introduction

One of the primary initial goals of the NIMH contract on Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) has been to develop a consensus cognitive battery for use in clinical trials, as the absence of such a battery has been a major impediment to standardized evaluation of new treatments designed to alleviate cognitive deficits in this disorder. In particular, development of a standard cognitive battery through a consensus of experts would establish an accepted measurement instrument for evaluation of pharmacological agents that target cognitive deficits in schizophrenia, thereby allowing a clear pathway for FDA approval of such new medications.

In considering the development of a MATRICS-NIMH consensus cognitive battery for use in clinical trials, a key step was to determine which cognitive domains should be represented. As reported by Kern et al. (2004) elsewhere in this issue, the broad sample of experts in relevant fields that were surveyed by the MATRICS Neurocognition Committee clearly stated that they believed that reliable coverage of the major separable cognitive deficits in schizophrenia was an "essential" feature for the consensus cognitive battery. Ideally, separable in this context would refer to cognitive deficits with distinct causes or neural substrates that may therefore respond to different types of pharmacological interventions. However, at a minimum, separable should refer to cognitive deficits in schizophrenia that are distinguishable at the statistical or analytic level, such as in the results of factor analytic studies. There is an extensive literature seeking to delineate the nature of cognitive deficits in schizophrenia (Braff, 1993; Goldberg and Green, 2002; Nuechterlein and Dawson, 1984) and it is clear that these deficits are enduring, core features of this illness (Censits et al., 1997; Gold, 2004; Green and Nuechterlein, 1999; Nuechterlein et al., 1992). However, there has until now been no consensus agreement on a standard way to divide the most prominent cognitive deficits into key dimensions or domains.

Extensive research using neuropsychological test batteries has demonstrated that schizophrenia patients, as a whole, do show certain characteristic profiles of cognitive deficits (Heaton et al., 2001; Heinrichs and Zakzanis, 1998; Saykin et al., 1991; Saykin et al., 1994). Some investigators have suggested that deficits in a number of cognitive domains may share a common cause (Andreasen et al., 1998; Cohen et al., 1999; Goldman-Rakic, 1994; Nuechterlein and Dawson, 1984). However, individual patients may show meaningful variations in the modal profile (Palmer et al., 1997, Weickert et al., 2000) and other researchers have suggested that different types of cognitive deficits may have different neurobiological substrates (e.g., working memory versus episodic memory) and may respond to different treatment approaches. Thus, it is important to represent the major separable cognitive domains in a battery for clinical trials. Unfortunately, the ways that the cognitive domains have been divided has varied from study to study, depending on the preferences of the individual investigative teams and the range of measures employed. To reach a consensus on the major separable cognitive factors in schizophrenia, the authors of this article served as a subcommittee of the MATRICS Neurocognition Committee to review the available empirical evidence and to make recommendations regarding the separable cognitive domains to be included in the MATRICS consensus cognitive battery for clinical trials.

2. Method

To delineate the major dimensions of cognitive deficit in schizophrenia, the authors established a set of principles for identification of the cognitive domains. The following principles were emphasized:

(1) Dimensions that were independent or only weakly intercorrelated were sought, such that they could be viewed as separable contributors to functional outcome and as potentially separate targets for new treatments.
(2) Only cognitive dimensions that had been replicated across several studies of schizophrenia patients were included.
(3) Research on separable neurocognitive factors in large normal samples [e.g., research with the Wechsler Adult Intelligence Scale-III (WAIS-III) and Wechsler Memory Scale-III (WMS-III) standardization samples] was considered relevant as an initial source of candidate dimensions (Tulsky and Price, 2003).
(4) Many sources of information are relevant to deciding whether or not specific cognitive domains should be considered separable, including the animal and human cognitive neuroscience literatures on the neurobiological substrates of different cognitive domains and differential responsivity to pharmacological intervention. However, results of factor analytic studies of cognitive performance in schizophrenia patients were viewed as a direct form of evidence regarding cognitive dimensions in schizophrenia, and one of the few sources of information available for all of the domains of interest for schizophrenia. Thus, all known factor analytic studies were sought, including both published and unpublished results to broaden the available database as much as possible.
(5) When relevant, the likely sensitivity of a cognitive dimension to intervention attempts was considered, based on the neuropsychological and cognitive neuroscience literatures.

Computer searches of the published scientific literature and individual inquiries of investigators who might have relevant unpublished results yielded 13 factor analytic studies of cognitive performance in schizophrenia (Allen et al., 1998; Dickinson et al., 2004; Gladsjo et al., in press; Gold, unpublished; Goldberg, Egan, and Weinberger, unpublished; Green et al., 2002; Hobart et al., 1999; Keefe et al., 2004; Kremen et al., 1992; Mirsky, 1987; Nuechterlein et al., 2003; Spaulding et al., 1989; Strauss and Summerfelt, 2003). The analytic methods, characteristics of samples, and cognitive tests used in these 13 studies are listed in Table 1. As is evident there, the most popular method for extraction of dimensions (9 of 13 studies) was principal components analysis, usually accompanied by a Varimax rotation method that seeks independent factors (Jolliffe, 1986; Nunnally, 1978). When principal components analysis was used, all studies except one used eigenvalue >1.0 as an initial guide to the number of factors to extract. Confirmatory factor analysis (Bollen and Long, 1998; Hoyle, 1995) was employed in three studies, typically using prior factor analytic solutions with normal subjects as a source of hypothesized factors in schizophrenia. Sample sizes varied substantially, from 34 to 209, and samples occasionally included patients with other psychoses or severe mental disorders rather than solely patients with schizophrenia. As can be seen in Table 1, the subject-to-variable ratios also show a range across studies, so the stability of loadings on factors may vary. While most of the samples involved outpatients, a few involved inpatients or a combination of outpatients and inpatients. Because consistent factors could be detected across these differences in factor analytic methods, sample composition, specific tests, and subject-to-variable ratio, the authors feel that greater confidence can be assigned to the conclusions.

Our MATRICS subcommittee examined the results of factor analytic studies to seek replicated factors at the level of the cognitive test measures loading on factors. That is, the factor names assigned by the authors of the individual studies were considered less important than the combination of cognitive measures that each factor represented. Tables of factors and the measures loading on them were constructed to summarize results across the 13 studies to examine consistency. In a few instances, it was not clear whether certain groups of cognitive measures should be combined in one factor or split into two factors. When possible, additional targeted factor analyses were conducted to resolve these issues, using relevant original data sets available to subcommittee members. Another method of resolving such ambiguities was to examine other studies of the interrelationships among

Table 1
Characteristics of factor analytic studies of cognitive performance in schizophrenia and related disorders

Study	Analytic method	Sample	Tests	No of variables in factor analyses	Percent of variance accounted for by factors
Allen et al. (1998)	CFA	169 male schizophrenia inpatients	WAIS-R subtests	11	NA
Dickinson et al. (2004)	Single common FA	97 stable schizophrenia outpatients	WAIS-III and WMS-III subtests	18	NA
Gladsjo et al. (in press)	CFA	209 outpatients with psychotic disorders	WAIS-R subtests, Trail Making Test, Boston Naming Test, Letter Fluency, Story Memory, CVLT, Figure Memory, Grooved Pegboard, WCST, Booklet Category Test	21	NA
Gold et al. (unpublished)	PCA, varimax	56 schizophrenia patients	AFV fluency, FAS fluency, Symbol Search, Digit Symbol, Logical Memory I, Word List I, Woodcock–Johnson Analysis/Synthesis, WCST, Arithmetic, Digit Span, CPT-IP	8 in each of two PCA analyses	83% and 76%
Goldberg, Egan, and Weinberger (unpublished)	PCA, varimax	86 schizophrenia patients	Arithmetic, Similarities, Picture Completion, Digit Symbol, WRAT Reading, Trail Making Test, verbal fluency for categories, Gordon CPT, N-Back, Logical Memory I, Visual Reproduction I, Verbal Paired Associates, WCST, CVLT	16	64%
Green et al. (2002)	PCA, varimax	62 schizophrenia outpatients	DS-CPT, Span of Apprehension, spatial work and reference memory tests, FAS fluency, CVLT, Digit Span Distractibility, Pin Test, WCST, Block Design, Trail Making Test	13	63%
Hobart et al. (1999)	PCA, varimax	150 outpatients with schizophrenia or major mood disorder	WAIS-III Vocabulary, Picture Arrangement, and Comprehension, WMS-III Logical Memory I and II, Visual Reproduction I and II, Woodcock–Johnson Listening Comprehension, Stroop, Trial Making Test, Gordon CPT, WCST, Finger Tapping, Purdue Pegboard	22	74%
Keefe et al. (2004)	PCA, oblique	150 patients with schizophrenia	BACS Digit Sequencing, Symbol Coding, Tower of London, Token Motor Task, Verbal Fluency, Verbal Memory	6	74%
Kremen et al. (1992)	PCA	34 patients with major psychotic disorders	Trail Making Test, Digit Symbol, Digit Span, WRAT-R Arithmetic, WMS Mental Control, WCST, auditory CPT, dichotic listening	11	77%
Mirsky (1987)	PCA	86 psychiatric patients and normal subjects	Digit Span, Arithmetic, Digit Symbol, Talland Letter Cancellation Test, Stroop, Trail Making Test, WCST, X and AX CPT	10	71%
Nuechterlein et al. (2003)	PCA, varimax	47 outpatients with a recent onset of schizophrenia	3–7 CPT, DS-CPT, Span of Apprehension, backward masking, CVLT, Digit Span Distractibility, Trail Making Test	10	65%
Spaulding et al. (1989)	CFA	125 patients with chronic schizophrenia	COGLAB subtests for backward masking, simple reaction time, reaction time redundancy effect, rebound effect, and anticipatory errors, a combined CPT and Span of Apprehension task	10	29%
Strauss and Summerfelt (2003)	PCA	83 patients with schizophrenia or bipolar disorder	Trail Making Test, WCST, letter fluency, Calev word list learning, Moss visuospatial memory span, Mooney Closure Test	6	35%

Note: CFA=confirmatory factor analysis. PCA=principal component analysis. WAIS=Wechsler Adult Intelligence Test. WMS=Wechsler Memory Scale. CVLT=California Verbal Learning Test. AFV fluency=fluency for names of animals, fruits, and vegetables. FAS fluency=fluency for words starting with F, A, and S. WCST=Wisconsin Card Sorting Test. CPT-IP=Continuous Performance Test, Identical Pairs. WRAT=Wide Range Achievement Test. DS-CPT=Degraded Stimulus Continuous Performance Test. X and AX CPT=continuous performance test with X or AX targets. 3-7 CPT=continuous performance test with 3-7 target. COGLAB=computerized cognitive laboratory.

the measures in schizophrenia, even if these studies had not employed factor analytic methods.

3. Results

The result of this process was the identification of six separable cognitive dimensions in schizophrenia. We present these cognitive domains ordered from relatively basic to high-level cognitive processes, rather than in the order in which factors emerged from individual studies, as the latter varied from study to study. To help the reader see the support for each dimension across studies and the nature of the cognitive domain, a table showing the studies identifying a similar factor and the primary measures loading on the factor is provided for each dimension. It is important to note that the absence of a factor in any particular study may reflect either the absence of measures in that cognitive domain or the lack of a factor that would be expected given the presence of relevant measures. Thus, statements that a similar factor was represented in a certain number of the 13 studies should not be taken to imply that all 13 studies would be expected to yield each factor. In judging whether individual studies supported a given separable cognitive dimension, the Neurocognition Committee took into account the nature of the measures included in those studies.

The first dimension, Speed of Processing, was represented within 8 of the 13 factor analytic studies, as shown in Table 2. Cognitive measures loading highly on this factor emphasize the speed with which digit/symbol pairings can be completed, target symbols can be located, number or number/letter sequences on a page can be identified and connected, and colors can be named. Verbal fluency, often measured by the number of words starting with a given letter that can be generated in a brief time period, also loads on this factor, although it is not traditionally thought of as a measure of processing speed. The authors considered whether fluency should be a separate factor, but found that factor analytic results indicated that fluency most commonly loaded on this factor. The cognitive processes tapped by the tasks loading on this factor are relatively simple, often involve perceptual and motor components, and always emphasize speed of performance. This dimension has also been identified in studies of normal cognitive performance (Tulsky and Price, 2003).

Table 2
Speed of processing

Study	Measures
Dickinson et al. (2004)	Digit Symbol, Symbol Search
Gladsjo et al. (in press)	Digit Symbol, Trails A and B, Grooved Pegs
Gold (unpublished)	Digit Symbol, Symbol Search
Goldberg et al. (unpublished)	Trails A and B, Digit Symbol, Fluency
Hobart et al. (1999)	Stroop color and color-word, Trails A and B
Keefe et al. (2004)	Fluency, Symbol Coding, Token Motor Test
Kremen et al. (1992)	Trails A and B, Digit Symbol
Mirsky (1987)	Digit Symbol, Talland Letter Cancellation, Trails, Stroop

A second dimension, Attention/Vigilance, was found in 7 of the 13 studies (Table 3). The most prominent measures loading highly on this performance dimension were indices from versions of the Continuous Performance Test (CPT), a sustained attention task originally developed by Rosvold et al. (1956) and refined for research on schizophrenia (Cornblatt et al., 1988; Nuechterlein, 1983). Other measures loading on this dimension included shadowing one voice in a dichotic listening task and target identification in early perceptual processing in the forced-choice Span of Apprehension task (Asarnow et al., 1991) and under backward masking conditions (Breitmeyer, 1984; Green et al., 1994). In studies of WAIS and WMS versions in normal subjects, a factor combining attention and working memory is often identified, including subtests, such as Arithmetic, Digit Span, Letter–Number Sequencing, and Spatial

Table 3
Attention/vigilance

Study	Measures
Gold (unpublished)	CPT-IP 2-, 3-, and 4-digit conditions
Goldberg et al. (unpublished)	Gordon CPT, 1-back, WCST persev. errors
Green et al. (2002)	DS-CPT, Span, Spatial Memory
Hobart et al. (1999)	Gordon CPT vigilance and distractibility
Kremen et al. (1992)	Auditory CPT, Dichotic Listening
Mirsky (1987)	X CPT, AX CPT
Nuechterlein et al. (2003)	DS-CPT, 3–7 CPT, Backward Masking

Span (Tulsky and Price, 2003). However, when CPT performance indices and these subtests are examined in the same schizophrenia samples, the CPT indices tend to load together on a separate factor (Gold, unpublished; Goldberg et al., unpublished; Kremen et al., 1992; Mirsky et al., 1991; Nuechterlein et al., 2003), although some overlap with CPT versions with immediate memory components is evident (Nuechterlein et al., 2003). Thus, we concluded that an attentional factor that emphasizes vigilance is separable from a working memory factor in schizophrenia.

A Working Memory dimension was represented in 8 of the 13 studies, as shown in Table 4. The most common measures loading on this factor were the subtests Arithmetic, Digit Span, Letter–Number Sequencing, and Mental Control from versions of the WAIS and WMS (Tulsky and Price, 2003; Wechsler, 1981, 1987, 1995). However, other measures from an experimental psychopathology tradition in schizophrenia, such as the more complex levels of n-back tasks (Callicott et al., 2000; Cohen et al., 1999) and spatial working memory tasks (Goldman-Rakic, 1994; Keefe, 2000; Park et al., 1995), would be expected to load on this dimension. All involve temporary on-line storage of information and, in most cases, mental manipulation of information.

The MATRICS Neurocognition Committee considered whether separate verbal and nonverbal working memory dimensions should be included among the primary cognitive deficit dimensions in schizophrenia. Impairments in both verbal and nonverbal working memory domains have been documented in schizophrenia (Barch et al., 2002; Gold et al., 1997; Kim et al., 2004; Park et al., 1995), but there is debate as to whether deficits are more severe in one domain than another (Coleman et al., 2002; Tek et al., 2002). However, available factor analytic results reveal that verbal and nonverbal tests tend to form a single factor when both are represented (Dickinson et al., 2004), and other available research has generally found moderate to high correlations of verbal and nonverbal working memory deficits in schizophrenia (Strauss and Summerfelt, 2003). Thus, the Committee concluded that one dimension of working memory in schizophrenia fits available evidence. Although verbal measures of working memory have been used more extensively in schizophrenia research, nonverbal measures of working memory have the advantage of readily available animal models for drug development. As a result, the Committee recommended that both verbal and nonverbal subtests be included in the MATRICS-NIMH consensus cognitive battery to measure the working memory dimension.

A fourth dimension, Verbal Learning and Memory, was evident in 6 of the 13 factor analytic studies of schizophrenia (Table 5). Immediate and delayed recall of word lists that exceed working memory capacity (e.g., California Verbal Learning Test, Hopkins Verbal Learning Test) and immediate and delayed recall of paragraph-length story information (e.g., WMS-III Logical Memory I and II) were the most typical measures loading on this factor. Indices of paired associate learning, recognition measures of secondary or long-term memory, and recall of digit sequences also loaded on this factor in some studies.

The MATRICS Neurocognition Committee examined the evidence concerning episodic memory deficits in schizophrenia to determine whether verbal

Table 4
Working memory

Study	Measures
Allen et al. (1998)	Arithmetic, Digit Span
Dickinson et al. (2004)	Letter Number Sequencing, Spatial Span
Gladsjo et al. (in press)	Arithmetic, Digit Span
Gold (unpublished)	Letter Number Sequencing, Arithmetic, Digit Span
Goldberg et al. (unpublished)	Digits Forward, Backward
Kremen et al. (1992)	Arithmetic, Digit Span, Mental Control
Mirsky (1987)	Arithmetic, Digit Span
Nuechterlein et al. (2003)	Digit Span, Trails B, 3–7 CPT

Table 5
Verbal learning and memory

Study	Measures
Dickinson et al. (2004)	Logical Memory, Verbal Pairs
Gladsjo et al. (in press)	CVLT recall, Story Learning
Goldberg et al. (unpublished)	CVLT recall, Logical Memory, Verbal Pairs
Green et al. (2002)	CVLT, Fluency, Digit Span Distractibility
Keefe et al. (2004)	Verbal Memory, Digit Sequencing
Nuechterlein et al. (2003)	CVLT recall, CVLT recognition

and nonverbal learning/memory should be represented as a single dimension or as two dimensions. Paralleling the situation with working memory, impairments in verbal learning and memory (Gold et al., 1999; Heinrichs and Zakzanis, 1998; Saykin et al., 1991; Seidman et al., 1994) and in visual learning and memory (Heinrichs and Zakzanis, 1998; Nestor et al., 1993; Saykin et al., 1991, 1994) have been documented in schizophrenia. However, factor analytic studies that include verbal and visual tests of episodic memory in schizophrenia tend to isolate separable verbal and nonverbal factors (Dickinson et al., 2004; Gladsjo et al., in press), paralleling their separation in large normal samples (Tulsky and Price, 2003). Furthermore, a supplementary analysis of a sample of schizophrenia patients with episodic memory deficits (< 1 SD below normal on verbal and/or visual memory; Nayak et al., 2004) showed that 47% of the patients had either verbal or visual episodic memory deficits rather than both. Thus, the Committee concluded that verbal learning and memory deficits and visual learning and memory deficits should be represented as separate dimensions.

The factor analytic evidence for a Visual Learning and Memory dimension in schizophrenia is summarized in Table 6. Most factor analytic studies of cognitive performance in schizophrenia have not included visual memory tests, so the fact that only 3 of 13 studies identified such a factor is more a reflection of test selection rather than evidence that such visual memory tests do not form a distinct factor. The tests falling on this dimension require recognition of faces either immediately or after a delay, recall of family scenes either immediately or after a delay, memory for nonfamiliar figures, and reproduction of line drawings.

The sixth major cognitive dimension in schizophrenia that has been isolated by replicated factor analytic evidence is Reasoning and Problem Solving, as shown in Table 7. Seven of 13 studies identified such a dimension, sometimes labeled Executive Functioning rather than Reasoning and Problem Solving. The label Reasoning and Problem Solving has the advantage of distinguishing this domain from the executive processes of working memory (Baddeley, 1986), which would fall on the Working Memory factor in the current delineation of cognitive domains. Cognitive measures loading highly on this factor involve sorting cards by an abstract principle that changes over time (Wisconsin Card Sorting Test), nonverbal reasoning to complete a sequence of visual patterns (Matrix Reasoning) or to construct a visual pattern (Block Design), moving round disks between pegs in the smallest number of steps to achieve a specific order (Tower of London), and similar verbal and nonverbal problem-solving tasks. These high-level cognitive processes often demand relatively intact lower-level processes, but also involve additional complex strategic planning and decision-making skills.

One additional cognitive dimension, Verbal Comprehension, has also been isolated in factor analytic studies of schizophrenia, typically receiving high loadings from measures such as the WAIS-III subtests for Vocabulary, Similarities, and Information (Allen et al., 1998; Gladsjo et al., in press; Hobart et al., 1999). However, because this general verbal ability dimension is considered to be extremely resistant to change in schizophrenia and in neurologically impaired samples (Lezak, 1995), it was omitted from the cognitive domains recommended for the MATRICS-NIMH consensus cognitive battery as the Committee did not feel that it would be sufficiently sensitive to existing or future treatment effects in clinical trials.

Table 6
Visual learning and memory

Study	Measures
Dickinson et al. (2004)	Facial Recognition I and II, Facial Pictures I and II
Gladsjo et al. (in press)	Figure Learning, Figure Delay
Hobart et al. (1999)	WMS-III Visual Reproduction 1 and 2

Table 7
Reasoning and problem solving

Study	Measures
Dickinson et al. (2004)	Matrix Reasoning, Block Design, Pict. Comp., Pict. Arrangement
Gladsjo et al. (in press)	Block Design, Category, WCST
Green et al. (2002)	WCST categories and persev. errors
Hobart et al. (1999)	WCST categories and persev. errors
Keefe et al. (2004)	Tower of London
Kremen et al. (1992)	WCST categories and errors
Mirsky (1987)	WCST errors

4. Discussion

As detailed above, the review of available factor analytic evidence for separable cognitive dimensions in schizophrenia yielded six domains that could be recommended for inclusion in the MATRICS-NIMH consensus cognitive battery for clinical trials: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, and Reasoning and Problem Solving. A seventh dimension, Verbal Comprehension, was identified but not recommended for inclusion due to the extreme resistance to change that characterizes such overlearned verbal skills. Results of two additional factor analytic studies of cognitive performance in schizophrenia that we were not aware of at the time of our discussions are consistent with these conclusions (Friis et al., 2002; Kurtz et al., 2001). As described in the introduction, many other sources of information are relevant to understanding whether specific cognitive domains are separable at a neural level and potentially responsive to different types of pharmacological interventions, and we do not claim to have "carved cognition at its joints" based on the results of these factor analytic studies. However, these studies provide an important starting point for generating a consensus cognitive battery that begins to capture the variations in cognitive function that exist among individuals with schizophrenia.

A particular issue that is worthy of note is debate over the extent to which a generalized cognitive deficit cutting across many cognitive functions accounts for impairment in schizophrenia. Two of the studies using exploratory factor analytic methods found that a single factor accounted well for the common variance in cognitive measures among chronic schizophrenia patients (Spaulding et al., 1989) or a mixed sample of schizophrenia and bipolar patients (Strauss and Summerfelt, 2003). In contrast, the clear majority of the exploratory factor analytic studies found that cognitive performance variations in schizophrenia were best accounted for by multiple independent or only weakly correlated factors, based on considerations of amount of variance accounted for, eigenvalues, and scree plots. Furthermore, confirmatory factor analysis in a study with the largest sample of schizophrenia patients indicated that a six-factor model produced the best fit (Gladsjo et al., in press). Thus, we concluded that the evidence, across all available studies, favored sufficient separation of the selected cognitive dimensions to include them as different cognitive domains in a battery intended to examine treatment effects in clinical trials. The results of such factor analyses provide evidence about the number of discrete dimensions that are assessed by typical cognitive batteries. These factor analytic findings do not directly address the between-group differences that may be observed across these discrete dimensions. Indeed, another study using a specialized statistical modeling procedure, single common factor analysis, found that a common factor accounted for the majority of the variance distinguishing schizophrenia patients from healthy subjects in six cognitive domains from the WAIS-III and the WMS-III (Dickinson et al., 2004). The presence of a substantial common factor in between-group variance, however, should not be interpreted as implying that this factor is due to a unitary, common underlying neural cause or a common etiological source. The common factor documented by Dickinson et al. does, however, imply that a substantial portion of between-group variability observed across relatively independent cognitive domains is shared. Further research will be needed to determine the extent to which variance in these statistically separable cognitive domains is due to common contributors and can be impacted by single versus separate interventions.

The results of this review of the empirical evidence, as well as the results of the survey of a group of 68 experts in relevant fields (Kern et al., 2004), were presented to the experts from academia, government, and industry who met at the initial MATRICS conference in Potomac, MD, in April of 2003. As explained in detail in the Kern et al. article in this issue, the survey revealed that the cognitive domains that the experts chose most often for inclusion in a consensus cognitive battery for schizophrenia were executive, concept formation, and cognitive control processes, attention/vigilance, short-term memory, long-term memory, problem solving and decision making, speed of processing, and social cognition. Thus, while the grouping of the cognitive domains was somewhat different in the survey of experts than in the factors emerging from the review of the empirical evidence, all domains identified in this survey, with the exception of social cognition, were included in the dimensions that were derived from the review of factor analytic research on cognitive performance in schizophrenia.

A discussion followed at the April 2003 MATRICS meeting to debate the pros and cons of including social cognition as a domain in the consensus cognitive battery. Because studies of social cognition in schizophrenia are relatively new, the absence of a social cognition factor in factor analytic studies of cognitive deficits in this disorder reflects the absence of such social cognition measures in these studies rather than evidence against such a dimension. The recent rise in interest in social cognition impairment in schizophrenia (Corcoran, 2001; Kee et al., 1998, 2003; Lancaster et al., 2003; Mueser et al., 1996; Penn et al., 1997) was viewed as an indication that social cognition should be considered as an additional cognitive domain for the consensus cognitive battery. It is, of course, not possible at this point to determine the extent to which social cognition is a relatively unitary dimension that is separable from the neurocognitive dimensions already summarized, as we know of no factor analytic studies that have addressed this issue. However, there are some indications that social cognition deficits may serve as a mediator between neurocognitive deficits and functional outcome in schizophrenia (Brekke et al., 2003), suggesting that improvements in social cognition might play an important role in increasing everyday functioning in schizophrenia. Because the absence of social cognition measures in the battery would mean that the next generation of clinical trials for cognition-enhancing treatments for schizophrenia would have no standardized assessment for this potentially important domain, the MATRICS Neurocognition Committee concluded that the MATRICS-NIMH consensus battery should include social cognition as a seventh cognitive domain.

In summary, the review of the empirical evidence from factor analytic studies, the survey of a broad sampling of experts, and discussion at the MATRICS conference led to the conclusion that seven major cognitive deficits in schizophrenia should be represented as separate domains in the MATRICS-NIMH consensus cognitive battery for schizophrenia: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Social Cognition. The MATRICS Neurocognition Committee decided that the next step in the construction of the battery was to consider candidate tests within each of these seven domains, using the criteria for test selection that we have described elsewhere (Green et al., 2004; Kern et al., 2004). This approach will allow the examination of a profile of cognitive deficits, using brief measures with strong psychometric properties for each domain. While our categorization of the major separable cognitive deficits in schizophrenia was completed for the purpose of selecting domains for the MATRICS-NIMH consensus cognitive battery, we believe that this identification of cognitive factors in schizophrenia has broad implications for further research on the nature of cognitive impairments in this disorder.

Acknowledgements

An earlier version of this paper was presented at: Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Conference #1: Identifying Cognitive Targets and Establishing Criteria for Test Selection, Bethesda, MD. Support for this conference came from NIMH Contract MH22006 (S.R. Marder, P.I., M.F. Green, Co-P.I.). Additional support for the preparation of this article came from Center grant MH66286 (K.H. Nuechterlein, P.I.).

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