The Cogstate Schizophrenia Battery (CSB) as a Co-Primary Outcome for Trials in Cognitive Impairment Associated with Schizophrenia

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Background

Extensive evidence shows cognitive impairment to be a core symptom of schizophrenia that has a negative impact on function. The MATRICS/FDA/NIMH workshop developed guidelines for the design of clinical trials of drugs that could ameliorate cognitive impairment associated with schizophrenia (CIAS). One important consequence was the development of a battery of performance-based (PerfO) outcome assessments. The use of the MATRICS Consensus Cognitive Battery (MCCB) as a co-primary outcome is recommended by FDA, whilst EMA describe the battery as "acceptable but other, comparable, test batteries may also be used provided their validity is demonstrated". Following the development and application of the MCCB, substantial concerns have been raised regarding patient and trial burden, and cross-cultural adaptability. In this context, the Cogstate Schizophrenia Battery (CSB) has been developed as a computerized cognitive test battery, meeting consensus requirements, but with significantly reduced burden on patients and clinical trial sites. In addition, the use of culture neutral stimuli on each of the component tests add to the utility of the CSB for international trials.

Methods

Information was summarized to describe the intended concepts of interest, context of use, and details of the application of the CSB. In addition, a review of the literature was performed to collate data related to content validity, reliability, construct validity, and ability to detect change. Data were collated according to the FDA clinical outcome assessment qualification package framework.

Content Validity

Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative

The MATRICS initiative identified seven "separable cognitive domains" based on a literature review of normative data and factor analytic studies, but also incorporating expert opinion and potential pharmacologic sensitivity (Green et al, 2004).

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
7. Social cognition*

**Social cognition was added later due to concern regarding its omission and potential importance as a domain*

Table 1: CSB Conceptual Framework

MCCB (duration approx. 90 mins)	CSB (duration approx. 40 mins)	Total Score
Speed of processing	Detection	Cognition
Verbal learning	International shopping list	
Working memory	One-back	
Reasoning and problem solving	Groton maze	
Visual learning	One-card learning	
Social cognition	Social emotional cognition	
Attention vigilance	Identification	

Construct Validity

Table 2: Convergent validity between CSB and MCCB

	MCCB		CSB		Convergent Validity (r)
Domain	***Test/item***	***Paradigm***	***Test/item***	***Paradigm***	
Speed of processing	Trail Making Part A	Sequencing	Detection	Simple reaction time	0.56
	BACS Symbol Coding	Symbol coding	Detection	Simple reaction time	0.76
	Category fluency	Verbal fluency	Detection	Simple reaction time	0.79
Verbal learning	HVLT	Verbal list learning	ISLT	Verbal list learning	0.78
Working memory	WMS-III Spatial Span	Spatial span	Two-back	N-back	0.69
	Letter-number span	Digit span	One-back	N-back	0.75
Reasoning and problem solving	NAB-Mazes	Maze tracing	Groton maze	Hidden-pathway maze learning	0.56
Visual learning	BVMT-R	Figure drawing	One-card learning	Pattern separation	0.76
Social cognition	MSCEIT	Social emotional vignette understanding	SECT	Emotion recognition / Odd man out	0.59
Attention vigilance	CPT-IP	Continuous performance	Identification	Choice reaction time	0.57
Global	Summary score		Global score		0.83

Reliability

Table 3: Test retest reliability for the CSB and component test items

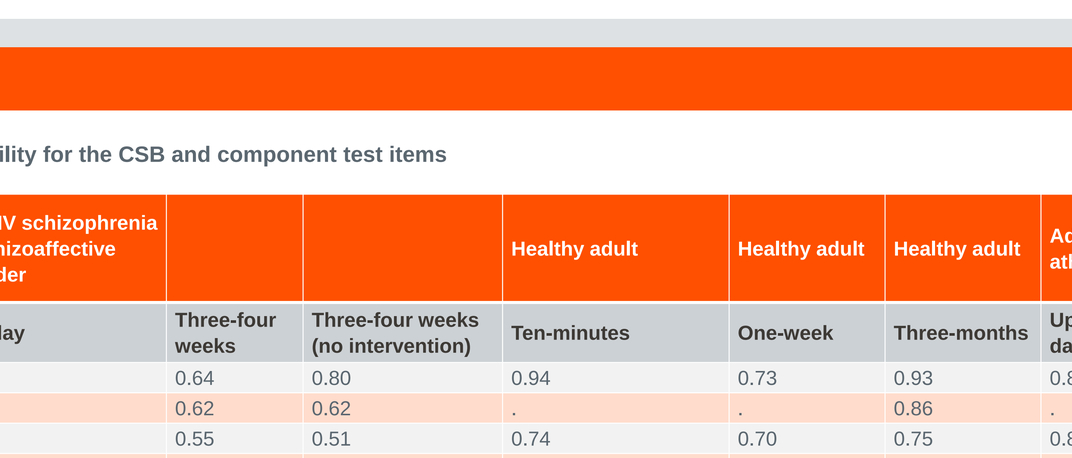
Test/item	DSM-IV schizophrenia or schizoaffective disorder			Healthy adult	Healthy adult	Healthy adult	Adult, male athletes	Chronic schizophrenia
	One day	Three-four weeks	Three-four weeks (no intervention)	Ten-minutes	One-week	Three-months	Up to seven days	One to four-hours and one-month
Detection	0.72	0.64	0.80	0.94	0.73	0.93	0.85	0.79
ISLT	0.56	0.62	0.62	.	.	0.86	.	.
One-back	0.49	0.55	0.51	0.74	0.70	0.75	0.83	.
Two-back	.	.	.	.	.	.	.	.
Groton maze	0.68	0.63	0.77	.	.	.	.	0.78
One-card learning	0.73	0.75	0.76	.	.	0.77	0.93	0.79
SECT	0.75	0.70	0.63	.	.	.	.	.
Identification	0.72	0.66	0.72	0.81	0.71	0.92	0.86	0.81
Global score	0.85	0.81	0.80	.	.	.	.	.
	Pearson correlation (r)	r	r	Intra-class correlation coefficient (ICC)	ICC	ICC	ICC	ICC

Table 4: Internal consistency reliability for the CSB and component test items

	Cronbach's Alpha	
Global score	**.79**	
Test/item	**Reliability if item is dropped**	**Item-total corr.**
DET	.74	.79
IDN	.74	.79
GML	.77	.53
ISL	.79	.45
OCL	.77	.55
ONB	.76	.63
SECT	.78	.49

Ability to Detect Change

Figure 1: Cross-sectional and longitudinal association of CSB and UPSA-B



Conclusions and Future Directions

The CSB is a valid and reliable assessment of cognition, able to detect relevant changes; and is a suitable co-primary outcome measure for clinical trials in cognitive impairment associated with schizophrenia.

- Content validity of the CSB is based on the 7-domain structure identified by the MATRICS initiative (Table 1)
- Construct validity at the item and domain level has been established for the (Table 2)
- Strong evidence for adequate test-retest reliability has been demonstrated across multiple studies (Table 3)
- Internal consistency reliability is also good, supporting the content validity of the battery, but also its length in respect of number of component items, and robustness to missing data
- Ability to detect change in respect of association to changes in function has also been repeatedly demonstrated (Figure 1)