



## Cognitive and clinical predictors of functional capacity in patients with first episode schizophrenia

Lone Vesterager<sup>a,b,\*</sup>, Torben Ø. Christensen<sup>c</sup>, Birthe B. Olsen<sup>c</sup>, Gertrud Krarup<sup>c</sup>, Marianne Melau<sup>a</sup>, Hysse B. Forchhammer<sup>d</sup>, Merete Nordentoft<sup>a,b</sup>

<sup>a</sup> Psychiatric Centre Copenhagen, Copenhagen University Hospital, Bispebjerg Bakke 23, DK-2400, Copenhagen, Denmark

<sup>b</sup> University of Copenhagen, Faculty of Health Sciences, Blegdamsvej 3B, DK-2200, Copenhagen, Denmark

<sup>c</sup> Psychiatric Hospital Risskov, Aarhus University Hospital, Tretommervej 3, DK-8240, Aarhus, Denmark

<sup>d</sup> Department of Neurology, Copenhagen University Hospital Glostrup, Nordre Ringvej 57, DK-2600, Glostrup, Denmark

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### ABSTRACT

**Background:** The predictors of functional capacity in first episode schizophrenia among seven separable cognitive domains and clinical variables are unknown.

**Aim:** To investigate predictors of functional capacity in first episode schizophrenia and the associations between functional capacity and measures of real-world functioning.

**Methods:** Socio-demographic, clinical, and cognitive measures from a sample of patients with first episode schizophrenia spectrum disorders aged 18–34 years (N=117) were examined at baseline, 4-month follow-up, and 10-month follow-up and used to predict concurrent and longitudinal functional capacity. Symptoms were assessed with the Positive and Negative Syndrome Scale, cognitive functioning with the MATRICS Cognitive Consensus Battery, and functional capacity with the brief version of the University of California San Diego Performance-based Skills Assessment. Linear and logistic regression analyses were adjusted for age, gender, and site.

**Results:** Working memory, negative symptoms, and social cognition accounted for 41% of the variance in functional capacity at baseline. Longitudinally, verbal learning, working memory, and negative symptoms predicted 4-month functional capacity. Working memory and visual learning predicted 10-month functional capacity. Functional capacity was associated to global functioning in the univariate analysis, but in multivariable analyses global functioning, financial independence, and independent living were predicted by negative symptoms or general symptoms explaining 15–23% of the variance.

**Conclusions:** The strongest single predictor of functional capacity is working memory, followed by negative symptoms. Clinical symptoms, but not functional capacity, predicted real-world functioning. The usability of the UPSA-B in first episode schizophrenia is discussed. Neurocom, ClinicalTrials.gov Identifier: NCT00472862, <http://clinicaltrials.gov/ct2/show/NCT00472862?term=neurocom&rank=1>.

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### 1. Background

Cognitive dysfunction is a core feature of schizophrenia and a strong predictor of functional outcome. Development of cognitive remediation and enhancement therapies has stressed the importance of measuring functional improvement and awareness on the distinction between the patient's actual *performance* in real life and *capacity*. Performance-based assessment of functional capacity with its non-reliance on patient's insight is regarded a feasible and ecologically valid way to

evaluate everyday functioning (Moore et al., 2001; McKibbin et al., 2004; Leifker et al., 2009; Patterson and Mautsach, 2010).

Identification of cognitive and clinical domains involved in functional capacity would propose important targets for cognitive remediation and other interventions aiming to improve functioning. The associations between functional capacity and socio-demographic, clinical, and cognitive variables have been explored in patients with schizophrenia in their mid-thirties to sixties (Twamley et al., 2002; Bowie et al., 2006; Keefe et al., 2006a; McClure et al., 2007; Cardenas et al., 2008; Mautsach et al., 2010), but not in a sample of young adults with first episode schizophrenia.

The University of California San Diego Performance-based Skills Assessment (UPSA) is the most commonly used functional capacity measure and is evaluated to have the strongest properties among performance-based and interview-based measures of functioning (Green et al., 2011). It has been attributed with substantial construct

\* Corresponding author at: Psychiatric Centre Copenhagen, Research Department, Copenhagen University Hospital, Building 13A, 3rd Floor, Bispebjerg Bakke 23, DK-2400, Copenhagen, Denmark. Tel.: +45 50 53 11 10; fax: +45 38 64 75 04.

E-mail addresses: [lone.vesterager@regionh.dk](mailto:lone.vesterager@regionh.dk) (L. Vesterager), [torben.christensen@rn.dk](mailto:torben.christensen@rn.dk) (T.Ø. Christensen), [birtolse@rm.dk](mailto:birtolse@rm.dk) (B.B. Olsen), [gertrud.krarup@regionh.dk](mailto:gertrud.krarup@regionh.dk) (G. Krarup), [marianne.melau@regionh.dk](mailto:marianne.melau@regionh.dk) (M. Melau), [hypp@glo.regionh.dk](mailto:hypp@glo.regionh.dk) (H.B. Forchhammer), [mn@dadlnet.dk](mailto:mn@dadlnet.dk) (M. Nordentoft).

validity as a mediator of neuropsychological performance on real-world functioning and it captures from 15 to 37% of the variance in real-world outcomes like independent living and social behavior (Twamley et al., 2002; Bowie et al., 2006; Heinrichs et al., 2006). In 2007, a brief version (UPSA-B) comprising the two most significant subscales was introduced as an equally good measure of functional capacity with comparable psychometric properties (Keefe et al., 2006b; Mausbach et al., 2007; McClure et al., 2007; Cardenas et al., 2008; Mausbach et al., 2010; Green et al., 2011).

The MATRICS initiative (Buchanan et al., 2005; Nuechterlein et al., 2008) has outlined seven distinct cognitive domains with special relevance to schizophrenia: speed of processing; attention/vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; and social cognition. A moderate to strong association between functional capacity and cognitive composites has consistently been reported (Bowie et al., 2006; Silverstein et al., 2010; Silverstein et al., 2011), however, investigations are missing on the relative contribution to functional capacity of the seven separable cognitive domains.

The current study was designed to determine in a sample of patients with first episode schizophrenia spectrum disorders 1) how clinical and cognitive domains predict concurrent and longitudinal functional capacity; and 2) how functional capacity reflects global functioning, financial independency, and residential status.

## 2. Methods

### 2.1. Study design and participants

This study is a secondary study of a randomized clinical trial (Vesterager et al., 2011). Eligible participants were recruited from outpatient settings; specialized clinics for treatment of early psychosis in the two largest cities in Denmark, Aarhus and Copenhagen, and had to be in a sub-acute phase of illness, have sufficient comprehension of Danish, and no history of organic disorder or concurrent substance abuse. Out of 235 eligible patients a total of 117 patients with first episode schizophrenia spectrum disorder were included and assessed at baseline, at 4 months, and at 10 months. At 4-month follow-up 98 (84%) were available for assessments and 92 (79%) at 10-month follow-up. Participants ranged from 18 to 34 years of age, with a mean of 25.0 (SD 3.3), and were characterized by a mild to moderate severity of psychopathology with a mean PANSS total score of 54.2 (SD = 12.4). After complete description of the study to the participants, written informed consent was obtained. All assessments were completed by trained neuropsychologists (TØC and LV) and trained assistants. Baseline descriptive statistics for the participant sample are presented in Table 1.

### 2.2. Measures

Functional capacity was measured using the UPSA-B. Translation and adaptation to a Danish context were required to use the UPSA-B in this study (Vesterager et al., 2011). The UPSA-B is a performance-based measure designed to evaluate the abilities to perform everyday tasks that are considered necessary for independent functioning in the community (Mausbach et al., 2007). Each of the two subscales, finances and communication, contributes 50 points, and total scores range from 0 to 100 points; higher scores reflect better performance. The UPSA-B requires about 10 min to complete and, involves props like a telephone, a utility bill, money, and a letter.

#### 2.2.1. Cognition

Cognition was assessed using the MATRICS Cognitive Consensus Battery (MCCB) (Keefe et al., 2011). Administration requires about 65 min. The following 10 tests were administered in this standard order:

**Table 1**

Baseline characteristics of patients with first episode schizophrenia spectrum disorders in a study of clinical and cognitive predictors of functional capacity.

Domain	Variable	Valid (N = 117)	%	Mean	SD	Range
Socio-demographic						
	Male	63	53.8			
	Schizophrenia	98	83.8			
	Receiving antipsychotic medication	104	88.9			
	High school completed	59	50.4			
	Living independently <sup>a</sup>	102	87.2			
	Financial independency <sup>b</sup>	37	31.6			
	Days of hospitalization (lifetime)	113		58.6	98.0	0–575
	Age (years)	117		25.0	3.3	18–34
Global functioning	GAF	116		46.6	10.5	19–81
Functional capacity	Finance	117		40.2	7.3	13.6–50
	Communication	117		37.3	9.5	11.1–50
	UPSA-B total	117		77.5	13.3	33.8–100
Cognition <sup>c</sup>	Speed of processing	117		43.4	10.1	14–65
	Attention and vigilance	115		40.7	9.5	20–63
	Working memory	115		47.1	9.3	22–70
	Verbal learning	117		45.1	10.3	21–78
	Visual learning	117		45.5	11.0	19–63
	Reasoning and problem solving	117		52.9	9.0	31–65
	Social cognition	106		41.7	11.7	4–64
	Cognitive composite	104		42.8	9.7	21–63
Self-esteem	Rosenberg Self-Esteem Scale	109		23.1	5.5	10–37
Symptoms	Positive Scale	117		11.8	4.0	7–26
	Negative Scale	117		15.4	5.9	7–28
	General Psychopathology Scale	117		27.1	6.6	16–43
	PANSS total	117		54.2	12.4	32–80

<sup>a</sup> Living alone or with partner/spouse/friend was categorized as independent living, whereas living with parents, or in a psychiatric residential facility was categorized as non-independent living.

<sup>b</sup> Financial independence was defined as earned income, economical support for educational purposes, and temporary sick leave payment, whereas social assistance and disability pension were categorized as financial non-independence.

<sup>c</sup> MCCB derived T-scores.

- Trail Making Test Part A is a timed test of visual scanning and psychomotor speed.
- Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding is a measure of speed of processing that requires the subject to write numbers corresponding to symbols as quickly as possible for a 90-second period.
- Hopkin's Verbal Learning Test – Revised (HVLT-R) measures immediate recall of a word list.
- Wechsler Memory Scale III (WMS-III) Spatial Span measures non-verbal working memory by testing the subject's ability to remember the locations of a series of blocks to which the administrator points.
- University of Maryland Letter Number Sequencing (LNS) is a verbal working memory test that requires the subject to remember and mentally reorganize orally presented strings of numbers and letters according to a specific set of rules.
- Neuropsychological Assessment Battery (NAB) Mazes is a timed test of executive functioning requiring the subject to complete increasingly difficult mazes.
- Brief Visuospatial Memory Test – Revised (BVMT-R) is a test of immediate visual recall and reproduction of geometric figures presented for 10 s.
- Category Fluency (Animal Naming) is an oral test of speed of information processing.
- Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT)

Managing Emotions is a multiple-choice test of social cognition. Vignettes of various situations are presented along with ways to cope with the emotions depicted in these vignettes. The subject is required to indicate the effectiveness of each solution, ranging from one (very ineffective) to five (very effective). A total score was derived using the MSCEIT General Consensus method.

- Continuous Performance Test – Identical Pairs (CPT-IP) is a computerized test of attention and vigilance.

The MCCB scoring program yields seven domain scores and a composite score which are standardized to the same T-score measurement scale with a mean of 50 and an SD of 10 based upon the normative data from the MATRICS PASS (Nuechterlein et al., 2008).

### 2.2.2. Clinical measures

Severity of psychiatric symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The positive, negative, and general psychopathology subscales were used as separate variables. Higher scores reflect more severe symptoms.

Self-esteem was evaluated with the Rosenberg's Self-Esteem Scale (Rosenberg, 1965) which is a self-rated ten-item measure. Items are rated on a four-point scale from strongly agree to strongly disagree (e.g. "I take a positive attitude toward myself", "I feel I do not have much to be proud of"). Scoring of negatively worded items were reversed before summing up and higher scores indicate higher self-esteem.

### 2.2.3. Real-world functioning

Global functioning was assessed using the Global Assessment of Functioning Scale (GAF), which comprises a symptom subscale and a functioning subscale. Higher scores indicate better global functioning. Independency in living status and financial status was extracted from socio-demographic data obtained in the baseline interview and categorized as dichotomous variables prior to statistical analysis.

## 2.3. Statistical analyses

Univariate linear regression analyses were performed of each PANSS subscales, self-esteem, and MCCB domains as predictors of functional capacity. We used uncorrected T-scores of cognitive domains to allow examination of age and gender as separate predictors. Multivariable linear regression analyses with backward exclusion based on F-test were conducted at baseline. Due to ceiling effects on UPSA-B at 4-month and 10-month assessments we used the median-divided UPSA-B to conduct univariate logistic regression analyses and multivariable logistic regression analyses with backward exclusion based on Wald-test. Cognitive T-scores without demographic correction for the seven MCCB domains, PANSS subscales, and self-esteem were entered into the multivariable analyses. Age, gender, and site were entered in all of the analyses as covariates. As patients were randomized to cognitive remediation plus a comprehensive psychosocial program or the comprehensive psychosocial program alone, analyses of 4-month and 10-month results were adjusted for treatment allocation.

## 3. Results

### 3.1. Attrition

Analysis of attrition (data not shown) revealed relatively low attrition (21.4% at its highest at 10-month follow-up) and no statistically significant associations. There was a trend towards poorer baseline verbal learning (Wald = 3.73, df = 1, p = 0.054) being associated with non-attendance at 10-month assessments.

### 3.2. Prediction of concurrent functional capacity

All cognitive domains were significantly associated with functional capacity at baseline as shown in Table 2. Functional capacity was not significantly associated to gender, site, receiving antipsychotic medication, having completed high school, or diagnosis of schizophrenia, however, age (Beta = 0.24, F = 7.02, df = 1, 116, p < 0.01) was positively associated with functional capacity at baseline.

### 3.3. Functional capacity and clinical variables

Negative and general symptoms were significantly associated with functional capacity at baseline and at 4 months, but not significantly at 10 months. At all three times of assessment there was a consistent lack of association between positive symptoms and functional capacity, a finding in line with previous studies (Twamley et al., 2002; Bowie et al., 2006). Also, self-esteem was not associated with functional capacity at any times of assessment.

### 3.4. Multiple regression analysis of concurrent functional capacity

The multivariable analysis was carried out to single out the strongest concurrent predictors of functional capacity (Table 2). Working memory explained 30% of the variance in functional capacity, negative symptoms contributed with further 7% variance explained, and social cognition added 4% to the variance explained. Thus, a total of 41% of the variance in concurrent functional capacity was accounted for by three different predictor variables.

### 3.5. Longitudinal prediction of functional capacity

At 4 months and at 10 months ceiling effects were substantial on the UPSA-B. When defining ceiling effects as having zero or just one mistake on the UPSA-B, the optimal area was reached by 12 out of 117 patients (10.3%) at baseline, by 30 out of 98 (30.6%) at 4-months, and by 22 out of 92 (23.9%) at 10-months.

Table 3 shows multivariable analyses performed to identify the strongest longitudinal predictors of functional capacity: verbal learning

**Table 2**

Linear regression analysis of variables predicting concurrent functional capacity of patients with first episode schizophrenia spectrum disorders (N = 117).

	Baseline functional capacity			
	Univariate		Multivariable <sup>a,b</sup>	
	Beta	p	Beta	p
Age	0.24	<0.01		
Male gender	0.04	0.67		
Site (Copenhagen)	−0.05	0.56		
Antipsychotic medication	−0.03	0.75		
Schizophrenia	−0.03	0.77		
High school	0.08	0.37		
Speed of processing <sup>a</sup>	0.36	<0.001		
Attention and vigilance <sup>a</sup>	0.26	0.01		
Working memory <sup>a</sup>	0.50	<0.001	0.38	<0.001
Verbal memory <sup>a</sup>	0.38	<0.001		
Visual memory <sup>a</sup>	0.35	<0.001		
Problem-solving <sup>a</sup>	0.21	0.02		
Social cognition <sup>a</sup>	0.34	0.001	0.19	0.03
Cognitive composite <sup>a</sup>	0.50	<0.001		
Positive Scale <sup>a</sup>	−0.09	0.40		
Negative Scale <sup>a</sup>	−0.56	<0.001	−0.34	<0.001
General Psychopathology Scale <sup>a</sup>	−0.27	0.01		
PANSS total <sup>a</sup>	−0.48	<0.001		
Self-esteem <sup>a</sup>	0.00	1.00		

<sup>a</sup> Analyses were adjusted for age, gender, and site.

<sup>b</sup> Multivariable analysis, N = 104, R<sup>2</sup> = 0.41, F = 11.21, df = 6, 103, p < 0.001.

explained 30% of the variance in functional capacity, working memory contributed with further 9% variance explained, and negative symptoms added 4% to the variance explained. Verbal learning, working memory, and negative symptoms accounted for a total of 47% of the variance in 4-month functional capacity. At 10 months functional capacity was predicted by working memory, which explained 24% of the variance, and visual learning, which added 6% to the variance explained. Working memory and visual learning jointly accounted for a total of 30% of the variance in 10-month functional capacity.

### 3.6. Functional capacity and real-world functioning

Univariate analysis showed a significant association between functional capacity and global functioning (Beta = 0.04, Wald = 7.00,  $df = 1$ ,  $p < 0.01$ ), but in the multivariable analysis only negative symptoms significantly predicted global functioning (Beta = -0.18, Wald = 15.30,  $df = 1$ ,  $p < 0.001$ ). Functional capacity was not significantly associated to financial independence or independent living. In multivariable analyses financial independence was predicted solely by general psychopathology symptoms (Beta = -0.11, Wald = 7.76,  $df = 1$ ,  $p < 0.01$ ), and independent living was predicted solely by negative symptoms (Beta = -0.14, Wald = 4.52,  $df = 1$ ,  $p = 0.03$ ) (Table 4).

## 4. Discussion

This novel and relatively large ( $N = 117$ ) sample of young patients enabled us to investigate clinical and cognitive domains' different contribution to the prediction of concurrent and longitudinal functional capacity free of the adverse effects of long illness duration, hospitalization, and years of treatment with antipsychotic medication. Furthermore, assessments were conducted at three points in time and with relatively low attrition. The use of a comprehensive assessment battery allowed for delineation of the separable cognitive and clinical domains involved in functional capacity.

Concurrent functional capacity was associated to all seven cognitive domains out of which working memory was the strongest single predictor, both concurrently and longitudinally, by accounting for up to 1/3 of the variance in functional capacity. Negative symptoms, social cognition, verbal learning, and visual learning explained further variance. Functional capacity was only modestly associated with real-world measures of functioning.

### 4.1. Cognition and functional capacity

The strong associations between cognitive and functional capacity measures correspond to results that were found in older (Twamley et al., 2002) and in first episode patients (Williams et al., 2008) and indicate that the UPSA-B is a highly 'cognitive' measure. As noted earlier (Heinrichs et al., 2010), the distinction between functional capacity and the abilities measured by standard cognitive tests might be larger in theory than in practice and the similarity may be attributable to the performance-based nature of both tests.

These results also generate hypotheses to why cognitive composites and functional capacity are not always strongly associated (Silverstein et al., 2010; Silverstein et al., 2011). Perhaps the heterogeneity of patients' cognitive profiles influences cognitive composites in different ways, and that high performance on other cognitive domains simply does not convert into functional capacity as measured with the UPSA-B.

The domain of working memory appears to be central in the prediction of functional capacity. This may be attributed to the demanding nature of the subtests, as the LNS was rated as the most demanding/least tolerable of the tests included in the MCCB (Nuechterlein et al., 2008). Due to its requirements of manipulating symbols according to a set of rules, it may be a test that effectively distinguishes between cognitive impaired and cognitive well-functioning patients. In line with the differentiation between maintenance-only and maintenance-plus-manipulation (executive) tasks (Perry et al., 2001; Kim et al., 2004), the LNS and to some extent the backwards part of the Spatial Span should actually be labeled executive working memory tasks.

Social cognition contributed variance to the prediction of concurrent functional capacity above and beyond that associated with working memory and negative symptoms. The key abilities for performance on the MSCEIT Managing Emotions branch may resemble those required in the role-play part of the UPSA-B like higher-level inferential processes (Mancuso et al., 2011) or meta-cognitive ability to grasp the other person's need of particular information.

Although there is a well-documented overlap between cognition and negative symptoms (Milev et al., 2005), our data confirm that negative symptoms independently account for a small proportion (4–7%) of the variance in functional capacity.

Given that overall cognition, working memory, and verbal learning are improvable through cognitive remediation (Reeder et al., 2004; Dixon et al., 2010; Wykes et al., 2011) and that negative symptoms can be reduced through cognitive-behavioral therapy and integrated psychosocial treatment programs (Thorup et al., 2005; Dixon

**Table 3**

Logistic regression analyses of variables predicting longitudinal functional capacity of patients with first episode schizophrenia spectrum disorders ( $N = 98$ )<sup>a</sup>.

	4-month functional capacity						10-month functional capacity					
	Univariate			Multivariable <sup>b</sup>			Univariate			Multivariable <sup>c</sup>		
	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p
Speed of processing	0.06	7.41	0.01				0.02	1.05	0.31			
Attention and vigilance	0.03	1.60	0.21				0.04	2.64	0.10			
Working memory	0.13	14.11	<0.001	0.09	6.051	0.01	0.09	9.96	<0.01	0.08	6.43	0.01
Verbal memory	0.11	13.86	<0.001	0.08	6.069	0.01	0.04	3.56	0.06			
Visual memory	0.02	3.37	0.07				0.07	7.75	<0.01	0.05	4.22	<0.05
Problem-solving	0.01	0.18	0.67				0.01	0.23	0.63			
Social cognition	0.03	2.29	0.13				0.03	1.39	0.24			
Cognitive composite	0.11	12.50	<0.001				0.07	6.72	0.01			
Positive Scale	-0.04	0.49	0.49				-0.05	0.50	0.48			
Negative Scale	-0.15	9.62	<0.01	-0.12	4.082	<0.05	-0.08	2.62	0.11			
General Scale	-0.09	5.35	0.02				0.01	0.03	0.87			
PANSS total	-0.08	9.55	<0.01				-0.02	0.80	0.37			
Self-esteem	0.04	0.74	0.39				-0.01	0.12	0.73			

<sup>a</sup> All analyses were adjusted for age, gender, site, and treatment allocation.

<sup>b</sup> Multivariable analysis  $N = 96$ , Nagelkerke  $R^2 = 0.47$ ,  $\chi^2 = 41.82$ ,  $df = 7$ ,  $p < 0.001$ .

<sup>c</sup> Multivariable analysis,  $N = 91$ , Nagelkerke  $R^2 = 0.30$ ,  $\chi^2 = 22.88$ ,  $df = 6$ ,  $p = 0.001$ .

**Table 4**Prediction of global functioning, financial independence, and independent living of patients with first episode schizophrenia spectrum disorders (N = 117)<sup>a</sup>.

	Financial independence <sup>b</sup>						Independent living <sup>c</sup>						Global functioning <sup>f</sup>					
	Univariate			Multivariable <sup>d</sup>			Univariate			Multivariable <sup>e</sup>			Univariate			Multivariable <sup>g</sup>		
	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p	Beta	Wald (df = 1)	p
Functional capacity	0.01	0.02	0.74				0.04	3.26	0.07				0.04	7.00	<0.01			
Speed of processing	0.01	0.16	0.69				−0.02	0.38	0.54				0.06	8.72	<0.01			
Attention and vigilance	0.02	0.98	0.32				−0.05	2.27	0.13				0.02	0.82	0.37			
Working memory	0.01	0.15	0.70				−0.03	0.67	0.41				0.02	0.70	0.40			
Verbal memory	−0.01	0.20	0.65				0.00	0.01	0.92				0.03	2.35	0.13			
Visual memory	0.01	0.09	0.76				0.03	1.10	0.29				0.03	3.17	0.08			
Problem-solving	0.01	0.22	0.64				0.01	0.12	0.73				0.03	2.27	0.13			
Social cognition	0.00	0.02	0.90				0.01	0.20	0.65				−0.00	0.02	0.90			
Cognitive composite	0.01	0.03	0.56				0.01	0.08	0.78				0.02	1.24	0.27			
Positive Scale	−0.04	0.49	0.48				−0.09	1.64	0.20				−0.03	0.40	0.53			
Negative Scale	−0.09	3.94	<0.05				−0.14	4.52	<0.05	−0.14	4.52	0.03	−0.18	15.30	<0.001	−0.18	15.30	<0.001
General Scale	−0.11	7.76	<0.01	−0.11	7.76	<0.01	−0.03	0.30	0.58				−0.10	8.23	<0.01			
PANSS total	−0.06	8.06	<0.05				−0.05	3.26	0.07				−0.08	14.14	<0.001			
Self-esteem	0.10	5.04	0.03				0.01	0.03	0.86				0.04	1.10	0.30			

<sup>a</sup> All analyses were adjusted for age, gender, and site.<sup>b</sup> Financial independence was defined as earned income, economical support for educational purposes, and temporary sick leave payment, whereas social assistance and disability pension were categorized as financial non-independence.<sup>c</sup> Living alone or with partner/spouse/friend was categorized as independent living, whereas living with parents, or in a psychiatric residential facility was categorized as non-independent living.<sup>d</sup> Multivariable analysis, N = 117, Nagelkerke  $R^2 = 0.15$ ,  $\chi^2 = 12.74$ ,  $df = 4$ ,  $p = 0.01$ .<sup>e</sup> Multivariable analysis, N = 115, Nagelkerke  $R^2 = 0.22$ ,  $\chi^2 = 14.70$ ,  $df = 4$ ,  $p < 0.01$ .<sup>f</sup> Median-divided Global Assessment of Functioning (GAF).<sup>g</sup> Multivariable analysis, N = 116, Nagelkerke  $R^2 = 0.23$ ,  $\chi^2 = 22.29$ ,  $df = 4$ ,  $p < 0.001$ .

et al., 2010), this study does not only confirm that functional capacity can be improved (Leifker et al., 2010), but it also underlines that there are distinct ways to improve the components of functional capacity.

#### 4.2. Functional capacity and real-world functioning measures

Our findings differ from previous studies showing that UPSA-B explains from 15 to 30% of the variance in real-world outcomes (Twamley et al., 2002; Bowie et al., 2006; Heinrichs et al., 2006). In the current study, functional capacity as measured by the UPSA-B did not add unique validity to the prediction of real-world outcomes above and beyond that of clinical symptoms. The explanations for this missing association between functional capacity and real-world functioning may also be attributed a) the characteristics of the patient sample or to b) the measures used.

- Despite heterogeneous patient characteristics including both well-functioning and poor-functioning patients, it is, however, noteworthy that the vast majority of participants had T-scores >40 in all cognitive domains, that is within the normal range for a non-psychiatric population. American norms are frequently used in clinical neuropsychology in Scandinavian countries (Harvey et al., 2009), and the use of the MCCB-derived domains enables comparison to studies of different populations (Kern et al., 2011). Although not standardized to a Danish population, the relatively high T-scores indicate a sample selection that restricts the generalizations to be made of this study: modest cognitive and functional capacity impairment might be overruled by clinical symptoms in the prediction on real-world functioning.
- The GAF is an impressionistic scale and a more nuanced scale of real-world functioning would probably have captured more differential aspects of real-world functioning. Furthermore, categorizing independent living and financial independence dichotomously are bound to be crude measures neglecting all gray areas in independency and

need of support. Motivation is very probably an intervening variable in the association between functional capacity and real-world functioning, but was not assessed. Finally, the lack of association between functional capacity and real-world independency in the current study may reflect the local Danish opportunities of economical assistance as young patients with a debut of psychosis are not necessarily expected to support themselves or to live on their own.

#### 4.3. Ceiling effects on the UPSA-B

Longitudinal prediction was limited by ceiling effects on the functional capacity measure. The fact that the UPSA was developed for an older population of patients (Patterson et al., 2001; Twamley et al., 2002) and thus could display ceiling effects in younger patients has been predicted (Harvey et al., 2007) and observed in empirical studies (Heinrichs et al., 2006; Keefe et al., 2006b). Inclusion of supplemental, more challenging, items is critical in a younger, less impaired sample. A way of addressing the possibility of practice effects could be through provision of alternate forms of the UPSA-B for repeated uses. Unfortunately, only one version of the UPSA-B is presently available. Furthermore, modern technology seems to have outdated the financial subtest to some extent. To reflect more recent demands steps have already been taken towards development of computerized virtual-reality assessment of functional capacity (NeuroCog Trials, 2012).

#### 4.4. Implications and future research

For young adults with first episode schizophrenia the strongest single predictor of functional capacity both concurrently and longitudinally is working memory. Negative symptoms, social cognition, verbal learning, and visual learning further explain variance. Real-world functioning is primarily predicted by negative and general psychopathology symptoms.

The clinical implications of these findings are that in a relatively well-functioning sample of patients with first episode schizophrenia both negative symptoms and cognition should be addressed to improve functional capacity, but in terms of real-world functioning clinical symptoms appear to be overriding. Replication of these findings is needed as well as further research in the effect of domain-specific cognitive improvements on functional capacity and real-world functioning.

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#### Contributors

Lone Vesterager, Torben Christensen, Birthe B. Olsen, Gertrud Krarup, Marianne Melau, Hysse B. Forchhammer, Merete Nordentoft designed the study and wrote the protocol. Lone Vesterager and Merete Nordentoft carried out the statistical analyses. Lone Vesterager wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

#### Conflict of interest

All authors declare no competing interests.

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#### References

- Bowie, C.R., Reichenberg, A., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2006. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am. J. Psychiatry* 163, 418–425.
- Buchanan, R.W., Davis, M., Goff, D., Green, M.F., Keefe, R.S.E., Leon, A.C., 2005. A summary of the FDA-NIMH-MATRICES workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr. Bull.* 31, 5–19.
- Cardenas, V., Mausbach, B.T., Barrio, C., Bucardo, J., Jeste, D., Patterson, T., 2008. The relationship between functional capacity and community responsibilities in middle-aged and older Latinos of Mexican origin with chronic psychosis. *Schizophr. Res.* 98, 209–216.
- Dixon, L.B., Dickerson, F., Bellack, A.S., Bennett, M., Dickinson, D., Goldberg, R.W., 2010. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr. Bull.* 36, 48–70.
- Green, M.F., Schooler, N.R., Kern, R.S., Fiske, F.J., Granberry, W., Harvey, P.D., Karson, C.N., Peters, N., Stewart, M., Seidman, L.J., Sonnenberg, J., Stone, W.S., Walling, D., Stover, E., Marder, S.R., 2011. Evaluation of functionally meaningful measures for clinical trials of cognition enhancement in schizophrenia. *Am. J. Psychiatry* 168, 400–407.
- Harvey, P.D., Velligan, D.I., Bellack, A.S., 2007. Performance-based measures of functional skills: usefulness in clinical treatment studies. *Schizophr. Bull.* 33 (5), 1138–1148.
- Harvey, P.D., Helldin, L., Bowie, C.R., Heaton, R.K., Olsson, A.K., Hjarthar, F., Norlander, T., Patterson, T.L., 2009. Performance-based measurement of functional disability in schizophrenia: a cross-national study in the United States and Sweden. *Am. J. Psychiatry* 166, 821–827.
- Heinrichs, R.W., Statucka, M., Goldberg, J., Dermid Vaz, S., 2006. The University of California Performance Skills Assessment (UPSA) in schizophrenia. *Schizophr. Res.* 88, 135–141.
- Heinrichs, R.W., Ammari, N., Miles, A.A., Dermid Vaz, S., 2010. Cognitive performance and functional competence as predictors of community independence in schizophrenia. *Schizophr. Bull.* 36, 381–387.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.
- Keefe, R.S.E., Poe, M., Walker, T.M., Kang, J.W., Harvey, P.D., 2006a. The schizophrenia cognition rating scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. *Am. J. Psychiatry* 163, 426–432.
- Keefe, R.S.E., Poe, M., Walker, T.M., Harvey, P.D., 2006b. The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. *J. Clin. Exp. Neuropsychol.* 28, 260–269.
- Keefe, R.S.E., Fox, K.H., Harvey, P.D., Cucchiaro, J., Siu, C., Loebel, A., 2011. Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. *Schizophr. Res.* 125, 161–168.
- Kern, R.S., Gold, J.M., Dickinson, D., Green, M.F., Nuechterlein, K.H., Baade, L.E., Keefe, R.S.E., Mesholam-Gately, R.I., Seidman, L.J., Lee, C., Sugar, C.A., Marder, S.R., 2011. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. *Schizophr. Res.* 126, 124–131.
- Kim, J., Glahn, D.C., Nuechterlein, K.H., Cannon, T.D., 2004. Maintenance and manipulation of information in schizophrenia: further evidence for impairment in the central executive component of working memory. *Schizophr. Res.* 68, 173–187.
- Leifker, F.R., Bowie, C.R., Harvey, P.D., 2009. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. *Schizophr. Res.* 115, 82–87.
- Leifker, F.R., Patterson, T.L., Bowie, C.R., Mausbach, B.T., Harvey, P.D., 2010. Psychometric properties of performance-based measurements of functional capacity: test-retest reliability, practice effects, and potential sensitivity to change. *Schizophr. Res.* 119, 246–252.
- Mancuso, F., Horan, W.P., Kern, R.S., Green, M.F., 2011. Social cognition in psychosis: multidimensional structure, clinical correlates, and relationship with functional outcome. *Schizophr. Res.* 125, 143–151.
- Mausbach, B.T., Harvey, P.D., Goldman, S.R., Jeste, D.V., Patterson, T.L., 2007. Development of a brief scale of everyday functioning in persons with serious mental illness. *Schizophr. Bull.* 33, 1364–1372.
- Mausbach, B.T., Harvey, P.D., Pulver, A.E., Depp, C.A., Wolyniec, P.S., Thornquist, M.H., Luke, J.R., McGrath, J.A., Bowie, C.R., Patterson, T.L., 2010. Relationship of the Brief UCSD Performance-based Skills Assessment (UPSA-B) to multiple indicators of functioning in people with schizophrenia and bipolar disorder. *Bipolar Disord.* 12.
- McClure, M.M., Bowie, C.R., Patterson, T.L., Heaton, R.K., Weaver, C., Anderson, H., Harvey, P.D., 2007. Correlations of functional capacity and neuropsychological performance in older patients with schizophrenia: evidence for specificity of relationships? *Schizophr. Res.* 89, 330–338.
- McKibbin, C.L., Brekke, J.S., Sires, D., Jeste, D.V., Patterson, T.L., 2004. Direct assessment of functional abilities: relevance to persons with schizophrenia. *Schizophr. Res.* 72, 53–67.
- Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am. J. Psychiatry* 162, 495–506.
- Moore, D.J., Palmer, B.W., Patterson, T.L., Jeste, D.V., 2001. A review of performance-based measures of functional living skills. *J. Psychiatr. Res.* 41, 97–118.
- NeuroCog Trials. I. Virtual Reality Functional Capacity Assessment Tool (VRFCAT). 20-6-2012. Ref Type: Online Source.
- Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese III, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am. J. Psychiatry* 165, 203–213.
- Patterson, T.L., Mausbach, B.T., 2010. Measurement of functional capacity: a new approach to understanding functional differences and real-world behavioral adaptation in those with mental illness. *Annu. Rev. Clin. Psychol.* 6, 139–154.
- Patterson, T.L., Goldman, S., McKibbin, C.L., Hughs, T., Jeste, D.V., 2001. UCSD performance-based skills assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr. Bull.* 27, 235–245.
- Perry, W., Heaton, R.K., Potterat, E., Roebuck, T., Minassian, A., Braff, D.L., 2001. Working memory in schizophrenia: transient 'online' storage versus executive functioning. *Schizophr. Bull.* 27, 157–176.
- Reeder, C., Newton, E., Frangou, S., Wykes, T., 2004. Which executive skills should we target to affect social functioning and symptom change? A study of a cognitive remediation therapy program. *Schizophr. Bull.* 30, 87–100.
- Rosenberg, M., 1965. Society and the Adolescent Self-Image. Princeton University Press, NJ.
- Silverstein, S.M., Jaeger, J., Donovan-Lepore, A.M., Wilkness, S.M., Savitz, A., Malinovsky, I., Hawthorne, D., Raines, S., Carson, S., Marcello, S., Zukin, S.R., Furlong, S., Dent, G., 2010. A comparative study of the MATRICS and IntegNeuro cognitive assessment batteries. *J. Clin. Exp. Neuropsychol.* 32, 937–952.
- Silverstein, S.M., All, S.D., Jaeger, J., 2011. Cognition-UPSA score relationships: a further analysis of Silverstein et al. (2010) data and some caveats. *Psychiatry Res.* 187, 424–431.
- Thorup, A., Petersen, L., Jeppesen, P., Ohlenschlaeger, J., Christensen, T., Krarup, G., Jorgensen, P., Nordentoft, M., 2005. Integrated treatment ameliorates negative symptoms in first episode psychosis—results from the Danish OPUS trial. *Schizophr. Res.* 79, 95–105.
- Twamley, E.W., Doshi, R.R., Nayak, G.V., Palmer, B.W., Golshan, S., Heaton, R.K., Patterson, T.L., Jeste, D.V., 2002. Generalized cognitive impairments, ability to perform everyday tasks, and level of independence in community living situations of older patients with psychosis. *Am. J. Psychiatry* 159, 2013–2020.
- Vesterager, L., Christensen, T., Olsen, B., Krarup, G., Forchhammer, H., Melau, M., Gluud, C., Nordentoft, M., 2011. Cognitive training plus a comprehensive psychosocial programme (OPUS) versus the comprehensive psychosocial programme alone for patients with first-episode schizophrenia (the NEUROCOM trial): a study protocol for a centrally randomised, observer-blinded multi-centre clinical trial. *Trials* 12, 35.
- Williams, L.M., Whitford, T.J., Flynn, G., Wong, W., Liddell, B.J., Silverstein, S., Galletly, C., Harris, A.W.F., Gordon, E., 2008. General and social cognition in first episode schizophrenia: identification of separable factors and prediction of functional outcome using the IntegNeuro test battery. *Schizophr. Res.* 99, 182–191.
- Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am. J. Psychiatry* 168, 472–485.