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Executive function in first-episode schizophrenia: A three-year longitudinal study of an ecologically valid test

Kristy C.M. Liu [a], Raymond C.K. Chan [b], Kevin K.S. Chan [a], Jennifer Y.M. Tang [a], Cindy P.Y. Chiu [a], May M.L. Lam [a], Sherry K.W. Chan [a], Gloria H.Y. Wong [a], Christy L.M. Hui [a], Eric Y.H. Chen [a,*]

[a] Department of Psychiatry, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong
[b] Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, 4A Datun Road, Beijing 100101, China

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ABSTRACT

Executive function impairment is a key cognitive deficit in schizophrenia. However, traditional neuropsychological tests of executive function may not be sensitive enough to capture the everyday dysexecutive problems experienced by patients. Additionally, existing literature has been inconsistent about longitudinal changes of executive functions in schizophrenia. The present study focuses on examining the longitudinal change of executive functions in schizophrenia using the Modified Six Elements Test (MSET) that was developed based on the Supervisory Attentional System model and shown to be sensitive to everyday dysexecutive problems. In the present study, MSET performance was assessed in 31 medication-naïve first-episode schizophrenic patients at four times over a period of three years, while the 31 normal controls were assessed once. Patients demonstrated impairment in MSET as compared to controls. Importantly, the MSET impairment persisted from the medication-naïve state to clinical stabilization and the three years following the first psychotic episode though patients improved in a conventional executive test (Modified Wisconsin Card Sorting Test). Performance was not related to intelligence, educational level, symptom changes, age-of-onset, or duration of untreated psychosis. Better MSET performance at medication-naïve state predicted improvement in negative and positive symptoms over the three-year period. These findings may suggest that MSET impairment is a primary deficit in schizophrenia that occurs early in the course of the illness and remains stable irrespective of clinical state for at least three years following the first episode of schizophrenia.

1. Introduction

Executive impairment is one of the most robust and central deficits to be associated with schizophrenia and is seen across stages of the illness (Chan et al., 2006a,b; Fioravanti et al., 2005; Rund, 2002). Schizophrenic patients tend to show impairment in tests sensitive to frontal lobe lesions, including Wisconsin card sorting, verbal fluency and trail making (Chan et al., 2006b; Liddle and Morris, 1991).

The neuropsychological tests traditionally used in examining executive functions may not be sufficiently sensitive to detect the dysexecutive syndrome experienced by patients in everyday life. Studies have shown that even though people with frontal lobe lesions exhibit many characteristics of a dysexecutive syndrome in their daily lives, some may not demonstrate impairment on performing conventional executive tests (Shallice and Burgess, 1991). To better capture the everyday executive functioning in patients, the Modified Six Elements Test (MSET) was incorporated into the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996). In the MSET, subjects have to plan their time so as to complete at least part of each of the six subtasks while at

* Corresponding author. Tel.: +852 2255 4488; fax: +852 2255 1345.
E-mail address: eyhchen@hku.hk (E.Y.H. Chen).

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the same time complying with certain simple rules. Unlike most conventional executive function tests, with provided goals and defined structure, MSET requires subjects to structure the tasks themselves. In this respect, MSET resembles the open-ended nature of problem solving in everyday life. Indeed, it has been shown to be sensitive to everyday executive functioning in people with frontal lobe lesions (Shallice and Burgess, 1991) and patients with schizophrenia (Chan et al., 2006a,b). Among all the tests in BADS, MSET has been found to be superior in ecological validity and sensitivity when applied to people with schizophrenia (Chan et al., 2006a,b; Evans et al., 1997; Katz et al., 2007; Krabbendam et al., 1999), and other psychiatric and neurological disorders (Burgess et al., 1998; Chan and Manly, 2002; Norris and Tate, 2000). For example, Katz et al. (2007) found a moderate to strong correlation between MSET performance and several key areas of daily functioning (instrumental activities of daily living, communication, and work readiness) in patients with schizophrenia as measured by the Routine Task Inventory (Allen, 1989, as cited in Katz et al., 2007). MSET performance has consistently been impaired in people with chronic and with first-episode schizophrenia (Chan et al., 2004, 2006a,b; Evans et al., 1997; Katz et al., 2007).

The specific executive components measured by different conventional executive function tests are still not well understood, probably due to the lack of theoretical guidance in the development of these tests (Chan et al., 2008a). The Supervisory Attentional System (SAS) model (Norman and Shallice, 1986) proposes a classification of executive function components and has been useful in explaining the nature of dysexecutive syndrome (Chan et al., 2004, 2006b). There are two systems in the SAS model, namely, contention scheduling and supervisory attention. The former system is responsible for routine and over-learned behaviours and allows prioritization of such actions (e.g., making coffee when the phone rings). The latter system, on the other hand, is responsible for regulating goal-directed behaviours in non-routine and novel situations (Norman and Shallice, 1986).The MSET is based on the latter system. It requires test-takers to attempt at least part of the six sub-tasks while at the same time complying with simple rules. To achieve high performance on this test, test-takers must consistently and optimally mobilize the most appropriate schemata across the sub-tasks. Therefore, in terms of SAS systems, MSET was developed to capture the regulation of the non-routine component of the supervisory attention system. Moreover, MSET has demonstrated construct validity in measuring the 'action/attention inhibition' and 'output generation' components of executive functions proposed in the SAS (Chan et al., 2004).

In the existing literature, studies that provide longitudinal data of executive functioning in schizophrenia have primarily utilized conventional executive function measures. These empirical findings have been inconsistent as some found longitudinal stability, while others reported decline or improvement (e.g. Gold et al., 1999; Hill et al., 2004; Hoff et al., 2005; Rund, 1998; Stirling et al., 2003; Szoke et al., 2008). Some possible explanations for the mixed findings include heterogeneous patient profiles, varied methodological designs, and inconsistency of executive tests employed across the studies. Alternatively, it may be that conventional executive function tests probe various aspects of executive functions (Evans et al., 1997) and that the temporal change of these components differs. In light of the mixed findings, the present study attempts to elucidate the longitudinal trajectories of the individual components of executive function through application of MSET.

In the present study, longitudinal assessment of MSET performance was carried out in medication-naïve, first-episode patients with schizophrenia-spectrum disorders, for a period of three years after the first presentation of illness. The present study aims to address the following questions: (1) whether patients show impairments in MSET performance; (2) whether MSET performance improves after antipsychotic treatment; (3) how MSET performance evolves over the three years following the first psychotic episode and; (4) whether MSET performance is related to demographics, clinical variables, duration of untreated psychosis, or outcome in first-episode schizophrenia.

2. Methods

2.1. Participants

Participants were 31 medication-naïve patients with first-episode schizophrenia-spectrum disorders chosen from a larger cohort recruited for longitudinal studies by our research team (some of the baseline data has been reported by Chan et al., 2006b). All patients were Cantonese-speaking, Han Chinese, and met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Consensus clinical diagnoses were made by two experienced psychiatrists based on DSM-IV. Patients were excluded if they had significant medical illness or if they were clinically judged to have high risk of suicidal behaviour. The healthy control sample consisted of 31 volunteers recruited from the general public and matched with the patient group for gender, age, and years of education. Controls were screened with a questionnaire designed by our team (available upon request) to ensure the absence of personal or family history of psychiatric illness, general medical or neurological illness, and history of special school attendance. The study was approved by the relevant Institutional Review Boards and written informed consent was attained from all subjects prior to participation. Assessment of patients was carried out at the point of first contact (medication-naïve), after clinical stabilization, at the end of the first year and at the end of the third year. Healthy controls were assessed only once.

2.2. Assessments

2.2.1. Clinical assessments

Positive and Negative Syndrome Scale (PANSS; Kay et al., 1988) was used to assess symptoms in patients; ratings were made based on clinical interviews and medical records. The inter-rater reliability of the three raters was 0.83 for the PANSS (by intra-class correlation coefficient). The Interview for the Retrospective Assessment of the Onset of Schizophrenia (Hafner et al., 1992) was used to assess duration of untreated psychosis (DUP) and for obtaining information about educational level. Functioning was measured using the Social and

Occupational Functioning Scale (SOFAS; American Psychiatric Association, 1994).

2.2.2. Cognitive assessments

2.2.2.1. Intelligence. Intelligence was calculated at the first assessment in both patients and normal controls using the Information, Arithmetic, Digit Span, Digit Symbol and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised for Cantonese speaking populations (Hong Kong Psychological Society, 1989).

2.2.2.2. Modified Six Elements Test (MSET). The MSET (Burgess et al., 1996) is a simplified version of the original Six Elements Test developed by Shallice and Burgess (1991). It consists of three types of tasks (viz. dictation, simple arithmetic and picture naming), each having two subtasks. The dictation task requires participants to tell a story on a specific topic ('a holiday' for subtask A; 'a happy event' for subtask B). The simple arithmetic task consists of 60 simple arithmetic questions. The picture naming task contains of 60 brightly colored pictures which must be identified in writing. Each participant was administered the task individually. Participants were required to attempt at least part of each subtask within 10 min; they received instructions that the subtasks of the same task could not immediately follow each other. They were also told that the aim of the test was not to finish all the subtasks as fast as possible. A digital timer was provided for participants to monitor time. Four scores were calculated for the MSET: (1) the number of subtasks completed; (2) the number of rule-breaking behaviour (rule error); (3) the number of times the subject has spent over 217 s on one subtask (time error) and; (4) the summary score of the above three scores (total profile score) (Wilson et al., 1996).

The Chinese version of the task has been adapted to be used in patients with first-episode and chronic schizophrenia and healthy adults in Hong Kong, and has been shown to be sensitive to deficits in attention allocation and planning (Chan et al., 2004, 2006a,b).

2.2.2.3. Modified Wisconsin Card Sorting Test. The Modified Wisconsin Card Sorting Test (MWCST: Nelson, 1976) was chosen as the conventional executive test with which to compare to MSET. Participants were required to sort 48 stimulus cards according to defined rules. When the participants had given six correct responses consecutively, a change of rule occurred. The number of categories completed and perseverative errors were calculated.

2.3. Data analysis

All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS) version 17.0. To compare standard MSET scores and MWCST scores between patients and controls, an analysis of covariance (ANCOVA) was carried out with IQ, age, gender, and educational level as covariates. A repeated measures ANOVA for MSET scores and MWCST scores with four within-subject levels (medication-naïve, stabilized, year one, and year three) was performed to investigate the changes of MSET scores and MWCST scores over time. Correlational analyses were carried out between MSET scores and demographic, clinical, and outcome variables.

3. Results

3.1. Sample characteristics

Participant characteristics are presented in Table 1. There were no significant differences between patients and normal controls in age, years of education, or gender ratio (Table 1). Of the 11 patients with diagnosis of schizophreniform disorder, nine converted to schizophrenia and two to schizoaffective disorder within three years. Twenty-nine patients were medication-naïve in the first assessment and the majority of patients remained on stable medication during follow ups, as presented in Table 2. PANSS scores of patients are presented in Table 3. A repeated measures ANOVA showed that there were significant changes of PANSS scores over time.

3.2. MSET and MWCST performance at the first episode

MSET and MWCST scores of patients at initial presentation were compared to that of healthy controls (Table 4). Results from the ANCOVA, controlling for the effects of IQ, age, gender and educational level, showed that patients attempted significantly fewer subtasks, committed more time errors, and had lower total profile scores than the normal controls in

Table 1
Sample characteristics.

	Patients (n = 31)	Controls (n = 31)	χ^2 or t	p-value
Age, mean (SD), years	27.58 (9.99)	26.79 (10.29)	$t = 0.31$	.759
Gender, M/F	21/10	14/17	$\chi^2 = 3.22$	.073
Educational level, mean (SD), years	11.29 (3.43)	11.10 (1.81)	$t = 0.28$	.782
DUP, median (IQR), days	110.00 (45.50–298.75)			
Diagnoses, number (%)				
Schizophrenia	18 (58.06)			
Paranoid type	16 (51.61)			
Catatonic type	0			
Disorganized type	0			
Undifferentiated type	2 (6.45)			
Residual type	0			
Schizoaffective disorder	2 (6.45)			
Schizophreniform disorder	11 (35.48)			

SD: standard deviation; DUP: duration of untreated psychosis; IQR: inter-quartile range.

Table 2
Drug treatment of patients.

	Initial presentation	Clinical stabilization	Year 1	Year 3
Antipsychotic drugs, numbers (%):	2 (6.5)	31(100)	27 (83.9)	29 (93.5)
Amisulpride	0	3 (9.7)	6(19.4)	5(16.1)
Aripiprazole	0	1(3.2)	1(3.2)	3(9.7)
Clozapine	0	1(3.2)	1(3.2)	1(3.2)
Flupenthixol	0	0	1(3.2)	3(9.7)
Haloperidol	1 (3.2)	2(6.5)	1(3.2)	2(6.5)
Olanzapine	0	8(25.8)	8(25.8)	6(19.4)
Quetiapine	1 (3.2)	4(12.9)	1(3.2)	2(6.5)
Risperidone	0	4(12.9)	5(16.1)	5(16.1)
Sulpiride	0	1(3.2)	1(3.2)	1(3.2)
Trifluoperazine	0	5(16.1)	3(9.7)	1(3.2)
Ziprasidone	0	2(6.5)	1(3.2)	1(3.2)
CPZ equivalent doses, mean, mg/day	104.15	274.78	239.1	220.3
Concurrent drugs, numbers (%):				
Antidepressants	0	4(12.9)	5(16.1)	5(16.1)
Anticholinergics	0	11(35.5)	8(25.8)	6(19.4)
Benzodiazepines	2(6.5)	3(9.7)	3(9.7)	3(9.7)

CPZ: chlorpromazine.

MSET, and completed fewer categories and committed more perseverative errors in MWCST.

3.3. Longitudinal change of MSET and MWCST scores

A repeated measures ANOVA showed that there was no significant longitudinal change for any MSET score (Table 5). To exhaustively explore the possible changes of MSET scores between time points, in particular that from medication-naïve state to clinical stabilization, paired sample *t*-tests were used to compare MSET scores for all combinations of time point pairs. Again, for all MSET scores, no significant changes were observed between any time points. In contrast, results of repeated measures ANOVA showed that there were significant changes in the two MWCST scores.

3.4. Demographic and clinical correlates of MSET performance

In patients, females committed more time errors than males ($t = -2.567$, $p = .016$); amongst controls, there was no gender difference in MSET scores. Neither IQ nor educational level was correlated with MSET scores in patients or normal controls. Age of onset and DUP were not correlated with MSET scores in patients, and MSET scores did not differ significantly between patients with different diagnoses. At initial presentation, positive symptoms were correlated with time errors ($r = .443$, $p = .013$), but there was no significant correlation between change in MSET performance and change in negative or positive symptoms.

Table 4
MSET and MWCST performance of patients at the first episode.

	Patients (n = 31)	Controls (n = 31)	*F*	*p*-value
MSET:				
Subtasks attempted, mean (SD)	5.19 (1.20)	5.90 (0.40)	9.33	.004
Rule error, mean (SD)	1.00 (1.21)	0.58 (1.03)	0.71	.402
Time error, mean (SD)	0.45 (0.57)	0.23 (0.43)	5.85	.019
Total profile score, mean (SD)	2.58 (0.99)	3.48 (0.68)	13.78	<.001
MWCST				
Categories completed, mean (SD)	3.70 (2.10)	5.35 (1.14)	9.38	.003
Perseverative errors, mean (SD)	6.43 (5.39)	1.80 (2.40)	11.55	.001

MSET: Modified Six Elements Test; MWCST: Modified Wisconsin Card Sorting Test; SD: standard deviation.

3.5. MSET performance and outcome

MSET scores at initial presentation were not correlated with change in SOFAS score, while rule error scores at initial presentation correlated negatively with changes in negative symptoms ($r = -.362$, $p = .046$), and time error scores at initial presentation correlated negatively with changes in positive symptoms ($r = -.453$, $p = .010$).

4. Discussion

The current study provided longitudinal data on an ecologically valid measure of executive dysfunction in a medication-naïve cohort of first-episode schizophrenic patients. We found that first-episode patients exhibited impairment in MSET performance at medication naïve state regardless of DUP, age of onset, IQ or educational level. Stability of MSET impairment was observed longitudinally from the medication-naïve state through the first three years of illness which contrasted with the improvement seen in the patients' performance on a conventional executive test (MWCST). Importantly, better MSET performance at the initial medication-naïve state predicted greater improvement in symptoms at the end of the third year, but was not related to three-year functional outcome.

Table 3
PANSS scores of patients.

	Initial presentation	Clinical stabilization	Year 1	Year 3	*F*	*p*-value	Significant contrasts [a]
Overall score, mean (SD)	76.32(12.31)	44.32(11.21)	39.80(9.02)	39.19(10.36)	104.55	<.001	1>2, 3, 4
Positive scale, mean (SD)	20.23(3.42)	8.84(2.73)	7.73(2.00)	7.77(2.16)	168.78	<.001	1>2, 3, 4; 2>3, 4
Negative scale, mean (SD)	14.65(5.86)	11.42(4.92)	10.10(5.05)	10.35(5.30)	7.89	.009	1>2, 3, 4; 2>3
General psychopathology scale, mean (SD)	37.16(8.21)	20.90(5.69)	18.73(4.27)	17.90(4.44)	87.05	<.001	1>2, 3, 4; 2>3, 4

PANSS: Positive and Negative Syndrome Scale; SD: standard deviation.
[a] As measures by LSD comparisons, significance value at $p < .05$. For simplification, numbers are used to denote the different clinical stage: 1: initial presentation, 2: clinical stabilization, 3: Year 1, 4: Year 3.

Table 5
MSET and MWCST performance of patients in the 3 years following a first psychotic episode.

	Initial presentation	Clinical stabilization	Year 1	Year 3	*F*	*p*-value
MSET:						
Subtasks attempted, mean (SD)	5.19 (1.20)	5.10(1.51)	5.32(1.19)	5.35(1.12)	0.43	.519
Rule error, mean (SD)	1.00(1.21)	0.74(1.21)	0.68(1.05)	0.81(1.20)	0.51	.678
Time error, mean (SD)	0.45(0.57)	0.71(1.10)	0.52(0.63)	0.42(0.62)	1.11	.301
Total profile score, mean (SD)	2.58(0.99)	2.74(1.44)	2.97(1.17)	3.00(1.10)	1.37	.257
MWCST:						
Categories completed, mean (SD)	3.70(2.10)	4.33(2.16)	5.20(1.45)	5.20(1.67)	6.80	<.001
Perseverative errors, mean (SD)	6.43(5.39)	5.23(6.17)	1.97(3.37)	2.30(3.75)	10.15	.003

MSET: Modified Six Elements Test; WCST: Modified Wisconsin Card Sorting Test; SD: standard deviation.

The impairment in MSET performance, as found in the present study, is consistent with previous findings of chronic and medicated first-episode patients (Chan et al., 2004; Evans et al., 1997; Katz et al., 2007). It also adds to the scarce data concerning medication-naïve patients (Chan et al., 2006b) and is consistent with the findings of impairments in conventional executive functions tasks in medication-naïve patients (Mohamed et al., 1999). The presence of MSET impairment early in the course of illness, before the effects of medication or progression of illness, suggests that it is a deficit fundamental to schizophrenia.

The lack of correlation of MSET performance with both IQ and educational level shown in the present study, together with previous empirical findings about the consistency of MSET impairment in intellectually intact psychosis patients (Chan et al., 2006b; Evans et al., 1997), suggests that MSET impairment is unlikely to be entirely a consequence of general intellectual impairment in schizophrenia, and instead may reflect a specific deficit over and above intellectual impairment.

To the best of our knowledge, the present study is the first to provide data about the longitudinal change in MSET performance of schizophrenic patients. Our results indicate stability of MSET impairment in a group of medication-naïve first-episode patients alongside improvement in performance on a conventional executive test, suggesting that the two tasks measure different components of executive functioning. In particular, MSET impairment was already present in the medication-naïve state and persisted through clinical stabilization, suggesting that the impairment was not alleviated by antipsychotic medication. The relative temporal stability of MSET performance, together with the present findings that MSET performance is not dependent on symptom changes, suggests that MSET deficit in first-episode schizophrenia is not likely to be state-dependent. However, this postulation is tentative and further evidence is needed from replications of the present findings.

The lack of correlation between MSET performance and DUP and age of onset raises the question of when MSET deficit in schizophrenia occurs. The present findings indicate that deficits precede the commencement of antipsychotic medication. Other evidence has shown that deterioration in cognitive functioning occurs well in advance of clinical symptoms (e.g. Cannon et al., 2000; Chan et al., 2008b; Laws et al., 2008), even among individuals who are in the prodromal stage of psychosis (e.g. Brewer et al., 2005). However with respect to MSET impairment, the exact period when the impairment commences is yet to be determined.

Katz et al. (2007) have found that BADS was a significant predictor for two outcome areas (instrumental activities of daily living and communication) within a sample of chronic schizophrenic patients. In the present study, we found that MSET performance was correlated with clinical outcomes over a three-year period following a first episode. With a prospective longitudinal design, the present study provides valuable data about the relationship of executive functions (as measured by MSET) early in the course of the illness and later clinical outcome. It also suggests the importance of measuring executive functions for rehabilitation of patients.

Several limitations should be addressed before drawing any conclusions. First, the present study focuses on one specific test of the BADS. Thus, results can only be applicable to the specific components of executive functions measured by MSET, and generalization of the present findings remained to be explored. Second, although the present study provided valuable data about executive functions at the early course of first-episode schizophrenia, the study duration was three years preventing detection of development of executive functioning over a more extended period. Indeed, prospective longitudinal studies of cognitive functions that follow psychosis patients for longer than 5 years have been scarce (Gold et al., 1999; Hoff et al., 2005; Stirling et al., 2003) despite the invaluable information they would contribute to the field. Third, this study has established that MSET deficit occurred at the early stage of psychosis prior to the intervention with antipsychotic medication. However, ascertaining the exact onset of this deficit was beyond the scope of the study; greater understanding of the onset is important as it could guide early intervention efforts. Further longitudinal studies of people at high risk of psychosis are needed to address this issue.

5. Conclusion

By using an ecologically valid measure of executive functions, the present study has shown that executive impairment as measured by MSET is a specific and fundamental deficit in schizophrenia that occurs early in the course of the illness. More importantly, such deficits remain stable irrespective of clinical state from the medication-naïve period to clinical stabilization and in the three years following the first episode of psychosis, which suggests that the MSET deficit in first-episode schizophrenia is not likely to be state-dependent.

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Contributors

Eric Chen and Raymond Chan designed the study. Kristy Liu managed literature searches and analyses, and wrote the first draft of the manuscript. Kristy Liu, Raymond Chan, Kevin Chan, Jennifer Tang and Eric Chen contributed to data analysis. All authors contributed to interpretation of results, participated in critical revision of manuscript drafts and approved the final version.

Conflict of interest

All authors declare that they have no conflicts of interest.

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