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ORIGINAL PAPER

Executive dysfunctions differentially predict amotivation in first-episode schizophrenia-spectrum disorder: a prospective 1-year follow-up study

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Abstract
Amotivation is a major determinant of functional outcome in schizophrenia but it is understudied in the early course of illness. There is a paucity of longitudinal research investigating predictors of amotivation. In this study, we aimed to examine baseline cognitive and clinical predictors of amotivation at 6 and 12 months of follow-up in patients aged 18–55 years presenting with first-episode DSM-IV schizophrenia-spectrum disorder (FES). Of 145 patients recruited at intake, 116 and 113 completed assessments at 6- and 12-month follow-up, respectively. Amotivation was measured by avolition-apathy and anhedonia-asociality subscale scores of the Scale of the Assessment of Negative Symptoms. Cognitive assessment was administered at baseline. As executive dysfunction has been more consistently found to be associated with negative symptoms and amotivation in prior literature, we adopted fractionated approach to subdivide executive function into distinct components encompassing switching and flexibility, response initiation, response inhibition, planning and strategy allocation, sustained attention and working memory. Our results showed that baseline amotivation ($p=0.01$) and switching and flexibility ($p=0.01$) were found to independently predict amotivation at 6 months follow-up. Baseline amotivation ($p<0.01$) and switching and flexibility (albeit with trend-wise significance, $p=0.06$) were also retained in final multivariate regression model for 12-month amotivation prediction. No other executive components or cognitive domains predicted amotivation at follow-up. Findings of our study thus indicate amotivation at initial presentation as a critical determinant of subsequent motivational deficits over 1 year of treatment for FES patients. Cognitive flexibility might be specifically related to the development of amotivation in the early stage of illness.

Keywords Amotivation · Executive function · Fractionation · Cognitive flexibility · Switching · First-episode schizophrenia

Introduction

Negative symptoms are a core feature of schizophrenia and are critically associated with functional disability [1]. Literature has shown that negative symptoms comprise two distinct sub-domains, namely motivational impairment (i.e., amotivation) and diminished expression (DE) [2]. Recent data has found that amotivation is more prevalent and persistent over time than DE [3, 4], and is a major predictor of concurrent and longitudinal functional outcome in chronic and first-episode schizophrenia, above and beyond the contributions of DE, other symptom dimensions and even cognitive deficits [5–11].

Substantial evidence has indicated that schizophrenia patients exhibit generalized cognitive impairment across multiple domains of cognition [12]. Previous studies further demonstrated significant associations between negative symptoms and cognitive deficits [13]. In particular, many, though not all, prior researches have revealed that among various cognitive domains, impairment in executive function may be more specifically related to negative

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symptom severity [14, 15]. Of note, it is acknowledged that executive function is not a unitary construct but consists of multiple individual cognitive processes. The supervisory attentional system (SAS), proposed by Norman and Shallice [16, 17], is a well-studied model which provides theoretical framework for sub-classification of executive function into fractionated components. The SAS is responsible for regulating goal-directed behaviors in novel, non-routine situations [18]. Disruption of this system may result in failure in goal formulation, planning, and proper selection between alternative sequences of actions for goal attainment. Fractionation of executive function into specific components based on the SAS model thus provides a systematic approach (versus viewing executive function as a single cognitive domain) to comprehensively examine relationships of executive deficits with symptom dimensions, especially amotivation in schizophrenia [19, 20]. Alternatively, there is emerging evidence demonstrating efficacy of cognitive remediation on reducing negative symptoms in schizophrenia patients [21]. One recent study further revealed that beneficial effect of cognitive remediation on negative symptoms was mediated by improvement in executive function [22]. Hence, clarifying cognitive processes underlying amotivation is crucial for the development of effective intervention for motivational deficits in schizophrenia.

It should be noted that previous research investigating the relationship between cognitive functions and amotivation in schizophrenia was hampered by several important methodological limitations. First, the majority of past studies measured negative symptoms using a single composite score without further delineation into two symptom sub-domains, thereby precluding investigation of specific cognitive deficits associated with amotivation. Second, very few studies have adopted theoretically based, fractionated approach in examining executive function and its relationship with amotivation. Instead, most evaluated executive function either as a unified cognitive process or based only on a few cognitive tests that may not adequately capture the multidimensional nature of executive function. This may obscure potential significant differential associations of executive function components with amotivation. Third, most previous studies focused on patients with chronic schizophrenia. However, accumulating evidence has indicated that amotivation emerged in the initial stage of illness strongly predicts subsequent motivational deficits [4, 23] and poor functional outcome [3, 6, 9], and thus has been regarded as a critical therapeutic target for promoting early recovery. Yet, despite its clinical significance in early illness phase, the relationship between amotivation and cognitive dysfunction is understudied in first-episode schizophrenia. Fourth, there is a paucity of longitudinal investigation examining prediction of baseline cognitive functions on amotivation at follow-up in schizophrenia, and none was conducted in first-episode samples.

In the current report, we present a prospective 1-year follow-up study in a representative cohort of Chinese patients presenting with first-episode schizophrenia-spectrum disorder (FES) in Hong Kong with an aim to identify baseline clinical and cognitive predictors of amotivation at 6 and 12 months of follow-up. Given that executive dysfunction has been more consistently found to be related to negative symptoms and motivational impairment in prior literature, we adopted fractionated approach, on the basis of SAS model, to the assessment of executive function which was subdivided into a number of separable cognitive components encompassing response initiation, switching and flexibility, strategy allocation and planning, response inhibition, working memory and sustained attention [19, 20]. This enabled more refined evaluation of executive deficits and identification of differential impacts of executive components on amotivation in the initial year of treatment for FES.

Methods

Participants and setting

One hundred forty-five consecutive patients aged 18–55 years presenting with first-episode DSM-IV [24] schizophrenia, schizophreniform disorder or schizoaffective disorder were recruited from outpatient and inpatient psychiatric units that provided service for a catchment area (i.e., Hong Kong Island) in Hong Kong with a population of approximately 1.3 million. Patients with known neurological disorder, substance abuse or learning disability were excluded. Of the initial cohort, 116 and 113 patients completed 6- and 12-month follow-up assessments, respectively. Completers did not differ from non-completers in demographics, baseline clinical characteristics and cognitive performance. The study was approved by local institutional review board and all participants provided informed consent.

Clinical assessments

Diagnosis was ascertained using all available information including the Chinese bilingual Structured Clinical Interview for DSM-IV (CB-SCID-I/P) [25], informant histories and medical records. The Interview for Retrospective Assessment of the Onset of Schizophrenia (IRAOS) [26] was administered to determine duration of untreated psychosis (DUP) which was defined as the time interval between onset of psychotic symptoms and service entry. Psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS) [27]. Separate symptom dimension scores (positive symptoms, disorganization, excitement and

depression) were derived from PANSS ratings based on previous factor-analysis conducted in first-episode psychosis [28]. Negative symptoms were measured by Scale of Assessment of Negative Symptoms (SANS) [29]. We generated two negative symptom sub-domain scores, i.e., amotivation and diminished expression (DE) based on the method applied by previous research [9, 30]. Amotivation consisted of items of Avolition-apathy and Anhedonia-asociality subscales (excluding global items) in SANS; and DE comprised items of Affective flattening subscale (excluding global item) and poverty of speech item of Alogia subscale. Intra-class correlation coefficients for PANSS general psychopathology, positive and negative symptom subscales, and SANS total score were 0.87, 0.84, 0.73 and 0.82, respectively. Psychopathological assessment was conducted at intake, 6 and 12 months.

Cognitive assessments

A standardized battery of cognitive assessments was administered at intake to all participants. Processing speed was measured by digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R-HK) [31]. Verbal memory was measured by logical memory subtest of the Wechsler Memory Scale-Revised (WMS-R-HK) [32]. Working memory was assessed by Letter-Number Span (LNS) test [33]. Sustained attention was evaluated by monotone counting test [34] Intellectual function was estimated using the subtest short-form of the WAIS-R-HK [35].

A comprehensive set of executive function tests comprising Modified Wisconsin Card Sorting test (MWCST) [36], Trail making test (TMT) Part A and B [37], category verbal fluency, Hayline Sentence Completion test (HSCT) [38] and Modified Six Elements test (MSET) [39] was administered to evaluate specific components of executive function, based on the fractionated approach adopted in previous research in schizophrenia. The Chinese versions of HSCT and MSET were employed in the current study and have previously been applied in local Chinese FES populations [40–42]. Under the framework of SAS model, working memory (i.e., online updating) and sustained attention were also conceptualized as individual components of executive function. A group of healthy controls ($n = 37$), matched by age, gender and educational level, was evaluated with the same battery of cognitive assessments as patients. Specific components of executive function [19, 20] and cognitive test measures that captured these components are detailed as below.

Response initiation

Category verbal fluency, TMT Part A and HSCT Part A were used to assess response initiation. In HSCT Part A, 15 sentences were verbally presented in which the last word was missing but was strongly cued by the context of the sentence. Participants were instructed to appropriately complete the sentences and total number of the correct responses was recorded to assess semantic initiation capacity.

Switching and flexibility

A number of perseverative errors committed in MWCST and TMT Part B performance were used as indices for switching and cognitive flexibility component of executive function.

Planning and strategy allocation

This component was measured using a number of categories completed in MWCST and a total profile score of MSET. The MSET assessed strategy allocation and involved three types of task including simple arithmetic, picture naming and dictation, with each having two subtasks. Participants were required to attempt at least part of each subtask within 10 min without consecutively completing subtasks of the same task. The total profile, which corresponded to an index of attention allocation and planning capacity, was computed on the basis of the number of subtasks completed, the number of rule-breaking errors, and the number of times a participant spent over 217 s per subtask.

Response inhibition

The HSCT Part B was employed to assess participants' ability to suppress inappropriate response. Participant was presented with 15 sentences in which the last word was omitted but was strongly suggested by the rest of the sentence, and was then required to give a word that made no sense in the sentence context. To correctly perform the task, the participant was required to inhibit a strongly cued automatic response and to provide an unrelated answer. Total error score was computed according to the error classification and scoring procedure outlined by Burgess and Shallice [38] as an index for executive inhibitory control. The number of rule-breaking errors committed in MSET was also used to assess response inhibition.

Data analysis

The primary analysis focused on identifying baseline clinical and cognitive predictors of amotivation at 6 and 12-month follow-up. First, a series of univariate linear regression analyses were conducted with amotivation at follow-up as dependent variable, and demographic, clinical and cognitive variables as candidate predictors. Second, those variables that showed P value < 0.10 in preceding analyses were then entered into multivariate regression models to determine which factors independently predicted amotivation at

6- and 12-month follow-up. Standardized z score for each of the cognitive tests was computed based on performance of healthy controls. Composite score for individual components of executive function (i.e., response initiation, switching and flexibility, strategy allocation and planning, and response inhibition) was calculated by averaging z scores of the respective cognitive test measures included in that specific component. When applicable, scores of specific cognitive tests were multiplied by − 1, so that the lower scores always indicated poorer performance. DUP was log-transformed due to its skewed distribution. The level of statistical significance other than univariate analyses was set at $P < 0.05$.

Results

Characteristics of the sample

Table 1 summarizes demographics, baseline clinical characteristics and cognitive functions of the patient sample. Of the 116 patients who completed 6-month follow-up assessment, 56% were male. The mean (SD) age of the sample at intake was 26.1 (9.6) years, and the mean (SD) educational level was 11.3 (2.7) years. The median DUP for the sample was 187 days. At 12 months, 113 patients completed follow-up assessment, with 54.9% being male. The mean (SD) age and the mean (SD) educational level of the completers were 26.8 (10.1) years and 11.0 (3.0) years, respectively. The median DUP of this sample was 185.5 days. The majority were diagnosed with schizophrenia (6-month completers: 87.9%; 12-month completers: 89.4%). Patients performed significantly worse than healthy controls on all cognitive tests, with a range from 0.3 (digit symbol) to 1.8 (MWCST perseverative errors) standard deviations below that of controls, and was consistent with findings of the literature on cognitive impairment in FES patients [43].

Univariate associations with amotivation at follow-up

Associations of amotivation at 6- and 12-month follow-up with demographic, baseline clinical and cognitive variables are shown in Tables 2 and 3, respectively. Scatter plots illustrating significant relationships between SANS amotivation at follow-ups and individual executive function components are also shown in Figure S1 as supplementary materials. Amotivation at 6-month follow-up was significantly related to age at entry, gender, educational level, PANSS disorganization and depression scores, SANS amotivation and DE scores, IQ estimate, logical memory measure, and composite scores of initiation, switching and flexibility, as well as planning and strategy allocation. Amotivation at 12-month follow-up was significantly associated with age at entry, educational attainment, PANSS disorganization and depression scores, SANS amotivation and DE scores, performance on digit symbol and logical memory tests, and switching and flexibility component score.

Predictors of amotivation at follow-up

As shown in Table 4, baseline amotivation levels and switching and flexibility component score independently predicted amotivation at 6-month follow-up. Multivariate regression analysis also revealed that baseline amotivation and switching and flexibility component were retained in the final equation for prediction of 12-month amotivation, though the latter only closely approached statistical significance ($P = 0.06$).

Discussion

In the current investigation, we sought to identify baseline cognitive and clinical predictors of amotivation over 1-year follow-up in patients presenting with FES. To the best of our knowledge, this is the first longitudinal study examining predictive capacity of cognitive functions on motivational impairment in FES sample, using fractionated approach to deconstruct broadly defined, multi-dimensional executive function into distinct cognitive components for analysis. Our results indicate that baseline amotivation and cognitive flexibility (i.e., switching and flexibility) component of executive function independently predicted amotivation at 6- and 12-month follow-up.

Our finding that baseline amotivation predicted motivational impairment at follow-up concurs with previous research which showed that diminished motivation at entry was significantly associated with 1-year amotivation in first-episode psychosis patients [5]. This further underscores the critical role of motivational impairment that emerged in the initial phase of illness in determining subsequent severity of amotivation in FES. Intriguingly, our results revealed a specific relationship between executive dysfunction and amotivation, with switching and flexibility, but not other executive components or cognitive domains, being found to selectively predict amotivation at follow-up. In particular, our data demonstrated that switching and flexibility component significantly predicted amotivation at 6 months and was also retained in the final regression model (albeit with trend-wise significance, $P = 0.06$) for prediction of amotivation at 12 months. This provides evidence supporting the stability of predictive role of cognitive flexibility on amotivation over the first year of treatment for FES. Cognitive flexibility refers to an ability to adjust and shift between cognitive processes and behaviors in response to changing environment and demands [44], and is crucial for goal-directed behavior

Table 1 Demographics, baseline clinical characteristics and cognitive functions of patients with first-episode schizophrenia-spectrum disorder

Variables of interest	Patients with 6-month follow-up ($n=116$)	Patients with 12-month follow-up ($n=113$)
	Mean (SD)/*N* (%)	Mean (SD)/*N* (%)
Demographics		
Age at entry	26.1 (9.6)	26.8 (10.1)
Male gender	65 (56.0)	62 (54.9)
Years of education	11.3 (2.7)	11.0 (3.0)
Baseline clinical characteristics		
Psychiatric diagnosis		
Schizophrenia	102 (87.9)	101 (89.4)
Schizoaffective disorder	5 (4.3)	3 (2.7)
Schizophreniform disorder	9 (7.8)	9 (8.0)
Median DUP, days[a]	187	185.5
PANSS positive symptom score	22.1 (4.9)	21.9 (5.0)
PANSS disorganization score	14.9 (6.4)	14.6 (6.3)
PANSS depression score	11.8 (4.5)	11.4 (4.2)
PANSS excitement score	7.1 (3.3)	6.9 (3.0)
SANS amotivation score	8.0 (8.6)	8.4 (8.7)
SANS DE score	5.9 (8.0)	6.1 (8.1)
Baseline cognitive functions		
IQ estimate	104.8 (23.5)	103.3 (22.1)
Digit symbol	−0.3 (0.2)	−0.3 (0.2)
Logical memory	−0.4 (1.0)	−0.3 (1.0)
Executive function components		
Working memory[b]	−1.0 (1.6)	−1.1 (1.7)
Sustained attention[c]	−0.4 (1.2)	−0.4 (1.2)
Response initiation	−0.9 (1.4)	−1.0 (1.4)
HSCT-A correct responses	−1.1 (3.0)	−1.2 (3.1)
TMT-A time[d]	−1.1 (2.1)	−1.2 (2.3)
Category verbal fluency	−0.8 (0.9)	−0.8 (0.8)
Switching and flexibility	−1.1 (2.0)	−1.2 (2.0)
MWCST perseverative errors[d]	−1.7 (3.3)	−1.8 (3.4)
TMT-B time[d]	−0.7 (1.7)	−0.8 (1.7)
Planning and strategy allocation	−1.0 (1.3)	−1.0 (1.3)
MWCST categories completed	−1.0 (1.7)	−1.0 (1.8)
MSET total profile score	−1.1 (1.5)	−1.1 (1.5)
Response inhibition	−0.6 (1.2)	−0.6 (1.3)
HSCT-B total errors[d]	−0.8 (1.9)	−0.8 (1.9)
MSET rule-breaking errors[d]	−0.6 (1.4)	−0.5 (1.3)

DUP Duration of untreated psychosis, *DE* Diminished expression, *HSCT-A* Hayline Sentence Completion Test Part A, *HSCT-B* Hayline Sentence Completion Test Part B, *MSET* Modified Six Elements Test, *MWCST* Modified Wisconsin Card Sorting Test, *PANSS* Positive and Negative Syndrome Scale, *SANS* Scale for Assessment of Negative Symptoms, *TMT-A* Trail Making Test Part A, *TMT-B* Trial Making Test Part B

[a]Mean DUP of patients with 6-month and 12-month follow-up was 385.6 days (588.0) and 396.6 days (830.3), respectively

[b]Working memory was measured by Letter-number span test

[c]Sustained attention was measured by monotone counting test

[d]Polarity of the respective cognitive measures was reversed by multiplying with −1 so that higher scores indicated better performance

Table 2 Relationships of amotivation at 6-month follow-up with demographics, and baseline clinical and cognitive measures in patients with first-episode schizophrenia-spectrum disorder[a]

Variables of interest	β	*t*	*P*	95% CI	
				Lower bound	Upper bound
Demographics					
Age at entry	−0.20	−2.21	0.03	−0.28	−0.02
Gender	−0.16	−1.69	0.09	−4.71	0.38
Years of education	−0.18	−1.97	0.05	−0.91	0.00
Baseline clinical characteristics					
Log DUP	0.06	0.61	0.54	−1.30	2.45
PANSS positive symptom score	0.06	0.59	0.56	−0.18	0.34
PANSS disorganization score	0.31	3.46	0.001	0.14	0.53
PANSS depression score	−0.27	−2.98	0.004	−0.69	−0.14
PANSS excitement score	0.08	0.88	0.38	−0.22	0.57
SANS amotivation score	0.57	7.32	<0.001	0.33	0.58
SANS DE score	0.40	4.64	<0.001	0.20	0.49
Baseline cognitive functions					
IQ estimate	−0.25	−2.62	0.01	−0.11	−0.02
Digit symbol	−0.16	−1.47	0.15	−11.59	1.74
Logical memory	−0.29	−2.72	0.01	−3.24	−0.50
Executive function components					
Working memory	−0.09	−0.85	0.40	−1.27	0.51
Sustained attention	−0.19	−1.69	0.13	−2.30	0.19
Response initiation	−0.23	−2.09	0.04	−2.06	−0.05
Switching and flexibility	−0.37	−3.48	0.001	−1.91	−0.52
Planning and strategy allocation	−0.29	−2.67	0.01	−2.66	−0.39
Response inhibition	−0.05	−0.46	0.65	−1.47	0.93

DUP Duration of untreated psychosis, *DE* Diminished expression, *PANSS* Positive and Negative Syndrome Scale, *SANS* Scale for Assessment of Negative Symptoms

[a] Univariate linear regression analyses were conducted

and consequent specific goal attainment. Disruption in switching and flexibility ability may thus underlie impaired motivation in schizophrenia patients. In fact, this also echoes findings of extensive neuroimaging literature on executive dysfunction and amotivation in schizophrenia. Substantial evidence has indicated that dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), thalamus and basal ganglia are critically involved in switching and cognitive flexibility of executive processing [45]. Previous studies have demonstrated reduced activation in left DLPFC, ACC and thalamus in schizophrenia patients while performing executive function tests including set-switching task [46, 47]. Conversely, negative symptom severity was found to be positively correlated with prefrontal cortical gray matter reduction [48]. More specifically, there is evidence showing that schizophrenia patients with high levels of amotivation had significantly greater frontal lobe volume reduction [49]. One recent study further revealed significant associations of persistent amotivation with more pronounced cortical thinning in left orbitofrontal cortex and ACC in first-episode psychosis patients [50]. Hence, this indicates that abnormalities in neural circuitry implicated in executive function, and cognitive flexibility in particular, might contribute to diminished motivation in schizophrenia.

Although our results were broadly consistent with the majority of prior studies in first-episode and chronic schizophrenia which demonstrated that performance on executive function test examining set-switching was associated with negative symptoms [14, 15, 51]; mixed findings were observed across those few studies that specifically addressed relationships between amotivation and individual cognitive functions in schizophrenia. Some studies revealed lack of association of amotivation with any domains of cognitive function [52–54], while one report showed that amotivation was related to verbal memory (but no executive function was measured) [55]. Three studies indicated a significant relationship between amotivation and executive dysfunction [49, 56, 57], with two further demonstrating that set-switching was linked to amotivation [49, 57]. One recent study also showed that cognitive flexibility (as measured by difference between TMT-B and TMT-A times) was significantly related to behavioral subcomponent of apathy (i.e., lack of initiative and low everyday productivity) in chronic schizophrenia [58]. Findings in first-episode studies were

Table 3 Relationships of amotivation at 12-month follow-up with demographics, and baseline clinical and cognitive measures in patients with first-episode schizophrenia-spectrum disorder[a]

Variables of interest	β	t	P	95% CI	
				Lower bound	Upper bound
Demographics					
Age at entry	−0.17	−1.84	0.07	−0.21	0.01
Gender	−0.14	−1.49	0.14	−3.95	0.56
Years of education	−0.17	−1.82	0.07	−0.72	0.03
Baseline clinical characteristics					
Log DUP	0.08	0.84	0.41	−0.97	2.39
PANSS positive symptom score	0.05	0.55	0.59	−0.16	0.29
PANSS disorganization score	0.27	2.94	0.004	0.09	0.44
PANSS depression score	−0.21	−2.28	0.03	−0.57	−0.04
PANSS excitement score	0.11	1.16	0.25	−0.16	0.60
SANS amotivation score	0.61	8.15	<0.001	0.32	0.53
SANS DE score	0.48	5.72	<0.001	0.23	0.48
Baseline cognitive functions					
IQ estimate	−0.31	−3.24	0.02	−0.26	−0.06
Digit symbol	−0.20	−1.86	0.07	−8.93	0.31
Logical memory	−0.23	−2.13	0.04	−2.18	−0.07
Executive function components					
Working memory	−0.02	−0.13	0.89	−0.67	0.58
Sustained attention	−0.13	−1.19	0.24	−1.44	0.36
Response initiation	−0.18	−1.57	0.12	−1.41	0.17
Switching and flexibility	−0.30	−2.69	0.01	−1.30	−0.19
Planning and strategy allocation	−0.16	−1.41	0.16	−1.53	0.26
Response inhibition	0.00	−0.03	0.97	−0.92	0.89

DUP Duration of untreated psychosis, *DE* Diminished expression, *PANSS* Positive and Negative Syndrome Scale, *SANS* Scale for Assessment of Negative Symptoms

[a]Univariate linear regression analyses were conducted

Table 4 Final multiple regression models for prediction of amotivation at 6 and 12-month follow-up

Variables in the equation	β	t	P	95% CI	
				Lower bound	Upper bound
Final model for amotivation at 6 months[a]					
SANS amotivation	0.31	2.84	0.01	0.08	0.43
Switching and flexibility	−0.32	−2.87	0.01	−1.66	−0.30
Final model for amotivation at 12 months[b]					
SANS amotivation	0.46	4.33	<0.01	0.15	0.41
Switching and flexibility	−0.20	−1.83	0.06	−1.04	0.02

DE Diminished expression, *PANSS* Positive and Negative Syndrome Scale, *SANS* Scale for Assessment of Negative Symptoms

[a]Age at entry, gender, educational level, and baseline PANSS disorganization, PANSS depression, SANS DE, IQ estimate, logical memory, response initiation, planning and strategy allocation were included in stepwise linear regression analysis but were excluded from the final model. Final model: adjusted $R^2 = 0.28$, $F = 7.89$, $P < 0.001$

[b]Age at entry, educational level, and baseline PANSS disorganization, PANSS depression, SANS DE, logical memory and digit symbol were included in stepwise linear regression analysis but were excluded from the final model. Final model: adjusted $R^2 = 0.29$, $F = 10.70$, $P < 0.001$

even less consistent in this respect. Thus far, there were only four published reports examining relationship of amotivation or negative symptoms with cognitive functions in FES patients [40, 51, 56, 59]. Most had a small sample size (three studies with $N < 80$, ranging between 22 and 78) [40, 56, 59]. Only two studies examined amotivation rather than

global negative symptom severity [52, 56]. One revealed that working memory and response initiation component of executive function were associated with amotivation [56], while another study, which did not employ fractionated approach in executive function measurement, failed to demonstrate any significant relationship between amotivation and executive impairment [52]. Of note, such discrepant findings might be partly attributable to methodological variation across studies including recruitment of participants at different phases of illness (with majority focused on chronic schizophrenia), selection of specific executive function tests, and measurement of executive function as a single cognitive domain versus a multifaceted construct with separable components. Importantly, until now, most past studies were cross-sectional and there has been no longitudinal research examining cognitive predictors of amotivation in FES. Findings on the concurrent relationship of amotivation with cognitive functions might not, however, be generalizable to prospective investigation of cognitive prediction on motivational impairment. Alternatively, given the paucity of existing data, further longitudinal research is warranted to verify our preliminary findings on the predictive value of cognitive flexibility on amotivation in FES.

Several methodological limitations warrant consideration in interpreting the study results. First, amotivation was measured by ratings derived from the relevant subscales in SANS instead of employing an instrument that is designed to specifically assess motivational deficits. Adoption of the latter would provide a more refined assessment of amotivation, and may therefore generate a more accurate prediction model for motivational impairment. Alternatively, assessment of amotivation could be improved using next-generation negative symptom scales (e.g., BNSS [60] and CAINS [61]) which were developed on the basis of modern conceptualization of negative symptoms [62] and address the limitations of existing rating instruments by including items measuring anticipatory pleasure and distinguishing internal experience from behavior for avolition and asociality. Second, individual executive components were composed of an unequal number of cognitive measures, and those comprised only single measure (working memory and sustained attention) may be less stable in representing the component construct. Third, the number of participants included in the study was modest with a dropout rate of 20 and 22.1% at 6 and 12 months of follow-up, respectively. Nonetheless, comparison analyses revealed no significant differences between completers and non-completers in demographics, and baseline clinical and cognitive measures, indicating that participant attrition was unlikely to bias the study results. Fourth, the sample size of healthy controls for cognitive comparison was relatively small. Although our data on FES patients' cognitive functions based on standardized *z* scores were generally consistent with the findings of previous research on cognitive deficits in first-episode populations, recruitment of a larger sample of healthy participants for patient–control comparison would provide a more accurate estimation of the degrees of cognitive impairment in FES patients. Fifth, the study has a relatively short follow-up duration. Reassessment at a later time will clarify the longer-term impact of baseline executive function components on predicting amotivation in FES patients.

In conclusion, our results indicate that motivational deficits emerged at initial presentation robustly predict higher levels of amotivation over the first year of treatment for FES patients. Our finding that amotivation at follow-up was selectively predicted by cognitive flexibility and not by any other executive components or cognitive domains underscores the importance of examining executive function at the level of separable, theoretically derived cognitive components. This also suggests cognitive flexibility of executive function as a potential therapeutic target of cognitive remediation for improvement of diminished motivation. Additionally, given that amotivation is a chief determinant of functional disability, further longitudinal research investigating dysfunctional cognitive processes underlying motivational deficits is required to facilitate development of effective interventions to ameliorate amotivation and therefore its adverse impact on functional outcome.

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Compliance with ethical standards

Conflict of interest Author E.Y.H.C. has participated in the paid advisory board for Otsuka, has received educational grant support from Janssen-Cilag, and has received research funding from Astra-Zeneca, Janssen-Cilag, Eli Lilly, Sanofi-Aventis and Otsuka. E.H.M.L has been a member of the paid advisory boards for Eli Lilly and AstraZeneca. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD (2006) Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. Am J Psychiatry 163:418–425
2. Messinger JW, Tremeau F, Antonius D (2011) Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. Clin Psychol Rev 31:161–168
3. Fervaha G, Foussias G, Agid O, Remington G (2015) Motivational deficits in early schizophrenia: prevalent, persistent, and key determinants of functional outcome. Schizophr Res 166:9–16

4. Norman RMG, Manchanda R, Harricharan R, Northcott S (2015) The course of negative symptoms over the first five years of treatment: data from an early intervention program for psychosis. Schizophr Res 169:412–417
5. Faerden A, Finset A, Friis S et al (2010) Apathy in first-episode psychosis patients: one year follow-up. Schizophr Res 116:20–26
6. Foussias G, Mann S, Zakzanis KK, van Reekum R, Agid O, Remington G (2011) Prediction of longitudinal functional outcomes in schizophrenia: the impact of baseline motivational deficits. Schizophr Res 132:24–27
7. Barrett EA, Barrett EA, Nesvåg R et al (2013) Apathy, poor verbal memory and male gender predict lower psychosocial functioning one year after the first treatment of psychosis. Psychiatry Res 210:55–61
8. Fervaha G, Foussias G, Agid O, Remington G (2014) Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. Acta Psychiatr Scand 130:290–299
9. Galderisi S, Rossi A, Rocca P et al Italian Network For Research on Psychoses (2014) The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatry 13:275–287
10. Chang WC, Hui CLM, Chan SKW, Lee EHM, Chen EYH (2016) Impact of avolition and cognitive impairment on functional outcome in first-episode schizophrenia-spectrum disorder: a prospective one-year follow-up study. Schizophr Res 170:318–321
11. Chang WC, Kwong VWY, Hui CLM, Chan SKW, Lee EHM, Chen EYH (2017) Relationship of amotivation to neurocognition, self-efficacy and functioning in first-episode psychosis: a structural equation modeling approach. Psychol Med 47:755–765
12. Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12:426–445
13. Dominguez MDG, Viechtbauer W, Simons CPJ, van Os J, Krabbendam L (2009) Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. Psychol Bull 135:157–171
14. Nieuwenstein MR, Aleman A, de Haan EHF (2001) Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies. J Psychiatr Res 35:119–125
15. Dibben CRM, Rice C, Laws K, McKenna PJ (2009) Is executive impairment associated with schizophrenic syndromes? A meta-analysis. Psychol Med 39:381–392
16. Norman DA, Shallice T (1986) Attention to action: willed and automatic control of behavior. In Davidson RJ, Schwartz GE, Shapiro D (eds) Consciousness and self-regulation: advances in research and theory. Plenum, New York, pp 1–18
17. Shallice T (1988) From neuropsychology to mental structure. Cambridge University Press, Cambridge
18. Gilbert SJ, Burgess PW (2008) Executive function. Curr Biol 18:110–114
19. Donohoe G, Robertson IH (2003) Can specific deficits in executive functioning explain the negative symptoms of schizophrenia? A review. Neurocase 9:97–108
20. Chan RCK, Toulopoulou T (2006) Fractionation of executive function in schizophrenia: relationships to clinical and neurological manifestations. In: French DP (ed) Schizophrenic psychology: new research. Nova Science, New York, pp 1–39
21. Cella M, Preti A, Edwards C, Dow T, Wykes T (2017) Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis. Clin Psychol Rev 52:43–51
22. Farreny A, Augado J, Ochoa S, Haro JM, Usall J (2013) The role of negative symptoms in the context of cognitive remediation for schizophrenia. Schizophr Res 150:58–63
23. Mezquida G, Cabrera B, Bioque M et al (2017) The course of negative symptoms in first-episode schizophrenia and its predictors: a prospective two-year follow-up study. Schizophr Res 189:84–90
24. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, DC
25. So E, Kam I, Leung CM, Chung D, Liu Z, Fong S (2003) The Chinese-bilingual SCID-I/P Project: Stage 1: reliability for mood disorders and schizophrenia. HK J Psychiatry 13:7–18
26. Hafner H, Riecher-Rossler A, Hambrecht M et al (1992) IRAOS: an instrument for the assessment of onset and early course of schizophrenia. Schizophr Res 6:209–223
27. Kay SR, Opler LA, Fiszbein A (1987) Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276
28. Emsley R, Rabinowitz J, Torreman M, the RIS-INT-35 Early Psychosis Global Working Group (2003) The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. Schizophr Res 61:47–57
29. Andreasen NC (1984) Scale for the assessment of negative symptoms (SANS). University of Iowa, Iowa City
30. Foussias G, Mann S, Zakzanis KK, van Reekum R, Remington G (2009) Motivational deficits as the central link to functioning in schizophrenia: a pilot study. Schizophr Res 115:333–337
31. Hong Kong Psychological Society (1989) The Wechsler Adult Intelligence Scale-revised (Cantonese version). Hong Kong Psychological Society, Hong Kong
32. Hong Kong Psychological Society (1989) The Wechsler Adult Memory Scale-revised (Cantonese version). Hong Kong Psychological Society, Hong Kong
33. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR (1997) Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry 54:159–165
34. Wilkins AJ, Shallice T, McCarthy R (1987) Frontal lesions and sustained attention. Neuropsychologia 25:359–365
35. Chan ELS, Chen EYH, Chan RCK (2005) Three-subtest short form of the Wechsler Adult Intelligence Scale for patients with psychotic disorders: a preliminary report. HK J Psychiatry 15:39–42
36. Nelson HE (1976) A modified card sorting test sensitive to frontal lobe defects. Cortex 12:313–324
37. Reitan RM (1955) The relation of the Trail Making Test to organic brain damage. J Couns Psychol 10:330–340
38. Burgess PW, Shallice T (1996) Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia 34:263–273
39. Burgess PW, Alderman N, Evans J, Wilson B, Emslie H, Shallice T (1996) Modified six elements test. In: Wilson BA, Alderman PW, Burgess PW, Emslie H, Evans JJ (eds) Behavioral assessment of the dysexecutive syndrome. Thames Valley Test Company, Bury St. Edmunds
40. Chan RCK, Chen EYH, Law CW (2006) Specific executive dysfunction in patients with first-episode medication-naive schizophrenia. Schizophr Res 81:51–64
41. Liu KC, Chan RC, Chan KK et al (2011) Executive function in first-episode schizophrenia: a three-year longitudinal study of an ecologically valid test. Schizophr Res 126:87–92
42. Chan KKS, Xu J, Liu K, Hui CL, Wong GH, Chen EY (2012) Executive function in first-episode schizophrenia: a three-year longitudinal study of the Hayling Sentence Completion Test. Schizophr Res 135:62–67
43. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ (2009) Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23:315–336

44. Cana J, Quesada JF, Antoli A, Fajardo I (2003) Cognitive flexibility and adaptability to environmental changes in dynamic complex problem-solving tasks. Ergonomics 46:482–501
45. Dajani DR, Uddin LQ (2015) Demystifying cognitive flexibility: implications for clinical and developmental neuroscience. Trends Neurosci 38:571–578
46. Minzenberg MJ, Laird A, Thelen S, Carter CS, Glahn DC (2009) Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry 66:811–822
47. Eisenberg DP, Berman KF (2010) Executive function, neural circuitry, and genetic mechanisms in schizophrenia. Neuropsychopharmacology 35:258–277
48. Chua SE, Wright IC, Poline JB et al (1997) Grey matter correlates of syndromes in schizophrenia. A semi-automated analysis of structural magnetic resonance images. Br J Psychiatry 170:406–410
49. Roth RM, Flashman LA, Saykin AJ, McAllister TW, Vidaver R (2004) Apathy in schizophrenia: reduced frontal lobe volume and neuropsychological deficits. Am J Psychiatry 161:157–159
50. Mørch-Johnsen L, Nesvåg R, Faerden A et al (2015) Brain structure abnormalities in first-episode psychosis patients with persistent apathy. Schizophr Res 164:59–64
51. Leeson VC, Robbins TW, Matheson E et al (2009) Discrimination learning, reversal, and set-shifting in first-episode schizophrenia: stability over six years and specific associations with medication type and disorganization syndrome. Biol Psychiatry 66:586–593
52. Ergul C, Ucok A (2015) Negative symptom subgroups have different effects on the clinical course of schizophrenia after the first episode: a 24-month follow up study. Eur Psychiatry 30:14–19
53. Hartmann-Riemer MN, Hager OM, Kirschner M et al (2015) The association of neurocognitive impairment with diminished expression and apathy in schizophrenia. Schizophr Res 169:427–432
54. Lim J, Lee SA, Lam M et al (2016) The relationship between negative symptom subdomains and cognition. Psychol Med 46:2169–2177
55. Brebion G, Bressan RA, Pilowsky LS, David AS (2009) Depression, avolition, and attention disorders in patients with schizophrenia: associations with verbal memory efficiency. J Neuropsychiatry Clin Neurosci 21:206–215
56. Faerden A, Vaskinn A, Finset A et al (2009) Apathy is associated with executive functioning in first episode psychosis. BMC Psychiatry 9:1
57. Konstantakopoulos G, Ploumpidis D, Lulis P, Patrikelis P, Soumani A, Papadimitriou GN, Politis AM (2011) Apathy, cognitive deficits and functional impairment in schizophrenia. Schizophr Res 133:193–198
58. Raffard S, Gutierrez LA, Yazbek H et al (2016) Working memory deficit as a risk factor for severe apathy in schizophrenia: a 1-year longitudinal study. Schizophr Bull 42:642–651
59. Greenwood KE, Morris R, Sigmundsson T, Landau S, Wykes T (2008) Executive functioning in schizophrenia and the relationship with symptom profile and chronicity. J Int Neuropsychol Soc 14:782–792
60. Kirkpatrick B, Strauss GP, Nguyen L et al (2011) The Brief Negative Symptom Scale: psychometric properties. Schizophr Bull 37:300–305
61. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP (2013) The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry 170:165–172
62. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR (2006) The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 32:214–219