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Longitudinal trajectories of subjective cognitive complaints in patients with major depressive disorder and similar objective cognitive trajectories

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Abstract

Background We examined the factors influencing various subtypes of subjective cognitive change in patients who shared similar objective cognitive trajectories within 6 months.

Method We used data from an observational, prospective, cohort study, including 598 patients with major depressive disorder (MDD) in latent class mixed models based on the digit symbol substitution test performance. Participants were stratified into four distinct objective cognitive layers: "low cognitive performance," "lower-middle cognitive performance," "upper-middle cognitive performance," and "high cognitive performance." Within each of the four layers, the trajectories of subjective cognitive complaints were identified. Multinomial regression was employed, with cognitive complaint trajectories as the outcome, and depressive symptoms, clinical features, and other covariates as predictors.

Results The factors influencing the subjective trajectories varied among the different objective layers. Patients with comorbid anxiety disorders or functional syndromes had more prominent self-reported cognitive symptoms and a slower rate of improvement. Younger age and lower education level were also influential factors for delayed remission of subjective cognitive function. Disease severity and antidepressant type did not contribute to dedifferentiating subjective cognitive trajectory subtypes within different subjective cognitive trajectories.

Conclusion Despite similar objective cognitive trajectories, subjective perceptions of these cognitive changes are heterogeneous. These findings deepen our understanding of the multifaceted nature of cognitive change in individuals with MDD and underscore the importance of considering a range of factors when interpreting and treating cognitive impairment at an early stage.

Keywords Major depressive disorder, Objective cognition, Subjective cognition, Trajectory, Characteristic

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Introduction

Major depressive disorder (MDD) is a prevalent and debilitating condition that affects over 120 million people worldwide and is a leading contributors to disability [1]. The symptoms of MDD typically include mood disturbances, low self-esteem, incoherent thinking, lack of interest, poor concentration, and indecisiveness [2, 3, 4]. Cognitive impairments, such as inattention, slowness, and indecisiveness, persist throughout the course of MDD [5, 6, 7, 8] and have long been related to the effect of the illness on poor functional outcomes and lack of symptom relief from antidepressant treatment [9, 10, 11].

Cognitive impairment can be measured using neuropsychological tests and self-report measures, which reflect an individual's cognitive ability and perception of ability, respectively. Both objective and subjective measures of cognitive ability have been established as significantly associated with depression treatment outcomes, psychosocial functioning, and life satisfaction [12, 13]. However, some previous studies have found no significant associations between objective cognitive functioning and subjective cognitive complaints [4, 14, 15] due to different processing mechanisms. Unlike self-reports, neuropsychological tests allow for objective cognitive assessments that are less influenced by patient insight, values, and concurrent situational events. Subjective cognitive complaints is not only shaped by objective cognitive impairments but is also affected by self-relevant or mood-congruent cognitive bias.

There has been evidence of directional and magnitude differences between objective cognitive function and subjective cognitive complaints related to unsatisfying treatment outcomes and psychosocial functioning in MDD [16, 17, 18]. Meanwhile, the discrepancy score or the type of discrepancy computed from a single time point at the start of treatment correlated strongly with treatment response and improved with function [16, 19, 20]. This discrepancy also suggests that there is a diversity of cognitive subtypes. Therefore, we hypothesized the significance of developing distinct trajectories for changes in objective cognitive functioning and subjective cognitive complaints during a follow-up scenario, aiming to comprehend changes in the cognitive abilities of individual patients with depression in terms of change and to identify cognitive subtypes from a clinical point of view. We constructed various objective cognitive function trajectories for patients with depression and explored the characteristics of patients who showed differences in changes in subjective cognitive complaints among the various objective cognitive function trajectories.

Methods

Participants and settings

This study employed data from an epidemiological, noninterventional, prospective, cohort study. The Prospective Research Observation to Assess Cognition in Treated Patients with MDD (PROACT) study was conducted between March 2016 and July 2017 at 15 psychiatric hospitals or units in general hospitals in four regions of China (North, South, East, and West), representing diverse clinical settings in China. The study was approved by the independent ethics committee of each study site. All patients provided written informed consent for participation. The study followed the International Conference on Harmonization Good Clinical Practices guidelines and the ethical principles of the Declaration of Helsinki.

Study inclusion and exclusion criteria have been reported [5]. Generally, inclusion criteria for the study included (1) outpatients who were aged 18–65 years; (2) patients with major depressive disorder (MDD), according to the International Classification of.

Diseases-10 (ICD-10);(3)patients who initiated a new antidepressant therapy at the baseline visit as decided by their physician; (4) patients who had moderate to severe depression, which was defined as ≥ 17 on a total score of the Hamilton Depression Rating Scale-17 Items (HDRS-17).Patients with comorbid psychotic or bipolar disorders, alcohol or substance dependence, use of combination therapy (currently using more than one antidepressant or adjunctive antipsychotic or mood stabilizer) were excluded. Patients in this cohort were followed up at 1,2,6 months within 6 months after the initiation of the new antidepressant monotherapy after the baseline investigation.

Measures

Demographics and clinical characteristics

The participants' basic social-demographic and clinical characteristics were collected through the case report form designed for the present study.

Perceived impairments questionnaire-depression (PDQ-D)

The PDQ-D [21] was used to measure subjective cognitive complaints, which assessed self-perceived impairment over the past week across four domains of cognitive function including attention/concentration, prospective memory, retrospective memory, and planning/organization. Each domain was composed of five questions scored from 0 (never) to 4 (always), yielding a total score ranging from 0 (no complaint) to 80 (severe complaints). A higher score indicates that the complaint is more pronounced The Chinese version of the PDQ-D has shown good psychometric validity for assessing the subjective cognitive complaints in patients with MDD [22].

Digit symbol substitution test (DSST)

The DSST is a neuropsychological coding test in which the patient is required to substitute simple symbols for digits over a 90-second period to assess performance of objective cognitive function. The score was calculated based on the number of correct symbols substituted and yielded a score ranged 0–133, with higher scores indicating better objective cognitive performance. The DSST has been shown to be sensitive to impairments in several domains, including motor speed, attention, and visuoperceptual function, which have been identified as being affected in patients with MDD. The Chinese version of DSST has been validated in Chinese population [23]. The DSST has also demonstrated its ability to detect changes in cognitive function, making it a promising clinical decision-making tool for monitoring the progression of MDD over time [24].

Hamilton depression rating scale-17 items (HDRS-17)

The HDRS-17 was used to measure depressive symptoms. The total HDRS-17 score ranges from 0 to 52, with a higher score indicating greater severity of depressive symptoms [25]. The Chinese version of HDRS-17 was validated and widely used in measurement of the severity of depressive symptoms in patients with MDD [26].

EuroQol five dimensions questionnaire (EQ-5D)

The EQ-5D is a self-report form designed to measure the patient's health-related quality of life [27]. It is composed of five questions about the respondent's state of health, measuring mobility, self-care, the performance of usual activities, pain or discomfort, and anxiety or depression. Each item is rated on a 5-point scale ranging from 1 (no problem) to 5 (extreme problem), a weighted total score of items ranging from −0.4162 to 1, with higher scores indicating better health-related quality of life [28]. The Chinese version of EQ-5D-5 L became available in 2012 [29] and can used in measuring health-related quality of life burden in China [30].

Statistical analysis

SAS 9.4 and R were used for statistical analysis in this study. First, we employed latent class mixed models (LCMMs) using the "lcmm" R package [31, 32] to identify an optimal number of latent classes of individuals sharing similar DSST trajectories. It starts with one linear class and determines the best-fitting models by adding more classes and including intercepts and slopes of the quadratic function. Models with increasing number of classes were compared using statistical (the Bayesian Information Criterion (BIC), Akaike's Information Criterion (AIC), and substantive (entropy) and empirical criteria (enough participants (> 5%) occupied each class) to determine the best-fitting model. The LCMMs were performed on 1767 observations, representing 589 patients, and the 4-class model were chosen. We then divided the sample into four strata based on the latent classes obtained, each representing a DSST trajectory layer (Supplement Table S1). Second, we identified an optimal number of cognitive complaint trajectories (PDQ-D) within each layer of the objective cognitive trajectory (DSST) using the same approach as described above. Within each layer, we found that the 2-class or 3-class model had the lowest BIC; therefore, these models were selected as the best, each exhibiting a specific trajectory of subjective cognitive complaint over 6 months (Supplement Table S2). Then, a multinomial regression was applied, with the classes of PDQ-D trajectory as the outcome variable within each DSST layers. The predictors were all from baseline survey, including sociodemographic variables (age, sex, employment, and education), baseline depressive severity (HDRS-17 score), disease features (time since this episode, recurrence or first episode), comorbidity-anxiety disorders or functional syndrome (including sleep disorders, chronic pain, and chronic fatigue), and health-related quality of life (EQ-5D score). The interrelated changes among subjective cognitive complaints, objective cognitive performance, and disease severity at different visit time points were analyzed using a repeated measures linear mixed-effects model(MMRM).

Results

Sample description

In total, 598 participants were included in the growth curve modeling to determine objective cognitive trajectories. Among the study participants, 68.6% were female, and 45.2% had a university level education or higher. More than 50% of patients had first-episode depression. A substantial (71.9%) proportion of patients had experienced disease duration of longer than eight weeks during this episode, with a mean HRDS-17 score of 23.3 (SD = 4.4). More than 30.6% of patients had combined functional syndrome, and 23.4% had anxiety disorders.

The mean PDQ-D score of the patients decreased from a baseline of 33.7 (SD = 16.2) to 17.7 (SD = 15.4) at 6 months, while the mean DSST score increased from 50.2 (SD = 16.5) at baseline to 58.7 (SD = 17.5) at 6 months. We constructed a repeated measures linear mixed-effects model with PDQ-D and DSST scores at each visit as the dependent variables and HAMD-17 scores at each visit as the independent variable. The results indicated that the time effect on improvement for both PDQ-D ($P = 0.0053$) and DSST ($P < 0.001$) was significant, and both were significantly associated with changes in HAMD-17 (P values < 0.001). Other baseline characteristics of the study population are presented in Table 1.

Table 1 Characteristics of patients in the four objective cognitive trajectory layers

Variables	Whole sample	Layer #1	Layer #2	Layer #3	Layer #4		
		Low DSST performance	Lower-middle DSST performance	High DSST performance	Upper-middle DSST performance	*P*	Comparisons among layers
N (% of the sample)	598(100%)	97(16.2)	189(31.6)	106(17.7)	206(34.5)		
Age group						< 0.001	1 ≠ 2 ≠ 3 ≠ 4
18–26	123(20.6)	0(0.0)	19(10.1)	45(42.5)	59(28.6)		
26–35	175(29.3)	8(8.2)	47(24.9)	45(42.5)	75(36.4)		
36–55	240(40.1)	50(51.6)	103(54.5)	16(15.1)	71(34.5)		
56–65	60(10.0)	39(40.2)	20(10.6)	0(0.0)	1(0.5)		
Female; *n* (%)	410(68.6)	72(74.2)	122(64.6)	77(72.6)	139(67.5)	0.2855	-
Employment status						< 0.001	
Employed	426(71.2)	35(36.1)	128(67.7)	93(87.7)	170(82.5)		1 < 2 < (3 = 4)
Unemployed	172(28.8)	62(63.9)	61(32.3)	13(12.3)	36(17.5)		
Education attainment [*n* (%)]						< 0.001	1 ≠ 2 ≠ 3 ≠ 4
No degree	134(22.4)	47(48.4)	58(30.7)	4(3.8)	25(12.1)		
High school, junior college	194(32.4)	41(42.3)	78(41.3)	17(16.0)	58(28.2)		
University, post graduate school or above	270(45.2)	9(9.3)	53(28.0)	85(80.2)	123(59.7)		
First episode	343(57.4)	51(52.6)	104(55.0)	68(64.2)	120(58.2)	0.3348	-
Recurrence	255(42.6)	46(47.4)	85(45.0)	38(35.8)	86(41.8)		
Contaminant functional syndromes						< 0.0001	1 < 2 < (3 = 4)
Yes	183(30.6)	44(45.4)	72(38.1)	17(16.0)	50(24.3)		
Concomitant anxiety disorder							
Yes	140(23.4)	40(41.2)	50(26.5)	15(14.2)	32(15.5)	< 0.001	1 < 2 < (3 = 4)
Assessment at baseline							
HDRS-17 score	23.3 ± 4.4	24.9 ± 4.4	23.5 ± 4.5	21.4 ± 3.7	23.2 ± 4.3	< 0.001	1 > (2 = 3) > 4
EQ-5D utility score	0.7 ± 0.1	0.7 ± 0.2	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	< 0.001	(3 = 4 = 2) > 1
DSST score	50.2 ± 16.5	26.5 ± 6.4	42.2 ± 7.5	73.1 ± 7.6	56.9 ± 7.1	< 0.001	3 > 4 > 2 > 1
PDQ score	33.7 ± 16.2	32.2 ± 16.6	35.0 ± 16.6	31.6 ± 15.5	34.3 ± 15.9	0.2463	-
Antidepressant							
SSRI	384(64.2)	58(59.8)	119(63.0)	76(71.7)	131(63.6)	0.3116	-
SNRI	152(25.4)	33(34.0)	48(25.4)	23(21.7)	48(23.3)	0.1684	-
Other	62(10.4)	6(6.2)	22(11.6)	7(6.6)	27(13.1)	0.1426	-
Assessment at month 6							
Remission rate (HRDS-17 ≤ 7)	342(64.5)	53(62.4)	105(61.4)	68(72.3)	116(64.4)	03323	-
HRDS-17 score	6.9 ± 5.6	7.1 ± 5.4	7.5 ± 5.6	5.6 ± 5.6	6.9 ± 5.5	0.0607	-
DSST score	58.7 ± 17.5	32.8 ± 7.2	50.4 ± 7.9	81.7 ± 7.8	67.1 ± 7.5	< 0.001	3 > 4 > 2 > 1
PDQ score	17.7 ± 15.4	16.0 ± 16.2	19.7 ± 16.1	14.2 ± 13.2	18.3 ± 15.2	0.0293	(1 = 2 = 3) > 4

Characteristics of different objective cognitive layers

Layer #1 ("low cognitive performance") included 97 participants (16.2% of the sample) with a mean DSST of 26.5 at baseline (SD = 6.4) which increased significantly to 32.8 (SD = 7.2) by month 6. At baseline, the mean HRDS-17 score was 24.9 (SD = 4.4). The remission rate of depressive symptoms (HRDS-17 ≤ 7) at month 6 was 62.4%.

Layer #2 ("lower-middle cognitive performance") included 189 participants (31.6% of the sample), with a mean DSST of 42.2 at baseline (SD = 7.5), reaching a mean DSST of 50.4 at month 6 (SD = 7.9). At baseline, the mean HRDS-17 score was 23.5 (SD = 4.5). The remission rate of depressive symptoms (HRDS-17 ≤ 7) at month 6 was 61.4%.

Layer #3 ("high cognitive performance") included 106 participants (17.7% of the sample), with a mean DSST of 73.1 at baseline (SD = 7.6), reaching a mean DSST of 81.7 at month 6 (SD = 7.8). At baseline, the mean HRDS-17 score was 21.4 (SD = 3.7). The remission rate of depressive symptoms (HRDS-17 ≤ 7) at month 6 was 72.3%.

Layer #4 ("upper-middle cognitive performance") included 206 participants (34.5% of the sample), with a mean DSST of 56.9 at baseline (SD = 7.1), reaching a mean DSST of 67.1 at month 6 (SD = 7.5). At baseline, the mean HRDS-17 score was 23.2 (SD = 4.3). The remission

rate of depressive symptoms (HRDS-17 ≤ 7) at month 6 was 64.4%.

The characteristics of participants within the 4 strata are described in Table 1. Figure 1 shows the objective cognitive trajectory in the 4 layers.

Characteristics of different cognitive complaints trajectories

The trajectories of subjective cognitive complaints for each layer of objective cognition are shown in Fig. 2. They are also described in Table 2.

In the participants with low DSST scores ($n = 97$), 83.5% ($n = 81$) reported severe cognitive complaints at baseline (mean = 26.9, SD = 11.3), whose score decreased to a mean of 11.3 (SD = 10.0) at month 6. Consistently, 16.5% ($n = 16$) reported severe complaints on the PDQ-D at baseline (mean = 58.6, SD = 13.5), which decreased to an unsatisfactory mean score of 39.2 (SD = 20.8) at month 6. In both latent classes, the change over time was found to be significant (both P values < 0.001).

In the participants who showed a lower-middle score for the DSST ($n = 189$), 16.9% ($n = 32$) reported severe cognitive complaints at baseline (mean = 56.1, SD = 11.5), whose score decreased slowly to a mean of 39.2 (SD = 20.8) at month 6. A total of 89 (47.1%) participants reported moderate subjective complaints (mean = 39.2, SD = 10.6), whose score decreased by half at 6 months, to 19.9 (SD = 11.4). Within this layer, 36.0% ($n = 68$) of the participants reported mild cognitive complaints, with their score decreasing to 8.4 (SD = 6.9) at 6 months.

In participants who showed an upper-middle score for the DSST ($n = 206$), 59.3% ($n = 122$) reported severe subjective cognitive distress, compared with 40.8% ($n = 84$) with less severe subjective cognitive complaints. Among the severely impaired patients, 2 subgroups of improvement speed were found, with 72 (35.0%) patients reporting severe impairment at baseline, achieving more rapid improvement at 6 months (mean = 15.3, SD = 8.9), whereas a further 50 (24.3%) patients with significant high perceived cognition complaints at baseline remained at a higher level of impairment (mean = 39.1, SD = 12.2) after 6 months of treatment.

In the participants who showed a high DSST score ($n = 106$), 30% of patients complained of more severe cognitive symptoms, and the total PDQ-D score declined from 46.3 (SD = 11.0) at baseline to an average of 28.7 (SD = 16.4); for the rest of the patients within this trajectory group, self-reported levels declined from 25.2 (SD = 12.5) at baseline to an average of 8.7 (SD = 5.3).

Characterization between classes

Figure 3 shows the regression results comparing social demographics and clinical features across a subclass of subjective complaint trajectories, stratified by objective cognitive trajectories(Supplement table S3).

In comparison with individuals with fewer subjective cognitive complaints, education was negatively

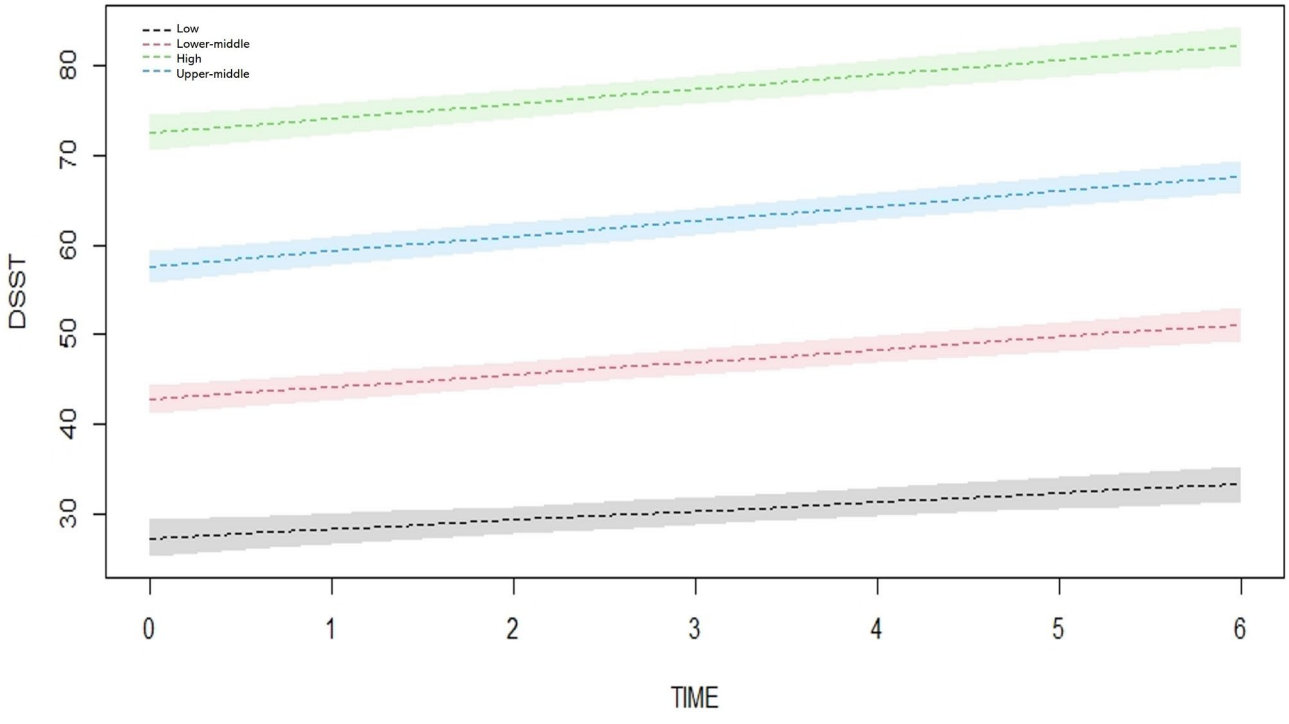

Fig. 1 Trajectories of objective cognitive function (DSST test performance) over 6 months using latent class mixed model

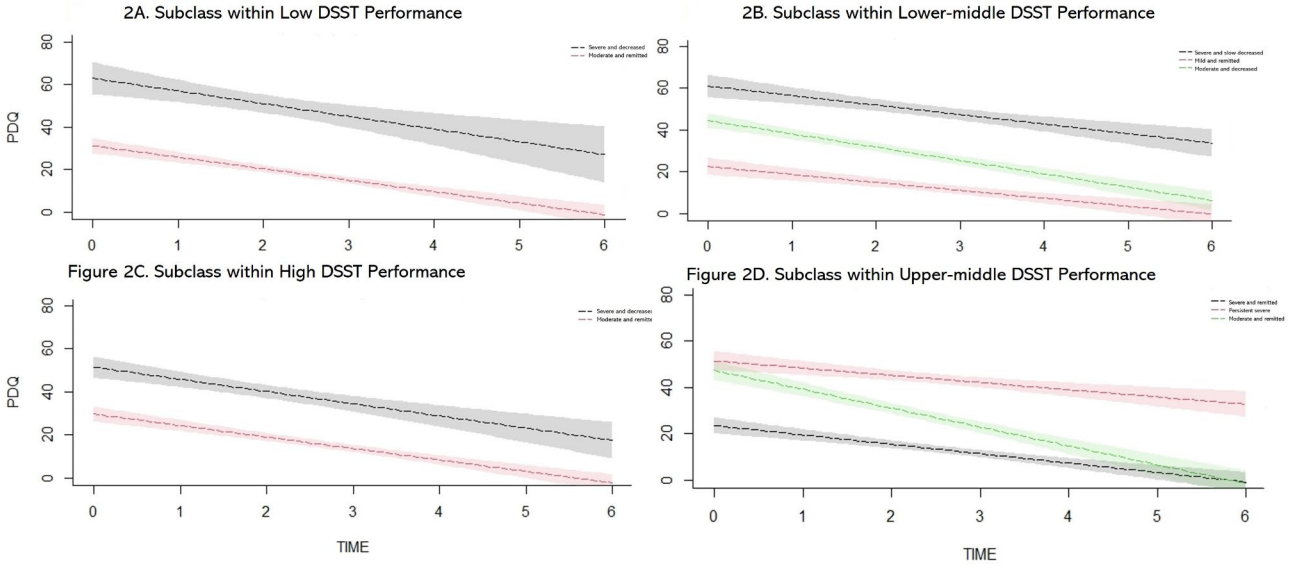

Fig. 2 **A**. Trajectories of subjective cognitive complaint(PDQ-D score) of patients with low DSST performance, including two subclasses: severe and decreased, and moderate and remited; **B**. Trajectories of subjective cognitive complaint(PDQ-D score) of patients with lower-middle DSST performance, including three subclasses: severe and slow decreased, mild and remitted, moderate and decreased; **C**. Trajectories of subjective cognitive complaint(PDQ-D score) of patients with high DSST performance, including two subclasses: severe and decreased, moderate and remitted; **D**. Trajectories of subjective cognitive complaint(PDQ-D score) of patients with Upper-middle DSST performance, including three subclasses: severe and remitted, persistent severe, moderate and remitted

associated with the probability of their subjective complaints slowly declining (all *P* values < 0.05), except for patients with severe (low DSST performance) cognition impairment. The education gradient was negatively associated with the probability of experiencing slow improvement in both the upper-middle and lower-middle cognitive performance groups ($P < 0.05$); patients with higher education levels had a slower decline in subjective cognitive complaints. Regarding clinical characteristics and pharmacological treatment, comorbidity with anxiety disorders might slow the remission rate of subjective cognitive complaints in the moderate-high or moderate-low DSST group ($P < 0.05$). The decline in depression severity was consistent with the decline in subjective cognitive complaints in the patients with high scores on the DSST ($P < 0.05$). In addition, for patients who performed better on the DSST, those with more subjective cognitive complaints received a greater proportion of selective serotonin reuptake inhibitor prescriptions, while accompanied by functional impairment, the speed of cognition complaint decline might be slowed. Higher health-related utility was associated with a lower probability of having persistently or slowly declining subjective cognitive complaints ($P < 0.05$) for patients with lower-middle or high DSST scores.

Interrelation change between subjective cognitive complaints with objective cognitive performance.

We constructed a Mixed-Effects Model for Repeated Measures (MMRM), taking PDQ-D at various time points as the dependent variable, DSST at different time points as the independent variable, and incorporating age, gender, education level, comorbidity, and other variables as covariates. The results showed that changes in PDQ-D at different time points were influenced by changes in DSST ($F = 64.70$, $P < 0.001$), and age ($F = 15.53$, $P < 0.001$), gender ($F = 5.03$, $P = 0.0253$), functional syndrome ($F = 4.86$, $P = 0.0279$), and anxiety disorder ($F = 4.70$, $P = 0.0306$) all had a significant impact on the changes in PDQ-D during the follow-up period.

Discussion

The current study investigated the 6-month longitudinal trajectories of subjective complaints within various changes in subjective cognitive complaints and its association with clinical characteristics among a sample of patients with MDD. In contrast to previous studies that focused on the discrepancy between subjective cognitive complaints and objective cognitive performance, which employed limited data points or maintained the concurrent trajectory of subjective and objective cognitive function, this study included four data points over the course of 6 months with a sample of patients receiving initial antidepressant monotherapy.

Overall, during the 6 months follow-up period, both subjective cognitive complaints and objective cognitive performance showed significant change in conjunction with the improvement of depressive severity. Additionally, we identified four distinct objective cognitive trajectories: high cognitive performance, upper-middle cognitive performance, lower-middle cognitive

Table 2 Description of latent classes of subjective cognitive complaints stratified by objective cognitive trajectory layer

Layer	Layer #1		Layer #2			Layer #3		Layer #4		
	Low DSST performance		Lower-middle DSST performance			High DSST performance		Upper-middle DSST performance		
Cognitive Complaint Trajectory	Severe and decreased	Moderate and remitted	Severe and slow decreased	Mild and remitted	Moderate and decreased	Severe and decreased	Moderate and remitted	Moderate and remitted	Persistent severe	Severe and remitted
N (% of the Layer)	81(83.5)	16(16.5)	32(16.9)	89(47.1)	68(36.0)	74(69.8)	32(30.2)	50(24.3)	72(35.0)	84(40.8)
Age group										
18–26	0(0.0)	0(0.0)	7(21.9)	11(12.4)	1(1.5) *	26(35.1)	19(59.4)*	15(30.0)	24(33.3)	20(23.8)
26–35	5(6.2)	3(18.8)	12(37.5)	22(24.7)	13(19.1)	34(46.0)	11(34.4)	21(42.0)	29(40.3)	25(29.8)
36–55	42(51.8)	8(50.0)	12(37.5)	46(51.7)	45(66.2)	14(18.9)	2(6.3)	14(28.0)	19(26.4)	38(45.2)
56–65	34(41.2)	5(31.3)	1(3.1)	10(11.2)	9(13.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.2)
Female	57(70.4)	15(93.8)	20(62.5)	57(64.0)	45(66.2)	52(70.3)	25(78.1)	40(80.0)	50(69.4)	49(58.3) *
Education attainment										
No degree	41(50.6)	6(37.5)*	4(12.5)	31(34.8)	23(33.8) *	2(2.7)	2(6.2)	4(8.0)	14(19.4)	7(8.3)
High school/ junior college	36(44.4)	5(31.3)	16(50.0)	29(32.6)	33(48.5)	11(16.9)	6(18.8)	18(36.0)	19(26.4)	21(25.0)
University, or above	4(4.9)	5(31.3)	12(37.5)	29(32.6)	12(17.7)	61(82.4)	24(75.0)	28(56.0)	39(54.2)	56(66.7)
First episode	44(54.3)	7(43.8)	18(56.3)	45(50.6)	41(60.3)	51(68.9)	17(53.1)	28(56.0)	42(58.3)	50(59.5)
Contaminant functional Syndromes										
Yes	38(46.9)	6(37.5)	12(37.5)	34(38.2)	26(38.2)	16(21.6)	1(3.1) *	7(14.0)	12(16.7)	31(36.9) *
Employment status										
Employed	27(33.3)	8(50.0)	23(71.9)	59(66.3)	46(67.7)	65(87.8)	28(87.5)	43(86.0)	61(84.7)	66(78.6)
Unemployed	54(66.7)	8(50.0)	9(28.1)	30(33.7)	22(32.4)	9(12.2)	4(12.5)	7(14.0)	11(15.3)	18(21.4)
Concomitant anxiety disorder										
Yes	33(40.7)	7(43.8)	4(12.5)	24(27.0)	22(32.4)	11(14.9)	4(12.5)	7(14.0)	4(5.6)	21(25.0) *
Antidepressant										
SSRI	50(61.7)	8(37.5)	23(71.9)	57(64.0)	39(57.4)	52(70.3)	24(75.0)	34(68.0)	47(65.3)	50(59.5)
SNRI	27(33.3)	6(37.5)	7(21.9)	26(29.2)	15(22.1)	17(23.0)	6(18.8)	9(18.0)	17(23.6)	22(26.2)
Other	4(4.9)	2(12.5)	2(6.2)	6(6.7)	14(20.6) *	5(6.8)	2(6.2)	7(14.0)	8(11.1)	12(14.3)
Assessment at baseline										
HDRS-17 score	24.6 ± 4.3	26.4 ± 4.9	25.4 ± 4.8	23.3 ± 4.6	22.8 ± 3.9[a]	20.8 ± 3.7	22.8 ± 3.5*	23.9 ± 4.1	23.4 ± 4.7	22.6 ± 4.1
EQ-5D utility score	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.1	0.7 ± 0.1	0.8 ± 0.1 [b]	0.8 ± 0.1	0.7 ± 0.1*	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1
DSST score	27.0 ± 6.0	24.1 ± 7.8	41.4 ± 9.7	42.3 ± 7.1	42.6 ± 7.0	73.7 ± 8.0	71.9 ± 6.4	57.5 ± 5.1	55.8 ± 8.0	57.4 ± 7.3
PDQ score	26.9 ± 11.3	58.6 ± 13.5*	56.1 ± 11.5	39.2 ± 10.6	19.8 ± 9.6[c]	25.2 ± 12.5	46.3 ± 11.0*	48.5 ± 12.3	41.1 ± 10.3	20.1 ± 8.7[c]
Assessment at month 6										
HDRS-17 score	6.3 ± 4.6	11.3 ± 6.9	11.7 ± 6.8	7.8 ± 5.2	4.9 ± 4.0 [c]	3.7 ± 3.5	10.5 ± 7.1*	10.6 ± 6.9	5.7 ± 3.8	5.7 ± 4.9 [a]
EQ-5D utility score	0.9 ± 0.1	0.8 ± 0.2*	0.8 ± 0.2	0.9 ± 0.1	0.9 ± 0.1 [d]	1.0 ± 0.1	0.8 ± 0.2*	0.8 ± 0.2	0.9 ± 0.1	0.9 ± 0.1 [d]
DSST score	33.1 ± 7.2	31.3 ± 7.3	31.3 ± 7.3	50.7 ± 8.3	49.7 ± 6.8	81.9 ± 8.1	81.0 ± 6.9	64.8 ± 6.6	68.1 ± 7.1	67.6 ± 8.1 [d]
PDQ score	11.3 ± 10.0	39.2 ± 20.8*	39.2 ± 20.8	19.9 ± 11.4	8.4 ± 6.9 [c]	8.7 ± 5.3	28.7 ± 16.4*	39.1 ± 12.2	15.3 ± 8.9	8.6 ± 7.5 [c]
Remission rate at month 6	48(68.6)	5(33.3) *	8(25.8)	50(61.0)	47(81.0) *	58(85.3)	10(38.5) *	15(34.9)	47(72.3)	54(75.0) *

a.1> (2 = 3); b.3 > 2 > 1; c.1 > 2 > 3; d.1< (2 = 3); *$P < 0.05$

performance, and low cognitive performance. Nearly half of the patients did not perform well on objective cognitive tests (low and lower-middle). Patients in all four cognitive performance groups showed relief in objective cognitive complaints, although no breakthrough improvements were observed. Although individuals within each group demonstrated a consistent objective cognitive performance trajectory over 6 months, they displayed at least 2 or 3 distinct patterns of subjective cognitive complaints. Patterns of subjective cognitive complaints change within the same objective cognitive performance trajectory are influenced by a variety of factors, including age, education, comorbidities, and disease-related utility.

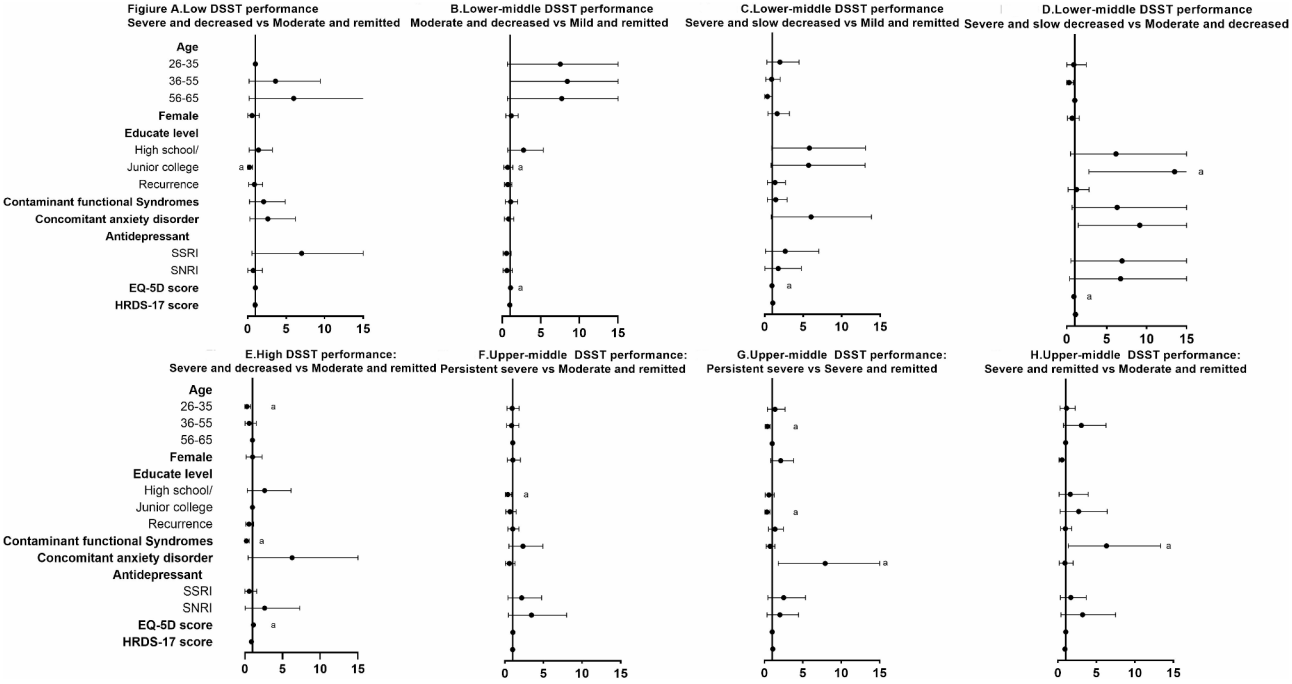

Fig. 3 **A**. Forest plot of the adjust odds ratios for the association of indicators with severe and decreased subjective cognitive complaints subclass and moderate and remitted cognitive complaints subclass in patients with low DSST performance; **B**. Forest plot of the adjust odds ratios for the association of indicators with moderate and decreased subjective cognitive complaints subclass and mild and remitted cognitive complaints subclass in patients with lower-middle DSST performance; **C**. Forest plot of the adjust odds ratios for the association of indicators with severe and slow decreased subjective cognitive complaints subclass and mild and remitted cognitive complaints subclass in patients with lower-middle DSST performance; **D**. Forest plot of the adjust odds ratios for the association of indicators with severe and slow decreased subjective cognitive complaints subclass and moderate and decreased cognitive complaints subclass in patients with lower-middle DSST performance; **E**. Forest plot of the adjust odds ratios for the association of indicators with severe and decreased subjective cognitive complaints subclass and moderate and remitted cognitive complaints subclass in patients with high DSST performance; **F**. Forest plot of the adjust odds ratios for the association of indicators with persistent severe subjective cognitive complaints subclass and moderate and remitted cognitive complaints subclass in patients with upper-middle DSST performance; **G**. Forest plot of the adjust odds ratios for the association of indicators with persistent severe subjective cognitive complaints subclass and severe and remitted cognitive complaints subclass in patients with upper-middle DSST performance; **H**. Forest plot of the adjust odds ratios for the association of indicators with severe and remitted subjective cognitive complaints subclass and moderate and remitted cognitive complaints subclass in patients with upper-middle DSST performance; *$P < 0.05$; See Table S3 in the Supplement for the odds ratios and 95% confidence intervals

The present study supports that there is heterogeneity in the cognitive function of patients with depression, and that there is a persistent feature independent of symptom improvement, consistent with previous studies [33, 34]. Bernhardt et al. [35] concluded that most of the improvement in cognitive function shown in patients with depression after they had received treatment was primarily attributable to the practice effect rather than to cognitive rehabilitation.

This study revealed that depression severity during depressive episodes was significantly associated with objective cognitive impairment, consistent with the results of a systematic review by McDermott et al. [36]. In terms of longitudinal follow-ups, however, the association between depression severity, antidepressant prescription, and subjective cognitive complaints was only present in the patients with MDD without objective cognitive function. This is in line with the study by Shilyansky et al. [10], which reported that despite antidepressant treatment there was no change in cognitive function compared with a control group tested during the acute phase of a depressive episode, and that these impairments were similar irrespective of clinical remission. The results also echo the "state" hypothesis [37] about cognition, and that cognitive function impairment should be treated as a core symptom of depression that requires specific interventions.

The results of this study show that in addition to the MDD group with severe objective cognitive impairment there is a significant slowdown in the recovery of subjective cognitive complaints if the patients' symptoms are accompanied by functional syndromes or anxiety disorders. The results of cross-sectional studies [38, 39] have shown that anxiety symptoms occupy a non-negligible part of the variance in subjective cognitive complaints after controlling for the severity of depressive symptoms, and this study is an extension of previous research suggesting that comorbid anxiety disorders might contribute

to persistent negative appraisals of the patient and their self-perceived competence. Patients with chronic sleep disorders tend to emphasize waking problems, such as fatigue and impaired performance [40]; thus, subjective cognitive complaints are significantly more prominent in patients with functional dysfunction.

We observed a significantly higher score for subjective cognitive complaints at baseline and a flatter decline during follow-up among patients with younger age and lower educational background. Poorer subjective memory and concentration impairments in younger participants compared with their older counterparts were also reported in a study of younger patients with MDD [41]. Subjective cognitive complaints can be prominent in younger patients, mainly due to the interference in academic engagement and interpersonal functioning [42]. These scenarios might be perpetuated when there is a lack of support that high-level education can bring.

Strengths and limitations

This study has several limitations. First, our sample and follow-up period may be insufficient to delineate additional cognitive change trajectory groups, such as those exhibiting deterioration during the course of the disease. Second, due to the lack of information in this cohort, we did not include the duration of depression, which has been identified as a putative predictor variable. Third, only DSST was used as an objective cognitive measure, which does not cover the broader dimensions of cognitive functioning, even though this instrument has demonstrated sensitivity in antidepressant treatment.

Despite these limitations, this study has several strengths, including a relatively long follow-up duration with multiple data points. We observed the trajectory of change in patients with depression treated with antidepressants in a long duration single episode.

Conclusion

In summary, our findings delineate four trajectories of objective cognitive performance over 6 months in patients with MDD, and a complex heterogeneity of changes in subjective cognitive complaints. In clinical practice, these findings can serve as critical indicators for profiles and interventions related to prognosis. Further studies are warranted to explore potential modifiable factors of poor cognition trajectories and to investigate associations between cognition trajectories and treatment failure. The results further highlight the relevance of complementary assessment methods to fully capture aspects of cognitive ability in patients with MDD.

Abbreviations

DSST	Digit symbol substitution test
EQ-5D	EuroQol Five Dimensions Questionnaire
HDRS-17	Hamilton Depression Rating Scale-17 Items
ICD-10	International Classification of Diseases-10
LCMM	Latent class mixed model
MDD	Major depressive disorder
MMRM	Repeated measures linear mixed-effects model
PDQ-D	Perceived Impairments Questionnaire-Depression
SD	Standard deviation

Supplementary Information

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Supplementary Material 1

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Author contributions

X.C and L.F was responsible for the conception of the study. X.Z and X.C analyzed the data and wrote the main manuscript text, and Y.W. prepared Figs. 1, 2 and 3; Table 1 and 2. All authors reviewed the manuscript.

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Data availability

The data that support the findings of this study are available on request from the corresponding authors.

Declarations

Ethics approval and consent to participate

All patients provided written informed consent for participation. The PROACT study followed the International Conference on Harmonization Good Clinical Practices guidelines and the ethical principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of Beijing Anding Hospital, Capital Medical University (No: (2019) Research (90)).

Consent for publication

Not applicable.

Competing interests

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