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Original

Long-term trajectories of clinical staging in first-episode psychosis and their associated cognitive outcome: A 21-year follow-up study

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ABSTRACT

Cognitive deficits are already present before psychosis onset but are a key feature of first-episode psychosis (FEP). The objective of this study was to investigate the cognitive outcomes of a cohort of FEP patients who were diagnosed using the clinical staging approach and were followed for up to 21 years.

We analyzed data from 173 participants with first-admission psychosis who were followed-up for a mean of 20.9 years. The clinical staging assessment was adapted from the clinical staging framework developed by McGorry et al.[1] Cognitive assessment was performed using the MATRICS Consensus Cognitive Battery (MMCB) at the end of follow-up.

FEP patients who were longitudinally diagnosed in the lowest clinical stages (stages 2A and 2B) showed better performance in attention, processing speed, and MCCB overall composite score than those in the highest clinical stages (stages 4A and 4B). There was a significant linear trend association between worsening of all MCCB cognitive functions and MCCB overall composite score and progression in clinical staging. Furthermore, the interval between two and five years of follow-up appears to be associated with deficits in processing speed as a cognitive marker.

Our results support the validation of the clinical staging model over a long-term course of FEP based on neuropsychological performance. A decline in some cognitive functions, such as processing speed, may facilitate the transition of patients to an advanced stage during the critical period of first-episode psychosis.

Introduction

Over the last three decades, research has consistently shown that cognitive impairment is a core feature of psychosis.[2,3] This deficit shares a common profile of impairment in cognitive functioning across psychosis subtypes, with different degrees of intensity.[4] Cognitive impairment has strong pervasive detrimental effects on the functionality of patients with psychosis, but its relationships with psychotic symptomatology, although significant, are less robust.[5,6]

Clinical staging models based on the pathological expression of the underlying biological processes of diseases enable clustering of patients based on etiology, pathophysiology, and severity. In medical illnesses without defined biological bases, clinical staging is mainly based on clinical progression, which is a very useful tool to aid in the early detection and systematic management of the illness, to target illness progression and help in prognosis, and to propose phase-specific therapies or interventions. This staging paradigm reflects the era of personalized medicine.

At least nine models of clinical staging that mainly focus on psychotic disorders have been reported.[7–15] Two additional staging models were based exclusively on psychopathological scales, such as the PANSS scale[16,17] (see for a comparative review of the models in references[18,19]).

Although all models comprised stages from the prodromal phase to the chronic stage, only two included stage 0, namely

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asymptomatic at risk[13] and premorbid phase.[12] McGorry's model[13] has been the most studied and worldwide diffused model and it continues its development with new refinements.[20] In addition, some authors have suggested that the inclusion of mood symptoms and cognitive deficits could improve the staging model.[10] In addition, it has been suggested that the premorbid and prodromal phases may be partly shared with bipolar disorder[21] have commonalities with other non-schizophrenic disorders.[7,22] Other authors have proposed transdiagnostic clinical staging models for youth mental disorders.[23,24]

The clinical staging model of psychosis provides a new framework aimed at developing preventive strategies for psychosis[20] and to improve the clinical utility of current nosological diagnostic systems.[25] While there is extensive research and evidence focused on the early stages prior to the full-threshold FEP (stage 2) from the asymptomatic at-risk stage (stage 0) to short-lived remitting psychotic episodes in clinical at-risk psychosis (stage 1c), there is less evidence regarding differential validation across stages and markers of transition across stages once the FEP merges. Most studies have focused on the earlier stages and their progression, and many others have used a cross-sectional design, and very few long-term studies have been carried out.[14] In addition, few studies have addressed the search for neurobiological correlates of specific stages using complementary techniques such as neuroimaging or neurocognitive assessments.

The relationship between the psychosis staging model and cognitive performance has been examined in five previous studies. One study assessed neurocognitive functioning in a sample of youth at risk of serious mental illness across different clinical stages (stages 0 to 1b) but not stage 2 or more.[26] Three cross-sectional studies were conducted in stable outpatients with schizophrenia[10] or schizophrenia spectrum disorders[27] and acutely admitted patients with schizophrenia[28]. Only one longitudinal study has examined the cognitive correlates of clinical staging in a large mixed sample including outpatients or inpatients with a non-affective psychotic disorder over a 6-years follow-up.[30] However, the extent to which clinical staging assignment after long-term follow-up of FEP patients is associated with cognitive impairment has not been addressed. Moreover, no previous studies have used the MATRICS Consensus Cognitive Battery (MCCB), the most widely used and standardized neuropsychological test battery for assessing cognition in schizophrenia.[31]

This study aimed to explore the long-term trajectories of clinical staging in FEP patients and their respective cognitive outcomes. We hypothesized that cognitive deficits would worsen with the progression of clinical staging.

Methods

Sample

The sample of this study was obtained from the SEGPEPs study, which is a longitudinal naturalistic study of FEP patients who were admitted for first-episode psychosis between January 1990 and December 2008 and thoroughly reassessed for varied outcome domains. All patients lived within a catchment area with a population of approximately 200,000 in the public health system (Pamplona, Spain). We have provided a full description and methods of the SEGPEPs study.[32]

The SEGPEPs inclusion criteria were as follows: (a) a diagnosis of FEP fulfilling the DSM-III-R or DSM-IV criteria, (b) age between 15 and 65 years, (c) residing in the catchment area of the hospital, (d) completing the inpatient treatment period and a 6-month assessment after discharge, (e) having close relatives available to provide broad background information, and (f) providing written informed consent. Additionally, for this study, we included only patients with available neuropsychological assessments at follow-up ($n = 173$).

Exclusion criteria were (a) previous antipsychotic treatment for more than two months, (b) a suspected or confirmed diagnosis of drug-induced psychosis, (c) a history of serious medical or neurological disease, and (d) intellectual disability as defined by an IQ <70.

Baseline and follow-up assessments

At the time of FEP, senior authors (VP or MJC) evaluated the participants. Two psychiatrists (LMI and EGJ) with extensive experience in psychosis research evaluation traced and assessed the patients between January 2018 and May 2021. They conducted direct interviews with patients and a close significant informant and collected all available information from clinical records through the computerized database of the regional health service. The Comprehensive Assessment of Symptoms and History (CASH)[33] was used for the baseline and follow-up assessments. The scale for the assessment of positive symptoms (SAPS)[34] and the scale for the assessment of negative symptoms (SANS)[35] were included in the CASH. The final assessments were blinded to the baseline assessment of each participant. All patients were re-diagnosed using all available information using the DSM-5 criteria.[36] The social and occupational functioning assessment scale (SOFAS)[37] was used to evaluate psychosocial functioning.

DSM-5 final diagnosis at the follow-up were as follows: schizophrenia ($n = 75$, 43.9%), schizophreniform disorder ($n = 4$, 2.3%), brief reactive psychosis ($n = 14$, 8.1%), delusional disorder ($n = 1$, 0.6%), schizoaffective disorder ($n = 33$, 19.1%), bipolar disorder ($n = 31$, 17.9%), major depression ($n = 8$, 4.6%), and atypical psychosis ($n = 6$, 3.5%).

The lifetime and current use of antipsychotic and anticholinergic drugs were collected using the CASH and transformed into dose-year scores for all patients.

Assessment of clinical staging

The methodology used to assess staging has been described previously.[14] Stages were defined based on the general staging framework developed by McGorry et al.[1] and Scott et al.[38] and the major course types described in classic European long-term follow-up studies of psychotic disorders.[14] Recurrence, persistence, symptom progression, and declining function. Six stages were defined as follows: stage 2A (single episode with full remission), stage 2B (multiple episodes with full remission), stage 3A (episodic course with partial remission and stable course), stage 3B (episodic course with partial remission and progressive course), stage 4A (chronic/continuous and stable course), and stage 4B (chronic/continuous and progressive course). Staging levels were determined across predefined temporal periods (baseline 2-years, 5-years, 10-years, 15-years, 20-years and final follow-up assessment points), and their transitions over the follow-up period are shown in Supplementary Table 1. The period for the assessment of baseline staging ranged from the age at illness onset to the 6-month assessment after the index admission. The assessment of clinical staging at the end of the follow-up was the last observation of clinical staging.

The senior authors (VP and MJC) assigned the staging of patients at every point of assessment using the Life Chart interview from the CASH, with all available information from the patient and a close relative and informatized register. Construct validity using a wide range of psychopathological and functioning validators and good inter-rater reliability for clinical stages in this sample has been previously described.[14]

Cognitive assessment

A Spanish equivalent test of the Word Accentuation Test (WAT),[39] the Spanish National Adult Reading Test,[40] was used to assess premorbid intelligence.

The MATRICS Consensus Cognitive Battery (MCCB)[31] was administered during follow-up. It consists of ten standardized cognitive domains that assess seven different cognitive functions: attention/vigilance, speed of processing, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The MCCB scoring tool provides a global composite score, based on the results of the included tests. Two experienced neuropsychologists (AST and GGB) administered the MCCB in a single session when possible using the same test presentation order. Normalized values (*T*-scores) after controlling for the influence of age, sex and education were used in the analyses.

Cognitive assessments were performed by two neuropsychologists (AST and GGB) who were blinded to the staging status of the patients.

Statistical analyses

Sociodemographic, psychopathological, illness-related, treatment, and functioning variables were compared between the patients who were lost to follow-up and those who completed the study using independent *t*-tests.

Differences in cognitive functions between the final clinical stages at follow-up were assessed using the nonparametric Kruskal–Wallis test because equal group size and normality of most variables could not be assumed. If the Kruskal–Wallis test showed significant differences across groups, post hoc tests were conducted using the false discovery rate (FDR) and the Benjamini–Hochberg method to control for type I error inflation.[41] Given the nature of the main outcome variable (successive staging levels), we examined its linear association by using the Jonckheere test. The effect sizes of the differences between stages in the Kruskal–Wallis tests were calculated using Epsilon squared (ε^2) for continuous variables. Following Tomczak and Tomczak[42] general guidelines, we interpreted ε^2 values of 0–0.01 as negligible; 0.01–0.04 as weak; and 0.05–0.16 as moderate effect sizes, respectively.

We ran generalized linear mixed models (GLMM) to assess the effects of staging on cognitive MCCB after allowing for the effect of other covariates, such as age at follow-up, sex, premorbid IQ, dose-years of antipsychotics, and dose-years of anticholinergics. For these analyses, variable staging was considered continuous from stage 2A to stage 4B. Separate mixed linear analyses were performed for each MCCB cognitive function and overall cognitive score. Mixed modeling analyses allowed estimates to be obtained after assuming that the missing data were random. The results from the mixed models are displayed as coefficients with 95% confidence intervals. The significance level was set at $p = 0.05$.

SPSS version 22 (IBM Corp., 2013) was used for all statistical analyses. The level of significance for the two-tailed test was set at a critical p value of 0.05, except where otherwise noted.

Ethics

This study was approved by the Navarra Clinical Research Ethics Committee and adhered to the 2008 revision of the Declaration of Helsinki and ethical guidelines of the appropriate national and institutional committees on human experimentation.

Results

The original SEGPEP sample suffers from two attritions. Of 510 patients in the baseline FEPs group, 243 (47.6%) were included in the follow-up study. The different causes of withdrawal from the study have been described previously.[32] No significant differences were found in baseline sex, global psychopathology (SAPS and SANS global scores), global functioning (SOFAS), and distribution of DSM-5 diagnoses at baseline admission between follow-up and non-follow-up subjects, except for age, which was significantly lower in the follow-up sample ($p < 0.001$).[32]

In the present study, we included one hundred seventy-three (71.1%) of the 243 patients underwent neuropsychological testing. No significant differences were found in baseline demographic variables (age and sex), global psychopathology (SAPS and SANS global scores), global functioning (SOFAS), distribution of DSM-5 diagnoses, premorbid IQ, and lifetime and current use of antipsychotic and anticholinergic drugs between patients with and without neuropsychological examination. However, patients without testing had lower socioeconomic status, lower level of education, and were more usually male and single at follow-up than those completing the neuropsychological assessment.

Fifty-two patients were male (52.1%), and the average age and follow-up time were 48.2 ± 10.8 and 20.2 ± 5.6 years, respectively. Patients with MCCB did not differ significantly from the excluded individuals in terms of age, global psychopathology, global functioning, current CPZ dosages, and DSM-5 diagnosis distribution (Table 1).

The staging level distribution at the follow-up time (after 20.2 ± 5.6 years) was as follows: stage 2A (8 patients, 4.6%); stage 2B (38 patients, 22.1%); stage 3A (63 patients, 36.4%); stage 3B (28 patients, 16.2%); stage 4A (22 patients, 12.7%); and stage 4B (14 patients, 8.1%) (Table 1).

Given the low number of patients in 2A and 2B, they were conflated in one group (stage 2AB) for pairwise comparisons between the stages. A visual inspection of the performance in MCCB cognitive functions revealed a similar pattern of impairment across stages, with increasing severity related to advanced staging (Fig. 1).

MCCB cognitive domains and overall composite score differences between clinical staging groups

There were significant differences between staging groups in the Kruskal–Wallis tests after applying the Benjamini–Hochberg correction, except for reasoning and problem solving. Stage 2AB patients showed significantly better cognitive performance in all MCCB cognitive domains and overall composite scores than patients in advanced stages. Specifically, patients in the 2AB stage showed better performance in attention, processing speed, and MCCB overall composite scores than patients in the 4A and 4B stages. Moreover, 2AB patients had significantly better processing speed, working memory, visual learning, and MCCB overall composite scores than patients in the closer stage (3A stage patients) (Table 2). The effect size of the differences in clinical staging was moderate for all significant cognitive domains, and the differences showed a strongly significant linear trend (Table 2).

Effect of the clinical staging group on the MCCB performance

Linear mixed-model analyses demonstrated a significant effect of staging on all MCCB cognitive functions and overall MCCB composite scores. These significant effects were found after allowing for the influence of covariates (age at follow-up, sex, premorbid IQ, dose-years of antipsychotics and dose-years of anticholinergics) (Table 3).

The influence of covariates was also examined. Premorbid IQ had a significant positive effect on all MCCB cognitive functions and the MCCB overall composite score. Older age at follow-up was significantly associated with lower performance in terms of processing speed, working memory, reasoning, and problem solving. Male sex

Table 1
Sociodemographic and clinical features of the participants ($n = 173$).

	n (%)	Mean (SD)
Age, years		48.2 (10.8)
Age at onset		25.9 (9.29)
Duration of untreated psychosis (DUP) (months)		14.5 (36.19)
Education (years)		11.5 (3.29)
Duration of follow-up, years		20.2 (5.64)
SAPS at follow-up (global ratings total score)		2.6 (3.31)
SANS at follow-up (global ratings total score)		5.5 (4.37)
No. of psychiatric admissions		8.1 (7.81)
SOFAS		62.7 (18.06)
Dose-years of antipsychotics		55.9 (42.4)
Dose-years of anticholinergics		13.0 (25.6)
Word Accentuation Test (IQ)		99.5 (12.3)
MATRICS Consensus Cognitive Battery (MCCB)		
Attention/vigilance		40.3 (10.6)
Speed of processing		35.1 (12.3)
Working memory		40.3 (12.4)
Verbal learning		35.3 (15.7)
Visual learning		37.3 (15.2)
Reasoning and problem solving		37.3 (10.6)
Social cognition		45.1 (11.8)
MCCB overall composite score		34.3 (13.5)
Gender (male)	90 (52.1)	
Lifetime DSM-5 diagnosis		
Schizophrenia	76 (43.9)	
Schizophreniform	4 (2.3)	
Brief reactive psychosis	14 (8.1)	
Delusional disorder	1 (0.6)	
Schizoaffective disorder	33 (19.1)	
Bipolar disorder	31 (17.9)	
Major depression	8 (4.6)	
Atypical psychosis	6 (3.5)	
Clinical staging at follow-up		
2A	8 (4.6)	
2B	38 (22.1)	
3A	63 (36.4)	
3B	28 (16.2)	
4A	22 (12.7)	
4B	14 (8.1)	

DSM-5: diagnostic and statistical manual, fifth edition; SAPS: scale for the assessment of positive symptoms; SANS: scale for the assessment of negative symptoms; SOFAS: social and occupational functioning assessment scale. Stage 2A: single episode with full remission; stage 2B: multiple episodes with full remission; stage 3A: multiple episodes with partial and stable remission; stage 3B: multiple episodes with partial remission and progressive course; stage 4A: chronic/continuous and stable course; stage 4B: chronic/continuous and progressing course.

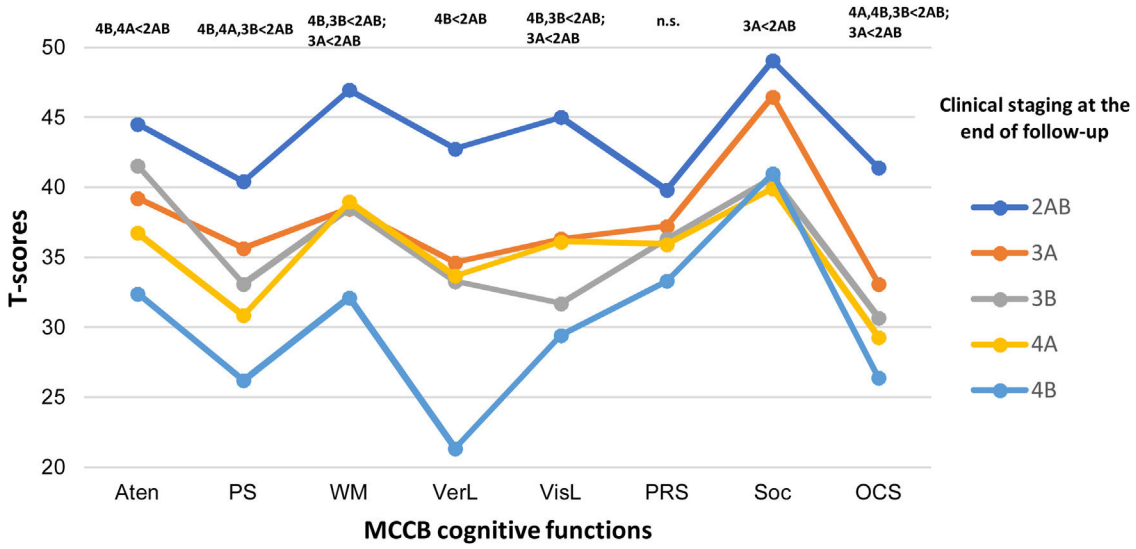

Fig. 1. Neuropsychological profiles of final clinical staging at the long-term follow-up of first-episode psychosis patients ($n = 173$). MCCB: MATRICS Consensus Cognitive Battery; Aten: attention; PS: processing speed; WM: working memory; VerL: verbal learning; VisL: visual learning; PRS: reasoning and problem solving; Soc: social cognition; OCS: overall composite score. Stage 2A: single episode with full remission; stage 2B: multiple episodes with full remission; stage 3A: multiple episodes with partial and stable remission; stage 3B: multiple episodes with partial remission and progressive course; stage 4A: chronic/continuous and stable course; stage 4B: chronic/continuous and progressing course.

Table 2
Neuropsychological performance in MATRICS Consensus Cognitive Battery (MCCB) at the 21-year follow-up across clinical stages (Kruskal–Wallis tests).

	2AB (n = 46)	3A (n = 63)	3B (n = 28)	4A (n = 22)	4B (n = 14)	Between groups$_{(df=5)}$	p	p^{**}	Post hoc comparisons	Effect size***	Linear trend (p)
MATRICS Consensus Cognitive Battery (MCCB)											
Attention/vigilance	44.5 (10.9)	39.2 (9.3)	41.5 (8.8)	36.7 (9.0)	32.4 (15.5)	H = 11.98	<0.017	<0.019	4B,4A<2AB	.08	<0.002
Speed of processing	40.4 (11.1)	35.6 (11.8)	33.1 (9.1)	30.8 (13.6)	26.2 (15.3)	H = 17.41	<0.002	<0.002	4B,4A,3B<2AB	.10	<0.001
Working memory	46.9 (10.6)	38.4 (12.0)	38.5 (10.7)	39.0 (12.8)	32.1 (13.7)	H = 19.20	<0.001	<0.002	4B,3B<2AB; 3A<2AB*	.11	<0.001
Verbal learning	42.7 (14.3)	34.6 (13.9)	33.2 (15.5)	33.6 (15.8)	21.3 (18.1)	H = 18.20	<0.001	<0.002	4B<2AB	.10	<0.001
Visual learning	45.0 (11.7)	36.3 (13.8)	31.7 (15.7)	36.1 (17.1)	29.4 (18.3)	H = 17.78	<0.001	<0.002	4B,3B<2AB; 3A<2AB*	.10	<0.001
Reasoning and problem solving	39.8 (10.6)	37.2 (10.1)	36.3 (10.5)	35.9 (11.3)	33.3 (11.7)	H = 5.98	<0.201	<0.201	ns	.03	<0.021
Social cognition	49.1 (10.8)	46.5 (11.0)	40.6 (11.3)	39.9 (13.4)	41.0 (11.8)	H = 14.35	<0.006	<0.009	3B<2AB	.08	<0.001
MMCB overall composite score	41.4 (11.6)	33.1 (13.1)	30.7 (11.2)	29.3 (15.0)	26.4 (14.1)	H = 19.32	<0.001	<0.002	4A,4B,3B<2AB; 3A<2AB*	.13	<0.001

* Significantly different compared to previous stage (e.g., stage 3A vs stage 2B).
** Benjamini–Hochberg p value.
*** ε^2 (Epsilon squared). ε^2 = 0–0.01 indicates a negligible effect. ε^2 = 0.01–0.04 indicates a weak effect. ε^2 = 0.05–0.16 indicates a moderate effect.

was negatively and significantly associated with poor performance in all cognitive domains except attention and verbal learning. Treatment with antipsychotic drugs over the course of the illness had a negative and significant influence on the speed of processing, visual learning, reasoning and problem solving, social cognition, and the MCCB overall composite score. Additionally, treatment with anticholinergics (dose-years) had a detrimental and significant effect on verbal learning (Table 3).

Effects of transition from lower-to higher-severity stages on MCCB performance over long-term follow-up

To examine whether cognitive impairment has endured since the early periods after FEP, we performed statistical comparisons between patients with full remission (stages 2A and 2B) and those with other progressed stages (from stages 3 to 4) during the first 5 years after illness onset (at 2-years and 5 years of follow-up) (Table 4). Patients with incomplete remission at the 2-years follow-up showed a significantly lower processing speed on neuropsychological assessment at the end of the follow-up (H = 5.01, df = 2, p < 0.025). However, when the comparison of clinical stages was carried out at 5-years those patients with partial remission showed significantly lower performance in all cognitive functions and the MCCB overall composite neuropsychological score, except for reasoning, problem solving, and social cognition (Table 5).

Discussion

The present study aimed to examine the association between clinical staging and cognitive performance in long-term first-episode psychosis. The long-term follow-up of this cohort allowed us to establish the clinical staging of patients at every point of assessment over the course of >20 years from the beginning of FEP. The following four main findings were obtained: first, patients with a single episode or acute episodes with full remission (stages 2A and 2B in our study) showed significantly better cognitive performance in all cognitive domains, except reasoning and problem solving, than FEP patients with partial remission, progressive, or chronic/continuous courses (stages 3A to 4B in our study) over the entire follow-up period. Second, performance on working memory, visual learning and the MCCB overall composite score specifically marked the progression from two closer stages (from the 2AB stage of patients with episodes with full remission to the 3A stage or patients with episodic course with partial and stable remission). Moreover, patients in stage 3B (episodic course with partial remission and progressive course) showed an additional significant worsening in processing speed and social cognition.

Third, a significant linear trend was observed in the association between stage progression and poor performance in all cognitive domains. This linearity for staging was also demonstrated in mixed linear models after controlling for the effect of covariates that potentially influence cognitive impairment at the long-term follow-up. Fourth, cognitive decline in patients progressing through more severe stages during the first 2 years after FEP was evidenced by impairment in processing speed at the end of follow-up. Moreover, cognitive impairment in patients with worsening clinical staging between 2 and 5 years after the PEPs widened the scope of impairment to more cognitive functions.

Over the course of long-term follow-up, patients who remained in clinical stage 2 (with full remission) significantly outperformed those who progressed in terms of cognitive performance, which is consistent with the mounting data in untreated patients[43] or treated[44] patients with first-episode schizophrenia. Cognitive deficits are established before the prodromal phase of psychosis.[45] Those in the prodromal phase or in the early years after the onset of psychosis did not exhibit cognitive decline[45,46] but they also appeared to improve after the first years of follow-up.[47] Furthermore, long-term follow-up studies[48–50] have also documented subsequent cognitive decline over a two-decade period following the initial hospitalization.

Regarding studies using the clinical staging model, our results are in agreement with the significantly greater cognitive impairment associated with advanced clinical stages found in three cross-sectional studies of schizophrenia patients[10,27,29] and in a 6-year follow-up study.[30] Patients in the lowest stage (2AB) showed significantly better cognitive performance than those in the highest stage. We found significant differences in all cognitive functions, except reasoning and problem solving, which were assessed in the MATRICS battery using the Mazes test. Differences in the composition of executive function across studies may account for this discrepancy, since one study was assessed using the Trail Making Test Form B, WAIS similarities, and matrix reasoning,[10] and in other studies with the block design task.[30]

Progression in clinical staging was associated with impairment in two cognitive functions in our study; specifically, processing speed and working memory were not detected in the 6-years follow-up study.[30] These results are in agreement with a meta-analysis examining the widespread impairment of baseline neurocognitive functioning in individuals at clinically high risk for

Table 3
Mixed linear models of MCCB cognitive functions at the 21-year follow-up and staging adjusted with covariates (age at follow-up, gender, WAT_IQ, dose-years of antipsychotics and dose-years of anticholinergics.

	Estimate	SE	df	*t*	Sig.	95% CI lower bound	95% CI Upper bound
Attention/vigilance							
Age at follow-up	0.03	0.03	934	1.24	.213	−0.02	0.10
Gender	−0.71	0.66	934	−1.01	.282	−2.00	0.58
Staging	−1.34	0.26	934	−4.98	.001	−1.86	−0.81
WAT_IQ	0.15	0.02	934	5.55	.001	0.10	0.21
Dose-years of antipsychotics	−0.01	0.01	934	−1.26	.208	−0.03	0.01
Dose-years of anticholinergics	0.01	0.01	934	1.12	.261	−0.01	0.05
Speed of processing							
Age at follow-up	−0.27	0.03	1089	−8.36	.001	−0.33	−0.20
Gender	−2.65	0.68	1089	−3.87	.001	−4.01	−1.31
Staging	−1.90	0.27	1089	−7.01	.001	−2.43	−1.36
WAT_IQ	0.12	0.02	1089	4.25	.001	0.06	0.18
Dose-years of antipsychotics	−0.02	0.01	1089	−3.02	.003	−0.04	−0.01
Dose-years of anticholinergics	.015	0.01	1089	1.01	.313	−0.01	0.04
Working memory							
Age at follow-up	−0.04	0.03	1089	−1.48	.013	−0.11	0.01
Gender	−1.74	0.71	1089	−2.44	.015	−3.13	−0.34
Staging	−1.14	0.28	1089	−4.06	.001	−1.69	−0.59
WAT_IQ	0.28	0.03	1089	9.16	.001	0.22	0.34
Dose-years of antipsychotics	−0.01	0.01	1089	−0.32	.748	−0.02	0.01
Dose-years of anticholinergics	−0.02	0.01	1089	−1.58	.113	−0.05	0.01
Verbal learning							
Age at follow-up	−0.06	0.04	1089	−1.58	.113	−0.15	0.01
Gender	−0.68	0.90	1089	−0.76	.446	−2.45	1.08
Staging	−1.74	0.35	1089	−4.90	.001	−2.40	−1.04
WAT_IQ	0.25	0.03	1089	6.41	.001	0.17	0.32
Dose-years of antipsychotics	−0.02	0.01	1089	−1.88	.060	−0.04	0.01
Dose-years of anticholinergics	−0.05	0.01	1089	−3.01	.003	−0.09	−0.02
Visual learning							
Age at follow-up	−0.01	0.04	1082	−0.25	.803	−0.09	0.06
Gender	−6.68	0.86	1082	−7.69	.001	−8.38	−4.97
Staging	−1.42	0.34	1082	−4.12	.001	−2.09	−0.74
WAT_IQ	0.23	0.03	1082	6.23	.001	0.16	0.31
Dose-years of antipsychotics	−0.03	0.01	1082	−2.46	.014	−0.05	−0.01
Dose-years of anticholinergics	−0.02	0.01	1082	−1.39	.165	−0.06	0.01
Reasoning and problem solving							
Age at follow-up	−0.26	0.02	1075	−9.36	.001	−0.32	−0.21
Gender	−2.53	0.60	1075	−4.16	.001	−3.72	−1.33
Staging	−0.53	0.24	1075	−2.19	.029	−1.01	−0.05
WAT_IQ	0.07	0.02	1075	2.84	.004	0.02	0.01
Dose-years of antipsychotics	−0.02	0.01	1075	−3.16	.002	−0.04	−0.01
Dose-years of anticholinergics	0.01	0.01	1075	0.55	.581	−0.01	0.03
Social cognition							
Age at follow-up	−0.03	0.03	1037	−1.18	.236	−0.10	0.02
Gender	−3.80	0.71	1037	−5.31	.001	−5.20	−2.39
Staging	−1.07	0.28	1037	−3.74	.001	−1.64	−0.51
WAT_IQ	0.04	0.03	1037	1.54	.124	−0.01	0.10
Dose-years of antipsychotics	−0.03	0.01	1037	−3.36	.001	−0.05	−0.01
Dose-years of anticholinergics	0.03	0.01	1037	1.97	.048	0.01	0.06
MMCB overall composite score							
Age at follow-up	−0.03	0.03	929	−0.86	.387	−0.11	0.04
Gender	−4.46	0.81	929	−5.45	.001	−6.07	−2.86
Staging	−1.55	0.33	929	−4.59	.001	−2.22	−0.89
WAT_IQ	0.27	0.03	929	7.65	.001	0.20	0.34
Dose-years of antipsychotics	−0.03	0.01	929	−2.45	.014	−0.05	−0.01
Dose-years of anticholinergics	0.01	0.02	929	0.60	.546	−0.02	0.05

WAT_IQ: Word Accentuation Test (intelligence quotient).

psychosis and domain-level differences in reasoning and problem solving, working memory, and processing speed.[51]

The third main finding was that visual learning, social cognition, and the MCCB overall composite score were significantly associated with progression in clinical stages in the linear mixed-model analyses, after allowing for the effect of covariates. These findings imply that the progression of cognitive impairment could be explained by the worsening of clinical staging after the first six years. According to a study by Jonas et al.,[49] there appears to be a stronger correlation between the age of a patient and cognitive decline that occurs 14 years prior to the onset of psychosis. This has led to the proposal that patients with FEP may exhibit a neurodegenerative pattern later in life.

An interesting finding of this study was that patients already over clinical stage 2 after two years of FEP showed impairment only in the speed of processing in the cognitive assessment at the follow-up. These results may provide evidence for the construct of a critical period for psychosis.[52,53] This finding is also in agreement

Table 4
Transitions of clinical staging from baseline clinical staging to clinical staging at 2, 5, 10 years, and clinical staging at the end of follow-up.

	Staging at 2 years		Staging at 5 years		Staging at 10 years		Staging at the end of follow-up	
	Stage 2AB	Stages 3 to 4	Stage 2AB	Stages 3 to 4	Stage 2AB	Stages 3 to 4	Stage 2AB	Stages 3 to 4
Baseline clinical staging								
Stage 2AB	68	22	56	34	47	43	40	50
Stages 3 to 4	6	77	8	75	6	77	6	77

Stage 2A: single episode with full remission; stage 2B: multiple episodes with full remission; stage 3A: multiple episodes with partial and stable remission; stage 3B: multiple episodes with partial remission and progressive course; stage 4A: chronic/continuous and stable course; stage 4B: chronic/continuous and progressing course.

Table 5
MCCB cognitive differences between patients that transitioned from stages 2 to stages with partial remission or progression during the critical period of follow-up (Kruskal–Wallis tests).

	Clinical staging at 2 years of follow-up				Clinical staging at 5 years of follow-up			
	2AB ($n = 74$)	3A to 4B ($n = 99$)	Between groups$_{(df=2)}$	p	2AB ($n = 64$)	3A to 4B ($n = 109$)	Between groups$_{(df=2)}$	p
MATRICS Consensus Cognitive Battery (MCCB)								
Attention/vigilance	42.0 (9.63)	39.0 (11.2)	$H = 2.56$	ns	44.5 (10.4)	37.6 (9.9)	$H = 14.04$	<0.001
Speed of processing	37.3 (11.74)	33.4 (12.6)	$H = 5.01$	<0.025	39.3 (11.4)	32.7 (12.3)	$H = 11.77$	<0.001
Working memory	42.5 (12.15)	38.6 (12.4)	$H = 2.77$	ns	44.5 (11.8)	37.8 (12.1)	$H = 10.19$	<0.001
Verbal learning	37.7 (16.04)	33.6 (15.4)	$H = 2.38$	ns	39.1 (15.9)	33.2 (15.3)	$H = 5.61$	<0.018
Visual learning	39.4 (14.07)	35.8 (15.9)	$H = 1.87$	ns	40.9 (13.9)	35.2 (15.6)	$H = 5.42$	<0.020
Reasoning and problem solving	37.7 (10.26)	37.0 (11.0)	$H = 0.37$	ns	38.9 (10.6)	36.3 (10.6)	$H = 2.59$	<0.107
Social cognition	45.7 (12.54)	44.6 (11.3)	$H = 0.64$	ns	47.1 (11.1)	43.8 (12.1)	$H = 2.55$	<0.110
MMCB overall composite score	36.8 (12.92)	32.4 (13.7)	$H = 3.10$	ns	39.0 (12.5)	31.2 (13.3)	$H = 11.20$	<0.001

Stage 2A: single episode with full remission; stage 2B: multiple episodes with full remission; stage 3A: multiple episodes with partial and stable remission; stage 3B: multiple episodes with partial remission and progressive course; stage 4A: chronic/continuous and stable course; stage 4B: chronic/continuous and progressing course.

with the lower scores in processing speed in young people with attenuated psychiatric syndromes (stage 1b) compared to healthy controls[26] and in individuals at ultra-high risk for psychosis,[54] since our 2AB patients showed a decrease of approximately 1 standard deviation below control levels (40.4 ± 11.1) (Table 2).

Moreover, this finding is also relevant because it is in agreement with the extensive research on the speed of processing impairment over the last decades. Processing speed is one of the most frequently reported cognitive deficits in psychotic patients.[55,56] Furthermore, it has been reported that its impairment is a particularly potent predictor of nonclinical psychotic experiences in children.[57] It is not only predisposing to, but its impairment is gradually worsening in those who develop schizophrenia illness.[58,59] Other premorbid cognitive impairments have been shown to be suggestive of future schizophrenia, such as visuospatial and working memory impairments.[60–63] However, the role of processing speed disturbances in psychosis has been emphasized because it has been hypothesized that its impairment may be a basic cognitive impairment or a mediating factor on other cognitive disturbances in psychosis.[64] Processing speed disturbances in psychosis are clearly distinguished from accelerated aging effect.[65]

Clinical heterogeneity is prevalent in all forms of psychosis, and is probably more common in individuals with FEP. Finding alternative clinical models to DSM categories that are either better for external validation or purportedly closer to the neurological substrate is one way to account for the heterogeneity problem of psychosis.[66–68] In this study, we used the cognitive function of our FEP patients at long-term follow-up to analyze the longitudinal trajectories of the clinical staging model.

Conclusions

The progression of FEP in clinical stages showed a significant linear trend with worsening cognitive performance during the follow-up period. The clinical staging model allowed for the differentiation of cognitive impairment between stages. Additionally, deficits in processing speed appeared to be a cognitive marker linked to the period between two and five years of follow-up, which corresponds to the critical period of psychosis.

Limitations

This study has some limitations. First, our cohort had two attritions. One was related to failing to re-contact patients, and the other was due to the lack of re-engagement of part of the sample to complete cognitive assessments. These attritions reduce the strength of the potential generalization to the entire FEP population. Second, the clinical staging model used in this study was slightly different from previous staging models[1,38,69] because it aimed to establish long-term clinical staging focusing on recurrence, persistence, and progression. Small differences among the models may affect comparability across studies. Third, our study used a follow-back design to assess clinical staging. This design is not exempt from limitations owing to the lack of a continuous assessment to accurately establish clinical staging and their transitions over the years. However, our model used a comprehensive set of predictors and outcome validators to verify its validity and feasibility.[14,70] Fourth, cognitive examination was only performed at the final appointment for all patients, precluding or reducing the strength of potential associations between clinical staging and changes in cognitive performance. Moreover, this was a naturalistic study,[32] and drug treatments and interventions were individually applied to patients by their community psychiatrist and were not standardized during the follow-up period. This design did not control for potential preventive strategies to reduce the transition or worsening of clinical staging in the long term. Fifth, there are many potential variables that may impact on cognitive performance in FEP patients, such as premorbid variables (i.e., antecedents of psychosis; obstetric complications, neurodevelopmental delays, trauma, cognitive reserve, etc.)[71,72] and environmental ones (family ambient during childhood, abuse at school, drug abuse, social exclusion, etc.) (Peralta et al., 2024, submitted). The list of potential confounding variables are large enough to be included in the statistical techniques we nowadays have available. Within potential variables having a

deleterious effect on cognitive performance on the basis of the literature, we chose for this article sex,[73] premorbid IQ,[74,75] dose-years of antipsychotics, and dose-years of anticholinergics to control for the pervasive effect of male gender, low premorbid intelligence, and high loadings of antipsychotic and anticholinergic loadings along their illness course.[76–78] However, we did not include substance abuse during the course of the illness as a covariate, despite being highly prevalent in the FEP population.

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Conflict of interests

The authors state that they have no conflict of interests.

Appendix A. SEGPEPs Group

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.sjpmh.2024.02.001.

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