INDIVIDUAL TRAJECTORIES OF COGNITIVE PERFORMANCE IN FIRST EPISODE PSYCHOSIS: A 2-YEAR FOLLOW-UP STUDY.

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Abstract

Background: Individual changes over time in cognition in patients with psychotic disorders have been studied very little, especially in the case of first episode psychosis (FEP).

Methods: We aimed to establish whether change in individual trajectories in cognition over two years of a sample of 159 FEP patients were reliable and clinically significant, using the reliable change index (RCI) and clinically significant change (CSC) methods. We also studied a sample of 151 matched healthy controls. Patients and controls were assessed with a set of neuropsychological tests, as well as premorbid, clinical and functionality measures. We analysed the course of cognitive measures over time, using analysis of variance, and the individual trajectories in the cognitive measures with the regression-based RCI (RCI_{SRB}) and the CSC.

Results: The RCI_{SRB} showed that between 5.4% and 31.2% of the patients showed deterioration patterns, and between 0.6% and 8.8% showed improvement patterns in these tests over time. Patients showing better cognitive profiles according to RCI_{SRB} (worsening in zero to two cognitive measures) showed better premorbid, clinical and functional profiles than patients showing deterioration patterns in more than three tests. When combining RCI_{SRB} and CSC values, we found that less than 10% of patients showed improvement or deterioration patterns in executive function and attention measures.

Conclusions: These results support the view that cognitive impairments are stable over the first two years of illness, but also that the analysis of individual trajectories could help to identify a subgroup of patients with particular phenotypes, who may require specific interventions.

KEYWORDS: first episode psychosis, longitudinal, cognition, reliable change index, schizophrenia, clinically significant change

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1. INTRODUCTION

Cognitive deficits are present in patients with psychotic disorders from the first episode [1] and even earlier [2]. However, the course of cognitive deficits is still a matter of debate. In general terms, the bulk of research points to stability of cognitive deficits over time. However, some studies have found patterns of deterioration [3-5] or improvement over time in some cognitive functions [6-8]. In addition, longitudinal studies of cognition in patients with psychosis usually compare group means at the different assessment time points to determine whether there has been improvement or deterioration over time, and few studies have examined individual trajectories of patients' cognitive performance over time in detail [9,10]. This is particularly important in clinical research, where researchers may be interested in the efficacy of a treatment or in considering whether an individual patient has improved in a particular cognitive domain. In the last three decades, the Reliable Change Index (RCI) has been used to assess change in clinical psychology and neuropsychological literature. This method represents a more sophisticated method for examining individual change, compared to other methods, such as comparing discrepancy scores between two observations with normative data, or the standard deviation index (see [11] for a review). The RCI includes different methods to assess change. The first one was proposed by Jacobson et al. [12,13], and more recently, other methods have been proposed to refine the assessment of change [11]. These methods have modified the original formula to control for practice effects [14] or for baseline performance and other relevant variables [15]. In the field of neuropsychology, it is especially relevant to account for practice effects when assessing change.

In this study, we aimed to analyse individual trajectories, and determine: 1) whether individual changes observed in cognitive tests were reliable; 2) whether any reliable changes found were also clinically significant; and 3) whether patients showing significant deterioration or improvement patterns over time had distinct clinical or demographic characteristics. Based on previous longitudinal studies [7,16-19], our hypothesis was that the predominant pattern observed in patients would be of stability in cognitive scores. In addition, we hypothesized that the study of individual trajectories would permit us to identify a subgroup of patients with deterioration patterns in some cognitive tests, and that these patients would differ in clinical and demographic characteristics from patients showing stability or improvement patterns in the cognitive tests.

2. METHODS

The present study is part of the "Phenotype-genotype and environmental interaction. The application of a predictive model in first psychotic episodes" or PEPs study, which is a multicentre, longitudinal, naturalistic, follow-up study in Spain designed to evaluate clinical, neuropsychological, neuroimaging, biochemical and genetic variables in a sample of 335 first-episode (FEP) psychosis patients and 253 matched healthy controls [20]. Patients and control subjects were recruited in the sixteen centres participating in the PEPs project from April 2009 to April 2011.

Patients of the PEPs study were assessed on five occasions: at baseline (recruitment), at two months (when the neurocognitive assessments were first administered), six months, one year and two years (when the neurocognitive battery was repeated). Overall, the mean follow-up period for re-testing was of 23.64 months for patients (s.d. = 2.38) and 22.69 months for controls (s.d. = 2.45). For the purposes of this study, we used data of the two months and two years visits.

2.1 Participants

The PEPsCog study, a substudy focused on cognitive characteristics, included patients of the PEPs study who completed seven or more of the ten tests included in the neurocognition module (266 patients and 225 controls). At follow-up, we maintained the same criteria, that is, we included patients who at follow-up had completed seven or more neurocognitive tests. The PEPsCog study sample and inclusion criteria at baseline are described in Cuesta et al. [1]. In brief, patients were between 16 and 35 years old, had experienced psychotic symptoms for less than 12 months before the time of their inclusion in the study, were fluent in Spanish and provided written informed consent. They were recruited during their attendance at the centres participating in the study, so most of them were inpatients at baseline, and then were followed in their natural treatment environment on an outpatient basis, so decisions regarding treatment were made by the corresponding psychiatrist. Controls were matched with the patients for age (±10%) and the socio-economic status of their parents (± 1 level). At follow-up, the sample consisted of 159 patients and 151 controls, which represented an attrition rate of 40.23% in patients and 32.89% in controls.

The study was approved by the Navarra Clinical Research Ethics Committee (CEIC).

2.2. Clinical assessments

Demographic data had been collected for all participants at baseline. At follow-up, we reviewed these data, assessing changes in years of education, marital status and living accommodation.

Premorbid adjustment was assessed retrospectively with the Premorbid Adjustment Scale (PAS; [21] based on information from patients and parents or close relatives.

Psychopathological status was assessed with the Positive and Negative Symptoms Scale [22,23], the Young Mania Rating Scale (YMRS [24]), and the Montgomery-Asberg Depression Rating Scale (MADRS [25,26]).

Pharmacological treatment was also recorded at each visit. Antipsychotic treatment was converted to chlorpromazine equivalents [27].

Diagnoses were reviewed at the two-year visit with the Structured Clinical Interviews for Axis I and II Disorders (SCID-I and II [28,29]). The SCID-I and II have a Spanish translation available [30,31]. These are semi-structured diagnostic interviews designed to assess current and past psychopathology and personality disorders in adults, according to DSM-IV criteria. The use of a semi-structured interview such as the SCID has been shown to improve the reliability of diagnostic assessments [32]. Using the same diagnostic tools on every visit helped us to check the stability of the diagnoses and to register any change.

Patients were grouped into three diagnostic categories: 1) schizophrenia spectrum disorders, which included schizophrenia, schizophreniform and schizoaffective disorders; 2) affective psychosis spectrum, including bipolar I and II disorders, and manic and depressive episodes with psychotic symptoms; and 3) other psychoses, including brief psychotic disorders, psychoses not otherwise specified and toxic psychoses.

2.3. Neuropsychological assessments.

Patients and controls were assessed twice with a set of neuropsychological tests The tests and the scores selected for the purposes of this work are listed in Table 1.

The tests were administered in two sessions of 1-1.5h by experienced neuropsychologists, who had achieved a good to excellent inter-rater reliability (intraclass correlation coefficients >0.80) in two of the tests of the battery: the WAIS Vocabulary subtest and the WCST.

2.4. Data analysis.

Demographic and clinical characteristics of patients and controls were compared with t-tests and chi-squared tests.

To analyse the differences in neuropsychological performance between groups and between assessments (at two months and at two years), we applied repeated measures analysis of variance (ANOVA), including demographic variables in which patients and controls differed significantly as covariates.

Then, to study the individual trajectories of patients and controls over time in the neuropsychological tests, we used RCI. Among the different methods available to calculate the RCI, we chose the complex regression-based change formula (RCI_{SRB}) [15] This method uses stepwise linear regression to predict Time 2 scores using Time 1 scores, and also including variables which could be clinically relevant. To calculate the RCI, we used data from the controls, considered a relevant sample to compare with our patients. The predicted score for Time 2 (T_2') is calculated with the regression line of the control group for each cognitive variable: $T_2' = bT_1 + c$. The RCI score is the result of subtracting the predicted score from the actual Time 2 score, and then dividing by the standard error of the regression equation (SEE): $RCI_{SRB} = (T_2 - T_2')/SEE$. This resulting RCI is then compared with a normal distribution table. We used the cutoff point of ±1.645, because it includes 90% of cases. In other words, in a normal distribution, only 5% of the cases would score above +1.645, and only 5% of cases would fall below -1.645.

Once we identified patients who showed an abnormal pattern of changes in cognitive performance over time, compared to controls, we explored the demographic and clinical characteristics of these subsamples. We also determined which patients showed abnormal changes in the greatest number of cognitive tests, to ascertain whether these patients showed similar clinical profiles.

Finally, we determined the clinically significant change (CSC), which represents the extent to which change over time is clinically meaningful. To calculate the cutoff point for each cognitive measure, we used the criterion C proposed by Evans et al. [42].

The reason for using this measure was to determine whether the patients individually had moved from a clinical distribution to a normative one over time. The formula used to calculate the cutoff point was as follows:

$$CSC=[(mean_{patients} \times SD_{controls})+(mean_{controls} \times SD_{patients})]/(SD_{controls}+SD_{patients})$$

All analyses were performed using IBM SPSS version 20.0 [43].

3. RESULTS

Demographic and clinical characteristics of the sample are shown in Table 2. Controls had more years of education than patients, a higher estimated premorbid IQ and higher global functioning assessed with the Global Assessment of Functioning scale (GAF) [44] than patients. No differences were found in age, sex or parental socioeconomic status between patients and controls.

Patients obtained significantly lower scores in the clinical ratings at the two-year visit compared to baseline assessments, except in the case of the YMRS, for which no significant differences were found. Mean daily antipsychotic doses were also significantly lower at the two-year visit than at baseline.

Repeated measures ANOVAs, including years of education as a covariate, revealed a significant effect of time in letter-number, WCST total errors, TAVEC delayed recall, Stroop word-colour and MSCEIT scores. Significant differences between patients and controls were found in all the test scores. However, the time x group interaction was only significant for the WCST categories and total errors scores, showing improvement in both scores. When applying the Bonferroni correction, time and time x group effects were not significant for any of the measures, while group effects remained significant except for CPT scores (Table 3).

The analysis of RCI_{SRB} revealed that between 5.4% and 31.2% of patients showed a deterioration pattern in at least one of the cognitive measures, while only between 0.6% and 8.8% showed an improvement pattern over time. The neuropsychological measures in which the highest percentages of patients had deterioration patterns were the TMT-B, TAVEC immediate and delayed recall (around 30% of the sample), followed by the MSCEIT, FAS and TMT-A (around 20% of the sample). At the other extreme, the measures in which the smallest percentages of patients showed deterioration were the Digit span, WCST perseverative errors and CPT

d' measures, with less than 10% of the sample showing a worsening pattern over time (Table 4).

According to these results we calculated the median of the number of measures in which the patients showed deterioration patterns (M=2). Hence, we grouped the patients into two groups: patients who showed deterioration patterns in two or fewer measures, and those who showed deterioration patterns in three or more measures. Then, we analysed the differences between the two groups in clinical and demographic measures with Student's t (Table 5). We did not find significant differences between groups in age, sex or parental socioeconomic status. Patients with deterioration patterns in less than three cognitive measures had more years of education, higher estimated premorbid IQ and better global functioning at both the two-month and the two-year visits, better functioning in daily activities and better premorbid adjustment in early and late adolescence and better total adjustment score, than patients with deterioration patterns in three or more cognitive measures. The distribution of diagnoses was also significantly different in the two groups, there being a higher percentage of patients with affective psychoses and other psychoses in the group of patients with better cognitive trajectory (0 to 2 measures with deteriorating patterns). Regarding clinical symptoms, patients with less cognitive impairment also had fewer symptoms in all the clinical syndromes explored. In accordance with this, the first group was receiving lower doses of antipsychotics (Table 5).

Once we had tested whether individual change over time was reliable in our sample of patients, we aimed to ascertain whether this reliable change was also clinically significant. Table 4 shows data concerning CSC, and the results of combining patients who showed reliable and CSC over time. As can be seen, few patients showed reliable and clinically significant improvement or worsening patterns in WCST perseverative and total errors, TMT-A, TMT-B and CPT d' scores, and none in the rest of measures. In other words, few patients showed such a higher change in these tests' performance, with respect to baseline and to controls, to consider that they had moved from a clinical to a non-clinical performance.

Finally, we compared demographic, clinical and cognitive differences between patients included in the study and those who had not completed seven or more cognitive tests at the two-year visit, or withdrew from the study during the follow-up. We aimed to rule out the possibility that the stability patterns found in our sample were due to these differences. We found that patients who participated in the study were

significantly younger than patients who were not included (mean ages of 23.65±5.64 and 25.07±5.34 years; t=2.05, p=0.041, respectively). No differences were found in sex or socioeconomic parental status, or in any clinical or cognitive measures.

4. DISCUSSION

Our main findings are as follows: First, FEP patients showed cognitive impairment with respect to controls in all the cognitive measures. Second, we found a stability pattern of cognitive performance in the first two years following the FEP, after accounting for practice effects and baseline performance. Third, when we analysed the individual trajectories of FEP patients, we found that between 5% and 31% of the patients showed reliable deterioration patterns in at least one cognitive measure, while less than 10% of patients showed reliable improvement patterns. Fourth, the analysis of individual trajectories allowed us to identify a subgroup of patients with cognitive deterioration patterns; specifically, when comparing the clinical and demographic profiles of patients who showed deterioration in zero to two measures, with those who showed deterioration in more than two measures, we found that the former had better profiles in all the clinical syndromes explored, better adjustment in adolescence and better functioning profiles, as well as a higher proportion of affective psychoses and other psychotic disorders than the latter. And fifth, we observed a combination of reliable and clinically significant change in few patients in six of the 14 cognitive measures, namely, those which assessed attention, processing speed and executive functions.

We found consolidated poor performance impairment in the patients with respect to controls, but similar trajectories over the two-year follow-up for both groups. These differences support the view that cognitive deficits are present at least since the onset of psychotic symptoms, even though poor premorbid adjustment seems to be a key antecedent for the development of cognitive impairment in patients developing psychosis, in agreement with previous research in FEP [1,45-47].

Our findings also support the idea that the course of cognitive deficits is stable over the first years following the onset of psychotic symptoms in FEP patients, as has been reported by other authors [48,9]. In a recent meta-analysis, Bora and Murray [49] reported that there was no evidence of cognitive decline in FEP patients, but the cognitive deficits observed were present from illness onset. Our results support these data, in that only a few FEP patients showed a significant decline or improvement over

the two years of follow-up. These results suggest that cognitive deficits follow a neurodevelopmental model, since no evidence of cognitive decline was observed, at least in the short term. Longitudinal studies with longer follow-up periods show similar stability patterns [7,16,17]. However, cognitive impairments have also been related to longer duration of illness [50], and neuroimaging studies reveal the presence of progressive brain deficits in schizophrenia [51,52] which may be related to functional outcomes [53]. Other studies such as the meta-analysis of Szoke et al. [8] refer to patterns of improvement in cognition over time, but considering the short periods of follow-up of some of the studies included, the absence of a control group to account for practice effects in many of them, and also the non-naturalistic designs, the results should be interpreted with caution [54].

Individual cognitive patterns of deterioration or improvement, governed by an illness course not explained by the neurodevelopmental model, may be obscured by group means. Further, repeat cognitive testing may be subject to practice effects, which may be confused with real cognitive improvement. The inclusion of a control group and the use of RCI methods can help to elucidate whether changes in performance over time are due to practice [55]. For example, Bora and Murray [49] report improvement over time in most of the cognitive domains assessed, but they recognize that these improvements can be partly explained by practice effects.

Few studies have reported data on cognitive performance using RCI methods in patients with psychotic disorders [56,10,57-59,16,9], and only two of them included FEP patients [10,9]. For example, Gray et al. [45] used three different RCI methods to establish reliable change in the MCCB [60] based on a large sample of patients with schizophrenia. They concluded that it was necessary to observe a change of about 10 T-score units to conclude that a reliable change had occurred. From the methods used in their work, they found that the RCI_{SRB} was the most useful for patients who had baseline scores far from the group mean. With these data, they developed confidence intervals for every cognitive domain of the MCCB to assess reliable change. Penades et al. [59] applied the RCI to detect change in relation to two different interventions, controlling for practice effects in a sample of chronic patients with schizophrenia. Cuesta et al. [10] also employed the RCI to assess the clinical efficacy of an intervention, in that case, comparing the effectiveness of two medications on cognitive performance.

Our results showed a predominant pattern of cognitive stability over two years at group level, but we also identified up to 49 and 13 patients who showed deterioration and improvement patterns in at least one cognitive measure, respectively. Hence, having RCI_{SRB} values could help to identify patients needing special attention concerning cognitive impairment and showing deterioration trajectories of illness that may represent a particular illness phenotype, and hence require specific interventions.

Cognitive assessments in our study were performed two months after inclusion in the study. We considered that this period of time (with flexibility of ±1 month) is sufficient for treatment to be established and for patients to show psychopathological stability. Hence, our results may suggest that cognitive deficits observed at the first assessment were not only a consequence of the acute manifestations of the episode. Considering this, the analysis of the two groups of patients suggests that worse outcomes in cognition, functioning and symptoms are related. We must differentiate between premorbid factors and illness-related factors. Patients with better cognitive course showed higher premorbid IQ, more years of education and better premorbid adjustment at every stage of life except for childhood, than patients with poorer cognitive outcomes at two years. These results are congruent with the cognitive reserve hypothesis [61]-[62], which proposes that patients with higher premorbid intellectual function are more able to cope with the brain insult caused by the illness. According to Barnett et al. [61], in psychotic disorders, this cognitive reserve may result in fewer psychotic symptoms and better functional outcomes. Higher premorbid IQ and IQ at the first episode have been related to better functional outcomes, fewer negative symptoms both at onset and at three and four-year follow-up and shorter index admissions [63,64]. In our sample, patients with better cognitive trajectories over time also had fewer symptoms, were on lower antipsychotic doses and showed higher global functioning than patients showing deterioration cognitive patterns in more than two measures. We also found a higher proportion of patients with affective psychoses and other psychotic disorders in the group with better cognitive patterns. In other words, the influence of clinical factors and the consequent higher antipsychotic doses may have a deleterious effect on cognition. Although we cannot establish causal relationships, our results suggest that cognitive preservation is related to better prognosis in the course of disease.

Our results regarding CSC showed that the scores to account for significant change over time were very high, and hence only patients with extreme scores at baseline showed a clinically significant improvement or worsening over time. In fact,

only few patients achieved CSC in three tests (WCST, TMT and CPT) reflecting the highest changes in attention, processing speed and executive functions measures: up to ten patients showed worsening patterns and up to 13 patients showed improvement patterns. These results could reflect that the cutoff score selected for each of the tests was too stringent or that the tests selected are insufficiently sensitive to cognitive change. However, in a previous report based on this sample [1], we described that patients showed cognitive impairment at baseline, but the differences were around -1.5 standard deviations with respect to controls. Thus, considering this magnitude of impairment, we did not expect that many patients would show large changes in their test scores at follow-up. In addition, these results are consistent with the stability patterns observed at the group level, where we found significant time x group interactions in only two measures of the WCST. These results are congruent with those of the meta-analysis by Bora and Murray [49] in that they also found significant improvements (although at group level) in these tests, as well as in a list learning test.

Strengths and limitations

As far as we know, only two previous studies [9,10] have used RCI methods to characterise cognitive patterns over time in FEP patients. In addition, CSC has not been considered previously in samples with FEP. Our work highlights the importance of taking into account individual trajectories, especially to design interventions. The study of individual trajectories may help to refine the search for prognostic factors to design treatment, which otherwise could be obscured by group means. In addition, they are interesting tools to determine individual trajectories, especially when analysing the results of an intervention. Hence, these methods could be relevant to apply in clinical practice.

The large sample and the longitudinal design are also two strengths of this work. The downside of the longitudinal design is the high attrition rates that we observe at the two-year visit. However, we did not find significant differences in clinical, cognitive and premorbid characteristics between patients who had longitudinal data and those who withdrew from the study.

Our findings have several clinical implications: first, there is a heterogeneity in trajectories that deserves further studies to better identify and predict cognitive and functional outcome. Second, any attempt to prevent cognitive impairment in patients with psychoses should target premorbid states and focus on early intervention, because

most of the harm is caused at the time of the FEP or even before. Last, cognitive status and symptomatic status are correlated and it may be as important to tackle psychotic symptoms as cognitive deficits.

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Appendix 1.

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Conflict of interest

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Table

Table 1. Neuropsychological tests and scores selected for cognitive assessment.

Cognitive domain	Type of test	Description of test and measures used for domain summary scores
Premorbid IQ	Wechsler Adult Intelligence Scale-III, Vocabulary Test [33]	Give oral definitions for words. Measure: direct score and standardized score. Estimated premorbid IQ is calculated from the standardized score: (SS x 5) + 50
Attention	Continuous Performance Test-II (CPT; [34]	Respond to a series of letters on a computer screen by pressing a key when you detect letters other than the letter "X". The assessment contains six blocks that vary in the rate of submission of the letters. Measure: Mean response sensitivity (D-prime).
Processing Speed	Trail Making Test (Form A) [35]	Connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in proper order. Measure: Time to complete this (form A)
Executive Function	Wisconsin Card Sorting Test, (WCST-128; [36]	Complete a complex task of categorization set shifting, and respond to feedback from the computer. Measure: Number of completed categories, total errors and perseverative errors.
	Trail Making Test (Form B)[35]	Draw lines connecting characters that are sequentially alternating between numbers and letters. Measure: Time to complete this (form B).
	Stroop Test, Color-Word Interference effect [37]	Name the colour in which the colour names are printed and disregard their verbal content. Measure: Number of correct responses in the Word-Colour section
	Controlled Oral Word Association Test, FAS-Test [38]	Generate as many words as possible beginning with F, A and S in three separate trials of 60 s. Measure: The sum of all correct responses
	Test Barcelona, Animal Words [39]	Produce as many animal names as possible in a 1-minute interval. Measure: Number of correct responses
Working Memory	Wechsler Adult Intelligence Scale-III, Digit Span Test [33]	Repeat a number sequence in the same order as that presented and in the reverse order. Measure: the total number of series correctly repeated forwards and backwards.
	Wechsler Adult Intelligence Scale-III, Letter-Number Sequencing [33]	Listen to a combination of numbers and letters read aloud by the tester and reorganize the sequence listing first the numbers in ascending order and then the letters in alphabetical order. Measure: number of correct sequences.
Verbal Memory	California Verbal Learning Test, Spanish version (TAVEC)[40]	Recall as many words as possible from a list of 16 words read aloud by the tester. The procedure is repeated 5 times, and recall is tested immediately and after a delay. Measure: total number of words recalled immediately and after a delay.
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT[41]	Rate the helpfulness of certain moods and assess the effectiveness of strategies to manage emotions. Measure: total managing emotion's section score.

Table 2. Demographic and clinical characteristics of the sample. Means and standard deviations.

	Patients (n=159)	**Controls (n=151)**	**D.f.**	**Student's t or X^2 ***
Age (years)	25.83 (5.68)	27.01 (6.17)	308	t=-1.74 (p=0.08)
Sex n(%): (F/M)	55 (34.6)/104 (65.4)	55 (36.4)/96 (63.6)		X^2=0.11 (p=0.74)
Education	12.39 (3.46)	14.76 (3.23)	300	**t=-6.13 (p<0.001)**
Estimated Prem IQ (2 years)	95.67 (13.76)	108.76 (11.37)	306	**t=-9.09 (p<0.001)**
GAF baseline (2 months)	63.51 (15)	93.17 (5.61)	305	**t=-23.08 (p<0.001)**
GAF 2 years	73.34 (14.61)	92.76 (4.19)	284	**t=-15. 23 (p<0.001)**
Parental socioeconomic status (H-R scale) High Medium-high Medium Medium-low Low Unknown	 35 (22) 19 (11.9) 37 (23.3) 54 (34) 13 (8.2) 1 (0.6)	 36 (23.8) 34 (22.5) 39 (25.8) 35 (23.2) 7 (4.6)		X^2=10.97 (p=0.052)
Diagnosis (2 years) **Schizophrenia spectrum** **Affective psychoses** **Other psychoses**	 90 (56.6%) 27 (17%) 42 (26.4%)			
Clinical ratings (patients)				
	Baseline (2 months)	**2 years**		
PANSS Positive Syndrome Negative Syndrome General psychopathology Total	 11.08 (5.01) 16.32 (6.87) 28.34 (9.32) 55.74 (19.06)	 10.06 (3.87) 13.97 (6.21) 24.89 (8.18) 48.92 (16.55)	 145	 **t=2.66 (p=0.009)** **t=4.58 (p<0.001)** **t=4.86 (p<0.001)** **t=4.97 (p<0.001)**
MADS	9.49 (8.54)	5.47 (6.17)	143	**t=5.08 (p<0.001)**
YMRS	1.71 (3.33)	1.76 (3.53)	146	t=-0.14 (p=0.885)
AP Doses (chlorpromazine equivalents)	451 (360.28)	188.71 (268.77)	157	**t=9.77 (p<0.001)**

*** Bold values indicate p<0.05**. D.f.: degrees of freedom; F: female; M: male; Prem IQ: Premorbid Intelligence Quotient; GAF: Global Assessment of Functioning; H-R scale: Hollingshead-Redlich scale [10]; PANSS: Positive and Negative Syndrome Scale; MADS: Montgomery-Asberg Depression Scale; YMRS: Young Rating Mania Scale; AP Doses: Daily doses of antipsychotics in chlorpromazine equivalents.

Table 3. Repeated measures analysis of variance between patients and controls in the cognitive measures. Means and standard deviations.

		Patients		Controls		Time effect ANOVA F(p)[a]	Group effect ANOVA F(p) [a]	Time x group effect ANOVA F(p) [a]
	D.f.	**Baseline**	**2 years**	**Baseline**	**2 years**			
Digit span	**1, 299**	14.04 (3.1)	14.24 (3.69)	16.95 (3.72)	17.24 (3.91)	2.26 (p=0.134)	**32.10 (p<0.001)***	0.44 (p=0.507)
Letter-number	**1, 298**	8.98 (2.84)	9.42 (2.94)	11.45 (2.57)	12.05 (2.75)	**4.97 (p=0.026)**	**44.31 (p<0.001)***	1.07 (p=0.302)
WCST-Categories	**1, 276**	4.78 (1.84)	5.24 (1.54)	5.71 (1)	5.78 (0.86)	0.39 (p=0.536)	**17.14 (p<0.001)***	**4.85 (p=0.029)**
WCST Perseverative errors	**1, 275**	17.01 (12.72)	12.78 (11.77)	10.30 (6.01)	8.48 (10.55)	3.35 (p=0.068)	**17.14 (p<0.001)***	1.20 (p=0.274)
WCST Total errors	**1, 275**	31.08 (17.06)	22.55 (14.6)	18.78 (11.16)	15.05 (9.05)	**7.77 (p=0.006)**	**27.77 (p<0.001)***	**6.78 (p=0.010)**
TMT-A	**1, 298**	39.52 (20.64)	35.85(19.2)	26.26 (8.74)	24.73 (8.18)	3.61 (p=0.058)	**47.59 (p<0.001)***	0.36 (p=0.055)
TMT-B	**1, 296**	87.75 (42.48)	86.65 (47.68)	56.40 (21.59)	53.60 (17.74)	0.29 (p=0.593)	**53.74 (p<0.001)***	0.02 (p=0.897)
TAVEC immediate recall	**1, 295**	9.84 (3.49)	11.05 (3.35)	13.54 (2.25)	14.23 (1.87)	2.14 (p=0.145)	**101.65 (p<0.001)***	2.28 (p=0.132)
TAVEC delayed recall	**1, 294**	10.30 (3.41)	11.46 (3.21)	13.90 (2.03)	14.52 (1.82)	**4.24 (p=0.040)**	**102.92 (p<0.001)***	2.03 (p=0.160)
Stroop Word-colour	**1, 290**	39.32 (11.1)	42.3 (11.43)	50.23 (11.98)	52.85 (11.39)	**5.92 (p=0.016)**	**50.15 (p<0.001)***	0.01 (p=0.939)
Semantic fluency (animals)	**1, 289**	17.09 (4.55)	17.75 (4.8)	22.8 (5.11)	23.52 (4.86)	1.61 (p=0.206)	**94.44 (p<0.001)***	0.11 (p=0.743)
Phonologic fluency (FAS)	**1, 285**	28.96 (9.58)	31.5 (10.07)	38.67 (9.92)	41.67 (10.05)	0.71 (p=0.399)	**53.54 (p<0.001)***	0.07 (p=0.792)
CPT-d'	**1, 264**	0.71 (0.59)	0.80 (0.52)	0.98 (0.64)	0.99 (0.51)	2.34 (p=0.128)	**5.59 (p=0.019)**	0.36 (p=0.548)
MSCEIT-IQ	**1, 259**	91.87 (11.97)	94.01 (12.40)	101.57 (12.06)	104.48 (11.24)	**6.33 (p=0.012)**	**48.31 (p<0.001)***	1.05 (p=0.306)

[a] Including Years of education as covariate

Bold values indicate p<0.05; *Bonferroni correction: p<0.004

D.f.: degrees of freedom; WCST: Wisconsin Card Sorting Test; TMT: Trail Making Test; TAVEC: California Verbal Learning Test, Spanish version; CPT: Continuous Performance Test; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test

Table 4. Reliable Change Index of the patients, based on the linear regression of the control group, and Clinically Significant Change.

		RCI_{SRB}				**CSC**				**RCI_{SRB} + CSC**	
		Improve		**Worsen**		**Improve**		**Worsen**		**Improve**	**Worsen**
	Total n	n	(%)	n	(%)	n	(%)	n	(%)	n (%)	n (%)
Digit span	159	4	2.5	12	7.6	0	0	0	0	0	0
Letter-number	159	5	3.1	17	10.7	0	0	0	0	0	0
WCST-Categories	146	7	4.8	24	16.4	0	0	0	0	0	0
WCST Persev. errors	147	1	0.7	8	5.4	31	21.1	11	7.5	1 (0.7)	8 (5.4)
WCST Total errors	147	13	8.8	24	16.3	25	17	2	1.4	13 (8.8)	2 (1.4)
TMT-A	159	4	2.5	30	18.9	8	5	3	1.9	4 (2.5)	3 (1.9)
TMT-B	157	4	2.6	47	29.9	8	5.1	10	6.4	4 (2.6)	10 (6.4)
TAVEC immediate recall	157	1	0.6	47	29.9	0	0	0	0	0	0
TAVEC delayed recall	157	5	3.2	49	31.2	0	0	0	0	0	0
Stroop Word-colour	153	5	3.3	18	11.8	0	0	0	0	0	0
Semantic fluency (animals)	147	2	1.4	16	10.9	0	0	0	0	0	0
Phonologic fluency (FAS)	153	5	3.3	31	20.3	0	0	0	0	0	0
CPT-d'	135	9	6.7	10	7.4	8	5.9	6	4.4	8 (5.9)	6 (4.4)
MSCEIT-IQ	134	6	4.5	29	21.6	0	0	0	0	0	0

WCST: Wisconsin Card Sorting Test; TMT: Trail Making Test; TAVEC: California Verbal Learning Test, Spanish version; CPT: Continuous Performance Test; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test

Table 5. Demographic and clinical differences between patients with deterioration patterns over time in 0 to 2 cognitive measures and patients with deterioration patterns in more than 2 cognitive measures. Means and standard deviations.

	0-2 measures (n=99)	**>2 measures (n=60)**	**Student's t or X^2 ***
Age (years)	26.04 (5.55)	25.48 (5.92)	t=0.6 (p=0.551)
Sex (%):(F/M)	30/69	25/35	X^2=2.13 (p=0.144)
Education (years)	13.17 (3.39)	11.12 (3.2)	**t=3.75 (p<0.001)**
Estimated Prem IQ (2 years)	101.33 (10.74)	86.27 (13.15)	**t=7.81 (p<0.001)**
GAF baseline (2 months)	65.73 (14.32)	59.76 (15.5)	**t=2.39 (p=0.018)**
GAF 2 years	75.84 (12.59)	69.04 (16.83)	**t=2.56 (p=0.012)**
Parental socioeconomic status (H-R scale)			X^2=10.19 (p=0.07)
High	25	10	
Medium-high	12	7	
Medium	27	10	
Medium-low	30	24	
Low	4	9	
Unknown			
Diagnosis (2 years)			**X^2=7.32 (p=0.026)**
Schizophrenia spectrum	48	42	
Affective psychoses	21	6	
Other psychoses	30	12	
Clinical ratings			
PANSS 2 years			
Positive Syndrome	9 (2.75)	12.15 (5.14)	**t=-4.83 (p<0.001)**
Negative Syndrome	12.45 (5.39)	16.73 (6.73)	**t=-4.24 (p<0.001)**
General psychopathology	23.30 (6.85)	27.95 (9.78)	**t=-3.38 (p=0.001)**
Total	44.75 (13.29)	56.82 (19.77)	**t=-4.42 (p<0.001)**
MADS	4.59 (5.53)	7.34 (7.59)	**t=-2.35 (p=0.021)**
YMRS	0.95 (2.02)	3.36 (5.18)	**t=-3.34 (p=0.001)**
AP Doses (chlorpromazine equivalents)	126.58 (189.63)	290.18 (340.91)	**t=-3.41 (p=0.001)**
Premorbid Adjustment Scale (PAS)			
Childhood	5.4 (3.72)	6.47 (4.77)	t=-1.57 (p=0.120)
Early adolescence	7.44 (4.87)	9.86 (5.33)	**t=-2.86 (p=0.005)**
Late adolescence	8.85 (5.73)	10.86 (6.27)	**t=-1.99 (p=0.048)**
Adult	2.80 (2.71)	3.22 (2.87)	t=-0.84 (p=0.405)
Total	39.67 (21.12)	49.07 (23.3)	**t=-2.52 (p=0.013)**

***Bold values indicate p<0.05;** F: female; M: male; Prem IQ: Premorbid Intelligence Quotient; GAF: Global Assessment of Functioning; H-R scale: Hollingshead-Redlich scale [10]; PANSS: Positive and Negative Syndrome Scale; MADS: Montgomery-Asberg Depression Scale; YMRS: Young Rating Mania Scale; AP Doses: Daily doses of antipsychotics in chlorpromazine equivalent.