Review

The course of the schizophrenia and its impact on cognition: a review of literature

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There has been increasing interest about cognition in schizophrenia during recent years. The greater focus of the investigators has been focused greater interest on the relation of cognitive deterioration with positive and negative symptoms, and functionality. However very few studies, if any, have specifically focused on the course of cognition in schizophrenic patients throughout the years. Those who have attempted to answer this question have done so by comparing cross-sectional studies of patients at different stages of their disease. Only a minority have used a longitudinal methodology in their studies. This article reviews a total of 31 cross-sectional and 43 longitudinal studies published in patients with a diagnosis of schizophrenia. The diversity of criteria and methods used significantly limits the conclusions that can be drawn. After a comprehensive review of the literature on this topic, the authors have come to the conclusion that there are two opposite trends: 1) Cognition in schizophrenia follows a progressive decline over the years of evolution of the disease (a conclusion predominant in studies with cross-sectional methodology) and 2) Cognition in schizophrenia remains stable once it appears during the first stages of the disease (a conclusion predominant in longitudinal studies). The authors conclude that the question about the likely decline of cognition in schizophrenia cannot be answered due to the lack of rigorous and thorough follow-up studies.

Keywords: Cognition, Progression, Schizophrenia, Longitudinal studies, Cross-sectional studies, Methodology

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Curso evolutivo de la esquizofrenia y su impacto en la cognición: una revisión de la literatura

Durante los últimos años ha habido un creciente interés sobre el problema de la cognición en la esquizofrenia. El mayor foco de interés de los investigadores ha descansado sobre la relación del deterioro cognitivo con los síntomas positivos y negativos de la enfermedad así como con la funcionalidad. Sin embargo muy pocos estudios se han centrado, específicamente, en determinar el curso del deterioro cognitivo a lo largo de la evolución de la enfermedad. La mayoría de quienes lo han intentando han empleado una metodología consistente en comparar transversalmente el estatus cognitivo de pacientes en diversos estadios evolutivos de la enfermedad. Solo una minoría ha empleado una metodología longitudinal. Este artículo revisa un total de 31 estudios transversales y 43 longitudinales en pacientes con esquizofrenia. La gran variabilidad de criterios y métodos dificulta enormemente la obtención de conclusiones a partir de los diversos hallazgos. Tras una exhaustiva revisión de la literatura sobre este asunto, los autores aprecian que hay dos tendencias principales: 1) El deterioro cognitivo evoluciona progresivamente a lo largo de la enfermedad (tesis predominante en los estudios de metodología transversal) y 2) El deterioro cognitivo permanece estable una vez que hace aparición (la tesis predominante de los estudios longitudinales). Los autores concluyen que la pregunta sobre la posible evolución del deterioro cognitivo no puede aún ser respondida por la carencia de suficientes estudios longitudinales con metodología rigurosa y suficientemente extensos.

Palabras clave: Cognición, Evolución, Esquizofrenia, Estudios longitudinales, Estudios transversales, Metodología

INTRODUCTION

In a review made by our group in 2007,[1] we presented the studies existing on cognitive deterioration in schizophrenia and its course. However due to the growing volume of publications in recent years, that review is now obsolete, thus making a new update necessary, which we are

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presenting herein. The question on whether cognitive deterioration in schizophrenia becomes more severe with evolution of the disease or if on the contrary it remains stable continues unanswered. This question is key to advancing in the knowledge on the physiopathology of this disease. Its response in one sense or the other would reaffirm or challenge the supposition held since more than one century ago that schizophrenia is a disease that advances relentlessly until deterioration of all the mental functions.

The bibliography on the neurocognitive deterioration in schizophrenia has maintained an exponential growth since 2007. However, the approach to this body of knowledge is difficult and even confusing. The methodology of the studies is too heterogeneous: samples having unequal size, longitudinal and cross-sectional approaches, patients in different stage of evolution of their disease, cognitive domains and also the use of different measurements, etc. This very important discrepancy in the methodology and in the conclusions requires a more detailed analysis.

The present work has attempted to summarize this information using a structure that facilitates its understanding, following the model already used by Testa et al. en 2009.[2] Two criteria have been followed to organize the review: 1) Study method: cross-sectional versus longitudinal; 2) Type of population studied: patients with short evolution (first psychotic episodes (FPE), patients with long evolution (chronic schizophrenia (CS) and patients at high risk of suffering schizophrenia (HR).

METHODOLOGY

A search was conducted in Pub-Med and Medline for the period February 2010 to March 2012 and the following terms in the data bases: "schizophrenia," "cognition," "longitudinal," "cross-sectional," "neuropsychology," "neurocognition," "psychosis." The publications were divided into 2 groups according to the design: cross-sectional and longitudinal.

The search resulted in the cross-sectional studies summarized in Tables 1 to 5. (Tables 1-5). The resulting longitudinal studies are summarized in Tables 6-8, the latter for studies with a follow-up of at least 1 year. (Tables 6-8).

RESULTS

A.- Cross-sectional studies

Cross-sectional studies have mostly dominated the neuropsychological literature, providing information on the characteristic cognitive profile of each one of the different states of the disease: high risk (HR), first psychotic episodes (FSE) and chronic or long course schizophrenia (CS).

1.- Neurocognition in high risk population

The studies comparing patients in situations called "high risk" (HR) or "ultra high risk" (UHR) consider two hypotheses: a) the presence of normal or quasi-normal cognitive level in this type of patient[3] and b) manuscripts that refer to the presence of deterioration in the prodromic state of the disease in several domains, such as verbal learning, spatial recognition memory and working memory.[4] The cross-sectional studies that have investigated neurocognition in persons having the "UHR" status are summarized in Table 3.

Studies with patients having high risk" (HR) or "ultra high risk" (UHR) coincide in mentioning that the subgroups of patients who end up evolving toward schizophrenia have a more severe profile of cognitive deterioration than those who remain stable in the diagnosis.[5, 6] Furthermore, in the Myles-Worsley et al. studies,[7] greater presentation of schizophrenic symptoms was not associated to greater cognitive severity, nor was significant interaction observed between genetic risk and clinical state and cognition. This study suggests that cognitive affectation is more affected by genetic status than by clinical symptoms.

Studies that compare cognitive performance of control samples with HR (that show basic predictive symptoms), UHR, FSE and CS, coincide in indicating a severity grade of cognitive deterioration that ranges from their absence in the controls to greater severity in patients having a long evolution.[3] These results would support the hypothesis the cognitive deterioration advances with the years of disease evolution.

2.- Neurocognition in first psychotic episodes (FSE)

The cross-sectional studies that have dealt with neurocognition in patients with first psychotic episodes (FSE) are summarized in Table 4.

Moritz et al.[9] showed how neurocognitive affectation of FSE and patients with CS differ from the control population, but that this does not occur between groups of patients. They suggested, consequently, that the deficits do not deteriorate over time. However, the dominant hypothesis of our study group is the opposite: the course of the diseases evolves towards deterioration of cognitive functions, suggesting that there is a deterioration in chronic patients, as that described by Hutton et al.[10] or Pantelis et al.[11] in attention capacity.

There is a tendency towards grading severity of the cognitive deterioration based on the group studied. In FSE, the cognitive deficits are milder than in patients with CS and more accentuated than in the cohort of HR patients.[8,12-15] This cognitive deterioration in FSE cannot be attributed to treatment or institutionalization factors since it is already present, even in antipsychotic medication naive patients.[16]

Table 1 List of meta-analyses of Cross-sectional Studies in cognition in Schizophrenia

AUTHORS	STUDY	OBJECT	N	EFFECT SIZE	RESULTS
Irani F et al. 2011	Metaanalysis of 29 cross-sectional studies and 14 longitudinal ones	Cognition in general and also specific subdomains	3064	Effect sizes small for longitudinal studies (-0.097) and large and heterogeneous for cross-sectional studies (-1.19) in general cognition and for specific domains (-0.7 and -1.14).	The deterioration is clear during the different life stages but does not worsen in follow-ups between 1 and 6 years. It is necessary to evaluate the moderator role of sociodemographic variables.
Knowles EE et al. 2010			4135	Greater effect size for coding tasks (g=1.50), followed by category fluency (g=1.31). The effect size magnitude of coding tasks is largely attributed to the heterogeneity. The meta-regression analysis indicates 3 moderator variables of effect size: publication year, difference of IQ with controls and daily dose equivalent to chlorpromazine. No other significant relations.	Affectation of processing speed in schizophrenia is considerably affected by moderator factors, specifically the dose of antipsychotic medication.
Irani F et al. 2010	Meta-analysis	Processing speed in schizophrenia	N (cross-sectional studies)= 2110 schizop. and 1738 controls. N (longitudinal studies)= 914 schizop.	Result in cross-sectional studies: Effect size in: • Global cognition (d= -1.19) • Specific neuropsychological domains (d= -1.04) • Estimated I.Q. (d= -0.84) • Language (d= -1.30) • Immediate memory (d= -1.25) • Executive function (d= -1.14) Results in longitudinal studies: • Global cognition (d= -0.097) • Specific neuropsychological domains (d= -0.11)	In 1-6 year follow-up stability in late schizop. In cross-sectional studies, affectation in Global cognition and in neurocognitive parameters. They influence moderator factors as the following: Institucionalization, presence of more symptoms + and -, low education level, elderly age, male gender, race, onset age and disease duration. The medication (dose, etc.) apparently has no effect.
Rajji & Mulsant, 2009	Metaanalysis of 29 cross-sectional studies and 14 longitudinal studies	Neuropsychology in schizophrenia of in elderly age	FPE Early onset Schizop Late onset Schizop.	ES≥0.8 in all the cognitive areas measured in FPE and Early onset Schizop. Early onset Schizop. greater deficit than FPE in: arithmetic, function, I.Q., processing speed and verbal memory. Late onset schizop. shows minimal affectation in arithmetic and vocabulary, but greater affectation in attention, fluency, global cognition, I.Q. and visuospatial construction.	Individuals with early onset Schizop. present severe general cognitive deficits while those with late onset Schizop. present relatively preserved cognitive functions.
Doughty OJ et al. 2009	Meta-analysis (29 studies)	Affectation of semantic memory in schizophrenia		Elevated effect size for naming objects and verbal fluency. Mean effect size for object matching. Small effect size for categorization.	Uneven profile of affection that may indicate degradation of semantic knowledge that can not be a good measure to explain the affectation of semantic memory in schizophrenia.

Table 1 Continuated

AUTHORS	STUDY	OBJECT	N	EFFECT SIZE	RESULTS
Ragland JD et al. 2009	Meta-analysis (36 studies)	Deficits in prefrontal activation during episodic memory in schizophrenia	123 schizop. 137 controls		Prominent prefrontal dysfunction in schizophrenia suggests cognitive deficits fundamentally in episodic memory.
Bora E et al. 2009	Meta-analysis (36 studies)	Theory of the mind (TM) in schizophrenia	1181 (67% males) schizophrenia 936 (58,3% males) controls	Effect size (d of Cohen) both for representation of TM in general and in individual tasks is wide (d= 0.90-1.08). In patients in "remission" level of affectation of TM is less than in patients "not in remission" (d=1.21) but still and all significant (d=0.80).	Affectation of general I.Q. significantly contributes to affectation of TM only in patients in "remission."
Woodberry KA et al. 2008	Meta-analysis (18 studies)	Premorbid I.Q. in schizophrenia	2142 Schizop 3001 control	Mean effect size in Global cognition prior to schizophrenia (d= -0.54).	Significant affectation in premorbid I.Q.. Even so, onset of psychosis related with greater I.Q. deterioration in patients.
Cohen AS et al. 2007	Meta-analysis (13 studies) and 1 study	neuropsychology of deficit schizophrenia	Meta-analysis: 365 deficit schizop. 552 non-deficit schizop. 197 controls	Effect size small in 11 of the 15 cognitive parameters measured. Mean effect size in 4 (in deficits): Language (ES=0.51; 95% I.Q.= -1.81-2.83) Global cognition (ES=0.52; 95% I.Q.= 0.23-0.82) Social cognition (ES=0.56; 95%I.Q.= -2.09-3.21) Oflatory discrimination (ES=1.11; 95%I.Q.=NA) Variability in ES through different categories measures is not significant (Qtotal[61]= 53.82, P> .05; Qwithin[48]= 47.08, P>.05).	Greater cognitive affectation in deficit schizophrenia patients than in non-deficit [ES=0.41]. The cognitive parameters affected in deficit schizop. do not follow a defined anatomic pattern of affectation.
Fioravanti M et al. 2005	Meta-analysis (113 studies)	Cognitive deficits in adults with schizophrenia	4365 schizop. 3429 controls	Greater significant difference between cases and controls in memory (SMD -1.18[-1.31, -1.05] p<0.00001) and language (SMD -1.01 [-1.18, -.85] p< .00001) and less in I.Q. (SMD -1.01 [-1.13, -.89] p< .00001). Data of studies based on I.Q., memory, language, executive function and attention show significant heterogeneity through the studies (respectively χ^2 (46)= 185.07, χ^2(57)=303.23 , χ^2(35)=127.70, χ^2(37)= 185.07, χ^2(47)=111.18, all the p at least < .0001).	Significant and consistent affectation of intelligence, memory, language, attention and executive functions in patients with long-term schizophrenia. However, significant variability is observed between studies. This suggests a multifaceted nature of the cognitive deficits in the population with schizophrenia.
Pelletier M et al. 2005	Meta-analysis (84 studies)	Clinical and cognitive moderators in recognition memory in schizophrenia		*d*=0.76.	Poor recognition memory in schizophrenia, related with other cognitive deficits and sensitive to clinical moderator variables (duration of disease - chronicity - of the disease, use of recognition memory test for figurative details increase the ES in relation to verbal recognition memory,...).

Table 1 Continuated

AUTHORS	STUDY	OBJECT	N	EFFECT SIZE	RESULTS
Sitskoorn MM et al. 2004	Meta-analysis (37 studies)	Cognitive deficits in relatives of patients with schizophrenia	1639 relatives of patients with schizophrenia 1380 controls	Greater effect size of verbal memory verbal (d= 0.54 , 95% I.Q.= 0.43-0.66) and executive function (d=0.51, 0.36-0.67). Attention shows lower effect sizes (d= 0.28, 0.06-0.50).	Cognitive deficits found in patients with schizophrenia are also found in relatives (not affected) of patients with schizophrenia.
Aleman et al. 1999	Meta-analysis (70 studies)	Affectation of memory in schizophrenia	3315 schizop.	Effect size in recognition memory (d=1.21). Effect size in short term memory: forward (d=0.71); backward (d=0.82).	Affectation in recall and recognition memory (verbal and visual),and in short term and working memory (although to a lesser degree).

Table 2 List of systematic reviews of Cross-sectional studies in cognition in Schizophrenia

AUTHORS	STUDY	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	RESULTS
Sponheim et al. 2010	Own sample of 41 FPE and 106 Chronic schizophrenia (CS)	Measure of cognition by age and final diagnosis	147 patients and their equivalent healthy controls	Problem solving tests, psychomotricity, and memory.	The deterioration was present in all the functions studied independently of the disease phase and there is no evidence of progression in the course. The deterioration is based on variables and time of disease, age and final diagnosis.
Rajji & Mulsant, 2008	Review (42 studies; 19 longitudinal and 23 cross-sectional)	Evolution of cognitive symptoms in schizophrenia of ≥50 years (late-life schizophrenia)	3560 (small samples, principally institutionalized patients)	Multiple batteries (in general limited neuropsychological evaluations).	Presentation of cognitive deterioration in schizophrenia at 65 years, initiating in visuospatial skills.
Matza et al., 2006	Review (9 studies)	Relation of cognitive status and functionality in schizophrenia	961	Multiple cognitive batteries and different functionality scales (ADAS-L, AIPSS, CDR, MCAS, QLS, SAFE, SACS, SBS).	Significant relation between cognitive status and functional status in schizophrenia
Heinrichs & Zakzanis, 1998	Review (204 studies)	Neurocognitive deficit in schizophrenia	Case-control	Multiple batteries (22 variables measured). d>.60 in the 22 parameters measured (no I.Q. includes the 0).	General cognitive deficit in schizophrenia.

Table 3	List of cross-sectional studies in cognition in UHR*				
AUTHORS	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	RESULTS	CONCLUSIONS
Thompson et al.2011	Review de studies in social cognition in UHR	7 studies	Multiple batteries of social cognition	UHR show clear deterioration in the different areas of social cognition.	Deterioration in social cognition could be a marker of risk of the disease and, undoubtedly, an objective of treatment in early intervention programs.
Pflueger et al. 2007	Neurocognition in UHR	60 UHR 51 control	Multiple batteries	UHR present deficits in intelligence, executive function, working memory and attention,. Verbal intelligence, executive function and above all working memory are those that are most differentiated from the control group.	UHR present neurocognitive affection prior to FPE, working memory being the most marked (in comparison to the control group).
Myles-Worsley et al. 2007	Neurocognition in UHR (based on Genetic risk vs. clinical risk)	310 (98 of high genetic risk, of whom 54 were symptomatic; 212 genetically low risk, 113 clinically high risk) 99 control	Multiple batteries including MATRICS)	Affectation is statistically significant in the Genetic Risk group in: Immediate memory for logic, verbal working memory (measured with digit spam and the letter-number sequencing tasks), CPT of numbers and forms and fine motor skills. Affectation is statistically significant in the Clinical Risk group in: perceptive organization and spatial working memory measured with WISC-III. No significant effects of interaction of the genetic risk and clinical status in neurocognition.	Genetic risk and clinical risk cause independent effects in the neurocognition of patients at high risk, the Genetic risk causing greater impact. However, affectation in visuospatial processing appears with the symptoms.
Bartok et al. 2005	Neurocognition in pre-psychotic patients	11	Multiple neurocognitive battery (11 tests): CANTAB.	Statistically significant affectation in comparison with scales of test in: Paired-associated learning ($p<0.001$); spatial recognition memory ($p<0.05$); rapid visual processing ($p<0.05$); spatial working memory ($p<0.05$).	Cognitive deficits can be found in pre-psychotics in frontal, prefrontal and attention functions.
Hawkins et al. 2004	Neurocognition in high risks subjects	36 symptomatic UHR 36 chronic schizop 36 FPE 36 control	Multiple batteries	UHR Vs. chronic schizop.: better results in all the measures except (no statistical significance) in: WMS-R visual reproductions and COWAT (FAS). UHR Vs. Control: worse results in all the measures except (no Statist. Sign) in: TMT-A and WMS-R visual reproductions parts I and II. UHR Vs. FPE: better score (Stat. Sign.) in: WAIS-R Digit symbol, TMT-A, TMT-B, CVLT total, WMS-R visual reproductions I and II.	Similar results between the UHR group and chronic group in verbal fluency and in visual memory (immediate recall), but better results in processing speed and verbal memory both in comparison with chronics and in that of the FPE.

Table 3 Continuated

AUTHORS	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	RESULTS	CONCLUSIONS
Weiser et al. 2003	Neurocognition in Schizotypal personality	326 SPED** 901 Schizop 293,820 control	Neurocognitive battery (4 tests)	RPM-R<0.001 Arithmetic-R<0.001 Similarities-R<0.001 Otis <0.001 Years of schooling <0.001 Significant differences in all the parameters measured between Schizop. and SPD with controls. Between Schizop. and SPD significant differences in attention and processing speed.	Neurocognitive deficits in Schizop and SPD in relation to control subjects. Better results in comparison to Schizop in abstract reasoning. Both groups similar results in attention and processing speed.

**Utra-High-Risk*; ***Schyzotipal Personality Disorder*

Table 4 List of cross-sectional studies in cognition in FPE

AUTHORS	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	RESULTS	CONCLUSIONS
Sponheim et al. 2010	Measurement of cognition by age and final diagnosis	Own sample of 41 FPE and 106 CS	147 patients and their health control equivalents	Problem solving tests, psychomotricity and memory.	The deterioration was present in all the functions studied independently of the disease phase and there is no evidence of progression in the course. The deterioration is based on variables as time of disease, age and final diagnosis.
Pantelis et al. 2009a	Attention divided into FPE: relation with working memory	48 FPE compared with 40 chronic schizop and 67 control	CANTAB attentional set-shifting (IDED) SWM tasks	Spatial working memory (SWM): statistically significant affectation in FPE (z=3.38, p=0.001) and chronic schizop. (z=3.82; p<0.001) in comparison to the controls. No differences between them (FPE and chronic schizop.). FPE does not differ from controls in IDED once affectation in working memory is controlled.	Affectation of attention divided into chronic and intact schizophrenia in FPE. Working memory affected in all the stages of schizophrenia.
Lappin et al. 2007	Relation between DUP and cognitive function in FPE	180 FPE with Schizop 93 Other psychosis	Multiple batteries (6 tests)	Affectation in: Verbal I.Q.: p=0.04 Verbal learning: p=0.02 Verbal working memory: p= 0.04.	The greater the DUP, the greater the neurocognition affectation in the first moment of presentation of the FPE.
Eastvold et al. 2007	Neurocognition in prodromes and FPE	40 subjects are risk 15 FPE 36 control	Multiple batteries	1)VP:F(2,91)=6.86, p<0.002 2)Working Mem.: F(2,91)=12.24, p<0.001 3) Episodic verbal mem.: F(2,91)=12.24, p<0.001, 4) Executive F.: F(2,91)=6.69, p:<0.002, 5)I.Q.: F(2,91)=12.42, p<0.001.	The subjects at risk have neurocognitive deficits in all the domains in comparison to the controls, although less severe than that observed in FPE. The subjects at risk who develop psychosis after have greater neurocognitive affectation in the prodromes than those who do not develop psychosis.

Table 4 Continuated

AUTHORS	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	RESULTS	CONCLUSIONS
Simon et al. 2007	Neurocognition in prodromes of schizophrenia	93 pat. at risk (69 UHR and 24 risk) 43 FPE 49 control	Multiple batteries	General cognitive functioning: F:3.216; p<0.05. Letter-number spam (F:0.013); UHR:12.8 (3.7), R: 14.8 (2.8), FPE: 12.5 (4.0), Control: 14.3 (3.3). Verbal fluency: (F:0.013); UHR: 9.5 (3.9), R: 9.4(2.4), FPE: 7.1(4.0), Control: 9.3(3.6). Immediate verbal mem.: (F:0.040); UHR: 51.8(14.1), R: 53.8(10.2),FPE: 45.6(18.5),Control: 53.7(11.7) Delayed verbal mem.: (F:0.015); UHR:10.8(3.4), R:11.3(3.6), FPE:9.4(4.7), Control:12.0(3.3).	The two groups at risk have intermediate neurocognitive affectation between the FPE and the control group. Greater affectation in UHR than in patients at risk. The greater affectation in general was in: auditory working memory, processing speed/verbal fluency and verbal declarative memory.
González-Blanch et al. 2006	Neurocognition in FPE	131 FPE 28 control	Multiple batteries (11 tests)	Affectation (once controlled factors such as gender, premorbid I.Q., and years of schooling): Processing speed and executive functioning: p<0.001 Motor skill: p= 0.008 Sustained attention: p= 0.002	Marked neurocognitive affectation in FPE .
Joyce et al. 2005	Neurocognition in FPE	93 FPE 50 control	Multiple batteries	Affectation in working memory (p<0.001). 40% of the sample had generalized cognitive affectation. Low premorbid I.Q. related to earlier onset of the disease (p<0.05).	At the onset of the disease, the cognitive heterogeneity is present amount the patients, with high proportion (40%) having generalized cognitive affectation. Working memory affected in most. Low premorbid I.Q. as risk factor for earlier initiation of the disease.
Tuulio-Henriksson et al. 2004	Age of onset and cognitive functioning in schizophrenia	237 schizop	Multiple batteries	Statistically significant affectation in Learning and verbal memory (p=0.002). No statistically significant association with working memory (p=0.16) and I.Q.(p=0.19).	In patients with early onset of the disease, the verbal memory functions are affected.
Banaschewski et al. 2000	Relation between neurocognition and sychopathological symptoms in early onset schizophrenia	99 early onset schizop	Multiple neurocognitive battery BPRS, SANS, SAPS	No significant relation between analysis of orthogonal factors and canonical correlation analysis between neurocognitive and psychopathological parameters Significant relation between premorbid alterations (motor and Language alterations) or onset characteristics (age, more disorganized pattern,...).	Premorbid alterations are risk factors of greater neurocognitive affectation (fundamentally in attention, verbal fluency and non-verbal reasoning).
Mohamed S et al. 1999	Neurocognition in FPE of schizophrenia	94 schizop (73 never medicated, 14 treatment<1 week, 7 treatment <2 weeks). 305 control	Multiple neurocognitive battery (30 tests)	Greater cognitive affectation in patients. Effect size 0.75 when both groups are compared (in 25 of the 30 tests). Greater affectation on digital subscales of WAIS (ES: -0.52) and understanding (ES: -0.42).	Marked neurocognitive affectation in patients with schizophrenia not caused by the duration of the disease, treatment or institutionalization.

Table 5 List of cross-sectional studies in cognition in Chronic Schizophrenia (CS) or long evolution schizophrenia

AUTHORS	STUDY	OBJECT	N	EFFECT SIZE	RESULTS
Irani F et al.2010	Metaanalysis of 29 cross-sectional studies and 14 longitudinal studies	Neuropsychology in schizophrenia of advanced age	(cross-sectional studies)= 2110 schizop. and 1738 controls. (longitudinal studies)= 914 schizop.	Results in cross-sectional studies: Effect size en: • Global cognition (d= -1.19) • Specific neuropsychological domains (d= -1.04) • Estimated I.Q. (d= -0.84) • Language (d= -1.30) • Immediate memory (d= -1.25) • Executive function (d= -1.14). Results in longitudinal studies: • Global cognition (d= -0.097). • Specific neuropsychological domains (d= -0.11). Moderators influence results of cross-sectional studies and not in longitudinal studies: • Age • Gender • Level of education • Race • Institucionalization • Duration of disease • Positive and negative symptoms • Medication	In follow-up of 1-6 years neurocognitive stability in schizop. in late age. In cross-sectional studies, deficit affectation in global cognition and in individual neurocognitive parameters in relation to their pairs. In this case, moderator factors such as the following have an effect: Institucionalization, presence of greater symptoms + and -, low education level, advanced age, male gender, possibly race and onset age and duration of disease. The medication (dose...) apparently do not influence it.
Rajji & Mulsant, 2009	Meta-analysis (29 studies)	Relation between cognition and age of onset of schizophrenia	FPE Early onset Schizop Late onset schizop	ES≥0.8 in practically all the cognitive areas measured in FPE and Early Onset Schizop. Early onset Schizop greater deficit than FPE in: arithmetic, Executive function, I.Q., Processing speed and verbal memory. Late onset schizop. shows minimum	Individuals with early onset Schizop. present severe general cognitive deficits while those with late onset Schizop. present relatively conserved cognitive functions.
Rajji & Mulsant, 2008	Review (42 studies; 19 longitudinal and 23 cross-sectional)	Evolution of cognitive symptoms in schizophrenia of ≥50 years (late-life schizophrenia)	3560 (small samples, principally of institutionalized patients)	Multiple batteries (in general limited neuropsychological evaluations.	Presentation of cognitive deterioration in schizophrenia at 65 years, with initiation in visuospatial skills.

Table 5 Continuated

AUTHORS	STUDY	OBJECT	N	EFFECT SIZE	RESULTS
Cohen AS. et al. 2007	Meta-analysis (13 studies) and 1 study	Neuropsychology of the deficit schizophrenia	Meta-analysis: 365 Deficit schizop 552 non-deficit schizop 197 controls	Effect size small in 11 of the 15 cognitive parameters measured. Mean effect size in 4 (in deficits: Language (ES=0.51; 95% I.Q.= -1.81-2.83) Global cognition (ES=0.52; 95% I.Q.= 0.23-0.82) Social cognition (ES=0.56; 95%I.Q.= -2.09-3.21) Olfatory discrimination (ES=1.11; 95%I.Q.=NA) Variability in ES through the different categories measures is not significant (Qtotal[61]= 53.82, P> .05; Qwithin[48]= 47.08, P>.05).	Greater cognitive affectation in deficit schizophrenic patients than in non-deficit ones [ES=0.41]. The cognitive parameters affected in deficit schizop. does not follow a defined pattern of affectation.
Twamley et al. 2006				Multiple batteries: Digits Backwards, Digits Forward, LNS.	Deficits in all the areas, with a direct relation between greater negative affectation and worse cognitive results.
Fioravanti M. et al. 2005	Meta-analysis (113 studies)	Cognitive deficits in adults with schizophrenia	4365 schizop. 3429 controls	Greater significant difference between cases and controls in memory (SMD -1.18[-1.31, -1.05] p<0.00001) and Language (SMD -1.01 [-1.18, -.85] p< .00001) and the minor difference in I.Q. (SMD -1.01 [-1.13, -.89] p< .00001). Data from studies based on I.Q, memory, Language, Executive function and attention show significant heterogeneity through the studies (respectively $\chi^2(46)$= 185.07, $\chi^2(57)$=303.23 , $\chi^2(35)$=127.70, $\chi^2(37)$= 185.07, $\chi^2(47)$=111.18, all the p at least < .0001).	Significant and consistent affectation of intelligence, memory, Language, attention and executive functions in patients with long-course schizophrenia. However, significant variability is observed between studies, which suggests a multifaceted nature of the cognitive deficits in the population with schizophrenia.
Silver et al. 2003			Chronic Schizop	Verbal working memory. Spatial working memory. Executive functioning.	Working memory is principal cognitive affectation in CS, which has an limiting effect on other cognitive areas for an adequate functionality.

Table 6 List of Meta-analysis of Longitudinal studies

AUTHORS	STUDY	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP	RESULTS
Mesholam-Gately et al. 2009	Meta-analysis (47 studies)	Neurocognition of first episodes (FE) of schizophrenia. Longitudinal and cross-sectional studies	Schizop 1st episode =2204 Control= 2775	Multiple batteries (43 tests): • Immediate verbal memory • Attention: Processing speed • Non-verbal memory • General cognitive skill • Language functions • Visuospatial skills • Verbal memory ... and learning strategies • Executive function • Attention: working memory	Longitudinal and cross-sectional studies.	Moderate-severe affectation in 10 cognitive domains in ES (Effect size -0.64 a -1.20), similar to the deficits present in SQZ established. Affectation greater in immediate verbal memory (SMD= -1.20) and Processing speed (SMD= -.96).
Szöke et al. 2008	Meta-analysis (53 studies)	Longitudinal studies of cognition in schizophrenia	Schizop=2476 Control= 324	Battery: • Memory: o Visual: Rey CFT, WMS o Verbal: CVLT o Logic: WMS, HVLT, RAVLT • Executive function: Lexical and Semantic VF, Stroop test, WCST, TMT-B. • Attention: Digit span, DSDT, Stroop, TMT-A. • Others: o Verbal concept formation: similarities o Psychomotor, Sustained attention: Digit symbol o Visuospatial conceptualization: Cubes o Vocabulary skills: vocabulary o Perceptive organization: Rey CFT (copy) o Verbal naming: Boston Naming test	Minimum: 1 month (mean: 4 months).	Improvement in most of the cognitive parameters, probably due to practice (learning) more than to cognitive rehabilitation. Semantic Verbal Fluency remains stable both in schizophrenics (ES= -0.02) and in controls (ES= 0.10) (possible endophenotype).

Table 7 List of works of the Review of Longitudinal studies in cognition in Schizophrenia

AUTHORS	STUDY	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP	RESULTS
Bozikas et al. 2011	Review of the literature	Cognition in FE	1012	Multiple batteries	Min 12 months.	Cognitive impairment remains stable
Lewandowski et al. 2011	Review of studies	Comparison between bipolar patients and with schizophrenia	630	Multiple batteries	Longitudinal studies.	Patients with schizophrenia have deterioration before the debut of the disease that is more pronounced in the first years of the disease and remains stable afterwards.

Table 7 Continuated

AUTHORS	STUDY	OBJECT	N	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP	RESULTS
Gracia Domínguez et al. 2009	Review (58 studies)	Correlation between psychopathological dimensions of the psychosis and cognition in non-affective psychosis	5009	Multiple batteries	Cross-sectional and longitudinal studies.	Modest significant association between negative symptoms, disorganized ones and cognitive deficits. No association with positive and depressive psychopathology. Association independent of age, gender and chronicity of the disease. Highly significant association between negative symptoms and verbal fluency (P=0.005); disorganization and reasoning and problem solving (p=0.004) and attention/vigilance (p=.03).
Rajji et al. 2008	Review (42 studies; 19 longitudinal and 23 cross-sectional)	Evolution of cognitive symptoms of ≥50 years (late-life schizophrenia)	3560	Multiple batteries (in general limited neuropsychological evaluations)	Minimum=1 year and Maximum=10 years.	Presentation of cognitive deterioration in schizophrenia at 65 years, initiating in the visuo-spatial skills.
Ojeda et al. 2007	Review (30 longitudinal studies)	Evolution of cognitive symptoms in schizophrenia	1318	Multiple batteries	Minimum 1 year.	Tendency that from the onset of the disease, significant cognitive symptoms are already present that remain stable between 2-5 years and whose deterioration increase with the evolution of the disease.
Matza et al. 2006	Review (9 longitudinal studies)	Relation between cognitive affectation and changes in functionality	961	Multiple batteries	Minimum=3 months Maximum=6 years.	Relation between cognitive affectation and affectation in functionality.
Kurtz et al. 2005	Review (10 studies)	Neurocognitive deficits over time in schizophrenia	834	Multiple batteries: I.Q. total, verbal memory, non-verbal memory, verbal and visual skills, MinimentalT, CERAD.	Minimum of 1 years and maximum of 10 years. Mean=3.92 years.	2 pathways: Stability during first 5 years in FPE or chronic schizop <65 years. Schizop >65 years global cognitive deterioration (2.5 years).

Table 8 List of longitudinal studies in cognition in UHR, FPE, and CS with minimum follow-up period of 1 years (Modified of Ojeda et al.., 2007)

AUTHORS	N	TYPE	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP (YEARS))	RESULTS
Moran et al. 1960	30	Schizop	Vocabulary	6	Stability.
Smith 1964	24	Schizop	I.Q.	8.4	Stability.
Klonoff et al. 1970	66	Schizop	WAIS	8	Improvement.
Flekkoy et al. 1975	72	Schizop	Word Association	16.6	Stability, tendency to improvement.
Nuechterlein, 1985	14	Schizop	CPT, Ds-CPT	1	Stability.
Rund 1989	14	Schizop+CG	Memory CP, digits	4	Stability.
Bilder et al. 1991	28	Schizop	Battery 4 tests	1	Improvement.
Sweeney et al. 1991	39	Schizop	Battery 7 tests	1	Stability in memory, fluency and verbal and visual memory. Improvement in recognition memory, orientation and psychomotricity
Nuechterlein et al. 1992	17	Schizop+CG	CPT, SPAN	1	Stability in attention. Greater stability in memory.
Hoff et al. 1992	17	Schizop, 1st episode	Battery 7 tests	2	Improvement in attention, concentration, psychomotor speed, conceptual problem solving. Stability in Language and verbal and spatial memory. Deterioration in verbal memory.
Rund et al. 1993	22	Schizop+CG	Backward masking	2	Stability.
Nopoulos et al. 1994	35	Schizop	Battery 5 tests	1 (n=17) 2 (n=18)	Stability. Improvement in attention and verbal flexibility.
Harvey et al. 1995	224	Geriatric schizop	MMSE	1	Stability.
Rund y Landro 1995	22	Schizop+CG	React T., CPT, dígits, short and long term memory	1	Stability with tendency to improvement.
Waddington et al. 1996	41	Geriatric schizop	10 orientation questions	5 y 10	Mild tendency to deterioration.
Rund et al. 1997	14	Schizop	Battery 4 tests	1-2	Stability in long-term memory, flexibility and improvement in short-term memory.
Russell et al. 1997	34	Schizop	WAIS	19	Stability.
Gold et al. 1999	49	Schizop. 1st episode	Battery 5 tests	5	Improvement in manipulative I.Q., stability in verbal I.Q. and deterioration in psychomotor speed.
Ho et al. 1998					
Hoff et al. 1999	42	Schizop+CG	Battery of 6 tests	2 y 5	Stability.
Hofer et al. 2000	16	1st episode schizop	Battery of 3 tests	2	Stability.

Table 8 Continuated

AUTHORS	N	TYPE	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP (YEARS))	RESULTS
Moritz et al. 2000		Schizop	Battery of 4 tests	1	Stability.
Friedman et al. 2001	118	Geriatric schizop+ CG and others	MMSE, CDR	6	Stability up to 65 years and deterioration for samples of older ages.
Grawe et al. 2001	29	Schizop	Battery of 6 tests	3	Deterioration regarding situation in first period.
Heaton et al. 2001	142	Schizop+CG	Battery of 9 tests	Mean of 3	Stability.
Tuninger et al. 2001	18 de 34	Chronic schizop	Battery of 9 tests	2	Stability.
Albus et al. 2002	50+50	FPE + CG	Multiple batteries	2	Stability.
Caspi et al. 2002	44	1st episode schizop+ CG	Battery of 4 tests	Psychotic episode remitted	Deterioration in spatial reasons and processing speed. Stability in measures of and other types of abstract reasoning.
Friedman et al. 2002	124	Chronic schizop	Multiple batteries	4	Significant deterioration in verbal memory, psychomotor speed and processing speed.
Townsend et al. 2002	83	1st episode schizop	Battery of 7 tests plus WAIS and Schizop Memory Weschler	1	Stability in all the measures.
Brodaty et al. 2003	27	Geriatric schizop+ CG	MMSE, Camcog, AVD	1 and 5	Deterioration in all the measures.
Stirling et al. 2003	37	Schizop	Battery of 8 tests	10 and 12	Stability in fluency and verbal memory, Executive functions. Deterioration in visuoconstructive skills and visual memory.
Hill et al. 2004	45+33	Schizop+CG	Battery of 5 tests	2	Global cognitive deterioration clear from onset of the disease that is maintained stable over time.
Meagher et al. 2004	129	Geriatric schizop.	MMSE, EXIT	3	Global deterioration in 25% .
Hoff et al. 2005	21+8	1st episode schizop+CG	Battery of 12 tests	10	Schizop and CG improvement in verbal intellectual functioning. Stroop color-word test and motor speed. Schizop improvement more evident in immediate visual memory.
Milev et al. 2005	99	1st episode Schizop	Multiple batteries	7	Functional affectation in those who have alterations in attention, verbal memory and processing speed.
Albus et al. 2006	71+71	FPE+CG	Multiple batteries	5	Neuropsychological affectation present from onset of disease that is maintained stable during the first 5 years.
Chemerinski et al.2006	334	Chronic schizop	MMSE, ADAS-L cog	6	Stable MMSE . ADAS-L cog deterioration.
Keefe et al. 2006	37+59+47	COPs+1st episode schizop+CG	Multiple batteries	6 months and 1 years	Attention and processing speed affected in prodromes Improvement over time in all except those who develop psychosis (stable).

Table 8 Continuated

AUTHORS	N	TYPE	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP (YEARS))	RESULTS
Savla et al. (2006	143+66	Chronic schizop +CG	DRS	1	Stability
Seidman et al. (2006	26+59	Schizop+CG	WAIS-R (vocabulary, block design), Digit Spam test	28 (at 7 and 35 years)	At 7 years, patients with Schizop cognitive affectation, above all, attention and working memory; at 35 years worsening in both test of WAIS.
Niendam et al. (2007	35	UHR	Multiple batteries	8.3 months	50% improvement in Processing speed and visual memory. 50% stability.
Rund et al. (2007	207/138/11	1st episode Schizop.	Multiple batteries (8 tests)	Onset, 1 years and 2 years	Global stability. Better premorbid academic adjustment predicts less deficit in working memory in T0, 1 year and 2 years. Worse results in working memory and verbal learning are related with greater number of relapses during 1st years.
Frangou et al. (2008	20+20	Early onset schizop. + CG	Battery of 5 tests	4	Stability in general (during adolescence). Deterioration in immediate verbal memory and attention. Improvement in processing speed.
Wölwer et al. (2008	125	1st episode schizop	Battery of 7 tests	1	Stability. TMT test as best predictor of possible cognitive deterioration.
Eberhard et al. (2009	162	Schizop	Battery of 11 tests	5	Improvement of verbal memory and visuoespatial skills in patients in remission. No directly significant relation between cognition and remission, but yes with vocational and social functioning.
Kremen et al. (2010	15+10	CG+ Schizop.	PPVTest	33	Patients who develop the disease have deterioration of receptive vocabulary during childhood and deterioration (although slower) between childhood and middle age of life.
Becker et al. (2010	41+ 17	UHR + CG	Multiple batteries	T0 and 18 months	Cognitive stability during first psychotic episode. Affectation of verbal memory prior to FPE.
Fusar-Poli et al. (2010	15	UHR	Spatial working memory and neuroimaging (fMRI)	T0 and 12 months	Mild improvement in performance on cognitive test.
Bonner–Jackson et al. (2010	244	Schizop	Processing speed, working memory	20 years	Stability of cognitive performance.
Reichenberg et al. 2010	1037	UHR	Acquisition of verbal and visual knowledge, reasoning, working memory, Processing speed, attention, visuospatial skills	30 years	Patients show significant differences early in life (years entre 7-13) with greater prominence of the verbal reasoning skills, attention, working memory and processing speed.

Table 8 Continuated

AUTHORS	N	TYPE	NEUROPSYCHOLOGICAL TESTS	FOLLOW-UP (YEARS))	RESULTS
Jepsen et al. 2010	53	FE	Weschler Intelligence	5 years	No differences. Stability of I.Q.
Shah et al.(2011	Review de 3898 studies	Chronic schizop	Multiple batteries	Several	The evidence is mixed but points to slight majority of studies that suggest mild deterioration in this stage of the disease.
Lin et al. (2011	230	UHR	Learning and verbal memory, Processing speed, attention, verbal fluency, general cognition	7.26 years	Deterioration in all the specific domains studied but not in generation cognition. Some of these indicators successfully predict future functional performance.
Scott Stroup et al. (2011	1158 patients	Schizop	Multiple batteries	18 months	Most of the patients remain stable or improve.
Horan et al. (2011	55	FPE	Social cognition	12 months	Stability in deficits.
Liu et al. (2011	62	FPE	Executive functions	3 years	Performance remains stable.

Schizop= schizophrenia; CG=control group; UHR=Ultra High Risk (patients at high risk);COPS= Criteria of Prodromic State in high risk patients; FPE= first psychotic episode.

Studies on FSE have not shown a pattern of cognitive affectation different from the rest of the groups of patients with schizophrenia. This affectation tends to be generalized, affecting all of the domains studied. Riley et al.[17] principally found deficits in verbal learning. Other groups have demonstrated specific results of affectation of the executive functions.[10, 18] However, in all of the studies, mention is made to deterioration planning, initiation, inhibition. immediate and sustained attention, cognitive flexibility, working memory and verbal fluency.[15, 19-21]

González-Blanch et al.,[22] using a sample of 131 patients compared to 28 healthy controls, found that deterioration is more marked in other functions such as processing speed, executive functioning, motor skill and sustained attention.

Another one of the questions considered in these studies is when cognitive deterioration appears in the person having FSE. Joyce et al.[15] compared 93 FSE with 50 healthy controls. At the time of diagnosis, the patients already showed deterioration, 40% of them with generalized cognitive affectation.

Those cross-sectional studies that have evaluated the presence of premorbid factors coincide in indicating the relationship between premorbid variables and severity and extension of deterioration. Thus, some language or motor development disorders or characteristics such as onset age of the disease constitute risk factors for greater involvement in attention, verbal fluency and nonverbal reasoning.[23] Premorbid I.Q. seems to be another one of the most relevant and repeated factors according to the metaanalysis of 18 studies of Woodberry et al.[24] However, lower I.Q. could also be associated to subtypes of disease of earlier appearance as suggested by the results of Joyce et al.[15] Nonetheless, this is contradicted by the previous findings of Tuulio-Henriksson et al.[25] Another one of the factors commonly analyzed is "duration of untreated psychosis" (DUP). For example, Lappin et al.[26] observed that the greater the duration of DUP (defined as the period between the appearance of psychotic phenomena and the first contact with the mental health services), the greater the neurocognitive involvement existing in the FSE, fundamentally in the areas of verbal IQ, verbal learning and verbal working memory.

3.- Neurocognition in chronic or long evolution schizophrenia

The results of the studies made in populations with chronic schizophrenia almost unanimously coincide in observing a generalized deterioration of all the cognitive domains (Table 5). This is supported by meta-analyses that jointly analyze this type of study. Thus, Irani et al.,[27] in a recent meta-analysis that evaluated neurocognition in older patients concluded that the results of cross-sectional studies demonstrate a deficit both in global cognition as well as individual neurocognitive parameters (language, immediate memory, executive function and global IQ) in relation to the control group. They also indicate a set of variables that could accentuate cognitive deterioration in these subgroups: older age, male sex, greater institutionalization, presence of major symptoms, low educational level, race, earlier onset age and greater duration of the disease. They did not obtain any conclusive results on the influence of antipsychotic medication.

Is there a specific profile of cognitive deterioration for CS? The response seems to be negative. Fioravanti et al.[28] published a meta-analysis in which they identified significant and consistent deterioration in intelligence, memory, language, attention and executive functions in a sample of 4365 patients with advanced schizophrenia. In spite of this, significant variability is also found between studies which, in the opinion of the authors, point to the multifaceted nature of the cognitive affectation in schizophrenia. In a more recent study by Sponheim et al.,[29] the authors concluded that in chronic schizophrenia, cognitive deterioration is generalized and more marked than in the samples of FSE, especially in problem solving tasks and psychomotricity.

Many groups have specifically focused on the study of working memory, proposing that it is a central characteristic of schizophrenia. They suggest alterations on visuospatial working memory tasks, "*Delayed response (DR) task,*" and other paradigms of working memory.[10, 30-47]. Twamley et al.[42, 48] studied short-term verbal memory, working memory and sequences of numbers and letters in a large sample of patients. They described deficits in all the tasks, with a direct relationship between greater affectation of negative symptoms and worse results in these tasks. Silver et al.[49] investigated verbal and spatial working memory deficits and their effect on executive measures. They concluded that working memory is the principal cognitive deficit affectation in CS, limiting in turn other cognitive areas for adequate functionality.

Another one of the questions is if the different cognitive functions deteriorate at the same speed. This question is difficult to answer using the cross-sectional studies methodology. In a sample of 3560 patients with CS, Rajji and Mulsant[50] found a marked deterioration in executive functions, visuospatial skills and verbal fluency, with less affectation in memory, attention and working memory. Interestingly, these have been the domains that have shown the most significant dysfunctionality in the initial phases of the disease, which the authors have interpreted as the fact that the domains that are affected most in the beginning do not present a registry of progression while those that appear later are more progressive and continue deteriorating over time.

The onset moment of the disease may also affect the severity of the cognitive deterioration after years of evolution of the disease. One year later in a meta-analysis, these same authors,[52] compared the cognitive deficits in individuals with early-onset with late onset and adults with FSE. Individuals with early-onset schizophrenia have severe general cognitive defects while those with delayed onset have relatively conserved cognitive functions, with more restricted affectation in attention, verbal fluency, global cognition, IQ and visuospatial skills. Furthermore, the cognitive pattern found suggests that these deficits are specific and not only a result of advanced age.

B.- Longitudinal studies

The hypothesis of progressive neuropsychological deterioration in schizophrenia suggested by the results of the cross-sectional studies finds scare or null support in the results of the longitudinal studies. Initially, the hypothesis of progressive deterioration, consistent with the traditional postulate of the evolution of schizophrenia towards the defect , predominated.[52,53] However, twenty years later, the evidence from the longitudinal studies has been repeatedly pointing in the opposite direction: the stability of the cognitive deficits in schizophrenia. Two metaanalyses (see Table 6) and the four reviews conducted in relation with it (see Table 7) coincide in this. The remaining studies of individual teams are shown in Table 8.

The meta-analysis of Szöke[54] analyzes a total of 53 longitudinal studies of cognition in schizophrenia. With a total of 2476 patients, the authors include longitudinal studies in adult patients with schizophrenia with a minimum follow-up period of one month. The mean follow-up time was 4 months and mean age of the patients 37 years. Only 12 of the 53 studies analyzed included a control group (total no.=324). The patients with schizophrenia showed significant improvement over time in most of the cognitive parameters measures, as well as the controls that showed similar levels of improvement, except on an attention test (*Stroop*). This phenomenon could be explained by the test-retest learning present in all the groups.

Another later meta-analysis[55] included a total of 47 longitudinal and cross-sectional studies published between 1994 and 2008, on cognition in FSE (they excluded affective psychosis, personality disorders with possibility of psychosis and syndromes having high clinical risks). They analyzed the results of 10 cognitive areas. The findings suggest that a significant affection is already present in the first episode, similar to the grade present in the already established disease and with maximum affectation in the areas of immediate verbal memory and processing speed. They also found a more extensive affectation of I.Q. in the FSE regarding the premorbid period. However, when said situation was compared with later phases of the disease, they observed that the difference was not significant, thus concluding that the deterioration occurs between the pre-morbid phase and the FSE phase, followed by a stability in the global deficit.

However, other reviews conducted have pointed to greater complexity in the findings. It is likely that the evolution of cognitive deterioration varies based on the group of patients studied and because their rhythm is also different based on the disease stage (FSE versus schizophrenia in middle age of life). Table 7 shows all the longitudinal studies analyzed for this review.

In a review of 10 longitudinal studies on the neurocognitive course over time in schizophrenia (n=834), Kurtz et al.[56] found two different courses of the cognitive deficits based on functional state (they defined these as institutionalized or in community) and age of the patient (young, middle age or elderly). The results in patients in community (ages 20 to 65 years) suggest a clear generalized cognitive affectation compared to the controls, and stable in most of the cognitive domains during the 5 years of follow-up. The studies conducted in patients over 65 years offered other results. As these patients are more deteriorated, the cognitive evaluation in this population is generally limited to measuring the general mental status (e.g.: *Mini mental state*), *screening* (e.g.: CERAD) or cognitive evaluation of brief dementias. The results suggest in that patients who are in their 50's, general cognitive deterioration is more marked after a longitudinal follow-up of 10 years, while in patients who are in their 60's, this general cognitive deterioration is already seen at 2.5 years of follow-up.

Considering this heterogeneity of the evolution of cognitive deterioration, and bearing in mind the longitudinal studies, we can conclude:

- Cognitive deterioration is already present prior to the disease onset.
  This statement depends on the moment we consider "onset" or "debut" of the disease, usually the appearance of the first episode with psychotic symptoms. In this sense, the longitudinal studies in HR or UHR populations conclude that the cognitive alterations are already present prior to the FSE .
  Prospective studies have found that individuals with HR present greater affectation of attention in childhood than in the general population.[57, 58] Keefe et al.[59] conducted a one-year follow-up on patients who met the criteria of "prodromic state" with elevated risk of psychosis and compared them with two groups: the FSE and healthy controls. Individuals with risk presented worse results than the controls, but better than the individuals with FSE in the evaluations at 6 and 12 months. In the prodromic state, they had greater

affectation of attention and processing speed and it is greater in those who later developed psychosis. On the contrary, those who did not develop it did not show significant differences in relation to the controls.

A recent study[60] gathered a group of 41 patients with UHR and 17 controls, with baseline and longitudinal evaluation at 18 months. The authors indicated that 17 of the 41 UHR individuals developed psychosis between the first and second evaluation. They obtained results graded on the basis of the severity of the patients: a) the subgroup that developed psychosis did not show significant deterioration between evaluations; b) the UHR subgroup showed improvement between the two evaluations; c) the control subgroup showed better results than the UHR group and than those who developed psychosis in verbal learning, memory and verbal fluency from the first evaluation.

However, the study having the greatest follow-up time in a general population is that of the Reichenber et al. group.[61] Their study included 1037 cases followed-up for a total of 30 years with a very high retention rate (93%), making it a reference study in this field. The conclusions of the study revealed that the cases that end up evolving to psychosis had deficits in verbal and visual skills and in conceptualization tasks from very early stages of life that did not become worse once the disease debuted. However, other deficits such as processing speed, attention, working memory and spatial problem solving capacity significantly decreased after the disease, regardless of the premorbid level reached.

- During the first months/years of the FSE evolution, cognitive deterioration remains stable although it is likely that there are groups with different evolutive patterns.

  Some groups have indicated that the cognitive deterioration is already present at the beginning of the disease, but that it evolves towards normality during the first and second year after initiating treatment. In this model, the studies of two groups coincide.[62, 63] The patients with FSE had worse results than controls in all of the cognitive areas studied. However, at 5 years, they found improvements in most of the cognitive domains, without significant differences between patients and controls. Only verbal fluency and memory improved less in the persons with schizophrenia than in the controls.

  However, other studies have reached somewhat more complex conclusions in relation to a homogenous stability of the cognitive deterioration. For example, Hill et al.[64] believe that some cognitive domains, such as memory and visual perception, improve early (at six weeks of treatment). Others, such as verbal memory, require six months to normalize and the remaining ones remain stable during the first two years. In a study in individuals with early onset (before 17 years), Frangou et al.[65] comparing them to with controls, did not observe significant differences with healthy persons in I.Q. and in planning. However, they described greater deterioration at four years of onset of the disease in verbal memory and attention and improvement in processing speed.

  Other groups[66-72] also observe stability of cognitive deterioration during the first years of follow-up, including general intellectual performance[73] and social cognition parameters.[74] However, the course is not homogenous in all those persons suffering schizophrenia. Patients with a good level of premorbid academic functioning have better scores on working memory during the entire period and the presence of more severe deficits in working memory and verbal learning is related with a greater number of relapses during the first year, however this does not occur during the second one. This statement was ratified in more recent studies with follow-up times of up to 20 years.[75]

  More recent works have tended to evaluate the neurocognitive relationship at the onset of the disease and functional capacity (social, laboral, etc.). Standing out along this line is the study conducted by Milev et al.[76] Their study demonstrated that attention and negative symptoms predict global psychosocial functioning at 7 years. This association between the evolution of cognitive deterioration and functional repercussion has also been seen in UHR patients. Niendam et al.[77] suggested two types of evolution: patients who improved in processing speed and visual memory (50% of the sample) and equally in their functionality 8 months later. On the contrary, the other 50%, who do not improve from the functional point of view, present stability of the cognitive deterioration over time.

- There are not enough data at present to determine if cognitive deterioration advances or remains stable in long-term schizophrenia (CS).

  As in the cross-sectional studies, longitudinal studies on CS are limited because they use simple cognitive scales. The studies as a whole tend to coincide, again, in the relative stability of the cognitive deterioration. Chemerinski et al.[78] reached this conclusion in a 6-year follow-up, Rund[66] during a 1 and 2 year follow-up and Wölberg[79] in another study of one-year's duration.

  Other groups still assume the stability of cognitive deterioration. For example, in a study with 124 institutionalized patients, Friedman et al.[80] observed that at the end of four years the subjects had observable stable deterioration in verbal memory, processing speed and psychomotor speed, especially when the samples were compared with other psychiatric disorders such as bipolar disorder.[81]

  The hypothesis of progressive cognitive deterioration is supported by the results of Meagher et al.[82] who pointed

out a cognitive deterioration of 25% of the sample, this deterioration being greater in men than in women. Kremen et al.[83] conducted the study having the longest follow-up (33 years) in a sample of 25 persons who were administered a vocabulary test at the age of 5 or 9 years and then around 40 years. Ten out of these 25 patients developed schizophrenia. The patients who developed the disease showed receptive vocabulary deterioration during childhood and deterioration (although slower) between childhood and middle age of life.

Seidman et al.,[84] in one of the longest longitudinal studies conducted up to now, gathered a sample of 85 individuals evaluated with two subtests of WAIS-R (Vocabulary and Cubes) at the age of 7, and then at 35 (28 year follow-up). They concluded that those persons who subsequently developed schizophrenia already had some significant alterations at the age of seven, especially in attention, verbal skills and working memory. When they were 35 years old, a significant cognitive deterioration was observed in those suffering schizophrenia in the two tasks evaluated, and also in the global I.Q. scale.

The rhythm of advance of cognitive deterioration could vary based on the age of the patient. In this sense, Rajji et al.,[50] in a review of 42 studies, 19 of them longitudinal, showed that the greatest cognitive decline began at about 65 years in the patients with late onset schizophrenia, affecting in the first place the visuospatial skills. This conclusion is limited by the short follow-up periods of these studies in principally institutionalized samples. However, a more recent review of Irani et al.,[27] that included both cross-sectional and longitudinal studies, concluded that the cognitive deterioration observed in patients over 65 years followed up in various periods from 1 to 6 years did not show progression in the deterioration when adequate adjustments were made in the sociodemographic variables, such as level of premorbid educational level. In spite of this, the reviews made by Rajji et al.[50] and by Shah et al.[85] in 2011 established that the population of elderly patients with schizophrenia presented a significant deterioration compared to other periods of the disease, independently of the presence or not of other risk factors.

Most of the studies coincide in relating cognitive deterioration to functional impact. Friedman et al.[80] found that the evolutive cognitive changes also predict changes in functional status, a conclusion ratified later by Eberhard et al.[86]

DISCUSSION

The response to the question on whether cognitive deterioration of schizophrenia is progressive or remains stable depends on the methodology used in the study consulted. In agreement with cross-sectional results, cognitive deterioration of schizophrenia advances progressively as the disease progresses. According to the longitudinal results, deterioration tends to remain stable once it appears.

Most of the cross-sectional studies confirm that cognitive deterioration progresses as the disease progresses. The cohort of patients with CS showed clearly greater severity to that presented by those suffering FSE, and these, in turn, greater than healthy persons. According to these data, there is no specific profile of cognitive deterioration for each group. It affects all the functions in a generalized way and could be present before the disease debuts. In the HR samples, persons who progress toward the disease have greater deterioration than those who do not. This confirms neurocognition as one of the possible endophenotypes of schizophrenia and facilitates the detection of genetic factors involved in the vulnerability to schizophrenia.

These results are consistent with the traditional idea of schizophrenia as a disease that advances towards deterioration of all the mental functions: the Kraepelinain "*dementia praecox.*" The cross-sectional method facilitates the study of a possible relation between variables but does not make it possible to determine a cause-effect relation between them. The comparison of samples from different historic cohorts is problematic. These are populations that have been subjected to different variables (education, familial, eating, environmental stimulation, pharmacological treatment and rehabilitator models, models of health care and diagnostic modes) that clearly affect the premorbid cognitive level and evolution of neuropsychological deterioration once the disease is present.

Therefore, the so-called divergence between the cross-sectional and longitudinal results should not be surprising. Considering the latter, the cognitive deterioration is already present prior to the debut of the disease. In the second place, once the schizophrenia debuts, the deterioration tends to remain stable, if it does not improve, with the initiation of antipsychotic treatment during the first months (even two years). It is likely that some cognitive functions improve more than others: processing speed and visual memory capacity seem to improve,[64, 65] while verbal memory and attention do not so such a favorable course. Finally, we have a significant gap of knowledge on what happens with the course of the cognitive deterioration in CS. The studies have reduced sample sizes (Table 7), short follow-ups or not very fine measures of deterioration. Thus, the empirical evidence is of very low quality. The data suggest, however, that the deterioration remains stable during the middle ages of life and that at the end of maturity (65 years), there may be an increase in the progression speed.

However, the longitudinal studies published also have limitations. The main one is that the follow-up periods are

too short. There are only 35 years that exceed on year of follow-up and two studies that exceptionally exceed 28 years.[83]

Thus, we believe that the response on the progression of cognitive deterioration in schizophrenia continues without a definitive response in 2012. There are data in favor and against the hypothesis of stability. Perhaps, and of greater relevance, there are suspicions that the progression does not have a constant rhythm but alternates periods of progression with others of stability from the silent premorbid years to the period of senescence. However, it is necessary to initiate and maintain very prolonged prospective studies. We are aware of the difficulty since it would involve two or three generations of different investigators. Nonetheless, the lack of knowledge on the evolutive course of schizophrenia is too great and contrasts with the extent of information we have for other areas of the physiopathology of schizophrenia.

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