Course of cognitive symptoms in schizophrenia: a review of the literature

N. Ojeda[2]
P. Sánchez[1]
E. Elizagárate[1]
A. B. Yöller[1]
J. Ezcurra[1]
I. Ramírez[1]
J. Ballesteros[3]

[1] Hospital Psiquiátrico Alava
Vitoria. Spain
[2] Universidad de Deusto
Psychology Department
Bilbao. Spain
[3] Universidad del País Vasco
Neurosciences Department
Leioa. Spain

Longitudinal studies are the only ones capable of responding to the question of whether cognitive deficits present in schizophrenia follow a stable course and establishing its evolutive relationship with other clinical symptoms of the disease. This article reviews a total of 30 studies published in patients with a first psychotic episode or chronic or geriatric patients, with a minimum follow-up period of 1 year. The diversity in criteria and methods used significantly limits the conclusions that can be drawn on this subject. However, the global tendency of the results suggests that significant and measurable cognitive symptoms are present at the onset of the disease and these remain stable in the subsequent period between 2 and 5 years. Their deterioration increases with the course of the disease, especially in hospitalized patients, it not exceeding the deterioration level presented in other degenerative diseases. The authors are aware that unifying research criteria and overcoming the methodological limitations may offer results that change the conclusions herein gathered in the future.

Key words:
Schizophrenia. Cognition. Course. Longitudinal studies. Methodology.

Actas Esp Psiquiatr 2007;35(4):263-270

Evolución de los síntomas cognitivos en la esquizofrenia: una revisión de la literatura

Los estudios longitudinales son los únicos capaces de dar respuesta a la cuestión de si los déficit cognitivos presentes en la esquizofrenia siguen un curso estable y establecer cuál es su relación evolutiva con otros síntomas clínicos de la enfermedad. Este artículo revisa un total de 30 estudios publicados en pacientes bien con un primer episodio psicótico, como crónicos o geriátricos con un período mínimo de seguimiento de 1 año. La disparidad de criterios y metodologías empleadas limita significativamente las conclusiones que pueden extraerse sobre esta materia. Sin embargo, la tendencia global a la que apuntan los resultados sugiere que ya en el inicio de la enfermedad están presentes síntomas cognitivos significativos y medibles que permanecen estables en el período posterior entre los 2 y los 5 años y cuyo deterioro se acentúa con la evolución de la enfermedad, especialmente en los pacientes institucionalizados, sin llegar a superar el nivel de deterioro que presentan otras patologías degenerativas. Los autores son conscientes de que la unificación de criterios de investigación y la superación de las limitaciones metodológicas pueden ofrecer en el futuro resultados que modifiquen las conclusiones aquí recogidas.

Palabras clave:
Esquizofrenia. Cognición. Evolución. Estudios longitudinales. Metodología.

PRESENT STATUS OF SCIENTIFIC KNOWLEDGE ON THE COURSE OF COGNITIVE DETERIORATION IN SCHIZOPHRENIA

The presence of cognitive deterioration in patients with schizophrenia is well described in the literature. Kraepelin and Bleuer referred to attention, memory and executive function difficulties and the tendency of the previously published studies was to evaluate and focus on the ascertainment of deficits in these specific skills. Since the end of the 1980's, a change has been observed in the focus of interest of the studies that has evolved to incorporate more extensive neuropsychological evaluation, even including complete batteries. The results of some of these publications suggest that the deterioration of patients with schizophrenia heavily extends to other areas such as processing speed[1], visuospatial tasks[2], or verbal fluency[3]. This change in methodological approach served for some authors to conclude that the patients had a more diffuse cognitive deficit or that even some of the cognitive skills measured were within normal limits[4]. Based on this, it was suggested that most of the cognitive deficits that had been identified in schizophrenia had also been observed in other diseases, although in different degree. Stated otherwise, there would not be a specific neuropsychological deficit of schi-

Correspondence:
Natalia Ojeda
Universidad de Deusto
Departamento de Psicología
Av. de las Universidades, 24
Bilbao. Spain
E-mail: nojeda@fice.deusto.es

zophrenia[5]. More recently, some authors[6] have decided to focus the characterization of the profile not only on the selection of the areas affected but also on the severity grade presented by each one of them. Presence of alterations, regardless of the deterioration profile, has been described both in samples of first psychotic episodes[7,8], as well as in chronic patients[9] and, of course, in samples of geriatric patients[10]. Thus, they are present in the early phases of the disease and undoubtedly persist in spite of the treatment. On the other hand, and in agreement with that known as a hypothesis of neurodevelopment, the possibility that these deficits are present from the premorbid period prior to the diagnosis of the disease, acting as possible risk factor, has also been suggested[11,12]. However, do they appear before the clinical symptoms that we use for the diagnosis? What is the evolutive course followed by these deficits since their appearance? Does this course have a relationship with the course of the remaining clinical symptoms and other medical or sociodemographic variables? The absence of conclusive data indicating a direct relationship of the cognitive situation regarding the clinical symptoms, especially the positive symptoms, and the functional performance of the patient, has limited the importance given by the clinicians to cognition in the disease. Dealing with this question means transferring the debate on the hypothesis of neurodegeneration and neurodevelopment to the field of the cognitive. And the response could only be obtained from controlled longitudinal studies that originate from first psychotic episodes (FSE) samples (lacking access to general epidemiological samples in premorbid situations) and with a future stable follow-up, not inferior to 3 or 5 years[13]. The review of the literature indicates that there are no studies published with these characteristics. The large volume of publications that have approached this question has done so based on the results of cross-sectional studies[14]. However, these include the bias that the generational differences between the samples compared are the alternative explanation to those derived from intrasubject variability[15,16]. There are three reviews published up to date on the course of cognitive deterioration in schizophrenia that include longitudinal studies. The first, published by Heaton and Drexler (1987)[16], included both the few longitudinal studies published up to date and mostly cross-sectional studies. In the second, Harvey, in 19954, limited himself to studies on geriatric samples and thus did not deal with the deterioration spectrum in previous phases. The last review published by Rund in 1998[17] included a total of 15 longitudinal studies and concluded that there is a tendency to stability of cognitive deterioration in the samples analyzed. We have counted a total of 15 other longitudinal studies published since 1998 that analyze this question. Some of them correspond to studies that had already published data before 1998 and which, after a longer follow-up over time, clarified or modified some of their findings[18]. This article thus reviews the results of 30 studies having a longitudinal design that have been identified in scientific publications with a follow-up of the samples not inferior to one year. The search terms «cognition», «neuropsychology», «schizophrenia», and «longitudinal» were used in the data bases for the review of the literature we present. There are some publications whose follow-up period is inferior (for example19 for 6 months). However, this review has only included studies with a minimum follow-up period of 1 year and periods not inferior to 6 months between each administration of the cognitive tests.

Table 1 includes the summary list of these studies and some of their main characteristics. The first approach to the studies published verifies the methodological disparity existing between them. This makes it difficult, or impossible, to make a direct comparison and retort of the findings. Thus, we must take a cautious position regarding the results observed.

The evolution of the cognitive deficits in first psychotic episodes (FSE)

Some of the first studies published on FSE confirmed the presence of deficits in the debut of the disease. However, they suggested that the cognitive situation partially improved after the first years of follow-up. Sweeney and his team[20] confirmed this significant improvement in tasks of attention, verbal fluency, psychomotricity and, in this case, also visual and verbal memory. This also dealt with patients who had not initiated any type of treatment and whose clinical picture was still not stable. Thus, the improvement observed by this group in the first year could be related with the treatment and stabilization of the positive symptoms. What it does demonstrate is the existence of primary alterations that are not caused by confounding variables such as medication, institutionalization or the evolution of the disease symptoms. Along the same line, Hoff and his team[21,22] presented the results of a follow-up in patients with FSE at 2 and 5 years of the 1st examination. Their results after 2 years of evolution showed that the patients had stable capacity in language and visual memory tasks. However, the scores obtained in tasks such as attention and concentration, psychomotor speed and resolution of conceptual tasks significantly improved. This improvement had a statistically significant relationship with the improvement of the positive symptoms. The authors interpreted the improvement in cognition as an effect of learning and practice in both samples. This information has great relevance, since most of the studies published do not have a control sample that endorses the same effect of learning as in the case of this study[23]. The findings of Hofer[24] are in the middle ground. The authors evaluated 16 FPE with measures of attention, learning and psychomotor speed. Reevaluations at 2 years suggest general stability of symptoms and mild improvement (non-significant) in motor speed tasks.

In one of the most recent longitudinal studies in FPE with a 2 year follow-up[25], the authors did not find any significant improvement or any relationship between the cognitive course and the other clinical symptoms. On the contrary,

Table 1 List of longitudinal studies on cognition in patients with schizophrenia

Study	N	Type	Neuropsychological test	Follow-up (years)	Results
Moran et al. (1960)	30	Sch	Vocabulary	6	Stability
Smith (1964)	24	Sch	IQ	8,4	Stability
Klonoff et al. (1970)	66	Sch	WAIS	8	Improvement
Flekkoy et al. (1975)	72	Sch	Word association	16,6	Stability, tendency to improvement
Nuechterlein (1985)	14	Sch	CPT, Ds-CPT	1	Stability
Rund (1989)	14	Sch + CG	Memory CP, digits	4	Stability
Bilder et al. (1991)	28	Sch	Battery 4 tests	1	Improvement
Sweeney et al. (1991)	39	Sch	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	Sch + CG	CPT, SPAN	1	Stability in attention, less stability in memory
Hoff et al. (1992)	17	Sch 1st episode	Battery 7 tests	2	Improvement in attention, concentration, psychomotor, speed in language and verbal and spatial memory. Deterioration in verbal memory
Rund et al (1993)	22	Sch + CG	Backward masking	2	Stability
Nopoulos et al. (1994)	35	Sch	Battery 5 tests	1 (n = 17) 2 (n = 18)	Stability Improvement in attention and mental flexibility
Harvey et al. (1995)	224	Sch geriatric	MMSE	1	Stability
Rund and Landro (1995)	22	Sch + CG	React T, CPT, digits, Short and long term memory	1	Stability with tendency to improvement
Waddington et al. (1996)	41	Sch geriatric	10 questions of orientation	5 & 10	Mild tendency to deterioration
Rund et al. (1997)	14	Sch	Battery 4 tests	1-2	Stability in long term memory, flexibility, improvement in short term memory
Russell et al. (1997)	34	Sch	WAIS	19	Stability
Gold et al. (1999)	49	Sch 1st episode	Battery of 5 tests	5	Improvement in manipulative IQ, stability in verbal IQI and deterioration in psychomotor speed
Ho et al. (1998)	Sch	Sch		2	Mild improvement in all measurements evaluated
Hoff et al. (1999)	42	Sch + CG	Battery of 6 tests	2 & 5	Stability
Hofer et al. (2000)	16	Sch 1st episode	Battery of 3 tests	2	Stability
Moritz et al. (2000)		Sch	Battery of 4 tests	1	Stability
Friedman et al. (2001)	118	Sch geriatric + CG and others	MMSE, CDR	6	Stability up to age 65 and deterioration for samples of superior age
Grawe et al. (2001)	29	Sch	Battery of 6 tests	3	Deterioration regarding situation in first episode
Heaton et al. (2001)	142	Sch + CG	Battery of 9 tests	Mean of 3	Stability
Tuninger et al. (2001)	18 of 34	Sch chronic	Battery of 9 tests	2	Stability
Caspi et al. (2002)	44	Sch 1st episode + CG	Battery of 4 tests	Psychotic ep. remitted	Deterioration in spatial reasoning and processing speed. Stability in measurements of attention and other types of abstract reasoning
Townsend et al. (2002)	83	Sch 1st episode	Battery of 7 tests plus WAIS Wechsler Memory Scale	1	Stability in all the measurements
Brodaty et al. (2003)	27	Sch geriatric + CG	MMSE, Camcog, DLA's	1 and 5	Deterioration in all the measurements
Tirling et al. (2003)	37	Sch	Battery of 8 tests	10 and 12	Stability in fluency and very memory, executive f. Deterioration in visuoconstrictive skills and visual memory

CG: means that the study includes control group; Sch: schizophrenia.

they also describe a marked tendency to stability and all the measurements, except in visuospatial reasoning and processing speed, with observable deterioration. The authors did not include measurements of verbal memory, so that they could not retort the findings of Hoff et al.

In spite of the transcendence of the longitudinal results in FPE samples, the follow-up period of the samples is generally very limited. There are only two studies to our knowledge that have published follow-up data for periods greater than 5 years[26,27]. Andreasen[26] presented the data of a longitudinal study that included measurements of cognitive performance, cerebral volume and clinical symptoms. The author confirmed the presence of a defectual performance from the appearance of the disease, that could even be present in patients before the debut of the clinical symptoms. In the initial follow-up at one year, the group was stable in the measurements with mild, but significant tendency, to improvement in measurements of attention and executive functions[28]. This tendency is confirmed in the results after the first two years of onset[29]. This team describes stable performance, with mild improvement in attention, executive functions and information processing speed. The data show stability but with mild deterioration in the same measurements in relationship with the control group. Follow-up examinations at 9 years, and in a subsample at 12 and 15 years, point to the fact that the cognition course has a slow but progressive deterioration during this subsequent phase in spite of the therapeutic intervention with the sample and that it would affect all the cognitive areas explored. This is more outstanding in processing speed, psychomotor speed and memory. In addition, they point out that it is not parallel to that of other measurements, that are also progressively defective, as measurements of cerebral volume or in negative symptoms. Other authors who have published follow-up data of samples of first episodes in periods between 1 and 2 years also confirm this tendency to stability in the first years of evolution[30,31]. The Townsend study has the advantage that it has included the largest battery described up to date in this type of investigation and has controlled factors such as time of untreated psychosis and the patients' gender in its analysis. The group has a stability profile in the performance of reasoning measurements, memory, fluency and verbal comprehension, attention and information processing speed. In this study, the sample of patients received treatment with new generation antipsychotics, whose interaction with cognitive performance seems to be more limited.

The 2003 Stirling study 27 presents FPEs results with evolution to schizophrenia with a 10-12 year follow-up. The results show a significantly lower performance than for the normal population for most of the areas evaluated (between 0.5 and 1 standard deviation). The authors specify the possibility that there is a differential pattern of performance and evolutive course for different cognitive areas. Thus, although no significant differences are observed regarding normal performance at the time of the FPE in tests such as Puzzles or Short Stories of WAIS and Memory for Design (MFD) (visual memory), these skills subsequently show deterioration in the follow-up evaluations. They observed an initially low performance in verbal fluency, memory of faces and executive function tasks that then tend to improve and to be stabilized. The observation of deterioration in these skills points to cognitive areas that are not included between the classically mentioned ones in the deterioration profile of schizophrenia: attention, verbal memory and executive functions[21,32,33]. An important limitation of the Stirling study (2003) is that they included patients who had presented their first episode in any period prior to the two years before initiating the study as sample of FPE. This criterion is generally defined by other authors as samples with a recent psychotic episode more than a first episode and, as we have already seen through the results of the 2 year follow-up studies, this time may be sufficient for the cognitive situation of the patients to have evolved from its situation in the onset of the episode.

THE EVOLUTION OF COGNITIVE DEFICITS IN PATIENTS WITH LONG-EVOLUTION OR CHRONIC SCHIZOPHRENIA

The first longitudinal study on cognition in schizophrenia was published by Moran[34] and team in 1960, and focused on 55 chronic patients. Thirty of them were reevaluated 6 years later. From their results, the authors concluded that there was stability of performance during the follow-up period, in spite of a mild tendency to deterioration that was summarized in inadequacy in the use of language. However, the authors related this fact to the normal aging process more than to a disease of the patients. Since the Moran study, there have been at least 17 studies published whose samples were not exclusively made up of FPEs or geriatric patients (see next section). The results are very diverse: six studies reported stability of the cognitive symptoms, four affirmed improvement, two deterioration, three stability with mild improvement in some measurements and two stability with mild worsening in some areas. In general, it is observed that the studies with 1 year follow-up periods mostly speak about stability of cognitive performance[5,17,35,36,37]. In another study in 2001[38], there was also no significant deterioration observed in patients having similar characteristics during a 2 year follow-up. In this case, these were non-hospitalized patients with a course greater than 2 years since they had been diagnosed of the disease. The Nopoulos group28 observed stability in most of the measurements administered and mild improvement in some of the attentional measurements. However, this sample is part of the same study on which Andreasen (2004) presented data of 10 and 12 year longitudinal follow-up, showing moderate deterioration of all the cognitive measurements, including the results in attention. It should be mentioned that among the studies that also report deterioration, those having the most years of follow-up made in the samples, 12 and 19 years respectively, are found[27,39].

The course of cognitive deficits in studies of geriatric patients

Interest in this type of population has increased, given that the chronicity, seriousness and advanced age of this population should provide evidence on the existence of neurodegenerative conditions and thus support the hypothesis of a progressive decline in the disease. As reported by Barrantes-Vidal[40] in the prospective clinical-pathological studies with this type of population, it has been found that two thirds of the patients fulfilled diagnostic criteria of dementia according to the DSM-IV. Other authors suggest that the severity of cognitive deterioration in elderly patients with schizophrenia could be, at least, superior to that presented by young patients, and that the deterioration would be even clearer in institutionalized patients, with a long course of the disease and poor long-term prognosis. To the contrary, some studies that verify stability or minimum cognitive changes in samples of patients who have had a satisfactory course and prognosis of the disease in general terms have also been published[38,41,42]. These authors even suggest that having schizophrenia could act as a risk factor of the likelihood of developing dementia. Although some epidemiological studies of predictive factors of dementias have not found a clear relationship[43] (Eurodem study), other authors stress that the presence of alterations of any nature in the CNS could have an influence, increasing vulnerability to develop other diseases such as denentia[44,45]. One of the difficulties when evaluating geriatric patients with schizophrenia is finding samples whose score in the initial assessment does not significantly differ from that of normal subjects or other groups they are compared with[46]. This fact suggests that if the samples are not intentionally selected at the time of initiating the study in order to be comparable, the patients will have a significantly inferior performance to that of the reference group from the onset. Harvey[4] and his team conducted an initial follow-up of one year in a sample of 336 hospitalized geriatric patients with schizophrenia. Approximately 30 % of the sample had an initial moderate or severe level of deterioration in the baseline evaluation when two years had passed since the onset of the study. The authors also found greater functional limitation. On the contrary, authors such as Jeste[43] concluded that the patients with schizophrenia in late phases of evolution of the disease do not have greater deterioration than the samples with onset of the disease in earlier phases, pointing to the stability of the symptoms. No research in geriatric samples has found improvement in the follow-up except for Gouzoulis et al.[48] who conducted the first evaluation of the subjects during the psychotic phase of the patients, before the pharmacological control.

Again, the studies that have had longer follow-up periods suggest that cognitive deterioration in geriatric patients with schizophrenia is greater than that occurring in the normal population of the same age (Waddington et al., 1996; Friedman et al., 2001). The most recent longitudinal study in geriatric patients is that published by Brodaty et al. (2003) in patients with late episode of the disease. After the 5 year follow-up, the authors describe a high incidence of dementia among the patients evaluated, not only suggesting generalized deterioration but also that the psychosis could be a prodromic signal of the appearance of a dementia in the patients. The joint assessment of the longitudinal study data in geriatric patients with schizophrenia suggests that the patients show an initial deterioration that is located in intermediate levels between normal subjects and patient with dementia that lead to very elevated dependence levels in hospitalized patients. In addition, there are indicators that suggest that psychosis could be an anticipation of a dementia type neurodegenerative condition in patients with late episode.

DISCUSSION

The review of the studies published affirms the great disparity of methodology and existing results. This not only makes direct comparisons and retort of the findings difficult, but rather impossible. Even so, their interpretation has been mainly included within in the hypothesis of neurodevelopment and neurodegeneration. We could conclude that those longitudinal studies with samples of patients with FPEs and chronic patients who have had follow-up periods greater than 1 year already suggest the existence of a clear cognitive deterioration in the first episode, that probably improves or remains stable when the clinical situation stabilizes and subsequently worsens with the passing of the years and clinical relapses. Studies in more recent FPE that have included greater number of neuropsychological measurements suggest the possibility that the deterioration is present before the first diagnosis. There is greater coherence in the conclusions derived from studies in chronic samples where, in some cases, the authors find a significant grade of deterioration in spite of using less demanding cognitive tests for the evaluation. In relationship with the follow-up period, it should be stated that most of the longitudinal studies published include mean periods of reevaluation between 1 and 2 years. However the potential effect of learning is better controlled when the assessments are not repeated in periods less than one year, when tests that have different formats are used to facilitate the retest, or when samples of control subjects, who also have the same learning effect between assessments, are included. This latter case even has obvious limitations, since it supposes that the capacity of learning and retention retest of the patients is comparable to that of normal subjects. The studies that include follow-ups after 2 or 5 years generally show tendency to stability or mild deterioration of the cognitive symptoms. This possible onset of the decline is clearer in studies that exceed 5 years of longitudinal course. It is also surprising that it is much more difficult to find results pointing to improvement of the cognitive situation of the patients, regardless of the sample time, in the more recent studies published after the year 2000. This fact seems to coincide in time with the ten-

dency to include more extensive and demanding neuropsychological assessment protocols. The main limitations of these studies come from characteristics related with the disease itself, its clinical characteristics and pharmacological treatment. Analysis of the samples enrolled show that hospitalized patients are often included in the same group as community patients (Harvey 2001) or that the authors do not always homogeneously understand terms as chronic (Tuninger et al., 2001).

In the long term follow-up of the sample, there is a «sampling death» that again provides biases in the characteristics of the sample that is maintained in the study. The idea has been postulated that they are patients who show greater treatment compliance, who need greater control by the therapeutic team and thus who would show characteristics on the clinical level, with a differential evolutive course that is not representative of all the group. In his review published in 1998, Rund (1998) indicated his concern about drawing conclusions on this material due to the diagnostic difficulties. The author points out that the differences of criteria between the DSM-III and DSM-IV (that affect the studies conducted between 1968 and 1994) could limit, in the beginning, the comparison of the studies published during this period. More important is the bias stressed by Sharma et al. (2202), derived from the comparison of samples that fulfill DSM-IV diagnostic criteria for schizophrenia vs. only ICD-10 criteria. On the contrary to the ICD-10, the DSM-IV, to establish the diagnosis, requires a minimum time of 6 months presence of the symptoms, with involvement of the daily life activities (DLA).

In the studies where more than one area of functioning has been explored, a tendency to explore those capacities that have been traditionally described as deficient in the disease, that is, attention, memory and executive functions, is seen. However, this has left a bibliographic gap in relationship with the performance of these patients in other skills, as, for example, visuospatial performance. Absence of references to these skills has sometimes led to assuming that performance in them was normal in schizophrenia. Some recent, non-longitudinal, studies stress the evidence that certain subgroups of patients have a significant deterioration in visuospatial and visuoconstructive capacities (Leiderman et al., 2004), and even suggest a greater deterioration of them in the course of the disease in regards to the already classical ones of attention and memory (Schwartz et al., 2003). On the other hand, most of the studies that have included measurements of information processing speed or psychomotor speed in their cognitive evaluations show the existence of significant deterioration in these functions from the onset of the disease (Ueland et al., 2004; Kravariti et al., 2003). Another finding that seems to occur repeatedly and independently of the methodological disparity is the persistence over time of worse performance in verbal memory, suggesting that this is a selective deficit of the disease (Hoff et al., 1999).

In addition, there are studies in which the same instruments have been used to measure different cognitive aspects and there is a tendency to use less demanding measurements in the samples of chronic and geriatric patients. The Matrics project, by initiative of the University UCLA (USA), is the largest attempt made up to date to overcome the disparity of neuropsychological protocols, the lack of consensus on which each test is measured and the absence of instruments with similar formats for the retest.

ACKNOWLEDGEMENTS

To Astra Zeneca for its support in the research on schizophrenia that allowed for the elaboration of this publication.

REFERENCES

1. Kravariti E, Morris RG, Rabe-Hesketh S, Murray RM, Frangou S. The Maudsley Early-Onset Schizophrenia Study: cognitive function in adolescent-onset schizophrenia. Schizophr Res 2003; 65:95-103.
2. Schwartz BL, Howard DV, Howard JH Jr, Hovaguimian A, Deutsch SI. Implicit learning of visuospatial sequences in schizophrenia. Neuropsychology 2003;17:517-33.
3. Bokat CE, Goldberg TE. Letter and category fluency in schizophrenic patients: a meta-analysis. Schizophr Res 2003;64: 73-8.
4. Harvey PD, Lombardi J, Kincaid MM, Parrella M, White L, Powchik P, et al. Cognitive functioning in chronically hospitalized schizophrenic patients: age-related changes and age disorientation as a predictor of impairment. Schizophr Res 1995;17:15-24.
5. Rund BR, Landro NI. Memory in schizophrenia and affective disorders. Scand J Psychol 1995;36:37-46.
6. Harvey PD, Moriarty PJ, Bowie C, Friedman JI, Parrella M, White L, et al. Cortical and subcortical cognitive deficits in schizophrenia: convergence of classifications based on language and memory skill areas. J Clin Exp Neuropsychol 2002;24: 55-66.
7. Good KP, Rabinowitz J, Whitehorn D, Harvey PD, DeSmedt G, Kopala LC. The relationship of neuropsychological test performance with the PANSS in antipsychotic naive, first-episode psychosis patients. Schizophr Res 2004;68:11-9.
8. Sharma T, Hughes C, Soni W, Kumari V. Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. Psychopharmacology (Berl) 2003;169:398-403.
9. Harvey PD. Cognitive impairment in elderly patients with schizophrenia: age related changes. Internat J Geriatric Psychiatry 2001;16:S78-S85.
10. Pantelis C, Yucel M, Wood SJ, McGorry PD, Velakoulis D. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. Aust N Z J Psychiatry 2003;37: 399-406.
11. Silverstein ML, Mavrolefteros G, Turnbull A. Premorbid factors in relation to motor, memory, and executive functions deficits in adult schizophrenia. Schizophr Res 2003;61:271-80.

12. Elliot R, Sahakian BJ. The neuropsychology of schizophrenia: relations with clinical and neurobiological dimensions. Psychol Med 1995;25;581-94.
13. Bombín I. Análisis de la evolución de los déficit cognitivos en la esquizofrenia: un estudio neuropsicológico transversal. Tesis doctoral presentada en la Universidad de Deusto. Bilbao, 2004.
14. Nuechterlein KH, Dawson ME, Gitlin M, Ventura J, Goldstein MJ, Snyder KS, et al. Developmental processes in schizophrenia disorders: longitudinal studies of vulnerability and stress. Schizophr Bull 1992;18:387-426.
15. Strauss ME. The differential and experimental paradigms in the study of cognition in schizophrenia. J Psych Res 1978;14: 316-20.
16. Heaton R, Paulsen JS, McAdams LA, Kuck J, Zisook S, Braff D, et al. Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. Arch Gen Psychiatry 1994;51: 469-76.
17. Rund BR. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr Bull 1998;24:425-35.
18. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE. Longitudinal neuropsychological follow-up study of patients with first episode schizophrenia. Am J Psychiatry 1999;156: 1336-41.
19. Hudges C, Kumari V, Soni W, Das M, Binneman B, Drozd S, et al. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophr Res 2002;59:137-46.
20. Sweeney JA, Haas GL, Keilp JG, Long M. Evaluation of the stability of neuropsychological functioning after acute episodes of schizophrenia: one-year follow-up study. Psyc Res 1991;38: 63-76.
21. Hoff AL, Riordan H, O'Donnell D, Stritzke P, Neale C, Boccio A, et al. Anomalous lateral sulcus asymmetry and cognitive function in first episode schizophrenia. Schizophr Bull 1992;18: 257-72.
22. Hoff AL, Sakuma M, Razi K, Heydebrand G, Csernansky JG, DeLisi LE. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. Am J Psychiatry 2000;157: 1824-8.
23. Dickinson D, Iannone VN, Wilk CM, Gold JM. General and specific cognitive deficits in schizophrenia. Biol Psychiatry 2004;55: 826-33.
24. Hofer H, Merlo MCG. Neuropsychological performance in first episode patients: evidence for normalisation of cognitive functioning. Schizophr Res 2000;41:269.
25. Caspi A, Reichenberg A, Weiser M, Rabinowitz J, Kaplan Z, Knobler H, et al. Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. Schizophr Res 2003;65:87-94.
26. Andreasen N. Course of cognitive symptoms in schizophrenia: its relation to neuroanatomy and negative symptoms. Conferencia pronunciada en las Jornadas Neuroimagen en Psiquiatría. Madrid, 2004.
27. Stirling J, White C, Lewis S, Hopkins R, Tantam D, Huddy A, et al. Neurocognitive function and outcome in first episode schizophrenia: a 10-year follow-up of an epidemiological cohort. Schizophr Res 2003;65:75-86.
28. Nopoulos P, Flashman L, Flaum M, Arndt S, Andreasen N. Stability of cognitive functioning early in the course of schizophrenia. Schizophr Res 1994;14:29-37.
29. Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC. Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. Am J Psychiatry 1998;155:1196-201.
30. Townsend LA, Ross MGN, Malla AK, Rychlo AD, Ahmed RR. Changes in cognitive functioning following comprehensive treatment for first episode patients with schizophrenia spectrum disorders. Psychiatric Res 2002;113:69-81.
31. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in first-episode and recent onset schizophrenia. Am J Psychiatry 199;156:1342-8.
32. Lezak MD. Neuropsychological assessment, 3.ª ed. New York: Oxford University Press, 1986.
33. Galderisi S, Maj M, Mucci A, Cassano GB, Invernizzi G, Rossi A, et al. Historical, psychopathological, neurological, and neuropsychological aspects of deficit schizophrenia: a multicenter study. Am J Psychiatry 2002;159:983-90.
34. Saykin AJ, Shatasel DL, Gur RE, Kester B, Mozley LH, Stafiniak P, et al. Neuropsychological findings in neuroleptic naïve patients with first-episode schizophrenia. Arch Gen Psychiatry 1994;51: 124-31.
35. Nuechterlein KH. Converging evidence for vigilance deficit as a vulnerability indicator for schizophrenic disorders. En: Alpert M, editor. Changes and Constancies. New York: Guilford Press, 1985; p. 175-98.
36. Moritz S, Krausz M, Gottwalz E, Lambert M, Perro C, Ganzer S, et al. Cognitive dysfunction at baseline predicts symptomatic 1 year outcome in first-episode schizophrenia. Psypathology 2000; 33:48-51.
37. Tuninger E, Levander S. Neuropsychological impairments in patients treated with depot neuroleptics: a longitudinal study. Acta Psychiatr Scand 2001;104(Suppl. 408):75-80.
38. Heaton R. Stability and course of neuropsychological deficits in schizophrenia. Arch Gen Psychiat 2001;58:24-32.
39. Russell AJ, Munro JC, Jones PB, Hemsley DR, Phil M, Murray RM. Schizophrenia and the Myth of intellectual decline. Am J Psych 1997;154:635-9.
40. Barrantes-Vidal N. Neuropsicología y teoría del neurodesarrollo de la esquizofrenia. En: Obiols JE, editor. Neurodesarrollo y esquizofrenia: aproximaciones actuales. Barcelona: Ars Médica, 2001.
41. Davidson M, Harvey P, Welsh KA, Powchik P, Putnam KM, Mohs RC. Cognitive functioning in late-life schizophrenia: a comparison of elderly schizophrenic patients and patients with Alzheimer's disease. Am J Psychiatry 1996;153:1274-9.
42. Brodaty H, Sachdev P, Koschera A, Monk D, Cullen B. Long-term outcome of late-onset schizophrenia: 5-year follow up study. Br J Psychiatry 2003;183:213-9.
43. Jeste DV, Harris MJ, Krull A, Kuck J, McAdams LA, Heaton R. Related Articles, Links Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. Am J Psychiatry 1995;152:722-30.

44. Jellinger KA. Dementia as a complication of schizophrenia. J Neurol Neurosurg Psychiatry 2001;71:707-8.
45. Bush A, Beail N. Risk factors for dementia in people with Down syndrome: issues in assessment and diagnosis. Am J Ment Retard 2004;109:83-97.
46. Palmer BW, Heaton RK, Paulsen JS. Is it possible to be schizophrenic and neuropsychologically normal? Neuropsychology 1997;11:437-47.
47. Harvey PD, Parrela M, White L, Mohs RC, Davidson M, Davis KL. Convergence of cognitive and adaptive decline in late-life schizophrenia. Schizophr Res 1999;35:77-84.
48. Gouzoulis-Mayfrank E, Voss T, Mörth D, Thelen B, Spitzer M, Meincke U. Semantic hyperpriming in thought disordered patients with schizophrenia: state or trait?- a longitudinal investigation. Schizophr Res 2003;65:65-73.