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SCHIZOPHRENIA AND RELATED PSYCHOSES

STUDIES OF THE EARLY STAGES OF PSYCHOSIS

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Notes:

* Articles that have been published or that are in press are included in the main body of the manuscript whereas articles currently under submission are included in the Appendix section; according to regulations of the *Universidad Autónoma de Barcelona*.

* Manuscript and reference style of articles are according to the Journal's requirements where they have been published, accepted or submitted for publication.

SCHIZOPHRENIA AND RELATED PSYCHOSES: STUDIES OF THE EARLY STAGES OF PSYCHOSIS

CONTENTS

Chapter 1. Introduction. Schizophrenia and related psychoses

Schizophrenia is one of the biggest challenges in mental health and research due to its disproportionate share of mental health costs and the complex underlying mechanisms that have placed it as the most disabling psychiatric disorder (Mueser & McGurk, 2004). The World Health Organization (WHO) has reported incidence rates ranging from 1.6 to 4.2 per 10 000 inhabitants/year (Jablensky, Sartorius, Ernberg, & Anker, 1992). A recent systematic review of epidemiological data indicates that, if the diagnostic category of schizophrenia is considered in isolation, the lifetime prevalence and incidence are 0.30−0.66% and 10.2–22.0 per 100 000 person-year, respectively (McGrath et al., 2004).

Although incidence rates could be seen as low to moderate, the combined economic and social costs of schizophrenia place it among the world's top ten causes of disability-adjusted life-years, accounting for an estimated 2.3% of all burdens in developed countries, and 0.8% in developing economies (Mueser & McGurk, 2004). Direct costs of schizophrenia include treatment provided in inpatient, outpatient, and long-term care, as well as criminal justice costs, medication costs, and publicly owned capital such as state mental health facilities. Indirect costs mostly arise from the productivity loss suffered by individuals with schizophrenia, family members, and caregivers (McEvoy, 2007).

Delusions and hallucinations are the most characteristic psychotic symptoms of schizophrenia, but they are not exclusive as they can occur in other diagnostic categories of psychotic disorder (i.e., non-affective, affective, substance-induced, and organic). Schizophrenia symptoms can be clustered into three main categories: (i) psychosis (encompassing delusions and hallucinations—also called the positive-symptom dimension); (ii) alterations in drive and volition (affective flattening, alogia, avolition, and social withdrawal—the negative-symptom dimension); and (iii) alterations in thought and affect

(disorganized speech and behaviour, formal thought disorder, inappropriate affect – the disorganized dimension) (American Psychiatric Association (APA), 2000). Moreover, alterations in neurocognition (e.g. difficulties in memory, attention, and executive functioning—the cognitive-symptom dimension) are also common in schizophrenia (van Os & Kapur, 2009).

Although the nosological boundaries between schizophrenia and other psychiatric disorders are indistinct with overlapping diagnostic categories (Tandon, Keshavan, & Nasrallah, 2008a), the criteria used to distinguish between different psychotic disorders are based on duration, dysfunction, associated substance use, bizarreness of delusions, and presence of depression or mania (van Os & Kapur, 2009). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000) schizophrenia is categorized as a non-affective psychosis along with the schizophreniform, schizoaffective, delusional, brief psychotic, shared psychotic, and not-otherwise-specified psychotic disorders. However, even though the DSM-IV-TR presents schizophrenia and related psychoses as discrete conditions, it also states that "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder" (APA, 2000, p. xxxi)". Thus, the study of schizophrenia offers important advances in our comprehension of its aetiology, epidemiology, treatment and outcome that can be equally or partially applied to other non-affective and even affective psychoses.

Furthermore, there is the notion of a psychosis continuum ranging from normal personality variation to psychosis, which implies that the same symptoms that are seen in patients with psychotic disorders can be measured in non-clinical populations (Verdoux & van Os, 2002). In this context, a psychosis phenotype, expressed at levels below

psychopathology, is commonly referred to as psychosis proneness, psychotic experiences, schizotypy or at-risk mental states. Hence, even though the prevalence of the clinical disorder is low, the prevalence of psychotic symptoms can conceivably be much higher (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; Verdoux & van Os, 2002) (Figure 1). In support to the concept of a psychosis continuum, some studies have found not only similar clusters (positive, negative and cognitive disorganization) of symptoms and traits in both schizophrenia and non-clinical populations (Barrantes-Vidal et al., 2003), but also common indexes of early developmental disturbances such as asymmetric dermatoglyphics (Rosa et al., 2000) and atypical hand dominance (Dragovic, Hammond, & Jablensky, 2005; Shaw, Claridge, & Clark, 2001). The study of psychotic features under psychopathological threshold might enhance our comprehension of the underlying aetiological mechanisms contributing to the risk for psychotic illness.

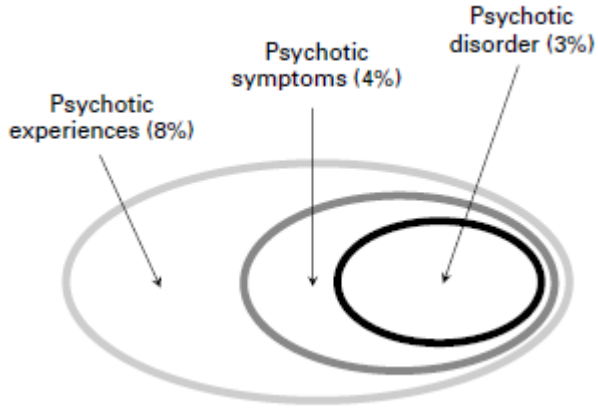

Figure 1. Psychosis: variation along a continuum (from van Os et al., 2009)

The aetiology of schizophrenia is a complex issue, involving genetic factors and gene-environment interactions that together contribute over 80% of the liability for developing schizophrenia (Tandon et al., 2008a; 2008b). Although a number of chromosomal regions and genes have been linked to the risk for developing the disease, up to this time, no single gene variation has been consistently associated with a greater likelihood of developing the

illness and the precise nature of the genetic contribution remains unclear (Tandon et al., 2008b). Environmental factors linked to a higher likelihood of developing schizophrenia include cannabis use, prenatal infection or malnutrition, perinatal complications, and a history of winter birth; the exact relevance or nature of these contributions is also unclear (Tandon et al., 2008a; 2008b).

The notion of schizophrenia as a neurodevelopmental disorder is a hypothesis that has received ample support. This hypothesis proposes that complications during pregnancy and at birth can obstruct the normal early development of the central nervous system that is characterized not only by cellular proliferation and neuronal migration but also by cell death. Insults might hinder neuronal fallout and impair the organization of axonal connections, leading to immature cell and connection patterns. Thus, an early neural damage in life may account for the onset of schizophrenic symptoms; the lesion lies dormant until the brain matures sufficiently to call into operation systems that are then found already damaged from early stages (Murray & Lewis, 1987; Weinberger, 1996). As mention earlier, neurodevelopmental disturbance markers have been particularly present in schizophrenia and psychosis-proneness populations (Dragovic et al., 2005; Rosa et al., 2000; Shaw et al., 2001).

The background of the modern notions of schizophrenia can be traced back to the work of Kraepelin and Bleuler. Kraepelin conceived the initial concept of *dementia praecox* as a particular type of dementia which occurred early in life and followed gradual deterioration to dementia (Sanbrook & Harris, 2003). Years later, Bleuer emphasised the core symptoms of the disorder as difficulties in thinking straight (loosening of associations), incongruous or flattened affect, loss of goal-directed behaviour or ambivalence due to conflicting impulses and retreat into an inner world (autism), and proposed the term “schizophrenia” to designate

this syndrome (Mueser & McGurk, 2004). We now know that there are neuropathological correlates of schizophrenia, but they are not necessarily signs of neuropathological deterioration; thus, although schizophrenia is undeniably serious, a deteriorating course is more the exception than the rule (McGorry, Nordentoft, & Simonsen, 2005).

Studies of the early stages of psychosis

Kraepelin's original concept of *dementia praecox* has been undeniably a crucial contribution to the understanding of schizophrenia. However, the concept was also responsible for portraying an overly pessimistic view regarding the prognosis of psychotic illnesses (Sanbrook & Harris, 2003).

After the first episode of psychosis most patients might suffer subsequent relapses and persistent symptoms, but there is also a small percentage of patients who would not. Indeed, Kraepelin later acknowledged himself that about 4% of his patients recovered completely, and 13% had a significant remission (Barnes & Pant, 2005). The International Study of Schizophrenia (ISoS) conducted by the World Health Organization (WHO) has shown that 13.8% of incidence cases experienced only one episode of psychosis and had a good outcome (Harrison et al., 2001). However, before the early intervention began to gain recognition (approximately in the mid 1990s), the diagnosis and treatment of schizophrenia were traditionally delayed until a full diagnosis could be made in order to avoid unnecessary and unpleasant side effects and stigma. In recent decades new data and developments have impacted on this traditional approach. First, evidence emerged suggesting that existing treatments for psychosis might also affect the natural history of the disorder. Second, the introduction of novel antipsychotics (e.g. clozapine, risperidone and olanzapine) proved to have equal efficacy to traditional neuroleptics and had fewer side-effects. Finally, the demonstration by the pioneering work of McGorry et al. that subgroups of patients with

'prodromal' symptoms and at a very high risk for 'converting' to psychosis in the short-term future could be identified (McGlashan, 2005) opened the ambitious aim of early detection and intervention.

This recent schizophrenia preventive approach is based on the clinical staging diagnosis concept, which differs from conventional diagnostic practice in that it defines the extent of progression of disease at a particular point in time, and where a person lies currently along the continuum of the course of illness (McGorry, 2007). The differentiation of early and milder clinical phenomena from those that accompany illness extension, progression and chronicity lies at the heart of the concept. It enables the clinician to select treatments relevant to earlier stages, and assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course (McGorry, Killackey, & Yung, 2008). A staging framework moves beyond the confines of the typical diagnostic approach, introducing subtypes along a longitudinal dimension. Hence, it has the potential to encompass a broader range of clinical phenotypes and to organize them in a coherent and mutually validating manner (McGorry, 2007).

In brief, at present time there is a general agreement that schizophrenia no longer means an inescapable path to deterioration, and that a first episode of psychosis might follow various courses, from full recovery to chronic course (APA, 2000; Ciompi, 1980; Jablensky et al., 1992; Shepherd, Watt, Falloon, & Smeeton, 1989). Also, there is a current perspective that sees psychosis features on a continuum involving attenuated manifestations which may or not evolve into psychosis (Krabbendam, Myin-Germeys, Bak, & van Os, 2005). Therefore, interest has grown to predict outcome at different stages of the psychosis continuum (Figure 2), studying factors that might signal the onset of illness and/or predict outcome after the first episode of psychosis.

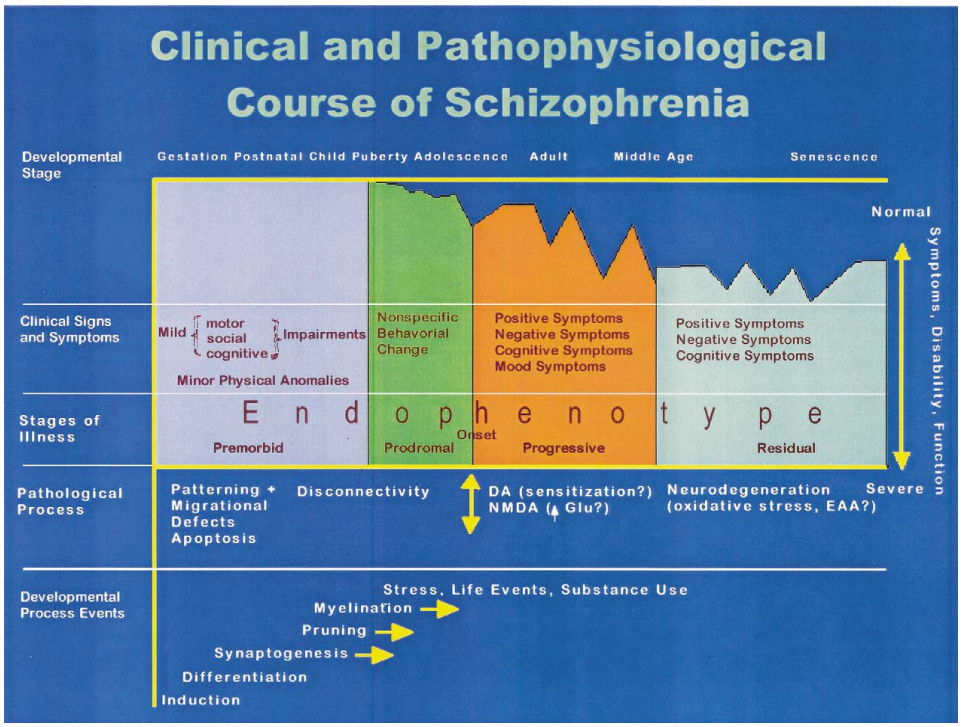

Figure 2. Clinical and pathophysiological course of schizophrenia (from Lieberman et al., 2001)

Indicators of vulnerability to psychosis

The rationale for early detection of schizophrenia is based on several observations: 1) diagnosis and treatment of schizophrenia are often seriously delayed, 2) consequences of the disease are very severe already in the early preclinical, undiagnosed phase of the disorder, and 3) early treatment seems to improve the course of the disease. It can therefore be stated quite safely that patients should be diagnosed and treated as early as possible (Riecher-Rössler et al., 2006). Efforts have been to improve early detection of schizophrenia, using well-defined criteria for psychotic breakdown (Yung et al., 2003). Furthermore, efforts have aimed also at detecting individuals at risk for psychosis onset, before the diagnostic criteria are fulfilled (Yung, 2007). For instance, the "at –risk mental state" criteria by Yung et al. (1996) have obtained up to a 41 % transition rate to psychosis in identified "ultra-high risk" people within a year of detection (Phillips, Yung, & McGorry, 2000), whereas, the criteria for prodromal syndromes by Miller et al. (2002) have obtained a

46% and 54% transition rates to psychosis of people identified as prodrome within 6 and 12 months, respectively.

Research has also regarded a psychosis-proneness phenotype distributed below clinical threshold in non-clinical populations (van Os et al., 2009). The notion of a psychosis-proneness phenotype has widely relied on the conceptual schizotaxia-schizotypy model for the pathogenesis of schizophrenia proposed Meehl (1990). This model states that "schizotaxia" is a genetic neurophysiological predisposition to both schizotypy and schizophrenia; whereas schizotypy is seen as the predisposition to schizophrenia at the level of the organization of the personality. Regardless of environmental and upbringing circumstances all people with a genetic schizotaxial vulnerability are programmed to develop schizotypal traits, but only a few, under the influence of other personality traits and negative experiences in life, will develop schizophrenia (Krabbendam et al., 2005; Vollema & van, 1995). Evidence suggests that schizophrenia and highly psychosis-prone populations partly concur in indexes of abnormal development such as atypical lateralization, asymmetric dermatoglyphics and impaired cognitive function (Rosa et al., 2000).

The study of *vulnerability markers to psychosis* (i.e. expressions of the underlying etiological process) and of *risk factors for psychosis* (i.e. conditions enhancing the likely transition to the disorder, but not a part of it) is an important task that will shed light on the aetiology of the psychosis spectrum, and allow the early detection and treatment of those in need.

Predictors of the short-term course outcome of psychosis

Although the severity of different symptoms varies across patients and through the course of illness (Tandon, Keshavan, & Nasrallah, 2008a), long-term follow-up studies (e.g. Eaton, Thara, Federman, & Melton, 1995; Harrison et al., 2001; Harrow, Grossman, Jobe, & Herbener, 2005; Wiersma, Nienhuis, Slooff, & Giel, 1998) have suggested that the course of psychosis is most stormy at the onset and early in its manifest course, reaching a natural plateau of psychopathology and disability thereafter. Moreover, there is evidence of the early course of illness as the strongest predictor of long-term outcome (Harrison et al., 2001). Thus, the early phase of psychosis can be viewed as a "critical period" during which it is possible to determine the long-term trajectory of the psychosis and to direct resources appropriately (Birchwood, 2000).

In consequence, numerous studies have aimed at analyzing the predictive factors (e.g. Bertelsen et al., 2009; Häfner et al., 2003; Lenior, Dingemans, Schene, & Linszen, 2005; Svedberg, Mesterton, & Cullberg, 2001) and providing innovative treatment alternatives (e.g. Garety et al., 2006; Petersen et al., 2005)in the short-term course of illness. Overall, findings suggest that poor outcome is predicted by male gender, early age of onset, prolonged period of untreated illness, and severity of cognitive and negative symptoms, and that early intervention during first episode of psychosis improves outcome (Tandon, Keshavan, & Nasrallah, 2008a). Nevertheless, underlying cultural differences might impact not only the epidemiology, aetiology and phenomenology of psychoses, but also their course and outcome (Kulhara & Chakrabarti, 2001). Hence, the importance of replicating the reliability of prognostic factors in different populations (e.g. Apiquián-Guitart, Fresán-Orellana, García-Anaya, Lóyzaga-Mendoza, & Nicolini-Sánchez, 2006; Jablensky et al., 1992).

Quality of Life of patients and their relatives: A feasible aim in treatment

Relapse (with or without hospitalization) and symptom remission have been the traditional outcome measures in psychosis, but other measures have also been widely present in the literature, such as psychopathology dimensions, cognitive function, treatment adherence, aggression/hostility, substance-use, social and occupational functioning, mortality and suicidality (Barnes & Pant, 2005; Malla & Payne, 2005).

Overall, research in mental health seems to have conventionally considered negative outcome (e.g. mortality, relapses, and dysfunction) and the means to prevent it. Nevertheless, the traditional focus on symptoms and illness has been gradually changing towards a wider concept of health that involves also satisfactory individual functioning, optimal use of available resources, and the capacity to overcome adversities. Positive psychological states are not only an essential part of health, but they can also influence illness onset, course and recovery. Positive feelings of esteem, control and an optimistic view of life are vital resources to rely on when facing stressful situations that might lead to illness (Vázquez, Hervás, Rahona, & Gómez, 2009). The relevance of studying risk factors in order to prevent unfavourable outcome is unquestionable; however, patients might also have positive aspects in their lives that, properly managed, might be protective and improve prognosis.

Furthermore, the development of atypical antipsychotic drugs has allowed a conceptual extension of therapeutic outcome criteria to adopt more positive and wide-reaching measures such as quality of life (Lambert & Naber, 2004; Pinikahana, Happell, Hope, & Keks, 2002). Quality of life involves the "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The WHOQOL Group, 1998). Quality of

life has emerged as a unifying concept in assessing the impact of sickness on people's day-to-day lives, measuring the human costs and benefits of interventions through their effects in various domains of life (e.g. social contacts, economy, expectancies) (Pinikahana et al., 2002). This concept has risen interest in mental health research and studies have been performed in various disorders, including schizophrenia (Eack & Newhill, 2007), and across cultures (e.g. Gaite et al., 2002; Urzúa-Morales & Jarne-Esparcia, 2008).

Moreover, this approach has been extended to patients' relatives as well, as illness might also have consequences in their lives. As the de-institutionalization of patients has been promoted, the role of families as providers of informal care has increased. Initially, attention was paid to family environment as a significant factor in the onset and course of psychosis, leading to the development of several psychosocial interventions centred on the family unit to prevent patients' relapse (Barbato & D' Avanzo, 2000). However, families cannot be seen as a fixed causal factor of the patients' clinical status; their interactions with the patient might well generate burden and affect their quality of life. Even though the focus on families was initially due to their role upon patients' outcome, it is fair to recognize their need for support as they might also be affected by their relatives' illness. Studies have shown that a caregiver's decreased quality of life is associated with lack of social support, economic burden, illness course and family relationships problems (Caqueo-Urízar, Gutiérrez-Maldonado, & Miranda-Castillo, 2009). Given that most patients live with their parental or own family, further research is needed to explore the quality of life not only of patients but also of their daily carers.

Outline and aims of the study

The introduction presented a general outline of schizophrenia and other psychoses previous to the main discussion of three important changes in the perspective that have

guided the study of these syndromes: 1) schizophrenia is a point of the psychosis continuum 2) the course of psychosis is heterogeneous and can be fairly predicted and influenced in its early phase, and 3) psychosis outcome has expanded beyond symptom remission in order to embrace patients' quality of life and even that of their relatives. The present doctoral dissertation provides evidence of the heterogeneity of illness course in the early years following a first psychotic episode replicating the prognostic value of previously related factors in two populations of patients from different countries. Chapters 2 will present a study with first-episode psychosis patients from the city of Barcelona (Spain) analysing retrospectively baseline sociodemographic factors and features of the premorbid phase, context of the first psychotic episode, and dimensions of psychopathology. Chapter 3 will present a replication of the study presented in Chapter 2 in a population of first-episode psychosis patients from the city of Merida (Mexico). Chapter 4 will present a summary of these two studies along with other three which are included as complementary material in the Appendix section. Appendix 1 will present a study with emphasis in psychosis proneness indicators, that is, the non-clinical stage of the psychosis continuum, focusing on the relationship between psychosis-proneness dimensions with laterality indexes, a proxy of neurodevelopmental disturbance. Appendix 2 will present a study regarding the quality of life of short-term course psychosis patients, analysing the prognostic value of illness course and the mediating effect of both illness perception and functioning. Appendix 3 will present a study addressing the quality of life of patients' relatives along with their levels of expressed emotion and burden, analysing the prognostic value of both patients' and relatives' features. Finally, the Summary section will address the main contributions of all the above mentioned studies and further research proposals.

Following, an outline of the studies is presented according to the sequence of the arguments offered in this Introduction.

Indicators of vulnerability to psychosis

In Appendix 1, atypical handedness patterns and their association to psychosis proneness in an adolescent community sample will be studied. Previous research in the area will be expanded by: 1) analyzing a variety of atypical handedness indexes (left, mixed, ambiguous, inconsistent), 2) measuring comprehensively the multidimensionality of psychosis-proneness (positive, disorganized and negative dimensions) and, 3) analyzing the association of different patterns of atypical handedness with nonclinical dimensions of both *trait* (schizotypy) and sub-clinical *symptom* (psychotic-like experiences) levels.

Predictors of the short-term course outcome of psychosis

The strength of prognostic factors might vary in different populations and the replication of studies provides evidence of the common and specific factors that reliably predict outcome. Studies on illness course have used diverse definitions for both outcome and predictors. The studies presented in Chapters 2 and 3 employ a retrospective design to examine the predictive validity of demographic, clinical, and psychosocial characteristics in short-term course first-episode psychosis patients of the cities of Barcelona (Spain) and Merida (Mexico). Outcome is operationalized according to three widely used criteria: diagnosis, presence of residual psychotic symptoms, and number of psychotic episodes. Findings from the Spanish and Mexican samples will be presented and discussed independently in Chapters 2 and 3, respectively.

Quality of Life of patients and their relatives: A feasible aim in treatment

Quality of life has become an important issue in patient care and in research. Attention has been paid to unveil its reliable predictors and possible mediating factors. The study described in Appendix 2 will explore whether the effect of illness course on patients'

QoL is mediated by their illness perception or overall functioning in a sample of short-term course first-episode psychosis patients.

Learning about the specific and common underlying factors affecting expressed emotion, burden and quality of life is essential to optimize family interventions, thereby improving the outcome of both patients and relatives. Appendix 3 will present a study exploring whether relatives' illness perception and psychological distress would be stronger predictors of their quality of life, expressed emotion and burden than the patients' clinical and functional status.

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Chapter 2. Predictors of outcome in the early course of first-episode psychosis

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Predictors of outcome in the early course of first-episode psychosis

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ABSTRACT – *Background and Objectives*: The identification of characteristics that predict clinical and functional outcomes in patients with schizophrenia and related psychotic disorders is essential for enhancing our understanding of the pathophysiology and the treatment of the disorder. The present study employed a retrospective design to examine the predictive validity of demographic, clinical, and psychosocial characteristics of first-episode patients on diagnosis, presence of residual psychotic symptoms, and number of psychotic episodes three to five years later.

Methods: Information on baseline predictor variables and outcome was obtained from the clinical records of 44 patients who had their first psychotic episode between 1999 and 2003 and whose available follow-up period was at least 3 years long (mean = 5.7 years, SD = 1.3 years).

Results: Male gender, single marital status, and poor premorbid adjustment were significantly associated with residual symptoms at follow-up. Poor insight at onset was significantly associated with subsequent relapses. Diagnosis of schizophrenia (as opposed to other psychotic disorders) at the follow-up assessment showed no significant association with any of the baseline predictors.

Conclusions: Consistent with previous findings, the constellation of male gender, single status, poor premorbid adjustment and poor insight appeared to predict especially poor outcome. Residual symptoms appear to be an especially useful index of clinical and functional status for examining the course and outcome of first-episode psychosis.

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Introduction

Schizophrenia is one of the most disabling mental disturbances; however, it can no longer be conceived as a hopeless and inevitable pathway to deterioration[1]. During the five years after the first psychotic episode (the so-called "critical period"), most patients are likely to relapse and/or present residual symptoms. Eventually, however, psychotic disorders appear to reach a plateau and follow a more stable course[2,3]. Nevertheless, some studies have documented great heterogeneity in illness course, such that between 12-22% of patients never relapse or present residual symptoms[4]. The identification of characteristics that predict clinical and functional outcomes in newly diagnosed psychotic patients should enhance our understanding of such disorders and provide guidance for treatment.

Research and intervention programs in early psychosis aim to reduce suicide and relapse rates, prevent social and cognitive deterioration and ameliorate persisting symptoms[5,6]. In this study area, *outcome* has been defined by a variety of clinical, functional and quality of life measures[5]. A widely used outcome criterion, and perhaps the most available, is *diagnosis*, which can be reliably established after approximately six months of onset[7]. Schizophrenic psychoses show, compared to schizoaffective and affective psychoses, a poorer global outcome, more deteriorating course, greater presence of negative symptoms, and more persistent impairments in several aspects of social life, such as communication and cognitive functions[8,9]. *Illness course* is also extensively reported as an outcome measure, varying from a full recovery to a chronic deteriorating course[7,10-12]. Some studies, simplifying the course of psychosis as "poor" or "good", have defined course by relying either on the presence of residual symptoms[4,13] or on the occurrence of subsequent relapses[14]. However, there is a shortage of studies comparing the impact of using either one or the other, particularly on their ability to evaluate the utility of putative prognostic indicators.

Apart from outcome definitions, studies have also diverged in the analysis of premorbid and first-episode characteristics that might be predictive of outcome. Sociodemographic variables, clinical features, conditions of the premorbid phase, context of presentation of the first episode of psychosis, and type of treatment have been the most common factors related to early and long-term outcome. Literature on this topic is abundant, suggesting that among many factors, early age at onset, male gender, single status, poor premorbid adjustment, lack of insight, and symptom severity at onset, are highly related to poor outcome[2,15], though not all findings concur[5,6].

Research so far has identified important predictors of outcome. Nevertheless, and to the best of our knowledge, there is a shortage of studies analysing the association of premorbid and first episode variables with different outcome definitions. Therefore, this study aims at (i) replicating the prognostic value of factors previously related to the early course of psychosis in retrospectively assessed first-episode psychotic patients, and (ii) assessing their prognostic value according to three different outcome criteria (final diagnosis, presence of psychotic residual symptoms, and number of psychotic episodes).

Methods

Design and Case Selection

This is a retrospective case series study focusing on the early course of psychosis in a cohort of patients from an outpatient clinic in Barcelona, Spain. Data were collected through the review of clinical files after obtaining formal authorization and ethical approval from the Hospital Committee. Inclusion criteria were: (1) occurrence of a first episode of psychosis between 1999 and 2003; (2) age at onset between 18-45 years; and (3) a primary current DSM-IV-TR[7] diagnosis of schizophrenia or other psychotic disorders (schizophreniform, schizoaffective, delusional, brief, or not otherwise specified). Exclusion criteria were: (1) psychoses of affective, organic, or toxic type, (2) an evident intellectual disorder, and (3) no follow-up information available. We identified 44 first-episode patients who met the criteria for inclusion in the study. These included 28 men and 16 women, with an average age at first episode of 27.6 years (SD = 7.6). All cases included had an available follow up of at least 3 years (mean = 5.7, SD = 1.3). Most patients (61.4%) had never interrupted their contact with the mental health service for any period of six months or longer. All patients had received antipsychotic medication.

Measures and Variables

Based upon findings in previous studies[4,13,14], the predictors identified at the first episode included (1) sociodemographic data, (2) premorbid phase, (3) features of the context of the first episode, and (4) dimensions of psychotic psychopathology. For psychopathology clinicians rated the presence of symptoms corresponding to each of its three dimensions (psychoticism, disorganization, and negative symptoms) by translating the clinical records information into PANNS selected items[16].

Outcome was classified according to three criteria. First, current diagnosis was established according to DSM-IV-TR[7] criteria by experienced senior clinicians (EV, JMB, MM). After reaching clinical consensus, diagnoses were dichotomized into: 1) schizophrenia and, 2) other psychoses. A second criterion grouped cases as 1) with residual symptoms or, 2) with no residual symptoms at the time of the outcome assessment. A third criterion considered the number of psychotic episodes during the follow-up period (including the initial episode), classifying cases as 1) single episode or, 2) multiple episodes.

Results

Table I presents a series of binary (sociodemographic variables) and multinomial (premorbid phase, context of the first episode, and

Table I
Logistic regression analyses of baseline variables predicting the three different outcome criteria

Outcome: Last diagnosis

VARIABLE Category / Range	Schizophrenia N = 29 Mean (SD) or %	Other psychosis N = 15 Mean (SD) or %	*Odds Ratio* *(95% CI)*
1. SOCIODEMOGRAPHIC VARIABLES			
Age at onset (years)	28.6 (7.9)	25.9 (7.0)	0.95 (0.87 – 1.04)
Gender Male / Female	65.5% / 34.5%	60.0% / 40.0%	1.27 (0.35 – 4.58)
Marital status Single / ever married	62.1% / 37.9%	66.7% / 33.3%	0.82 (0.22 – 3.03)
Educational level Basic / Medium or higher	55.2% / 44.8%	53.3% / 46.7%	1.08 (0.31 – 3.76)
Work or study Yes / No	79.3% / 20.7%	80.0% / 20.0%	0.96 (0.20 – 4.52)
2. PREMORBID PHASE VARIABLES			
Premorbid adjustment Poor / Good	69.0% / 31.0%	60.0% / 40.0%	1.34 (0.35 – 5.14)
Identified trigger Yes / No	44.8% / 55.2%	33.3% / 66.7%	1.57 (0.41 – 5.98)
Type of onset Sudden, Acute / Insidious	55.2% / 44.8%	66.7% / 33.3%	0.61 (0.16 – 2.25)
3. CONTEXT OF FIRST PSYCHOTIC EPISODE VARIABLES			
Hospitalization Yes / No	55.2% / 44.8%	53.3% / 46.7%	0.96 (0.26 – 3.58)
Substance abuse Yes / No	34.5% / 65.5%	40.0% / 60.0%	0.84 (0.22 – 3.18)
Level of insight Null / Partial	79.3% / 20.7%	60.0% / 40.0%	2.54 (0.63 – 10.27)
4. PSYCHOPATHOLOGY SYMPTOM COUNTS			
Psychoticism	2.1 (0.9)	2.2 (0.9)	1.21 (0.50 – 2.91)
Disorganization	0.8 (0.5)	0.7 (0.5)	0.58 (0.12 – 2.74)
Negative	1.7 (1.1)	1.1 (1.1)	0.60 (0.32 – 1.11)

*$p < 0.05$

Note: separate regressions were computed for premorbid phase, context, and psychopathology variables with the predictors for each analysis entered simultaneously.

Outcome: Presence of residual symptoms (R.S.)

VARIABLE Category / Range	With R.S. n = 36 Mean (SD) or %	With NO R.S. n = 8 Mean (SD) or %	*Odds Ratio* *(95% CI)*
1. SOCIODEMOGRAPHIC VARIABLES			
Age at onset (years)	27.3 (7.8)	29.4 (6.8)	1.04 (0.94 – 1.15)
Gender Male / Female	72.2% / 27.8%	25.0% / 75.0%	**7.80*** (1.34 – 45.28)
Marital status Single / ever married	72.2% / 27.8%	25.0% / 75.0%	**7.80*** (1.34 – 45.28)
Educational level Basic / Medium or higher	50.0% / 50.0%	75.0% / 25.0%	0.33 (0.06 – 1.88)
Work or study Yes / No	75.0% / 25.0%	100.0% / 0.0%	0.00 (0.00 – 0.00)
2. PREMORBID PHASE VARIABLES			
Premorbid adjustment Poor / Good	75.0% / 25.0%	25.0% / 75.0%	**7.77*** (1.22–49.44)
Identified trigger Yes / No	47.2% / 52.8%	12.5% / 87.5%	4.90 (0.48 – 49.69)
Type of onset Sudden, Acute / Insidious	55.6% / 44.4%	75.0% / 25.0%	0.36 (0.05 – 2.49)
3. CONTEXT OF FIRST PSYCHOTIC EPISODE VARIABLES			
Hospitalization Yes / No	52.8% / 42.2%	62.5% / 37.5%	0.48 (0.08 – 2.82)
Substance abuse Yes / No	36.1% / 63.9%	37.5% / 62.5%	1.25 (0.22 – 7.23)
Level of insight Null / Partial	77.8% / 22.2%	50.0% / 50.0%	4.21 (0.76 – 23.22)
4. PSYCHOPATHOLOGY SYMPTOM COUNTS			
Psychoticism	2.1 (0.9)	2.4 (0.7)	1.27 (0.48 – 3.36)
Disorganization	0.7 (0.5)	1.0 (0.0)	7.26 (0.58 – 90.60)
Negative	1.5 (1.1)	1.3 (1.2)	0.74 (0.34 – 1.63)

*$p < 0.05$

Note: separate regressions were computed for premorbid phase, context, and psychopathology variables with the predictors for each analysis entered simultaneously.

Outcome: Number of episodes

VARIABLE Category / Range	Single episode n = 14 Mean (SD) or %	Multiple episodes n = 30 Mean (SD) or %	*Odds Ratio* *(95% CI)*
1. SOCIODEMOGRAPHIC VARIABLES			
Age at onset (years)	28.5 (6.7)	27.3 (8.1)	1.02 (0.94 – 1.11)
Gender Male / Female	64.3% / 35.7%	63.3% / 36.7%	0.96 (0.26 – 3.60)
Marital status Single / ever married	50.0% / 50.0%	70.0% / 30.0%	2.33 (0.63 – 8.62)
Educational level Basic / Medium or higher	57.1% / 42.9%	53.3% / 46.7%	0.86 (0.24 – 3.08)
Work or study Yes / No	78.6% / 21.4%	80.0% / 20.0%	1.09 (0.23 – 5.19)
2. PREMORBID PHASE VARIABLES			
Premorbid adjustment Poor / Good	71.4% / 28.6%	63.3% / 36.7%	0.64 (0.15 – 2.64)
Identified trigger Yes / No	35.7% / 64.3%	43.3% / 56.7%	1.48 (0.38 – 5.72)
Type of onset Sudden, Acute / Insidious	50.0% / 50.0%	63.3% / 36.7%	1.70 (0.47 – 6.21)
3. CONTEXT OF FIRST PSYCHOTIC EPISODE VARIABLES			
Hospitalization Yes / No	35.7% / 64.3 %	63.3% / 36.7%	2.54 (0.61 – 10.48)
Substance abuse Yes / No	28.6% / 71.4%	40.0% / 60.0%	1.72 (0.38 – 7.78)
Level of insight Null / Partial	50.0% / 50.0%	83.3% / 16.7%	**4.88*** (1.08 – 21.97)
4. PSYCHOPATHOLOGY SYMPTOM COUNTS			
Psychoticism	2.0 (0.8)	2.2 (0.9)	0.80 (0.38 – 1.71)
Disorganization	0.6 (0.6)	0.8 (0.4)	0.68 (0.18 – 2.53)
Negative	1.6 (1.2)	1.4 (1.1)	1.26 (0.70 – 2.26)

*$p < 0.05$

Note: separate regressions were computed for premorbid phase, context, and psychopathology variables with the predictors for each analysis entered simultaneously.

psychopathology) logistic regressions computed to analyze the prediction of the three outcomes by the selected prognostic variables.

Patients who are male, who had never been married nor lived with a stable partner at the time of first admission, or had a poor premorbid adjustment, were significantly more likely to suffer from residual symptoms at the outcome assessment. Poor insight at first-episode predicted further relapses (multiple psychotic episodes).

Consideration was given to creating a composite outcome measure based upon the three outcome variables. However, the outcome variables did not correlate significantly with one another and an additive combination (reverse scoring of number of episodes) not surprisingly produced an unreliable variable (coefficient alpha = 0.35). Furthermore, it was not entirely clear what the nature of the composite variable was. As an alternative, a principal component analysis was conducted on the three outcome variables resulting in one interpretable component that accounted for 44% of the variance. This continuous variable was transformed to remove positive skew and correlated with the prognostic variables. However, only level of insight at the first episode correlated significantly with the outcome factor (with good insight associated with the non-psychotic/less residual/fewer episodes pole of the factor). Therefore, the possibility of constructing a composite outcome measure did not turn out to be informative and suggests the need of qualitatively taking into account a profile associated with the 3 outcome measures.

Discussion

This longitudinal retrospective study corroborates the significant association of male gender, single status, and poor premorbid adjustment with poor outcome as defined by the subsequent presence of residual symptoms. Also, poor insight was associated with the occurrence of multiple psychotic episodes. Dimensions of psychopathology were not associated to any of the three outcome definitions. Outcome defined by final diagnosis could not be predicted by any of the selected baseline factors.

Predictors of outcome

Both biological and psychosocial hypotheses have been put forward to explain gender differences in psychosis outcome (in this study indicated by males showing more residual symptomatology). Some authors have suggested that gender does not have a direct effect on symptomatology, but rather that it is related to underlying differences on social behaviour patterns. Men's socially unfavourable illness behaviour (e.g., low acknowledgment of illness) would contribute to their poorer social course and overall outcome, whereas women's higher tendency to prosocial behaviour, such as cooperativeness and compliance, would influence a more favourable outcome[17]. This pattern would be consistent with research showing that schizophrenic women have a better social functioning than schizophrenic men, regardless of age of onset and symptomatology[18,19]. In the biological domain, factors such as later brain maturation in males are hypothesised to render them more vulnerable to prenatal and perinatal neurodevelopmental insults, which may cause structural brain abnormalities that, in the case of schizophrenia, have been associated to chronic negative symptoms (i.e., residual status) and premature onset. Additionally, it has been suggested that estrogens may have a protective role for females by facilitating an earli-

er maturation of the brain and, thus, making them less vulnerable to neurodevelopmental impairment[20]. Thus, men would be more prone to a hypothesized poor-prognosis, neurodevelopmental subtype of schizophrenia, for which early environmental brain insults play an important etiologic role, whereas women would be more prone to a hypothesized good-prognosis, affective subtype, probably more genetically related to affective disorders[21].

Individuals who were single at onset also showed poorer outcome (residual symptomatology). Although results are not reported, statistical tests showed us that this association was not due to age at onset, gender, premorbid adjustment, or continued contact with the mental health service. Marital status (ever married or lived with a stable partner) has been shown to have an independent onset-delaying effect, even more marked in males, which suggests that it is not earlier age of onset (related to male gender) what prevents individuals from getting married, but rather that being married is what delays onset, and it could as well prevent the emergence and chronicity of residual symptomatology[22].

Poor premorbid adjustment was significantly associated to residual symptomatology. This association seems to be developmentally meaningful, as residual symptoms could be understood as the continuation of the dysfunction already present before the psychotic exacerbation. Poor premorbid adjustment has been associated with more negative symptoms in the early course of illness, less improvement in negative symptoms, and overall poorer clinical and social functioning[23]; whereas good premorbid adjustment has been related to better clinical outcome, not only in chronic schizophrenia, but also in affective psychoses (i.e. bipolar disorder, major depression with psychosis)[23] and in psychotic disorders that are substance induced[24].

Poor insight was also associated to poor outcome, but this time defined by occurrence of multiple psychotic episodes, not by residual symptoms. This result is consistent with previous reports indicating that individuals experiencing a first episode of psychosis who have little insight are at increased risk of discontinuing their medication[25], disengaging from treatment[26], and thus increasing the chances of relapse. In this study, though, insight and continued contact with the mental health service showed no significant association.

In this study, opposite to what was expected, none of the three dimensions of psychopathology was associated with outcome. Outcome in psychosis might well be predicted by baseline psychopathology, particularly by negative symptomatology[27]. Negative symptoms (e.g. social withdrawal and anhedonia), rather than the characteristic positive and even disorganization symptoms, seem one of the strongest factors discriminating people who later develop schizophrenia [28,29]. Moreover, the association of negative symptoms at onset with later residual symptomatology appears significant and even stronger than their association with other dimensions of psychosis (e.g. psychoticism and disorganization) or dimensions of premorbid personality [30]. It might be that in the current study clinicians mostly focused on the recording of the more striking positive and disorganized symptoms, either because of an assessment bias or because negative symptoms at the time of first episode tend to be masked by those symptoms that cause severe behavioural disturbances.

Analysis of three outcome criteria

The three outcome criteria showed no significant associations among them, suggesting the relevance of using each of them to map with completeness the course and out-

come of first-episode psychosis. None of the selected sociodemographic, premorbid, first-episode or psychopathology variables could significantly distinguish between patients who developed schizophrenia from those who had a different kind of psychosis. Although the result could be due to insufficient statistical power, an alternative possibility is that none of these predictors is specifically associated with schizophrenic or non-schizophrenic psychoses, which would be consistent with research supporting that despite schizophrenia, schizoaffective disorder, and affective illness are prototypical entities, they share common features and a general set of aetiological and risk factors[31,32].

Presence of residual symptoms was the most distinguishable outcome from baseline indicators. Over time, the treatment of schizophrenia and related psychoses has evolved, making the improvement of psychosocial functioning and quality of life feasible aims, in addition to the amelioration of positive symptoms[33,34]. However, episode remission is not enough for recovery because persistent symptomatology, even if at a low level of severity, can interfere with behaviour and functioning, hindering patients' chances of social reintegration[35]. Thus, the possibility of identifying at first-episode patients likely to suffer residual symptomatology has significant implications for treatment and service planning.

The number of relapses could only be associated with baseline level of insight. Relapses have an important effect not only on the clinical, but also on the social functioning of patients[36]. Exacerbation of symptoms and hospitalizations might cause cumulative deterioration in functioning and a diminished ability to maintain employment and relationships[35]. Thus, early intervention treatment programs in psychosis work hardly to prevent relapses and to promote the maintenance of a stable clinical status[34]. Abundant research, replicated as well in the present study, highlights the important role of insight at illness onset as a prognostic factor[37].

In summary, schizophrenia and other related psychoses cannot longer be seen as a definite conviction to deterioration, as the course of the disorder has shown to be heterogeneous. Here, three alternative definitions of outcome were analysed: final diagnosis, presence of residual symptoms, and number of psychotic episodes. Findings indicate that being male, single marital status at onset, poor premorbid adjustment, and lack of insight are significant predictors of "poor" outcome in the early course of first-episode psychotic patients. Furthermore, these factors better distinguish patients' outcome when this is defined as presence of residual symptomatology. Thus, residual symptomatology stands out as an important measure of the outcome / course of the disorder and attention must be placed to its standardized assessment and follow-up.

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Chapter 3. Predictors of short-term course in Mexican first-episode psychosis patients

Abstract

Background and objectives: The identification of prognostic factors in patients with schizophrenia and related psychotic disorders should enhance our understanding of the aetiology of these disorders and improve their treatment. The first years following an initial episode of psychosis are a "critical period" for biological and psychosocial influences that affect future outcome. Both, short-term outcome and baseline predictors have been defined by different measures, making the comparison among studies difficult. Studies of the predictive value of baseline demographic and clinical characteristics in the Mexican population are still limited. Hence, the present study aims to: 1) replicate the prognostic value of selected patient characteristics previously related to the short-term course of psychosis in Mexican first-episode psychosis patients, and 2) retrospectively assess their prognostic value in the prediction of diagnosis, presence of psychotic residual symptoms, and number of psychotic episodes at least three-years later.

Methods: Information on baseline predictor variables (sociodemographic, premorbid phase, context of the first episode, dimensions of psychopathology) and clinical outcome (diagnosis, residual symptomatology, psychotic episodes) was obtained from the clinical records of 51 patients with a short-term course of psychosis and whose available follow-up period was at least 3 years long (mean=5.8, SD=2.1).

Results: Poor premorbid adjustment and hospitalization at first psychotic episode were significant predictors of a schizophrenia diagnosis. Lower educational level and an insidious type of onset significantly predicted the presence of residual symptoms. Hospitalization at

first psychotic episode and higher scores on the psychotic dimension at onset significantly predicted subsequent psychotic episodes.

Discussion: Low educational level increased the risk of residual symptoms, possibly because it hinders treatment continuity. Poor premorbid adjustment was related to a schizophrenia diagnosis at the follow-up assessment, supporting previous findings of their high ratings for premorbid impairment, including social withdrawal and dysfunctional peer relationship. Insidious onset was predictive of persistent residual symptoms; an association possibly mediated by the duration of untreated psychosis (DUP). Being hospitalized at first episode was a significant prognostic factor for schizophrenia diagnosis and multiple psychotic episodes; the severity and nature of symptoms at first episode that require hospitalization might account for these associations. Replicating previous findings, multiple-episode patients scored significantly higher than the single-episode patients on the psychoticism dimension. Most baseline factors did not predict diagnosis. This seems congruent with a dimensional view of psychosis suggesting that even though schizophrenic and non-schizophrenic psychoses are classified as separate families of disorders, they exist along a continuum of psychosis that crosses diagnostic boundaries, sharing aetiological and risk factors. Currently, both the amelioration of severe psychotic symptoms and the improvement of psychosocial functioning and quality of life are feasible aims. Symptom exacerbation and hospitalizations might cause cumulative deterioration and impair the patient's social reintegration. Thus, relapse prevention is an important objective in treatment. The identification of reliable predictors of illness course has significant implications for treatment and service planning.

Conclusions: The predictive value of several factors was replicated in this sample of patients with psychotic illnesses, although predictors seem to relate differently to the three

short-term course measures. Comprehensively mapping the development and outcome of the first episode of psychosis requires the use of standardized measurement tools and the longitudinal assessment of multiple outcome measures.

Introduction

Schizophrenia is one of the most disabling mental disorders; however, it can no longer be conceived as a hopeless and inevitable pathway to deterioration[1]. The course following a first psychotic episode is clearly heterogeneous[2]. Although schizophrenia is typically viewed as a chronic and episodic disorder, between 12-22% of patients never relapse or experience residual symptoms after their first episode of psychosis[3,4].

Although the course of psychosis is heterogeneous (whether treated or untreated), its presentation seems most severe and disturbing during the onset and the first years of illness[5]. Eventually, between two and five years after the first episode, psychotic disorders appear to plateau and follow a more stable course[3]. These first years following the initial episode of psychosis (the so-called "critical period") are viewed as a crucial time during which biological and psychosocial changes have decisive effects on the patient. Characteristics assessed during the critical period provide promising predictors of patients' long-term outcome[5]. Moreover, evidence[6] indicates that the course and the severity of psychotic illnesses are predictable by year 3 (including on average, 12 months of untreated psychosis)[5].

Current early intervention programs and research are based on the premises that this "critical period" influences the long-term course of psychosis and that the critical period is particularly malleable to intervention[5]. Early intervention efforts aim at reducing suicide and relapse rates, preventing social and cognitive deterioration, and ameliorating persisting symptoms[7,8]. These programs have a greater impact on illness course and outcome when applied in the early phase of the disorder[9]. The identification of characteristics that predict clinical and functional outcomes in newly diagnosed psychosis patients should enhance our understanding of such disorders and provide guidance for treatment.

The complexity and heterogeneity of schizophrenia and related psychoses require reliable and valid measures of outcome to capture patients' functioning and impairment over time[3]. Schizophrenic psychoses show, compared to schizoaffective and affective psychoses, a poorer global outcome, more deteriorating course, greater presence of negative symptoms, and more persistent impairments in several aspects of social life, such as communication and cognitive functions[10,11]. A variety of clinical, functional and quality of life measures have been used to assess outcome[7], but this diversity makes the comparison among studies difficult[8].

The most widely used outcome is diagnosis, which can be reliably established after approximately six months of onset of psychosis[12]. Illness course is also extensively reported as an outcome measure, varying from a full recovery to a chronic deteriorating course[12]. Some studies, simplifying the course of psychosis as "poor" or "good", have defined course by relying either on the presence of residual symptoms[4,13] or on the occurrence of subsequent relapses into acute psychosis[14]. However, there is a shortage of studies comparing the impact of using either one or the other, particularly on their ability to evaluate the utility of putative prognostic indicators.

Studies have also differed in the premorbid and first-episode factors analysed as possible predictors of outcome. Sociodemographic variables, clinical features, premorbid characteristics, context of presentation of the first episode of psychosis, and type of treatment have been the most common factors related to short- and long-term prognosis. Literature on this topic is abundant, suggesting that various factors such as early age at onset, male gender, single status, poor premorbid adjustment, lack of insight, and symptom severity at onset are highly related to poor outcome[3,15], although not all findings concur[7,8].

Studies with Mexican first episode psychosis patients indicate that this population does not differ significantly in its baseline demographic and clinical characteristics when compared to populations from developed countries[16]. Although the predictive value of the DUP has been replicated in the Mexican population in a one-year follow-up study [17], the predictive value of other first episode psychosis characteristics after the critical period needs study.

Research so far has identified important predictors of outcome. However, there is a shortage of studies analysing the association of premorbid and first episode variables with different outcome definitions. Furthermore, studies of short-term course predictors in Mexican first-episode psychosis patients are also limited. Therefore, this study aims to: 1) replicate the prognostic value of factors (sociodemographic, premorbid, context of the first psychotic episode, and psychopathology dimensions) previously related to the short-term course of psychosis in retrospectively assessed Mexican first-episode psychosis patients, and 2) assess their prognostic value in the prediction of final diagnosis, presence of psychotic residual symptoms, and number of psychotic episodes.

Methods

Participants

This is a retrospective case series study focusing on the short-term course of psychosis in a cohort of patients who have received mental health care in the adult service of the Hospital Psiquiátrico Yucatán (HPY). The HPY is a public institution located in the city of Merida, Mexico, that offers inpatient and outpatient care to all patients in need. The HPY has a broad catchment area that includes patients from neighbouring states (e.g.

Campeche, Quintana Roo); however, for this study, sampling was restricted to the inhabitants of the city of Merida. Data were collected through the review of all clinical files after obtaining formal authorization and ethical approval from the Hospital Committee. Additional inclusion criteria were: 1) occurrence of a first episode of psychosis between 1999 and 2005; 2) age at onset 16-45 years; and 3) a primary current DSM-IV-TR[12] diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, delusional disorder, brief psychotic disorder, or psychosis not otherwise specified. Exclusion criteria were: 1) psychoses of affective, organic, or toxic type, 2) an evident intellectual disorder, and 3) no follow-up information available.

An initial random sample of 111 cases was selected. LG was responsible for the examination of the clinical histories and the review of current diagnoses according to DSM-IV-TR criteria[12] as some might have changed since onset. Nine cases were excluded: 3 affective psychoses, 2 organic psychoses, 2 toxic psychoses, 1 missing file, and 1 case with a duplicated file. Furthermore, 51 cases with a follow-up time period shorter than 3 years were omitted. The final sample of 51 short-term course psychosis patients included 23 men and 28 women, with an average age at first episode of 28.1 (SD=7.6). All cases in the sample were followed for at least 3 years (mean=5.8, SD=2.1) and had received antipsychotic medication.

Materials

The predictors identified at the first episode included: 1) sociodemographic data (gender, marital status, educational level, occupational status), 2) premorbid phase characteristics (premorbid adjustment, identified trigger, type of onset), 3) features of the context of the first episode (hospitalization, substance abuse, level of insight), and 4) dimensions of psychotic psychopathology. Classification of premorbid adjustment was

based on the medical record information about possible i) learning, ii) behavioural, iii) emotional or iv) social difficulties present at any time before the first psychotic episode. Based on the available information from clinical files, premorbid adjustment was categorized as poor or good. For psychopathology, the recorded presence of symptoms corresponding to each of its three dimensions was rated by translating the clinical records information into the most representative Positive and Negative Syndrome Scale (PANSS)[18] items based on the criteria provided by Andreasen et al.[19]. The psychoticism dimension included recorded symptoms of delusions, unusual thought content and hallucinatory behaviour; the disorganization dimension included symptoms of conceptual disorganization, mannerism or posturing; the dimension of negative symptoms included blunted affect, social withdrawal and lack of spontaneity.

Outcome was classified according to three criteria. First, DSM-IV-TR[12] last available diagnoses were dichotomized into: 1) schizophrenia, and 2) other psychoses. A second criterion grouped cases as: 1) with residual symptoms, or 2) with no residual symptoms, at the time of the outcome assessment. A third criterion considered the number of psychotic episodes recorded during the follow-up period (including the initial episode), classifying cases as: 1) single episode, or 2) multiple episodes.

First, Pearson correlations were run to explore possible associations among the three outcome criteria. Next, separate regressions were computed for sociodemographic, premorbid phase, context of first psychotic episode, and psychopathology variables with the predictors for each analysis entered simultaneously. Statistical analyses were computed with SPSS, version 15[20].

Results

Table 1 presents the results of the binary logistic regressions predicting the three outcome measures.

Current diagnosis and number of psychotic episodes were significantly correlated ($r = +0.32$, $p = 0.02$); that is, patients with schizophrenia were likely to have experienced more than one psychotic episode. The presence/absence of residual symptoms was not significantly associated with either current diagnosis ($r = -0.06$) or to the number of psychotic episodes ($r = +0.05$).

Sociodemographic variables

Sociodemographic factors at onset were not associated with a diagnosis of schizophrenia or reports of relapse at the follow-up. However, lower educational level at onset was associated with heightened risk of residual symptoms at the follow-up.

Premorbid phase variables

Poor premorbid adjustment was significantly associated with a subsequent diagnosis of schizophrenia. An insidious onset was associated with residual symptoms, and oddly with those who did not relapse (single episode). Nevertheless, it must be pointed out that 11 of the 19 patients (57.9%) with a single episode presented residual symptoms; furthermore, all 11 had an insidious onset.

Context of first psychotic episode

Patients who were hospitalized during their first psychotic episode were more likely to have a diagnosis of schizophrenia and to relapse (multiple episodes) by the follow-up

assessment. Substance abuse did not appear as a significant predictor of outcome, although only a small percentage of patients reported this abuse (n=6, 11.8%). Surprisingly, poor insight at the first-episode identified patients who subsequently were diagnosed with psychoses other than schizophrenia and who did not relapse.

Dimensions of psychopathology at onset

Psychotic symptoms present at onset significantly related to multiple episodes, whereas disorganization related to absence of residual symptoms. Negative symptoms did not predict any of the three outcome measures.

Table 1. Logistic regression analyses of baseline variables predicting the three different outcome criteria.

Outcome: Last diagnosis

VARIABLE **Category / Range**	**Schizophrenia** **n = 34** **Mean (SD) or %**	**Other psychosis** **n = 17** **Mean (SD) or %**	***Odds Ratio*** ***(95% CI)***
1. SOCIODEMOGRAPHIC VARIABLES			
Age at onset (years) (n=51)	27.3 (7.8)	29.7 (7.3)	1.04 (0.97 – 1.13)
Gender (n=51) Male / Female	52.9% / 47.1%	29.4% / 70.6%	2.70 (0.78 – 9.35)
Marital status (n=46) Single / ever married	69.0% / 31.0%	41.2% / 51.8%	3.18 (0.91 – 11.03)
Educational level (n=49) Basic / Medium or higher	53.1% / 46.9%	52.9% / 47.1%	1.01 (0.31 – 3.27)
Work or study (n=47) No /Yes	21.9% / 78.1%	13.3% / 86.7%	1.82 (0.33 – 10.05)
2. PREMORBID PHASE VARIABLES			
Premorbid adjustment (n=51) Poor / Good	55.9% / 44.1%	17.6% / 82.4%	**8.11*** **(1.81 – 36.42)**
Identified trigger (n=49) Yes / No	55.9% / 44.1%	52.9% / 47.1%	1.23 (0.34 – 4.54)

Type of onset (n=51) Insidious / Sudden,Acute	70.6% / 29.4%	82.4% / 17.6%	0.28 (0.06 – 1.36)
3. CONTEXT OF FIRST PSYCHOTIC EPISODE VARIABLES			
Hospitalization (n=51) Yes / No	52.9% / 47.1%	29.4% / 70.6%	**4.00*** **(1.01 – 15.85)**
Substance abuse (n=51) Yes / No	11.8% / 88.2%	11.8% / 88.2%	1.40 (0.19 – 10.08)
Level of insight (n=51) Poor / Partial	55.9% / 44.1%	82.4% / 17.6%	**5.20*** **(1.14 – 23.75)**
4. PSYCHOPATHOLOGY SYMPTOMS			
Psychoticism (n=51)	2.38 (0.78)	2.00 (0.94)	0.56 (0.26 - 1.21)
Disorganization (n=51)	0.41 (0.56)	0.29 (0.59)	0.75 (0.22 – 2.53)
Negative (n=51)	0.56 (0.79)	0.29 (0.59)	0.49 (0.18 – 1.31)

Outcome: Presence of residual symptoms (R.S.)

VARIABLE **Category / Range**	**With R.S.** **n = 31** **Mean (SD) or %**	**With NO R.S.** **n = 20** **Mean (SD) or %**	***Odds Ratio*** ***(95% CI)***
1. SOCIODEMOGRAPHIC VARIABLES			
Age at onset (years) (n=51)	29.1 (7.8)	26.4 (7.4)	0.95 (0.88 - 1.03)
Gender (n=51) Male / Female	51.6% / 48.4%	35.0% / 65.0%	1.98 (0.62 – 6.31)
Marital status (n=46) Single / ever married	60.7% / 39.3%	55.6% / 44.4%	1.24 (0.37 - 4.10)
Educational level (n=49) Basic / Medium or higher	66.7% / 33.3%	31.6% / 68.4%	**4.33*** **(1.27–14.82)**
Work or study (n=47) No /Yes	25.8% / 74.2%	6.3% / 93.8%	5.22 (0.59–46.07)
2. PREMORBID PHASE VARIABLES			
Premorbid adjustment (n=51) Poor / Good	51.6% / 48.4%	30.0% / 70.0%	1.78 (0.48 – 6.60)
Identified trigger (n=49) Yes / No	54.8% / 45.2%	55.0% / 45.0%	0.97 (0.27 – 3.48)
Type of onset (n=51) Insidious / Sudden,Acute	90.3% / 9.7%	50.0% / 50.0%	**8.28*** **(1.85–37.13)**

3. CONTEXT OF FIRST PSYCHOTIC EPISODE VARIABLES			
Hospitalization (n=51) Yes / No	45.2% / 54.8%	45.0% / 55.0%	1.38 (0.40 – 4.68)
Substance abuse (n=51) Yes / No	16.1% / 83.9%	5.0% / 95.0%	0.24 (0.02 – 2.42)
Level of insight (n=51) Poor / Partial	74.2% / 25.8%	50.0% / 50.0%	0.32 (0.09 – 1.11)
4. PSYCHOPATHOLOGY SYMPTOMS			
Psychoticism (n=51)	2.13 (0.89)	2.45 (0.76)	1.33 (0.62 – 2.86)
Disorganization (n=51)	0.23 (0.43)	0.60 (0.68)	**3.31*** **(1.02–10.78)**
Negative (n=51)	0.45 (0.68)	0.50 (0.83)	1.32 (0.58 – 3.03)

Outcome: number of psychotic episodes

VARIABLE **Category / Range**	**Multiple episodes** **n = 32** **Mean (SD) or %**	**Single episode** **n = 19** **Mean (SD) or %**	***Odds Ratio*** ***(95% CI)***
1. SOCIODEMOGRAPHIC VARIABLES			
Age at onset (years) (n=51)	26.8 (7.6)	30.2 (7.5)	1.06 (0.98 – 1.15)
Gender (n=51) Male / Female	43.8% / 56.3%	47.4% / 52.6%	0.86 (0.28 – 2.70)
Marital status (n=46) Single / ever married	60.7% / 39.3%	55.6% / 44.4%	1.24 (0.37 - 4.10)
Educational level (n=49) Basic / Medium or higher	56.7% / 43.3%	47.4% / 52.6%	1.45 (0.46 - 4.61)
Work or study (n=47) No /Yes	13.8% / 86.2%	27.8% / 72.2%	0.42 (0.10 - 1.82)
2. PREMORBID PHASE VARIABLES			
Premorbid adjustment (n=51) Poor / Good	46.9% / 53.1%	36.8% / 63.2%	2.16 (0.62 – 7.55)
Identified trigger (n=49) Yes / No	56.3% / 43.8%	52.6% / 47.4%	1.22 (0.37 – 4.07)
Type of onset (n=51) Insidious / Sudden,Acute	65.6% / 34.4%	89.5% / 10.5%	**0.18*** **(0.03 – 0.97)**

3. CONTEXT OF FIRST PSYCHOTIC EPISODE VARIABLES			
Hospitalization (n=51) Yes / No	53.1% / 46.9%	31.6% / 68.4%	**3.78*** **(0.99–14.39)**
Substance abuse (n=51) Yes / No	9.4% / 90.6%	15.8% / 84.2%	2.69 (0.41–17.65)
Level of insight (n=51) Poor / Partial	56.3% / 43.8%	78.9% / 21.1%	**4.04*** **(0.98–16.60)**
4. PSYCHOPATHOLOGY SYMPTOMS			
Psychoticism (n=51)	2.56 (0.62)	1.74 (0.93)	**0.23*** **(0.08 – 0.62)**
Disorganization (n=51)	0.41 (0.56)	0.32 (0.58)	1.68 (0.47 – 6.05)
Negative (n=51)	0.38 (0.55)	0.63 (0.96)	1.60 (0.65 – 3.98)

Discussion

Baseline characteristics are useful predictors of short-term outcome in psychosis, yet they relate differently to particular outcome measures: schizophrenia was predicted by poor premorbid adjustment and hospitalization, residual symptoms by lower educational level and an insidious onset, whereas multiple psychotic episodes were related to hospitalization and psychoticism.

Predictors of outcome

Sociodemographic variables

The mean age at psychosis onset of this sample is higher than that of some other first-episode studies, although it is consistent with other previous findings obtained in first-episode Mexican patients[21]. Thus, there seems to be a significant range in terms of age at onset, possibly due to sociological differences between regions of the country or to differences in the access to mental health care. In any case, further research should examine

how differences in age at onset might impact the relative importance of different predictors of later outcome.

An earlier age at onset, male gender, single marital status, lower educational level, and no daily occupation, among other sociodemographic factors, have been associated with a poorer outcome in first-episode psychosis patients[4,15]; nevertheless, in this study they were not significantly related to diagnosis or relapses. A low educational level at onset did increase the risk of residual symptoms -- possibly because it hinders treatment continuity. A review found that high education and good social functioning of patients with psychosis were associated with good adherence to treatment[22].

Premorbid phase variables

Poor premorbid adjustment has been associated with more negative symptoms in the short-term course of illness, less improvement in negative symptoms, and overall poorer clinical and social functioning. On the other hand, good premorbid adjustment has been related to better clinical outcome, not only in chronic schizophrenia, but also in affective psychoses[23], and in psychotic disorders that are substance induced[24]. Premorbid adjustment appears to be an important predictor of diagnosis. First-episode psychotic patients who later develop schizophrenia compared to those who develop bipolar disorder have not only shown more persistent positive and negative symptoms at follow-up, but also higher ratings of premorbid impairment, including social withdrawal and dysfunctional peer relationships[25,26].

In the present study, an insidious onset significantly predicted residual symptoms. This association might be mediated by DUP. An acute onset relates to shorter DUP in patients[27], possibly because the sudden changes and appearance of psychotic symptoms

might well be more noticeable to patients and relatives, prompting treatment seeking. On the other hand, an insidious type of onset has been found predictive of longer DUP[27] and poorer global psychopathological and psychosocial outcome[28]. Although an insidious type of onset usually relates to a poor outcome, in our study it was surprisingly related to single-episode outcome. However, this may simply reflect the relatively short follow-up period. Previous research has shown that relapses in the short-term course of illness are not related to the type of onset[15,28] though they seemed related to DUP and to the delay in intensive psychosocial treatment[28].

Context of first psychotic episode

The study of early psychosis has used hospitalization as an important outcome measure analysing predictive factors of re-hospitalization[29,30], time spent in hospital[31], and time between hospitalizations[30]. Here, we considered being hospitalized at first episode as a prognostic factor, resulting in significant risk for schizophrenia diagnosis and presence of multiple episodes at the reassessment, but not for residual symptoms. The severity and nature of symptoms at first episode that require hospitalization might account for the association with a later diagnosis of schizophrenia. It has been suggested that lacking objective measures of symptoms, hospitalization can be used as a "proxy" measure of a psychotic episode[32] usually characterised by a significant deterioration due to positive symptoms. For this study, we considered hospitalization as a sign of severity and it was a significant prognostic factor of short-term course. Multiple episodes were also related to hospitalization at first episode. In a retrospective study, Rosen and Garety[4] found that hospitalization at first episode turned out to be a significant predictor only when the outcome definition took into account relapses and not only residual symptoms. Being

hospitalized and under supervised treatment might have a more counteracting effect on residual symptoms, but not on the likelihood of relapse.

Poor insight has been associated with poorer cognitive functioning[33], and increased risk of relapse[15,34] and readmission[34]. On the other hand, good insight of illness has been related to higher levels of depression[33,35]. Furthermore, most evidence supports an association throughout the first years after an initial episode between poor insight and increased symptoms[33,35], though not all findings concur[34]. Various studies support the assumption of a causal chain connecting poor insight with poor treatment adherence and thus with impaired outcome and functioning; although this seems apparent during the treatment phase, the association with long-term adherence remains unclear[36]. In our study, insight was not considered at present but at the time of the first episode. Contrary to expectations, poor insight was significantly associated to other non-affective psychoses and single-episode outcome. These results are not easy to explain based on the information available and important factors that might mediate this effect (e.g. severity and nature of symptoms at onset, perception of condition as a mental disorder) must be considered on standardized prospective assessments.

Dimensions of psychopathology at onset

None of the three dimensions of psychopathology were associated with subsequent diagnoses. Although the result could be due to insufficient statistical power, an alternative possibility is that the nature of psychotic psychopathology at onset, though more severe in schizophrenic psychoses, is not specifically associated with later diagnoses. This would be consistent with research indicating that schizophrenia, schizoaffective disorder, and affective illness share common features and a general set of aetiological and risk factors[37,38].

Psychotic (positive) symptoms were more common than disorganized and negative symptoms at the onset for the whole sample and for all groups. This was not surprising, given that positive symptoms typically herald the onset of a first, acute episode, and because for many patients negative symptoms develop as part of a chronic course of the disorder. The psychotic dimension was only significant when predicting multiple- vs. single-episode patients, with the former group scoring higher. A 7-year follow-up of schizophrenic outpatients showed that lower positive symptoms were characteristic of those patients who did not relapse[39].

Only a few patients displayed disorganized symptoms in their clinical histories, although surprisingly those with higher scores were more likely to be part of the non-residual symptom group. Unfortunately, the retrospective nature of the study restricts information to explore further the prognostic nature of these results.

For our sample, negative symptoms were not significant predictors of outcome. Negative symptoms at onset tend to be associated with residual symptoms more than other dimensions of psychosis or premorbid personality[40]. Moreover, in a retrospective study comparing groups of patients with single or multiple psychotic episodes, negative symptoms at first contact was the only dimension of psychopathology that stood out as a significant prognostic factor[4]. However, we did not replicate this finding. However, this may reflect that information on negative symptoms was not as readily noted and recorded as were the more striking positive and disorganized symptoms that typically signal the onset of a psychotic episode. Furthermore, negative symptoms at the time of first episode might be masked by those symptoms that cause severe behavioural disturbances, or they might evolve later in the course of illness.

Analysis of outcome criteria

Among the three selected short-term course measures, only diagnosis and number of episodes were significantly related, as most patients presented schizophrenia and had suffered multiple psychotic episodes. However, their only common prognostic factor of "poor outcome" was hospitalization. Hence the importance of using different measures to map with completeness the course and outcome of first-episode psychosis.

Poor premorbid adjustment and hospitalization at first episode were the only significant predictors of schizophrenia; hence, at first episode, clinical assessment must place particular attention to patients who require hospitalization and who have presented previous difficulties, as they are in higher risk to develop schizophrenia. Most baseline factors did not predict diagnosis. Even though schizophrenia implies a general poorer outcome than other psychoses, both affective and non-affective[10,11], whether they differ etiologically is an issue still debated[37,41]. Some results suggest that even early in its course, schizophrenia is distinguishable not only from affective psychoses[42], but also from schizoaffective disorders[43]. Nevertheless, other findings suggest that schizophrenia has some overlapping features with schizoaffective disorder (e.g. cognitive performance)[41] and even with bipolar disorder[37]. A dimensional view of psychosis suggests that even though schizophrenic and non-schizophrenic psychoses are seen as distinct entities, they would exist along a continuum of psychosis that crosses diagnostic boundaries and would have in common aetiological and risk factors[38]. Moreover, whether schizophrenia can be predicted at onset has also important clinical implications, as it involves that it might not be appropriate to make predictions at first–episode regarding diagnosis. As it is well-known, stating a premature diagnosis of schizophrenia can have adverse consequences for clinicians

(e.g., therapeutic nihilism) and patients (e.g., hopelessness, stigma, demoralisation and depression).

A lower educational level and insidious onset were significantly related to patients with residual symptoms. These factors stand out as robust baseline predictors that hold predictive value over-and-above methodological similarities and differences among studies. The amelioration of core signs and symptoms is indispensable but not enough for recovery because persistent symptomatology, even if at a low level of severity, can interfere with behaviour and functioning, hindering patients' social, educational, and occupational development, and their chances of social reintegration[44]. Thus, the possibility of identifying patients at first-episode likely to suffer residual symptomatology has significant implications for treatment and service planning.

Higher functioning, lower positive symptoms, higher ability in self-care and higher IQ relate to single episode patients[39], whereas poor insight[15], poorer premorbid childhood functionality and noncompliance to the treatment highly contribute to relapse risk[45]. In the present study, hospitalization at first episode and psychotic symptoms significantly predicted multiple psychotic episodes. Relapses may have an important effect not only on the clinical, but also on the social functioning of patients. Exacerbation of symptoms and hospitalizations might cause cumulative deterioration in functioning and a diminished ability to maintain employment and relationships[44]. Thus, early intervention as well as standard treatment programs in psychosis must work to prevent relapses and to promote the maintenance of a stable clinical status[46].

Limitations

Though the study of the course of psychosis should ideally rely on a prospective design, a retrospective study provides valuable information over a period of time and is recommended as a sensible starting point when research on this topic is developing at a new site. The number of baseline measures had to be restrained depending on the availability from case-notes; this might be useful to draw attention on what factors clinicians pay attention to in daily practice, as well as on how they record information.

Subsequent research may include patients who are inhabitants of other communities, which could yield interesting data on the search of mental health care, availability of services and awareness of illness. Broadening the inclusion criteria to other types of psychosis such as affective, toxic and organic, might also provide useful information of the vast psychosis spectrum. In a prospective study, a thorough exploration of the premorbid phase, the onset characteristics, and clinical family background at first-psychotic episode would certainly enrich the possibility of significant and generalizable findings.

Conclusions

Historically, schizophrenia and related psychoses have been characterized erroneously as necessarily having a deteriorating course. However, the course of these disorders is heterogeneous with many patients showing good recovery. Three alternative definitions of short-term course were retrospectively analyzed in a Mexican sample of first-episode psychosis patients: final diagnosis, presence of residual symptoms, and number of psychotic episodes. Findings indicate that some baseline variables are useful predictors for this particular population, and they appear to relate differently to particular outcome measures. Given that not all predictors relate similarly to different outcome measures attention must be placed to the standardized and discreet assessment of varied predictors and outcome indexes.

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Chapter 4. Epilogue. Summary of findings and directions for future research

Studies of the early stages of psychosis

As introduced in Chapter 1, the concept of psychosis has significantly evolved, triggering the emergence of innovative early intervention programs. Current efforts aim at identifying those individuals at hight risk for psychosis onset in order to provide them with immediate and intensive treatment. As mentioned earlier, this new approach assumes a clinical staging diagnosis, which views disease as progressive states along a continuum, opening the possibility to encompass a broader range of clinical phenotypes from general to clinical populations (McGorry, 2007). Early intervention relies on evidence supporting that psychosis does not imply an ineludible pathway to deterioration. The course of psychotic illness has shown an ample range of patterns, from full recovery to chronic course (APA, 2000). Furthermore, the period of 3 to 5 years before and after the first psychotic episode, named the "critical period", is viewed as a crucial time to predict and influence the long-term trajectory of the psychosis (Birchwood, 2000). Therefore, the goal is to provide diagnosis and treatment at any point along the continuum of psychosis (prodromal, first episode, short-term course) assuming that immediate and intensive interventions will be both more effective and less harmful than treatments delivered later in the course (McGorry, Killackey, & Yung, 2008). In consequence, there is growing interest for studying psychosis in its early stages, exploring factors that might signal vulnerability for psychosis onset and/or predict illness course at short term.

Indicators of vulnerability to psychosis

Appendix 1 presented a study conducted with an adolescent sample from the general population that explored the presence of trait and symptom-like psychosis features and their association with atypical handedness patterns. Mixed handedness (using different hand for different actions) was more strongly related to psychosis-proneness than pure-left handedness (using left hand for all actions). Furthermore, this association was more evident in those who reported to use "either" hand for any action. Results support an association between a shift away from pure dextrality and psychosis-proneness, resembling the pattern observed in schizophrenia patients and their relatives, considered at risk for psychosis. The main finding of this study is that *both trait and symptom-like measures of positive psychosis-proneness are associated with patterns of atypical handedness, particularly with ambiguous handedness across primary actions.*

These results reinforce the notion of continuum between the nonclinical and the clinical psychosis phenotype, with atypical lateralization, expressed through hand preference, as an underlying factor of both schizophrenia and psychosis-proneness. Possible paths for further research could explore the effect of applying a more flexible criterion of inconsistent hand use across time for non-clinical samples. Moreover, the association of atypical handedness for primary and non-primary actions with psychosis-proneness seems an issue worth to test independently.

Predictors of the short-term course outcome of psychosis

Chapters 2 and 3 presented two studies following similar methodology and which explored reliable predictors of the short-term course of a first episode of psychosis in independent samples from Barcelona (Spain) and Merida (Mexico). First of all, both studies

provided evidence of the heterogeneity in the early course of psychosis, with a number of patients even showing a complete recovery. Furthermore, the predictive value of some factors previously associated to the short-term course of psychosis was replicated. Even though results from both samples vary, they support the notion that prodromal and onset features can be reliable predictors of short-term outcome and that they relate differently to the three most widely used outcome criteria: diagnosis, residual symptomatology and relapse course. The main finding of the studies is that *baseline factors can reliably predict the short-term outcome of first-episode psychosis patients. Nevertheless, their predictive value varies with the selected outcome criteria and origin of participants, which indicates the need to take such differences into account and the fact that they might explain some of the inconsistent findings reported in the literature.*

Through the review of clinical records of patients with a short-term course of first-episode psychosis from clinical settings from the cities of Barcelona (Spain) and Merida (Mexico) information on baseline predictors and clinical outcome was obtained. Male gender, single marital status, poor premorbid adjustment and poor insight appeared to predict poor outcome in the Spanish sample (Chapter 2). On the other hand, lower educational level, poor premorbid adjustment, insidious onset, hospitalization at first psychotic episode and higher scores on the psychotic dimension at onset seemed to predict poor outcome in the Mexican sample (Chapter 3). Furthermore, these predictors did not equally relate to the three outcome criteria: residual symptoms, relapses and diagnosis.

Despite numberous differences between these two research sites, results replicated the value of some first-episode psychosis predictive factors, while providing evidence of how their effect varies across cultures (significant predictors were not the same for both samples, and also relate differently to outcome measures).

Due to the retrospective nature of the design and various uncontrollable differences between research sites (e.g. sociodemographic circumstances, mental health service conditions, clinical record format) which could have biased the results, it was preferred not to combine samples.

Further lines of research might aim at conducting prospective designs involving the assessment of samples from different cultures in parallel. Awareness of predictors of poor outcome in psychosis is an invaluable tool for clinical intervention planning; however, it should always be kept in mind that psychosis clinical manifestations, diagnosis and treatment are subject to variations across cultures.

Quality of Life of patients and their relatives: A feasible aim in treatment

It is generally accepted that the course of psychosis since illness onset is highly heterogeneous and the concept of the psychosis continuum is gaining acceptance. Another important change in the perspective of outcome in mental health has also occurred. Remission and relapse have been two extensively used measures of outcome, but alternatively other measures of a functional nature have been increasingly capturing the interest of research in mental health (Malla & Payne, 2005). The development of atypical antipsychotic drugs has allowed a conceptual extension of therapeutic outcome criteria to adopt more positive and wide-reaching measures such as quality of life (Lambert & Naber, 2004).

Furthermore, the functional domain of psychosis outcome embraces not only the patients themselves but also their primary caregivers. Family environment plays an important role in the onset and course of psychosis (Barbato & D' Avanzo, 2000), but caregivers' functioning might also be affected in the context of the psychotic illness of a

relative with lack of social support, economic burden, illness course and family relationships problems (Caqueo-Urízar, Gutiérrez-Maldonado, & Miranda-Castillo, 2009). Given that most patients live with their parental or own family, further research is needed to explore the quality of life and related issues not only of patients but also of their daily carers.

Therefore, quality of life of both patients and relatives has become an important aim in mental health treatment. In regard to quality of life in the early course of psychosis two studies were presented, one addressing the quality of life of patients and the other the quality of life of their main caregiving relatives.

Appendix 2 presented a study that provides supporting evidence of a general decrement in the QoL of short-term course psychosis patients. Patients with a short-term course of illness after the first psychotic episode were interviewed in order to assess their quality of life and clinical course (diagnosis, relapses and residual symptoms). The main finding is that r*esidual symptoms, rather than subsequent relapses or diagnosis per se, have a deteriorating effect on the quality of life of short-term course psychosis patients. This effect seems fully mediated by their emotional representation of illness and functioning.*

Patients' skills and emotional responses towards the disorder need to be targeted in the clinical context in order to achieve a satisfactory level of personal and social reintegration after experiencing a psychotic disorder. Patients should be provided not only information about the disorder, but also emotional and coping skills training to help them elaborate the experience of psychosis and ease social reintegration.

Further exploration of this issue should bring into analysis the clinical status of patients, paying attention to the dimensionality of those residual symptoms that might overlap with the emotional representation of illness (e.g. anxiety, depression). Moreover, it

would be worth exploring possible particular protective factors of quality of life in Mexican patients.

Appendix 3 presented a study on relatives of patients with a short-term course of psychosis after the first-episode. Relatives were interviewed in order to assess their levels of expressed emotion, burden and quality of life. The main finding is that r*elatives' illness perception and psychological distress predicted their levels of expressed emotion, burden and quality of life better than the patients' clinical status.*

These findings promote attentiveness to the physical and mental well-being of the patients' caregivers. Families cannot be taken into consideration exclusively as "relapse triggers". Families have assumed the responsability of providing patients with daily informal care and relatives find themselves also in need of psychological support. Caregiving relatives' well-being is essential for themselves, the patients and other family members.

Additional research might explore specific dimensions of expressed emotion, burden and quality of life and their predictors. Other important factors to consider would be the families' expectations of their ill relatives' functioning from a cultural framework, satisfaction with mental health services, as well as indicators of objective quality of life.

Contributions and limitations

The present doctoral dissertation along with the appendixes 1 to 3 has presented different studies in the context of three important changes in the perspective that has guided the study of schizophrenia and related psychoses: 1) schizophrenia is a point of the psychosis continuum, 2) the course of psychosis is heterogeneous and can be fairly predicted and influenced in its early phase, and 3) psychosis outcome has expanded beyond

symptom remission in order to embrace patients' quality of life and even that of their relatives.

Evidence provided in Appendix 1 supports the hypothesis of the psychosis continuum by showing that a well-established risk factor for schizophrenia, neurodevelopmental disturbance, defined by the proxy phenotype of atypical handedness, is meaningfully associated with trait and symptom-like psychotic experiences in individuals from the general population, mirroring the associations reported in clinical schizophrenia. Thus, non-clinical psychosis phenotypes seem to be reliably studied in non-clinical populations.

Evidence from Chapters 2 and 3 supports the heterogeneity of the course of psychosis, and how early factors from the so-called critical period can fairly predict early outcome, while showing that the specific predictor-outcome associations vary accross cultures.

Appendixes 2 and 3 provide evidence of the diminishing effect of psychosis perception in the QoL not only of patients' but also of their relatives, an issue of growing interest in the study of functional measures in mental health.

Schizophrenia and related psychoses are certainly an ample area of study. Naturalistic studies and retrospective designs always imply the difficulty to determine causal factors and an undesirable lack of control of incidental variables. Given these limitations, the present work aims to offer a partial and insufficient but useful contribution to support the new perspectives on the conceptualization of psychosis and its outcome.

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Summary

Chapter 1 provides a general outline of schizophrenia and other psychoses previous to the main discussion of three important changes in the perspective that have guided the study of these syndromes: 1) schizophrenia is a point of the psychosis continuum, 2) the course of psychosis is heterogeneous and can be fairly predicted and influenced in its early phase, and 3) psychosis outcome has expanded beyond symptom remission in order to embrace patients' quality of life and even that of their relatives.

Chapter 2 reports a study replicating the predictive value of factors previously related to the short-term course of psychosis. In a sample of first-episode psychosis patients, from the city of Barcelona (Spain), who have passed the "critical period" of illness, male gender, single status, poor premorbid adjustment and poor insight appeared to predict especially poor outcome. Residual symptoms appeared to be an especially useful index of clinical and functional status for examining the course and outcome of first-episode psychosis.

Chapter 3 reports a study in a sample of first-episode psychosis patients from the city of Merida (Mexico) following the design and method of the study reported in Chapter 2. Although predictors seem to relate differently to the three short-term course criteria that were considered: diagnosis, residual symptomatology and relapsing course, lower educational level, poor premorbid adjustment, an insidious type of onset, hospitalization at first psychotic episode, and higher scores on the psychotic dimension at onset appeared to predict especially poor outcome.

Chapter 4 summarizes the main findings of all the studies presented in Chapters 2 and 3, and the studies presented in Appendixes 1, 2 and 3, with an emphasis on how they

provide supporting evidence for the new perspectives in the study of schizophrenia and related psychosis presented in Chapter 1.

Appendix 1 reports a study replicating the association between a shift away from pure dextrality with positive and negative dimensions of both *trait* (schizotypy) and sub-clinical *symptom* (psychotic-like experiences) psychosis-proneness levels in a representative sample of adolescents from the general population. Mixed-handedness seems a reliable marker of developmental disorders underlying both atypical lateralization and psychosis-proneness. Among various possible atypical-handedness patterns, ambiguous handedness across primary actions seems to be particularly related to psychosis-proneness.

Appendix 2 reports a study analyzing the effect of subsequent relapses, residual symptomatology, and diagnosis on the QoL of patients with a short-term course of psychosis and how it can be mediated by illness perception and overall functioning. Patients with residual symptoms showed a poorer QoL, and this effect was fully mediated by their emotional representation of illness and functioning. This study underscore sthe importance of targeting more intensively patients' skills and emotional responses towards the disorder in the clinical context in order to achieve a satisfactory level of personal and social reintegration after experiencing a psychotic disorder.

Appendix 3 reports a study exploring whether relatives' psychological distress and illness perception or patients' clinical and functional status were stronger predictors of relatives' expressed emotion, burden, and quality of life. Relatives' psychological distress and illness perception dimensions predicted both burden and quality of life, over and above patients' clinical and functional status. The study highlights the importance of paying attention to the possible impact of illness on the physical and mental well-being of the

caregivers. Providing relatives with psychological support for their own distress, might bring further benefits for both patients and relatives.

Appendix 1. Psychotic-like symptoms and positive schizotypy are associated with mixed and ambiguous handedness in an adolescent community sample

Abstract

Objective: To analyze the association of different patterns of atypical handedness with positive, disorganized and negative dimensions of both *trait* (schizotypy) and sub-clinical *symptom* (psychotic-like experiences) psychosis-proneness levels in a representative sample of adolescents from the general population.

Method: 728 adolescents were assessed for hand preference (Annett Hand Preference Questionnaire), schizotypy (Oxford-Liverpool Inventory of Feelings and Experiences) and psychotic-like experiences (Community Assessment of Psychic Experiences). A subsample of 129 was reassessed on the same measures to examine the stability of handedness.

Results: Writing-hand alone did not detect associations between laterality and psychosis-proneness. Mixed- rather than left- handedness was related to psychosis-proneness, and this was more evident when analyzing exclusively subjects with ambiguous handedness. When analyzing exclusively subjects with non-ambiguous handedness, strong-left handedness was related to psychosis-proneness. Inconsistent handedness showed a trend for an association with psychosis-proneness. The positive dimension showed a stronger association than the negative one with atypical handedness.

Conclusions: Trait and symptom-like measures of positive psychosis-proneness are associated with certain patterns of atypical handedness. Mixed-handedness seems a reliable marker of developmental disorders underlying both atypical lateralization and psychosis-

proneness. Among various possible mixed-handedness patterns, ambiguous handedness across primary actions seems to be particularly related to psychosis-proneness.

Key words: psychosis-proneness; handedness; schizophrenia

Significant outcomes:

- An association between a shift away from pure dextrality and both trait and symptom-like measures of psychosis-proneness was replicated in a representative sample of adolescents from the general population.
- The relationship between mixed handedness and psychosis-proneness was more evident for subjects with ambiguous handedness than for subjects with non-ambiguous handedness, and left-handedness had a significant effect for the non-ambiguous handedness group.
- A predominant association between the *positive* dimension and several patterns of atypical handedness was found in consistency with findings in clinical samples. This reinforces the view of continuity between the nonclinical and the clinical psychosis phenotype.

Limitations:

- Psychosis-proneness instruments were not originally designed for adolescents, even if they have later on shown satisfactory performance in this age range.
- Hand preference is a measure of laterality strongly susceptible to environmental influences.
- Asking participants to report rather than to demonstrate hand preference might have influenced the reliability of the results.

Introduction

Schizotypy phenotypes in the general population share etiopathogenic mechanisms and risk factors with schizophrenia, supporting the notion of psychosis as a continuum ranging from nonclinical to clinical deviance (1). The nonclinical psychosis phenotype (i.e., psychosis-proneness) is observed and reliably measured at the level of schizotypic personality features (using trait-like measures) and psychotic-like experiences (using symptom-based measures) (2-5). The study of psychosis-proneness in nonclinical samples allows the analysis of risk factors without the confounding effects of psychosis (e.g., medication, symptom severity, stigma).

An abnormality in cerebral lateralization has long been related to the etiology of schizophrenia (6,7) and more recently of schizotypy (8,9). This fits well with the view that schizophrenia is a neurodevelopment disorder that originates at the time when brain asymmetries are being established (10,11). Handedness is a simple way of capturing atypical lateralization–although there is a variety of hand preference patterns. Thus, the conceptualization and measurement of atypical handedness is a complex issue. *Mixed handedness* refers to using different hands for different actions (across-items inconsistency) (12), whereas *ambiguous handedness* refers to the use of different hands for the same action across time (within-item inconsistency) (13). However, some authors (14) had participants self-report rather than demonstrate handedness, referring to *ambiguous handedness* as the report of using "either hand" for an action. However, studies have not comprehensively examined the relation of psychosis-proneness with hand preference patterns, including inconsistency across both items and time.

There is consistent evidence of mixed handedness in schizophrenic patients (15). Similarly, several studies in nonclinical subjects have found that psychosis-proneness is

associated with mixed handedness (12,14,16-21), although some studies have found associations with both left and mixed handedness (22,23).

Most of these studies focused on the association of atypical handedness with *positive* schizotypy, which features cognitive-perceptual distortions of this multidimensional construct (24). Disorganized features have also been related to atypical handedness in nonclinical samples (19,25); however, such studies are limited due to preferential focus on positive dimension scales. Some studies suggested that mixed handedness and negative schizotypy are minimally related (17,25), although less strongly than with positive traits (19). However, other indicators of developmental instability, such as dermatoglyphic asymmetry and minor physical anomalies, tend to be associated with negative schizotypy (26-28). As atypical handedness is considered a marker of neurodevelopmental disturbance (29), it would be useful to clarify its relation with negative schizotypy.

Aims of the study

The present study aimed to replicate the association between atypical handedness and psychosis-proneness in a representative sample of adolescents from the general population. We expanded upon previous studies by: 1) including multiple handedness indexes, 2) comprehensively measuring the multidimensionality of psychosis-proneness (positive, disorganized and negative dimensions) and, 3) analyzing the association of different patterns of atypical handedness with nonclinical dimensions of both *trait* (schizotypy) and sub-clinical *symptom* (psychotic-like experiences) levels.

Methods

Subjects

Participants were community adolescents in secondary obligatory education randomly selected from the School Census of Barcelona. Parental consent and participant assent was obtained prior to participation. From the initial sample (n=927), 95 non-native Spanish speakers students were excluded due to limited command of the language. Another 99 students with elevated scores on the Eysenck Personality Questionnaire (30) Lie scale and five who did not complete the questionnaires were excluded. The final sample consisted of 728 subjects evenly distributed by sex (Time 1 sample). Mean age was 14.3 (SD=0.6) and was not significantly different for females (mean=14.4, SD=0.6) and males (mean=14.5, SD=0.6) ($t_{(720)}$=-1.51).

An average of seven months later, a subsample was recontacted to examine the temporal stability of handedness patterns. The Time 2 subsample included 129 participants. They did not differ from the total sample on sex ($\chi^2_{(1)}$ = 0.69) or age ($t_{(849)}$ = 1.82). Selected participants were assigned to an "index" or "control" group. The index group (n=53) included subjects who scored at least 2 SD above the mean on any of the schizotypy dimensions from the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)(31) or on the Community Assessment of Psychotic Experiences (CAPE) (5). The control group (n=76) included participants whose scores were less than 0.5 SD above the mean on all of these measures. The groups did not significantly differ on sex ($\chi^2_{(1)}$=0.03) or age ($t_{(127)}$=0.24).

Psychosis-proneness measures

Participants completed measures assessing schizotypy and psychotic-like experiences at the initial assessment. The OLIFE is a widely used questionnaire that contains self-administered subscales assessing schizotypy traits: Unusual Experiences (UnEx), Cognitive Disorganization (CogDis), and Introvertive Anhedonia (IntAn), related to positive, disorganized and negative schizotypy respectively. This questionnaire has shown an excellent reliability (32) and good validity (33). Note that the OLIFE Impulsive-Nonconformity subscale was not used in the present study. Psychotic-like experiences were assessed with the Spanish version of the CAPE (34), a self-administered instrument including Positive (CAPEPos), Negative (CAPENeg) symptom subscales. It has good validity and reliability (35,36) and has been used in general (37) and adolescent (38) population studies. Note that the CAPE Depressive symptom subscale was not included.

Handedness measures

Handedness was assessed with the 12-item self-report Annett Hand Preference Questionnaire (39) at both assessments. It inquires about hand preference for 6 primary and 6 non-primary actions (Table 6); answers are “right”, “either”, and “left”. Following Shaw et al. (14), subjects were grouped according to the following handedness criteria:

a) Writing Hand. 651 right-handed and 65 left-handed subjects were compared. Note that 12 subjects classified “either” were excluded for this comparison.
b) 3-way classification. Following Annett (40), the 7 original groups (see next paragraph) were reduced to 3: “strong right” (group 1), “mixed” (groups 2-7) and “strong left” (group 8).

c) 7-way classification. Subjects were assigned to one of the 7 groups (group 5 omitted for historical reasons), according to Annett (39,40). Group 1 is Right-pure; Group 2, Right-weak Left; Group 3, Right-mild Left; Group 4, Right-moderate Left; Group 6, Left-strong Right; Group 7, Left-weak Right; and Group 8, Left-pure.
d) Degree of "ambiguous handedness". The number of items to which a subject responded to use "either" hand.
e) Inconsistency across time (Time 2 subsample only). Number of handedness items answered inconsistently across the two assessments. Following Hayden et al. (13), subjects reporting 3 or more inconsistent items had "inconsistent hand preference" and subjects with 2 or fewer inconsistent answers had "consistent hand preference".

Hypotheses and data analyses

Based upon the literature, we hypothesized the following associations of handedness with psychosis-proneness. We expected the strongest associations of handedness to be with positive schizotypy, consistent with the majority of the previous findings.

a) Given that the literature supports an association of mixed, rather than pure left, handedness with psychosis-proneness, we expected no differences between left and right-handed writers.
b) We expected mixed handed participants to have elevated psychosis-proneness scores relative to both of the other groups and for left-handed to exceed right-handed participants.
c) We expected that the 7-way classification of handedness would corroborate the association of mixed, followed by left, handedness with psychosis-proneness.
d) We expected highly psychosis-prone subjects to display a higher degree of ambiguous handedness (i.e., using different hands for the same action, as Shaw et al. (14)).

e) We predicted the effect of mixed handedness for psychosis-proneness would be more evident for subjects with ambiguous handedness (any "either" score) than for subjects with non-ambiguous handedness.

f) We hypothesized that subjects with inconsistent hand preference across the two assessments would score higher on psychosis-proneness. Furthermore, this classification of handedness would show that "inconsistent hand preference" had the strongest association with psychosis-proneness, followed by "ambiguous hand preference", "mixed" handedness, consistent, and left dominant hand preference.

Results

Scores on the psychosis-proneness scales ranged from -1.3 SD to +4.9 SD, indicating that a wide range of variability on these constructs in the sample. Females had significantly higher scores on UnEx and CogDis, whereas males scored significantly higher on IntAn. No significant sex differences were found for the CAPE (Table 1). The correlations of the psychosis-proneness scales for the total sample and the Time 2 subsample were comparable (Table 2).

Classification by Writing-Hand

As hypothesized, participants identified as right-handed or left-handed based upon writing hand did not differ on the OLIFE or CAPE (Table 3). There were not any significant writing-hand x sex interactions.

Table 1. Mean scores and SD for the selected O-LIFE and CAPE subscales

	Total (N=728)	Female (n=364)	Male (n=364)	*t* value (d.f.=726)	Cohen's d value
O-LIFE					
UnEx	11.5 (5.9)	12.1 (6.0)	11.0 (5.8)	2.53**	0.19
CogDis	12.9 (5.0)	13.8 (4.7)	11.9 (5.1)	5.25***	0.39
IntAn	6.9 (3.0)	6.3 (2.6)	7.5 (3.2)	-5.72***	0.42
CAPE					
CAPEPos	29.9 (6.7)	30.0 (6.9)	29.8 (6.6)	0.23	0.02
CAPENeg	24.3 (5.0)	24.1 (4.8)	24.4 (5.2)	0.61	0.05

*p ≤ 0.05, **p≤0.01, ***p≤0.001.
A Cohen's d value of 0.20 represents a small effect size, 0.50 represents a medium effect size and 0.80 represents a large effect size.
UnEx: Unusual Experiences subscale. CogDis: Cognitive Disorganization subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale. CAPENeg: CAPE negative subscale.

Table 2. Correlations between selected O-LIFE and CAPE subscales for the total sample (N=728) and the re-assessed subsample (n=129).

N=728 / n=129	CogDis	IntAn	CAPEPos	CAPENeg
UnEx	+.47*** / +.56***	-.02 / +.07	+.70*** / +.79***	+.39*** / +.46***
	CogDis	+.16*** / +.36***	+.39*** / +.58***	+.51*** / +.64***
		IntAn	+.06 / +.06	+.28*** / +.40***
			CAPEPos	+.52*** / +.59***

*p ≤ 0.05, **p≤0.01, ***p≤0.001
UnEx: Unusual Experiences subscale. CogDis: Cognitive Disorganization subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale. CAPENeg: CAPE negative subscale.

Table 3. Mean scores and SD for the selected O-LIFE and CAPE subscales by writing-hand (n=716)

	Left (n=65)	Right (n=651)	t value (d.f.=714)	Cohen's d value
O-LIFE				
UnEx	11.5 (5.6)	11.5 (6.0)	0.00	0.00
CogDis	13.3 (4.7)	12.8 (5.0)	-0.70	0.05
IntAn	6.9 (2.5)	6.9 (3.0)	0.07	0.01
CAPE				
CAPEPos	29.8 (6.1)	29.9 (6.8)	0.15	0.01
CAPENeg	24.2 (5.1)	24.2 (5.0)	0.09	0.01

A Cohen's d value of 0.20 represents a small effect size, 0.50 represents a medium effect size and 0.80 represents a large effect size.
UnEx: Unusual Experiences subscale. CogDis: Cognitive Disorganization subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale. CAPENeg: CAPE negative subscale.
Note: 12 subjects who answered "either" were excluded of this particular analysis.

Three-way Classification of Handedness

The three groups differed significantly on UnEx, although *post-hoc* tests showed no significant differences between groups (Table 4). No significant differences resulted for the other OLIFE subscales, CAPE, or the sex x handedness interactions.

Table 4. Mean scores and SD for the selected O-LIFE and CAPE subscales by 3-way classification of handedness (n=728)

	Strong-Left (n=24)	Mixed (n=211)	Strong-Right (n=493)	F value (d.f.=2, 722)
O-LIFE				
UnEx	13.6 (5.9)	12.0 (5.9)	11.2 (5.9)	3.13*
CogDis	13.7 (4.4)	13.3 (4.6)	12.7 (5.2)	2.08
IntAn	6.8 (2.4)	7.1 (3.1)	6.8 (3.0)	0.07
CAPE				
CAPEPos	31.0 (6.9)	30.6 (7.4)	29.6 (6.4)	1.99
CAPENeg	24.1 (6.0)	24.6 (5.0)	24.1 (5.0)	0.58

*$p \leq 0.05$
UnEx: Unusual Experiences subscale. CogDis: Cognitive Disorganization subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale. CAPENeg: CAPE negative subscale.

Seven-way Classification of Handedness

Significant effects of the 7-way classification were found for UnEx and for CAPEPos (Table 5). None of the *post-hoc* comparisons were significant for the UnEx scores. On the CAPEPos, handedness group 1 scored significantly lower than groups 3 (p=0.03) and 4 (p=0.02), and group 4 also scored significantly higher than group 2 (p=0.02). The handedness x sex interactions were not significant.

Ambiguous Handedness

The Pearson correlation of psychosis-proneness measures with the number of items answered either hand preference was significant for UnEx ($r_{(726)}$ =+0.10, p=0.01), and CAPEPos ($r_{(726)}$ =+0.08, p=0.04), although they represent modest effect sizes. These associations were moderated by sex, as females showed significant correlations for both UnEx ($r_{(362)}$=+0.15, p=0.00) and CAPEPos ($r_{(362)}$ =+0.11, p=0.03), although results were not significant for males. Thus, highly psychosis-prone females, but not males, were less consistent in hand preference across items.

The percentage of subjects responding “either” to each of the Annett items varied widely (Table 6), indicating that some activities (notably primary actions) rarely involved ambiguous handedness. In order to examine whether psychosis-proneness was more strongly related with ambiguous handedness on such tasks, we calculated the correlation of the percentage of subjects endorsing “either” to each Annett item with their UnEx and CAPEPos scores following Shaw et al. (14). As writing-hand was analyzed previously, it was not considered for this analysis. As in Shaw et al. (14), most items answered “either” referred to non-primary actions, and higher UnEx scores were significantly and inversely related to the proportion of subjects using “either hand” for each action ($r_{(9)}$=-0.69, p=0.02).

Table 5. Mean scores and SD for the selected O-LIFE and CAPE subscales by Annett 7-way classification of handedness.

	Group 1 (n=493)	Group 2 (n=79)	Group 3 (n=67)	Group 4 (n=19)	Group 6 (n=30)	Group 7 (n=16)	Group 8 (n=24)	F value (d.f.=6, 714)	Significant comparisons
O-LIFE									
UnEx	11.2 (5.9)	11.8 (5.6)	13.2 (6.4)	12.4 (6.8)	10.3 (4.6)	10.6 (5.7)	13.6 (5.9)	2.22*	
CogDis	12.7 (5.2)	12.9 (4.3)	13.7 (4.8)	13.7 (4.8)	14.0 (4.4)	11.6 (5.2)	13.7 (4.4)	1.61	
IntAn	6.8 (3.0)	6.5 (3.0)	7.1 (2.9)	8.4 (3.2)	7.0 (1.9)	7.9 (4.8)	6.8 (2.4)	1.48	
CAPE									
CAPE Pos	29.6 (6.4)	29.1 (5.3)	32.3 (8.9)	34.6 (10.5)	29.0 (5.5)	28.8 (5.4)	31.0 (6.9)	4.25***	Group 1 < Group 3 Group 1 < Group 4 Group 2 < Group 4
CAPE Neg	24.1 (5.0)	23.7 (4.7)	25.4 (5.5)	25.8 (5.3)	24.2 (4.4)	25.3 (5.3)	24.1 (6.0)	0.97	

*p ≤ 0.05, **p≤0.01, ***p≤0.001.

Group 1: Right-pure; Group 2: Right-weak Left; Group 3: Right-mild Left; Group 4: Right-moderate Left; Group 6: Left-strong Right; Group 7: Left-weak Right; Group 8: Left-pure.
UnEx: Unusual Experiences subscale. CogDis: Cognitive Disorganization subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale. CAPENeg: CAPE negative subscale.

Further exploration showed that again the effect was due to females (UnEx, $r_{(9)}$=-0.72, p=0.01), as males did not corroborate the association (UnEx, $r_{(9)}$=-0.31). In other words, females using either hand for actions that few other people endorsed, showed higher UnEx scores than subjects using either hand for actions more commonly performed with either hand. Thus, the association between higher UnEx scores and the "either" handedness item appeared evident in female subjects who responded "either" to less commonly ambiguous primary actions.

Table 6. Percentage of sample endorsing "either" to each Annett item (except writing hand), ordered from low to high. Alongside the mean UnEx and CAPEPos scores of the subjects endorsing "either" to the corresponding item considered as a group.

Item	Subjects endorsing "either" n (%)	O-LIFE UnEx mean score	CAPE CAPEPos mean score
Hammering (P)	29 (4.0)	13.5	32.7
Scissors	30 (4.1)	13.0	24.9
Throwing ball (P)	38 (5.2)	12.9	31.5
Wielding racket (P)	46 (6.3)	11.9	29.6
Striking match (P)	60 (8.2)	12.7	30.7
Threading needle	66 (9.1)	12.7	31.1
Brushing teeth (P)	8 (11.1)	12.1	31.2
Dealing cards	87 (12.0)	12.1	30.9
Shoveling	129 (17.7)	11.9	30.2
Sweeping	155 (21.3)	12.0	29.8
Unscrewing jar	157 (21.6)	12.2	30.6

UnEx: Unusual Experiences subscale. CAPEPos: CAPE positive subscale. P: primary action.
Total number of items= 11 UnEx: r= -0.69, p= 0.02 CAPEPos: r= +0.09, p= 0.80

Further analysis of Mixed- vs. Ambiguous-handedness

Following Shaw et al. (14), we examined whether there was an additive effect of the ambiguous-handedness (number of actions for which "either hand" is used) and the

Table 7. Data divided according to "either" score on the Annett scale

a) Subjects with "zero either score" (not ambiguous) (n=341)

Annett 3-way Classification

UnEx	Strong Right (n=234)	Mixed (n=89)	Strong Left (n=18)
Mean(SD)	10.7 (6.0)	11.2 (5.5)	14.7 (5.7)

$F_{(2,338)}$=3.82 p=0.023

Post-hoc contrasts: Strong Right < Strong Left p=0.017

Annett 7-way Classification

	Group 1	Group 2	Group 3	Group 4	Group 6	Group 7	Group 8
CAPEPos	(n=234)	(n=36)	(n=28)	(n=13)	(n=9)	(n=3)	(n=18)
Mean(SD)	29.3 (6.6)	27.7 (4.6)	32.5 (8.9)	32.3 (7.9)	28.0 (4.0)	24.3 (5.9)	32.4 (7.1)

$F_{(6,334)}$= 2.76 p=0.012

Post-hoc contrasts: not significant

b) Subjects with "any either score" (ambiguous) (n=387)

Annett 7-way Classification

	Group 1	Group 2	Group 3	Group 4	Group 6	Group 7	Group 8
IntAn	(n=259)	(n=43)	(n=39)	(n=6)	(n=21)	(n=13)	(n=8)
Mean(SD)	6.8 (3.0)	6.2 (2.6)	7.0 (3.0)	10.2 (3.2)	7.2 (2.0)	8.2 (5.4)	8.7 (2.2)

$F_{(6,380)}$= 2.38 p=0.029

Post-hoc contrasts: Group 2 < Group 4 p=0.041

	Group 1	Group 2	Group 3	Group 4	Group 6	Group 7	Group 8
CAPEPos	(n=259)	(n=43)	(n=39)	(n=6)	(n=21)	(n=13)	(n=8)
Mean(SD)	29.8 (6.3)	30.2 (5.6)	32.1 (9.1)	39.5 (14.2)	29.5 (6.0)	29.9 (5.0)	26.7 (3.9)

$F_{(6,380)}$= 2.84 p=0.012

Post-hoc contrasts: Group 1 < Group 4 p=0.008; Group 7 < Group 4 p=0.051; Group 2 < Group 4 p=0.024; Group 8 < Group 4 p=0.015; Group 6 < Group 4 p=0.020

Group 1: Right-pure; Group 2: Right-weak Left; Group 3: Right-mild Left; Group 4: Right-moderate Left; Group 6: Left-strong Right; Group 7: Left-weak Right; Group 8: Left-pure.
UnEx: Unusual Experiences subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale.

standard scoring of mixed-handedness (using the right hand consistently for some actions and the left hand for others). To this end, the sample was subdivided based upon whether participants gave any "either" answer on the Annett scale. The resulting "zero either score" (not ambiguous) and "any either score" (ambiguous) groups were balanced (46.8% and 53.2% of the sample, respectively). We examined the effects of the 3-way and the 7-way classifications independently for the "zero either score" and the "any either score" groups. For the "zero either score" group, the 3-way classification had a significant effect for UnEx, and the 7-way classification differed significantly for CAPEPos. For the "any either score" group, the 7-way classification was significant for IntAn and CAPEPos (Table 7).

Hand Preference Inconsistency Across Time

Ninety-four of the 129 re-assessed participants at Time 2 were classified as having a "consistent hand preference" across the assessments. The consistent and inconsistent subjects did not differ significantly, although trends were observed for UnEx and CAPEPos (Table 8). The interactions of inconsistent hand preference and sex were not significant.

Table 8. Mean scores and SD for the selected O-LIFE and CAPE subscales by hand preference inconsistency across time (n=129).

	Inconsistent (n=35)	Consistent (n=94)	t value (d.f.=127)	Cohen's d value
O-LIFE				
UnEx	12.4 (7.6)	10.7 (5.9)	-1.40	0.25
CogDis	13.1 (5.8)	12.1 (5.1)	-0.95	0.17
IntAn	7.3 (3.9)	7.1 (3.5)	-0.29	0.05
CAPE				
CAPEPos	32.1 (9.2)	29.6 (7.1)	-1.67	0.30
CAPENeg	25.5 (6.7)	24.2 (6.0)	-1.10	0.20

*p ≤ 0.05, **p≤0.01, ***p≤0.001.
A Cohen's d value of 0.20 represents a small effect size, 0.50 represents a medium effect size and 0.80 represents a large effect size.
UnEx: Unusual Experiences subscale. CogDis: Cognitive Disorganization subscale. IntAn: Introvertive Anhedonia subscale. CAPEPos: CAPE positive subscale. CAPENeg: CAPE negative subscale.

Discussion

Consistent with previous studies of nonclinical samples (9), our findings support that a shift away from pure dextrality is related to psychosis-proneness. Annett's 7- and 3-way classifications showed that left-handers did not differ significantly from other groups. As reported by Annett and Moran (16), we found in the 7-way classification that pure left-handers showed lower psychosis-proneness scores than mixed-handers (e.g. for IntAn, CAPEPos and CAPEneg); other studies (14) have even found left-handers to have lower, not higher, scores than consistent right-handers. In our study, Annett's 7-way right-handers with strong/moderate left tendencies were more psychosis-prone than pure-right handed subjects. Thus, the effects might be explained as a function of mixed-handedness rather than simple non-right handedness, consistent with the hypothesis of disrupted lateralization in the etiology of schizophrenia.

Corroborating previous findings (14,16,18), writing hand alone was not associated with psychosis-proneness. Ambiguous handedness was associated with psychosis-proneness, particularly for females on the positive dimension at trait and symptom-like levels. Moreover, as in the study by Shaw et al. (14), this association appeared particularly dependent on female subjects who used "either" hand for less commonly ambiguous actions. Similarly, Annett and Moran (16) found that the highest schizotypy scores corresponded to right-handed writers who perform other primary actions with the left hand. These authors suggested that discordance for primary actions is not a general risk for both right- and left-handed writers, but only for the former, suggesting that the classification of mixed-handedness should be further refined to examine the specific subgroup of right-handed writers who perform other primary actions with the left hand.

Not only did these findings confirm the hypothesis that the effect of mixed handedness for psychosis-proneness is more evident for subjects with ambiguous handedness than for subjects with non-ambiguous handedness, but we found that left-handedness had a significant effect on the latter. Consistent with Shaw et al. (14), we found significant differences on UnEx scores for the non-ambiguous group. On the other hand, the ambiguous group showed differences on IntAn and CAPEPos scores. Therefore, when we observe subjects exclusively using one hand for a specific action (non-ambiguous), left-handers (not mixed) are significantly more psychosis prone than right-handers. On the other hand, when observing ambiguous-handers, the most mixed group (right with strong left tendency) scored significantly higher than both left- and right-handers. Furthermore, the effect of left-handedness on non-ambiguous groups was evident for positive schizotypy, whereas the effect of mixed-handedness on ambiguous groups was evident for negative schizotypy and positive symptom dimension. Note that this is only the second study, after Shaw et al. (14) to perform these analyses; therefore, replication is needed.

We also considered hand-preference inconsistency across time as a measure of atypical handedness as proposed by Hayden et al. (13). Although the inconsistent group scored higher than the consistent group on every scale on visual inspection, only a trend for significant differences was found.

Consistent with previous studies, we found a predominant association between the *positive* dimension and classifications of atypical handedness. Nevertheless, other indicators of neurodevelopmental impairment, such as developmental instability have stronger associations with negative schizotypy (26,28,41). Prenatal indicators of developmental disturbances occurring in a narrow prenatal time window, such as

dermatoglyphic anomalies, might relate to negative schizotypy, resembling the pattern found in schizophrenia (28); whereas later functional lateralization, reflected by handedness, might be more related to positive schizotypy.

This study indicated that both trait and symptom-like measures of positive psychosis-proneness are associated with patterns of atypical handedness. Although some psychosis-proneness instruments were originally designed for older adolescents and adults, they can be reliably applied to adolescents to estimate the expression of nonclinical symptom-oriented (38,42) and trait-oriented (26,43) psychosis vulnerability. Also, adolescent samples allow the study of nonclinical characteristics before the typical age of onset of frank psychotic symptoms in later adolescence or early adulthood (44). Indeed, subtle attenuated psychotic symptoms and traits are thought to be more common in adolescents than in adults (45). This high prevalence could be due to the characteristic self-consciousness of the developmental stage and susceptibility to suspicious thoughts and abnormal perceptions. Adolescents often have increased difficulties distinguishing between relevant and irrelevant stimuli, and they experience perceptual disturbances more readily than adults. Most subtle psychosis-proneness expressions arise in a challenging social context (e.g. ideas of reference and suspicion), but are transient and never progressing to clinical psychopathology. Thus, in adolescents, only some dimensions of the underlying and heterogeneous psychosis phenotype may correspond to a continuum with more severe psychopathology and predict later psychiatric disorder (42).

In summary, we have replicated that both schizotypy traits and nonclinical psychotic-like experiences are present and can be assessed in adolescents and relate to atypical handedness. Mixed-handedness seems a reliable marker of developmental disorders underlying both, atypical lateralization and psychosis-proneness. Among

various possible mixed-handedness patterns, ambiguous handedness across primary actions seems to be particularly related to psychosis-

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Appendix 2. Quality of life: relation to illness course, illness perception and functioning in short-term course psychosis patients

Abstract

Quality of Life (QoL) has emerged as an important issue in patient care and, in consequence, in research. The effect of the short-term course of the illness (e.g. subsequent relapses, residual symptomatology, and final diagnosis) on the QoL of patients requires study. Patients' illness perception and functioning have been related to QoL, although their possible role as mediators also needs to be explored. This study aimed at exploring the association of illness course with patients' QoL, and whether these relations were mediated by patients' illness perception or overall functioning in a sample first-episode psychosis patients. 61 participants with a short-term course of psychosis were interviewed and assessed for illness course (relapses, residual symptoms, and diagnosis), QoL, illness perception, and functioning. Patients' negative cognitive and emotional representation of illness and poor functioning were related to poor QoL. Patients with residual symptoms showed a poorer QoL, and this effect was fully mediated by their emotional representation of illness and functioning. These results underscore the importance of targeting more intensively patients' skills and emotional responses towards the disorder in the clinical context in order to achieve a satisfactory level of personal and social reintegration after experiencing a psychotic disorder.

Keywords:

Quality of Life, Short-term Psychosis, Illness Course, Illness Perception, Functioning

Introduction

Quality of Life (QoL) refers to the "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The WHOQOL Group 1998). Reflecting an emerging biopsychosocial perspective of health, QoL has become an important issue in patient care and, in consequence, in research. The concept of QoL has long been applied in medical conditions, and more recently expanded to psychiatric disorders (Awad and Voruganti 2000). Advances in antipsychotic medication have made clinical stability achievable for patients with psychotic disorders and QoL a feasible aim in the patient's process of reintegration to family and community life.

QoL has gained importance besides social and clinical outcome in schizophrenia, despite unresolved methodological issues (Browne et al. 2000). Research indicates that people with schizophrenia suffer significantly poorer QoL (review by Pinikahana et al. 2002). In fact, impaired QoL has been observed in first-episode psychosis patients (Bechdolf et al. 2005; Browne et al. 2000), prodromal (Bechdolf et al. 2005; Ruhrmann et al. 2008) and even psychosis-vulnerable subjects (Svirskis et al. 2007). Nevertheless, follow-up studies have shown that after a first psychotic episode is treated, QoL might plateau (Górna et al. 2008) and even improve (Foldemo and Bogren 2002; Malla et al. 2001; Ritsner et al. 2003).

Given the huge differences in mental health provision between high- and low-income countries, a better outcome in schizophrenia patients from the former might be expected. However, the World Health Organization (WHO) international collaborative research on schizophrenia found that the prognosis of schizophrenia in developing countries was groupwise uniformly milder, although a better course and outcome could

not be concluded (Jablensky et al. 1992). It has been argued that the diminished social support likely associated with high-standard competitive cultures is a concern. Despite access to top biomedical treatment, developed countries still have high rates of chronic disability and dependency associated with schizophrenia; thus, something essential to recovery must be missing from the social domain (Jablensky and Sartorius 2008).

Given that QoL is a desirable result of treatment, attention has been paid to identifying possible predictors. So far, literature has found that short delays in treatment, good premorbid adjustment (Malla and Payne 2005), social attachment and reassurance of worth (Caron et al. 2005), moderation of symptoms, frequency of contacts with family, friendship, age (Gaite et al. 2002), being married, having a home, residing in the community, being in a support program, and taking antipsychotic medication, among others (Pinikahana et al. 2002), are significant predictors of satisfactory QoL; however, cultural issues might moderate their effect (Gaite et al. 2002; Pinikahana et al. 2002).

Despite the increased clinical and research interest in QoL of schizophrenia patients, studies that focus on the short-term illness course of psychosis are still limited. Subsequent relapses, residual symptomatology and diagnosis, are three widely used criteria to operationalize illness course that can be established and predicted after the "critical period" (~3 years after first episode) (Birchwood 2000). Relapse has an important effect not only on the clinical, but also on the social functioning of patients. Exacerbation of symptoms and hospitalizations might cause cumulative deterioration in functioning and diminish the ability to maintain employment and relationships (Nasrallah and Lasser 2006), thus affecting QoL. Although relapsing patients might be expected to experience lower QoL than non-relapsing patients, evidence remains contradictory (Almond et al. 2004). In regard to psychopathology, residual symptoms seem to diminish

QoL (Malla and Payne 2005; Savilla et al. 2008; Thorup et al. 2010); particularly, positive and negative symptoms (Eack and Newhill 2007), with the latter more robustly so (Hirschberg 2006; Narvaez et al. 2008; Pinikahana et al. 2002). Schizophrenic psychoses show, compared to schizoaffective psychoses, a poorer global outcome, more deteriorating course, greater presence of negative symptoms, and more persistent impairments in several aspects of social life (Möller et al. 2000). Nevertheless, schizophrenic and schizoaffective psychoses seem not to differ in regard to QoL (Ritsner et al. 2003).

Insight has been proposed as a core mediator of the association between illness course and QoL, but results are contradictory. Although previous studies found an inverse or no significant association, recent studies have reported that greater insight into illness is significantly associated with an increase in depression and poor QoL (Karow and Pajonk 2006). Insight implies the individual's recognition of his/her psychopathology, entailing the awareness of the presence of specific symptoms, the impact of the disorder, and the need for treatment (Osatuke et al. 2008). Although the importance of insight in psychosis for treatment adherence and outcome is undeniable, a satisfactory level of insight might be hindered by academic education, defensive psychological mechanisms and fear of stigma.

Alternatively, from the self-regulatory model of Leventhal et al. (1984), the concept of "illness perception", or "illness appraisal", has emerged as an important factor in health psychology. The model proposes that when people face health difficulties, they create a private representation of their illness in order to make sense of and respond adequately to the situation. Whether seen as an illness or otherwise, the experience of psychosis raises individual's beliefs involving not only the acknowledgement of health

status, but also the appraisal of personal and social consequences (Watson et al. 2006). Among mental health patients, it is not unusual to find partial awareness of their illness that might be addressed as "personal difficulties", "stress", or "nervousness". This might be due to denial, a limited educational level, or even to mildness of symptoms. Unlike insight, illness perception does not require acknowledging the condition as a disorder; thus, patients can recognize being affected (or not) regardless of their comprehension and awareness of mental illness. Initially, illness representations were defined as "a patient's own implicit common sense beliefs about their illness" (Leventhal et al. 1984) but currently this definition has expanded to include an emotional dimension, in addition to the original illness cognitions (Broadbent et al. 2006; Moss-Morris et al. 2002). Illness perception has been related to QoL in certain medical conditions (e.g. Miglioretti et al. 2008; Scharloo et al. 2007), but this association still needs confirmation in psychosis.

Functioning and QoL seem to be strongly related in schizophrenia (Groznik et al. 2001; Norman et al. 2000) and schizoaffective (Norman et al. 2000) patients. This relationship has shown consistency across comparative European samples (Becker et al. 2005). Nevertheless, to the best of our knowledge, replication with Latin-American samples is missing. Moreover, despite having being identified as a strong predictor of QoL (Hegeman 2002) the role of functioning as a mediator is still to be explored.

The present study examined the association of illness course with QoL and the extent to which illness perception and global functioning mediated such relations in a sample of short-term course first-episode psychosis patients. It was hypothesized that 1) poor illness course would be related to poor QoL; 2) the relation of illness course to QoL would be mediated by both illness perception and level of functioning.

Methods

Sample

Participants for this study were all patients who had received mental health care in the adult service of the Hospital Psiquiátrico Yucatan (HPY). Although the HPY has a broad catchment area, sampling was restricted to the inhabitants of the city of Merida, where this hospital is located. After obtaining formal authorization and ethical approval from the Hospital Committee, clinical files were reviewed in search of patients who would meet the following criteria: (1) occurrence of a first episode of psychosis between 1999 and 2005 (so that all patients had passed the critical period); (2) age at onset 16-45 years; and (3) a primary current DSM-IV-TR (American Psychiatric Association 2000) diagnosis of schizophrenia or other psychotic disorder. Exclusion criteria were: (1) psychoses of affective, organic, or toxic type, (2) an evident intellectual disorder, and (3) inadequate contact information.

From a total of 158 potential cases, 55 had moved away and could not be located. From the remaining 103, 66 (64.1%) agreed to be interviewed (with no economic compensation involved). Five participants were unable to provide reliable data due to high symptom severity; thus, the final sample was 61 patients (55.7% female). At the time of the assessment, no participant was hospitalized. In terms of current DSM-IV-TR diagnoses, 41 patients had schizophrenia (14 paranoid, 2 disorganized, and 25 residual) and 20 patients had other types of psychoses (8 schizoaffective, 7 delusional, 2 schizophreniform, 2 brief, and 1 not otherwise specified). Mean illness course was 6.7 years (SD=1.9, range 3.8 – 11.2). Current mean age was 35.9 years (SD=10.0) and mean age at onset was 29.1 years (SD=9.8). There were no significant sex differences for either current ($t_{(59)}$= -1.06, p=0.29) or onset ($t_{(59)}$= -1.01, p=0.32) age.

Of the total sample, 25 patients (41%) were not currently following outpatient treatment. Four of them (2 with brief psychosis and 2 with schizophreniform disorder), had received medical discharge. The remaining 21 had dropped out from regular outpatient follow-up. However, these 21 patients did not show any difference in our outcome variable, QoL, compared to the 36 who followed out-patient treatment (CSCV-Favorable, $t_{(55)}$=-1.37; CSCV-Disfavorable, $t_{(55)}$=1.21). Therefore, current treatment status was not considered for the analyses.

Measures

Based on information from clinical files and interviews, the illness course of each patient was established for three dichotomously scored criteria: 1) any psychotic episodes (relapse) during the follow-up period, 2) presence of residual symptoms at the time of the interview, and 3) current DSM-IV-TR primary psychotic diagnosis.

Illness perception was measured with the Brief Illness Perception Questionnaire (Brief-IPQ; Broadbent et al. 2006), a nine-item self-report scale. The first 8 items assess three dimensions of illness perception: cognitive representation (beliefs about consequences and duration of illness, personal control over illness, usefulness of treatment, and severity of symptoms), emotional representation (negative emotions about illness) and comprehensibility (understanding of the disorder). Higher scores of cognitive and emotional representations indicate a negative perception of illness, whereas higher scores on comprehensibility indicate a favorable perception. The ninth item assesses assumed causes of illness by asking patients to list the three most important factors accounting for their illness. This item was substituted by a more comprehensive scale developed by Angermeyer and Klusmann (1988) that asks participants to rate in a four-point scale (“no”, “possibly”, “likely”, “very likely”) 30 possible causes of illness. Items

are categorized into biological (e.g., brain damage, genetics), personality (e.g. lack of will power), family (e.g. broken home), societal (e.g. stressful life events), and esoterical (e.g. evil spirits) causes. A category score (range 0 – 6) is rated according to the total number of items in that category selected as a "likely/very likely" cause of illness.

Quality of Life was assessed with the Sevilla Quality of Life Questionnaire (CSCV, Cuestionario Sevilla de Calidad de Vida), a 59-item self-rated questionnaire developed for patients with schizophrenia (Giner et al. 1997). This 5-point rating questionnaire has two scales: the Favorable-aspect scale (CSCV-Favorable) composed of vital satisfaction, self-esteem and harmony factors; and the Disfavorable-aspect scale (CSCV-Disfavorable) composed of lack of cognitive apprehension, loss of energy, lack of inner control, difficulty with emotional expression, difficulty with cognitive expression, oddness, fear of losing control, restrained hostility, and automatism factors.

Current functioning was assessed with the Global Assessment of Functioning (GAF) Scale (APA 2000), a widely used scale to evaluate overall functioning (from 0 to 100).

The original selected measures differ in their score range: the Brief-IPS scores on an 11-point rating scale, the SQLQ on a 5-point, and the cause of illness a 4-point rating scale. Anticipating that some participants might not be familiar with self-rating gradual agreement scales and in order to ensure the reliability of the data collection in this population we unified the rating of all scales. Items were read aloud by the interviewer and participants were requested to answer how much they agreed by pointing at one of four drawn squares, from the smallest ("not at all" =1) to the largest ("definitely yes" =4).

Data analysis

First, the QoL of groups defined by the three illness course criteria (relapses, residual symptoms, and diagnosis) were compared with *t*-tests, and the association of QoL with illness perception and functioning were estimated with Pearson correlations. Next, bivariate and partial correlations were applied to observe the direct and mediated effect (controlling for illness perception and functioning) of illness course on QoL. Sobel tests and bootstrapping procedures were used to determine the significance of each mediator individually. Finally, the resulting significant mediators were entered simultaneously to confirm their effect.

Results

Descriptive data for illness perception, quality of life and functioning measures are presented in Table 1. No significant differences by sex were found on any variable so the values are presented for the total sample.

Data for illness course and its effect on QoL are presented in Table 2. Following Cohen (1992), a *d*-value of .2 indicates a small effect, .5 a medium effect, and .8 a large effect size. As can be seen, the presence of residual symptoms was robustly associated with impaired QoL.

Data for the association of QoL with illness perception and global functioning are presented in Table 3. Overall, negative cognitive and emotional representations were significantly related to poorer QoL, whereas higher understanding of illness was related only to the QoL favorable aspects. Although the favorable aspects of QoL did not seem to

be related to the perception of illness causes, some unfavorable aspects did, pointing at an association between poor QoL and the attribution of illness mainly to personality and family factors. Not surprisingly, better global functioning was consistently associated to a better QoL.

Table 1. Mean and Standard Deviation of Illness Perception, Functioning and Quality of Life Scores (*n*=61)

Scales	Mean (SD)	Range
Illness perception		
Brief Illness Perception Questionnaire		
Cognitive representation	10.7 (2.9)	5.0 – 17.00
Emotional representation	5.0 (2.1)	2.0 – 8.0
Comprehensibility	2.9 (1.1)	1.0 – 4.0
Likely causes of illness		
Biological	1.4 (1.4)	0.0 – 6.0
Personality	2.0 (1.6)	0.0 – 6.0
Family	1.7 (1.7)	0.0 – 6.0
Societal	2.4 (1.6)	0.0 – 6.0
Esoterical	0.8 (1.2)	0.0 – 5.0
Global functioning		
Global Assessment of Functioning	75.3 (16.5)	35.0 – 100.0
Quality of life		
CSCV-Favorable	3.0 (0.7)	1.5 – 4.0
Vital Satisfaction	3.2 (0.7)	1.4 – 4.0
Self-esteem	2.9 (0.7)	1.0 – 4.0
Harmony	3.1 (0.8)	1.0 – 4.0
CSCV-Disfavorable	1.7 (0.6)	1.0 – 3.4
Lack of cognitive apprehension	1.6 (0.6)	1.0 – 3.0
Lost of energy	1.8 (0.7)	1.0 – 3.7
Lack of inner control	1.8 (0.8)	1.0 – 3.7
Difficulty with emotional expression	1.8 (0.8)	1.0 – 3.6
Difficulty with cognitive expression	1.7 (0.7)	1.0 – 3.3
Oddness	1.7 (0.8)	1.0 – 4.0
Fear of loosing control	1.5 (0.6)	1.0 – 3.7
Restrained hostility	1.5 (0.6)	1.0 – 3.7
Automatism	1.6 (0.7)	1.0 – 4.0

CSCV: Cuestionario Sevilla de Calidad de Vida (Sevilla Quality of Life Questionnaire)

Table 2. Differences in Quality of Life According to Illness Course (*n*=61)

	Relapses				Residual Symptoms				Diagnosis			
Quality of life subscales Mean (SD)	Multi-episode *n*=37	Single-episode *n*=24	*p*	Cohen´s d	With Symptoms *n*=30	Without Symptoms *n*=31	*p*	Cohen´s d	Schizophrenia *n*=41	Other psychoses *n*=20	*p*	Cohen´s d
CSCV-Favorable	2.9 (0.7)	3.2 (0.6)		0.46	2.8 (0.7)	3.3 (0.6)	**	**0.77**	2.9 (0.7)	3.2 (0.5)		0.49
Vital satisfaction	3.0 (0.8)	3.3 (0.7)		0.40	2.9 (0.8)	3.4 (0.6)	**	**0.71**	3.1 (0.8)	3.3 (0.7)		0.27
Self-esteem	2.8 (0.7)	3.0 (0.8)		0.27	2.6 (0.8)	3.2 (0.6)	**	**0.85**	2.8 (0.8)	3.0 (0.6)		0.28
Harmony	3.0 (0.9)	3.3 (0.6)		0.39	2.9 (0.8)	3.3 (0.7)	*	**0.53**	2.9 (0.8)	3.4 (0.5)	*	**0.75**
CSCV-Disfavorable	1.8 (0.6)	1.6 (0.5)		0.36	1.9 (0.7)	1.5 (0.4)	**	**0.70**	1.7 (0.6)	1.7 (0.7)		0.00
Lack of cognitive apprehension	1.7 (0.6)	1.5 (0.5)		0.36	1.6 (0.6)	1.6 (0.6)		0.00	1.6 (0.6)	1.6 (0.6)		0.00
Lost of energy	1.9 (0.7)	1.7 (0.7)		0.29	2.1 (0.8)	1.6 (0.5)	**	**0.75**	1.8 (0.7)	1.8 (0.8)		0.00
Lack of inner control	1.9 (0.7)	1.7 (0.8)		0.26	2.1 (0.8)	1.6 (0.6)	*	**0.71**	1.8 (0.8)	1.8 (0.8)		0.00
Difficulty with emotional expression	1.9 (0.8)	1.8 (0.8)		0.12	2.1 (0.8)	1.6 (0.6)	**	**0.71**	1.8 (0.8)	2.0 (0.7)		0.27
Difficulty with cognitive expression	1.8 (0.8)	1.5 (0.6)	*	**0.42**	1.9 (0.7)	1.5 (0.6)	*	**0.61**	1.8 (0.7)	1.6 (0.6)		0.31
Oddness	1.7 (0.9)	1.7 (0.9)		0.00	1.9 (0.9)	1.5 (0.7)		0.50	1.7 (0.8)	1.8 (1.0)		0.11
Fear of losing control	1.6 (0.7)	1.3 (0.4)	*	**0.53**	1.7 (0.8)	1.2 (0.3)	**	**0.83**	1.5 (0.6)	1.5 (0.7)		0.00
Restrained hostility	1.5 (0.6)	1.4 (0.6)		0.17	1.7 (0.8)	1.2 (0.3)	***	**0.83**	1.4 (0.5)	1.6 (0.8)		0.30
Automatism	1.7 (0.8)	1.4 (0.6)		0.42	1.8 (0.8)	1.4 (0.6)	*	**0.57**	1.6 (0.7)	1.6 (0.8)		0.00

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001
CSCV: Cuestionario Sevilla de Calidad de Vida (Sevilla Quality of Life Questionnaire)
Note: medium effect sizes in bold, large effect sizes in bold and italics

Table 3. Pearson Correlations of Quality of Life with Illness Perception and Functioning *n*=61)

	Illness perception								Global functioning
	Brief-IPQ			Likely causes of illness					
Quality of life subscales	Cognitive representation	Emotional representation	Comprehensibility	Biological	Personality	Family	Societal	Esoterical	GAF
CSCV-Favorable	-0.59***	-0.42***	0.30*	0.03	-0.09	-0.08	0.15	-0.06	0.54***
Vital Satisfaction	-0.59***	-0.51***	0.19	-0.03	-0.08	-0.12	0.07	-0.08	0.50***
Self-esteem	-0.43***	-0.23	0.33**	0.06	-0.03	-0.08	0.20	0.03	0.52***
Harmony	-0.57***	-0.41***	0.28*	0.05	-0.13	-0.01	0.12	-0.11	0.44***
CSCV-Disfavorable	0.62***	0.45***	-0.18	0.09	0.32**	0.26*	0.10	0.16	-0.43***
Lack of cognitive apprehension	0.40**	0.33**	-0.20	0.08	0.19	0.17	0.12	0.15	-0.17
Lost of energy	0.60***	0.53***	-0.21	0.17	0.39**	0.31**	0.12	0.19	-0.37**
Lack of inner control	0.64***	0.44***	-0.15	-0.01	0.33**	0.20	0.06	0.11	-0.43***
Difficulty with emotional expression	0.51***	0.36**	-0.18	0.04	0.39**	0.29*	0.12	0.19	-0.42***
Difficulty with cognitive expression	0.52***	0.44***	-0.22	0.19	0.23	0.29*	0.03	0.08	-0.44***
Oddness	0.45***	0.26*	-0.06	0.19	0.26*	0.37**	0.12	0.20	-0.35**
Fear of loosing control	0.56***	0.33**	-0.16	-0.03	0.30*	0.11	0.08	0.11	-0.42***
Restrained hostility	0.47***	0.37**	-0.09	0.05	0.19	0.16	0.11	0.12	-0.34**
Automatism	0.48***	0.30*	-0.07	-0.01	0.08	0.02	-0.03	0.01	-0.24

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001
CSCV: Cuestionario Sevilla de Calidad de Vida (Sevilla Quality of Life Questionnaire)

Given the high correlations among the 3 CSCV-Favorable (r values from 0.66 to 0.79, all $p \leq 0.001$, coefficient alpha of the three subscales of .89) and the 9 CSCV-Disfavorable (r values from 0.46 to 0.82, all $p \leq 0.001$, coefficient alpha of .94) subscales, it was decided to proceed in further analyses using only the global CSCV-Favorable and CSCV-Disfavorable scores. The residual symptom criterion was selected as the most reliable predictor of poor QoL, above diagnosis and relapses. Also, negative cognitive and emotional representations were the dimensions of illness perception clearly associated with QoL. Therefore, the final mediation analysis included residual symptoms as the predictor of CSCV-Favorable and CSCV-Disfavorable QoL, and cognitive and emotional representations of illness and global functioning as candidate mediators. Results are shown in Table 4. A significant direct effect of residual symptoms on both QoL dimensions can be observed. However, the effect was fully mediated by emotional representation of illness and functioning, as it was no longer significant when either of these two mediators were entered in partial correlations. Cognitive representation failed to partially mediate the effect of residual symptoms on either QoL measure. Sobel tests confirmed emotional representation and global functioning as significant mediators of the association of residual symptoms with QoL. Following Preacher and Hayes (2008), we recalculated the mediation effects using multiple mediator models, corroborated the statistically significant mediation effect of emotional representation and functioning.

Table 4. Tests of Mediation of the Association of Residual Symptoms and Quality of Life by Emotional Representation of Illness and Functioning

Predictor	Outcome	Direct effect	Mediator	Mediated effect	Single mediation Sobel test	Multiple mediation Sobel test	Multiple mediation Bootstrap 95% CI
Residual Symptoms	CSCV-Favorable	.36**	Cognitive representation	-.27*	-1.87	-	-
			Emotional representation	-.25	-2.01*	-2.15*	-.33 - -.05
			Global functioning	-.02	-3.19***	-3.41***	-.76 - -.24
	CSCV-Disfavorable	-.35**	Cognitive representation	.26*	1.89	-	-
			Emotional representation	.23	2.11*	2.18*	.05 - .32
			Global functioning	.11	2.11*	2.28*	-.03 - .54

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$
CSCV: Cuestionario Sevilla de Calidad de Vida (Sevilla Quality of Life Questionnaire)
Note: Direct effect is the bivariate correlation of Residual Symptom rating with the outcome measure; Mediated effect is the same correlation with the mediator partialed out. Single mediation Sobel test indicates the significance of mediation analyzed individually. Multiple mediation Sobel test indicates the significance of mediation with mediators entered simultaneously.

Discussion

As treatments are better able to provide symptomatic relief to patients with psychotic illnesses, focus has increasingly shifted to the impact of such disorders on QoL. The present results showed that residual symptoms have a greater deteriorating effect on patients' QoL than subsequent relapses or diagnosis; per se. Results also showed that this effect was mediated by their negative emotional representation of illness and poor functioning.

Illness perception has been found to be significantly associated with medication adherence, positive and negative symptoms, anxiety and depression in schizophrenia

patients (Lobban et al. 2005; Watson et al. 2006). This study provides evidence of an association between negative emotional illness perception and a diminished QoL. Studies have shown that anxiety and depression are strong predictors of changes in QoL across time (Huppert and Smith 2001; Priebe et al. 2000). Furthermore, it is the ability to cope with symptoms and the associated distress what substantially contributes to QoL in schizophrenia (Ritsner et al. 2003). Thus, the link between the emotional dimension of illness perception and QoL is a worth target for both treatment and research.

Our findings support the importance of comprehensive psychoeducation programs for patients. Stigmatization, isolation, guilt and shame, anxiety, uncertainty about future, quarrel with destiny and acceptance of the disorder seem to be some of the various issues that a patient needs to manage apart from gaining a satisfactory comprehension of the illness and treatment (Rummel-Kluge et al. 2006).

The association between functioning and QoL was replicated in this sample of short-term course psychosis patients in a sample from a developing country. From the illness intrusiveness conceptual framework, a poor functional level might disrupt daily life, compromising QoL by: 1) reducing gratification from psychologically valued activities and 2) diminishing personal control by limiting the ability to obtain positive outcomes and/or to avoid negative ones (Devins 2010). Evidence supports that family and social dimensions of life, which might provide attachment and reassurance of worth, are very important to patients' QoL (Caqueo-Urízar and Lemos-Giráldez 2008; Caron et al. 2005; Pitkänen et al. 2009).The reintegration of patients' to their daily family and community roles can be hindered by poor functionality, restringing their opportunities to obtain social reinforcement and improve QoL.

Residual psychopathology has been related to poor QoL (Jabs et al. 2004; Malla and Payne 2005), but our results provide a clear picture of the impact of residual symptoms, above that of relapsing course and diagnosis. Additionally, the study extends previous research by exploring how residual symptoms and QoL are linked through the mediation of illness perception and functional level.

Residual symptoms, rather than relapses and clinical diagnosis, affect QoL. However, its effect is mediated by emotional representation of illness and global functioning of patient. Attention to frank psychotic symptoms and helping the patient to understand illness are, needless to say, core tasks in treatment. Nevertheless, these results underscore the importance of targeting more intensively patients' skills and emotional responses towards the disorder in the clinical context in order to achieve a satisfactory level of personal and social reintegration.

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Appendix 3. Predictors of expressed emotion, burden and quality of life in relatives of short-term course psychosis patients

Abstract

Background: Expressed emotion, burden, and quality of life of relatives received attention due to the increasing interest in predicting and preventing relapse in psychotic patients, but they have subsequently acquired interest of their own. The objective of the study was to identify factors that might predict expressed emotion, burden, and quality of life in a sample of relatives of short-term course first-episode psychosis patients. The study explored whether relatives' psychological distress and illness perception or patients' clinical and functional status were stronger predictors of relatives' expressed emotion, burden, and quality of life.

Method: 65 patient-relative dyads were interviewed. Relatives self-reported on expressed emotion, burden, quality of life, psychological distress and illness perception. Patients' clinical and functional status was rated by interviewer. Pearson correlations and hierarchical multiple linear regressions were used for statistical analyses.

Results: Patients' functional status and relatives' psychological distress were significantly associated with expressed emotion, burden and quality of life. Patients' clinical status and relatives' illness perception were most strongly related to expressed emotion and burden. Relatives' psychological distress and illness perception dimensions predicted both burden and quality of life, over and above patients' clinical and functional status.

Conclusions: Results underscore the importance of paying attention to the possible impact of illness on the physical and mental well-being of the caregivers. Providing relatives the opportunity to express their concerns about the consequences of illness for the patient and themselves, as well as psychological support for their own distress, might bring further benefits for both patients and relatives.

Key words: Psychosis, Relatives, Expressed emotion, Burden, Quality of life, Psychological distress, Illness perception.

Introduction

As deinstitutionalization of patients with psychotic illnesses has been promoted, the active involvement of families in the care of their relatives has increased. Families play an important role in the recovery of patients from the first episode of psychosis through remission and relapses. Without support from and an alliance with clinical professionals, family members may experience worry, shame, stigma, guilt and even depression when facing the challenge of having a relative with a brief or chronic mental disorder (Barrowclough *et al.* 1996; Szmukler, 1996; Schene *et al.* 1998; Addington *et al.* 2005). Expressed emotion, burden, and quality of life of relatives are three concepts that emerged as part of the increasing interest in predicting and preventing relapse in psychotic patients, but have subsequently acquired recognition of their own as important aspects of families' psychological well-being.

Expressed Emotion (EE) refers to critical, hostile, or emotionally over-involved attitudes and interactions of family members toward a relative with a disorder or impairment (Barrowclough & Hooley, 2003). High EE is a predictor of relapse not only in schizophrenia (Bland, 1989; Butzlaff & Hooley, 1998; Miklowitz, 2004), but also across a range of psychiatric conditions (Butzlaff & Hooley, 1998; Hooley, 2007). Consequently, family intervention programs have been developed to reduce relatives' EE levels (Hahlweg & Wiedemann, 1999; Barbato & D' Avanzo, 2000). The evidence suggests that high EE families benefit more from family interventions (Kuipers *et al.* 1999; Askey *et al.* 2007), but caution must be taken in families with low EE, as it may increase the levels of EE (Askey *et al.* 2007). Also, the effect of high EE on relapse has not been replicated globally (e.g. Mexican-Americans) suggesting that cultural factors

might play an important role (Kopelowicz *et al.* 2002; Kealey, 2005; Kymalainen & Weisman de Mamani, 2008).

A parallel line of research has shifted the focus towards the consequences of severe mental illness for patients' caregivers. Family burden refers to a psychological state produced by the combination of physical work, emotional pressure, social restrictions, and financial difficulties arising from taking care of an ill relative (Caqueo-Urízar *et al.* 2009). It involves shame, embarrassment, and feelings of self-blame and guilt (Awad & Voruganti, 2008). Results indicate that relatives might suffer burden in different life domains, such as reduction of subjective health, restrictions in leisure time, daily routine and social contacts, occupational problems, and coping with the patients' symptoms and emotional problems (Möller-Leimkühler, 2005). Effective family interventions have been developed to treat burden in families (Nasr & Kausar, 2009), although not all findings concur (McDonell *et al.* 2003; González-Blanch *et al.* 2010).

A closely related and increasingly studied concept is Quality of Life (QoL), defined as the "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The WHOQOL Group, 1998, pg. 551). Although the QoL of schizophrenia patients has been widely studied, recent efforts have also focused on relatives' QoL (e.g. Fischer *et al.* 2004; Foldemo *et al.* 2005). Caregiving relatives of schizophrenia patients exhibit significantly lower QoL than the general population, resulting from fear of discrimination, concern about the care of the patient in later life and feeling a lack of security because of the patient (Fischer *et al.* 2004).

Support for relatives has focused on improving their knowledge about psychotic illnesses and reducing EE. Nevertheless, as the main providers of informal care for

patients, the recognition and support for other equally relevant concerns (e.g. guilt, economic restrains, patient's autonomy and risk for relapse) and unfulfilled needs (e.g. social support and satisfactory family relationships) that might affect relatives' QoL and put them at risk of psychopathology are necessary (Bloch *et al.* 1995; Caqueo-Urízar *et al.* 2009).

Patients' poor functioning and high symptom severity have generally been associated with increased EE (Rascón *et al.* 2008) and burden, (Foldemo *et al.* 2005; Parabiaghi *et al.* 2007; Roick *et al.* 2007) and poorer QoL in relatives (Angermeyer *et al.* 2006). Nevertheless, not all findings concur (Scazufca & Kuipers, 1996; Miklowitz, 2004; Möller-Leimkühler, 2005). Some studies suggest that burden is rather stable, and that symptom severity is not necessarily associated with a reduction in relatives' burden (Brown & Birtwistle, 1998).

The ongoing psychological distress experienced by relatives is also an important factor to be taken into account, as those with high levels of distress are likely to experience high EE (Barrowclough & Parle, 1997; Shimodera *et al.* 2000) and burden (Boye *et al.* 2001; Hanzawa *et al.* 2008). A causal relationship cannot be concluded in either direction; however, psychological distress implies mild symptoms that might be due to other factors apart from the probable stress of having an ill relative (e.g. health, work or economic problems of their own). Hence, it seems appropriate to consider the relatives' psychological distress as a suitable predictor of other related factors such as EE, burden, and QoL.

Underlying perceptions of relatives are important in explaining their reactions to illness (Miklowitz, 2004), and have implications both for identifying those at risk for poor adaptation and for designing strategies that might improve their well-being

(Barrowclough & Parle, 1997). Nevertheless, some specific dimensions of relatives' illness perception might be more influential than others. Caregivers' well-being seems to be related mainly to perceptions of the magnitude of the illness consequences for themselves, whereas their EE levels seem to be related to beliefs about their own (Barrowclough *et al.* 2001) or the patient's control (McNab *et al.* 2007) over the illness. Although some studies have found no association between illness perception and EE (Lobban *et al.* 2005), caregivers who rate patients as having little control have shown significantly poorer self-esteem and more stress and depression (Kuipers *et al.* 2007).

EE, burden and QoL are closely related concepts (Foldemo *et al.* 2005; Möller-Leimkühler, 2005; Caqueo-Urízar *et al.* 2009); however, they do not overlap completely. Hence, it is useful to explore all three in relation to previously related predictors in the same study. Learning about the specific and common underlying factors affecting EE, burden and QoL should enhance family interventions, thereby improving the outcomes of both patients and relatives. This should be of special importance in the short course of illness, when patients' relatives are most motivated for learning skills and the illness course is more malleable. Thus, the objective of the study was to identify factors that predict EE, burden and QoL levels in relatives of short-term course first-episode psychosis patients. The study aimed to explore whether relatives' illness perception and psychological distress are stronger predictors of EE, burden and QoL than patients' clinical and functional status. If patients' clinical and functional status accounts (almost) completely for relatives' adjustment and further impact on patients' risk for relapse and likelihood of receiving helpful support, it would seem to be less crucial to invest resources on refining current psychoeducational programs for relatives. However, if relatives' (mal)adjustment is related to specific factors, such as illness perception, relatively independent of patients' status, this would print out to the critical usefulness of

devoting therapeutic efforts tailored at this population. It was hypothesized that: 1) patients' poor clinical and functional status would relate to high EE and burden and to poor QoL in relatives; 2) relatives' high psychological distress and negative illness perception would relate to high EE and burden and to poor QoL; 3) relatives' psychological distress and negative illness perception would predict EE, burden and QoL better than patients' clinical and functional status.

Methods

Participants

The sample consisted of 65 patient-relative dyads recruited at the Yucatan Psychiatric Hospital (Mexico). Participation involved no economic compensation. Inclusion criteria were based on the following patient characteristics: (1) a primary DSM-IV-TR (APA, 2000) diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional, brief, or not otherwise specified, disorders; (2) occurrence of a first episode of psychosis between 1999 and 2005 (range of 3-10 years after first psychotic episode); (3) age at onset 15-45 years; (4) psychosis not of affective, organic, or toxic type, and (5) no evident intellectual disorder. At the time of the assessment, none of patients was hospitalized. In terms of current DSM-IV-TR diagnoses, 44 patients had schizophrenia (16 paranoid, 3 disorganized, 1 catatonic and 24 residual) and 21 patients had other types of psychoses (9 schizoaffective, 7 delusional, 2 schizophreniform, 2 brief, and 1 not otherwise specified). Patients' current mean age was 36.2 years (SD=9.9) and mean age at onset was 29.3 years (SD=9.7). There were no significant sex differences for either current ($t_{(63)}$=-0.80) or onset ($t_{(63)}$=-0.68) age. Mean illness course was 6.9 years

(SD=2.1). All patients had a short-term course of psychosis, that is, between 3 and 10 years had passed since the first psychotic episode. This range of time allows the inclusion of patients who have not been ill for a long time but have passed through the "critical period" of psychosis (Birchwood, 2000) when most significant decline occurs.

48 (73.8%) relatives were females. All relatives reported having contact with the patient at least once a week, and 58 (89.2%) lived with the patient. Relatives included 30 (46.2%) parents, 17 (26.2%) spouses, 7 (10.8%) siblings, 6 (9.2%) offspring, and 5 (7.7%) other relatives (grandmother, aunt, nephew, mother-in-law, and sister-in-law). Two of the relatives (3.1%) were illiterate, 38 (58.5%) had secondary or lower education (up to 9th grade), and the remaining 25 (38.5%) had partial/complete medium or higher education. Mean age of relatives was 48.7 years (SD=16.5) and did not differ significantly by sex ($t_{(63)}$= -1.10). Relatives' sex, age and educational level were not significantly related to any of the outcome measures.

Measures

EE was measured with the Family Questionnaire (FQ) (Wiedemann *et al.* 2002), a 20-item self-report instrument for measuring the EE status of relatives of patients with schizophrenia.

Burden was measured with the Caregiver Burden Interview (Zarith *et al.* 1980). Although originally designed for caregivers of people with dementia, it is used with relatives of schizophrenia patients (Hanzawa *et al.* 2008; Yusuf *et al.* 2009). It includes 22 items enquiring about relatives' relationships with the patient, physical and psychological well-being, finances, social life, and expectations.

QoL was measured with the WHOQOL-BREF (Lucas, 1998; The WHOQOL Group, 1998; Skevington *et al.* 2004), a 26-item instrument applicable cross-culturally to assess four main domains of subjective QoL: physical health, psychological well-being, social relationships, and satisfaction with the conditions of the immediate environment.

Psychological distress was measured with the 28-item General Health Questionnaire (GHQ-28; Goldberg & Hillier, 1979; Lobo *et al.* 1986). This instrument assesses somatic symptoms, anxiety-insomnia, social dysfunction, and depressive symptoms.

Illness Perception was measured with the Illness Perception Questionnaire – Schizophrenia Carers Version (IPQ-SCV; Barrowclough *et al.* 2001). Through 23 items relatives report on illness severity, its negative impact on psychological, social and economic functioning, its amenability to cure or control, and how chronic and/or fluctuating the illness is perceived to be. There are 6 subscales: consequences of illness for the patient, consequences of illness for the relative, control/cure of illness by patient and/or treatment, control/cure of illness by relative, chronic nature of illness, and episodic nature of illness.

The original selected measures differ in their score range: FQ and GHQ-28 are scored on a 4-point scale, whereas the Caregiver Burden Interview, WHOQOL-BREF, and IPQ-SCV are scored on a 5-point scale. Anticipating some participants might not be familiar with self-report Likert scales and to ensure the reliability of the data collection, we unified the rating of all scales: items were read aloud by the interviewer and participants responded by pointing at one of four drawn squares, from the smallest (“not at all” =1) to the largest (“definitely yes” =4).

Patients' current clinical status was rated with the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987; Peralta & Cuesta, 1994). The PANSS is widely used for the assessment of positive and negative symptoms, and general psychopathology. Patients' current functional status was rated with the Global Assessment of Functioning (GAF) Scale (APA, 2000), which rates overall functioning from 0 to 100.

Statistical analyses

First, Pearson correlations were used to analyse the associations between each of the predictor and outcome variables. Next, a series of hierarchical regressions were computed to predict EE, burden and QoL using patient and relative factors. The primary goal of the regression analyses was to examine whether relatives' psychological distress and illness perception accounted for variance in the dependent variables over-and-above patient factors (symptom severity and functioning). The following steps were entered in all regression analyses. The PANSS total score was entered at step 1 to examine the variance accounted for by patient symptom severity. Patients' GAF score was entered at the second step to examine variance accounted for by patient functioning. Relatives' total GHQ-28 was entered at step 3 to examine variance accounted for by relatives' psychological distress. The six IPQ-SCV subscales were entered as a block at step 4 to examine the variance accounted for by relatives' perception of the patient's illness. The individual scale scores, rather than the total score, were used to test specific relations of the subscales with the dependent variables.

Results

Descriptive data are presented in Table 1. EE and burden scores were generally low as 83.1% and 93.8% of sample respectively scored below the 2.5 mid-point. QoL showed overall satisfactory levels, as only 7.7% of sample scored below the mid-point. EE was significantly related to both QoL ($r=-0.27$, $p<0.05$) and burden ($r=0.72$, $p<0.001$), and these two were also significantly related to each other ($r=-0.33$, $p<0.01$).

Predictor and outcome variables showed low to moderate correlations, although most of them were significant (Table 2). Patients' functional status was significantly associated to EE, burden and QoL, whereas patients' clinical status was significantly associated only to the first two. Relatives' psychological distress was the factor most consistently related to relatives' EE, burden and QoL across all dimensions. Negative illness perception dimensions were mostly related to EE and burden. From all illness perception dimensions, only the relatives' view of negative consequences of the illness for themselves was related to all three outcomes.

Note that for the hierarchical regressions the total PANSS and GHQ-28 scores were used because 1) specific hypotheses were not offered about the impact of each PANSS or GHQ-28 dimensions, 2) positive intercorrelations were found among the PANSS symptom dimensions (.54 to .73) and the GHQ-28 subscales (.21 to .75), and 3) each PANSS and GHQ-28 dimensions were similarly related to outcome variables (Table 1). Given the differential associations between illness perception dimensions and the outcome variables, all subscales were entered in the analysis.

Table 1. Descriptive Statistics for Relatives (*n*=65) and Patients (*n*=65)

Variable	Scale	Mean (SD)	Range	Cronbach 's alpha
Relatives' outcome				
Expressed emotion	Family Questionnaire	1.9 (0.5)	1.2 – 3.0	0.84
Burden	Caregiver Burden Interview	1.8 (0.4)	1.1 – 3.0	0.82
Quality of life	WHOQOL-BREF	3.3 (0.5)	2.1 – 4.0	0.92
Patient predictor factors				
Clinical status	PANSS	49.3 (16.0)	30 – 93	0.89
	Positive symptoms	10.6 (4.1)	7- 25	0.68
	Negative symptoms	12.5 (5.9)	7 – 30	0.83
	General psychopathology	26.2 (7.9)	16 - 48	0.76
Functional status	GAF	72.5 (18.4)	30 - 100	-
Relative predictor factors				
Psychological distress	GHQ-28	1.6 (0.5)	1.0 – 3.2	0.92
	Somatic symptoms	1.7 (0.7)	1.0 – 3.7	0.80
	Anxiety-insomnia	1.6 (0.7)	1.0 – 3.9	0.85
	Social dysfunction	1.9 (0.7)	1.0 – 3.6	0.85
	Depression	1.2 (0.6)	1.0 – 3.7	0.94
Illness perception	IPQ-SCV	2.6 (0.4)	1.8 – 3.4	0.61
	Consequences-patient	2.6 (0.5)	1.0 – 3.4	0.31
	Consequences-relative	2.3 (0.6)	1.0 – 3.8	0.38
	Control-cure of illness	3.0 (0.5)	2.0 – 4.0	0.15
	Control-cure by relative	2.7 (0.9)	1.0 – 4.0	0.39
	Timeline-chronic	2.7 (1.1)	1.0 – 4.0	0.78
	Timeline-episodic	2.6 (0.9)	1.0 – 4.0	0.65

PANSS : Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; GHQ-28 : 28-item General Health Questionnaire; IPQ-SCV: Illness Perception Questionnaire – Schizophrenia Carers Version.

Table 2. Pearson Correlations Between Predictor (Patient and Relative Factors) and Relatives' Outcome Variables (n=65)

	Expressed emotion	Burden	Quality of life
Patient factors			
Patient clinical status			
PANSS	**0.47*** **	**0.36** **	-0.17
Positive symptoms	**0.37** **	**0.24***	-0.10
Negative symptoms	**0.40*** **	**0.38** **	-0.17
General psychopathology	**0.45*** **	**0.32** **	-0.18
Patient functional status			
GAF	**-0.50*** **	**-0.44*** **	**0.30** **
Relative factors			
Psychological distress			
GHQ-28	**0.46*** **	**0.46*** **	**-0.74*** **
Somatic symptoms	**0.45*** **	**0.36** **	**-0.64*** **
Anxiety-insomnia	**0.46*** **	**0.41*** **	**-0.54*** **
Social dysfunction	0.21	**0.34** **	**-0.58*** **
Depression	**0.31** **	**0.30** **	**-0.52*** **
Illness perception			
IPQ-SCV	**0.38** **	**0.51*** **	-0.11
Consequences-patient	**0.24***	**0.32** **	-0.00
Consequences-relative	**0.35** **	**0.45*** **	**-0.35** **
Control-cure of illness	-0.06	-0.11	**0.28***
Control-cure by relative	**0.25***	**0.30***	0.02
Timeline-chronic	**0.27***	**0.45*** **	-0.19
Timeline-episodic	0.13	0.19	-0.05

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001
Medium effect sizes (r≥0.30) in bold, large effect sizes (r≥0.50) in bold and italics.
PANSS : Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; GHQ-28 : 28-item General Health Questionnaire; IPQ-SCV: Illness Perception Questionnaire – Schizophrenia Carers Version..

Hierarchical regression for EE (Table 3) revealed that patients' clinical status and relatives' psychological distress significantly accounted for variance in EE. Neither patients' functional status nor any of the relatives' illness perception measures accounted for significant variance in the model.

Table 3. Hierarchical Regression for Expressed Emotion in Relatives of Short-term Course Psychosis Patients (*n*=65)

Step	Predictors	ß	ΔR^2	*p*
1	Patients' clinical status (PANSS Total score)		0.216	<0.001
2	Patients' functional status (GAF)		0.041	0.069
3	Relatives' psychological distress (GHQ-28 Total score)		0.128	<0.001
4	Relatives' illness perception (IPQ-SCV)		0.045	0.632
	Consequences-patient	0.061		0.620
	Consequences-relative	0.071		0.597
	Control-cure of illness	-0.014		0.906
	Control-cure by relative	0.181		0.108
	Timeline-chronic	0.081		0.504
	Timeline-episodic	-0.047		0.672
	Total $\underline{R}^2$		0.430	<0.001

PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; GHQ-28: 28-item General Health Questionnaire; IPQ-SCV: Illness Perception Questionnaire-Schizophrenia Carers Version.

In terms of burden (Table 4), each of the four steps accounted for a significant increment in variance. Among the illness perception subscales, perception of controllability of illness by relative and chronicity accounted for variance over-and-above the other variables in the model.

Table 4. Hierarchical Regression for Burden in Relatives of Short-term Course Psychosis Patients (*n*=65)

Step	Predictors	ß	ΔR^2	*p*
1	Patients' clinical status (PANSS Total score)		0.132	0.003
2	Patients' functional status (GAF)		0.057	0.040
3	Relatives' psychological distress (GHQ-28 Total score)		0.128	0.001
4	Relatives' illness perception (IPQ-SCV)		0.190	0.005
	Consequences-patient	0.063		0.582
	Consequences-relative	0.232		0.066
	Control-cure of illness	-0.122		0.259
	Control-cure by relative	0.265		0.013
	Timeline-chronic	0.272		0.018
	Timeline-episodic	0.003		0.977
	Total $\underline{R}^2$		0.507	<0.001

PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; GHQ-28: 28-item General Health Questionnaire; IPQ-SCV: Illness Perception Questionnaire-Schizophrenia Carers Version.

Patient functioning, relatives' psychological distress, and relatives' illness perception accounted for significant increments in QoL variance (Table 5). Among relatives' illness perception subscales, both illness consequences for patients and relatives, as well as controllability of illness by patients/treatment accounted for significant variance.

Finally, note that the combination of the patient and relative predictors accounted for 43% to 69% of the total variance in the dependent variables.

Table 5. Hierarchical Regression for Quality of Life in Relatives of Short-term Course Psychosis Patients (*n*=65)

Step	Predictors	ß	ΔR^2	*p*
1	Patients' clinical status (PANSS Total score)		0.030	0.165
2	Patients' functional status (GAF)		0.088	0.015
3	Relatives' psychological distress (GHQ-28 Total score)		0.443	<0.001
4	Relatives' illness perception (IPQ-SCV)		0.129	0.003
	Consequences-patient	0.188		0.041
	Consequences-relative	-0.259		0.011
	Control-cure of illness	0.247		0.005
	Control-cure by relative	0.160		0.055
	Timeline-chronic	0.023		0.796
	Timeline-episodic	0.005		0.951
	Total $\underline{R}^2$		0.690	<0.001

PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; GHQ-28: 28-item General Health Questionnaire; IPQ-SCV: Illness Perception Questionnaire-Schizophrenia Carers Version.

Discussion

Our results confirmed, to some extent, the first hypothesis that poor clinical and functional status of patients would be associated with high EE and burden and to poor QoL of their relatives. However, our most important finding was that relatives' psychological distress accounted for variance over-and-above the patient variables in the prediction of the three dependent variables, and relatives' illness perception accounted for significant variance for burden and QoL, over-and-above all of the predictors in the model. Relatives' burden was predicted by their perception of illness as chronic and of their own capacity to influence patients' illness. Relatives' perception of consequences of illness for patients and themselves, and of the controllability of illness by the patient and/or treatment, predicted QoL.

Relatives' perception of illness as being under the control of the patient and/or treatment rather than under their own control relieves burden and favours QoL. This suggests that attribution of control to external factors is an important aspect when coping with having an ill relative, reducing self-blame and the weight of responsibility. Furthermore, it has been suggested that beliefs on patient and treatment control over the illness should ideally be considered as independent factors. Fortune *et al.* (2005) found that caregivers holding a strong belief that their relative could exert personal control over their psychosis tended to report more distress, while stronger beliefs in treatment control was associated with less self-reported distress. Even though our sample included patients with no more than 10 years of illness, results showed that relatives' perception of illness as chronic predicted higher burden. Carers can be more pessimistic than patients regarding illness persistence, particularly those who are stressed (Kuipers *et al.* 2007). Results also showed that QoL of caregivers is resented by their perception of illness as affecting their own lives as well as patients'. This underscores the involvement and empathy of caregivers towards their ill relative. Psychosis affects to a greater or lesser degree the lives of patients and also of their close ones. Families have an important role in patients' illness but undeniably they find themselves also in need of support.

In consistence with some previous studies, overall patients' clinical and functional status was related to relatives' EE (Rascón *et al.* 2008) and burden (Parabiaghi *et al.* 2007), but not to QoL (Möller-Leimkühler, 2005). Initial research on EE viewed criticism and overinvolvement attitudes in families as threatens to a vulnerable patient, who in consequence relapsed. Alternatively, EE can be seen as a reflection of disturbances in the transactional patterns of the entire family system. The patient might have shown early temperamental, cognitive or behavioural disturbances as signs of liability to psychiatric disorders. In turn, other family members, due to their own personality and psychological

features, could be prone to react with frustration, anxiety, criticism, or overprotective guilt. The patient is influenced by these attitudes and his/her own behaviour feeds back on the family. Thus, a tense family dynamic establishes, likely to trigger relapse (Miklowitz, 2004). It is remarkable that even though on average patients showed a relatively low level of psychopathology, clinical and functional status were still related to their relatives' burden. A relative might feel particularly overwhelmed, confused or distressed by patient's (even) mild residual symptoms and poor functioning, wondering if the patient is really getting better, and how much longer it will take to recover. The associations of burden with the relatives' perception of illness as chronic and with the magnitude of the illness consequences for themselves and for the patients support this interpretation.

It was also hypothesized that relatives' psychological distress and negative illness perception would relate to high EE and burden and to poor QoL. Even though relatives' psychological distress was strongly related to their EE, burden and QoL levels, a causal relationship cannot be concluded in either direction. Relatives might react negatively because of their own temperamental disturbances, enhanced by the strain of taking care of an ill relative (Miklowitz, 2004). Psychological distress might well reflect a vulnerability to psychopathology shared among parents, siblings and offspring. Signs of disturbance under the clinical threshold in relatives should be addressed in order to prevent a transition to psychopathology and to enhance a more stable family environment for the patient. Overall negative illness perception was related to EE and burden, but not to QoL. Unlike EE and burden, QoL involves relatives' life dimensions beyond their relationship with the patient, and that might be reflected in a less consistent association with dimensions of illness perception. Interestingly, the perception of the magnitude of the illness consequences for the relative was related to high EE and burden, and to low QoL. Families cannot be seen exclusively as a causal factor of illness to be controlled; illness of

a family member affects the other members as well, particularly the one who assumes the role of main caregiver.

Overall this sample of relatives of short-term course psychosis patients did not show high levels of EE and burden, or severely affected QoL. Studies with similar results have proposed that one explanation for this could be that relatives in some way can become habituated to their situation (Foldemo *et al.* 2005). However, the inclusion in our sample of relatives of both patients who still suffer severe or subtle symptoms as well as patients who have improved and/or never relapsed (i.e. residual schizophrenia, schizophreniform and brief psychotic disorders) might account for these favourable results. Moreover, the cultural background of our sample is an important fact to take into consideration. Research has found that families of schizophrenia patients with a Mexican background are less critical of their ill relatives than Caucasians (Kopelowicz *et al.* 2002) and exhibit low EE levels (Kopelowicz *et al.* 2006; Dorian *et al.* 2008). Mexican-American caregivers seem particularly accepting of their relative's illness, showing non-blaming and low aversive responses to patient's behaviour (Dorian *et al.* 2008). Hence, it is important to consider the ethnic background of patients and their families when developing strategies for mental health care and research.

The present study contributed to our understanding of psychological well-being in relatives of short term-course first-episode psychosis patients. Relatives' psychological distress and illness perception dimensions stood over patients' clinical and functional status as significant predictors of both burden and QoL. Psychoeducational programs for families adequately provide information and train skills to cope with the ill relative, but possibly it is more needed to focus on the impact of illness on the physical and mental well-being of the caregivers themselves. Providing relatives the opportunity to express

their concerns about the consequences of illness for the patient and themselves, as well as psychological support for their own distress, might bring further benefits for both patient and relatives.

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Appendix 4. Curriculum vitae

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Posgraduate Education

PhD student of the Doctorate in Child, Adolescent and Adult Psychopatology
***Universidad Autónoma de Barcelona* (Spain).**
Supervisor: Professor Neus Barrantes-Vidal.

MSc Developmental Neuropsychology
***University of Essex* (United Kingdom)**
Supervisor: Professor Arnold Wilkins.

Undergraduate Education

BA Psychology

***Universidad Autónoma de Yucatán* (Mexico)** **1993 – 2000**

Supervisor: Silvia Bobadilla, MA.

Work Experience

- **Departamental Administrator**

  Justo Sierra O'Reilly College, Psychology Department Feb 2003 – Aug 2004

- **Spanish as a Second Language Teacher**

  Autonomous University of Yucatan, Faculty of Education May 2003 – Jul 2004

- **School Counsellor**

  Continental, Primary and Secondary School Ago 2001 – Feb 2003

- **English as a Second Language Teacher**

  Harmon Hall, Private School of English as a Second Language Sep 1999–Jul 2000

Other Qualifications

Languages

- Spanish native speaker
- Proficiency level of English
- Advanced level of French
- Basic level of Italian

Computer Skills

- Diploma in Computer Applications. Universidad Mesoamericana de San Agustin (Mexico).
- Statistical Package for the Social Sciences (SPSS, 15)

Appendix 5. List of articles

- Gómez-de-Regil, L., Kwapil, T.R., Blanqué, J.M., Vainer, E., Montoro, M., Barrantes-Vidal, N. (2010). **Predictors of outcome in the early-course of first-episode psychosis**. *European Journal of Psychiatry, 24(2), 87-97*.

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