Universitat Autònoma de Barcelona

A 10-YEAR LONGITUDINAL STUDY OF SUSTAINED ATTENTION ACROSS ADOLESCENCE IN A COMMUNITY SAMPLE:

Neurocognitive, Personality, and Biobehavioural Correlates

Doctoral thesis presented by

Eva Mª Álvarez Moya

Directed by

Prof. Jordi E. Obiols Llandrich

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"La inespecificidad es la pesadilla y el gran interrogante de todos los estudios biológicos psiquiátricos"

"Unspecificity is the nightmare and the big question of all psychiatric biological studies"

Julio Sanjuán

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THEORETICAL BACKGROUND

1. INTRODUCTION

High-risk studies, addressed to the ultimate objective of early detection of psychopathology, have generated a lot of research on the so-called vulnerability markers for schizophrenia. However, no specific markers have been identified so far. Most studies to date yield inconclusive results and few of them report positive cases for psychotic disorders in their follow-ups.

The most used strategy in high-risk research, i.e., the genetic high-risk strategy, has revealed, however, only moderately useful to identify such markers, as its results are hardly generalizable to all cases and it yields a high proportion of false positives (and false negatives).

Alternatively, other methodologies have been proposed, as the endophenotypical and the exophenotypical high-risk studies (cohort studies). As we will see later in this theoretical background, cohort studies take a psychobiological (endophenotypic) or a behavioural (exophenotypic) variable as the risk criterion and carry out a follow-up of those individuals from the general population who present such marker.

The present project is framed on the last group of studies. We will present here a longitudinal prospective study of the sustained attention deficit throughout adolescence in a Catalan community (general population) sample. The initial objective of this project, started in 1992, was to establish the capacity of the sustained attention deficit to predict later development of schizophrenia spectrum disorders. For this reason, we selected two cohorts from the general population according to the absence (Index cohort) or presence (Control cohort) of such sustained attention deficit. Therefore, our objective focused on the early-detection of psychotic disorders. Nevertheless, the long follow-up carried out (10 years) generated a high level of attrition in our sample up to the point that this initial objective had to be dismissed. The final sample size was too small to perform the kind of statistical analyses required to establish the predictive power of the sustained attention deficit in relation to the later

appearance of schizophrenia spectrum disorders. In addition, no clear psychotic cases were found at the end of the follow-up.

This inconvenience led us to reformulate our initial objective and to set up a new main objective: to explore the development of the sustained attention deficit throughout adolescence and to determine its correlates at different levels of functioning (neurocognition, personality, psychosocial, neurointegrative, etc.). Parallel, we tried to settle on the associations between different putative vulnerability/risk markers for psychopathology along the different phases of the project.

In the present report, we focused on three main aims: a) to establish the phenotypical profile of our cohorts in early adulthood (last assessment), b) to identify and describe different subgroups of subjects according to their profile of attentional development through adolescence, and c) to explore cross-sectional associations between a widely used putative vulnerability marker, i.e., psychometric schizotypy, and some endophenotypical variables, in particular neurocognitive factors. The analyses of previous phases of this project have been reported elsewhere (Barrantes-Vidal, Fañanás, Rosa, Caparrós, Riba, & Obiols, 2002; Obiols et al., 1997; Obiols, Serrano, Caparrós, Subirà, & Barrantes, 1999; Rosa et al., 1999).

Based on the objectives previously mentioned, the theoretical background will begin with a first section addressed to developmental issues, in general, and applied to schizophrenia, in particular. Secondly, we will introduce some aspects on high-risk research in schizophrenia. Thirdly, considering the main role that the sustained attention deficit has in our study, a special section will be dedicated to discuss general aspects on attention and cognitive development. Finally, we will focus on the concept of schizotypy and its relationship with schizophrenia spectrum disorders.

2. DEVELOPMENTAL PSYCHOPATHOLOGY AND SCHIZOPHRENIA

2.1 Developmental psychopathology

The term "developmental" is often used to refer to *childhood* issues, but development also occurs after childhood. In addition, this term can be used to refer to the changes and inconsistencies that an *individual* exhibits over time. Finally, "developmental" can refer to a *characteristic* (i.e., schizophrenia) that shows a sequence of preceding states.

According to Pogue-Geile (1997), a developmental function is not flat or uniform across age. The change can be **linear** (the rate of change is constant and not

associated with age) or **non-linear** (the rate of change across age may vary with age). Though both changes are developmental, the most truly developmental change is the non-linear one, as some age periods differ from others in their rate of change. In this respect, a non-linear mean developmental function implies that changes over time covary with age in a group. The reason for this covariation can be double: a) *age-environment covariation*: changes in acceleration with age can be created by a covariation between age and exposure to some environmental causal factors, and b) *age-gene expression covariation*: the expression of certain genes could covary with age.

A mean non-linear developmental function usually exhibits both *peak* acceleration as well as some *variation* in acceleration. The causes of both phenomena may (or may not) be different. Anyway, phenotypic changes over time may be due to either change in environmental exposure or gene expression. In this regard, it is important to distinguish between the causes of changes themselves and the causes of any covariation between them and age.

Developmental psychopathology (Cicchetti, 1989; Rutter, 1996) represents the bringing together of a number of disparate approaches and theoretical concepts to the study of psychopathology over the lifespan (Stroufe & Rutter, 1984; Rutter, 1988). This perspective highlights the importance of finding answers to questions about the ways in which risk and protective factors interact to produce disorder, considering that the study of normal development is fundamental to understand psychopathological conditions and vice versa. Individuals are viewed as developing along flexible trajectories which can be influenced at any point in the lifespan, to either increase or reduce the risk of disorder. It is in this context where the concept of "**heterotypic continuity**" appears. This term describes the differing age-dependent manifestations of the same underlying phenomenon or disorder. This is contrasted to the idea of "**homotypic continuity**", which makes reference to those disorders that present in a similar way at different ages. Incidentally, age at onset is regarded as a variable of key interest because factors influencing timing of onset may provide important clues to the primary causes of the disorder. From a developmental psychopathology point of view, psychopathological disorders are not seen to emerge from the unfolding of a disease process; rather they are seen to arise out of a dynamic, transactional relation between the developing capacities of the individual and the changing demands of the environment. Disorder may then arise at a point in development when the gap between an individual's capacities and the demands of the environment exceed a critical threshold (Hollis & Taylor, 1997).

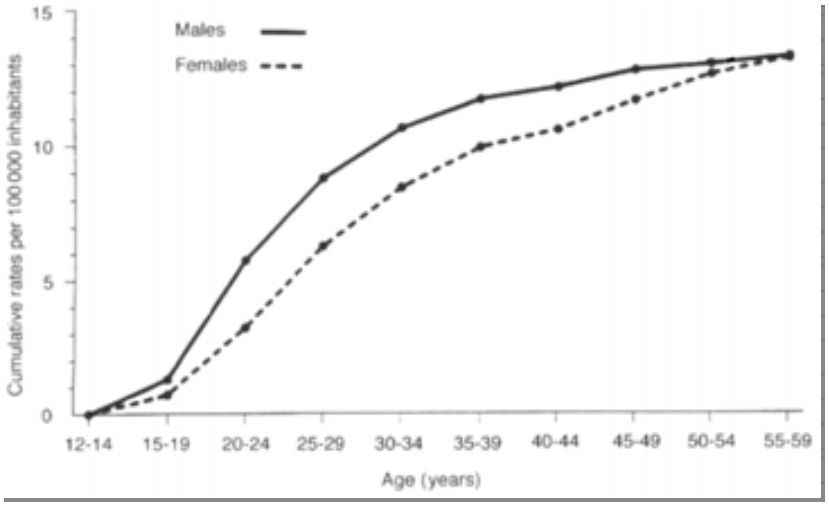
2.2 Schizophrenia as a developmental disorder

The notion of a developmental origin of schizophrenia was already present in XIXth century authors. For instance, Hecker (1871) stated that hebephrenia is a disease that invariably erupts after puberty, mostly in individuals with previous milestone retards. Clouston (1891) described the "adolescent/developmental insanity" that referred to a psychotic condition affecting adolescents and young adults, particularly males, and that in 30% of cases proceeded to a "secondary dementia". Later, Southard (1915) reported brain changes in psychotic patients considered to be of developmental origin (Lewis, 1989). Unfortunately, Krapepelin's wider concept of dementia praecox incorporated, and eclipsed, those first descriptions and findings, but these ideas were again retrieved in modern developmental theories of schizophrenia.

In this regard, schizophrenia is considered a non-linear mean developmental function for **onset** with peak acceleration in young adulthood. Our primary evidence for a role of developmental processes in schizophrenia comes from the nature of its age incidence distribution and its peak during the young adulthood (Hambrecht, Maurer & Häfner, 1992; Häfner, Hambrecht, Loffler, Munk-Jorgensen & Riecher-Rössler, 1998). Its age incidence distribution is cumulative along the lines of a developmental function. Therefore, the risk for onset of schizophrenia varies with an individual's age. Moreover, the existence of brain abnormalities in schizophrenia indicates that its onset is a sort of neuro-developmental phenomenon (Murray & Lewis, 1987; Murray, Lewis & Reveley, 1985), as we will see later.

One of the most rigorous studies on age incidence in schizophrenia is that of Häfner, Maurer, Löffler and Riecher-Rössler (1993) in Germany. They estimated a cumulative annual incidence of schizophrenia of 13.21 per 100,000 for male, and 13.14 per 100,000 for female. Although some recent studies have suggested that total risk for schizophrenia may be higher in males than females, most studies observe no sex differences (Hambrecht, Riecher-Rössler, Fätkenheuer, Louza, & Häfner, 1994). However, the shape of the age incidence distributions differs between males and females (Angermeyer & Kühn, 1988). At earlier ages, males show a steeper slope than females, whereas at later ages females show the steeper slope (see Figure 1.1). The peak annual incidence of hospital admission occurs in the age-band of 20-24 years for males, whereas for females the peak annual incidence is in the age-band for 25-29 years, with a second small peak at 45-49 years old.

Figure 1.1 *Cumulative age incidence distribution of hospital admissions for broad definition of schizophrenia (extracted from Hambrecht et al., 1992)*



Gender differences in schizophrenia (males show earlier age of onset –Castle, Wessely, & Murray, 1993; more negative symptoms and worse outcome –Castle & Murray, 1991; etc.) have been postulated to result from the modulating effects of sex on foetal brain development (Bullmore, O'Connell, Frangou & Murray, 1997). However, some controversial exists on the gender differences in age of onset of the disease. Thus, while most authors agree in the earlier age of onset for males, others have described some interesting specifications. In particular, it has been found a slight excess of females initiating the disease (or the first psychotic symptoms) around puberty (coinciding with menarche) followed then by an excess of males through adolescence (e.g., Galdós, Van Os & Murray, 1993). Therefore, the latter datum would explain the generalized agreement in the earlier age of onset for males. By the way, males seem to be more vulnerable than females to prenatal and birth complications (e.g., O'Callaghan, Gibson, Colohan, Buckley, Walshe & Larkin, 1992), so these hazards have been proposed as the critical early environmental effect that may contribute to the greater premorbid abnormalities observed in male schizophrenics, as well as to their earlier onset of schizophrenia (e.g., Cantor-Graae, McNeil, Nordstrom & Rosenlund, 1994; McGrath & Murray, 1995). Therefore, childhood abnormal characteristics may reflect sex-modulated vulnerability to environmental effects operating at a prenatal level (Bullmore et al., 1997). That is why some authors (Lewine, 1988; Pogue-Geile, 1997) suggest that developmental functions for schizophrenia should be separated for males and females.

In summary, schizophrenia should be considered as a "developmental" disorder, as its age of clinical onset shows a non-linear distribution, or developmental function. The peak acceleration of schizophrenia's developmental function is during the late teens

and early twenties and varies slightly depending on gender, but the reasons of these differences remain still unknown.

Next we will review neurodevelopmental theories, developmental genetics, neuroanatomical findings, and questions on psychopathological continuity across the lifespan in schizophrenia.

2.2.1 Neurodevelopmental models of schizophrenia

To date, three general models of schizophrenia development have been proposed, i.e., early-neurodevelopment models, late-neurodevelopment models, and stage (risk factors) models.

- *Early-neurodevelopment models of schizophrenia*

The (early) neurodevelopmental theory is the most popular of the developmental models mentioned before. It hypothesizes that the development of the brain and psychological pathologies that are specific to schizophrenia first occur "early" and are abnormalities in *in utero* brain development (Murray & Lewis, 1987; Weinberger, 1987; Pogue-Geile, 1991). This hypothesis states that in some critical moment of pre- or perinatal neurodevelopment (probably during the second trimester of pregnancy), a maturation impairment of certain brain structures may have occurred in the foetus. This damage would be a static lesion. The aetiology of individual differences in these early abnormalities has been hypothesized to be genetic (i.e., expressed *in utero*) and/or environmental (e.g., *in utero* viral infection such as influenza –Munk-Jørgensen & Ewald, 2001, or other obstetrical insults), with more emphasis recently being paid to environmental hypotheses. According to this model, this brain damage would remain relatively "silent" (clinically absent) during childhood, giving rise only to subtle behavioural symptoms. In adolescence, or early adult life, however, this lesion would manifest clinically in the form of psychotic symptoms.

In this regard, Bullmore et al. (1997) proposed the "dysplastic net hypothesis", which integrates the early neurodevelopmental model of schizophrenia and the theory that schizophrenic symptoms arise from abnormal neuronal connectivity (Frith et al., 1995; Gold & Weinberger, 1995). According to this hypothesis, dysconnectivity of the adult schizophrenic brain is determined by dysplastic *foetal* brain development. Disturbances on the brain network would lead to the decrease of interregional volume correlations in schizophrenic patients, in particular between frontal and temporal brain regions. The fact that during the second half of gestation exuberant axonal projections first invade the cortical plate and compete for synaptic territory has lead to the

supporters of this hypothesis to propose that the neurodevelopmental mechanisms determining adult patterns of cortico-cortical connectivity occur during this period. In addition, sex-modulated patterns of cerebral asymmetry become macroscopically evident during the second half of pregnancy. If brain development is indeed disordered at this stage in pregnancy, one would expect to find abnormal patterns of cerebral asymmetry in adult schizophrenics, a modulating effect of sex on abnormal brain structure and function, and psychological deficits compatible with impaired neurocognitive network function in adulthood. The origin of these pathogenic processes could lie on abnormalities in those genes controlling brain development in the second half of pregnancy (supported by evidence of abnormal cerebral asymmetry), and/or on diverse environmental risks in pregnancy (hypoxia-ischemia, viral infection) which might induce cortico-cortical dysconnectivity, possibly by the "final common pathway" of glutamatergic excitotoxicity.

Therefore, the critical neuropathological events for the development of schizophrenia are hypothesized to occur in foetal or early postnatal brain development, so premorbid abnormalities are viewed as manifestations or underlying brain pathology. The *in utero* developmental period has been emphasized primarily because of the dramatic brain changes that occur at that time. However, the question on why psychotic symptomatology does not appear until adolescence / young adulthood still remains unclear, so such hypothesis requires some additional mechanism to explain the long delay between these early abnormalities and the much later onset of schizophrenic symptoms. It is in this attempt to explain this "delay" where this model addresses the developmental aspects of schizophrenia and its age of peak clinical onset. In this respect, there are two explanatory approaches:

- Paul Meehl's point of view, which will be extendedly reviewed later, suggests that the onset of schizophrenia depends on both the addition of a series of pathogenic experiences necessary (but not sufficient) during childhood and adolescence, and the presence of early brain abnormalities due to an early expressed gene. The critical combination or number of risk factors is usually reached no earlier than young adulthood, leading to schizophrenia. These individuals with the mutant gene (*schizotaxic*) that are not exposed to the relevant noxious experiences will never develop schizophrenia, although they manifest a "*forme frustrée*", i.e., schizotypy (Meehl, 1962, 1989, 1990). Meehl never clarified why this accumulation of experiences peaks during young adulthood, however. In this model, environmental experiences across ages

serve both to affect the eventual risk for schizophrenia among schizotaxic subjects, and to delay the onset of schizophrenia until young adulthood.

- Recent early development models (e.g., Randall, 1980; Murray & Lewis, 1987; Weinberger, 1987) give a role for *normal* developmental brain changes during young adulthood in accounting for the "delay" in onset of schizophrenia symptoms. Thus, brain abnormalities sufficient to produce schizophrenia are present *in utero* but they do not "release"/manifest until developmental brain changes (brain maturation) that typically occur during adolescence and young adulthood (e.g., myelination of the corticolimbic circuits –Benes, 1989) appear. Yet these authors do not consider explicitly the causes of these normal brain development changes during young adulthood. According to them, normal later experiences and/or genetic expression serve only to time the onset of symptoms, but not to alter risk across individuals.

As a whole, the basis of early-neurodevelopmental models would be the following:

1) The neurodevelopmental disturbance should be visible premorbidly.

2) There is a trait neurobiological disorder (endophenotype) that should be present both at a premorbid level and after clinical onset of the disease (state level).

3) There would be an early brain lesion causing the neurodevelopmental damage and manifesting on the endophenotype, on premorbid neurobehavioural characteristics and on the subtype of schizophrenia.

4) There would be male predominance and pre- and/or perinatal complications (Goodman, 1991.

- *Late-development models of schizophrenia*

Late-development theories of schizophrenia hypothesize that brain abnormalities specific to schizophrenia appear *late*, usually during young adulthood and relatively close in time to the onset of clinical symptoms. These models address more directly the developmental aspect of schizophrenia, i.e., its peak age of onset in young adulthood, and they do not postulate different processes for the onset of pathogenesis and the onset of symptoms, unlike early-development models.

The most clearly proposed late-development model of schizophrenia is that by Feinberg (1982-93). This author suggests that schizophrenia may arise from brain

changes that normally take place during late adolescence / young adulthood. Thus, a failure to terminate certain normal brain changes (e.g., synaptic pruning) or abnormalities in the beginning of other brain processes (e.g., myelinization) during this period are some suggested possibilities for the onset of the neurodevelopmental impairment and the clinical symptoms of schizophrenia (e.g., Keshavan, Anderson, & Pettegrew, 1994), according to this model.

Anyway, although there are several hypothetical proposals, such abnormalities in normal brain processes that may lead to the development of schizophrenia during young adulthood have not been identified yet. Similarly, the precise normal brain changes affected during this period remain still unknown.

Considering that schizophrenia exhibits a developmental function for its onset, one should expect that the abnormalities that trigger it affect some normal developmental function/s. In this regard, *synaptic density* is one of the most consistently reported candidates to be affected in relation to the onset of this disorder (Feinberg, 1982-83; Feinberg, Thode, Chugani, & March, 1990; Keshavan et al., 1994).

Synaptic density shows a mean non-linear developmental function characterised by a dramatic increase until the age of 2 years old followed by a progressive decline that reaches a plateau in late adolescence. It results from two processes: an initial overproduction (synapse generation) and a subsequent pruning (synapse elimination) of neural elements (Huttenlocher, 1979, 1994). Additionally, these processes would be presumably controlled by "synaptic generation genes" and "synaptic pruning genes", respectively. This is the normal development of synaptic density, and the fact that its plateau is attained during the same lifetime period during which schizophrenia onset shows its highest acceleration has lead to some authors (Feinberg, 1982-83; Feinberg et al., 1990) to consider it the cornerstone of the pathogenesis of this disease.

Feinberg (1982, 1982-83, 1997; Feinberg et al., 1990) postulates that extensive maturational changes in the physiology and function of the human brain take place over the second decade of life, and that these changes would be the consequence of the late elimination of cortical synapses proposed by Huttenlocher (1979, 1994). From his point of view, such pervasive neuronal arrangements might sometimes go wrong and disrupt the integration of different brain circuits or systems ("neuronal disintegration"), therefore leading to the onset of schizophrenia. Incidentally, taking into account that normal brain changes are controlled by changes in gene expression, one can speculate that brain abnormalities in schizophrenia may be also due to abnormalities in such gene expression (genetic polymorphisms). Anyhow, it is

still unknown whether abnormalities on synaptic pruning result from elimination of "too few, too many, or the wrong" synapses (Feinberg, 1997; Pogue-Geile, 1991).

These authors have proposed that, in addition to genetic abnormalities on the extent of synaptic pruning, there may also be polymorphisms affecting the *rate* of pruning. The normal variation in this mechanism would be at the origin of individual differences in age at which pruning terminates. By the way, it has been speculated that the expression of these synaptic pruning rate genes would be modulated by genes on the sex chromosomes that would produce a slower rate of pruning among females. This normal process would probably account for the observed gender differences in age of onset for schizophrenia.

- *Stage models of schizophrenia*

Stage models of schizophrenia state that early brain pathology acts as a *risk factor* rather than a sufficient cause, so that its effects can only been understood in the light of the individual's later exposure to other risk and protective factors. According to this model, schizophrenia would be preceded by an invariable sequence of developmental stages, each with its age-specific manifestations (e.g., neuromotor difficulties in infancy, attentional problems in mid-childhood and early adolescence). The main difference from a deterministic (early) neurodevelopmental model would be that each stage acts as a filter with only a proportion of cases moving on to the next stage. The authors defending this model (Hollis & Taylor, 1997) justify it arguing that when continuous/dimensional measures such as IQ are studied, premorbid impairments appear to act as independent risk factors rather than specific precursors. In addition, this theory accounts for the age at onset distributions of disorders (Pickles, 1993).

Hollis & Taylor (1997) consider that neurodevelopmental abnormalities of schizophrenia are of a rather different nature to schizophrenia itself. Therefore, they cannot be seen as simply the presentation of schizophrenia in an immature organism (heterotypic continuity), as the immature evidently can develop the full clinical syndrome. However, the preschizophrenic abnormalities identified by high-risk studies (see next point) seem not to be specific to schizophrenia and sound as if they increased the risk for many psychiatric disorders. For that reason, they seem likely to rather represent a risk factor.

- *Evidences in favour and against the different models of neurodevelopment in schizophrenia*

According to Hollis & Taylor (1997), the success of any particular neurodevelopmental model should be judged by its ability to answer the following key questions:

1) It should account for the typical onset of schizophrenia in adolescence and young adulthood, whereas most developmental disorders begin in early childhood.

2) It should resolve the question of whether premorbid abnormalities in schizophrenia are best understood as precursors or non-specific risk factors.

3) It should explain the variability in age at onset, in particular the cause of "atypical" very early onset schizophrenia in childhood.

Support to the view that schizophrenia is a neurodevelopmental disorder comes from the typical onset in adolescence, the occurrence of structural and neurofunctional abnormalities at the onset of the illness, and the apparent lack of progression of these abnormalities with time in most cases (Murray & Lewis, 1987; Weinberger, 1987, 1995), as well as findings from retrospective (Jones, Lewis & Murray, 1994a; Done, Crow, Johnson, & Sacker, 1994), prospective (e.g., Fish, 1987; Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Mirsky, Hans, Nagler, Mirsky, Subrey, 1987), and neuropathological studies. From the latter, those finding lack of normal asymmetry, and/or abnormal callosal anatomy in the schizophrenic brain would be suggestive of disruption of brain development in the latter part of foetal life (Bullmore et al., 1997).

However, Hollis & Taylor (1997) argue that a developmental psychopathology perspective offers a probabilistic, rather than a deterministic, view of the development of schizophrenia. As a result, the idea that preschizophrenic childhood abnormalities are manifestations of a primary causal lesion occurring during foetal neurodevelopment appears difficult to sustain according to these authors. They propose an alternative neurodevelopmental (stage) model in which a variety of independent, non-specific risk factors (and protective factors) acting over the course of child and adolescence development would act to increase or decrease the vulnerability of an individual to key neurodevelopmental, cognitive and social changes occurring during this period, and therefore the probability of developing schizophrenia. Additionally, other premorbid impairments may be epiphenomena which, as non-specific correlates, play no causal role in the development of schizophrenia. Finally, they consider that the evidence for premorbid impairments as precursors is strongest for those that arise proximal to the onset of schizophrenia in early adolescence, such as affective instability, social withdrawal, and relative cognitive decline. Consequently, to understand more about the developmental processes

leading to the onset of schizophrenia, it may be necessary to shift our attention from distal processes (social-, cognitive-, and neuro-development in late-childhood and adolescence).

Late-development models are supported by anatomical evidence that suggests a relative reduction in brain tissue in schizophrenic patients (e.g., Selemon, Rajkowska & Goldman-Rakic, 1995). Thus, Feinberg (1997) has provided scientific evidence for his late development model from sleep EEG studies, nitrous oxide method studies of cerebral metabolic rate, event-related EEG potentials, and age-dependent changes in neurotransmitter responses. These findings taken together would support the notion of a major reorganization of the human brain taking place during the second decade of life.

Nevertheless, one of the limitations of the late maturational model is that it is not readily testable. The distinction between the late emergence of psychopathology due to the expression of abnormal late genes as opposed to psychopathology resulting from faulty implementation of normal, late genetic instructions is not testable either. Besides, Feinberg (1997) recognizes that the late-development model could only be applicable to subjects with good premorbid adjustment, as it cannot explain the existence of behavioural abnormalities in childhood.

Both early and late-development models of schizophrenia emphasize the development of schizophrenic pathophysiology but differ in terms of the age when brain abnormalities specific to schizophrenia are hypothesized to occur. As we saw above, early development models postulate different processes for early pathogenesis and late clinical onset, while late-development models postulate only a single process for both. However, any of them intends to understand the nature and causes of the developmental function of schizophrenia onset.

Keshavan (1997) tried to integrate early- and late-development models suggesting that early developmental lesions could lead to a reduced connectivity in certain brain regions (i.e., the prefrontal cortex) perhaps leading to negative symptoms, and a persistent synaptic expansion in certain projection sites of these brain structures, such as the cingulate and temporolimbic cortex and ventral striatum, possibly leading to positive symptoms. In other words, early brain injury could result in a dyspruned neural connectivity, i.e., loss of some neuronal connections that would normally have been retained, and a compensatory retention and/or proliferation of some other connections that would have normally been pruned out.

Concerning the stage model, data on age-dependent premorbid impairments comes largely from cross-sectional analyses of high-risk studies, and there is relatively little data on longitudinal, within-individual preschizophrenic development. As a result, research has not yet found any specific pattern of developmental progression of preschizophrenic symptoms (Hollis & Taylor, 1997).

Anyhow, in their attempt to explain the developmental basis of schizophrenia, most recent developmental models have primarily emphasized hypotheses concerning the development of the pathophysiology of schizophrenia (neurodevelopmental models), rather than the developmental aspects of it (i.e., age of onset).

✍ *Is there a "neurodevelopmental" subtype of schizophrenia?*

All these findings taken together lead us to consider schizophrenia as an aetiologically, physiopathologically and clinically heterogeneous disorder. Actually, since Kraepelin's description of *dementia praecox* (1883), several attempts to subtype schizophrenia have been done (e.g., Tsuang, Lyons & Faraone, 1990). The most recent of these attempts is the proposal of a *neurodevelopmental subtype* of this disease (Lewis & Murray, 1987; Murray et al., 1985; Murray, O'Callahan, Castle & Lewis, 1992).

Kraepelin (1883) was the first to describe what currently is known as the "neurodevelopmental" subtype, characterized by predominantly male, early onset, and a high deleterious course. In 1934, Rosanoff, Handy, Rosanoff-Plesset and Brush described two subtypes of schizophrenia according to clinical and aetiological factors: 1) subjects with a perinatal brain lesion that remained latent (or with behavioural manifestations) until the onset of psychosis in late adolescence / early adulthood (current neurodevelopmental subtype), and 2) subjects without perinatal brain lesion, predominantly female, with a genetic basis, and no behavioural disturbances at childhood. Recently, Murray et al. (1992) postulated three subgroups: 1) congenital (corresponding to the first Rosanoff et al.'s subgroup and due to genetic and environmental pre- and perinatal causes), 2) adult-onset schizophrenia, and 3) late-onset schizophrenia.

However, the acceptance of the neurodevelopmental subtype of schizophrenia as a separated nosological entity should be preceded by empirical evidence. In this respect, no endophenotypes specific to schizophrenia have been identified to date, and there are no studies examining the association among the different levels of a nosological entity (aetiology, physiopathology –endophenotype, premorbid (neurobehavioural) disturbances, and state clinical manifestations –schizophrenia with predominantly negative symptoms). Besides, several inconsistencies on clinical and

familial issues lead us to think that the neurodevelopmental subtype of schizophrenia is not independent on the other subtypes of schizophrenia. Then again, the consistent association of this subtype to negative symptoms makes us think that this term represents only a new label for the old concept of negative schizophrenia. In conclusion, the concept of "neurodevelopmental schizophrenia" represents a heuristic model with fundamental elements that have not been clearly formulated, and that is why it is so difficult to corroborate scientifically (Peralta, Cuesta & Serrano, 2001).

2.2.2 Genetic issues on the development of schizophrenia

Schizophrenia has a well established genetic basis, supported by twin, adoption and family studies (e.g. Farmer, McGuffin, Gottesman, 1987; Gottesman & Shields, 1982; Kendler & Gruenberg, 1984). Some of the findings that support the genetic basis for schizophrenia are the especially higher prevalence of familial schizophrenia in those patients with earlier onset of their disease (Sham et al., 1994), the presence of enlarged ventricular volumes (Cannon, Mednick, Parnas, Schulsinger, Preastholm & Vestergaad, 1993a; DeLisi, Goldin, Hamovit, Maxwell, Kurtz & Gershon, 1986; Honer, Bassett, Smith, Lapointe & Falkai, 1994; etc.) and the loss of brain asymmetry (Sharma et al., 1996) in relatives of schizophrenics.

Most investigators agree that multiple genetic loci are involved, either in a multifactorial threshold or oligogenic fashion (McGue & Gottesman, 1989). Furthermore, several attempts to identify the genes involved in the development of schizophrenia (neurodevelopmental genes) point to the following genetic impairments (Vicente & Kennedy, 1997):

- Abnormalities in genes controlling cell adhesion molecules such as NCAM involved in remodelling of synaptic connections in the adult.
- Defects in genes controlling the NMDA receptor, which is crucial in the processes of strengthening and weakening of synapses during "pruning".
- Faults in genes controlling neurotrophins and their receptors (mainly BDNF and NT-3), involved in motor dysfunction earlier in the developmental process.
- Abnormalities in early regulators such as the homeotic genes involved in controlling the expression of groups of molecules, therefore possibly affecting more than one process, which is consistent with the heterogeneity of alterations observed in schizophrenia.

Moreover, variation in age of schizophrenia onset has also been studied by means of family and twin studies of age at onset among affected cases. A propos of this variation in age of onset of schizophrenia, it is worth remembering that although the DNA does not change over time, gene expression does vary, as well across the different tissues within an individual over time. Actually, this dynamic aspect of genetic influence is the cornerstone of developmental genetics and developmental behavioural genetics (e.g., Plomin, 1986; Hahn, Hewitt, Henderson & Benno, 1990). Thus, genetic studies show that age of onset is correlated between affected first-degree relatives (i.e., parent-offspring and siblings) (Kendler, Tsuang & Hays, 1987). In general, it seems that genetic influences are important in variation in age of schizophrenia onset, but they may be largely uncorrelated with genetic influences that cause schizophrenia itself. Environmental influences (largely of the nonshared variety) also appear to be present, although the relevance given to them varies according to the different authors. Thus, some of them give a main role to genetic influences (e.g., Gottesman & Shields, 1982), while some others consider that the interaction of both environmental and genetic factors is essential (e.g., Tsuang, Stone & Faraone, 2001).

There can be no doubt that genetic factors contribute importantly to cases of schizophrenia, and the likeliest mode of transmission is polygenic (e.g., Cannon, Kaprio, Lonnqvist, Huttunen & Koskenvuo, 1998; McGue, Gotesman & Rao, 1985). However, Feinberg (1997) proposes an additional possibility to be considered: genetic factors may be themselves non-specific and act only to increase the probability that an error will occur in late regressive / constructive neuronal maturation. This error might emerge sporadically with a certain stochastic frequency (e.g., approximately 1%) in the absence of genetic predisposition (Bassett, Chow, AbdelMalik, Gheorghiu, Husted, Weksberg, 2003; Bassett, Chow, O'Neill, Brzustowicz, 2001; Dalman et al., 1999; Kunugi, Nanko, Murray, 2001). This interpretation would be consistent with the fact that the great majority of individuals who develop schizophrenia do not have a first degree relative with the disease. It could also help explain some paradoxes of schizophrenia (Sanjuán, 2001), such as why the diminished fertility of schizophrenics has not reduced the incidence of schizophrenia (persistence of schizophrenia), and why this incidence is roughly the same throughout the world (universality of schizophrenia).

Family and twin studies support the presence of a genetic basis in schizophrenia and have lead to the consideration of the biological relationship with a schizophrenic patient as the main risk factor for schizophrenia. However, some authors have proposed other non-familial mechanisms that could be acting on the vulnerability to

schizophrenia at a prenatal level, such as *de novo* mutations (e.g., Basset et al., 2001; Malaspina, 2001; Malaspina et al., 2002), stochastic factors (random or chance effects) during foetal development, prenatal maternal infections, obstetric complications, etc. (Bassett et al., 2003; Dalman et al., 1999; Jones, Rantakallio, Hartikainen, Isohanni & Sipila, 1998; Kunugi et al., 2001; etc.). These alternative aetiological factors may lead to mutations or abnormalities in genetic expression of the genes involved in neurodevelopment.

Prenatal and birth complications (PBCs) have been postulated to partially cause the abnormalities in brain development that eventually may manifest as schizophrenia. This statement arises from studies that report a greater number of labour and delivery complications at birth in schizophrenic patients in relation to normal controls (e.g., Cannon, 1996; Jablensky, 1995; Lewis & Murray, 1987). However, whether earlier impairment of brain development causes the excess of perinatal complications observed in schizophrenics remains an open question (Goodman, 1988, 1991). Certainly, a pre-existing neural tube defect can be the cause of perinatal complications (Nelson & Ellenberg, 1986). Such impairment of foetal brain development could be due to abnormalities in the genes controlling neurodevelopment but it could also result from adverse environmental events during pregnancy (e.g., influenza). However, most foetuses exposed to PBCs do not develop schizophrenia and most patients with schizophrenia have no history of PBCs. Bullmore et al. (1997) explained this fact suggesting that PBCs may only increase risk of later schizophrenia when certain critical neuronal circuits are compromised.

According to Pogue-Geile (1997), perinatal abnormalities may be also associated with early age of onset and may largely reflect nonshared environmental effects. He considers that these putative causes of variation in age of onset might also explain the peak acceleration across age in schizophrenia onset.

Concerning **life events**, it seems that they are common in schizophrenic patients just before their first hospital admission (Bebbington et al., 1993; Bebbington & Kuipers, 1988; Brown & Birley, 1968), so these events appear to act to bring forward the onset of illness rather than as a sufficient cause. Therefore, similarly to the case of PBCs, the results suggest that social adversity may increase the risk of schizophrenia, but only in subjects with a sufficient underlying genetic liability (Mednick, Parnas & Schulsinger, 1987; Tienari et al., 1987).

✍ *Interaction genetics-environment in the development of schizophrenia*

The interaction genes-environment (also named *ecogenetics*[1]) and the development can be conceptualized from different points of view. From a *nativist* (non-developmental) approach, a set of genes specifically targets domain-specific modules as the end-product of their epigenesis. Environment simply acts as a trigger that gives form (environmentally derived) to the innate ability. Alterations in genes are expected to result in very specific impairments in the endstate. The *empirical* point of view, in contrast, argues that much of the structure for building the human mind is discovered directly in the structure of the physical and social environment. Another option is neuroconstructivism. This is an approach to normal and atypical development that fully recognizes innate biological constraints but, unlike nativism, considers them to be initially less detailed and less domain-specific as far as higher-level cognitive functions are concerned (Karmiloff-Smith, 2002). Rather, development itself is seen as playing a crucial role in shaping phenotypical outcomes, with the postnatal period of growth as essential in influencing the resulting domain specificity of the developing cortex (Elman et al., 1996; Quartz & Sejnowsky, 1997). According to this approach, the interaction is not in fact between genes and environment. Rather, on the gene side, the interaction lies in the outcome of the indirect, cascading effects of interacting genes and their environments and, on the environment side, the interaction comes from the infant's *progressive* selection and processing of different kinds of input. Once a domain-relevant mechanism is repeatedly used to process a certain type of input, it becomes domain-specific as a result of its developmental history (Elman et al., 1996).

Environmental factors have been suggested to play a role in the pathogenesis of schizophrenia either by causing "phenocopies" (non-genetic cases), or by influencing expression of disease in genetically vulnerable individuals. Even they may be necessary for the disease to become manifest in individuals with predisposing genotypes (Sham, 1996).

Genotype-environment **interaction** refers to a genetically mediated sensitivity to environmental factors, or an environmentally mediated influence on gene expression (Kendler & Eaves, 1986) (see Figure 1.2 below). This concept has been empirically corroborated in several studies (e.g., Cannon et al., 1993b; Tienari et al., 1994). In contrast, genotype-environment **correlation** is a somewhat different type of relationship between genetics and environment where genes are considered not only to control for sensitivity to an environmental factor (interaction) but also to control for the exposure to it. Thus, subjects are genetically predisposed to select themselves into

[1] Van Os & Marcelis, 1998

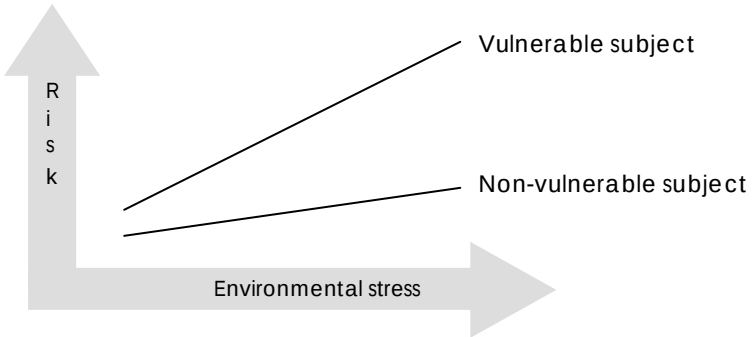
high-risk environments (Van Os & Marcelis, 1998). The genetic control of environmental exposure has been also corroborated by several studies (Marcelis et al., 1998; Tsuang et al., 1996).

It has been suggested that, in general, the interaction between genetic and environmental factors in the genesis of schizophrenia may emerge as a chain of transactional events, in which cognitive abnormalities may lead to altered family and peer relationships, and increasing vulnerability to educational demands. These factors may, in turn, magnify cognitive and social deficits and enhance the likelihood of transition into an acute disorder. According to this point of view, longitudinal studies should examine whether this chain of events accounts better for the development of the disorder than does the notion of a direct expression of a neuropsychological deficit (Berner, 2002; Hollis & Taylor, 1997).

- *Vulnerability theory in schizophrenia*

The attempts to combine environmental and genetic factors into the same aetiological frame are represented in, and conform, the so-called **vulnerability theory** (Zubin & Spring, 1977). This theory states that some individuals are more likely than others to develop schizophrenia and other psychoses. Consistently with the notion of genotype-environment interaction (see above), individuals are considered to differ in their sensitivity to adverse environments, so those genetically susceptible are more likely to develop clinical symptomatology when exposed to these adverse environments than those without a genetic vulnerability (Jones & Done, 1997; Van Os, Jones, Sham, Bebbington, Murray, 1998) (see Figure 1.2).

Figure 1.2 Ecogenetics and vulnerability-stress model in schizophrenia (adapted from Van Os & Marcelis, 1998).

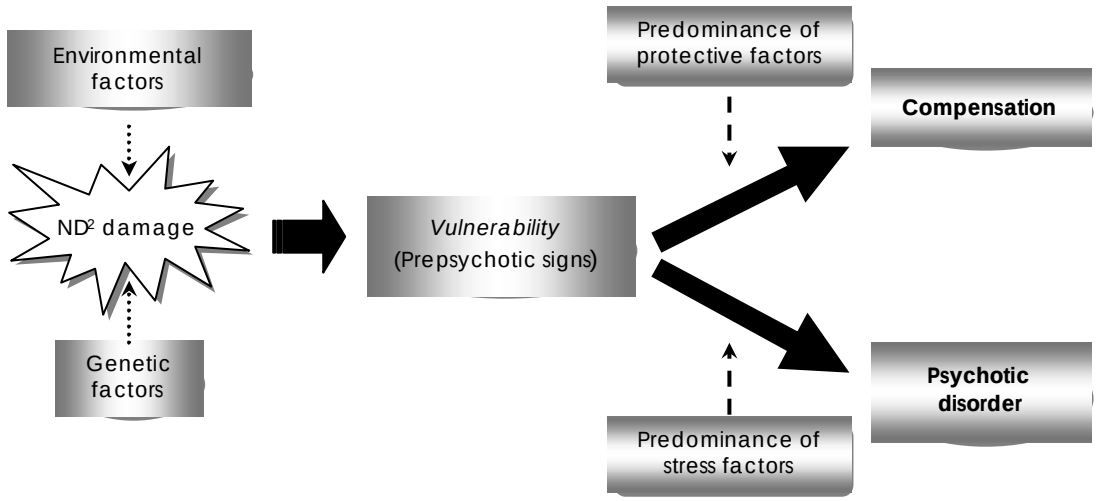


Therefore, in a high-risk/vulnerable subject, the predominance of stress factors (e.g. substance abuse or adverse life events) or protective factors (e.g. good breeding or medium-to-high intelligence level) will determine a later decompensation to clinical

symptomatology or rather maintenance at a subclinical level (see Figure 1.3, next page). Incidentally, one of the most interesting notions derived from the vulnerability-stress model (also diathesis-stress model) is the hypothetical existence of people with a genetic liability to psychosis that will never decompensate into the clinical disorder. Actually, this idea is supported by twin studies that find a monozygotic concordance far from 100% (Gottesman, 1991).

In an effort of integration, Keshavan (1997) suggested that vulnerability to schizophrenia is caused by an interaction of multiple genetic and environmental factors affecting early brain development. Thus, the timing of onset of the clinical manifestations of the disorder might be determined by late brain maturational processes, peripubertal neuroendocrine changes, and levels of psychosocial stresses.

Figure 1.3 The pathway of vulnerability



2.2.3 Neurobiological findings

Neuropathological alterations identified in schizophrenia include ventricular enlargement and volumetric abnormalities of temporal lobe structures, hippocampus, amygdala, and entorhinal cortex (Walker, 1994). There have also been observed cytoarchitecture and cell densities altered in limbic structures (Arnold et al., 1995), such as abnormalities in orientation of pyramidal cells in the anterior and middle hippocampal region, as well as disturbances of cell migration from inner to outer layers of the entorhinal cortex (Conrad, Abebe, Austin, Forsythe & Scheibel, 1991; Bogerts, 1993). Reversed hemispheric asymmetry (Bilder et al., 1994; Bullmore, Brammer, Harvey,

[2] ND: Neurodevelopmental

Murray & Ron, 1995) and dysgenesis of the corpus callosum (Lewis, Reveley, David & Ron, 1988) have also been reported and associated with risk for schizophrenia.

Given the heterogeneity of structural alterations reported in schizophrenia, it is hypothesized that the variety and severity range of symptoms observed in schizophrenia can be explained by defects in several brain regions affecting the same neural circuit that mediates higher cognitive functions such as memory and attention. Such neural circuitry would include neocortical associative areas, the limbic system and midline and thalamic structures, with possible involvement of the basal ganglia (Vicente & Kennedy, 1997). The possible involvement of the fronto-temporal network in schizophrenia has been especially remarked (Mesulam, 1990), as this network appears to have undergone a normal maturational process to reach functional maturity around adolescence (Goldman, 1971; Grattan & Eslinger, 1991). It is possible that if this network becomes essential for normal brain functioning, then abnormalities in it are revealed symptomatologically as schizophrenia. This network includes dorsolateral, anterior cingulated, and lateral orbitofrontal circuits, which would be involved in the most salient features of schizophrenia: executive dysfunction, apathy and disinhibition, respectively (Keshavan, 1997).

It has been postulated that many of the symptoms in schizophrenia could be explained by a deficit in frontal lobe executive functions. This deficit has been associated with a failure in social cognition, in a manner that a failure to cope with increasing social and cognitive demands would lead to the onset of psychotic symptoms. From a late-development approach, these executive functioning and social cognition deficits are considered to be paralleled at a neurobiological level by an altered process of synaptic pruning, so the timing of aberrant neurodevelopment may be later than that considered in "early" neurodevelopmental models of schizophrenia (Hollis & Taylor, 1997).

Thereby, some support to the neurodevelopmental model comes presumably from neuroimaging (Andreasen et al., 1992) and neuropathology studies (Jakob & Beckmann, 1986), which have demonstrated structural brain anomalies in schizophrenics that are compatible with aberrant neurodevelopment rather than neurodegeneration (Akbarian, Bunney, Potkin, Wigal, Hagman & Sandman, 1993; Murray, 1994).

From an early-neurodevelopment point of view, it has been proposed that the most likely period during which a neurodevelopmental aberration may give rise to the characteristic brain abnormalities of a schizophrenic brain is the second half of

pregnancy. This proposal is based on the fact that during this period profound changes in neuronal organization and gross cerebral appearance emerge. Defenders of the "dysplastic net hypothesis" (Bullmore et al., 1997) even argue that cognitive, negative and positive features of schizophrenia can be conceptualized as the functional expression of this abnormal network connectivity, whose origin would be at the second half of pregnancy. According to these authors, such abnormalities not only would manifest in adult schizophrenics but also in pre-schizophrenic individuals. In addition, adult patterns of hemispheric asymmetry are established during this stage. Indeed, the extent to which such lateralized patterns of cerebral organization are expressed during development is modulated by the factors determining handedness (Kertesz, Polk, Black & Howell, 1990) and sex (McGlone, 1980), although the precise mechanisms involved are unknown.

It has been speculated that the disordered cytoarchitectural organization in frontal, temporal and cingulate lobes should extend beyond neuronal laminar location to the ability to form correct afferent and efferent connections in order to have clinical meaning (Kotrla, Sater & Weinberger, 1997). Thus, abnormal connectivity of one cortical area could have widespread ramifications throughout interconnected cortical and subcortical regions (Rakic, Suner & Williams, 1991; O'Leary, Schlaggar & Tuttle, 1994).

On behalf of those theories defending a network impairment in this disease, it has been suggested that the possibility of recovery from schizophrenia (Harding & Zahniser, 1994) is more consistent with a functional imbalance of neural systems (possibly subcortical) than with the operation of an implacable, static structural defect (such an imbalance could be caused by either an early or a late developmental brain abnormality) (Feinberg, 1997).

At a neurochemical level, the major hypothesis of the origin of brain abnormalities in schizophrenia has been the dopamine theory, but new insights point to the role of the excitatory neurotransmitters glutamate (a hypofunction) (Kim, Kornhuber, Schid-Burgk & Holzmuller, 1980) as underlying abnormal synaptic pruning.

Anyhow, despite all these findings, the neurodevelopmental hypothesis remains largely untested to date. Neuroimaging and neuropathological studies provide us with a broad range of structures or circuits possibly underlying the neurodevelopmental aberration in schizophrenia, but no one of them has been reliably corroborated.

2.2.4 Psychopathological continuity from childhood to adulthood

Another issue related to the neurodevelopmental theory in schizophrenia is the extent to which premorbid abnormalities in childhood and adolescence do specifically predict schizophrenia in adulthood.

Actually, specificity is a classic problem of psychiatric studies (Sanjuán, 2001). In schizophrenia, premorbid impairments are far from specific, as various outcomes can appear in adult life (schizophrenia, affective psychosis, and others). In addition, the developmental abnormalities seen in pre-schizophrenics are quite different from the clinical symptomatology of adult psychosis (hallucinations, delusions, and thought disorder). However, it seems to be a continuity of negative symptoms (Foerster, Lewis, Owen & Murray, 1989). High-risk and retrospective studies reveal difficulties to explain this discontinuity. In contrast, in affective disorders childhood symptomatology and the adult disorder do show continuity (Van Os, Jones, Lewis, Wadsworth & Murray, 1997b). Furthermore, it has been speculated that the greater the loading of pre-existing developmental risk (premorbid abnormalities), the earlier that the psychotic process will occur for any given genetic risk (Hollis & Taylor, 1997).

An example of psychopathological continuity is ADHD. This syndrome does not disappear over time. Impulsivity, distractibility and attentional problems have been observed consistently over time (e.g., Manuzza, Klein, Bessler, Malloy & LaPadula, 1998; Ross & Ross, 1976), as well as restlessness, aggressiveness, emotional lability, and antisocial behaviour. Increased delinquency, psychiatric disorders (including schizophrenia), and alcoholism have been found in retrospective studies, but the major prospective studies have found only marginal evidence for such an increase (Spreen, Risser & Edgell, 1995). Cross-sectional studies, however, seems to provide clearest confirmation for an association between ADHD diagnosis and psychosis proneness (e.g., Keshavan, Sujata, Mehra, Montrose & Sweeney, 2003).

In the domain of schizophrenia, a clear example of psychopathological continuity is childhood-onset schizophrenia. This is supposed to be a more severe and aetiologically homogeneous form of schizophrenia with onset in childhood or adolescence. In spite of the moderate diagnostic continuity of this disorder in adulthood (around a 60%), empirical evidence seems to support continuity of adult schizophrenia into childhood and the use of adult diagnostic criteria to detect this disorder in infancy (e.g., Asarnow et al., 2002). However, the problems of potential phenocopies and comorbid states, together with immature cognitive and language abilities, make preadolescent diagnosis particularly problematic.

Currently, biological approaches (leaded by the neurodevelopmental theory) tend to see continuity from a modified point of view: early and later psychological abnormalities would be manifestations of the same underlying brain lesion (heterotypic continuity), and the normal development of surrounding brain areas and their corresponding functions would have a pathoplastic effect on those manifestations (Weinberger, 1987). In this regard, the neuroconstructivist approach considers that disorders might turn out to lie on more of a continuum than commonly thought. Thus, two very distinct phenotypical outcomes could start with only slightly differing neurobiological parameters but, with development, the effects of this small difference might be far reaching (Karmiloff-Smith, 2002).

At a neuropsychological level, cognitive abnormalities in pre-schizophrenic children could be either a qualitative deviation from normal development, or an extreme position on a continuum that can be attributed to the operation of the same factors that determine the normal range of variation (Hollis & Taylor, 1997).

In summary, the main idea of psychopathological continuity, which has a direct relationship with the neurodevelopmental theory, is reflected next:

> "An exciting future lies ahead, which promises to abandon the parochial distinction between child and adult psychiatric disorders. A way forward is to integrate research into developmental disorders across the lifespan, and provide new insights into both normal development and psychopathology." (Hollis & Taylor, 1997, p.229).

3. PRE-SCHIZOPHRENIA RESEARCH

In order to advance the neurodevelopmental models in schizophrenia, it would be necessary to characterize the premorbid deficit in this disorder and to establish the nature of the developmental neuropathology. In this respect, high-risk studies, birth cohort studies, follow-back (retrospective) studies and studies of childhood-onset schizophrenia[3] promise to shed light.

As we have seen, it appears that children destined to develop schizophrenia in adulthood can be differentiated from their peers across a variety of characteristics. Therefore, most of these studies (see Table 1.1) are focused on the search for phenotypic "risk"/"vulnerability" markers in pre-schizophrenic individuals. The rationale for this kind of research is to detect vulnerable individuals in the general population

[3] This kind of studies has already been mentioned in the previous point, so they will not be commented in the present point.

before they develop schizophrenia, with the eventual aim of implementing secondary (and ideally primary) prevention strategies.

Table 1.1 Methodologies for the study of pre-schizophrenic traits

- Birth cohort studies
- Retrospective studies
- Prospective studies
  - Genetic high risk
  - Endophenotypic high risk
  - Exophenotypic (psychometric) high-risk

3.1 Birth cohort and retrospective studies

Birth cohort studies (e.g., Jones et al., 1998; Wadsworth, 1991) consist of a prospective longitudinal follow-up from birth to death of a large birth cohort that is representative of the population at a certain historical moment. This kind of research is the best option for the study of schizophrenia development, but it is very difficult and costly to carry out. This strategy provides a broad window on the early development of schizophrenics with observations free of retrospective observer bias, but they do not target putative biobehavioural markers of schizophrenia, as they were not set up specifically to study this disorder (Hollis & Taylor, 1997).

The retrospective strategy, in contrast, starts from an individual who has already developed schizophrenia, and searches for his/her premorbid information by means of interviews to relatives (Wenar & Kerig, 2000), medical registers, academic reports, etc. (Jones & Done, 1997). Its objective is to make a reconstruction of his/her psychopathology origins in order to find vulnerability markers/factors that existed before the onset of the disorder. Some disadvantages of this strategy include the possibility of recall bias and the fact that the predictive significance of links between premorbid symptoms and schizophrenia can be overestimated, as it does not take into account the prevalence of the disorder. In addition, they show a difficulty to establish the extent to which these premorbid abnormalities are specific to schizophrenia (Hollis & Taylor, 1997).

Both types of methodology have been usually combined, as investigators search retrospectively for premorbid abnormalities in the birth cohort registers of those subjects (from the birth cohort) who have finally developed schizophrenia.

Thus, retrospective and birth cohort studies (e.g. O'Callaghan, Larkin, & Waddington, 1990; Jones & Done, 1997; Jones et al., 1994a) indicate that **psychomotor**

development delays (sitting, biped position, and walking behaviours), **early milestones of motor and language abnormalities**, **solitary play**, **subtle delays in intelligence**, and presence of **social anxiety/avoidance** (specially between 13 and 15 years old) are the most powerful predictors of schizophrenia.

3.2 High-risk studies

High risk studies, introduced by Pearson & Kley (1957) and Mednick & McNeill (1968), intend to predict who is at risk for schizophrenia, which factors predispose to the disorder and which circumstances yield the manifestation of the disorder in vulnerable subjects (Depue, Monroe & Shackman, 1979). They investigate certain variables in subjects considered at high statistical risk for the development of schizophrenia or other schizophrenic spectrum disorders (Erlenmeyer-Kimling & Cornblatt, 1987a).

Most high risk studies started in the 60's and 70's, but only a few of them carried out a follow-up long enough to get clinical diagnoses (Watson, Mednick, Olin, Cannon, Parnas, Schulsinger, 1999).

Contrarily to retrospective studies, high-risk studies use a **prospective longitudinal** strategy. Thus, an index, or high-risk, group (exposed to a variable selected as a risk criterion) and a control, or low-risk, group (not exposed to the risk variable) are defined and longitudinally assessed in different lifetime moments. Along these lines, there is a possibility of studying the same environmental stress factor, such as a parental divorce, at two levels of genetic liability: in vulnerable (at-risk) and non-vulnerable (low-risk) people (Parnas, Schulsinger & Mednick, 1990).

Currently, there are three general approaches for the identification of high-risk individuals: the genetic, the endophenotypic, and the exophenotypic (psychometric).

3.2.1 Genetic high risk studies

Genetic high-risk studies use the **biological relationship** (usually first-degree relatives) with schizophrenic patients as the risk criterion. Since the pioneering Barbara Fish's study in 1952 (Fish, 1987), the *New York Infant Study*, several high-risk studies have been carried out based on this criterion, e.g. the *Copenhagen High Risk Project* (Mednick et al., 1987) or the *New York High Risk Project* (Erlenmeyer-Kimling and Cornblatt, 1987b), among others (e.g. Marcus et al., 1987; Tienari et al., 1987). Offspring of schizophrenic parents (usually mothers) are the most frequent sample in this type of studies, though parents and siblings of affected patients are also a frequent research target group (Nuechterlein, 1987).

The rationale of genetic high risk studies is strictly empirical: considering that most mental disorders display a familial aggregation, siblings of an affected parent have a significantly higher risk for developing the disorder than their peers in the general population. When the disorder has a well established genetic basis, as in schizophrenia, this criterion is even more powerful, as a proportion of the offspring will have inherited a genetic diathesis for the disorder (Klein & Anderson, 1995).

Several risk factors for schizophrenia have been identified following this strategy, such as **obstetric complications** (e.g., Hultman, Sparen, Takei, Murray, Cnattingus, 1999; Mednick, 1970), **low birth weight** (e.g. Bennedsen et al., 1999; Marcus, Auerbach, Wilkinson, Burack, 1981), **abnormal familiar relationships** (e.g., Marcus et al., 1987; Tienari et al., 1985), **abnormalities in neuromotor development** (e.g. Fish, Marcus, Hans, Auerbach, Perdue, 1992; Walker, Savoie, Davis, 1994; Hans, Marcus, Nuechterlein, Asarnow, Styr & Auerbach, 1999), **behavioural disturbances** (aggressivity, disruptive conduct, passivity, withdrawal) informed by teachers (e.g. Parnas et al., 1990; Olin, John & Mednick, 1995), **attentional and information processing impairments** (e.g. Erlenmeyer-Kimling & Cornblatt, 1987b; Ernlenmeyer-Kimling et al., 2000), **abnormalities in saccadic eye movements** (Crawford, Sharma, Puri, Murray, Berridge & Lewis, 1998), childhood **social isolation**, **restricted affect**, **oddness** and **disordered speech** (Hodges, Byrne, Grant & Johnstone, 1999), patterns of **communication deviance** in the familiy (Wahlberg et al., 1997), etc. (see Niemi, Suvisaari, Tuulio-Henriksson & Lönnqvist (2003) for an updated review on genetic high risk studies).

Table 1.2 displays a list of advantages and limitations of genetic high-risk studies. As can be seen, validity is the strongest advantage of genetic high-risk studies. These studies use more etiologically homogeneous samples (Lewis, Reveley, Chitkara & Murray, 1987) and have more possibilities of detecting attachments between hypothetical risk factors and specific psychopathological outcomes (Klein & Anderson, 1995). However, their limitations (see Table 1.2) and the fact that some variables confer a risk on a subject even when there is no familiar history of the disorder (e.g. neurodevelopmental disturbances, as evidenced by dermatoglyphic abnormalities – Fañanás, Moral & Bertranpetit, 1991), have lead to the development of alternative high-risk strategies, named endophenotypic and exophenotypic high-risk approaches.

Table 1.2 Advantages and disadvantages of genetic high-risk strategies

- Advantages
  - Highly valid (Lewis et al., 1987)
- Disadvantages

Non-representative samples[4] (Lewine, Watt & Grubb, 1984; Cornblatt, 2002)
High rate of false positives (Lewine et al., 1984)
Relatively uneconomical (Klein & Anderson, 1995)

3.2.2 Endophenotypic and exophenotypic high risk (cohort) studies

The main difference between genetic high-risk studies and endophenotypic and exophenotypic high-risk studies is the definition of the risk criterion. Contrarily to genetic high risk studies, which use a biological relationship with a schizophrenic patient as the selection criterion, endo- and exophenotypic studies use subjects from the *general population* selected according to a *hypothetically-preceding-schizophrenia trait/ variable* (or a traits/variables configuration) (Chapman & Chapman, 1987; Claridge, 1994). These studies are also named **cohort studies** because they carry out a follow-up of a cohort of subjects defined according to their exposure to a certain risk criterion.

Endophenotypic[5] high-risk studies use biological indices to identify at-risk subjects, such as the electrodermal response (Venables, Dalais, Mitchell, Mednick & Schulsinger, 1983) and smooth pursuit eye movements (Siever, Coursey, Alterman, Buchsbaum & Murphy, 1984), or neuropsychological variables such as attention (Lenzenweger, Cornblatt & Putnick, 1991) and IQ (David, Malmberg, Brandt, Allebeck, Lewis, 1997). In contrast, exophenotypic high-risk studies use externally visible phenotypical variables such as psychosocial, personality or behavioural traits that, presumably, are early signs of schizophrenia (Chapman and Chapman, 1987). To date, schizotypal and schizoid traits are the most extensively studied exophenotypic variable in high-risk research for schizophrenia. The study on this factor is also known as the *psychometric high-risk paradigm* (Lenzenweger, 1994). In the next table (Table 1.3), some differences between both approaches can be observed.

Table 1.3 Advantages and disadvantages of endo- and exophenotypic high-risk studies (Klein & Anderson, 1995)

	ENDOPHENOTYPIC	EXOPHENOTYPIC
Advantages	-Provide closer to genotype markers. -Allows the identification of biologically homogeneous subtypes of the disorder.	-Possibility of screening for big samples from the general population at a minimum cost. -Possibility of generalization of the results to broader risk populations. -Possibility of using it in conjunction with other paradigms (including the genetic one), with the intention of identifying subgroups of individuals with a notorious high risk.

[4] Only a 15% of future schizophrenics patients have a schizophrenic first-degree relative
[5] Endophenotypic characteristics in schizophrenia refer to those data intermediating between the genotype and the phenotype for the disease and not externally visible (Gottesman, 1991; Gottesman & Gould, 2003).

Disadvantages	-Possibility of screening for big samples from the general population at a minimum cost. -Possibility of generalization of the results to broader risk populations. -Possibility of using it in conjunction with other paradigms (including the genetic one), with the intention of identifying subgroups of individuals with a notorious high risk.	-Exophenotypic variables are at a considerable distance from the genetic level (difficulty in relating them with the genotype). -High proportion of false positives due to a low prevalence of individuals at risk for a severe psychopathology. -Susceptibility to circularity in the definition of risk and the subsequent disorder. -Exophenotypic precursors of schizophrenic disorders can be relatively subtle and difficult to reliably assess. -Provides limited information about underlying risk processes

It is enquiring that for normally distributed risk factors such as IQ, the majority of affected individuals appears to arise from the majority of the population who are around the average value, so **very high-risk individuals are very rare** (Jones & Done, 1997).

Endophenotypic and exophenotypic high-risk research has identified several potential risk markers (many of them also identified by means of genetic strategies), as can be seen in Table 1.4. Incidentally, some authors consider that risk markers identified by genetic and non-genetic high-risk strategies are not comparable because this "maintains the illusion that the same type of genetic marker might be expressed in the form of a continuum of varied phenotypical manifestations, a possibility about we have no information" (Sarfati & Hardy-Baylé, 2002, p.895). Therefore, we should consider that the vulnerability in a first-degree relative of a schizophrenic patient is unlikely the same vulnerability of an individual with a certain risk factor (e.g. attentional deficit) but without genetic loading for schizophrenia.

Anyhow, cognitive variables of information processing such as sustained attention or span of apprehension, and psychophysiological variables such as smooth pursuit eye movements, have been the most consistently identified as putative risk markers for schizophrenic spectrum disorders in several studies. The rest of variables seen in Table 1.4 are less specific risk markers for schizophrenia and need more confirmation, above all in the case of electrodermal response, which has mainly negative results.

Table 1.4 Summary of endo- and exophenotypic variables identified as risk markers for schizophrenia spectrum disorders

Pre- and perinatal variables
✍ High maternal body mass index before pregnancy (Schaeffer et al., 2000)
✍ Low birth weight (Gunnell et al., 2003; Wahlbeck et al., 2001a)

- Maternal breath infections during the second trimester of pregnancy (Brown et al., 2000)
- Obstetric complications (hypoxia) (Cannon et al., 2000a ; Taylor, 1991)
- Atypical mother-child interaction at birth (Cannon et al., 2002)

Neuropsychological variables

- Sustained attention (Obiols et al., 1999; Lenzenweger et al., 1991)
- Span of apprehension (Venables, 1990)
- Reaction time (Drewer & Shean, 1993)
- Working memory (Holzman et al., 1995)
- Abstraction/concept formation (Spitznagel & Suhr, 2002)
- Cognitive inhibition (Williams, 1995)
- Low intelligence quotient (Cannon et al., 2000b; David et al., 1997)

Psychophysiological variables

- Smooth pursuit eye movement (Holzman et al., 1995)
- Event related potentials (Raine et al., 2002; Yee & Miller, 1994)
- Blinking reflex (Schell et al., 1995)
- Cortisol levels enhancement (Walker et al., 2001)
- Electrodermal response ? (Raine et al., 2002; Venables, 1993)

Neurological variables

- Minor physical anomalies (Weinstein et al., 1999)
- Neurological soft signs (Obiols et al., 1999)
- Neuromotor impairments (Rosso et al., 2000)
- Milestones acquisition delays (Cannon et al., 2002)

Neuroanatomical variables

- Enlargement of lateral cerebral ventricles (Elkis et al., 1995)
- Low birth weight/reduced cranium perimeter (Wahlbeck et al., 2001a)

Personality variables

- Psychometric schizotypy (Chapman et al., 1994; Kwapil, 1998)
- Schizotypal personality disorder (Miller et al., 2002)
- Personality disorder (not specified by the authors) (Lewis et al., 2000)

Social-familial, behavioural and emotional variables

- Deviant patterns of familial communication and affective styles (Goldstein, 1987; Kwapil et al., 2000)
- Higher number of siblings in household during childhood (Wahlbeck et al., 2001b)
- Academic achievement (Fuller et al., 2002)
- Internalizing problems in childhood (Cannon et al., 2002)
- Social and behavioural deviations and language abnormalities (Bearden et al., 2000)

Clinical variables

- Presence of isolated psychotic symptoms in childhood (Poulton et al., 2000)
- ICD-8 diagnoses of neurosis and substance misuse (Lewis et al., 2000)

3.2.3 Main high-risk studies

Some of the major genetic and non-genetic high risk studies are displayed next, as a sample of the proliferation of high-risk research since it was initiated in the 60s.

Table 1.5 Main high-risk studies for schizophrenia

Reference	Study	Risk criteria	Follow-up period
✍Fish, 1987	*New York Infant Study*	Genetic	1952-1982
✍Mednick et al., 1987	*Copenhagen High Risk Project*	Genetic	1962-1986
✍Marcus et al., 1987	*NIMH Israeli Kibbutz-City Study*	Genetic	1965-
✍Goldstein, 1987	*UCLA High Risk Study*	Non-genetic	1967-1982
✍Tienari et al., 1987	*Finnish Adoptive Family Study*	Genetic	1969-
✍Sameroff et al., 1987	*Rochester Longitudinal Study*	Genetic	1970-1975
✍Weintraub, 1987	*Stony Brook High Risk Project*	Genetic	1971-
✍Erlenmeyer-Kimling and Cornblatt, 1987b	*New York High Risk Project*	Genetic	1971-
✍Poulton et al., 2000	*Dunedin Multidisciplinary Health and Development Study* (New Zealand)	Non-genetic	1972-1999
✍Marcus et al., 1987	*Jerusalem Infant Development Study*	Genetic	1973-
✍McNeil and Kaij, 1987	*Swedish High -Risk Study*	Genetic	1973-1983
✍Chapman et al., 1994	--	Non-genetic	10 years
✍Kwapil, 1998	--	Non-genetic	10 years
✍Obiols et al., 1997	--	Non-genetic	1993-2003
✍Johnstone et al., 2000	*Edinburgh High Risk Study*	Genetic	1994-

High-risk strategies, in general, provide valuable information on the disordered development in schizophrenia, but they are expensive and their insights are limited due to several biases associated to them (false positives, false negatives, etc.). Therefore, we should expect that the combination of genetic and non-genetic high-risk studies enhances their power (Keshavan, 1997).

3.3 Vulnerability markers

Genetic and non-genetic high-risk research has identified possible candidates to be "vulnerability markers" for schizophrenia. These studies have focused mainly on *biobehavioural markers*, defined by Cornblatt (2002) as those deficits that can be detected early in development, many years before clinical symptoms appear. These deficits are assumed to reflect (i.e. "mark") the brain abnormalities underlying a biological vulnerability for later illness. However, not all the putative biobehavioural characteristics mentioned in previous points endorse the necessary requirements of a vulnerability marker.

Confusion is usual when using the term "vulnerability marker", as in a broader sense, this can be any sign that increases the probability that a given individual develops schizophrenia, e.g. drug addiction, academic performance, etc. However, these characteristics would be non-specific factors that show a mere statistical relationship with the process of disease (Hollis & Taylor, 1997; Sarfati & Hardy-Baylé, 2002). In a narrower sense, a vulnerability marker for schizophrenia should fulfil some conditions in order to be considered as a trait-marker or stable marker of the disease (Zubin and Spring, 1977; Azorín, 1997):

1. **Specificity**: it must be differently distributed in schizophrenic patients than in the general population or in other psychiatric disorders.

2. **Heritability**: it must be observed more frequently in first-degree relatives of schizophrenic patients than in the general population or in relatives of patients with other psychiatric disorders (not confound with a gene marker).

3. **Stability**: it must be independent of the clinical profile, and present before, during and after an acute episode.

4. **Replicability**: it must be replicable by different research teams.

According to these conditions, one of the most promising candidates to be considered as a vulnerability marker for schizophrenia are the abnormalities in smooth pursuit eye movement (SPEM) (Crawford et al., 1998; Lee & Williams, 2000).

However, very few abnormalities out of those mentioned before fulfil these requirements, so some authors (Hollis & Taylor, 1997) have proposed to distinguish among precursors, epiphenomena, and risk factors. **Precursors** are defined as behaviours or symptoms which, almost invariably, precede the onset of the disorder (endogenous expressions of the underlying pathological process). **Epiphenomena** are conceptualised as symptoms or behaviours associated to the disorder because they share some common causes, but they do not necessarily have a causal link with the onset of the disorder. Finally, **risk factors** are defined as symptoms or stressors that enhance the risk for the disorder but are not a manifestation of it. In schizophrenia, for instance, social withdrawal would be a precursor, minor physical anomalies would be epiphenomena, and low intelligence quotient would be a risk factor.

To date, most of the premorbid abnormalities that have been identified by high-risk strategies can only be considered as risk factors, as they have showed an overall lack of specificity or positive predictive value with respect to schizophrenia. Moreover,

those premorbid impairments that occur long before the onset of the disorder appear less likely to satisfy criteria as precursors of schizophrenia. In fact, because of the relatively low number of cases who finally develop schizophrenia in these studies, the majority of comparisons are made between "high" and "low" risk groups, rather than between pre-schizophrenics and controls. These facts would argue against an "early" neurodevelopmental model, though it has been suggested that the notion of premorbid impairments as precursors of schizophrenia might still be maintained from a "stage" approach (see previous point) (Hollis & Taylor, 1997).

Given that the present study was initially started with the aim of examining the validity of the sustained attention deficit as a vulnerability marker for schizophrenia spectrum disorders (from a dimensional point of view), special sections are dedicated to attention and schizotypy as vulnerability markers for these disorders[6].

4. ATTENTION AND COGNITIVE DEVELOPMENT

The development of attentional processes runs together with the development of the central nervous system (CNS) and cognitive functions. Therefore, in the present section we will expose some notes on general cognitive and CNS development, and special mention will be given to the development of attention and its characteristics as a vulnerability marker for schizophrenia.

4.1 Cognitive and CNS development

Next, we will review some general aspects of cognitive and CNS development, and the specific development of the different cognitive functions.

4.1.1 General cognitive development

According to Piaget (1952), the stages of normal cognitive development are the following:

1) Sensorimotor stage (the first 18 months of postnatal life)
2) Preoperational stage (childhood)
3) Concrete operations stage (period comprising the elementary school)
4) Formal operations stage (adolescence and adulthood)

[6] However, as we will comment on the *Methods* section, this initial objective has been reformulated in the present report.

The attempts to relate such stages of cognitive development with the development of the CNS have had only limited success (Diamond, 1991).

The achievement of these insights requires knowing the exact development of neural structures and pathways. In this regard, the concept of "**growth spurts**" (Dobbing & Smart, 1974) can be useful. Growth spurts are periods of development when the brain weight increases very rapidly. It seems that the neural growth spurt does not start until the number of neurons in the developing brain reaches the adult level (at about 30 weeks of gestation). The first growth spurt in the human brain occurs at that time with an enormous proliferation of glial cells. The second growth spurt involves a rapid myelination and starts in the second postnatal year continuing into the 3^{d} and 4th years (Spreen et al., 1995).

Several studies suggest that peaks and troughs occur at similar times in biological and cognitive measures, which is known as "**phrenoblysis**" (Epstein, 1978). Peak growths for cortical thickness have been identified between the ages 6 to 8, 10 to 12, and 14 to 16 years (and possibly also around 3 years). In this respect, Piaget (1952, 2002) suggests that the continuous maturation of the CNS goes until 15 or 16 years. Other authors postulate a somewhat later period for finishing cognitive maturation, from 17 to 21 years old (Pratt, 2002). Thus, unfavourable conditions during such growth spurt periods can be expected to retard cognitive development (Epstein, 1986).

These data lead us to the concept of "**critical periods**" in cognitive development. This term refers to some developmental stages when the organism is more vulnerable or receptive to environmental influences than at other stages. This idea contrasts with that of "plasticity", which refers to the ability of the CNS to change in response to these environmental influences (Luciana, 2003; Spreen et al., 1995). Colombo (1982) defined the critical period as the time between the anatomical or functional emergence of a biobehavioural system and its maturation. At a *prenatal* level, the exposure to teratogenic agents (infections, drugs, environmental pollutants, metabolic deficiencies) during the embryogenic period (from 18 to 55 days) or during foetal development (from the 56th day to birth) can produce functional and morphological deficits, or reduction in cell size and number, respectively. In this respect, a dose-response relationship between teratogenic exposure and development has been hypothesized, in a manner that large doses of teratogens during a period of rapid growth in the CNS can finally have an embryo lethal effect, while low doses of them could result in behavioural deficits and other functional impairments, such as learning impairments or abnormal activity patterns (Butcher, Hawrer, Bubacher, Scott, 1975). At a *postnatal* level, the developing brain is sensitive to the effects of environmental

deprivation (disruption/abnormalities in early attachment with the mother, malnutrition, deficient levels of environmental stimulation, etc.). For instance, it has been suggested that the first 24 months of life constitute the crucial period for the growth of associative tissue (coinciding with Piaget's sensorimotor stage), which would be responsible for complex ("higher") cognitive functions. As a result, earlier experiences of environmental deprivation (severe malnutrition) during these months can affect cognitive potential irreversibly, even if adequate nutrition is available after this period of development (e.g., Cravioto & Dilicardie, 1975). On the other hand, it has been proposed that language acquisition shows a critical period from 2 to 14 years old, parallel to cerebral lateralization (Lenneberg, 1967). However, later findings appear to indicate that Lenneberg's critical period for language learning should rather be regarded as a sensitive period.

By the way, there is frequent confusion between the terms "sensitive period" and "critical period". Fox (1970) recommended the use of the term "critical period" for times during which normal development needed to be triggered by stimuli, and the term "sensitive period" or times during which the organism is especially vulnerable to harmful influences.

Different neural systems and associated behavioural capabilities are affected by environmental input at highly variable time periods, supporting the idea that they develop along distinct time courses (e.g., Maurer & Lewis, 1998). For instance, the primary visual cortex suffers a burst in synaptogenesis at about 3 to 4 months of age, with the maximum density reached at 4 months. In contrast, synaptogenesis in the middle prefrontal cortex takes longer, reaching a maximum synaptic density at about 3.5 years of age. Furthermore, the time course for synapse elimination occurs significantly later in the middle frontal gyrus (until age 20) than in the primary visual cortex (by age 4) (Huttenlocher & Dabholkar, 1997). Indeed, PET and FDG (technique that traces glucose metabolism) studies confirm that the prefrontal cortex is one of the latest areas to show an increase glucose metabolism, while the primary sensory and motor cortex, the hippocampal region, and the cingulate cortex have the earliest increase in glucose metabolism, indicating that primary cortices develop before higher association cortices (Neville & Bavelier, 2002).

Therefore, the degree of interplay between genetic and environmental factors is highly variable across different neurocognitive systems, leading to different degrees and timing of sensitivities to environmental inputs for different brain functions (Bishop, 1997; Neville & Bavelier, 2002). In this manner, phenotypical outcomes could stem from small differences in one or more of the following parameters: developmental timing,

gene dosage, neuronal formation, neuronal migration, neuronal density, biochemical efficiency affecting firing thresholds, variations in transmitter types, dendritic arborisation, synaptogenesis, and pruning (Karmiloff-Smith, 2002). This relative timing or sequence of occurrence of events indicates that development occurs as a cascade of events and that any one event may influence those that follow it but not those that precede it (Nowakowski & Hayes, 2002).

On the other hand, Luria (1966) considered that development runs together with a "progressive lateralization of function". Consequently, cognition in children must be seen as a developing process that cannot be assumed to be firmly lateralized. In this respect, it has been hypothesized that most tasks, whatever their nature, are at first best solved with a right hemisphere strategy, but gradually become transferred to a left hemisphere strategy as routinized codes become available (Goldberg & Costa, 1981).

At a neurochemical level, cognitive development has been related to the dopaminergic system since dopamine might have a trophic action during maturation, which may influence the later cortical specification, particularly of pre-frontal cortical areas. Such an extension of cortical dopaminergic innervation could be related to an increased processing of cortical information through basal ganglia, either during the course of evolution or development (Nieoullon, 2002).

4.1.2 Development of specific cognitive functional systems

We will see in this subpoint some brief remarks on the development of executive functions, spatial abilities, and memory and learning.

- *Executive functioning development*

It has been proposed that the child gradually acquires executive strategies that require increasingly more complex mental sets about the rules of a dynamic physical world (Spreen et al., 1995). This process appears to approach a multistage developmental model, with the major development occurring between age 6 and 8, a fairly complete development by age 10, and mastery reached by age 12 (Passler, Isaac & Hynd, 1985). Other authors suggest that executive functioning is not completely mature until young adulthood, coinciding with the functional maturity of the prefrontal cortex, whereas posterior systems are mature in middle childhood (Segalowitz, Unsal & Dywan, 1992).

The evidence for the localization of executive functions in the prefrontal cortex comes from studies of patients with lesions on this brain area (e.g., Gualtieri, 1995). However,

behavioural functions *per se* cannot be localized in the frontal areas; rather, the frontal lobes seem to be essential for the control of "organized, integrated, fixed functional systems" (Stuss & Benson, 1986, p.229).

The crucial role of the prefrontal cortex in executive functioning is based on its neuroanatomical linkage with both the limbic (motivational) and the reticular activating (arousal) systems, as well as with other cortical regions (the motor areas of the frontal lobe and the posterior association cortex). This "bi-directional" linkage allows regulatory control both over the perceptual codings mediated by the posterior cortex, as well as over the attentional functions of the subcortical structures (Pribram & Luria, 1973; Trevarthen, 1990). These integrative systems, although functioning in a rudimentary fashion at an early age, are slower in maturation than any other structure in the human brain (Spreen et al., 1995).

- *Spatial abilities*

Studies with brain-damaged patients suggest that the right hemisphere is the primary substrate of spatial functions, but also of the perception of music and prosodic aspects of speech and emotional expression (e.g., Heilman & Valenstein, 1984). However, the temporal aspects of spatial functioning would be processed primarily by the left hemisphere (Witelson & Swallow, 1988).

The age of 10 has been postulated as an important "breaking point" in child development since spatial abilities have been shown to develop and lateralize after this age (Witelson & Swallow, 1988).

- *Memory and learning*

The neuroanatomical correlate of memory is the hippocampus, classically associated with long-term retention. However, as the child develops it has been hypothesized that it is not so much the capacity for memory that grows, but the strategies of learning and retrieving and, ultimately, the capacity for metamemory (more associated to frontal lobes). Thus, it is the growth of cognitive abilities in general rather than of the neural capacity for storage that develops in the child and enables increasingly more accurate recall (Spreen et al., 1995). In this regard, Gerhart & Kirschner (1997) postulated that, rather than bringing greater pre-specialization to neocortex, evolution has provided the human neocortex with a greater and more varied capacity to learn via the process of development itself.

4.2 Developmental aspects of attention

4.2.1 General reflections about attention

Attention is a highly complex field of study due to its heterogeneous nature. It can manifest in a variety of processes, such as mental concentration, vigilance, selective attention, search, activations and set (Moray, 1969).

Several distinctions of the attentional processes have been made so far (see Table 1.6). For instance, *overt* attention refers to those eye movements that shift gaze from one location to another, while *covert* attention makes reference to the shifts of visual attention between spatial locations or objects that occur independently of eye and head movements (Posner, 1980). Another distinction of visual orienting designs *exogenously* driven saccades as short-latency and reflexive eye movements triggered by stimuli that appear within the visual field, while *endogenously* driven saccades are commonly of longer latency and are described as intentional or volitional (Klein, Kingstone & Pontefract, 1992). Finally, the interest in how the brain exerts executive or supervisory control has lead to the distinction between *automatic* attention, which refers to those attentional processes that are executed with little motoric effort and typically involve sensory selection based on stimulus features, versus *controlled* attention evident when a task requires effort. Concerning this last classification, automatic attention is characterized by minimal response demands; the stimulus set is already a well-integrated part of long-term memory, so selections can be performed without awareness or deliberate intention. This characteristic permits to carry out multiple tasks simultaneously. However, controlled attention makes difficult to process more than one stimulus at a time, so it needs serial/sequential processing. Effortful attention involves deliberation and awareness, and is demonstrable on tasks that require response production in conjunction with vigilance of some sensory attribute over long time periods (sustained attention) (Cohen, 1993).

Table 1.6 Some classifications of the attentional processes

- Overt vs covert
- Endogenous vs exogenous
- Automatic vs controlled

Cohen (1993) suggested that attention depended on a minimum of four neurobehavioral factors, named a) sensory selection, b) response selection and control, c) attentional capacity, and d) sustained performance. On the one hand, **sensory selection** involves processes like filtering, focusing and automatic shifting (related to orienting response). **Response selection** and control would involve response intention, initiation and inhibition, active switching, and executive supervisory control. **Attentional capacity** would be influenced by structural (memory, neural processing speed, temporal-spatial representation...) and energetic (level of arousal, effort) factors. Finally, **sustained performance** is related to temporal distribution of the processes mentioned, and is influenced by all of them, as well as by fatigability and vigilance. These factors would not be orthogonal and they might share common neural mechanisms.

- *Vigilance and sustained attention*

Given the importance of sustained attention in the present project, special mention will be made to this function.

Vigilance is the ability of humans to keep watch for long periods of time. In terms of information processing, it involves attending for long periods while anticipating a signal's occurrence. By definition, vigilance requires sustained attention (Cohen, 1993).

According to the type of task, different vigilance errors can be observed. Thus, when one signal source is used, the subjects make few false-alarm errors but tend to miss items over time. In contrast, when using more stimuli, the subjects initially make many more false-alarm errors (Broadbent, 1963). These different types of errors, therefore, reflect the degree of confidence that subjects have when making a response.

After the first studies on vigilance (Broadbent, 1950, 1963; Mackworth, 1950; etc.), conducted for military purposes, Broadbent and other investigators later refined their techniques by applying signal detection methods to the analysis of vigilance. Signal detection analysis provides an index of the stimulus discriminability (d') and also the response criterion (ß). By using these methods, Baddeley & Colquhoun (1969) found that varying the signal presentation rate influenced the way response tendencies (ß) changed, but not stimulus discriminability. This finding was corroborated by other studies (e.g., Broadbent & Gregory, 1963), suggesting that the rate of presentation seemed to influence the subjects' expectancies and motivational state, though the reason was unclear.

Concerning sustained attention, when the information occurs at a high rate, there is likely to be an eventual decline in d' over a given time period. In contrast, when signals occur at a low rate, d' does not change significantly. Instead, there is a tendency toward higher ß levels, reflecting a change in the disposition to respond a particular way. Signals that have longer durations of onset do show a decline in d' over time, but they may show a change in ß, reflecting a change in the confidence of the subject. Therefore, it is primarily under conditions of high stimulus rate and low target rate that discrimination ability is reduced over time. This finding suggests that, under this condition, an informational overload eventually occurs. Generally, the temporal effects of performing for long durations with low rates of stimulus processing seem to have more impact on the response characteristics of the individual than on perceptual discrimination capacity (Cohen, 1993; Parasuraman, 1984).

Deficits in sustained performance may be due to failures of filtering, pigeonholing, arousal, response selection, or lack of effective reinforcements. Effective filtering requires a person to monitor an appropriate channel over time, and to resist distraction that causes the attention to shift to a task-irrelevant channel. Pigeonholing similarly requires that a person maintain an appropriate set of responses to a series of stimuli, and to consistently categorize stimuli into their correct response bins. Deficits in arousal result in a tonic decrement in sensitivity (d'). Neurologically or psychiatrically disturbed patients may be unable to inhibit well-learned but inappropriate responses to a stimulus. Finally, patients may be unresponsive to formerly reinforcing activities and consequences or may lack sensitivity to contingencies. They therefore fail to sustain attention on tasks despite intact cognitive processing. In this regard, it has been often remarked that patients with frontal lobe syndromes or head trauma show scarce deficits on traditional neuropsychological testing but are profoundly impaired in natural-world performance (e.g., Damasio, 1994). Thus, the experimental neuropsychological literature suggests that measures of vigilance may be a more sensitive measure of brain dysfunction than traditional tests of intellectual performance (Cohen, 1993). In addition, stability of the sustained attention deficit has also been demonstrated, as well as its state independence (Cornblatt & Keilp, 1994).

4.2.2 Neuroanatomical and neuropsychological features of attention

In spite of the heterogeneous nature of attention, some neuroanatomical structures have been proposed to underlie this function, i.e., the prefrontal cortex, the cingulate cortex, and subcortical systems.

Lesions on the prefrontal cortex yield deficits on a number of functions depending on the attentional control, such as learning tasks involving discrimination and delayed response, motility, visual search, sustained attention, and social-emotional functioning. Other related deficits include inhibition and suppression of interfering stimuli, disorders of spatial selective attention (more specifically related to damage to the frontal eye fields), and inattention to affective and social cues leading to an impoverishment of emotional experience (Palmer & Heaton, 2000). In addition, damage to this area may yield "impulsive" behaviour (e.g., Kojima & Goldman-Rakic, 1982), which is critical in attentional control, as impulsive responding does not allow an adequate consideration of the response alternatives. Capacities such as generation of long-term goal-directed behaviours, response sequencing, and generation of hypotheses about possible response outcomes based on previous learning, can be affected by this impairment (Cohen, 1993; Fuster, 1999). On the other hand, damage to the orbito-frontal cortex disrupts emotional experience, affecting ultimately the primary motivational value given to incoming information.

The anterior cingulate cortex is a paralimbic brain region richly interconnected with limbic and cortical areas, particularly the frontal cortex. It seems to be involved in the intensive aspects of attention, modulating and creating a temporal continuity for affective-motivational impulses relative to ongoing stimuli that arouse attention (Cohen, 1993).

At a subcortical level, attention seems to be influenced by the limbic system, the hypothalamus, and the reticular system (Mesulam, 1985). The damage to the reticular system yields a disruption of normal arousal and abnormalities of consciousness, the hypothalamus plays a role in creating a drive state, and the limbic system is unspecifically related to attentional control (Cohen, 1993).

Sustained attention, in particular, seems to show also a range of diffuse neuroanatomical correlates involving cortical (frontal, temporal, parietal), subcortical (limbic, basal ganglia), and functional systems including the pathways between the basal ganglia, thalamus, and frontal lobes (Riccio, Reynolds, Lowe & Moore, 2002).

- *Attention as an executive function*

Attentional end executive functions have demonstrated to be very difficult to separate, as executive functions coordinate most of the attentional processes and the latter underlie the correct executive functioning. In their proposal of the existence of three neural networks related to different aspects of attention and to different brain areas (see Table 1.7), Posner & Petersen (1990) remarked the interconnection between

attentional and executive aspects, above all in the executive control network, but also in orienting to visual stimuli, which requires self-regulation and other executive processes.

Table 1.7 Attentional networks and brain correlates (Posner & Petersen, 1990)

Network	Processes	Brain correlates
Alerting	Achieving and maintaining a state of high sensitivity to incoming stimuli	Right frontal and parietal lobes
Orienting	Selection of information from sensory input	Pulvinar, superior colliculus, posterior parietal lobe
Executive control	Mechanisms for resolving conflicts among thoughts, feeling and responses	Anterior cingulate and lateral prefrontal cortex

In addition to the complex interrelationship between both functions, a number of neuroimaging studies indicate that the different executive/attentional processes also show distinct neuroanatomical correlates (e.g. Corbetta, Kincade, Ollinger, McAvoy, Shulman, 2000; Garavan, Ross, Murphy, Roche, Stein, 2002; Sylvester et al., 2003). Still studies have been conducted trying to disentangle the molecular genetics of executive/attentional networks, suggesting that individual variation in executive / attentional performance may be yielded by several and different genetic polimorphisms (e.g., Fossella et al., 2002). Therefore, the classical study of both functions as separate processes seems to be far from valid.

4.2.3 Measurement of attention

In order to assess persistence and the ability to maintain vigilance, it is necessary to use a task that requires processing over long time periods. The effect of attentional variability that is independent of information load can be best assessed using tests that are relatively easy to perform (they make limited cognitive demand) but difficult to sustain because of their repetitive and lengthy nature. In this regard, the *Continuous Performance Test* (CPT) was developed to measure sustained attention and vigilance (Rosvold, Mirsky, Sarason, Bransome, Beck, 1956). Variables such as the number of stimuli to be processed on a given trial, the interstimulus interval, and the memory load of the task, can affect performance on this test. This fact suggests that task duration is not the only relevant attentional factor that the CPT assesses. It also measures the ability to sustain responding on a simple task that is likely to be of little inherent interest to the subject. Therefore, the CPT provides information about performance on specific task parameters with demand created by task duration (10 minutes in its original form)

and low information load (Cohen, 1993). Table 1.8 shows the most commonly used neuropsychological measures of attention.

Table 1.8 Neuropsychological assessment of attention (extracted from Cohen, 1993)

- Attention span
  - Digit Span
  - Corsi Blocks
  - Consonant trigrams
- Divided attention
  - Stroop test
  - Dichotic listening
- Switching
  - Trail-Making Test
  - Motor impersistence task
  - Go-no-go task
  - Wisconsin Card Sort
- Response intention and planning
  - Controlled word generation
  - Spontaneous verbal generation
- Sustained performance and vigilance
  - Continuous performance
  - Paced auditory serial addition
  - Cancellation tests
- Information-processing speed
  - Symbol Digit Modality Test

4.2.4 Development of attention during childhood and adolescence

The development of attentional processes takes place over a long time course from infancy to adolescence, reflecting a number of different mechanisms and significant individual differences (Cohen, 1993).

Infants are initially characterized by attentional responses that are provoked by stimulus change, which evokes an orienting response (motoric orientation to the spatial location of auditory, visual, and tactile stimuli). This response becomes apparent within the first few days to months after birth, but development makes the rate of habituation of the orienting response increase. In fact, the ontogeny of visually guided behaviours over the first few months of life can be partly viewed as a transition from exogenous or automatic eye movement control to a more predictive system influenced by endogenous control of orienting (Johnson, 1994, 2002).

As a child develops motor control, her or his perception becomes more selective, and her or his attentional capacity increases. In this way, children attend to stimuli that are task-relevant and improve their capacity to attend multiple features of a stimulus and their attentional flexibility (Cohen, 1993).

The direction of attention in response to verbal, symbolic, or memorized cues (endogenously driven orienting) would be present in 4month-old infants (Johnson, Posner & Rothbart, 1991), consistently with an increasing prefrontal endogenous control over shifts of attention and saccades. The dorsolateral prefrontal cortex, in contrast, seems not to be sufficiently developed to support tasks that require both inhibition and working memory until approximately 10 months (e.g., Diamond, 1991).

However, the ability of children to sustain attention (another manifestation of endogenously driven orienting), particularly in the absence of immediate reinforcement, is quite variable. Actually, the natural development of vigilance, or the ability to maintain attention when there are long periods between task-relevant signals, has not been well-described (Cohen, 1993). Even so, the hypothesized neural correlate of sustained attention on cortically mediated pathways inhibiting collicular mechanisms (possibly in the frontal cortex) has lead to expect that sustained attention appears approximately from 4 months of age on (Johnson, 2002).

By adolescence, spatial vigilance performance peaks. Verbal vigilance performance, in contrast, peaks in adulthood. By grade school, however, there are significant differences between children on vigilance tasks (Cohen, 1993). These differences have a profound impact on children's academic performance. For instance, normal grade-school children perform well on the CPT, whereas ADHD children have great difficulty with such tests (Barkley, 1988).

A recent study by Klenberg, Korkman & Lahti-Nuuttila (2001) in Finland studied the developmental sequence of attention and executive functions in 400 children aged 3- to 12 years. Impulse control and inhibition of irrelevant responses, auditory and visual attention, visual search, planning, and verbal and visual fluency tests were administered. The development proceeded sequentially, from motor inhibition and impulse control to functions of selective and sustained attention, and finally to executive functions of fluency. Significant relations between gender and development and between parent education and development were found in several subtests. In a factor analysis, inhibition, auditory attention, visual attention, and the EF of fluency clustered into separate factors. The authors concluded that the developmental staging and clustering of functions suggested that, although inhibition, attention, and executive functions are highly interrelated cognitive functions, their developmental sequences are separate from one another. Thus, some agreement seems to exist in that development of basic inhibitory functions seems to precede the development of more complex functions of selective attention, and executive functions continue to develop into adolescence (Gomes, Molholm, Christodoulou, Ritter & Cowan, 2000).

Cornblatt, Risch, Faris, Friedman & Erlenmeyer-Kimling (1988) compared the sustained attention profile of adults and adolescents with the CPT, and found that adolescents showed better performance on spatial than on verbal stimuli, whereas the adults showed similar performance levels on both tests. Even the spatial performance of adolescents was better than that of adults. This interaction between age and performance was due to differences in accuracy unrelated to response strategies (ß).

In this regard, it has been suggested that sustained attention develops during primary school ages. Thus, a study by Lin, Hsiao & Chen (1999) described a convex age-development curve for sensitivity and hit rate in the CPT scores of children from 6 to 15 years old.

Stability of the sustained attention deficit has been demonstrated, as well as its state independence (Cornblatt & Keilp, 1994).

4.3 Sustained attention deficit as a vulnerability marker for schizophrenia

Generally, mental disordered patients and their relatives show attentional deficits, so it has been suggested that the attentional performance may contribute to genetic vulnerability of complex psychiatric disorders (Falconer, 1996). In the general population, attentional performance seems to be also influenced by genetic factors. Actually, heritability of *Continuous Performance Test*[7] execution has been estimated in 0.49 in normal subjects (Cornblatt et al., 1988).

CPT performance deficits have been detected in children at risk for schizophrenia (offspring of schizophrenic patients) (Erlenmeyer-Kimling et al., 2000), and other first-degree relatives of schizophrenic patients (e.g. Chen, Liu, Chang, Lien, Chang, Hwu, 1998; Laurent et al., 2000), as well as in schizotypal individuals (e.g. Obiols, Garcia, de Trincheria & Domenech, 1993; Lenzenweger et al., 1991; Harvey et al., 1996a).

Results from studies with schizophrenic patients and children at-risk for schizophrenia, seem to indicate that impairments in CPT performance are specific both to schizophrenic patients (e.g. Cornblatt, Lenzenweger & Erlenmeyer-Kimling, 1989; Buchanan, Strauss, Breier, Kirkpatrick & Carpenter, 1997) and to high-risk samples (e.g. Nuechterlein, 1983; Cornblatt, Obuchowski, Roberts, Pollack, Erlenmeyer-Kimling, 1999). These findings and its developmental stability and independence of clinical state have led to some authors to consider it a suitable endophenotype for use in molecular genetic studies of schizophrenia (Cornblatt & Malhotra, 2001).

Cornblatt & Erlenmeyer-Kimling (1985) created a composite measure of attention (*attentional deviance index*) largely based on the CPT[8], and assessed its predictive validity. The results yielded a specificity of 91% and a sensitivity of 35% for predicting adolescent disturbances considered to foreshadow schizophrenia-spectrum disorders.

[7] We will focus on the CPT because it is one of the attentional tests that have generated more studies in high-risk research for schizophrenia and because it is the main focus of the first two goals of this project.
[8] This measure is composed by some indices from the *CPT-Identical Pairs* version, the *Attention Span Task*, and the WISC *Digit Span*.

Further, a model on the influence of early attentional deficits in later social deficits (and negative symptoms) has been proposed by Cornblatt & Keilp (1994).

5. SCHIZOTYPY

5.1 Schizotypy and "psychosis proneness": General aspects

The *Diagnostic and Statistical Manual of Mental Disorders IV-TR* (2000) groups the different personality disorders together in three clusters. As can be seen in Table 1.9, Cluster A is characterized by odd and eccentric behaviours, Cluster B includes dramatic, emotional and erratic behaviours, and Cluster C represents anxious and fearful behaviours.

Table 1.9 DSM-IV-TR personality disorders by cluster

Cluster A	Cluster B	Cluster C
✍Paranoid	✍Antisocial	✍Avoidant
✍Schizotypal	✍Borderline	✍Dependent
✍Schizoid	✍Histrionic	✍Obsessive-Compulsive
	✍Narcissistic	

Cluster A personality disorders are presumably the most related to the schizophrenic spectrum of disorders, especially the schizotypal personality disorder (Battaglia, Bernardeschi, Franchini, Bellodi & Smeraldi, 1995; Battaglia & Torgensen, 1996). Unlike psychometric schizotypy, cluster A personality disorders are categorical diagnoses that require a minimum degree of severity on its presentation in order to be applied. Therefore, they are valid only in clinical settings. Specifically, the *paranoid* personality disorder refers to a pattern of mistrust and suspiciousness which leads the individual to misinterpret the intentions of other people, the *schizotypal* personality disorder (see Table 1.10, next page) is a pattern of strong discomfort on personal relationships, cognitive or perceptive distortions, and behavioural eccentricities; and finally, the *schizoid* personality disorder represents a pattern of disengagement of social relationships and restraint of emotional expression (APA, 2000).

Schizotypy, in contrast, is an open concept, possibly including several discriminable phenomena and differently defined according to the approach. Thus, the *consensual* approach to schizotypy focuses on the DSM definition of Schizotypal Personality

Disorder, as we have just described. The *historical* point of view is based on early descriptions of schizophrenia borderline, latent schizophrenia, pseudoneurotic schizophrenia, ambulatory schizophrenia, schizotype, etc. The *theoretical* approach represents categorical and dimensional models of schizotypal personality. Finally, the *empirical* point of view is concentrated on clinical, biological and longitudinal studies (Lencz & Raine, 1995). Evidently, the results derived from the application of one or another approach are different and will be reviewed in the following points.

In order to introduce the notion, we could say that schizotypy is a construct reflecting a configuration of personality, behavioural and cognitive traits which show a similarity with schizophrenic symptomatology, but to a lesser degree of severity. That is why schizotypy is also frequently referred to as *psychosis-proneness* and is considered as one of the cornerstones of high-risk research. Actually, from a dimensional point of view, this configuration of personality traits has yielded the emergence of the "psychometric high risk paradigm" (Lenzenweger, 1994).

Cluster A personality disorders are then included in the concept of schizotypy and are considered to reflect, therefore, liability to psychosis. However, not all of them have received the same degree of interest in studies on vulnerability to psychosis. Most neuropsychological and neuroimaging studies are based on individuals with schizotypal personality disorder (SPD). Very few studies about specific neuropsychological performance or neuroimaging correlates of Paranoid or Schizoid personality disorders, as defined on the DSM, have been carried out. In addition, there is evidence for a considerable overlap among Cluster A personality disorders in their relation to schizophrenia (Varma & Sharma, 1993).

Table 1.10 DSM-IV-TR criteria for 301.22 Schizotypal Personality Disorder (APA, 2000)

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
   (1) ideas of reference (excluding delusions of reference)
   (2) odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations)
   (3) unusual perceptual experiences, including bodily illusions
   (4) odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped)
   (5) suspiciousness or paranoid ideation
   (6) inappropriate or constricted affect
   (7) behaviour or appearance that is odd, eccentric, or peculiar
   (8) lack of close friends or confidants other than first-degree relatives
   (9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self

B. Does not occur exclusively during the course of Schizophrenia, a Mood Disorder With Psychotic Features, another Psychotic Disorder, or a Pervasive Developmental Disorder.

5.2 Historical roots of the "schizotypy" concept

The concept of "schizotypy" basically took form according to two information sources (Kendler, 1985). On the one hand, there are a number of studies focused on the traits that characterise non-psychotic impaired relatives of schizophrenic patients. This kind of literature is called "**familial**" because of the emphasis on the observation of schizophrenic's relatives. On the other hand, there are clinical descriptions of patients who, without filling the full criteria for a clinical diagnosis of schizophrenia, showed fundamental symptoms of the disorder, but in an attenuated way. This literature is called "**clinical**" due to the emphasis on the observation of schizophrenic-like (schizotype) forms in clinical populations.

Schizotypic features were firstly noticed and introduced by Kraepelin (1919) and Bleuler (1911) with the term "*latent schizophrenia*". It described a type of personality disorder believed to be, essentially, a quantitatively less severe expression of schizophrenia. This term designed a kind of eccentric, irritable, socially isolated, etc. personality observed in relatives of schizophrenic patients. Table 1.11 displays some of those traits that these and other authors observed in relatives of their schizophrenic patients at the beginning of the XXth century.

Table 1.11 Personality traits observed by different authors in non-schizophrenic impaired relatives of schizophrenic patients (extracted from Kendler, 1985)

Characteristic	*Kraepelin*	*Bleuler*	*Gadelius*	*Rosanoff*	*Kretschmer*	*Barnett*	*Kallman*	*Slater*	*Inouye*	*Stephens et al.*
Eccentricity-oddness	X	X	X	X	X	X	X	X		X
Irritable-unreasonable		X	X	X		X	X	X	X	
Social isolation		X			X	X	X	X		X
Aloof, cold demeanor					X	X	X	X	X	X
Suspiciousness		X		X				X	X	X
Superstitiousness			X				X	X		
Poor psychosocial functioning	X				X			X		
Nervousness					X					X
Odd speech								X		X
Hypersensitivity					X				X	

The clinical literature on schizotypy started with Zilboorg (1941), who introduced the term "*ambulatory schizophrenia*" to describe superficially normal subjects with subtle abnormalities, named "autistic thinking", a tendency to confuse fantasy with the real world, taciturn attitude, etc. Later, Deutsch (1942) used the term "*personality as-if*" to describe individuals showing a deficit on emotional functioning, without affecting neither their social life nor their behaviour. Hoch & Polatin (1949) used the term "*pseudoneurotic schizophrenia*" to design a group of patients presenting pan-anxiety (diffuse and persistent anxiety), pan-neurosis (conversion symptoms, obsessions, depression, neurasthenia, etc.) and pan-sexuality (chaotic sexuality). Table 1.12 summarizes the characteristics observed by these and other authors in patients who did not fulfil the full criteria for a clinical diagnosis of schizophrenia but exhibited psychotic-like traits.

Table 1.12 Characteristics observed in non-schizophrenic patients showing psychotic-like symptoms (extracted from Kendler, 1985)

Characteristic	*Zilboorg*	*Deutsch*	*Hoch et al.*	*Rado*	*Meehl*
Disordered thinking	X		X	X	X
Lack of deep interpersonal relationships	X	X		X	X
Deviant sexuality	X		X		
Profound anger	X			X	
Interpersonal dependency		X		X	
Sensitivity to rejection				X	X
Anhedonia				X	X
Superficial intactness	X	X			
Brief psychotic symptoms			X		
Widespread anxiety			X		
Multiple neurotic symptoms			X		
Preoccupation with fantasy	X				
Acting-out behaviour			X		

Kendler (1985) advanced that clinical descriptions derived from the two kinds of observations (clinical and familial), though similar, did not coincide. According to Kelley & Coursey (1992), the "genetic-familial" tradition would focus more on negative symptoms (social isolation, oddness, eccentricity, coldness, aloofness), whereas the

"clinical" tradition would emphasize more positive symptomatology (thought disorder, brief psychotic experiences, etc.).

These first observations of schizotypal forms were basically descriptive, but lacked aetiological and process explanations (Lenzenweger & Korfine, 1995). Later, Meehl (1962) presented one of the most valuable and currently used models about schizotypy and its relationship to schizophrenia, overcoming the descriptive level of previous authors. The origins of Meehl's model seem to be on Rado's observations (1953, 1960). This author, educated on the psychodynamic tradition, made a sketch of an integrative model on the link between schizophrenia and schizotypal personality functioning. He suggested that schizotypic behaviour derived from a fundamental vulnerability to schizophrenia. Further, Rado coined the term "s*chizotype*" for the first time, as an abbreviation of the expression "**schizophrenic phenotype**". Besides, Rado postulated that a common schizophrenic diathesis might lead to several phenotypic manifestations, from a compensated schizotype to a deteriorated schizophrenia. Thus, this affirmation pointed to the existence of an **aetiological unit** underlying several clinical manifestations along the schizophrenic spectrum (Lenzenweger & Korfine, 1995).

5.3 Schizotaxia and vulnerability to psychosis

Paul Meehl got in touch with Rado's theory in the mid 50's and, in 1962, he published his renamed article "Schizotaxia, schizotypy, schizophrenia". In this paper he set up a theory based on the statement that clinical schizophrenia would be the result of a complex developmental interaction among several critical factors (Meehl, 1962, 1989, 1990):

1. A "**schizotaxic**" brain characterised by a hypothetical "ubiquitous[9] neural integrative defect" related to an aberration at a synaptic level named "hypokrisia" (hypokrisia would be determined by a single autosomic major gene: the "schizogene")[10].

2. **Social learning experiences** influenced by the environment leading to a schizotypic personality organization ("schizotype", according to Meehl).

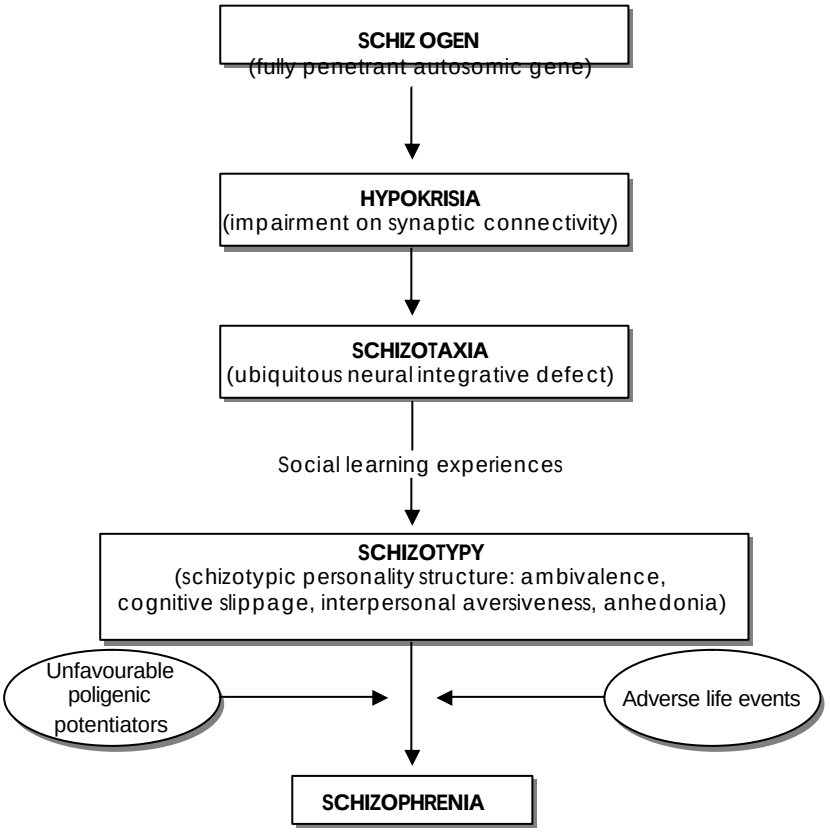
3. **Polygenic potentiators** (anxiety, anhedonia, introversion).

According to Meehl, a "modal" schizotype will not decompensate to schizophrenia. However, the intervention of unfavourable polygenic potentiators (anxiety,

[9] Affecting the whole Central Nervous System (Meehl, 1989).

introversion, etc.) and adverse life events (e.g. childhood traumas, important problems in adulthood) will make that about 10% of shizotypes develop schizophrenia (Meehl, 1989) (see Figure 1.4, next page). Anyway, every schizotype reflects his/her latent vulnerability to schizophrenia through a somewhat aberrant social and psychological functioning. Thus, schizotypy would manifest as **ambivalence**, **cognitive slippage** (attenuated formal thought disorder), **interpersonal aversive drift** (social fear) and **anhedonia** (deficit on the ability to experience pleasure). In summary, from Meehl's point of view, schizotypy –as a personality organization reflecting a latent vulnerability to schizophrenia, may manifest at several degrees: from a highly compensated schizotype (minimum presence of schizotypal signs and symptoms), through a schizotype showing a failure of compensation, to those who develop schizophrenia. Each one of these manifestations would share the same schizogene and the same schizotypal personality organization. Hence it is important the assumption that not every schizotype will develop schizophrenia (only a 10% according to Meehl). Nevertheless, all of them will show their underlying vulnerability, even in a subtle way, in form of an aberrant psychosocial functioning (Lenzenweger, 1994).

Figure 1.4 Sketch of Meehl's model (1962)



[10] Meehl estimates that the base prevalence of "schizotaxia" or the "schizotaxon" is a 10% in the general population.

5.4 Schizotypy and genetics

Meehl's model postulates the existence of certain behaviours and personality traits somewhat similar to schizophrenia in the general population. This behavioural and personality patterns have been extensively studied and observed in relatives of schizophrenic patients, and have received several names (latent schizophrenia, borderline schizophrenia, pseudoneurotic schizophrenia, schizotypy, etc.), as we mentioned above.

The adoptive study by Kety, Rosenthal, Wender & Schulsinger (1968) in Copenhagen demonstrated that these attenuated manifestations of schizophrenia show a familial relationship and, therefore, a genetic relationship with schizophrenia. Equally to Kety's seminal study, other authors have later suggested a genetic relationship between familial schizotypal forms and schizophrenia (e.g., Battaglia et al., 1999; Kendler & Diehl, 1993).

All of these disorders sharing aetiological factors with schizophrenia and reflecting an alternative phenotype for it were called "**schizophrenic spectrum disorders**" (e.g. Baron & Risch, 1987).

The Copenhagen Adoptive Study (Kety et al., 1968) reported an 8.7% prevalence of schizophrenic spectrum disorders (acute schizophrenia, borderline[11] or latent schizophrenia, "uncertain" schizophrenia, and schizoid or inadequate personality) in biological relatives of chronic schizophrenic adoptees, whereas the prevalence in biological relatives of control adoptees was 1.9%. Results showed a higher prevalence of borderline and chronic schizophrenia in biological relatives of chronic schizophrenic adoptees than in biological relatives of control adoptees. In a parallel study of the same group (Rosenthal, Wender, Kety, Schulsinger, Welner & Ostergaard, 1968), they observed a higher prevalence of schizophrenia in the adoptees born of a schizophrenic biological parent than in the adoptees born of control biological parents. In both studies, a higher prevalence of borderline schizophrenia in biological relatives of adoptees or parents with chronic schizophrenia was observed. However, when the proband (adoptee or parent) showed borderline schizophrenia, no higher prevalence of chronic schizophrenia in his/her biological relatives in relation to the

[11] "Borderline schizophrenia" criteria, according to Kety et al. (1968): 1) slight thought and speech aberrations, tendency to ignore reality, 2) brief episodes of cognitive distortion, depersonalisation, strangeness, etc., 3) anhedonia, 4) chaotic sexual drive (mixture of heterosexuality and homosexuality), apparent calmness but lacking in depth, 5) multiple and changing neurotic manifestations, widespread anxiety.

prevalence in biological relatives of control cases (without psychopathology) was observed (Torgersen, 1985).

SPD criteria, introduced in the DSM-III (Spitzer, Endicott & Gibbon, 1979) for the first time, derive from the Danish adoptive studies previously mentioned. The DSM-III requirements for a diagnosis of SPD combined Kety et al. (1968) criteria of borderline (latent) schizophrenia and "uncertain" schizophrenia (diffuse forms of schizotypal manifestation), as can be seen in Table 1.13.

Table 1.13 DSM-III criteria for Schizotypal Personality Disorder (Spitzer et al., 1979)

1. Magical thinking
2. Ideas of reference
3. Social isolation
4. Recurrent illusions
5. Bizarre speech
6. Inadequate rapport, coldness, aloofness
7. Suspiciousness
8. Hypersensitivity-exaggerated social anxiety

In 1981, Kendler, Gruenberg & Strauss made a new analysis of the Copenhagen adoptive registry applying the new SPD criteria appeared in the DSM-III. The result was that 13.6% of biological relatives of schizophrenic adoptees received an SPD diagnosis. However, every SPD case was assigned to biological relatives of chronic schizophrenic adoptees, and only one case appeared in biological relatives of acute schizophrenic adoptees (in relatives of borderline or uncertain schizophrenic adoptees appeared no SPD cases). More recently, Kendler, McGuire, Gruenberg, O'Hare, Spellman & Walsh (1993) also reported higher prevalences of DSM-III-R Cluster A personality disorders and avoidant personality disorder in first-degree relatives of schizophrenic patients. Interestingly, they found that the SPD also reflected liability to other psychotic disorders, though not to affective illness.

In this respect, Torgersen (1985) stated that the relationship of this personality disorder with schizophrenia was difficult to establish, in spite of adoptive and twin studies that indicate that SPD transmission has a well established genetic base. On the other hand, neither DSM-III SPD criteria (Spitzer et al., 1979), nor the borderline schizophrenia criteria (Kety et al., 1968) would reflect basic aspects of the symptomatology displayed by relatives of schizophrenics who show symptomatological characteristics associated to schizophrenic spectrum disorders. Likewise, according to Torgersen, DSM-III SPD criteria would include many individuals with non-related-to-schizophrenia personality disorders.

In response to Torgersen's critics, Kety (1985) stated that the low prevalence of chronic schizophrenia in biological relatives of people with schizophrenic spectrum disorders would be explained by the low prevalence of schizophrenia (approximately 1%), in comparison to the much higher prevalence of schizophrenic spectrum disorders (13.6% for SPD in the 1968's Danish sample of relatives). According to this author, the difference of rates might explain why is much more likely to find SPD or other schizophrenic spectrum disorders in biological relatives of chronic schizophrenics but, however, this finding is not inversely replicated.

Along these lines, it has been often wondered why the incidence of schizophrenia, a disorder traditionally associated to lower reproductive fitness, does not decrease in forthcoming generations. According to Battaglia & Bellodi (1996), the response to this interesting question might be in the SPD. Specifically, it seems that the reproductive fitness of SPD patients is not diminished, unlike in schizophrenia. This fact then would explain the opposite patterns of distribution of risks for schizophrenia and SPD in families.

5.5 Dimensional models of psychosis

Dimensional models (or *continuum* models) in psychopathology, unlike categorical models typically represented by classification systems of mental disorders as the DSM and the ICD, consider the existence of a continuity or connection among mental disorders, personality disorders and behavioural and psychological traits that we find in the broad mental health domain (Claridge, 1985).

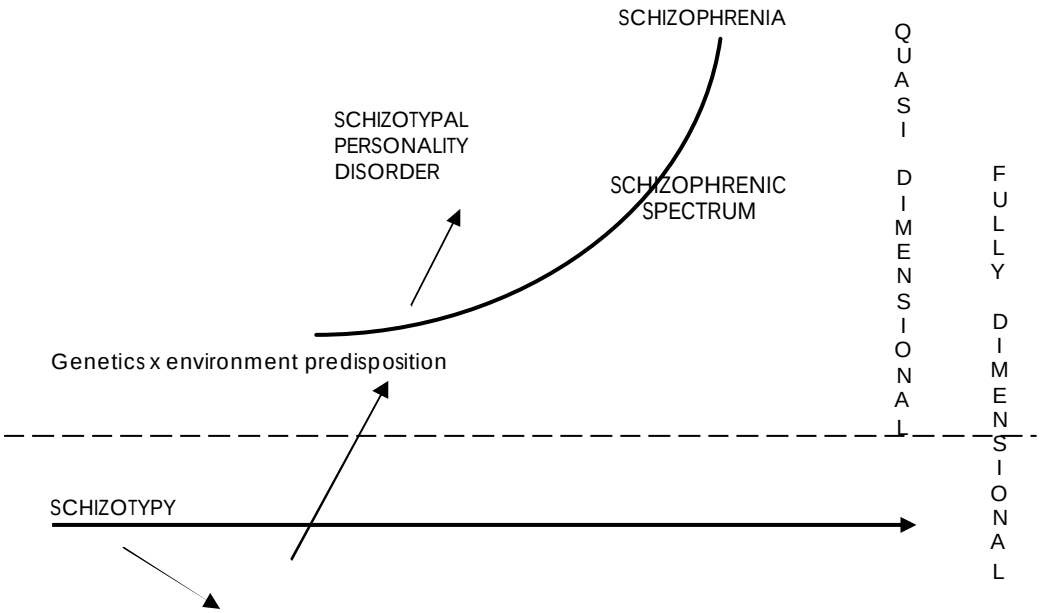
Dimensional models of psychosis, as opposed to categorical/dichotomic models, have their basis on the concept of "unitary psychosis" ("*einheitpsychose*"; Griesinger, 1861; Kerr & McClelland, 1991). In contrast to the Kraepelinian point of view, the dimensional approach to psychosis considers that schizophrenia spectrum disorders are distributed along a psychopathological *continuum* where affective, paranoid, and mixed syndromes would actually represent different forms (or stages) of psychosis sharing a common origin (Crow, 1986; Strauss, 1969; Van Os, Hanssen, Bijl & Ravelli, 2000).

The emergence of these models responded to the general awareness that the classical dichotomy between schizophrenia and affective disorders was unrepresentative of the reality of psychotic phenomena. This impression is confirmed by studies reporting a genetic and psychopathological overlap between schizophrenia and depression (Maier et al., 1993; Taylor, 1992; Taylor, Berenbaum & Jampala, 1993; Van Os et al., 1997b), a stronger association of dimensional measures

to course, treatment and outcome parameters (Peralta, Cuesta, Giraldo, Cardenas, Gonzalez, 2002; Rosenman, Korten, Medway & Evans, 2003; Van Os et al., 1996a, 1999a,b), and high prevalence of schizotypal and psychotic-like traits in the general population (e.g., Altman, Collins & Mundy, 1997; Johns & Van Os, 2001; Morimoto & Tanno, 2004; Rosa et al., 2000; Stefanis et al., 2002; Strauss, 1969; Van Os et al., 2000; Verdoux, Maurice-Tison, Gay, Van Os, Salamon & Bourgeois, 1998).

Claridge & Beech (1995) consider that there are two traditional approaches to dimensional models (see Figure 1.5). On the one hand, there is a psychiatric viewpoint on continuity, more typical of North American authors and called "quasi-dimensional" (based on the disease). From this perspective, the abnormal (ill) state is the point of reference in that dimensionality is reflected on different degrees of expression of the disease process. Derived descriptors of this approach are clinical signs and symptoms, which constitute the basic measure of this paradigm. From this point of view, schizophrenic spectrum disorders are seen as "*formes frustrées*" of schizophrenia. On the other hand, there is a more psychological and typical of European authors approach, called "fully-dimensional" (based on personality). In this case, the point of reference is normality-health (not the disease, as in the previous approach), but it also includes the quasi-dimensional view, extending the psychopathological continuum from the normal personality level to the disease level. From this perspective, certain configurations of personality would reflect a predisposition to abnormal domain (disease) disorders remaining, nevertheless, in a normal individual variation level (Claridge, 1987).

Figure 1.5 Diagram of comparison of quasi-dimensional and fully-dimensional approaches of schizotypy and schizophrenia (extracted from Claridge & Beech, 1995)



Personality traits
Cognitive style (Creativity?)
Nervous system type
Genetic variation

An essential difference between both perspectives is that fully-dimensional models consider that those traits describing deviance are represented in personality as "healthy diversity" (Claridge, 1994).

Meehl's model (1962) would combine aspects from both the quasi-dimensional and the fully-dimensional point of view. On the one hand, his model suggests continuity between schizotypic personality -derived from schizotaxia- and schizophrenia (*fully-dimensional model*) but, parallel, it considers schizotypy as an aberrant ("ill") manifestation of personality (*quasi-dimensional model*).

Hence, the dimensional or dispositional point of view of mental disorders assumes continuity between clinically diagnosable psychopathology and subclinical personality and behaviour (predisposition). This approach has led to the view of schizotypic personality traits as vulnerability markers to schizophrenia spectrum disorders and, therefore, to the emergence of the so-called "**behavioural high risk -or psychometric- paradigm**" (Chapman, Edell & Chapman, 1980; Lenzenweger, 1994).

The whole data suggest that dimensional models are conceptually superior to categorical considerations (Rosenman et al., 2003; Van Os et al., 1999a). However, due to the practical difficulties in applying dimensional models to the general practice, the employment of both strategies (categorical and dimensional) complementarily appears to be the best option.

Thus, the main assumption underlying the psychometric high risk paradigm is that major mental disorders would represent the most severe end of a continuum, whereas in the other end we would find phenotypically similar but symptomatologically more attenuated conditions (Klein & Anderson, 1995). With respect to schizophrenia, the *continuum* model derives from clinical observations of schizotypic forms usually preceding the onset of psychosis (e.g. Bleuler, 1911; Kraepelin, 1919), more common in relatives of schizophrenic patients than in the general population (Kendler, 1988).

5.6 Measurement and factorial structure of schizotypy

The development of the psychometric (exophenotypic-behavioural) high-risk paradigm has led to the proliferation of scales for schizotypic personality traits measurement and to the subsequent problem of determining if such different

instruments are measuring the same construct (Kelley & Coursey, 1992). These scales (see Table 1.14, next page) have been broadly used in non-clinical samples, with results overtly suggesting that some psychotic forms are represented in the general population (e.g., Claridge & Beech, 1995; Johns, Nazroo, Bebbington & Kuipers, 2002; Morimoto & Tanno, 2004; Peters, Day, McKenna & Orbach, 1999). Therefore, some of these psychotic-like forms should not be considered pathological, but rather as a part of normal individual variation (Johns & Van Os, 2001; Verdoux et al., 1998).

A significant problem of schizotypic pathology, at a diagnosis level, is its low prevalence in hospitals. Prevalences around 2% for paranoid personality disorder and 4% for SPD have been found in hospital samples (Loranger, 1990). This fact makes the search for adequate samples of study very difficult. Furthermore, hospitalised schizotypic cases very likely represent more severe expressions of the underlying vulnerability than usual in the general (non-clinical) population. Therefore, results derived from the study of these cases may not be fully representative of the "psychosis-proneness" concept. Thus, the optimal strategy to detect the presence of this *psychosis proneness*[12] would involve a random selection of individuals from the **general population** (Lenzenweger, 1994).

Table 1.14 Scales for the measurement of psychometric schizotypy

- "Schizoidia" (from the MMPI: Golden and Meehl, 1979)
- Chapman scales: "Perceptual Aberration": Chapman et al., 1978
  "Magical Ideation": Eckblad & Chapman, 1983
  "Social and Physical Anhedonia": Chapman et al., 1976
  Etc.
- "Schizotypal Traits Questionnaire" (STQ) (composed by two scales: "Schizotypal Personality" and "Borderline Personality") (Claridge & Broks, 1984)
- "Launay and Slade Hallucinatory Disposition Scale" (LSHS) (Launay & Slade, 1981)
- "Schizophrenism" (Nielsen & Petersen, 1976)
- "Psychoticism" (from the EPQ: Eysenck & Eysenck, 1975)
- "Schizotypal Personality Questionnaire" (SPQ) (Raine, 1991)
- "Peters et al. Delusions Inventory-21 items" (PDI-21) (Peters & Garety, 1996)
- "Oxford-Liverpool Inventory of Feelings and Experiences" (O-LIFE) (Mason et al., 1995)

Along these lines, the use of diagnostic interviews might seem the most adequate alternative. However, this detection methodology is highly costly in terms of time, and because of its condition of categorical diagnostic system (opposite to the dimensional model), would probably detect only cases of "expressed" liability. This would generate

[12] Psychosis proneness is understood as a genetic predisposition or diathesis for psychosis (Chapman et al., 1994) according to the vulnerability-stress model of schizophrenia (Meehl, 1990; Gottesman, 1991), which would express phenotypically in form of schizotypic traits.

a high level of false negatives that would compromise the task of detection of psychosis-prone individuals. In this regard, the identification of schizotypal (psychosis-prone) individuals in the general population might be more precise if carried out from a **dimensional** point of view.

Each one of the scales displayed in Table 1.14 measures one or several aspects hypothetically predisposing to psychosis. Indeed the pioneers of psychometric measurement of schizotypy, i.e., Chapman's, warned us about the need of several scales to tap all aspects of schizotypy (Claridge & Beech, 1995). However, there are some difficulties in establishing if these scales are measuring what we really want to measure (schizotypy-vulnerability to psychosis). Certainly, the status of schizotypy as a construct makes it very difficult to determine the validity of the existent measures of psychometric schizotypy.

On the other hand, it is worth taking into account that the psychometric approach to studies of vulnerability to psychosis does not try to deny the undeniable predictive value of genetic high-risk strategies, as both approaches are compatible. Furthermore, the positive predictive value of psychometric schizotypy in relation to schizophrenia is actually low. In fact, most of psychometrically-detected schizotypic subjects will never develop the disease. Therefore, the psychometric strategy is seen as an extra-tool for high-risk studies and not a substitute for other approaches to vulnerability (Battaglia et al., 1999; Lenzenweger, 1994).

The problem of individual variation in schizotypic traits, so difficult to overcome by current instruments of measure, leads us to think about schizotypy as a **multidimensional**, not a unitary, construct. From this point of view, a number of factor analyses of several scales presumably measuring schizotypy have been made with the purpose of disentangling the dimensional structure of this concept (Vollema & van den Bosch, 1995). Despite the different results depending on the analysed scales, some dimensions seem to be consistently identified in almost every factor analysis. In a review by Claridge & Beech (1995) on factor analytical studies, the authors concluded that there were two dimensions which appeared in almost every study, and another factor or dimension less delimited but also consistent. Firstly, there is a factor (or dimension) characterised by unusual perceptual experiences, and thinking styles and beliefs. Secondly, they described a factor represented by personality traits as "schizoid loneliness", "lacking emotions", and a trend to anhedonia. Finally, there is a factor characterised by psychotic-like forms not represented in the first factor, such as cognitive disorganization (attentional, decision making, and concentration problems,

etc.). As can be observed, the factorial structure of schizotypy is very similar (though not exactly) to that of schizophrenia (e.g., Liddle, 1987; Rossi & Daneluzzo, 2002).

Some factor analytic studies on the diagnostic criteria for SPD also report a similar structure to that reported in schizotypy (e.g., Battaglia, Cavallini, Macciardi & Bellodi, 1997). However, it seems that the agreement between psychometric schizotypy measures and the categorical diagnosis of SPD is low (e.g., Thaker, Moran, Adami & Cassady, 1993; Álvarez-Moya, Barrantes-Vidal, Navarro, Subirà & Obiols, *submitted*). In this regard, a somewhat different factorial structure has been recently reported in SPD patients by using a latent class analysis (Fossati et al., 2001). These authors found a first class characterised by odd thinking, inappropriate affect, and interpersonal features; a second class consisting of cognitive/perceptual difficulties; and a third class composed by paranoid features. Unlike previous studies, oddness, aloofness, and social withdrawal, rather than positive symptoms, best characterized SPD even in clinical samples. These differences on the SPD factorial structure and the lack of concordance with psychometric schizotypy have lead to postulate that the SPD diagnosis appears to be a heterogeneous category. Such heterogenenity would even affect the genetic loading of its different components/factors such that the more "negative" and "oddness" criteria would be significantly more concentrated among the schizotypal relatives of probands with schizophrenia (Battaglia & Torgensen, 1996). Actually, Bergman, Silverman, Harvey, Smith & Siever (2000) concluded from a factor analytic study with first-degree relatives of schizophrenic patients and SPD patients selected from clinical settings that the structure of schizotypal symptoms in the relatives is similar to the three-factor model of schizophrenia symptoms often reported, but not the same as the structure of schizotypal symptoms in clinically selected SPD patients.

Another approach to the dimensionality of schizotypy consists of grouping individuals, rather than the questionnaire scores, according to their profile of response to different psychometric schizotypy scales. Thus, three groups (clusters) have been consistently identified: high scorers on positive dimensions, high scorers on negative dimensions, and high scorers on all schizotypal dimensions (Barrantes-Vidal et al., 2002; Suhr & Spitznagel, 2001; Williams, 1995).

5.7 Schizotypy and neurocognition

Schizotypy also show neuropsychological correlates similar to that found in schizophrenia. Generally, neuropsychological studies of schizotypic samples (either from the general population or relatives of schizophrenics) have found a deficit in tasks involving fronto-lymbic circuits (Lencz, Raine, Benishay, Mills & Bird, 1995). Some of the

most frequently reported neurocognitive deficits in schizotypy are diplayed in Table 1.15.

Table 1.15 Neurocognitive deficits in schizotypy

- Negative priming (Beech et al., 1989; Ferraro & Okerlund, 1996)
- Backward masking (Balogh & Merritt, 1985)
- Longer reaction times (Simons, MacMillan & Ireland, 1982)
- Semantic priming (Fisher & Weinman, 1989)
- Latent inhibition (Baruch et al., 1988; Höfer, Della Casa & Feldon, 1999)
- Learning (Jones et al., 1992)
- Sustained attention (Venables, 1990; Condray & Steinhauer, 1992; Obiols et al., 1993)
- Span of apprehension (Asarnow et al., 1983)
- Concept formation and cognitive flexibility (Lyons et al., 1991; Raine et al., 1992a; Trestman et al., 1995)
- SPEM abnormalities (Kelley & Bakan, 1999; O'Driscoll, Lenzenweger & Holzman, 1998; Simons & Katkin, 1985)
- Short-term memory (Koh & Peterson, 1974)
- Mentalising (Langdon & Colteart, 1999)
- Spatial working memory (Park, Holzman & Lenzenweger, 1995; Wood et al., 2003)
- Pre-attentional processing of visual information (Sterenko & Woods, 1978)

Similar correlates have been reported in the SPD, i.e., abnormalities in the habituation of skin conductance orienting (e.g., Raine, Benishay, Lencz & Scarpa, 1997), in event-related potentials (e.g., Niznikiewicz et al., 2000; Trestman et al., 1996), in SPEM (e.g., Lencz et al., 1993), in executive functions (e.g., Cadenhead, Perry, Shafer & Braff, 1999; Diforio, Walker & Kestler, 2000; Gilvarry, Russell, Hemsley & Murray, 2001; Lyons, Merla, Young & Kremen, 1991; Trestman et al., 1995), etc. Neuroimaging studies have also confirmed differential metabolic patterns on medial frontal and medial temporal areas in SPD patients, as well as intermediate values between schizophrenic and normal volunteers in prefrontal areas (Buchsbaum et al., 2002).

OBJECTIVES AND HYPOTHESES

1. OBJECTIVES

With the aim of identifying subjects at high-risk for later psychopathology, in general, and schizophrenia spectrum disorders, in particular, we proposed the following objectives:

1.1 General aims

a) From a prospective point of view, to explore the evolution of a CPT-linked sustained attention deficit during adolescence and to determine its relationship to other markers of vulnerability to psychopathology at 10-years follow-up.

b) From a cross-sectional point of view, to determine the association among psychometric schizotypy and different markers of vulnerability to psychopathology in a sample of youngsters from the general population.

1.2 Specific aims

1.2.1 Prospective study

a.1 To explore the relationship between the absence/presence of a CPT-linked sustained attention deficit at early adolescence and the following variables:

- Current neuropsychological performance
  - Attention, as measured by the CPT-IP
  - Executive functions, as measured by the WCST, the Stroop Colours and Words Test, and semantic and phonetic verbal fluencies
  - Memory, as measured by the CVLT and a spatial working memory test
- Current neurointegrative variables
  - Neurological soft signs
  - Psychomotor performance, as measured by the Finger Tapping test
  - Laterality, as measured by the Annett Handedness Scale

- Personality
  - Psychometric schizotypy, as measured by the Oxford-Liverpool Inventory of Feelings and Experiences
  - Axis II personality traits, as measured by the SCID-II
- Current psychosocial variables
  - Social behaviour, as measured by the DOI scale (self-reported and parents version)
  - Coping strategies, as measured by the COPE scale
  - Stressful life events, as measured by an *ad hoc* scale.
- Current clinical status
  - DSM-IV Axis I mental disorders, as measured by the SCID-I
  - Premorbid adjustment in the previous year, as measured by the Premorbid Adjustment Scale
  - Premorbid social adjustment in childhood and adolescence, as measured by the Premorbid Social Adjustment Scale
  - Observational assessment of the presence of general clinical signs
- Prenatal / perinatal abnormalities
  - Prenatal and birth complications, as measured by an *ad hoc* questionnaire to the subjects' mothers.

a.2 To examine the development of sustained attention from early adolescence to early adulthood in order to determine possible subgroups of subjects with different profiles of attentional development.

a.2.1 To compare current neuropsychological performance, neurointegrative variables, schizotypy and axis II personality measures, clinical status, premorbid adjustment, psychosocial variables, and prenatal and birth complications (see aim a.1) among the different subgroups of attentional development in order to identify subjects at high-risk for later development of psychopathology.

1.2.2 Cross-sectional study

b. To explore the association among psychometric schizotypy, from a multidimensional approach, and neuropsychological variables (executive functions, attention and memory) in youngsters from the general population.

2. HYPOTHESES

2.1 Prospective study

a.1 Those subjects with a sustained attention deficit at early adolescence will show a poorer functioning / performance in all the areas mentioned than the subjects with no such a deficit in early adulthood. As to personality, we expect to find especially higher levels of Cluster A personality traits and negative schizotypy.

a.2 We expect to identify different subgroups of attentional development. One of these subgroups will show evidences for the neurodevelopmental subtype described in the literature.

a.2.1 There will be differences in all the areas mentioned according to the attentional development, with those subjects on the neurodevelopmental subgroup displaying worse current functioning in general, especially more Cluster A personality traits, negative schizotypy, and more prenatal and/or perinatal abnormalities than the other groups.

2.2 Cross-sectional study

b. A higher degree of psychometric schizotypy will be associated with poorer executive functioning, poorer attention and poorer spatial and verbal memory. This association will be especially evident for the negative dimension of schizotypy.

METHODS

1) SUBJECTS

The current sample consists of 80 subjects, aged 20-24 years old, whose sociodemographic characteristics are displayed in Table 1.

Table 3.1 Sociodemographic characteristics of the sample (n=80)

Gender	51.3% male
Age	$\bar{X}$ =22.0; SD=1.0
Education (years)	$\bar{X}$ =12.8; SD=2.1

In 1992, N=1498 adolescents from the general population aged 12-13 years old were screened with the *Continuous Performance Test – Identical Pairs* version, which measures sustained attention. This main sample was selected by means of a conglomerated sampling of all adolescents attending 8th EGB on public and private schools from Barcelona and Girona.

A subsample (n=301) was extracted from the main sample using the CPT-IP performance as the selection criteria. Thus, the 10% of worst performers (indicative of an attentional deficit) were designated as the "**index group**" (n=162), and a "**control group**" (n=139) was matched to the previous one by sex, classroom and age (more details about use of the CPT-IP to select the cohorts are provided next, in section *2. Material*). Both groups were assessed with a test battery including neuropsychological, personality and intelligence tests, as described elsewhere (Obiols et al., 1997).

The second phase, carried out in 1997-1998, was strongly decimated by attrition, since only 139 subjects out of the initial 301 subjects wanted to collaborate. A second test battery, consisting of some repeated measures of Phase I assessments, and other measures of psychosocial and personality traits, were administered to this sample (see next point).

After the second assessment, the sample was contacted by telephone in several occasions in order to minimise the attrition in the upcoming third phase. In fact, this is a non-clinical population who do not receive a compensation for their collaboration, so a "high-risk" of dropouts is always present. Despite our efforts and the economical compensation that we offered to those who wanted to collaborate in the last phase (Phase III; 2001-2003), attrition reduced the final sample size to n=80 subjects.

✍ *Missing analysis*

In relative numbers, 46.2% subjects of the initial sample (n=301) were assessed in Phase II, and of those assessed in Phase II, 57.5% were re-contacted and re-assessed in Phase III. That is a **26.6%** of the initial sample. Evidently, it has been a **high rate of attrition** from the first phase, but we must consider that we contacted in Phase III only those subjects that participated in Phase II, so the attrition during the last follow-up period (Phase II to Phase III) was not as marked as it may appear.

There were no differences on the distribution of Index and Control subjects in the missing sample (54.1% vs 45.9%, respectively) in relation to the final sample (52.5% vs 47.5%, respectively), or in gender distribution (53.6% males in the missing sample, 51.3% males in the final sample). However, there was a clear difference between the missing sample and the final sample on their IQ. Subjects of the missing sample showed a statistically lower IQ, as measured by the Raven Progressive Matrices, than subjects of the final sample ($p<0.001$). This difference was maintained by cohort, so Index subjects of the **missing sample** were statistically **less intelligent** than Index subjects of the final sample ($p<0.001$), and the same was applicable to Control subjects of both samples.

2) MATERIAL

Table 3.2 shows a summary of the instruments used along the three phases of the present study. However, we will only describe those instruments employed in the third phase, and those of Phase I that we used in the present analyses (see Barrantes-Vidal, 2000, for a description of instruments used in previous phases).

Table 3.2 Test batteries administered in the different phases of this project

	BATTERY I (1994)	BATTERY II (1997-1998)	BATTERY III (2001-2003)
NEUROPSYCHOLOGICAL VARIABLES			
Sustained attention	CPT-IP		
Executive functions		WCST	
	TMT-A, TMT-B		
	F.A.S.		F.A.S
			Animal Naming
			SCWT
Intelligence	Raven Progr. Matrices		
	WISC (short version)		
Memory		CVLT	
		Spatial Working Memory	
NEUROINTEGRATIVE / NEURODEVELOPMENTAL VARIABLES			
Psychomotor perform.		Finger Tapping	
Dermatoglyphics	a-b ridge count		
Neurological soft signs	9-signs *ad hoc* battery		9-signs *ad hoc* battery

Laterality	Annett scale (modif.)		Annett scale (modif.)
PERSONALITY VARIABLES			
Psychometric schizotypy	Chapman's scales: *Perceptual Aberration* *Social Anhedonia* *Physical Anhedonia*	O-LIFE	
Personality disorders			SCID-II
Obsessionality	Leyton Inventory		
FAMILIAL INFORMATION			
Obstetric complications, etc.	Questionnaire *ad hoc* (parents)		
CLINICAL VARIABLES			
General features		Observational assessment (examiners-rated)	
Axis I disorders			SCID-I
PREMORBID ADJUSTMENT			
General adjustment			PAS
Child. & adolesc. adj.			PSAS (mothers)
PSYCHOSOCIAL VARIABLES			
Social behaviour	Achenbach TRF	DOI-JA / DOI-JH	
Coping			COPE
Stressful events			Life Events checklist

2.1 Instruments (Phase III)

2.1.1 Neuropsychological measures

- *Continuous Performance Test*

The *Continuous Performance Test-Identical Pairs* version is a test designed for the measurement of sustained attention (or vigilance), understood as the overall level of performance on a task that demands sustained, focused attention, irrespective of time (Lenzenweger et al., 1991). Impaired performance on this test seems to be a valid endophenotypic indicator of schizophrenia genotype (Cornblatt & Keilp, 1994).

The CPT was originally developed as a diagnostic instrument for the investigation of brain damage (Rosvold et al., 1956) and consists of a series of single letters visually presented for about 10 minutes. Since then, several versions have been developed (X-CPT, AX-CPT, DS-CPT, etc.), from which the CPT-IP has become the most reported in high-risk studies for schizophrenia.

According to Cornblatt & Keilp (1994), the CPT shows no relationship with the IQ and involves some aspects of working memory. Their impaired performance has been related to subcortical (basal ganglia) dysfunction and laterality disturbances (Buchsbaum et al., 1992). As a whole, this test shows good psychometric properties.

The CPT-IP is a computerized version compounded by two trials consisting of a rapid visual presentation of a long series of very short duration (50ms) stimuli (first trial: four-digit numbers / second trial: nonsense shapes). Each trial has 150 stimuli and the subject is required to respond (click on a mouse) whenever a certain stimuli appears two consecutive times (identical pairs).

Efficiency on each trial is reflected on the **d'** (d-prime) and ? (beta) indexes, both based on the signal detection theory (Green and Swets, 1966). Other indexes registered in the present study were **omission errors**, **commission errors**, **distraction errors**, and **reaction time** (see Table 3.3).

Table 3.3 CPT-IP indexes reported in the present study

CPT-IP index	Description
d'	Measure of the subject's ability to discriminate a signal from background noise
?	Measure of a subject's tendency either to overrespond or underrespond. It is considered a measure of state disposition and motivation
Omission errors	Non-response to a target stimulus. Also called "misses"
Commission errors	Incorrect responses to nontarget stimuli in catch* trials. Also called "false alarms"
Distraction errors	Incorrect responses to nontarget stimuli in filler* trials (type of commission error)
Reaction time	Mean time (ms) required to respond to each stimulus

**Catch trial*: the stimulus is very similar, but not equal, to the target stimulus (e.g. 4302 following 4382); *Filler trial*: the stimulus is not similar to the target stimulus (e.g. 4302 following 8325)

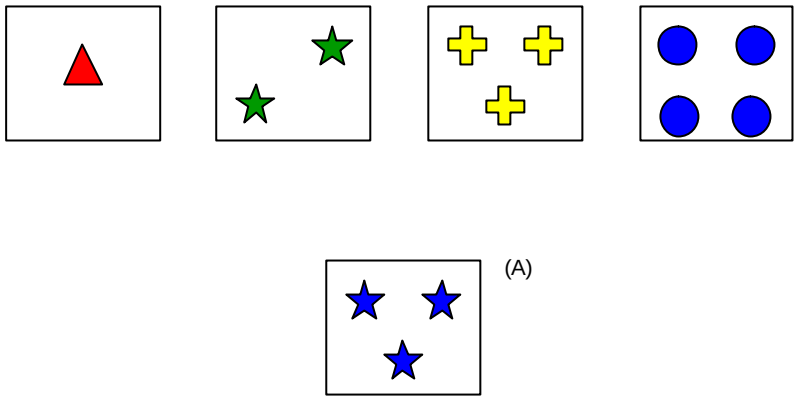
The assignation of subjects to Index or Control groups was based on the *d' numbers* (verbal d') and the *d' shapes* (spatial d'). A mean between both indexes was computed for each subject. Percentile 10 (worst performers) of this composite index in the whole sample (n=1498, see Part 2, point 3) was selected as a cut-point for group assignation. Thus, those subjects scoring ?1.11 on mean verbal-spatial d' were selected as "Index group" (n=162). Control group (n=139) was selected from the rest of subjects (scoring >1.11) matching them to Index group by sex, age, and classroom.

✍ *Wisconsin Card Sorting Test*

The *Wisconsin Card Sorting Test* (Heaton, 1981; Heaton, Chelune, Talley, Kay & Curtiss, 1993) is a neuropsychological instrument designed for the measurement of "frontal function". Originally created with the aim of measuring neuropsychological impairment on frontal-damaged patients, the WCST was firstly used in schizophrenic patients by Elizabeth Fey, in 1951.

The WCST is a card classification task that, in its computerized version (the most broadly used), has the following display:

Figure 3.1 Display of the WCST computerized version



This test consists in placing the card marked "A" under one of the 4 cards above. These 4 cards represent different attributes and possibilities of classification and never change during the test. Once the subject matches the A-card with a "model" card, a message appears in the middle of the screen indicating whether this movement was "CORRECT" or "INCORRECT". Next, a new card appears below, and the process starts again. This process is repeated 128 times in traditional WCST versions, typically used to measure neuropsychological impairment in psychotic or frontal-damaged patients.

However, considering that our sample is constituted by clinically normal people, we used a 64-trials version (Kongs, Thompson, Iverson & Heaton, 2000), that has been reported by other investigators to be also useful, besides of less time-consuming (Fey, 1951; Greve, 2001). The instruction given to the subject is the following: "*Next you will see a card that you have to sort out in one of these places (pointing the four model cards). When you have decided on the specific place, a message will appear in the middle of the screen indicating if this movement is Correct, or Incorrect*". Subject is neither informed about the change of criteria, nor about possible categories (Colour, Form, and Number).

Correction is computerized, and provides the following indexes:

- Number of **errors**
- Number of **perseverative responses**
- Number of **perseverative errors**
- Number of **non-perseverative errors**

- Number of achieved **categories**
- Number of **conceptual level responses**
- Number of **failures to maintain the set**
- (Number of **trials** required to complete the first category)
- ("**L*earning-to-learn***" index)

The number of trials to complete the first category were almost a constant in our sample (10, 11 trials for most subjects), and the “learning to learn” index gave us some problems of correction (computer failures), so both indexes were dropped out of the analyses.

- *Stroop Colours and Words Test*

The *Stroop Colours and Words Test* (Stroop, 1935; Golden, 1978) is used to measure "cognitive inhibition" (inhibitory control), which is considered an index of executive functioning because of the involvement of selective attention and shifting abilities in its performance. This test was administered with a paper-and-pencil format and contains 3 parts:

1) A list of 100 names of colours (Blue, Green, Red) written in black-ink.
2) A list of 100 non-readable items written in blue-, green-, and red-ink.
3) A list of 100 names of colours always written in an inconsistent ink-colour (interference task).

Execution consists of reading during 45 seconds each list. The first list is administered with the instruction: "Here you have a list of words representing colours. When I tell you, you will have to read as ready as possible these words, until I warn you to stop. If you finish all the words before I warn you, start again and continue reading until I tell you". Next, the second list is administered with the same instructions but the difference of naming the colour of each item, instead of reading. Finally, the last list is administered with the following instructions: "Here you have names of colours written in an inconsistent colour-ink. You will have to name the colour-ink of each word, but not reading".

The indexes reported were **number of words correctly read** on the first list, **number of colours correctly named** on the second list, and **number of correct responses on the interference task** (third list).

- *Controlled Oral Words Association Test and Animal Naming*

The *Controlled Oral Words Association Test* (Benton & Hamsher, 1978) is a phonetic verbal fluency test, also called F.A.S. Verbal fluencies are considered as an index of

executive functioning. The test consists of naming (orally) words starting with a certain letter, named "F", "A", and "S", during 1 minute for each word.

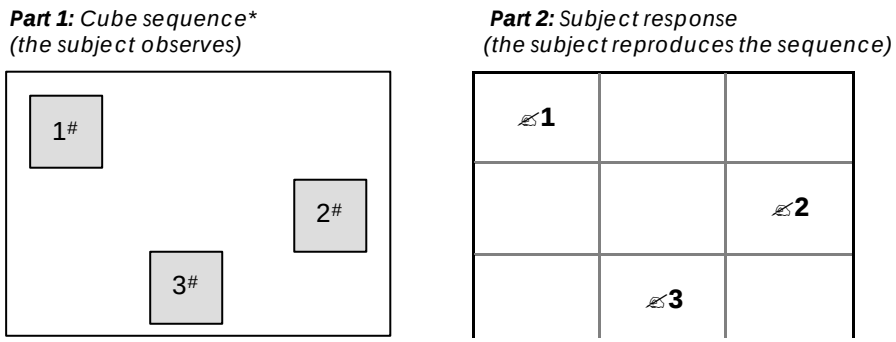
The *Animal Naming* is a semantic verbal **f**uency task consisting of naming (orally) animals during 1 minute.

The indexes analysed in the present study were **number of words generated** for each condition (*F.A.S.* and *Animal Naming*).

✍ *Spatial Working Memory*

We used a computerized spatial working memory (SWM) task provided by *Neurosoft Inc*©. This task consists of reproducing a sequence of movements performed by a cube, and requires retaining the position and order of appearance of such a cube. Each trial has two parts. Firstly, the subject is instructed to pay attention to a cube that appears in different parts of the computer screen (one at a time) doing a sequence. After that, a cell grille appears on the screen in order the subject can orient him/herself spatially. Then, the subject must reproduce (doing click on the different cells) exactly the same sequence as the cube did (same positions and same order) (see Figure 3.2).

Figure 3.2 Visual display of the SWM task: Example of the first trial



* The cubes remain visible in each position only for 50ms, and always one at a time.
# This number indicates the order of appearance in Part 1, and so the correct order of responses in Part 2.

This task is composed of 6 trials, starting with a 3-movements sequence, and progressively increasing the level of difficulty up to an 8-movements sequence.

The indices derived from this task were: a) **overall SWM accuracy** (percentage of correct responses in general), b) left **SWM accuracy** (percentage of correct responses on the left column), and 3) **right SWM accuracy** (percentage of correct responses on the right column).

No psychometric properties of this test have been reported. Moreover, the literature on SWM in schizophrenia and related psychoses lacks of consistent measurement methods addressed to this neuropsychological function. In addition to the scant reports on this issue, very different measures are used, so the comparison of results is difficult. Anyway, a recent study by Wood et al. (2003) used a SWM task quite similar to the one that we used. They found that subjects at an imminent high risk of developing psychosis were impaired in this ability.

- *California Verbal Learning Test*

The CVLT (Delis, Freeland, Kramer & Kaplan, 1987) is a relatively new test that is similar in many respects to the frequently used Rey Auditory Verbal Learning Test. A major advantage of the CVLT is that, in addition to providing conventional measures of overall recall, rate of learning, and indices of forgetting, it also provides information on an additional array of learning and memory characteristics (e.g., recognition memory, recall errors, qualitative aspects of learning (serial versus semantic clustering), and several other features of verbal learning and recall ability). The CVLT does not examine rote verbal memory in itself, but rather, some level of interaction between verbal memory and conceptual ability (Lezak, 1995).

The test involves oral presentation of a "shopping" list of 16 items (List A) over 5 immediate recall trials. The items on the list are presented in the same order on all five trials and examinees are asked to recall items in whatever order they please and to recall all of the items they can, including those they reported on previous trials. The list consists of four items from each of four categories (fruits, spices, clothing, and tools), but examinees are not informed of this. Adjacent words on the list are from different categories, which affords an assessment of the degree to which and examinee used the active, effective learning strategy of recalling the words in semantic clusters. Also, the items are not prototypical exemplars of their categories, so if examinees start guessing prototypical category members, these responses are correctly labelled as intrusion errors.

Following the five learning trials, a second, interference list (List B) is presented for one trial. List B is also composed of four items from each of four categories: two categories are the same as those in List A (fruits, spices) and two are the new (fish, utensils). Following recall of List B, free and category cued recall of List A is tested (termed the "short delay" trials). After a 20 min interval in which non-verbal testing takes place[13], "long delay" free recall, category cued recall, and recognition of List A are assessed.

The yes/no recognition test contains 16 List A target items and 28 distracters (8 List B items, 8 items phonemically similar to the target items, 8 items unrelated to the targets, and prototypical members of the List A categories).

Table 3.4 Description of the CVLT indices shows all CVLT indices and their descriptions, though on behalf of parsimony, not all of them were used in the present study (see *Results* section).

Table 3.4 Description of the CVLT indices

Variable	***Description***
RECALL MEASURES	
List A total (trials 1-5)	Total number of List A words recalled across trials 1-5
List A trial 1	Number of List A words recalled on trial 1
List A trial 5	Number of List A words recalled on trial 5
List B	Number of List B words recalled on the one immediate recall trial
List A short delay free recall	Number of List A words recalled immediately after the List B trial without re-presentation of List A
List A short delay cued recall	Number of List A words recalled when category names are provided
List A long delay free recall	Number of List A words recalled after a 20-min delay following the short delay cued recall trial
List A long delay cued recall	Number of List A words recalled when category names are provided
LEARNING CHARACTERISTICS	
Semantic clustering ratio	Ratio of List A words from the same category recalled together over chance-expected semantic clustering
Serial clustering ratio	Ratio of List A words recalled in the same order as they were presented over chance-expected serial clustering
Percent correct recall primacy region	Percentage of total words recalled that are from the primacy region of List A (first four words)
Percent correct recall middle region	Percentage of total words recalled that are from the middle region of List A (middle eight words)
Percent correct recall recency region	Percentage of total words recalled that are from the recency region of List A (last four words)
Increment in words recalled per trial (slope)	Slope of a least-squares regression line calculated to fit changes in correct response scores across trials 1-5
Percent recall consistency across trials 1-5	Percentage of List A words recalled on one of the first four trials that are also recalled on the very next trial
RECALL ERRORS	
Perseverations (free and cued total)	Total number of responses repeated on each trial summed across all free and cued recall trials of Lists A and B
Total free recall intrusions	Total number of nontarget items reported on all free recall trials of Lists A and B
Total cued recall intrusions	Total number of nontarget items reported on the two cued recall trials of List A
RECOGNITION MEASURES	
Recognition hits	Correct identification of List A words on recognition testing
Discriminability	Signal detection index of overall accuracy on recognition test incorporating number of misses and false-positive errors
False positives	Number of distracter items identified as List A items on the recognition test
Response bias	Difference in number of false positives and misses corrected for total number of errors made: reflects possible bias in response criterion on recognition testing
List B-shared	False identification of items from List B that are from the categories shared with List A
List B-nonshared	False identification of items from List B that are from categories not shared with List A
Neither list-prototypical	False identification of items found on neither list but that are prototypical of categories on List A
Neither list-phonemically similar	False identification of distracters that are phonemically similar to words

[13] During this period other neuropsychological tests were performed (see point *Third Phase Development*)

	on List A
Neither list-unrelated	False identification of words that share neither semantic nor phonemic features of words on either list
CONTRAST MEASURES	
List B compared to List A trial 1 recall	Change in recall of List B relative to trial 1 of List A; reflects vulnerability to proactive interference
Short delay recall of List A compared to trial 5	Change in recall on short delay free recall relative to trial 5 of List A; reflects vulnerability to retroactive interference and the short delay
Long delay free recall compared to short delay free recall	Change in recall on long delay free recall relative to short delay free recall; reflects vulnerability to the effects of long delay
Discriminability compared to long delay free recall	Change in recognition discriminability relative to long delay free recall; reflects impact of recognition testing format

CVLT performance correlates positively with education and women tend to outperform men on learning and recall measures, although no sex differences appear for the recognition trial or for error types (Kramer, Delis & Daniel, 1988).

Reliability studies report correlation coefficients of 0.77 to 0.86 (Delis et al., 1987). On the other hand, factor analytic studies yielded 6 factors: a general learning factor, learning strategy, acquisition rate, serial position effect, discriminability, and learning interference (Delis et al., 1988).

2.1.2 Neurointegrative measures

- *Neurological Soft Signs*

We used an *ad hoc* battery of neurological soft signs that measured signs of developmental delay in several functions (see Obiols et al., 1999), such as: 1) asymmetry and laterality, 2) motor coordination, 3) motor overflow, and 4) sensory-perceptual signs.

All items were scored on a 4-point scale ranging from 0 (absence) to 3 (clear presence). A **total NSS score** was computed for every subject by summing all item scores.

Table 3.5 Items included in the NSS battery

- Hand crossing
- Inferior extremities crossing
- Superior extremities crossing
- Right inferior extremity coordination
- Left inferior extremity coordination
- Right fingers opposition
- Left fingers opposition
- Syncinesias (right)
- Syncinesias (left)
- Right hand graphestesia
- Left hand graphestesia
- Foot rhythm

Some aspects of laterality were measured by hand crossing, and extremities crossing. Motor coordination included tests of fine motor coordination such as finger opposition and extremities coordination. Sensory-perceptual signs were assessed by means of graphestesia[14] tests, and syncinesias of the inferior extremities were measured during the evaluation of finger opposition and foot rhythm tasks.

NSS have been found both in schizophrenic patients (Schröder et al., 1992) and in healthy first-degree relatives of these patients (Niethammer et al., 2000; Torrey, 1994; Rossi et al., 1990).

At a neuroanatomical level, NSS appear to be related to diminished activation of the sensorimotor cortices and the supplementary motor area in schizophrenic patients (e.g., Günther et al., 1994; Schröder et al., 1999).

Buchanan & Heinrichs (1989) found that their measure of NSS (the NES scale) was not related to age and sex, both in control subjects and in schizophrenic patients, suggesting that these factors are not important determinants of neurological impairment. However, other studies yield inconclusive results on this respect (Heinrichs and Buchanan, 1988).

A study of validity and reliability of different NSS scales (Stokman, Shaffer, O'Connor, Wolff, 1986) revealed that, in general terms, all had acceptable psychometric properties, suggesting that neurological signs can be reliably assessed by different tools. NSS have also demonstrated to be stable over time in non-psychiatric subjects (Pine, Wasserman, Fried, Parides & Shaffer, 1997).

- *Annett Handedness Scale*

The Annett Handedness Scale (Annett, 1970) assesses hand preference according to the stated and demonstrated preference for 12 discrete actions: six primary actions (writing, throwing ball, hammering nail, brushing teeth, striking match, holding a racquet) and six secondary actions (sweeping –hand on top, shovelling –hand on top, unscrewing a jar lid, dealing cards, threading a needle –guiding hand, holding scissors).

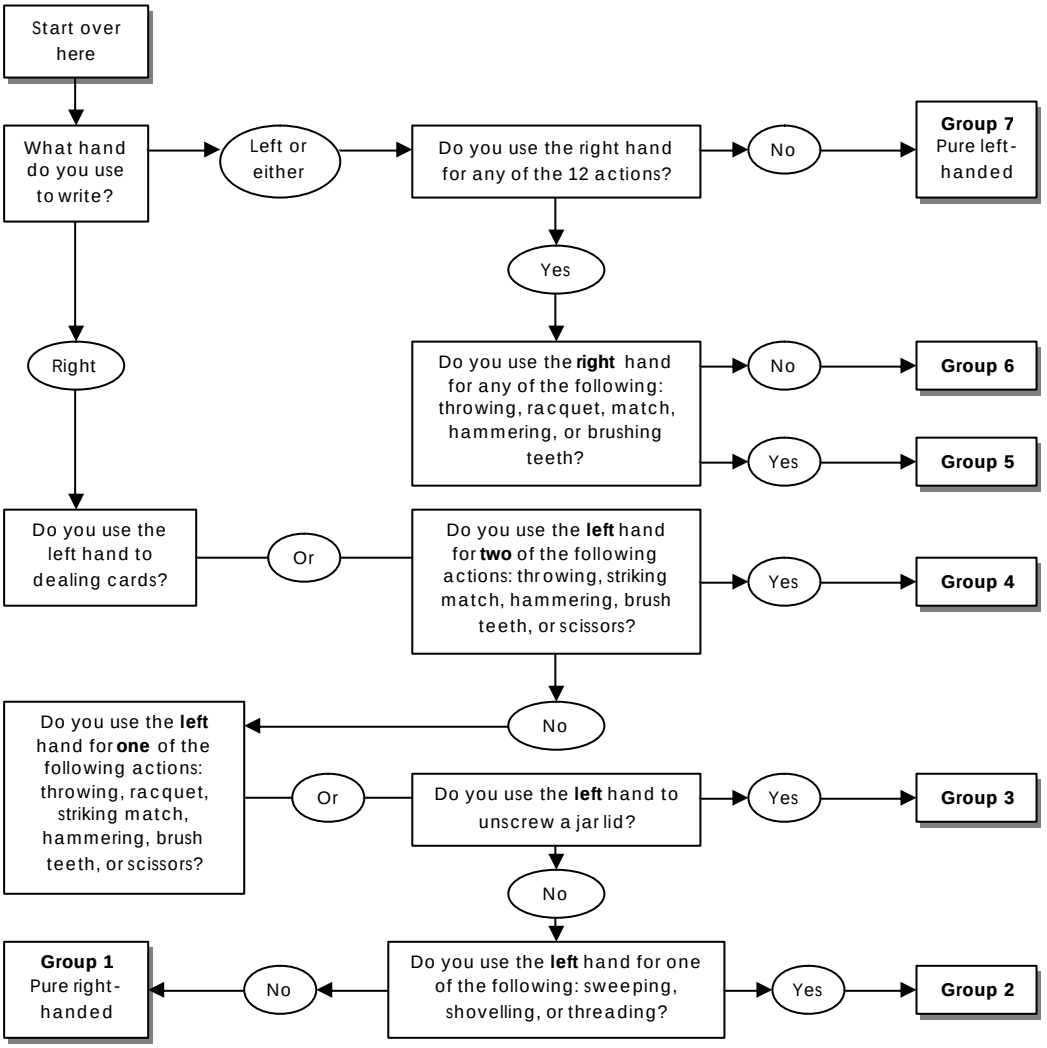
Although most versions of this scale register three possible response options (right, left, either), we added some middle responses that did not alter, however, the final score. These added responses were "usually right hand" (2-score in our register sheet) and

[14] Subject, with eyes closed, is asked to identify the number written on the tip of his/her palm.

"usually left" (4-score in our register sheet). Furthermore, we added two questions on eye- and feet-dominance, with the same scoring than the previous ones.

Responses of "either", "usually right", and "usually left" were coded as the writing hand in adherence to Annett's (1970) recommendation. Adopting Annett's own scoring method, subjects were assigned to one of seven handedness groups, ranging from full right to full left, through degrees of mixed handedness (see Figure 3.3).

Figure 3.3 Decision tree for scoring the Annett scale



In the present study, the Annett scale was scored in four different ways, though not all of them could be finally included in the statistical analyses:

a) According to Annett's (1970, 1985) revised classification system (see Figure 3.3), which divides participants into seven groups (for historical reasons numbered 1-

8 with 5 omitted) by means of a decision tree[15]. As can be seen in Figure 3.3, Group 1 designates fully right-handed individuals. Those in groups 2-4 are right-handed but have an increasing preference for using the left hand for other activities. Conversely, participants in Group 7 are fully left-handed, while those in groups 6 and 5 are left-handed but increasingly prefer to use the right hand for other activities. We could not perform statistical comparisons among these groups because there were no subjects enough in each one. Anyway, descriptive data will be offered.

b) Assigning subjects into three groups[4] ("strong right", "strong left", and "mixed"). "Strong right" and "strong left" were identical to Annett's groups 1 and 7, respectively. "Mixed" included all other subjects. We only detected n=1 "strong left" subject, so we added him to the "right" group, and compared "**mixed-handedness**" versus "**strong-handedness**" subjects.

c) By quantifying the degree of **either hand usage** (0-14[16]), as measured by the number of items for which a subject declared a preference for "either" hand. The variability on this variable was, however, so low that we dropped it out from the statistical analyses.

d) By summing all item-scores in order to obtain a **quantitative measure of laterality** (from 14, indicating pure right-handedness, to 70, indicating pure left-handedness, and the 35-score indicating pure mixed handedness).

This scale has been used extensively and is brief and easy to administer and score. In addition, its psychometric properties indicate good test-retest reliability (McMeekan & Lishman, 1975).

✍ *Finger Tapping*

The Finger Tapping Test (Reitan, 1969) is also called the *Finger Oscillation Test*, and its purpose is to measure motor speed of the index finger of each hand. It comes from the Halstead's test battery (1947) and is frequently used to assess subtle motor and other cognitive impairment.

In our version (*Neurosoft Inc.*©, 1990), the subject is placed in front of a computer screen and instructed to tap a mouse as rapidly as possible using the index finger of the right hand. Secondly, the same instruction is given with the left hand. Three 10-second trials are administered for each hand (6 trials in total) and, in order to minimise

[15] It does not include eye-dominance and feet-dominance items.

fatigue, trials per hand are alternated. Each trial is measured in a 10-point range from slowest to fastest and the subject can observe in the computer screen how a bar increases as he/she taps.

The finger tapping score is computed for each hand separately and is the mean of the three 10-second trials. In addition, performances of the right and the left hands are compared to determine if there is consistent evidence of poor performance with one hand relative to the other (ratio). Therefore, the indices provided by the computer program were the following: a) **mean left hand speed**, b) **mean right hand speed**, and c) **left/right ratio** (dominance score ranging from -100 to +100, where a positive score indicates right dominance, a negative score indicates left dominance, and the 0-score indicates no dominance). Due to computer failures in the generation of these indices, we had to drop out of the analyses the left/right ratio.

It seems that performance with each hand is quite stable over time, with reliability coefficients ranging from 0.58 to 0.93, both in normal and neurologically impaired subjects (e.g. Ruff & Parker, 1993). Likewise, performance with the preferred (dominant) hand tends to be superior to that with the non-preferred hand (e.g. Peters, 1990).

Finally, tapping frequency can be affected by variable levels of alertness, impaired ability to focus attention, or slowing of responses (Spreen & Strauss, 1998).

2.1.3 Clinical variables

✍ *Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I)*

The SCID-I (First, Spitzer, Gibbon, Williams, 1997a) is a semi-structured interview addressed to establish the most important Axis I diagnoses according to the DSM-IV (APA, 1994). There are two versions of this interview: the clinical version (CV), and the research version. We used the former because the research version is not adapted in our country.

The SCID-I-CV was designed to be used in clinical settings and to facilitate standardized evaluations. It only taps the most frequent DSM-IV diagnoses seen in clinical practice. Most of the diagnoses appeared in the SCID-I-CV are provided with their complete set of criteria (with their corresponding question). However, some disorders appear summarized; with only a brief description of it instead of its complete set of criteria (see

[16] We included eye-dominance and feet-dominance items.

Table 3.6 for a listing of those disorders summarized in the SCID-I-CV).

Table 3.6 SCID-I-CV psychiatric disorders with no diagnostic criteria

- Agoraphobia without history of panic disorder
- Social phobia
- Specific phobia
- Generalized anxiety disorder
- Somatization disorder
- Undifferentiated somatoform disorder
- Hypocondriasis
- Body dysmorphic disorder
- Anorexia nervosa
- Bulimia nervosa

This interview is divided into six relatively independent modules. Table 3.7 indicates symptoms, episodes and disorders included in the SCID-I-CV, excepting for those listed in the previous table (

Table 3.6). The diagnosis of these disorders is based on the assessment of their diagnostic criteria.

Table 3.7 Diagnoses tapped by the SCID-I-CV

Module A: *Affective episodes*	Major depressive episode Mania episode Hypomania episode Dysthimic disorder Affective disorder due to medical illness Affective disorder due to substances
Module B: *Psychotic symptoms*	Delusions Hallucinations Disorganized behaviour and language Catatonic behaviour Negative symptoms
Module C: *Psychotic disorders*	Schizophrenia Paranoid type Catatonic type Disorganized type Undifferentiated type Residual type Schizophreniform disorder Schizoaffective disorder Delusional disorder Brief psychotic disorder Psychotic disorder due to medical illness Psychotic disorder due to substances Not otherwise specified psychotic disorder
Module D: *Affective disorders*	Bipolar I disorder Bipolar II disorder Not otherwise specified bipolar disorder Major depressive disorder

	Not otherwise specified depressive disorder
Module E: *Substance use disorders*	Alcohol dependence Alcohol abuse Amphetamine dependence Amphetamine abuse Cannabis dependence Cannabis abuse Cocaine dependence Cocaine abuse Hallucinogens dependence Hallucinogens abuse Opiate dependence Opiate abuse Phencyclidine dependence Phencyclidine abuse Sedative/hypnotic/anxiolytic dependence Sedative/hypnotic/anxiolytic abuse Other (or unknown) substances dependence Other (or unknown) substances abuse
Module F: *Anxiety and other disorders*	Panic disorder with agoraphobia Panic disorder without agoraphobia Obsessive-compulsive disorder Posttraumatic stress disorder Anxiety disorder due to medical illness Anxiety disorder due to substances Not otherwise specified anxiety disorder Adaptive disorder

The SCID-I-CV is applicable to psychiatric patients and general medicine patients. Given its language and diagnostic covering, this interview is more appropriate to adult subjects (from 18 years old on) (First et al., 1997a). It is administered by means of two workbooks: the application workbook, that contains the questions to be asked and the DSM-IV diagnostic criteria, and the scoring workbook, that contains a summary of the DSM-IV diagnostic criteria, and where the clinician notes down their diagnostic decisions. During the interview, both workbooks are used. Before starting with the structured questions, the clinician assesses some general questions in the "General Overview". This is a part of the interview where the patient is asked to describe his/her problem with his/her own words. In addition, other questions about previous treatments, social functioning, etc. are asked in order to establish a provisional differential diagnosis before starting the structured interview.

Once the interview is finished, the clinician writes down the diagnosis/es in the SCID-I-CV Diagnoses Summary, indicating for each one if it is "current" (criteria are present during the last month) or "lifetime" (criteria were present some time in the patient lifetime).

We administered the whole interview and established diagnoses (see

Table 3.6 and Table 3.7) according to the "User's Guide" provided by the authors.

Psychometric properties of the SCID-I-CV indicate an acceptable reliability (Segal et al., 1995; Williams et al., 1992) and validity (Kranzler et al., 1995).

✍ *Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II)*

The *Structured Clinical Interview for DSM-IV Axis II Personality Disorders* (First, Gibbon, Spitzer, Williams & Smith, 1997b) is a semi-structured clinical interview organized according to the different categories of Axis II DSM-IV disorders. This interview assesses ten DSM-IV Axis II personality disorders, as well as the Depressive Personality Disorder, and the Passive-Aggressive Personality Disorder (included in the DSM-IV Appendix B). The SCID-II provides both categorical (present/absent) diagnoses and dimensional scores for each personality disorder. A Spanish version (translated by Pérez & Sangorrín, 2001) was used [17].

With a traditional clinical interview format, the SCID-II begins with some general open questions (see annexe 2) about the subject's behaviour and relationships, in order to provide us with information about subject's introspective ability. The first section starts with the standard sentence: "*Next I will ask you some questions about the kind of person you are, that is to say, how do you feel and behave in general*". After that, the presence of every DSM-IV personality disorder is assessed by means of questions corresponding to criteria conforming specific personality disorder diagnoses. The assessment starts with cluster C disorders (Avoidant, Dependent, Obsessive-Compulsive), follows with Passive-Aggressive and Depressive personality disorders, continues with cluster A disorders (Paranoid, Schizotypal, Schizoid), and finishes with cluster B disorders (Histrionic, Narcissistic, Borderline, Antisocial). Each question has a 3-points score (see Table 3.8), and was registered according to the scoring rules introduced in the "SCID-II User's Guide".

Table 3.8 Possible scores for each personality disorder criterion according to the SCID-II

? = Inadequate or insufficient information to codify the criterion as 1, 2, or 3
1 = Absent or False
2 = Subthreshold
3 = Threshold or True

The scoring for this interview is double. On the one hand, **categorical** diagnoses (Present / Absent) can be obtained by summing all criteria with a 3-score and checking if this sum transcends the threshold for each personality disorder. On the other hand, a **dimensional** score can be computed by summing the total number of fully present criteria per category.

We did not use the categorical formulation of personality disorders, as we did not found a number of frank personality disorders in our sample sufficient enough to make statistical analyses[18].

In order to maximise the information, we used two types of SCID-II scores. On the one hand, we used the dimensional score provided by the SCID-II (total number of fully present criteria per personality disorder), to that we will refer as ***narrow dimensional score***. On the other hand, we summed total scores per personality disorder including the subthreshold score, as can be seen in Table 3. 9. This compute yielded a looser dimensional score with a higher variability (as it also included doubtful personality traits) that allowed us to make more accurate statistical analyses. We will refer to this formulation as ***loose dimensional score***.

Table 3. 9 SCID-II scores conversion for obtaining "loose dimensional scores"

SCID-II (scores per item)	***Present study (converted scores)***
Absent or False: **1**	**0**
Subthreshold: **2**	**1**
Threshold or True: **3**	**2**

In addition, an **overall score** was computed for cluster A, cluster B, and Cluster C personality disorders, both for narrow dimensional scores and for loose dimensional scores. These general scores were obtained by summing the dimensional scores (narrow and loose separately) of those personality disorders included in each cluster.

Therefore, we analysed **dimensional scores for each personality disorder** (as mentioned before) and **for each cluster**, both from a narrow and from a looser point of view.

There are no studies about reliability and validity of the SCID-II for DSM-IV, but psychometric properties of the SCID-II for DSM-III-R have been established, indicating a reasonable reliability (First et al., 1995) and a moderate validity (Loranger et al., 1987).

✍ *Observational Assessment*

The observational assessment was filled in by the examineer just after ending the assessment session, in absence of the subject. We employed some signs of the

[17] We used the SCID-II for DSM-IV, not validated in our country yet, but only adapted. SCID-II for DSM-III-R, which is indeed validated in Spain, was rejected on behalf of the latest version.

[18] It should be considered that our sample consisted of *clinically normal* youngsters from the general population, so the lack of frank personality disorders or extreme scores was expectable.

Observational Rating Scale (Nagler, Marcus, Sohlberg, Lifshitz & Silberman, 1985) that was used in the Israeli High-Risk Study (Marcus et al., 1987). The assessment comprised twelve aspects that were grouped together in three main areas for statistical analyses (see Table 2.1), according to Barrantes-Vidal (2000). Each item was assessed on a 3-point Likert scale, with "*0*" indicating *absence* of such sign, "*1*" indicated *possible or doubtful presence*, and "*2*" indicated *fully presence* of the clinical sign. Therefore, the higher the score, the higher was the presence of clinical signs or abnormalities.

Table 2.1 Observational assessment: Items assessed per area

Behavioural
- Appearance
- Motor behaviour
- Behaviour during task performance
- Relationship with the examineer
- Aggressive attitude
- Suspicious attitude

Emotional
- Emotional expression (quality and quantity)
- Anxiety
- Autonomic activation

Verbal
- Language
- Verbal and non-verbal communication
- Paralinguistc signs

Premorbid Adjustment Scale

The Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin & Wyatt, 1982) is a rating scale designed to evaluate the level of functioning in four major areas at each of several periods of the subject's life: social accessibility-isolation, peer relationships, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties. Items evaluating age-appropriate functioning in these areas are repeated for each period of the subject's life: childhood (up to 11 years), early adolescence (12-15 years), late adolescence (16-18 years), and adulthood (19 years and beyond). The final section, labelled *General*, is more global, containing items meant to estimate the highest level of functioning that the subject achieved before becoming ill, as well as the time span and characteristics of onset of illness, and general information such as amount of education.

Although this scale was created to measure the period ending 6 months before the first psychiatric hospital admission or psychiatric contact, or 6 months before evidence of characteristic florid psychotic symptomatology (Cannon-Spoor et al., 1982), we

modified its applicability for research purposes. Thus, though our subjects were non-psychotic and selected from the general population, we administered this scale evaluating the 6 months before this assessment in order to have a general impression on the general adjustment of the subject, independent on the presence or absence of current psychopathology.

This scale was filled in by means of a personal interview. We administered the *Adulthood* section and the *General* section. Each section contains a number of items with a scoring range of 0-6. The "0" end of the continuum denotes the hypothetically healthiest end of the adjustment range, and the "6" the hypothetically least healthy end. There are descriptive phrases as rough anchor points, and the rater must select the number that corresponds most closely to the descriptive phrase nearest it. Though authors recommend dividing the total sum of item scores per section by the maximum possible score, we used total sums of all item scores per section. Thus, the indices computed per subject were the following:

- Adulthood scores:
  - **Sociability and withdrawal**
  - **Peer relationships**
  - **Aspects of adult socio-sexual life**
  - **Total Adulthood score**
- General scores:
  - **Education**
  - **Occupation**
  - (Cessation of work or school performance)[19]
  - **Constancy**
  - **Independence**
  - **General functioning**
  - **Social-personal adjustment**
  - **Interest in life**
  - **Energy level**
  - **General total score**
- **Overall score** (total sum of previous sections)

Premorbid adjustment impairments have been reported in individuals who finally developed schizophrenia (Done, Crow, Johnstone & Sacker, 1994; Jones, Rodgers, Murray & Marmot, 1994b).

[19] This item was drop out of statistical analyses because of an absence of variability (no subject scored higher than 0).

Psychometric properties of this scale are acceptable, with good interrater reliability and validity, and well related to outcome measures (course of the disorder, length of hospitalization, type of onset) (Cannon-Spoor et al., 1982).

- *Premorbid Social Adjustment Scale*

The *Premorbid Social Adjustment Scale* (PSAS; Foerster, Lewis, Owen, and Murray, 1991) is an adapted version of the PAS scale used to specifically assess sociability, peer relations, scholastic performance, adaptation to school, and interests. It is a brief semi-structured interview designed to be administered to mothers.

This instrument has five different questions related to the areas mentioned above. According to the information provided by mothers, each subject receives a score for each item, rated on a 7-point Likert scale that ranges from 1 (excellent adaptation) to 7 (extremely poor adaptation). Each item is rated separately for childhood (5-11 years) and adolescence (12-16 years).

We used this scale in addition to the PAS because the latter was only applicable to the preceding year, whereas the PSAS tapped much earlier periods of the subject's lifetime (childhood and adolescence). Moreover, the PSAS is strictly focused on childhood and adolescent social adjustment.

The indices computed for each subject were the following:

- **Sociability and isolation** (Childhood/Adolescence)
- **Peer relations** (Childhood/Adolescence)
- **Scholastic performance** (Childhood/Adolescence)
- **Adaptation to school** (Childhood/Adolescence)
- **Interests** (Childhood/Adolescence)
- **Total Childhood**
- **Total Adolescence**

Reliability of the PSAS has proved to be satisfactory for both lifetime periods assessed (Foerster et al., 1991).

A study by Cannon et al. (1997) applied this scale to mothers of schizophrenic patients and found that these patients showed a poorer premorbid social adjustment, especially during adolescence, in comparison to bipolar patients and to normal controls. In fact, these authors indicate as a main strength of their study the use of *mothers* as the source of information on premorbid adjustment because they are best placed to give accurate retrospective information about a child's early development.

Nevertheless, they consider that there may be a recall bias related to the mother's knowledge of her child's adult outcome, which could influence her memory of childhood behaviour. However, this bias is unlikely in our sample, since our subjects were not clinically affected by psychotic disorders or other major psychiatric disorders, so we can infer that their mothers were not influenced by the sort of recall bias possibly present in the Cannon et al. (1997) study. Foerster et al. (1991) study also found a poorer premorbid adjustment in schizophrenic patients. Furthermore, a poor premorbid adjustment, especially in childhood, predicted an early age at first admission, mainly in male.

2.1.4 Psychometric measures

- *Oxford-Liverpool Inventory of Feelings and Experiences*

The *Oxford-Liverpool Inventory of Feelings and Experiences* (Mason et al., 1995) is a self-report questionnaire consisting of 120 "Yes/No" items. This instrument was derived from factor analysis of the *Combined Schizotypal Traits Questionnaire* (CSTQ; Bentall, Claridge & Slade, 1989), a 420-item battery of scales measuring schizotypal traits. The CSTQ contained several scales tapping several aspects of schizotypy, as the next table displays:

Table 3.10 Scales forming the CSTQ

- Schizotypal Traits Questionnaire (STQ; Claridge & Broks, 1984)
- Chapman scales
- Launay & Slade's Hallucination scales (LSHS; Launay & Slade, 1981)
- Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975)
- Nielsen and Petersen's schizophrenism scale (Nielsen & Petersen, 1976)
- MMPI Schizoidia scale (Golden & Meehl, 1979)
- Delusions Symptoms States Inventory (DSSI; Foulds & Bedford, 1975)

The result of this process yielded 4 scales corresponding to 4 schizotypal dimensions: ***Unusual Experiences***, ***Cognitive Disorganisation***, ***Introverted Anhedonia***, and ***Impulsive Nonconformity***. These scales were complemented with the *Lie* subscale from the EPQ, in order to control for sincerity. Other items from the EPQ's Extraversion subscale and the STQ's STA subscale were added. Extraversion items were used in order to "dissimulate" the pathological tone of the instrument, and STA was added to provide a known comparison instrument. All items (24-30 per scale) were pseudo-randomised in order to avoid an excess of "pathological" items at the beginning of the

questionnaire. Psychometric properties of this instrument (Burch, Steel & Hemsley, 1998; Mason et al., 1995) are acceptable.

Unusual Experiences (Factor 1) scale includes items expressing perceptual, hallucinatory and magical thinking experiences, which is consistent with "positive" symptoms of psychosis. *Cognitive Disorganisation* (Factor 2) scale includes items representing attentional, concentration, and decision-making difficulties, as well as a sense of purposelessness, moodiness and social anxiety. *Introverted Anhedonia* (Factor 3) contains items expressing a lack of enjoyment from social situations and/or from other activities, indicating a dislike of emotional and physical intimacy, as well as an emphasis on independence and solitude. This scale would approach the "negative" symptoms of schizophrenia. *Impulsive Nonconformity* (Factor 4) includes items representing violent, self-abusive and reckless behaviours, though a more moderate score may indicate a preference for a free-living and non-conforming lifestyle often chosen by students (Mason et al., 1995).

A sample of some items that conforming each subscale is showed in the next table:

Table 3.11 Some items from the different O-LIFE subscales

- ***Unusual Experiences*** (Factor 1)
  - 21. *Are your thoughts sometimes so strong that you can almost hear them?*
  - 29. *Have you felt that you have special, almost magical powers?*
  - 70. *Have you felt that you might cause something to happen just by thinking too much about it?*
- ***Cognitive Disorganization*** (Factor 2)
  - 26. *No matter how hard you try to concentrate, do unrelated thoughts always creep into your mind?*
  - 42. *Are you sometimes so nervous that you are "blocked"?*
  - 95. *Do you often feel "fed up"?*
- ***Introverted Anhedonia*** (Factor 3)
  - 30. *Are you much too independent to really get involved with other people?*
  - 52. *Are people usually better off if they stay aloof from emotional involvements with most others?*
  - 115. *Do you feel very close to your friends?*
- ***Impulsive Nonconformity*** (Factor 4)
  - 4. *Do you often overindulge in alcohol or food?*
  - 64. *Do you ever have the urge to break or smash things?*
  - 83. *Have you ever taken advantage of someone?*

This instrument provides independent scores for each factor derived from a simple sum of the endorsed items.

- *Dimensions of Interpersonal Orientation (DOI)*

The "Dimensions of Interpersonal Orientation"[20] Kit is rooted in the "Socialization Battery" (Silva, 1992; Silva & Martorell, 1983, 1987; Silva, Martorell & Clemente, 1986), which was developed to assess several constructs related to the interpersonal behaviour of children and adolescents, especially with their peers. The constructs underlying both instruments are presented in Table 3.12.

Table 3.12 Description of the DOI kit constructs

Constructs	Description
Consideration for others	Social sensitivity; concern over and worry for others, particularly those who have problems and are ignored or rejected. Helping behaviour.
Respect/Social Self-control	Observance of social norms and rules which facilitate coexistence and mutual respect; community spirit and good citizenship; politeness, kindness.
Aggressiveness/Antisocial Behaviour	Verbal and physical aggressiveness; stubbornness, quarrelsomeness; defiant and mocking reactions; domineering, obstinate and undisciplined behaviour; resistance to and transgression of social norms.
Sociability vs. Withdrawal	Gregariousness; enjoying being with others and integrating into groups; joviality and good spirits, versus separation both passive and active from the others; introversion, isolation.
Social Ascendancy/Leadership	Popularity, initiative, self-confidence, and a helping spirit. Seen by others as leader and model. Organization and management of group activities.
Social Anxiety/Shyness	Fear, restlessness, diffidence, bashfulness, timidity, and sense of shame in social relationships. Social vulnerability.

Extracted from Silva, Martínez-Arias, Rapaport, Ertle, & Ortet, 1997.

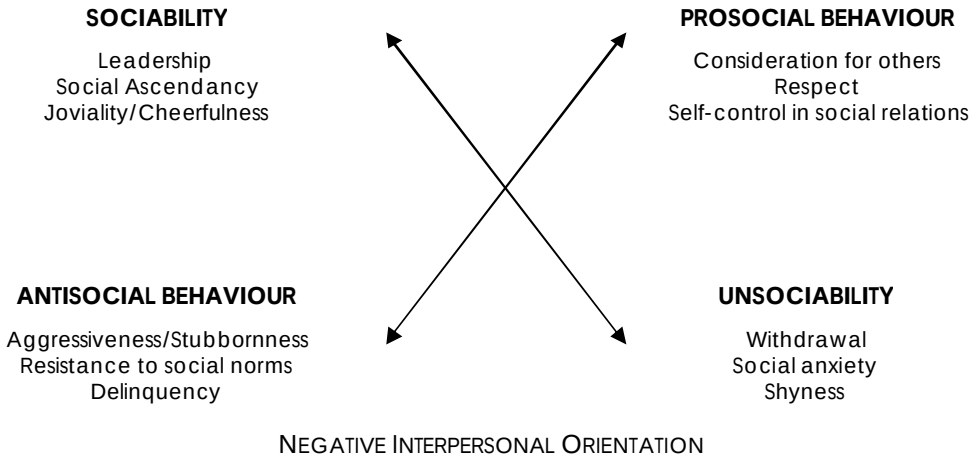
The DOI has four content-equivalent versions: two versions for older children and adolescents (DOI Junior Self-Report [DOI-JA in Spanish] and DOI Junior Other-Report [DOI-JH in Spanish]), and two versions for adults (DOI Adult Self-Report and DOI adult Other-Report). The only change from self- to other-report items in the transformation of pronouns "I" to "she/he", and there are only a few minor transformations from junior to adult items (Silva et al., 1997).

The scales that measure the six constructs of Table 3.12 are merged into two factors, as can be seen in Figure 3.4. The geometrical representation of these factors gives an X-shaped model (Silva, Martínez-Arias, Moro & Ortet, 1996a,b) with four poles representing basic interpersonal orientations: "approaching others" (Sociability), "distancing from others" (Unsociability), "being for others" (Prosocial Behaviour), and "being against others" (Antisocial Behaviour).

Figure 3.4 The X-shaped model

POSITIVE INTERPERSONAL ORIENTATION

[20] Spanish: "Dimensiones de Orientación Interpersonal"



Extracted from Silva, Moro & Ortet, 1994

Psychometric properties of this test have shown to be acceptable, with a good internal consistency, and a proved convergent and discriminant validity. On the whole, structural analyses give support to the DOI internal structure (Silva et al., 1996b, 1997).

We administered the adolescent version to subjects (DOI-JA) and to their parents (DOI-JH). Both consisted of 59 items with a response format based on a 4points scale, ranging from 1: *"Never or almost ne*ver", to 4: *"Always or almost always"*. Indexes extracted from both questionnaires were 8 in total: **6 factor** scores (corresponding to those described in Table 3.12), an **overall** score (indicating a more prosocial/sociable behaviour as higher the score, and a more unsociable/antisocial behaviour as lower the score), and a **sincerity** score (indicating more sincerity as higher the score).

✍ *COPE*

The COPE scale (Carver, Scheier & Weintraub, 1989) was developed with the aim of assessing people's coping styles and strategies. It was constructed according to a "rational" (theoretical) approach, and used two theoretical models as guidelines: the Lazarus model of stress (Lazarus, 1966) and a model of behavioural self-regulation (Carver & Scheier, 1981, 1983, 1985; Scheier & Carver, 1988).

As do earlier instruments, this test assesses people's active coping efforts. However, unlike previous inventories, this scale distinguishes among several distinct aspects of active coping: planning, active coping, suppression of attention to competing activities, and the exercise of restraint. In addition, it assesses a set of coping responses that may potentially impede or interfere with active coping: behavioural disengagement from continued efforts at goal attainment, mental disengagement

from one's goals, focusing on and venting of emotions, and use of alcohol or drugs as a way of disengaging (cluster of scales called "neurotic coping" by McCrae & Costa, 1986) (Carver et al., 1989).

The COPE scale has two versions: a *dispositional* one (i.e., what the subject *usually* does when under stress) and a *situational* one (i.e., what the subject did (or is doing currently) in a *specific coping episode* or during a *specific period of time*).

Fifteen conceptually distinct scales were initially included in this questionnaire. A description of all of them is offered in

Table 3.13.

Table 3.13 Description of the initial COPE scales

Scale	Description
Active Coping	Taking active steps to try to remove or circumvent the stressor or to ameliorate its effects
Planning	Thinking about how to cope with a stressor. Coming up with action strategies, thinking about what steps to take and how best to handle the problem
Seeking Social Support for Instrumental Reasons	Seeking advice, assistance, or information
Seeking Social Support for Emotional Reasons	Getting moral support, sympathy, or understanding
Suppression of Competing Activities	Putting other projects aside, trying to avoid becoming distracted by other events, even letting other things slide, if necessary, in order to deal with the stressor
Turning to Religion	Increasing their involvement in religious activities
Positive Reinterpretation and Growth	Managing distress emotions rather than dealing with the stressor per se. Construing a stressful transaction in positive terms
Restraint Coping	Waiting an appropriate opportunity to act presents itself, holding one-self back, and not acting prematurely
Acceptance	To accept the reality of a stressful situation
Focusing on and Venting of Emotions	Tendency to focus on whatever distress or upset one is experiencing and to ventilate those feelings
Denial	Refusal to believe that the stressor exists or of trying to act as though the stressor is not real
Mental Disengagement	Engagement in activities that serve to distract the person from thinking about the behavioural dimension or goal with which the stressor is interfering (daydreaming, sleep, TV…)
Behavioural Disengagement	Reducing one's effort to deal with the stressor, even giving up

	the attempt to attain goals with which the stressor is interfering (helplessness)
Alcohol-Drug Disengagement	Consuming alcohol or drugs to cope with the stressor
Humour	Joking about the stressor

Studies on construct validity of this questionnaire (Carver et al., 1989) confirmed this initial model, excepting for the fact that "Planning" and "Active Coping" items loaded together on one factor, as well as "Seeking Social Support for Instrumental Reasons" and "Seeking Social Support for Emotional Reasons". In addition, "Positive Reinterpretation and Growth" split into two different factors.

The Spanish adaptation of this test (Crespo & Cruzado, 1997) confirmed 10 factors out of the 15 initial factors proposed by Carver et al. (1989). The other 5 factors in the Spanish adaptation were light modifications of the original structure (see Crespo & Cruzado, 1997 for more information). The final factorial structure in the Spanish version of the COPE was the following:

1. **Seeking Social Support**
2. **Turning to Religion**
3. **Humour**
4. **Drug/alcohol use**
5. **Planning and Active Coping**
6. **Retirement of Coping**
7. **Focusing on and venting of Emotions**
8. **Acceptance**
9. **Denial**
10. **Restraint Coping**
11. **Concentrating Efforts to Solve the Situation** (similar to *Suppression of Competing Activities*)
12. **Personal Growth**
13. **Positive Reinterpretation**
14. **Activities Distracting from the Stressor** (similar to *Mental Disengagement*)
15. **Escaping** (sharing items from *Mental Disengagement* and *Behavioural Disengagement*)

Crespo & Cruzado (1997) made a second order factorial analysis in order to disentangle basic dimensions of coping. Such analysis yielded 6 factors explaining a 53% of variance: ***1) Problem-Focused Behavioural Coping*** (includes factors 5, 12, and negative loading of factor 6), ***2) Cognitive Coping of the Problem*** (includes factors 3, 8, 10, and 13), ***3) Cognitive Escape*** (includes factors 2, 9, and 15), ***4) Emotion-Focused***

Coping (includes factor 1 and 7), ***5) Behavioural Escape*** (includes factor 14 and negative loading of factor 11), and ***6) Alcohol or Drug Use*** (includes factor 4).

Psychometric properties of this scale are acceptable, as well in the Spanish adaptation (Crespo & Cruzado, 1997) as in the original version (Carver et al., 1989). Thus, internal consistency, test-retest reliability, and construct validity have shown to be good enough. Likewise, factor structure has confirmed the original theoretically-based structure for most scales.

Here we used the *dispositional* version, translated to Spanish by Cruzado, Vázquez and Crespo, and adapted to the Spanish population by Crespo & Cruzado (1997). It consists of 60 items with a 4-point Likert scale ranging from 1: "*I usually don't do this at all*" to 4: "*I usually do this a lot*". Indices derived from this scale were the 15 factors previously mentioned, and the 6 second-order factors obtained in the Spanish adaptation.

- *Life events*

Life events exposure was assessed by means of an *ad hoc* scale created by means of the combination of several life events scales.

We started from the *Social Readjustment Rating Scale* (SRRS), by Holmes & Rahe (1967). These authors developed a checklist of 43 life events "derived from clinical experience" and based on the underlying assumption that *change, whether desirable, undesirable or both, is stressful*. They considered psychological trauma as a cause of psychopathology, and defined it as those events that require a readjustment on the part of the individual, a change in his life. Therefore, they quantified this readjustment in terms of the so-called Life Change Units (L.C.U.s). The readjustment in terms of LCUs includes events with a positive as well as a negative connotation. Though several variations of the SRRS exist (e.g., Paykel, Prusoff & Uhlenhuth, 1971; Sammuelson, 1982), we used the Coddington (1972a, 1972b) version. This author developed different life event checklists according to age, from preschool subjects to senior high school subjects, and assigned specific LCUs to each life event depending on the age. Coddington (1972a) quantified the significance of various life events according to the Holmes & Rahe (1967) method, so 243 professional workers (teachers, paediatricians, and mental health workers) rank ordered a series of 43 life events in relation to age. Given the current mean age of our subjects (around 22 years old), we used the Senior High School checklist proposed by this author, consisting of 42 life events.

The absence of a distinction between positive and negative life events is one of the usual criticisms to Holmes & Rahe (1967) point of view (e.g. Newcomb, Huba & Bentler, 1981). Detractors of this point of view argue that since an event may have a different impact on one person relative to another, normative weightings lose this specific impact. That is why we used another approach to life events measure based on the *Life Events Checklist* (LEC; Johnson & McCutcheon, 1980) and on the Newcomb et al. (1981, 1986) life events scale. The LEC is a 50-item checklist that measures child and adolescent stress making a distinction between positive and negative life events. In addition, subjects are instructed to characterize endorsed events as "good" or "bad", and to rate the degree of impact on a 4-point scale (0="no effect", 1="some effect", 2="moderate effect", and 3="great effect"). The usual period of inquiry of the LEC is the preceding year. The Newcomb and cols. (1981, 1986) life events scale is a 39-item questionnaire constructed from a multidimensional point of view and applicable to adolescents. The scoring method is very similar to the previous one and adds seven interpretable dimensions of stress (family/parents, accident/illness, sexuality, autonomy, deviance, relocation, and distress).

Our final life events questionnaire consisted of a 58-item scale including the SRRS (Coddington's version, 1972a, 1972b), and those items from the LEC and the Newcomb et al. (1981, 1986) scale that did not appear in the SRRS. Moreover, we added some items on sexual/physical abuse reported by Williamson, Birmaher, Anderson, Al-Shabbout, and Ryan (1995), and included an optional item in which the subjects could note other events.

Subjects were instructed to mark those life events occurred over the preceding year, to indicate if endorsed events were "good" (+) or "bad" (-), and to rate the degree of impact on a 4-point scale, as mentioned in the LEC scale (see above). We computed the following scores for each subject:

- Total **LCUs** (items 1 to 42; Coddington's quantification)
- Total **number of positive life events** (all items)
- Total **number of negative life events** (all items)
- Total **degree of impact of positive life events** (all items)
- Total **degree of impact of negative life events** (all items)

Psychometric properties of these scales have not been studied regularly. Even so, some studies have reported an acceptable reliability and a good correlation with psychological adjustment for the LEC (Johnson & Bradlyn, 1988; Johnson & McCutcheon, 1980). The Newcomb and cols. scale was reliable and consistent across

samples according to a later report by the same authors (Newcomb et al., 1986). As regards the Coddington's version of the SRRS, the professionals that rated the different life events essentially agreed (with no relevant differences among them) in the relative importance of all items (Coddington, 1972a).

2.2 Phase I measures used in the analyses

The following measures were collected in the first phase of this study but we included them in the present analyses because of their unquestionable usefulness for corroborating our hypotheses. They are described by Barrantes-Vidal (2000), so here we will only offer a brief description.

2.2.1 Raven Progressive Matrices

The Raven Progressive Matrices-General Form (Raven, 1986) is a multiple-choice paper and pencil test composed of a series of visual pattern matching and analogy problems symbolized in nonrepresentational designs. It consists of 60 items grouped into five sets and it has no time limit, though most people take from 40 minutes to 1 hour. The first set of items calls for pattern matching and tests visuospatial skills associated with normal right hemisphere functioning. In the other sets, the task shifts from one pattern completion to reasoning by analogy, ranging from quite simple to increasing difficulty, and ultimately to very complex, in which mathematical concepts are involved (Lezak, 1995). These analogical reasoning problems seem to tap mainly left hemisphere functions.

2.2.2 Prenatal and birth complications

Given that Phase I assessment was carried out at school (unlike Phase III assessment), a questionnaire for parents was given to each subject in this context, together with a letter in which we informed their parents of the participation of their child in the study and of the confidentiality of this information.

Though the original questionnaire contained more information (see Barrantes-Vidal, 2000 for a detailed explanation of this questionnaire), we only extracted some items for Phase III analyses (see Table 2.2).

Table 2.2 Phase I-collected prenatal and birth complications analysed in Phase III

- Birth weight
- Pregnancy duration
- Complications during pregnancy (infection, flu, drugs, etc. in the mother)
- Complications during delivery (forceps use, caesarean section, very prolonged delivery, etc.)

The two first variables were quantitative and the two last ones categorical (yes/no).

2.3 Supporting material

Computerized tests (CPT-IP, WCST, Finger Tapping, and Spatial Working Memory) were administered by means of an IBM 760XL laptop, with a colour TFT screen.

The O-LIFE, the DOI-JH, the DOI-JA, the COPE, and the Life Events scale were administered by using self-report (paper-and-pencil) questionnaires.

The CVLT, the SCWT, verbal fluencies, the Annett scale, the Neurological Soft Signs scale, the SCID-I, the SCID-II, the PAS, the PSAS, the substance use scale, and the observational assessment were administered by the interviewer and registered in paper-and-pencil records.

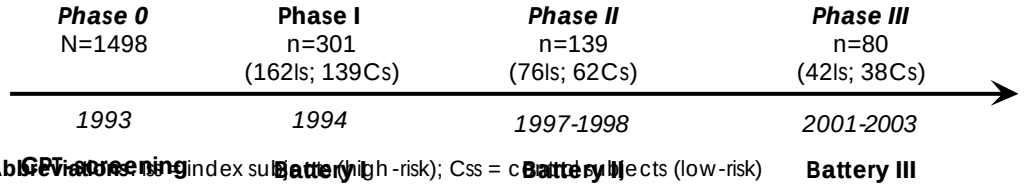
The SPSS v11.5 was used to keep the information in a data base and to make statistical analyses.

3) PROCEDURES

3.1 Design

This project is framed in a **prospective longitudinal study with two cohorts**. Such cohorts were defined in 1993 according to the presence/absence of a sustained attention deficit, as measured by the CPT-IP. This project developed in three phases distributed along 10 years of follow-up, as can be seen in Figure 2.1.

Figure 2.1 Sketch of the main study



Abbreviations: Is = index subjects (high-risk); Cs = comparison subjects (low-risk)

The initial sample of 301 subjects was first assessed in 1994, later in 1997-1998, and finally in 2001-2003.

Phase 0, Phase I, and Phase II have already been the object of other reports (see Barrantes-Vidal, 2000; Barrantes-Vidal et al., 2002; Obiols et al., 1997, 1999; Rosa et al.,

1999), so only the development of the third (and last) phase will be explained in the present project.

3.2 Third phase development

In order to increase the follow-up period, our first intention was to carry out the third phase assessments in two different moments in time, with approximately one year between both sessions. The procedure involved a first neuropsychological assessment, and a clinical assessment the second time. However, the high rate of attrition in the second phase forced us to consider making both assessments together. Therefore, the final procedure to carry out the third and last phase of the present study was the following:

During the first trimester of 2000, we sent letters to those subjects (and to their parents, separately) that had participated in the second phase. In these letters we remembered to the subject (and to their parents) his/her part in the second phase, and introduced them the third phase. In addition, we asked again for their collaboration and offered them an economical compensation (60€) for their participation. We also informed them that the current assessment would be very similar to the previous one, with the only difference of some additional tests. Finally, we told them that we would contact them by phone to confirm their collaboration. We also included our telephone number and names, and encouraged them to consult any possible doubts on this issue with us.

Parallel to dispatch such letters, we prepared the instruments and corrected some methodological questions of design, as mentioned above.

To our great surprise, 31 subjects phoned us before we contacted them and manifested to be willing to collaborate. These subjects were the first ones to be assessed.

At the beginning of 2001, we started to contact the subjects by telephone, beginning with those who had contacted us to collaborate. In this telephone call, we explained them how it was going to be the assessment, which sort of tests and interviews we were going to use, and how long it would take the whole assessment. Considering that this was the last time that we were going to assess them, we created a big battery (see Table 3.2) of tests aiming to cover as many aspects as we could. The duration of the whole assessment ranged between 2h30' and 3h, so we systematically suggested to subjects to make the assessment in two 1h30'-sessions (distributed in different days). However, most subjects preferred to make the assessment all at once. Considering the

difficulty in arranging a meeting with this kind of sample (most of them were working or studying almost all the day, and it was very difficult to find them at home), we made no objections to their decision. We also proposed them either coming to our laboratory to make the assessment, or making it at their home. Most subjects preferred the latter option.

In order to avoid the effects of fatigue on neuropsychological performance, the session started with the neuropsychological assessment (approximately 1h15') and continued with the clinical interviews, which do not require such a big cognitive effort and are less sensitive to fatigue. The order of tests administration was the following:

Table 3.14 Order of tests administration[21]

1) CVLT -I (short delay recall measures)
2) CPT-IP (firstly numbers and secondly shapes)
3) Finger Tapping
4) Spatial Working Memory
5) CVLT -II (long delay recall and recognition measures)
6) WCST-64
7) F.A.S.
8) Animal Naming
9) SCWT
10) Annett scale
11) NSS assessment
12) SCID-I
13) SCID-II
14) Substance use scale
15) PAS

At the end of the session, a dossier with the self-reported tests was given to the subject, together with oral instructions on how to fill them (instructions were also given in writing for each test). This dossier was collected some days later.

The PSAS was administered to the subject's mother either the same day of the assessment ("face to face"), whenever it was possible, or by telephone. Anyway, there was much missing for this scale, as it was really difficult to find them at home.

The payment was made by means of a bank transfer and the assessments were all made by one trained psychologist, in order to enhance data reliability.

The data were stored in a computerized data base, as well as in paper, respecting confidentiality by means of a code number for each subject.

[21] This list includes neither self-reported questionnaires (O-LIFE, DOI-JA, DOI-JH, COPE, Life events) nor the PSAS, which were administered to the subjects's mothers.

RESULTS

1) DESCRIPTIVE STATISTICS

We will offer "n_s", "means", "standard deviations", and "range" (min/max) of all variables in the whole sample (n=80). Normality conditions were examined for all variables, as well by means of Kolmogorov-Smirnov tests as by box-plot inspection. Although the former test was statistically significant in some cases, the visual inspection of box-plot diagrams revealed normal distributions in most cases. Those tests with a stronger psychopathological loading (SCID-II, PAS, PSAS) and a smaller range of responses (some indexes of the WCST, the CVLT, the Life Events scale, the NSS battery, and the Annett scale) were the most distant from normality. Nonetheless, given the suitable sample size, we applied parametrical tests in all cases, so this fact should be taken into account for the interpretation of results.

1.1 Neuropsychological indexes

Table 4. 1 Descriptive statistics of neuropsychological tests in the whole sample

			n	Mean	SD	min	max
		Raven total score	79	45.87	5.96	28	57
Attention	***CPT-IP Numbers***	***Omission errors***	80	4.47	3.72	0	23
		Commission errors	80	0.96	1.45	0	8
		Distraction errors	80	0.38	1.10	0	6
		Reaction time (ms)[22]	75	535.53	72.39	367	765
		d'	80	3.13	0.74	0.54	5.42
		?	80	4.97	3.83	0.13	14.77
	CPT-IP Shapes	***Omission errors***	80	5.29	3.76	0	21
		Commission errors	80	2.81	2.30	0	13
		Distraction errors	80	0.75	1.04	0	5
		Reaction time (ms)[1]	75	548.71	64.14	396	708
		d'	80	2.48	0.68	0.64	4.22
		?	80	2.29	2.06	0.02	14.15
		Mean d'	80	2.81	0.62	0.95	4.82
Executive	***WCST***	***Errors***	80	13.53	7.19	6	37
		Perseverations	80	6.91	4.62	3	26
		Perseverative Errors	80	6.31	3.70	3	23

[22] Missing was due to a computer failure.

			n	Mean	SD	min	max
		Raven total score	79	45.87	5.96	28	57
		Non-Perseverative Errors	80	7.21	4.71	2	22
		Conceptual Level Responses	79	46.87	10.47	13	58
		Categories	80	3.75	1.21	0	5
		Trials to complete 1st category	79	12.04	4.28	10	41
		Failures to Maintain the Set	80	0.35	0.64	0	2
	F.A.S.	*#Words generated*	80	39.50	10.27	8	59
	AN	*#Words generated*	80	21.53	5.42	10	38
	SCWT	*#Words read*	79	108.08	14.10	70	141
		#Colours named	79	70.71	11.53	44	106
		#W-C correct items	79	46.29	10.25	21	65
		Interference	79	3.69	7.86	-15.86	24.03
Memory	*CVLT*	*List A total*	80	57.93	8.40	29	72
		List A trial 1 (A1)	80	7.79	1.89	3	12
		List A trial 5 (A5)	80	13.64	1.82	9	16
		List B	80	6.59	2.05	3	11
		List A6.1	80	13.00	2.03	8	16
		List A6.2	80	13.70	1.69	9	16
		List A7.1	80	13.71	1.70	10	16
		List A7.2	80	14.01	1.65	9	16
		Semantic clustering ratio	80	2.15	0.80	0.50	4.18
		Serial clustering ratio	80	2.35	1.80	0.00	0.23
		%correct recall prim. region	80	27.75	4.80	15.52	48.28
		%correct recall middle region	80	44.49	5.40	23.91	55.22
		%correct recall recen. region	80	27.76	4.32	17.24	37.21
		Slope	80	1.38	0.54	-0.30	2.80
		% recall consistency	80	87.68	7.49	60.00	98.21
		Perseverations	80	6.19	4.83	0	21
		Total intrusions	80	2.44	3.61	0	19
		Recognition hits	79	15.42	0.81	13	16
		Discriminability	79	97.24	3.43	84.09	100.00
		List B vs. List A1 recall	80	-12.92	26.91	-62.50	75.00
		A6.1 vs A5	80	-4.42	10.48	-33.33	33.33
		A7.1 vs A6.1	80	2.55	6.69	-18.18	27.27
		Discriminability vs A7.1	79	14.02	13.08	-6.25	50.00
	SWM	*% overall accuracy*	80	67.18	13.85	25.80	93.30
		% left accuracy	80	58.77	21.13	0.00	100.00
		% right accuracy	80	76.81	17.11	26.70	100.00

We have presented above all the descriptives of the CVLT indices provided by the computerized correction programme. However, as we indicated in the Methods section, we only used for statistical analyses those that we considered most interesting:

- Recall measures
  - List A total
  - List B
  - List A6.1
  - List A6.2

- List A7.1
- List A7.2

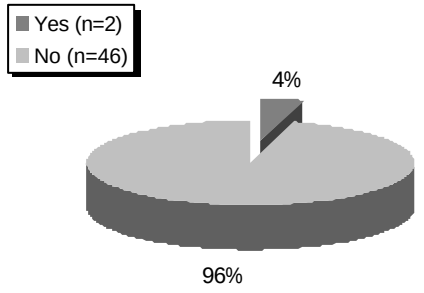
- Learning characteristics
  - Slope
  - Semantic clustering ratio
  - Serial clustering ratio
- Recall errors
  - Perseverations
  - Intrusions (total)
- Recognition measures
  - Recognition hits
- Contrast measures
  - List B versus List A1 recall
  - A6.1 versus A5
  - A7.1 versus A6.1
  - Discriminability versus A7.1

1.2 Neurointegrative variables

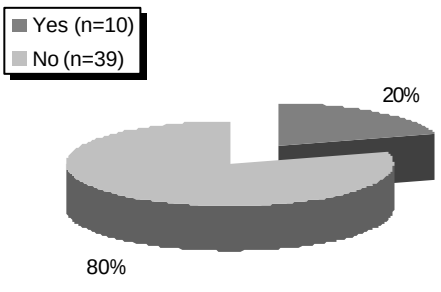
Table 4.2 displays descriptive statistics of quantitative neurointegrative variables, and Figure 4.1 offers a graphic representation of the Annett scale categorical indexes.

Table 4.2 Descriptive statistics of neurointegrative variables in the whole sample

		n	Mean	SD	min	max
Finger tapping	***Left hand***	80	4.27	0.76	2.30	6.60
	Right hand	80	4.74	1.00	1.90	8.67
NSS	***Total***	80	2.42	2.99	0	20
Annett	***Total sum***	80	21.11	10.13	14	69
PBCs	***Pregnancy Duration***	48	8.96	0.28	8	9.5
	Birth weight	49	3.36	0.56	1.80	4.82

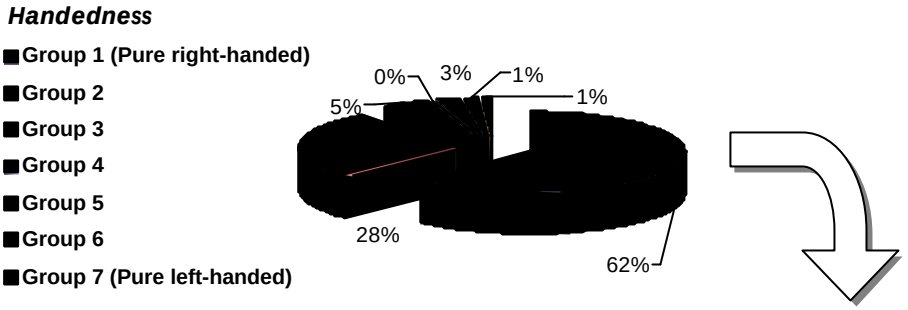


Complications during pregnancy



Complications at delivery

Figure 4.1 Transformation of the Annett scale handedness index into a binary variable



Strong handedness	Mixed handedness
n=51 (63.7%)	n=29 (36.3%)

Strong right-handed	Mixed	Strong left-handed
n=50 (62.5%)	n=29 (36.3%)	n=1 (1.3%)

As was mentioned in the *Methods* section, "strong right-handed" and "strong left-handed" subjects were included in the same group for statistical analyses.

1.3 Personality variables

The number of frank personality disorders was not big enough to perform statistical analyses in our sample; in addition, no one of those cases was a cluster A diagnosis (main interest of the original project). For these reasons, we present these data from a quantitative perspective, i.e. the number of present symptoms by personality disorder category, and the dimensional score for each personality disorder according to our own modification of the SCID-II guidelines (see *Instruments* for more information on this modification). Nevertheless, given that the number of criteria showed such a low range that statistical analyses (already tested in other reports) resulted non-reliable, we only used the SCID-II dimensional score in the analyses. Descriptive statistics of the O-LIFE factors are also displayed in the following table.

Table 4.3 Descriptive statistics of personality assessments in the whole sample

		n	Mean	SD	min	max
SCID-II (# criteria)	***Avoidant***	80	0.40	1.05	0	6
	Dependent	80	0.28	0.75	0	4
	Obsessive-Compulsive	80	0.53	0.83	0	3
	Passive-Aggressive	80	0.29	0.83	0	5
	Depressive	80	0.39	1.06	0	7
	Paranoid	80	0.33	0.65	0	3
	Schizotypal	80	0.21	0.54	0	3
	Schizoid	80	0.08	0.41	0	3
	Histrionic	80	0.11	0.36	0	2
	Narcissistic	80	0.15	0.60	0	4
	Borderline	80	0.29	0.70	0	3
	Antisocial	80	0.24	0.64	0	4

		n	Mean	SD	min	max
	Cluster A	80	0.61	1.15	0	7
	Cluster B	80	0.79	1.40	0	8
	Cluster C	80	1.20	1.85	0	11
SCIDII (Dimensional scores)	***Avoidant***	80	1.66	2.63	0	13
	Dependent	80	1.33	1.93	0	9
	Obsessive-Compulsive	80	2.64	2.09	0	8
	Passive-Aggressive	80	1.59	1.75	0	9
	Depressive	80	1.68	2.25	0	14
	Paranoid	80	1.60	1.79	0	7
	Schizotypal	80	1.18	1.65	0	8
	Schizoid	80	0.61	1.48	0	8
	Histrionic	80	0.85	1.34	0	7
	Narcissistic	80	1.29	1.96	0	10
	Borderline	80	2.59	2.21	0	9
	Antisocial	80	1.45	3.12	0	18
	Cluster A	80	3.39	3.58	0	19
	Cluster B	80	6.17	5.95	0	31
	Cluster C	80	5.62	4.68	0	28
O-LIFE	***Unusual Experiences***	80	6.66	5.54	0	24
	Cognitive Disorganization	80	8.73	5.99	0	23
	Introverted Anhedonia	80	5.44	3.41	0	15
	Impulsive Nonconformity	80	5.96	3.11	0	16

1.4 Psychosocial variables

Table 4.4 Descriptive statistics of psychosocial variables in the whole sample

		n	Mean	SD	min	max
COPE	***Seeking social support***	79	21.47	4.74	10	32
	Religion	79	5.75	2.37	4	15
	Humour	79	8.48	2.93	4	15
	Drug/alcohol use	79	5.15	2.30	4	16
	Planning & active coping	79	15.06	3.44	7	24
	Retirement coping	79	4.81	1.83	3	12
	Emotional expression	79	8.57	2.61	4	16
	Acceptance	79	10.70	2.33	4	16
	Denial	79	6.20	2.40	4	16
	Restraint coping	79	9.34	2.13	4	14
	Concentrate on solving	79	9.63	2.11	5	16
	Personal growth	79	6.39	1.14	4	8
	Positive reinterpretation	79	7.99	1.88	4	12
	Distraction from stressor	79	6.39	1.58	3	10
	Escaping	79	5.76	1.81	3	10
	Factor 1[a]	79	16.65	4.65	5	29
	Factor 2[a]	79	36.51	6.45	18	52
	Factor 3[a]	79	17.71	5.04	11	37
	Factor 4[a]	79	30.04	6.51	14	43
	Factor 5[a b]	79	3.24	2.27	-4	9
	Factor 6[a]	79	5.15	2.30	4	16
DO	***Consideration with others***	78	25.12	4.17	16	32
	Respect/Self-control	78	24.56	3.92	12	32

		n	Mean	SD	min	max
	Aggressivity/Antisocial	78	14.18	2.69	10	24
	Withdrawal vs. Sociability	78	7.47	3.74	-5	12
	Social ascend./leadership	78	17.31	3.88	9	25
	Social anxiety/shyness	78	15.64	4.43	8	30
	Lie	78	17.95	4.05	9	29
	Total JA	78	44.64	13.17	6	72
DOI-JH	***Consideration with others***	77	25.39	5.76	8	52
	Respect/Self-control	77	23.36	4.74	10	32
	Aggressivity/Antisocial	77	14.88	3.03	10	23
	Withdrawal vs. Sociability	77	6.69	3.86	-6	12
	Social ascend./leadership	77	19.09	4.87	8	32
	Social anxiety/shyness	77	15.19	4.23	8	28
	Lie	77	19.09	4.72	10	31
	Total JH	77	44.45	17.35	1	77
Life Events	***LCU***	79	258.44	202.57	0	1363
	# positive* events	79	4.56	3.13	0	15
	# negative* events	79	3.16	3.58	0	24
	Impact positive events*	78	12.22	8.84	0	45
	Impact negative events*	78	8.44	12.11	0	90

[a] COPE factors: **Factor 1**: Problem-Focused Behavioural Coping; **Factor 2**: Cognitive Coping of the Problem; **Factor 3**: Cognitive Escape; **Factor 4**: Emotion-Focused Coping; **Factor 5**: Behavioural Escape; **Factor 6**: Alcohol or Drug Use.

[b] Higher scores on this factor indicate a lesser use of *Behavioural Escape*.

1.5 Clinical variables

1.5.1 Premorbid adjustment

Table 4.5 Descriptive statistics of premorbid adjustment measures in the whole sample

		n	Mean	SD	min	max
PAS	***Sociability & withdrawal.A***	79	1.13	1.16	0	4
	Peer relations.A	79	0.67	0.90	0	3
	Socio-sexual life.A	79	0.77	1.38	0	5
	Adulthood total	79	2.57	2.38	0	9
	Education.G	79	0.72	0.73	0	2
	Occupation.G	79	0.41	1.07	0	6
	Constancy.G	79	0.94	1.42	0	5
	Independence.G	79	3.16	1.45	0	6
	General functioning.G	79	1.20	1.23	0	5
	Social-personal adjust.G	79	1.24	0.80	0	4
	Interest in life.G	79	1.95	0.85	0	4
	Energy level.G	79	1.81	1.39	0	4
	General total	79	11.57	5.61	3	36
	Total scale	79	14.14	7.09	4	43
PSAS[a]	***Sociability & isolation.C***	49	2.02	1.16	1	5
	Peer relations.C	49	1.57	0.82	1	5
	Scholastic perform.C	49	3.12	1.56	1	7
	Adaptation to school.C	49	1.29	0.61	1	3
	Interests.C	49	2.61	1.22	1	5
	Childhood total	49	10.61	3.44	5	20
	Sociability & isolation.A	49	2.16	1.20	1	5

	n	Mean	SD	min	max
Peer relations.A	49	1.61	0.81	1	5
Scholastic perform.A	49	3.69	1.64	1	7
Adaptation to school.A	49	1.65	1.20	1	5
Interests.A	49	2.80	1.27	1	5
Adolescence total	49	11.92	4.49	5	23

[a] There was much missing on this variable because of great difficulties in finding the subjects' parents at home.

1.5.2 Observational assessment

Table 4.6 Descriptive statistics of the observational assessment in the whole sample

	n	Mean	SD	min	max
Behaviour	78	0.67	1.21	0	5
Emotion	78	0.86	1.20	0	7
Verbal	78	0.44	1.04	0	5
Total	78	1.96	2.68	0	13

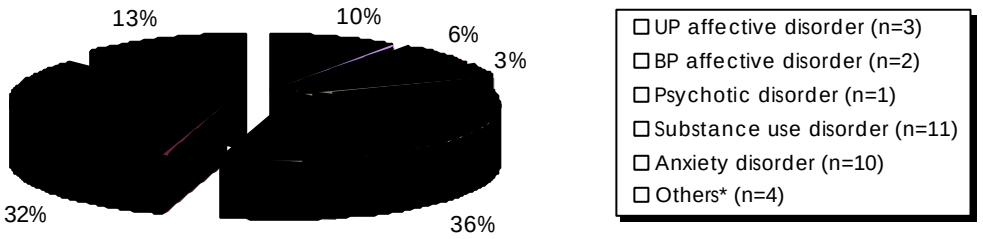
1.5.3 Axis-I psychiatric disorders

Table 4.7 Descriptive statistics of the presence of axis-I psychiatric disorders in the whole sample

	Frequency [23] n; %
Any past axis-I psychiatric disorder	19 (23.75%)
Any current axis-I psychiatric disorder	27 (33.75%)
Any lifetime axis-I psychiatric disorder	38 (47.5%)

Total sample size: n=80

Figure 4.2 Distribution of current [24] axis-I psychiatric disorders in the whole sample (n=27)



* Eating disorders, somatoform disorders, adaptative disorders
Note. Frequencies in parentheses do not coincide with the total number of subjects with a current psychiatric disorder (n=27) because there are some subjects with more than one diagnosis

[23] We adopted a broad definition of the presence of axis-I mental disorders, including those not otherwise specified and those without a clear affectation of daily functioning. That is why the frequency of psychiatric disorders is higher than it would be expected in a general population sample,

[24] Only current psychiatric diagnoses are showed because of our main interest in Phase III outcomes. Anyhow, the distribution of past diagnoses was the following: n=7 UP affective disorders, n=4 anxiety disorders, n=4 substance use disorders, n=2 eating disorders, and n=2 adaptative disorders.

2) HYPOTHESES TESTING

We will present the results and statistical analyses performed according to the objective. In general, statistically significant associations ($p<0.05$) will be marked in red-ink, while relevant trends to statistical significance will be marked in bold black-ink.

A) PROSPECTIVE STUDY

2.1 Phenotypical profile of the cohorts in Phase III

In order to introduce both cohorts (index/control), Table 4.8 contains information about age, years of education and intelligence, as well as the result of mean comparison tests (*t-test*) between both groups. We also offer gender representation and *chi-square* tests results.

Table 4.8 Comparison of control variables between cohorts

	Index cohort n=42	**Control cohort** n=38	**95%CI of the difference**	**t / ?²**	**Significance**
Age	$\overline{x}$ =22.1; SD=1.0	$\overline{x}$ =21.0; SD=1.0	-0.7 to 0.3	t= -0.85	p=0.400
Education	$\overline{x}$ =12.4; SD=2.2	$\overline{x}$ =13.2; SD=1.9	-0.1 to 1.7	t= 1.67	**p=0.099**
Raven	$\overline{x}$ =43.9; SD=6.0	$\overline{x}$ =48.0; SD=5.1	1.6 to 6.6	t= 3.23	**p=0.002**
Gender	52.4% male	50% male	---	?²= 0.045	p=0.832

As can be observed in Table 4.8, both cohorts were statistically different with respect to intelligence, with index subjects exhibiting worse Raven scores than control subjects. The groups did not differ in age and gender representation, but index subjects tended to display a lesser number of years of education.

✍ Statistical analyses

In general, we performed analyses of covariance with quantitative dependent variables in order to compare the cohorts on current measures. We adjusted these analyses for several variables that we will specify in each case. The categorical index of the Annett scale was analysed by means of a chi-square test and logistic regression adjusted for gender. Table 4.9 displays the consideration and scale of each variable in the analyses.

Table 4.9 Aim 1: Status and scale of the different variables analysed

	Status	**Scale**

Cohort	Independent	Categorical (k=2)
Gender	Control	Categorical (k=2)
Raven	Control	Quantitative
CPT-IP	Dependent	Quantitative
WCST	Dependent	Quantitative
SCWT	Dependent	Quantitative
FAS/Animal Naming	Dependent	Quantitative
CVLT	Dependent	Quantitative
Spatial Working Memory	Dependent	Quantitative
Finger Tapping	Dependent	Quantitative
Annett scale	Dependent	Categorical (k=2) Quantitative
NSS	Dependent	Quantitative
Observational assessment	Dependent	Quantitative
O-LIFE	Dependent	Quantitative
SCID-II	Dependent Control	Quantitative
DOIs	Dependent	Quantitative
Life Events scale	Dependent	Quantitative
COPE	Dependent	Quantitative
SCID-I	Dependent	Categorical (k=2)
PAS	Dependent	Quantitative
PSAS	Dependent	Quantitative
PBCs	Dependent	Categorical (k=2) Quantitative

2.1.1 Neuropsychological functioning

Considering the statistical difference with respect to intelligence found between cohorts, we adjusted these analyses for *intelligence*. In addition, we entered *gender* in equations in order to dismiss any possible interaction with neuropsychological functioning. All tables are provided with mean and standard deviations by cohort, adjusted difference (*d*), 95% confidence interval of the adjusted difference (*95%CI*), and adjusted degrees of significance of this difference (*p*).

- *Attention*

As can be seen in Table 4.10, Index subjects exhibited from 0.1 to 3.2 more omission errors on the CPT-IP shapes version than control subjects (p=0.032). In addition, they displayed a significantly worse shapes discriminability than control subjects, showing from 0.04 to 0.60 points less (p=0.027) in the d' indicator. Mean d' was also lower in Index subjects at a trend degree (p=0.093). Likewise, Index subjects exhibited, at a trend degree (p=0.111), a lower reaction time than control subjects did.

Table 4.10 Phase III attentional performance by cohort: Analysis of covariance

		Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	D	95%CI	p
CPT-IP numbers	***Omission errors***	4.90; 4.41	4.00; 2.76	---------- *NS* ----------		
	Commission errors	1.24; 1.76	0.66; 0.94	---------- *NS* ----------		
	Distraction errors	0.57; 1.40	0.16; 0.55	---------- *NS* ----------		
	Reaction time	529.44; 80.69	542.88; 61.30	---------- *NS* ----------		
	Verbal d'	3.01; 0.79	3.27; 0.67	---------- *NS* ----------		
	Verbal ß	4.85; 4.13	5.10; 3.51	---------- *NS* ----------		
CPT-IP shapes	***Omission errors***	6.57; 4.34	3.87; 2.33	1.69	0.15 to 3.23	**0.032**
	Commission errors	3.24; 2.84	2.34; 1.38	---------- *NS* ----------		
	Distraction errors	0.88; 1.29	0.61; 0.64	---------- *NS* ----------		
	Reaction time	535.05; 65.71	565.18; 58.98	-23.99	-53.67 to 5.69	**0.111**
	Spatial d'	2.25; 0.70	2.74; 0.56	-0.32	-0.60 to -0.04	**0.027**
	Spatial ß	2.47; 2.31	2.10; 1.76	---------- *NS* ----------		
	Mean d'	2.63; 0.64	3.01; 0.54	-0.23	-0.49 to 0.04	**0.093**

Sample size for this comparison: n=42 Index subjects; n=38 Control subjects

✍ *Executive functioning*

Results of analyses of covariance between cohort and executive functioning performance are displayed in Table 4.11.

Table 4.11 Phase III executive performance by cohort: Analysis of covariance

		Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	D	95%CI	p
WCST	***Errors***	15.71; 8.47	11.11; 4.40	4.33	1.01 to 7.64	**0.011**
	Perseverations	7.79; 5.72	5.95; 2.73	1.40	-0.74 to 3.54	**0.197**
	PE	7.10; 4.62	5.45; 2.05	1.36	-0.36 to 3.07	**0.119**
	NPE	8.62; 5.24	5.66; 3.50	2.97	0.77 to 5.17	**0.009**
	CLR	43.83; 12.25	50.32; 6.62	-6.04	-10.91 to -1.17	**0.016**
	Categories	3.38; 1.29	4.16; 0.97	-0.71	-1.27 to -0.15	**0.013**
	Trials to 1st cat.	12.54; 5.73	11.50; 1.61	---------- *NS* ----------		
	FMS	0.48; 0.74	0.21; 0.47	0.29	-0.00 to 0.59	**0.053**
SCWT	***#Words***	105.55; 14.32	110.95; 13.48	---------- *NS* ----------		
	#Colours	69.31; 13.32	72.30; 9.01	---------- *NS* ----------		
	#Word-Colour	44.07; 10.54	48.81; 9.44	---------- *NS* ----------		
	Interference	2.38; 7.50	5.18; 8.10	---------- *NS* ----------		
VF	***Total F.A.S.***	37.95; 10.06	41.21; 10.35	---------- *NS* ----------		
	Total AN	20.81; 5.20	22.32; 5.61	---------- *NS* ----------		

Sample sizes for these comparisons: WCST ✍ n=42 Index; n=38 Control; SCWT ✍ n=42 Index; n=37 Control; Verbal Fluency ✍ n=42 Index; n=38 Control.
Abbreviations. I: Index cohort**; C:** Control cohort**; PE**: Perseverative Errors; **NPE:** Non Perseverative Errors; **CLR:** Conceptual Level Responses; **FMS**: Failures to Maintain the Set; **Total AN**: Total number of words generated on the Animal Naming test. **VF**: Verbal Fluency.

As can be observed, Index subjects show a worse executive performance than Control subjects do in all indices. However, the adjusted difference between cohorts is statistically significant only in the WCST. At a 95% confidence interval, Index cohort

exhibits from 1.0 to 7.6 more total errors (p=0.011), from 0.8 to 5.2 more non-perseverative errors (p=0.009), from 1.2 to 10.9 less conceptual level responses (p=0.016), from 0.1 to 1.3 more categories achieved (p=0.013), and until 0.6 more failures to maintain the set (p=0.053) than do Control subjects.

No statistically significant differences between cohorts appeared in the SCWT or in verbal fluency tests.

- *Memory*

Results of covariance analyses between cohort and memory tests are displayed in Table 4.12. Given the large amount of indices provided by the CVLT, only those yielding statistically significant or relevant trend associations are displayed.

Table 4.12 Phase III memory performance by cohort: Analysis of covariance

		Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
CVLT	***List A total***	57.93; 8.47	57.92; 8.44	----------	*NS* ----------	
	List B	6.52; 2.10	6.66; 2.03	----------	*NS* ----------	
	List A6.1	12.74; 2.04	13.29; 2.00	----------	*NS* ----------	
	List A6.2	13.69; 1.63	13.71; 1.78	----------	*NS* ----------	
	List A7.1	13.62; 1.81	13.82; 1.59	----------	*NS* ----------	
	List A7.2	13.86; 1.75	14.18; 1.54	----------	*NS* ----------	
	Semantic clustering ratio	2.12; 0.70	2.19; 0.92	----------	*NS* ----------	
	Serial clustering ratio	2.29; 1.55	2.42; 2.06	----------	*NS* ----------	
	Slope	1.44; 0.46	1.33; 0.59	----------	*NS* ----------	
	Perseverations	6.33; 5.00	6.03; 4.69	----------	*NS* ----------	
	Intrusions (total)	1.64; 2.40	3.32; 4.47	-1.80	-3.21 to -0.39	**0.013**
	Recognition hits	15.40; 0.83	15.43; 0.80	----------	*NS* ----------	
	List B vs. List A1 recall	-14.04; 25.41	-11.70; 28.76	----------	*NS* ----------	
	A6.1 vs A5	-6.32; 11.99	-2.33; 8.17	-4.67	-9.68 to 0.34	**0.067**
	A7.1 vs A6.1	1.28; 6.20	3.96; 7.01	-2.80	-6.01 to 0.42	**0.087**
	Discriminability vs A7.1	14.76; 14.01	13.17; 12.08	----------	*NS* ----------	
SWM	***% overall accuracy***	63.53; 14.15	71.21; 12.48	-6.61	-13.00 to -0.22	**0.043**
	% left accuracy	54.03; 22.15	64.00; 18.87	-7.53	-17.23 to 2.17	**0.126**
	% right accuracy	73.87; 17.81	80.06; 15.90	-6.48	-14.60 to 1.64	**0.116**

Sample size: CVLT - n=42 Index; n=38 Control; SWM - n=42 Index subjects; n=38 Control subjects
Abbreviations: *A6.1:* short delay free recall; *A6.2*: short delay cued recall; *A7.1:* long delay free recall; *A7.2:* long delay cued recall; *SWM*: Spatial Working Memory.

With regard to verbal memory, Index subjects displayed a statistically significant lesser number of intrusions in the short- and long- term recall trials (p=0.013). At a trend level, Index subjects forgot more words than the Control cohort on the short-term free recall

trial in relation to the last List A trial (p=0.067). In addition, they tended to remember less words than Control subjects on the long-term free recall trial in relation to the short-term recall trial (p=0.087). Concerning contrast measures in general, it seems that recall of List B was systematically worse than recall of List A (first trial) in both cohorts. Short-term free recall was also worse than immediate recall of List A (last trial) in both groups. Moreover, both cohorts recalled more words on the long-term free recall trial than on the short-term trial. Finally, both groups showed a better discriminability in relation to long-term free recall.

With respect to spatial working memory, Index subjects exhibited a generally poorer spatial working memory performance, as they exhibit from 0.2 to 13% lesser overall accuracy than Control subjects do (p=0.043), as well as a lesser left and right accuracy (at a trend degree).

2.1.2 Neurodevelopmental variables

We performed analyses of covariance with cohort as the independent variable, and finger tapping performance, number of NSS, total sum of Annett scores, and PBCs (quantitative indices) as the dependent variables. These analyses were adjusted for *gender*. All tables are provided with mean and standard deviations by cohort, adjusted difference (*d*), 95% confidence interval of the adjusted difference (*95%CI*), and adjusted degrees of significance of this difference (*p*). The relationship between cohort and handedness, as derived from the Annett scale, was analysed by means of a chi-square test and a losgistic regression analysis adjusted for gender. As regards the categorical PBCs indices, we performed a chi-square test[25].

- *Finger Tapping*

Table 4.13 displays the results of covariance analyses with cohort and finger tapping performance.

Table 4.13 Phase III finger tapping performance by cohort: Analysis of covariance

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
Left hand	4.12; 0.64	4.45; 0.84	-0.32	-0.63 to -0.01	**0.042**
Right hand	4.61; 0.81	4.88; 1.18	-0.36	-0.85 to 0.12	**0.135**

Sample size for this comparison: n=42 Index subjects; n=38 Control subjects

[25] We did not perform a logistic regression analysis with cohort and PBCs given that no causal relationship can be assumed from cohort to PBCs (only from PBCs to cohort might be done an analysis in these terms, but that is not the object of this project).

As can be seen, Index subjects display a statistically significant lesser number of taps per second in the left hand than Control subjects do (p=0.042), as well as a trend to a lesser right hand speed (p=0.135).

✍ *Neurological Soft Signs*

The results of the analyses of covariance with cohort and total number of neurological soft signs are showed in Table 4.14.

Table 4.14 Phase III neurological soft signs by cohort: Analysis of covariance

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
NSS total	3.17; 3.68	1.61; 1.65	1.58	0.29 to 2.87	**0.017**

Sample size for this comparison: n=42 Index subjects; n=38 Control subjects

This table reveals that Index subjects showed a statistically significant higher number of neurological soft signs than Control subjects.

✍ *Laterality*

Logistic regression analyses were performed in order to test the predictive capacity of the cohort in relation to handedness, entering gender as a covariate. In addition, chi-square tests with both variables were performed in order to test possible statistical differences on the distribution of mixed-handedness in both cohorts (see Table 4.15).

Table 4.15 Phase III handedness by cohort: Logistic Regression Analyses and Chi-square tests

	Index cohort	Control cohort	Logist. regr.	Chi-square
Strong handedness	n=23 (54.8%)*	n=28 (73.7%)	B=0.84; df=1;	?²=3.09;
Mixed handedness	n=19 (45.2%)	n=10 (26.3%)	**p=0.082**	**p=0.079**

*Column percentages

As can be observed, the cohort was statistically associated with mixed-handedness (p=0.082) and the difference on the percentage of mixed-handedness among Index subjects (45.2%) *versus* Control subjects (26.3%) was also significant (p=0.079), both at a trend level.

After such analysis, and in order to dismiss the possible effect of grouping together the only left-handed subject with those right-handed (see section *Methods*, subpoint *2.1.2 Neurointegrative measures*), we dropped out this case from the analyses and repeated them. The results on the Chi-square test varied slightly and the statistical significance increased up to p=0.065, as this subject came from the Index cohort.

The result of the analysis of covariance with the total Annett score is presented in Table 4.16. No statistically significant associations were found between both variables, as can be observed.

Table 4.16 Phase III total Annett score by cohort: Analysis of covariance

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
Total sum	22.14; 11.76	19.94; 7.88	---------- NS ----------		

Sample size for this comparison: n=42 Index subjects, n=37 Control subjects.

- *Prenatal and birth complications*

The results of the analyses of covariance with the two cohorts on PBCs are showed in Table 4.17. Though the means go in the expected direction, no statistically significant or trend associations were found.

Table 4.17 Prenatal and birth complications by cohort: Analyses of covariance

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
Pregn. Duration	8.92; 0.29	9.00; 0.27	---------- NS ----------		
Birth weight	3.33; 0.66	3.41; 0.40	---------- NS ----------		

Sample size for this comparison: n=27 Index subjects, n=22 Control subjects.

Chi-square tests revealed no statistically significant or trend associations between cohort and complications during pregnancy or complications during delivery. However, it is noticeable the fact that 7% of Index subjects had complications during pregnancy, while no Control subject did (see Table 4.18).

Table 4.18 Prenatal and birth complications by cohort: Chi-square tests

		Index cohort	Control cohort	Chi-square test
Complications during pregnancy	Yes	n=2 (7.4 %)*	n=0 (0.0%)	$?^2$=1.62; p=0.203
	No	n=25 (92.6%)	n=21 (100.0%)	
Complications during deivery	Yes	n=5 (17.9%)	n=5 (23.8%)	$?^2$=0.26; p=0.609
	No	n=23 (82.1%)	n=16 (76.2%)	

* Column percentages

2.1.3 Personality variables

We performed analyses of covariance with cohort as the independent variable and personality measures (SCID-II and O-LIFE) as dependent variables. The analyses were adjusted for *gender* and *Cluster A, B, or C* traits. We considered the latter adjustment

because of the well-known covariance among personality traits from different clusters. Thus, when a certain personality cluster was analysed, total scores on the rest of clusters were included in the model as covariates. When O-LIFE scores were analysed, we entered number of Cluster B and Cluster C traits in the covariance model as covariate variables. All tables are provided with mean and standard deviations by cohort, adjusted difference (*d*), 95% confidence interval of the adjusted difference (*95%CI*), and adjusted degrees of significance of this difference (*p*).

Axis II Personality Assessment

The results of the analysis of covariance of axis II personality traits by cohort adjusted for gender and other personality clusters are showed in Table 4.19. Given the large amount of indices derived from this analysis, we only offer those yielding statistically significant or relevant trend associations.

Table 4.19 Phase III axis-II personality disorders (dimensional scores): Analyses of covariance

		Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
SCID-II dimensional scores	***Avoidant***	2.17; 3.17	1.11; 1.74	----------*NS*----------		
	Dependent	1.57; 2.39	1.05; 1.23	----------*NS*----------		
	Obsessive-Compulsive	3.02; 2.16	2.21; 1.96	----------*NS*----------		
	Passive-Aggressive	1.93; 1.90	1.21; 1.49	----------*NS*----------		
	Depressive	2.29; 2.75	1.00; 1.25	0.76	-0.12 to 1.64	**0.090**
	Paranoid	1.98; 1.97	1.18; 1.49	----------*NS*----------		
	Schizotypal	1.50; 2.02	0.82; 1.04	----------*NS*----------		
	Schizoid	0.79; 1.63	0.42; 1.29	----------*NS*----------		
	Histrionic	1.05; 1.59	0.63; 0.97	----------*NS*----------		
	Narcissistic	1.71; 2.35	0.82; 1.27	0.65	-0.21 to 1.52	**0.137**
	Borderline	2.62; 2.02	2.55; 2.42	----------*NS*----------		
	Antisocial	1.50; 3.39	1.39; 2.83	----------*NS*----------		
	Cluster A	4.26; 4.31	2.42; 2.21	----------*NS*----------		
	Cluster B	6.88; 6.51	5.39; 5.24	----------*NS*----------		
	Cluster C	6.76; 5.58	4.37; 3.03	1.35	-0.41 to 3.11	**0.132**

Sample size for these comparisons: n=42 Index; n=38 Control

As can be observed, no statistically significant associations were evident after adjustment. Thus, Index subjects tended to show more depressive traits and, to a lesser degree, more narcissistic and total Cluster C personality traits.

The following graphic shows a representation of the cohort differences on all the SCID-II personality disorders assessed.

- *Psychometric Schizotypy*

The results of covariance analyses between cohort and O-LIFE scores are showed in Table 4.20.

Table 4.20 Phase III psychometric schizotypy by cohort: Analysis of covariance

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
Unusual Experiences	6.67; 5.97	6.66; 5.11	---------- *NS* ----------		
Cognitive Disorganization	9.64; 6.49	7.71; 5.28	---------- *NS* ----------		
Introvertive Anhedonia	6.50; 3.70	4.26; 2.64	1.80	0.35 to 3.24	**0.015**
Impulsive Non Conformity	5.93; 3.23	6.00; 3.02	---------- *NS* ----------		

Sample size for this comparison: n=42 Index subjects; n=38 Control subjects

On the one hand, Index subjects showed a statistically significant higher degree of Introvertive Anhedonia (negative schizotypy), even after adjustment. On the other hand, Cluster C traits seemed to explain the difference between cohorts on Cognitive Disorganization, as this difference was statistically significant before adjustment but it disappeared after the inclusion of such traits in the covariance model.

2.1.4 Psychosocial variables

We performed analyses of covariance between cohort, on the one hand, and social behaviour (DOI-JA, DOI-JH) and coping measures (COPE), on the other hand. We adjusted these analyses for gender. All tables are provided with mean and standard deviations by cohort, adjusted difference (d), 95% confidence interval of the adjusted difference (95%CI), and adjusted degrees of significance of this difference (p). All the analyses were a posteriori adjusted for Cluster C traits in order to confirm the results. The relationship between cohort and life events exposure was measured via mean comparison tests (t-test), although adjustments for gender and Cluster C traits were performed a posteriori in order to dismiss any possible confounding effect of these variables.

✍ *Coping*

Table 4.21 shows the results of analyses of covariance between cohort and COPE scores adjusted for gender.

Table 4.21 Phase III coping measures by cohort: Analysis of covariance

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
Seeking social support	20.46; 4.20	22.55; 5.10	-2.06	-4.07 to -0.04	**0.045**
Religion	6.00; 2.51	5.47; 2.20	---------- *NS* ----------		
Humour	7.88; 2.87	9.13; 2.89	-1.28	-2.49 to -0.06	**0.040**
Drug/alcohol use	5.27; 2.41	5.03; 2.21	---------- *NS* ----------		
Planning & active coping	14.27; 3.19	15.92; 3.54	-1.65	-3.16 to -0.15	**0.032**
Retirement coping	5.41; 2.10	4.16; 1.20	1.26	0.48 to 2.03	**0.002**
Emotional expression	8.63; 2.62	8.50; 2.62	---------- *NS* ----------		
Acceptance	10.27; 2.05	11.16; 2.54	-0.89	-1.92 to 0.14	**0.090**
Denial	6.98; 2.77	5.37; 1.57	1.61	0.59 to 2.63	**0.002**
Restraint coping	9.49; 1.86	9.18; 2.40	---------- *NS* ----------		
Concentrate on solving	9.24; 1.79	10.05; 2.37	-0.81	-1.74 to 0.13	**0.089**
Personal growth	6.20; 1.12	6.61; 1.13	-0.41	-0.91 to 0.09	**0.110**
Positive reinterpretation	7.54; 1.67	8.47; 2.00	-0.94	-1.76 to -0.11	**0.026**
Distraction from stressor	6.63; 1.37	6.13; 1.76	0.50	-0.20 to 1.21	**0.159**
Escaping	6.17; 1.87	5.32; 1.66	0.85	0.06 to 1.65	**0.035**
Factor 1	15.05; 4.33	18.37; 4.41	-3.33	-5.30 to -1.36	**0.001**
Factor 2	35.17; 6.35	37.95; 6.33	-2.81	-5.61 to -0.01	**0.049**
Factor 3	19.15; 5.73	16.16; 3.64	3.01	0.85 to 5.17	**0.007**
Factor 4	29.10; 6.08	31.05; 6.88	-1.89	-4.54 to 0.76	**0.160**
Factor 5*	2.61; 2.03	3.92; 2.33	-1.31	-2.29 to -0.33	**0.009**
Factor 6	5.27; 2.41	5.03; 2.21	---------- *NS* ----------		

Sample size for this comparison: n=41 Index subjects; n=38 Control subjects
*A positive score on this factor indicates a lesser use of *Behavioural Escape*.

As can be observed, Index subjects show a statistically significant poorer use of social support (p=0.045), humour (p=0.040), planning and active coping (p=0.032), and positive reinterpretation (p=0.026) than Control subjects do when coping with difficulties. In contrast, they use to retire coping more frequently than Control subjects do (p=0.002), and use denial (p=0.002) and escape from difficulties (p=0.035) more

frequently than the Control group. At a trend level, the Index cohort shows a lesser acceptance of the problem (p=0.090), a poorer concentration on solving the problem (p=0.089), and a higher use of distraction to cope with difficulties (p=0.159). Likewise, they tend to integrate the experience as a part of their personal growth with a lesser frequency than the Control group do (p=0.110).

Regarding the COPE factors, Index subjects showed a statistically significant poorer use of problem-focused behavioural coping (p=0.001) and cognitive coping (p=0.049), and a higher use of behavioural escape (p=0.009) and cognitive escape (p=0.007). In addition, the Index cohort tended to use less frequently emotion-focused coping strategies (p=0.160).

These results were maintained after adjustment for Cluster C traits.

- *Social behaviour*

Table 4.22 displays the results of analyses of covariance between cohort and DOI-JA / DOI-JH scores by cohort adjusted for *gender*. As can be seen, Index subjects perceive themselves (DOI-JA), at a trend level, as showing a poorer social ascendance/leadership (p=0.136), more social anxiety/shyness (p=0.143), and a less prosocial (more unsociably) behaviour (p=0.134) than Control subjects.

Table 4.22 Phase III social behaviour measures by cohort: Analysis of covariance

		Index cohort $\overline{x}$; SD	Control cohort $\overline{x}$; SD	d	95%CI	p
DOI-JA	***Consideration with others***	25.22; 4.45	25.00; 3.89	---------- *NS* ----------		
	Respect/Self-control	24.17; 4.00	25.00; 3.84	---------- *NS* ----------		
	Aggressivity/Antisocial	14.29; 2.54	14.05; 2.88	---------- *NS* ----------		
	Withdrawal vs. Sociability	7.05; 4.02	7.95; 3.40	---------- *NS* ----------		
	Social ascend./leadership	16.68; 4.07	18.00; 3.59	-1.32	-3.06 to 0.42	**0.136**
	Social anxiety/shyness	16.32; 4.63	14.89; 4.14	1.46	-0.51 to 3.44	**0.143**
	Lie	17.66; 4.21	18.27; 3.91	---------- *NS* ----------		

	Total JA	42.51; 14.19	47.00; 11.66	-4.49	-10.38 to 1.41	**0.134**
DOI-JH	***Consideration with others***	25.05; 6.86	25.74; 4.41	----------	*NS*	----------
	Respect/Self-control	22.56; 4.98	24.18; 4.39	-1.62	-3.75 to 0.51	**0.135**
	Aggressivity/Antisocial	15.26; 3.09	14.50; 2.97	----------	*NS*	----------
	Withdrawal vs. Sociability	5.92; 3.92	7.47; 3.69	-1.49	-3.20 to 0.21	**0.086**
	Social ascend./leadership	18.69; 4.39	19.50; 5.34	----------	*NS*	----------
	Social anxiety/shyness	16.23; 4.43	14.13; 3.78	2.12	0.24 to 4.00	**0.027**
	Lie	18.97; 4.67	19.21; 4.84	----------	*NS*	----------
	Total JH	40.74; 17.33	48.26; 16.73	-7.19	-14.73 to 0.35	**0.061**

Sample size for these comparisons: DOI-JA ≙ n=41 Index subjects; n=37 Control subjects; DOI-JH ≙ n=39 Index subjects; n=38 Control subjects.

According to the parents version (DOI-JH), Index subjects would show a statistically significant higher social anxiety/shyness than Control subjects would (p=0.027), and a trend to be less sociable (higher withdrawal) (p=0.086), less respectful/self-controlled (p=0.135), and more unsociable/antisocial (p=0.061) than the Control group.

However, after adjusting these results for Cluster C scores (indicating presence of anxious/depressive traits), those trends to significance that came into sight in the DOI-JA disappeared (leadership: p=0.407; shyness: p=0.654; Total JA: p=0.635). Somewhat similar occurred with the DOI-JH, so those trends for Index subjects to show a higher withdrawal and a lesser prosocial behaviour also disappeared (p=0.286, and p=0.225, respectively). In addition, the statistically significant difference between cohorts on DOI-JH social anxiety/shyness became non-significant after adjustment, but maintained a light trend to statistical significance (p=0.190). Even so, the trend to less respect/self-control exhibited by Index subjects was maintained after adjustment for Cluster C scores.

In order to test the possible influence of the cohort in the agreement between subjects and their parents on the DOI, we performed Pearson correlations between -JA and -JH versions separately in both cohorts.

As can be observed in Table 4.23, there is a statistically significant agreement between subjects and their parents as to the assessment of their degree of shyness, and in the general social behaviour score in both groups, though this agreement is especially

significant in Index subjects. However, only Index subjects show an agreement with their parents as to their consideration with others, their sociability and their social ascendance. In contrast, an agreement between subjects and parents on the subject's degree of self-control and aggressivity is present only in the Control group.

Table 4.23 Pearson correlations between the DOI-JA and the DOI-JH scales of social behaviour according to the cohort

	Index group	Control group
Consideration with others	**?=0.45; p=0.004**	?=0.19; p=0.263
Respect/Self-control	?=0.08; p=0.630	**?=0.51; p=0.001**
Aggressivity/Antisocial	?=0.15; p=0.375	**?=0.48; p=0.003**
Withdrawal vs. Sociability	**?=0.62; p<0.001**	?=0.17; p=0.303
Social ascend./leadership	**?=0.46; p=0.004**	?=0.16; p=0.340
Social anxiety/shyness	**?=0.71; p<0.001**	**?=0.33; p=0.042**
Lie	**?=0.60; p<0.001**	**?=0.52; p=0.001**
Total JA	**?=0.59; p<0.001**	**?=0.38; p=0.019**

Sample size for this analysis: n=38 Index subjects; n=37 Control subjects

- *Life events*

A mean comparison test (t-test) was performed between cohort and several indexes from the Life Events scale. These results were *a posteriori* confirmed by means of an analysis of covariance adjusted for *gender* and *Cluster C* personality traits, but the lack of differences between results derived from one and another analysis lead us to present the simplest of them: the t-test.

Table 4.24 Life events exposure in Phase III by cohort: T-test analysis (n=79)

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	t	95%CI	p
LCU	300.95; 236.58	212.58; 147.76	-1.97	-177.56 to 0.82	**0.052**
# positive* events	5.29; 3.63	3.76; 2.28	-2.26	-2.88 to -0.18	**0.027**
# negative* events	3.76; 4.36	2.53; 2.38	-1.54	-2.82 to 0.36	**0.128**
Impact positive events*	13.90; 9.71	10.35; 7.45	-1.80	-7.48 to 0.38	**0.076**
Impact negative events*	10.34; 15.28	6.32; 6.75	-1.47	-9.44 to 1.41	**0.145**

Sample size for this comparison: n=41 Index subjects; n=38 Control subjects
* Subjective and idiosyncratic assessment of each subject

As we can observe, Index subjects were exposed to a statistically significant higher number of positive (subjective assessment) life events than Control subjects. Furthermore, they tended to display more LCU (p=0.052) –indicating a higher degree of stressful life events exposure independently on the sign, and a stronger perceived impact of positive life events exposure (p=0.076). Finally, Index subjects showed a

trend to be exposed to more negative events (p=0.128) and to be more affected by this exposure (p=0.145) than the Control group. These results were maintained after adjusting for gender and Cluster C traits.

In summary, Index subjects displayed a higher exposure to and affectation by life events, independently on the sign. This higher perceived exposure to life events was not explained by gender or anxious/depressive personality traits.

2.1.5 Premorbid adjustment

We performed analyses of covariance between cohort and premorbid adjustment measures (PAS, PSAS) adjusted for *gender*. Table 4.25 is provided with mean and standard deviations by cohort, adjusted differences (*d*), 95% confidence interval of the adjusted difference (*95%CI*), and adjusted degrees of significance of this difference (*p*).

Table 4.25 Phase III premorbid adjustment measures by cohort: Analyses of covariance

		Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	d	95%CI	p
PAS	***Sociability & withdrawal.A***	1.24; 1.32	1.00; 0.96	----------	*NS* ----------	
	Peer relations.A	0.78; 1.01	0.55; 0.76	----------	*NS* ----------	
	Socio-sexual life.A	0.76; 1.30	0.79; 1.47	----------	*NS* ----------	
	Adulthood total	2.78; 2.43	2.34; 2.34	----------	*NS* ----------	
	Education.G	0.80; 0.75	0.63; 0.71	----------	*NS* ----------	
	Occupation.G	0.37; 1.04	0.45; 1.11	----------	*NS* ----------	
	Constancy.G	0.95; 1.36	0.92; 1.50	----------	*NS* ----------	
	Independence.G	3.12; 1.47	3.21; 1.45	----------	*NS* ----------	
	General functioning.G	1.17; 1.05	1.24; 1.42	----------	*NS* ----------	
	Social-personal adjust.G	1.49; 0.93	0.97; 0.54	0.55	0.18 to 0.92	**0.004**
	Interest in life.G	2.05; 0.92	1.82; 0.80	----------	*NS* ----------	
	Energy level.G	2.07; 1.35	1.57; 1.39	0.50	-0.17 to 1.17	**0.140**
	General total	12.02; 4.50	11.27; 6.62	----------	*NS* ----------	
	Total scale	14.80; 5.92	13.68; 8.15	----------	*NS* ----------	
PSAS	***Sociability & isolation.C***	2.12; 1.27	1.92; 1.06	----------	*NS* ----------	
	Peer relations.C	1.60; 0.96	1.54; 0.66	----------	*NS* ----------	
	Scholastic perform.C	3.52; 1.61	2.71; 1.43	0.65	-0.26 to 1.56	**0.157**

Adaptation to school.C	1.44; 0.71	1.13; 0.45	0.37	-0.00 to 0.74	**0.051**
Interests.C	2.72; 1.06	2.50; 1.38	---------- *NS* ----------		
Childhood total	11.40; 3.74	9.79; 2.96	1.58	-0.33 to 3.48	**0.102**
Sociability & isolation.A	2.44; 1.29	1.88; 1.03	0.56	-0.11 to 1.24	**0.099**
Peer relations.A	1.72; 0.94	1.50; 0.66	---------- *NS* ----------		
Scholastic perform.A	4.08; 1.63	3.29; 1.57	0.77	-0.10 to 1.63	**0.081**
Adaptation to school.A	1.80; 1.22	1.50; 1.18	---------- *NS* ----------		
Interests.A	3.04; 1.06	2.54; 1.44	0.50	-0.23 to 1.22	**0.174**
Adolescence total	13.08; 4.52	10.71; 4.23	2.33	-0.12 to 4.78	**0.062**

Sample size for these comparisons: PAS ✍ n=41 Index subjects; n=38 Control subjects; PSAS ✍ n=25 Index subjects; n=24 Control subjects.

With respect to the PAS, Index subjects showed a statistically significant worse premorbid social-personal adjustment (p=0.004), scoring from 0.2 to 0.9 points higher than Control subjects on this item. We can also appreciate a trend for Index subjects to score higher in the Energy item (p=0.140). This would indicate that these subjects tend to cope with life with less energy and motivation than do Control subjects.

Concerning the PSAS, the results are very similar to the previous scale, as Index subjects displayed a trend to score higher in several items, indicating a poorer premorbid social adjustment in general. Specifically, this cohort tended to exhibit a poorer scholastic performance, both in childhood (p=0.157) and especially in adolescence (p=0.081), a poorer adaptation to school in childhood (p=0.051), and a poorer sociability (more isolation) (p=0.099) and less hobbies and interests (p=0.174) in adolescence. In general, the Index cohort tended to show a poorer premorbid social adjustment than did Control subjects, both in childhood (p=0.102) and adolescence (p=0.062).

2.1.6 Clinical variables

In order to relate the cohort with the Observational Assessment scores, we performed an independent samples t-test. The results were later confirmed by means of analyses of covariance adjusted for gender, though we present the unadjusted results. Table 4.26 shows means and standard deviations by cohort, unadjusted differences (*d*), 95% confidence interval of the difference (*95%CI*), and degree of significance of this difference (*p*).

Table 4.26 Phase III Observational Assessment by cohort: T-test

	Index cohort $\bar{x}$; SD	Control cohort $\bar{x}$; SD	t	95%CI	p

Behaviour	0.83; 1.20	0.50; 1.22	---------- *NS* ----------		
Emotion	1.05; 1.34	0.66; 1.02	1.45	-0.15 to 0.93	**0.151**
Verbal	0.50; 1.15	0.37; 0.91	---------- *NS* ----------		
Total	2.38; 2.79	1.53; 2.53	1.32	-0.41 to 2.02	**0.190**

Sample size for this comparison: n=40 Index subjects; n=38 Control subjects

As can be observed, though the Index cohort showed higher scores on the Observational Assessment in all cases (indicating a higher overall presence of psychopathological traits), no statistically significant differences between cohorts appeared. However, a trend to statistical significance was detected for Index subjects to show a higher number of clinical emotional traits and, at a lesser degree, a trend to show a higher number of psychopathological traits in total. These results were maintained after adjusting for gender.

SCID-I diagnoses were analysed by means of a chi-square test in order to explore the differences on the distribution of psychiatric diagnoses by cohort. No differences were found (p=0.982).

2.2 Cluster analysis of the developmental pattern of sustained attention through adolescence: Relationship with Phase III measures

2.2.1 Cluster analysis of the developmental pattern of sustained attention

In order to carry out the cluster analysis of sustained attention measures through adolescence, we used the mean *CPT d's* (mean of spatial d' and verbal d') along the three phases and computed an **individual percent of change (IPC)** inter-phases for each subject. From a developmental perspective, we created such measure in order to take into account the individual change during adolescence, rather than the change in relation to a normative cut-point. We calculated the individual percent of change from Phase I to Phase II, and from Phase II to Phase III, according to the following formula:

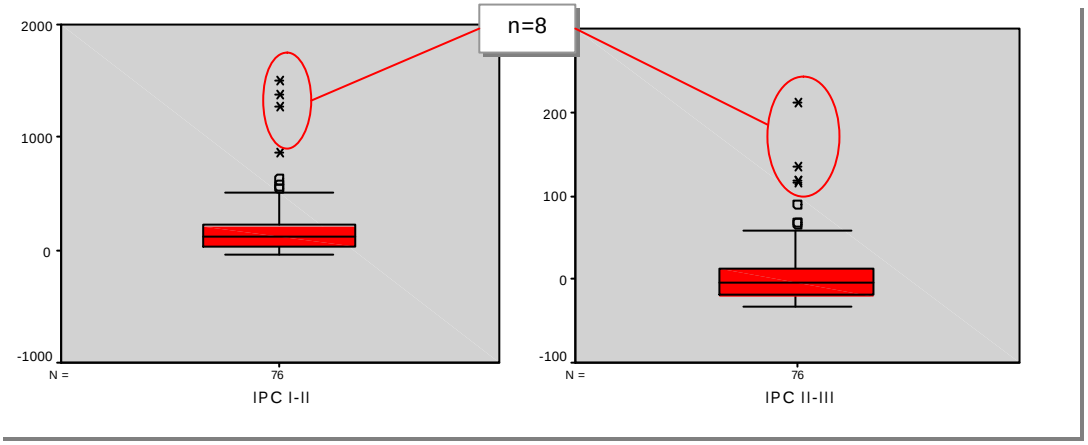
$$\textbf{\textit{IPC I-II}}\ (\text{from Phase I to Phase II}) = \frac{\bar{x}\ d'\text{Phase II} - \bar{x}\ d'\text{Phase I}}{\bar{x}\ d'\text{Phase I}} * 100$$

$$\textbf{\textit{IPC II-III}}\ (\text{from Phase II to Phase III}) = \frac{\bar{x}\ d'\text{Phase III} - \bar{x}\ d'\text{Phase II}}{\bar{x}\ d'\text{Phase II}} * 100$$

We also computed an IPC from Phase I to Phase III, but it yielded redundant results in the cluster analysis, so it was removed and only the two indices mentioned were used.

The distributions of these two measures (IPC I-II and IPC II-III) were examined by means of box-plot diagrams (see Figure 4.3), which revealed the presence of extreme outlyers in both indices. These subjects (n=8) were removed from the cluster analysis, that finally was carried out with 68 subjects.

Figure 4.3 Box-plot representation of IPCs (n=76[26])



A two-step cluster analysis with automatic creation of factors was performed. It yielded 3 clusters whose characteristics are seen in Table 4.27.

As can be observed, the first cluster showed a ~98% increase on the CPT-IP mean d' from Phase I to Phase II, and a lighter increase (~27%) from Phase II to Phase III. The second cluster displayed a somewhat higher d' increase from Phase I to Phase II (~126%), but suffered a small decrease (~14%) from Phase II to Phase III. The third and final cluster exhibited an almost five-fold d' increase from Phase I to Phase II (~477%) and, alike the second one, it showed a small decrease from Phase II to Phase III (~11%).

Table 4.27 Cluster analysis results

Centroids

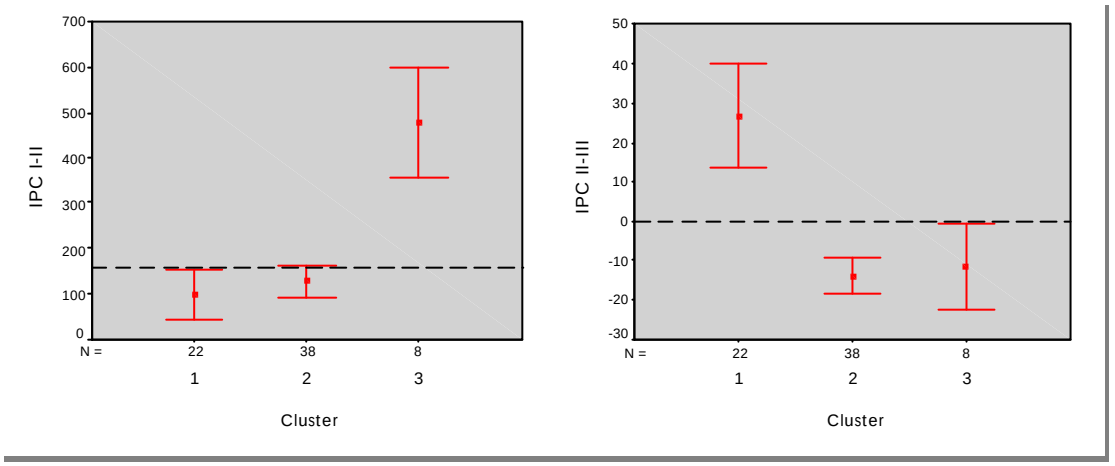
	IPC I-II		IPC II-III	
	Mean	*SD*	*Mean*	*SD*

[26] There were 4 system missings for these computes

Cluster					
1	n=22	98.26	103.53	26.91	24.00
2	n=38	126.24	86.48	-13.98	11.26
3	n=8	477.41	109.53	-11.51	9.75
Combined		158.50	150.56	-0.46	24.99

Note. Means reflect percentages of d' change

Figure 4.4 Simultaneous CI95% for the clusters means



Note. The reference lines are the global means (IPC I-II=158.50 and IPC II-III=-0.46)

As can be observed in the following graphics (see

Figure 4.4), the main difference from Phase I to Phase II was marked by Cluster 3, while the main difference from Phase II to Phase III was attributable to Cluster 1. An ANOVA analysis with Scheffé comparisons was performed among clusters on IPC I-II and IPC II-III variables in order to test the significance of the differences observed in these

graphics. Indeed, from Phase I to Phase II (IPC I-II) Cluster 3 differed at a statistically significant level ($p<0.001$) from Clusters 1 and 2, while both Cluster 1 and Cluster 2 showed no statistically significant differences ($p=0.549$) between them. The percentage of change from Phase II to Phase III (IPC II-III) was different at a statistically significant level between Cluster 1 and Clusters 2 and 3 ($p<0.001$), while the difference between the latter ones was statistically non-significant ($p=0.928$).

In order to get a notion of the attentional scores obtained by subjects from each cluster, Figure 4.5 (next page) offers a graphic representation of the mean CPT d' scores by cluster along the three phases of the present study.

As can be seen, Clusters 1 and 2, though differing on their developmental pattern of attention, have finally converged in the same degree of sustained attention (see point 2.2.3), whereas Cluster 3, though showing the same developmental pattern as Cluster 2 (increasing d' from Phase I to Phase II and decreasing d' from Phase II to Phase III) has finally obtained a lower d', in comparison to the rest of clusters.

Figure 4.5 Mean CPT d' scores by cluster along the three phases