study by Gregory, Claridge, Clark & Taylor (2003) provides an example of interaction between gender and handedness reporting an association between schizotypy and mixed-handedness only in males.

What seems to be clear is that there exists evidence for a leftward shift in the distribution of handedness in schizophrenia suggesting increased mixed-handedness (Green, Satz, Smith & Nelson, 1989; Nelson, Satz, Green & Cicchetti, 1993; Satz & Green, 1999). Likewise, it has been suggested that the development of handedness is related to the genetics of cerebral lateralisation, which might be disrupted in schizophrenia (Annett, 1999; Crow, 1997; Crow et al., 1989, etc.) and in first-degree relatives of schizophrenic patients (e.g., Grosh, Docherty & Wexler, 1995; Orr, Cannon, Gilvarry, Jones & Murray, 1999). However, this hypothesis has also been challenged by studies that report these patterns of atypical asymmetry in the temporal lobe in other psychiatric disorders (e.g., Hynd, Semrud-Clikeman, Lorys, Novey & Eliopulos, 1990) and “typically human” asymmetries in chimpanzees (Gannon, Holloway, Broadfield & Braun, 1998).

Anyhow, our results suggest that normal gender differences on laterality should be taken into account when studying this variable as a putative risk marker for psychosis or other psychopathologies.

On the other hand, we found a clearly lower birth weight in Cluster 3, in comparison to the other clusters, especially Cluster 2. This finding involves the possible existence of a vulnerability acquired at a prenatal level in this group and, together with the higher mixed-handedness, they give support to early-developmental models of vulnerability, and so to the hypothetical presence of early neurodevelopmental damage in Cluster 3 subjects. In this respect, Zornberg Buka & Tsuang (2000) highlighted the importance of distinguishing between the relative risks of different types of obstetric complications, because grouping them may produce inconsistent results. Thus, Seidman et al. (2000) found that, among a series of obstetric complications, low birth-weight had the strongest association with neuropsychological impairments at age 7 years. Then our results add evidence to these findings. However, it is worth taking into account that obstetric complications (including birth-weight) seem not to be specific to schizophrenia (Verdoux, 2004; Verdoux & Sutter, 2002), since they have been also reported, though to a lesser extent, in other psychiatric illnesses such as mood disorders.

As to the trend for Cluster 1 to show a lower birth weight than Cluster 2, the maintenance of this result even after adjustment for gender led us to dismiss the possible influence of this variable on such difference. Thus, we are compelled to take into account the likelihood that Cluster 1 also presents subtle early-neurodevelopmental impairment acquired at prenatal stages, though to a lesser extent than Cluster 3. The truth of this statement might have two implications: on the one hand, the hypothesis that Cluster 1 subjects represent the impact of a late-neurodevelopmental impairment associated to maturation and female gender would be challenged because of the mentioned data suggesting early-neurodevelopmental alterations; on the other hand, the overall better functioning of Cluster 1 with respect to Cluster 3 in almost all areas in spite of the likely presence of such early-neurodevelopmental damage might be partly due to the higher incidence of female gender in this group, and therefore to a possibly protective effect of this variable. The protective effect of female gender on vulnerability has been suggested in several occasions (e.g., Riecher-Rössler & Häfner, 1993; Seeman, 1895). Even so, Cluster

inconsistency of handedness measures.
was not entirely composed by female, so this statement would be only applicable to a subgroup out of this cluster.

In general, our results give support to the hypothesis that the cluster with the hypothetical neurodevelopmental impairment (Cluster 3) also shows the poorest neurointegrative performance and more prenatal abnormalities than the other two clusters.

2.2.4 Personality correlates

Cluster 3 tended to score higher than Cluster 2 on avoidant personality and higher than Cluster 1 and 2 on Introvertive Anhedonia and Cognitive Disorganization. On the whole, these findings characterize Cluster 3 as mainly associated to negative and disorganized personality traits, as the association between avoidant personality and negative symptoms (e.g., Kendler et al., 1993) is unquestionable. Our hypothesis in this regard is only partially supported, as we failed to find higher levels of Cluster A personality traits in Cluster 3 subjects.

The possibilities of debate on this finding have been mostly explained in the previous point (2.1.3) when discussing the association between Index cohort and negative schizotypy. Thus, those subjects with a sustained attention deficit stable through adolescence show negative and disorganized features, the latter probably the most directly associated to their cognitive impairment. The absolute lack of relationship of this cluster to any “positive” feature gives still more support to the notion that neurocognitive vulnerability (to schizophrenia?) runs associated with negative forms of the schizophrenic spectrum in the general population (Cornblatt, 2002; Tsuang et al., 2002). Actually, in schizophrenic patients attentional disturbances seem to be more consistently associated with negative features (e.g. Nuechterlein et al., 1986; Asarnow et al., 1991; Cornblatt and Keilp, 1994; Buchanan et al., 1997; Hwu et al., 2002), though some studies did not find this relationship (e.g. Ito et al., 1997). In addition, the association that we found seems to be “purged” of more “neurotic” traits that, in contrast, were present in the Index cohort. This finding still gives more support to the notion of schizotaxia (Meehl, 1969; 1989; 1990; Tsuang et al., 2001; Tsuang et al., 2002) and to the possibility that attenuated versions of the deficit syndrome (Carpenter et al., 1988) may exist in the general population along a continuum of severity.

Cluster 1, in contrast, tended to show higher scores on borderline personality in relation to Cluster 2, as well as generally higher Cluster B scores. They displayed no higher schizotypy in relation to the other clusters. It appears, therefore, that Cluster 1 exhibits more “immature” personality traits. Interestingly, this immature personality appears in a cluster of subjects that seem to present a retard in their cognitive development, though finally they achieve a virtually normal performance.

Therefore, Cluster 1 seems to correlate with immature personality traits while Cluster 3 is associated to negative features, possibly of the schizophrenic spectrum.

2.2.5 Psychosocial correlates

34 These results are adjusted for gender and Cluster A and Cluster C traits.
Cluster 3 differed from Cluster 1 and Cluster 2 specifically on their higher use of cognitive escape strategies when coping with daily stressors. These subjects also tended to use problem-focused behavioural coping strategies less than the other clusters did. This result is similar to that found in Index subjects but they are again more filtered, leading to the conclusion that the presence of poor attentional resources (and poor general neurocognitive functioning, as was described before) gives way to deficits in the use of coping strategies, as suggested by Wilder-Willis et al. (2002). This fact might explain the higher use of cognitive escape and the presence of avoidant behaviours seen before in this cluster.

Likewise, Cluster 3 was characterized by poor social behaviour, i.e., less sociability, more social anxiety, less leadership capacity and social ascendance, and a trend to a generally poor prosocial (more unsociable) behaviour. Again, the Cluster 3 social behaviour profile was very similar to that found in the Index cohort, but more limited and focused on social withdrawal / internalizing behaviours. Therefore, Cornblatt’s model (Cornblatt & Keilp, 1994) on the genesis of negative and positive symptoms in high-risk subjects with sustained attention deficit is even more applicable in this cluster.

Evidently, the existence of a transactional relationship between coping deficits and social retirement in Cluster 3 subjects is highly probable.

Therefore, our hypothesis that the hypothetically neurodevelopmental cluster (Cluster 3) would show more psychosocial impairments is supported by our data.

### 2.2.6 Clinical correlates

Clinical correlates in Cluster 3 are in agreement with the rest of characteristics mentioned in previous points and so, they also give support to hypothesis a2.1. Thus, these subjects showed a poorer previous adjustment than the other clusters, especially in the social area and, to a lesser degree in relation to interests, suggesting the presence of anhedonic, passive and apathetic features in these subjects since childhood. Similarly, a recent study by Silverstein, Mavrolefteros & Turnbull (2003) has reported an association between premorbid social deficits and adult neuropsychological performance in schizophrenic patients.

They also displayed a stronger emotional disturbance with respect to the other clusters. In this regard, we must remember that emotional disturbances according to the observational assessment that we carried out include not only an excess but also a defect in the emotional response. Though we could not corroborate this point (because the variability of the specific items was so low to make statistical comparisons), we anticipate that the latter kind of disturbance would be the most representative of this cluster. This fact would be consistent with previous adjustment and personality findings in this group.

### 2.2.7 General conclusion and comments

The cluster analysis of sustained attention measures from early adolescence to early adulthood identified three developmental groups, as can be seen in Table 5.6.

*Table 5.6 Phenotypical profile of the three developmental clusters: Short summary table*
Firstly, a small cluster of subjects with a sustained attention deficit stable through adolescence was observed. This cluster displayed a profile of attentional development similar to that found in the cluster of best performers, which will be commented later. However, they never reached the “normal” level of attentional performance with respect to such best-performers cluster (though in early adulthood their differences were not statistically significant). Therefore, we will call them “worst-performers cluster” from now on. The apparent sustained attention deficit of this group was correlated in early adulthood with a number of neuropsychological impairments, mainly represented by executive and spatial working memory dysfunctions. Social withdrawal, emotional disturbances such as anhedonia and social anxiety, apathy, slight signs of thought disorder, coping deficits and poor previous social adjustment were also characteristic of this cluster of subjects. In addition, neurointegrative abnormalities such as mixed handedness and laterality or slight psychomotor difficulties, as well as a clearly low birth weight were present in this cluster. Again, this profile of abnormalities gives support to the validity of the schizotypia concept before mentioned. Furthermore, altogether these abnormalities point to the possibility that this cluster represents the (early) neurodevelopmental subtype of vulnerability to (possibly) schizophrenia spectrum disorders (Castle & Murray, 1991; Castle, 1996; Goodman, 1991; Murray et al., 1992). By the way, retrospective studies have described profiles of impairment highly similar to that found in our “worst-performers”-neurodevelopmental group (e.g., Sobin et al., 2001). One of the main characteristics mentioned supporting the possibility that this cluster represents the neurodevelopmental subtype is the presence of low birth-weight. This variable has been suggested as a modest but definite risk factor for schizophrenia (e.g., Gunnell et al., 2003), and has been associated with poor premorbid functioning (alike in our sample) and neurocognitive impairment (again as in our sample) (Kunugi et al., 2001). The only difference of our data with the subtype described in the literature would be the male predominance, a characteristic that we failed to find in Cluster 3 subjects. In this regard, the small sample size of this group might not reflect real gender differences, so we expect that a higher size would have revealed interesting sex differences. In fact, a similar subgroup with male predominance was already identified in the first phase of the present study (Barrantes-Vidal et al., 2002) by means of a cluster analysis of psychometric schizotypy measures in this sample.
Secondly, a somewhat bigger group of subjects showed a generally best neuropsychological performance than the worst-performers cluster, but **subtle impairment on some executive functioning and spatial memory indices**. This minor neuropsychological impairment was, however, much less marked than that of the previously mentioned cluster. Interestingly, their attentional development through adolescence was different from the other two groups. These subjects showed a **linear development** of their sustained attention scores that, even being under the previous group in middle adolescence, achieved however the same level than that of the best performers group in early adulthood. This fact leads us to speculate that they showed a **retard in their (cognitive) attentional development**, as while the best- and the worst-performers clusters seemed to have finished their attentional development in mid adolescence, this cluster continued developing till early adulthood. In addition, this development was, in general, much less steep (slowest) than that of the other groups. We have no more longitudinal data that allows us to test if these subjects will continue developing or either they will stop their progression. However, the fact that they have reached adulthood compels us to anticipate that they will stabilize from now on. This cluster displayed a trend to present **immature and emotionally unstable** personality traits, **female predominance**, and mostly strong handedness. Moreover, a **trend to show low birth weight** (in comparison to the best-performers cluster) was observed. No poor previous adjustment or clinical signs in the observational assessment, as well as no coping or social deficits were observed in these subjects. Therefore, we will name this group as “developmentally-delayed” from now on. Additionally, we hypothesize that the developmental delay observed in these subjects might be due to a slight neurodevelopmental impairment that would give way to immaturity and emotional disturbances, as well as subtle neuropsychological deficits.Actually, delays on cerebral maturation have been associated to presence of psychopathology (Crow et al., 1996; Saugstad, 1998, 1999). On the other hand, the role of gender in this cluster is unclear, but we suspect that a protective effect of female gender (as suggested by Häfner, Behrens, de Vry & Gattaz, 1991; Häfner et al., 1998; Riecher-Rössler & Häfner, 1993; Seeman, 1985; etc.) might be responsible for the lesser mixed-handedness and the lesser general impairment showed by these subjects.

Thirdly, the biggest cluster was composed by subjects who showed an **overall good functioning on all the areas** analysed. This group, to that we have referred as the “best-performers”, displayed a **male predominance** and higher **mixed-handedness**. Its attentional development showed a **non-linear mean function** similar to that of the worst-performers cluster, but always with higher sustained attention scores. Thus, they appeared to finish their attentional development during middle adolescence. The higher percentage of mixed-handedness in this group might be explained by the effect of male gender. This point, though not extensively studied, seems to find some support in studies that suggest a higher prevalences of mixed-handedness in males and more strong-handedness (left and right) in females (surprisingly on the contrary of theories on language specialization) (e.g., Coren, 1995; Pedersen, Sigmundsson, Whiting & Ingvaldsen, 2003; Tan, 1988; Tan & Kutlu, 1991). Anyway, the male predominance in this group was not as marked as the female predominance in the developmentally-retarded cluster.

As to the development of sustained attention, the profile of the best-performers group (presumably “normally” developed) describes it as suffering a steep increase from early to middle adolescence, and a
light decrease from middle adolescence to early adulthood, when it possibly stabilizes. These data suggest that the development of (sustained) attention follows an asymptotic non-linear developmental function. Such a statement finds support in a study by Lin et al. (1999), who described a similar pattern of development of CPT scores (a convex age-development curve) in children and adolescents from 6 to 15 years old.

With regard to the differences between the worst-performers profile and that of the Index cohort, we believe that the selection of groups according to sustained attention performance yielded a highly heterogeneous Index cohort. Along these lines, a sustained attention deficit detected at early adolescence might well be the expression of a static neurodevelopmental damage affecting attentional processes and cognitive functioning across the lifetime, or either it might represent a certain point in the cognitive development of a still (abnormally) immature brain that, eventually, will achieve a normal level of functioning. This assortment of hypothetical aetiologies for the sustained attention deficit in the same cohort would have given rise to the broader and even erratic range of impairments identified in the Index cohort. This assumption might also account for the high level of covariation among neurocognitive and personality traits that was identified in this cohort.

Altogether, we may state that the cluster analysis of sustained attention performance through adolescence segregated two groups (plus a third “normal” group) that reflected different paths of vulnerability to psychopathology. It is possible that every one of these groups reflects vulnerability to a certain group of psychiatric disorders that we cannot establish because of lacking data on future outcomes. Even so, we may speculate a schizophrenia spectrum disorders outcome for the “worst-performers” cluster, and an affective (unipolar and bipolar) outcome for the “developmentally delayed” cluster. By the way, the apparent quantitative difference on the neurodevelopmental impairment of both “pathological” groups (worst-performers and developmentally-delayed) and the truth of the previous speculations would mean that affective and schizophrenic outcomes both have the same underlying basis. The differences in the final outcome (multifinality principle) would be due to the degree of neurodevelopmental impairment (more severe for schizophrenic outcomes) and to the intervention of different risk factors (social withdrawal, poor coping strategies, etc.) and/or gene-environment interactions during development. This possibility has been suggested by some authors (Berner, 2002; Verdoux, 2004; Verdoux & Sutter, 2002), who consider that a given risk factor (perinatal complications, in particular) may be associated with several adverse health outcomes but this fact does not preclude the existence of a causal relationship between earlier risk factors and schizophrenia. From this point of view, our results would give support to the concept of “unitary psychosis” by grouping together the origins of the vulnerability to affective and schizophrenic disorders.

2.3 Relationship between psychometric schizotypy and neurocognitive variables

2.3.1 Positive schizotypy
Positive schizotypy (Unusual Experiences) was associated with an impulsive style of response in the sustained attention test and a trend to more inattentiveness, as well as to poor left spatial working memory. This association between positive schizotypy and neurocognitive (attention and spatial memory) deficits has been reported by other authors with more evident results (Lenzenweger, Cornblatt & Putnick, 1991; Park, Holzman & Lenzenweger, 1995). However, this factor was associated with good immediate and short-term verbal memory and, at a trend level, with higher inhibitory control. This trend to good inhibitory control constrasts with the majority of studies that report poor executive performance in subjects with positive schizotypy (e.g., Lenzenweger & Korfine, 1994; Park et al., 1995; Poreh et al., 1995; Suhr et al., 1997; Tallent & Gooding, 1999). Nevertheless, there are several studies yielding negative results on this relationship (e.g., Duchene et al., 1998; Lin et al., 2000; Spitznagel & Suhr, 2002). Concerning the higher verbal memory ability, associations between elevated linguistic capacities and positive schizotypy traits have been reported elsewhere (e.g., Brugger et al., 1993). However, the lack of association between both variables is more frequent (e.g., Lenzenweger & Gold, 2000). In this regard, it has been suggested that there exist people in the general population that experience strong perceptual aberrations of positive schizotypy but show no evidence of psychosis (e.g., Johns & Van Os, 2001; Verdoux et al., 1998), or even disposition to it (“happy schizotypes”; McCreery, 1993).

2.3.2 Disorganized schizotypy

Disorganized schizotypy (Cognitive Disorganization) correlated with poor spatial sustained attention and poor spatial working memory, especially left accuracy. It also correlated, at a trend level, with poor inhibitory control and poor semantic verbal fluency. Only in the Control cohort, this factor was associated with poor concept formation, poor flexibility of thinking, poor short- and long-term verbal memory but good discriminability. In Index subjects, however, Cognitive Disorganization correlated with good short- and long-term verbal memory but, in contrast, with poor discriminability in comparison to long-term memory capacities (at a trend level). The reversed pattern of associations between verbal memory and cognitive disorganization according to the cohort was a striking result. We hypothesize that Control subjects, who presumably have a normal attentional level, would be affected by the anxiety component of this schizotypal factor (non-adaptive anxiety), thus performing badly in verbal memory (and executive functioning). In contrast, Index subjects presumably suffering from an attentional deficit, would be favoured by higher levels of anxiety (adaptive anxiety). Even though, this speculation does not permit to explain the reversed pattern of associations with recognition measures. In general, few studies have explored the association between the disorganized factor of schizotypy and neurocognitive functioning (Álvarez-Moya & Barrantes-Vidal, 2003). Most of the published studies employ only measures of negative and/or positive schizotypal factors (e.g., Laurent et al., 2001; Lenzenweger & Korfine, 1994; Park et al., 1995), or even they do not distinguish the different schizotypal dimensions and make use of a general measure of schizotypy (e.g., Raine et al., 1992b; Spaulding et al., 1989). Therefore, finding corroboration for our results in this regard is difficult. Daneluzzo et al. (1998) reported a relationship between disorganized aspects of psychometric schizotypy and poor concept formation, as measured by the WCST. Nuechterlein et al. (2002) also found several perceptual and attentional deficits in a disorganized factor that they extracted by means of a factorial analysis of Cluster A personality traits.
in relatives of schizophrenic patients. Then more studies are needed in order to replicate these findings. Anyway, what seems clear from our results on disorganized schizotypy is that it may correlate with neuropsychological functioning in a different manner as a function of the presence or absence of an attentional deficit. Likewise, the high covariation between this schizotypal factor and neurotic traits might lead to establish false associations between disorganized schizotypy and neuropsychological performance, as our results might be explained by such neurotic traits, rather than by this schizotypal factor. Anyhow, we were not able to test this point because of the clear difficulty in adjusting our analyses (Pearson correlations) for neurotic traits.

2.3.3 Negative schizotypy

Negative schizotypy (Introvertive Anhedonia) was clearly related to executive dysfunction, as evidenced by poor concept formation, poor verbal fluency, and a trend to poor inhibitory control. The association with the two first types of impairments (concept formation and verbal fluency) has been consistently reported in the literature on negative schizotypy (e.g., Chen, Lam, Chen & Nguyen, 1996; Franke et al., 1993; Laurent et al., 2001; Tallent & Gooding, 1999), as well as in schizophrenic patients with predominantly negative symptoms (e.g., Berman, Viegner, Merson, Allan, Pappas & Green, 1997; Breier et al., 1990; Brazo et al., 2002; Suslow, Junghans, Weitzsch & Arolt, 1998). Nonetheless, findings on poor inhibitory control are more confusing, with some authors reporting an association with positive features of schizotypy (e.g., Suhr, 1997), and others (the majority) reporting negative results on the relationship between schizotypy and cognitive inhibition (e.g., Moritz et al., 1998; Peters et al., 1994; Spitznagel & Suhr, 2002). Studies with schizophrenic patients, however, report more consistently an association between impaired cognitive inhibition and positive symptoms (e.g., Frith, 1979; Williams, 1996; Peters et al., 2000; Brazo et al., 2002). Even so, some authors have postulated a relationship between negative schizotypy and inhibitory control, but only when the former coexists with positive features (Williams & Beech, 1997). In this regard, we must remember that such association was present only at a slight trend level in our sample, so it might be misleading. Negative schizotypy also correlated with clearly poor spatial working memory performance, especially right accuracy. A recent study by Wood et al. (2003) also found an association between spatial working memory and negative psychotic features in a sample of ultra-high-risk subjects. The association between negative schizotypy and spatial working memory has been also reported by other authors (e.g., Gooding & Tallent, 2003; Lemos, Inda, López, Paino & Besteiro, 1999; Wood et al., 2003). This schizotypal factor also correlated with poor verbal recall and, to a lesser degree, poor long-term recall. As to its apparently inconsistent association with a lesser number of intrusions in the verbal memory task, we believe this fact might be explained by the association of this factor with a lesser spontaneity in word production. The relationship between negative schizotypy and verbal memory impairments has been reported by several authors. On the other hand, despite the several studies that observe an association between negative schizotypy and sustained attention deficit (e.g., Chen, Hsiao & Lin, 1997; Chen, Liu, Chang, Lien, Chang & Hwu, 1998; Obiols et al., 1993), we did not detect this association in our sample. In fact, only disorganized schizotypy correlated with deficits in sustained attention performance in our sample. Given the significant correlation between negative and disorganized schizotypal features in our

35 Defined by the authors as those at high risk of early transition to first-episode psychosis (see McGorry, Phillips & Yung, 2001).
sample and the lack of studies addressing specifically the association of disorganized schizotypy with sustained attention, we might hypothesize that the relationship reported by other authors between negative schizotypy and sustained attention may have been yielded by the covariation of negative schizotypy with disorganized features, and not by the negative component per se. This lack of association between negative schizotypy and CPT performance has been also reported in high-(genetic)risk subjects (e.g., Franke, Maier, Hardt, Hain & Cornblatt, 1994).

2.3.4 Impulsive nonconformity

Impulsive Nonconformity correlated with a moderately good neuropsychological performance, as evidenced by good cognitive inhibiton, good verbal learning (both at a trend level) and, especially, good right spatial working memory. In this case, given the absence of instruments, apart from the O-LIFE, addressed to measure this factor seen as a schizotypal dimension, almost no reports on the association of Impulsive Nonconformity with neuropsychological performance have been found. Our findings suggest that Impulsive Nonconformity would not be associated with neuropsychological impairment, but rather it would confer a superior neuropsychological capacity. Nonetheless, we believe that this result may be present in subjects with normal scores on this factor, as no maximum scores were observed in our sample (most subjects ranged between 3 and 9 points, out of a maximum of 23 points). Therefore, it might be that these traits are adaptive when they appear at normal levels in the general population. In fact, Mason et al. (1995) consider that these personality traits may reflect a non-conforming and free-living lifestyle typical of young people, rather than a personality disturbance. As to the effect of extreme scores on neurocognitive functioning, we should expect some degree of impairment considering the literature on impulsivity and neuropsychological functioning, but no data on this respect was available in our results.

2.3.5 General conclusion and comments

To sum-up, our hypothesis that schizotypy, especially the negative factor, would be related to neuropsychological impairment was supported by our data. Specifically, negative and disorganized schizotypal dimensions were associated to clear neuropsychological impairment, while positive schizotypy showed an inconsistent pattern of neuropsychological execution, with some good-performance tasks and some other bad-performance tasks. Impulsive nonconformity, however, correlated with better neuropsychological functioning.

Cohort effects were relevant on the disorganized dimension, as reversed patterns of association to verbal memory appeared according to this variable. However, considering the non-specific association of disorganized schizotypy with all the rest of schizotypic factors and so its possible lack of own validity (at least in our sample), these results might not be related to schizotypy per se. As we mentioned before, neurotic traits may account for a relevant part of the results yielded by this factor (Claridge, 1994) and several factorial analyses of schizotypy questionnaires fail to validate this dimension (e.g., Kelley & Coursey, 1992; Martinez, Ferrando, Lemos, Inda, Paine & López, 1999; Rawlings & MacFarlane, 1994; see Vollema & Van den Bosch, 1995, for a review on this issue). Moreover, prospective studies of schizotypy measures as vulnerability markers for schizophrenia report
positive results only for positive and negative dimensions (e.g., Chapman et al., 1994; Kwapił, 1998). In this regard, disorganized schizotypy would have acted as a proxy risk factor (Kraemer et al., 2001) in our sample. This suggests that such dimension maybe does not represent a specific schizotypal factor, but rather it would be unspecifically covarying with the rest of schizotypic factors. In contrast, negative schizotypy was the most specific and independent factor, as it correlated only with disorganized schizotypy, while the other two factors (positive schizotypy and impulsive nonconformity) correlated both between them and with disorganized schizotypy. These net of relationships, therefore, might have been influencing the pattern of neuropsychological performance identified for each factor, but this point could not be tested from a correlational model as the one we used.

On the other hand, the spatial working memory test was the most consistent indicator of cognitive impairment across the different dimensions of schizotypy. This consistency in yielding results was also noticeable in other analyses reported in previous points (clear spatial working memory impairment was present in the Index cohort and in the worst-performers cluster), so we may conclude that this test seems to be very sensitive for detecting cognitive impairment in the general population. Actually, spatial working memory deficits in subjects at risk (genetic and non-genetic) for schizophrenia has been consistently reported in the literature (e.g., Gooding & Tallent, 2003; Park et al., 1995; Park & McTigue, 1997; Wood et al., 2003). Given the close association of this ability to executive functioning (Keefe, 2000), we speculate that spatial working memory might be one of the first and most sensitive indicators of executive dysfunction in vulnerable subjects.

Altogether, the associations between schizotypic dimensions and cognitive performance that we observed in our sample, especially the association of negative schizotypy with neurocognitive impairment, bear a resemblance to those found in schizophrenic subjects. Then again our results give support to the idea that personality traits and clinical symptoms are extremes of the same continuum, ranging from the normal personality till the disease level (fully-dimensional models) (e.g., Claridge, 1994; Claridge & Beech, 1995; Van Os et al., 2000).

### 2.4 Methodological flaws and advantages of the study

The characteristics of our sample (adolescents from the general population), and the type of design (prospective follow-up with three phases) generated a high level of attrition, mainly in the second phase of the study. This fact yielded a small final sample size that has given rise to low variability in some indices, abnormal distributions of many variables, possible loss of positive cases for schizophrenia spectrum disorders, etc.

It remains to be assessed the specificity of the sustained attention deficit as a vulnerability marker for schizophrenia spectrum disorders. Their association with affective features, both in our study as in the literature, make us doubt on their specific association with schizophrenic outcomes. We could not test this point because of a lack of positive cases for psychotic disorders and a sample size long enough to perform that kind of statistical analyses.

Given our interest in psychopathological continuity, stratification of our analyses for gender would have surely yield very interesting tints on the results and might have helped us to corroborate gender
differences observed in schizophrenia in our sample. However, the small sample size prevented us from segregating even more our groups on behalf of increasing the statistical power of our results.

A psychometric measure of anxiety and depression might have been more useful to adjust our results than the SCID-II measure of Cluster C symptoms that we employed. In this regard, given that anxious/depressive traits were not the objective of our project, we preferred to take advantage of a measure that was going to be administered anyhow instead of adding even more psychometric tests to the already too long assessment.

The assessment of NSS was too short and, probably, incomplete. This might explain why we failed to find a higher number of NSS in the “developmental” cluster, although we did observe a trend in Index subjects. However, as in the previous case, the long duration of the assessment and the fact that these signs were not the main objective of our study, precluded us from employing a more exhaustive battery of soft signs.

Information from parents, specifically that of PBCs and the PSAS, might be influenced by the retrospective bias traditionally associated to follow-back studies. Our study took a prospective longitudinal design (opposed to retrospective/follow-back studies) in order to avoid these biases, but this kind of information, especially PBCs, was otherwise very difficult to achieve. Even so, the retrospective bias is usually present in studies that start from clinically affected subjects, as their relatives are more prone to report and remember specifically negative characteristics in these subjects during their infancy or adolescence due to their necessity of finding a cause for the current state of their relative. However, our patients were not clinically affected, so this “necessity” had no reason to exist in most cases.

As to the correlational/cross-sectional study, stratification for gender would have been again necessary, as well as adjustment for several variables that may have influenced the relationship between schizotypy and neurocognitive performance. However, these adjustments were not possible because of sample size matters.

As comprehensive models of psychopathology (e.g. Crow, 1980; Andreasen and Olsen, 1982; Liddle, 1987; Venables, 1995) that try to relate schizophrenic symptoms with cognitive anomalies, we also tried to relate personality (schizotypic) traits with neurocognitive impairments. The inconvenience of this type of approaches is that they do not address aetiological issues (Sarfati and Hardy-Baylé, 2002). That is why we give a main role for the results obtained in the prospective analysis.

If we consider the background of high-risk research in schizophrenia, the general impression is that the identification of vulnerable subjects in the general population will be more accurate if we look for a pattern of vulnerability traits, instead of a single marker (e.g. Claridge, 1994; Michie et al., 2000). In this study we only used the sustained attention deficit as the criterion for selecting the cohorts from the general population, but future research of this kind should employ more than one risk marker in order to improve accuracy and specificity of early detection. To that effect, Kraemer et al. (2001) claim for the aggregation of risk factors in order to gain clearer understanding of what causal processes might be involved in the genesis of a given psychiatric disorder.
Nevertheless, not all were methodological limitations on the present project, as can be seen in the following table:

**Table 5.7 Advantages of the study**

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<th>Advantage</th>
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<td>Long follow-up period (10 years)</td>
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<td>Three assessments at different moments of the adolescent stage till early adulthood</td>
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<td>Use of subjects from the general population (free of biases associated to the use of clinical samples)</td>
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<tr>
<td>Multidimensional and comprehensive assessment</td>
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### 2.5 General discussion

From a prospective longitudinal approach, we found signs of vulnerability in subjects from the general population with an endophenotypically-defined risk for schizophrenia spectrum disorders. This vulnerability was manifested in a broad range of impairments at several levels of functioning (neurocognition, neurointegrative, personality, psychosocial and clinical areas). However, we failed to find positive cases for psychotic disorders or frank Cluster A personality disorders, nor even a significantly higher number of Cluster A personality traits in Index subjects. Nevertheless, we found a statistically non-significant higher number of paranoid, schizotypal and schizoid symptoms and significantly higher levels of negative schizotypy in this group.

From a developmental approach, we detected three groups of subjects differing on their profile of sustained attention development. One of these groups might reflect the neurodevelopmental subtype of vulnerability to schizophrenia spectrum disorders, as evidenced by their visible neurocognitive impairment, neurointegrative abnormalities and possibly neurodevelopmental damage, and a range of psychosocial and clinical correlates supporting this notion. However, the absence of differences in gender distribution in this group leads us to consider this possibility at a speculative level.

The similarity of profiles between the Index cohort and the worst-performers (neurodevelopmental subtype?) cluster was not absolute. Thus, the Index cohort showed a broader range of impairments and so a more unspecific vulnerability to psychopathology maybe because it included those subjects with a stable sustained attention deficit and those with a delay in their (cognitive) attentional development that eventually achieved a normal level of performance. However, the worst-performers cluster presented a more specific profile of impairments, maybe more related to vulnerability to schizophrenia spectrum disorders in particular, as it only included those subjects with a stable sustained attention deficit.

The difference between the other two clusters seemed to be related to gender differences and to the possible intervention of other risk mechanisms differing from that found on the neurodevelopmental subtype (worst-performers cluster). Thus, the “developmentally-delayed” cluster, which showed a profile of impairment much less severe than that of the “worst-performers” group and a higher presence of females, might reflect higher vulnerability to affective disorders.

The cross-sectional assessment of the relationship between psychometric schizotypy and neuropsychological performance also revealed different profiles of impairment according to the
schizotypal dimension, suggesting that the negative factor would be the most valid and clearly associated to neurocognitive impairment. In this respect, other authors also report a more consistent association between this factor and neurocognitive measures (Lemos et al., 1999), find it more frequently in first-degree relatives of schizophrenic patients (e.g., Clementz, Grove, Katsanis & Iacono, 1991), and give support to its taxometric validity in normal-population samples (Blanchard, Gangestad, Brown & Horan, 2000; Kelley & Coursey, 1992). The disorganized factor might reflect a mixture of non-specific, maybe neurotic, traits that correlated with all the schizotypic dimensions and, therefore, might not be a valid measure of this schizotypal factor in our sample. Positive schizotypy displayed an inconsistent profile of neuropsychological performance that makes difficult to determine it status as a vulnerability marker and, finally, impulsive nonconformity was associated to good neurocognitive performance. From all these data, we conclude that negative schizotypy would be the most valid candidate to be considered a vulnerability marker for schizophrenia spectrum disorders.

All in all, the neurocognitive impairments and clinical/emotional disturbances detected both in the Index cohort and in the neurodevelopmental (worst-performers) cluster (mainly affecting spatial performance) might involve a right brain hemisphere affection. In addition, spatial working memory and WCST impairments (both dealing with spatial (non-verbal) concepts) were the clearest neurocognitive correlates of negative schizotypy. Higher right hemisphere impairment for visuospatial functions in schizotypy has been already postulated by several authors (Goodarzi, Wykes & Hemsley, 2000; Jutai, 1989; Richardson & Stein, 1993; Stein, Riddell & Fowler, 1989).

On the other hand, the confirmation of the neurodevelopmental origin of our worst-performers cluster would point to the sustained attention deficit as an endophenotypical expression of a neurodevelopmental damage and, therefore, to their consideration as a good indicator of vulnerability to (possibly) schizophrenia. Furthermore, the absence of an attentional impairment on the developmentally-delayed cluster despite its profile of impairment on other neurocognitive and personality areas, gives still more support to the validity of this endophenotype as a likely risk marker for schizophrenia spectrum disorders in particular. Incidentally, other profiles of vulnerability to different psychiatric disorders might exist in the general population according to our data. Thus, the developmentally-delayed group might reflect a vulnerability more specific to affective disorders and highly mediated by female gender.

Likewise, the neurodevelopmental subtype of schizophrenia reported in the literature (Goodman, 1991; Murray et al., 1992; Rosanoff et al., 1934) has been characterized by an early-onset. Our data failed to replicate this finding because no psychotic cases have been identified yet. However, the most severe profile of impairments described in the neurodevelopmental subtype of schizophrenia might include an insidious onset, rather than an acute breakdown. As a result, the worst-performers cluster in our sample might be displaying the first insidious signs of an eventual psychotic disorder (ultra-high-risk subjects?). Evidently, this reasoning is speculative but by no means should be dismissed.

By the way, the exposure to a certain factor at times may not manifest as a change until sometime later, i.e. there can be time “lags” between environmental exposure / gene expression and changes in the measured phenotype. This fact leads us to think of a “threshold” that must be exceeded so that observable changes in the phenotype can appear (Pogue-Geile, 1997). From this point of view, the
worst-performers cluster might have accumulated the highest amount of risk factors in relation to the other two clusters identified, but such amount would not be sufficient yet to reach the threshold of the disease onset.

In any case, the whole information yielded by our results gives support both to the concept of continuity between personality dimensions and clinical psychotic symptoms (dimensional models), and to the concept of “unitary” psychosis (because of the high covariation among affective and “schizophrenia spectrum” features in our sample). Additionally, support is given to the concept of *schizotaxia*.

Taking together our results, a developmental approach to early detection of vulnerability to psychopathology, in particular to schizophrenia spectrum disorders, seems to be more useful and specific than a cross-sectional (static) point of view. That is because developmental aspects may be influencing performance in different ways at different times (heterotypic continuity), so the neglect of these aspects when establishing the cohorts might give rise to several false negatives or false positives for the risk marker in question. Unfortunately, the developmental approach is much more difficult and complex to implement than the cross-sectional.

As far as we know, this is the first non-genetic high-risk study that employs the sustained attention deficit as the criterion for selecting high-risk subjects. We believe that our results are very promising, and advocate for the need of further research to support them.

### 3. Practical Implications of Our Research

Longitudinal prospective high-risk studies are highly costly and difficult to perform. However, considering the devastating effects of this disease, both in the individual and his/her family, this is a necessary effort in order to establish intervention programs at a primary prevention level. This possibility, science-fiction not so long ago, is currently being carried out in the USA (*Hillside Recognition and Prevention (RAP) Program*; Cornblatt, 2002) with highly promising results. Nevertheless, we are still far from such level given that no specific endo- or exophenotypes have been detected yet in relation to schizophrenia. Anyway, the acknowledgement that certain variables may act as risk or vulnerability markers for future illness (whatever it is) should be taken into account in order to establish preventive programs addressed to those individual deficits that predispose to the forthcoming emergence of psychopathology. From a psychological point of view, and on behalf of ethical standards, that kind of intervention should primarily address psychosocial aspects (cognitive and social skills training, psychoeducation, family intervention, etc.) and use pharmacological interventions only for those cases clearly prodromic. In this context, and in spite of Cornblatt’s “efforts”, secondary prevention seems to be the most plausible and nearest alternative to date.

Likewise, in the context of high-risk research, our group is currently carrying out a new project with a double-goal of early detection and prevention of psychotic disorders. This study, alike that introduced in this project, is also focused on adolescents from the general population, but has tried to overcome methodological deficiencies of the present project by means of a newer and improved methodology of cohort selection. Unlike the present project and parallel to the early detection goal, this new study has
set up a psychoeducational program addressed to adolescents, parents and teachers. Considering the total absence of prevention programs for schizophrenia in our country, this second goal, though modest, is a first step to primary prevention in psychosis.
CONCLUSIONS

1) As was hypothesized, Index subjects (those with a sustained attention deficit detected at early adolescence) showed a pattern of deficits at 10-year follow-up characterized by:

- Poor attentional abilities, executive dysfunction, verbal memory abnormalities and spatial working memory deficits.
- The pattern of neurocognitive impairment detected affected especially those tests managing spatial concepts (spatial attention, WCST, spatial working memory).
- Poor neurointegrative performance, as evidenced by poor psychomotor performance, more NSS and more mixed-handedness.
- High levels of negative schizotypy.
- High levels of neurotic and immature personality traits.
- No psychotic disorders or higher prevalence of other axis I psychiatric disorders.
- No Cluster A personality disorders or higher presence of these traits.
- Poor coping abilities, as evidenced by higher use of escaping and denial strategies at the expense of behavioural and active coping strategies.
- Poor social behaviour, as evidenced by more withdrawal, more social anxiety and shyness, less respect and self-control and less social ascendance (both unsocial and antisocial).
- More life events, both positive and negative, according to the subjective point of view of the subject.
- Poor previous social adjustment, more apathy, and poor scholastic performance both in childhood and adolescence, as well as during the previous year.
- More clinical signs of emotional disturbance.

2) We identified three groups with different patterns of sustained attention development across adolescence. In agreement with our hypothesis, one of these groups might reflect the neurodevelopmental subtype described in the literature.
3) The group of best-performers appeared to show an asymptotic non-linear developmental function of sustained attention from early adolescence till early adulthood. This group was characterized by:

- Good functioning/performance in all the areas assessed.
- Noticeable incidence of mixed-handedness (lower than in the worst-performers/neurodevelopmental group, however).
- Male predominance.

4) Another group appeared to show a delay in their sustained attention development, displaying a progressive linear increase of their attentional scores from early adolescence till early adulthood and achieving finally the level of the best-performers group. This group was characterized by:

- Slight executive and spatial working memory abnormalities, affecting only some few indices (perseverations and failures to maintain the set, and overall accuracy, respectively).
- Low incidence of mixed-handedness but a trend to low birth weight.
- Female predominance.
- Cluster B personality traits.

5) The “neurodevelopmental” (worst-performers) cluster showed a non-linear mean developmental function of their sustained attention scores, alike the best-performers cluster, but showed a stable sustained attention deficit through adolescence. This group was characterized by:

- 100% Index cohort composition.
- No gender differences.
- Poor neurocognitive performance, as evidenced by poor sustained attention, poor executive functions, poor spatial working memory. Again the most impaired tests were those managing spatial concepts.
- Poor neurointegrative performance, as evidenced by poor psychomotor performance and more mixed-handedness, and possible neurodevelopmental damage, as suggested by lower birth weight.
- More avoidant personality traits.
- More negative and disorganized schizotypy.
- Poor coping strategies, as evidenced by a predominant use of cognitive escape.
- Poor social behaviour, as evidenced by more withdrawal and social anxiety / shyness and less social ascendance (more unsocial).
Poor previous social adjustment, as evidenced by sociability difficulties and isolation, and poor level of interests, both in childhood and adolescence, as well as during the previous year.

More clinical signs of emotional disturbance.

6) The profiles of impairment of the Index cohort and the “neurodevelopmental” (worst-performers) cluster were similar but more accurate in the latter, as the cluster analysis seemed to have filtered only those subjects with a stable sustained attention deficit.

7) Our “neurodevelopmental” cluster might reflect a vulnerability more specific to schizophrenia spectrum disorders, while the developmentally-delayed group might represent a vulnerability more specific to affective disorders.

8) Mixed-handedness played an uncertain role in our results due to its high incidence in the “best-performers” cluster.

9) The spatial working memory test was the most sensitive for detecting neurocognitive impairment, probably reflecting some degree of executive dysfunction.

10) Attrition might have yielded the loss of positive cases for psychotic disorders.

11) The pattern of deficits detected in Index subjects and especially in the “neurodevelopmental” cluster might reflect the concept of schizotaxia.

12) The attentional deficit appears to be a non-specific marker of vulnerability to psychopathology that, in conjunction with other risk factors, may determine a higher vulnerability either to schizophrenic or to affective outcomes.

13) A developmental approach to early detection of psychiatric illnesses, in particular schizophrenia spectrum disorders, may be more useful and specific than a cross-sectional selection of cohorts but, all at once, much more complex to implement.

14) Negative schizotypy seemed to be the most valid indicator of psychometric vulnerability to psychopathology (probably to schizophrenia spectrum disorders), as evidenced by their clearer association to neurocognitive (mainly executive) impairments such as:

- Executive dysfunction: poor concept formation, lack of cognitive flexibility, poor inhibitory control, poor semantic and phonetic verbal fluency.

- Slight signs of poor verbal memory.

- Poor (especially right) spatial working memory.

15) Disorganized schizotypy was non-specifically associated to all the rest of schizotypal factors, as well as to neurotic features, so it might not reflect a valid measure of such concept in our sample. It also showed a profile of neurocognitive impairment mainly affecting attention and executive functions,
but we should put into question these associations given their mentioned lack of independent entity.

16) An effect of interaction between disorganized schizotypy and cohort in their relationship to verbal memory was evident such that Index subjects showed better short- and long-term verbal memory than discriminability, while Control subjects showed better discriminability than short- and long-term verbal memory.

17) Positive schizotypy showed an inconsistent pattern of associations with neurocognitive performance, as evidenced by its correlations with good verbal memory and good inhibitory control (both at a trend level), and parallel with inattentiveness, impulsive style of response and, to a lesser degree, with poor left spatial working memory.

18) Impulsive nonconformity showed an overall pattern of good neurocognitive performance and a trend to display a more impulsive style of response.

19) Altogether, our results give support to continuum/dimensional models of psychopathology, on the one hand, and to the concept of “unitary” psychosis, on the other.

36 This impairment might be considered a sign of executive dysfunction


