PSYCHOTIC LIKE EXPERIENCES AND 22q11 MICRODELETION SYNDROME: TWO POSSIBLE MODELS FOR THE INVESTIGATION OF GENE-ENVIROMENT INTERACTION IN PSYCHOTIC ONSET

BY

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A “euro-label” joint doctoral thesis submitted to The University of Birmingham and to The Sapienza University of Rome

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October 2012

ABSTRACT (in english)

Psychotic disorders can be defined as disorders of adaptation to social context (van Os, 2010). Although heritability is often emphasized (Insel, 2011), onset must be considered as the end-point of a pathway which involves: 1) genetic heritability; 2) environmental factors (i.e. early life adversity, growing up in an urban environment, minority group position, and cannabis use) (van Os, 2010); 3) psychopathological factors (i.e. psychotic-like experiences, affective dysregulation) (Birchwood et al. 2009; Smeets et al. 2010; van Os et al. 2009).

Therefore, the current challenge consists in combining different scientific fields aiming at a deeper comprehension of psychotic disorders caused, precisely, by gene/enviroment interaction (van Os, 2009).

Taking off these considerations, this thesis will present research conducted in Rome (i.e. Children Hospital Bambino Gesù and Sapienza University of Rome) and in Birmingham (Department of Psychology, University of Birmingham) by the Author during his PhD. These research is focused on two possible models which can help to better understand the role played by gene/enviroment interaction in the pathogenesis of psychotic disorders.

The first model, related to what we previously called psychopathologcal factors, concerns the so-called psychotic-like experiences and is therefore situated in the sphere of the psychopathological factors involved in the pathway to psychosis. The second model, related to what we previously called genetic heritability, concerns a genetic syndrome with the highest known prevalence of psychotic disorders (i.e. 22q11 microdeletion syndrome) and therefore belongs to the area of genetic heritability factors.

The thesis starts with a comprehensive review of these topics. Subsequently, the main findings of the research conducted during the PhD will be described and analyzed.
Implications are explored, in terms of clinical practice, aetiological pathways, potential treatments and intervention strategies.

ABSTRACT (in italian)

I disturbi psicotici nel loro insieme sono stati recentemente definiti come “disturbi di adattamento rispetto al contesto sociale” (van Os, 2010). Pertanto, sebbene l’aspetto della predisposizione genetica venga sempre più preso in considerazione (Insel, 2011), l’esordio psicotico deve essere inquadrato come il punto di arrivo di un percorso che, partendo da una suscettibilità genetica, è poi determinato da diversi “fattori ambientali” (traumi infantili, urbanizzazione, uso di cannabis, etc.) (van Os, 2010) e “clinici” come ad esempio la presenza nel corso del tempo di sintomi psicotici sottosoglia (psychotic-like experiences, PLEs) (van Os et al, 2009) e di quella che è stata definita “affective dysregulation” (Birchwood et al, 2009; Smeets et al, 2010).
La sfida attuale relativa al tentativo di comprendere la patogenesi di questi disturbi è quindi oggi rappresentata dalla necessità di mettere insieme le diverse discipline necessarie ad analizzare questo modello di malattia determinato appunto dall’interazione gene - ambiente (van Os, 2009).
Partendo da queste osservazioni, nella presente tesi di dottorato verranno esposti i risultati delle ricerche da me condotte presso l’ IRCCS Bambino Gesù di Roma, l’ università “Sapienza” di Roma e l’ università di Birmingham nel corso del dottorato, su due possibili

modelli utili per la comprensione dell'interazione gene/ambiente nella patogenesi dei disturbi psicotici. Il primo riguarda le PLEs ed appartiene pertanto al gruppo dei fattori "clinici" che influenzano il percorso verso la psicosi, il secondo diversamente riguarda la sindrome da microdelezione del q22 ed attiene pertanto al gruppo dei fattori di suscettibilità genetica.

La tesi inizia con un'approfondita review sugli argomenti trattati, Successivamente vengono presentati i principali risultati delle ricerche condotte dall' Autore durante il suo dottorato.

DEDICATION

To all the people I met during these years, to those who are still alongside of me, and to those who have followed others routes.

AKNOWLEDGEMENTS

I would like to acknowledge the exceptional guidance and support that Professor Max Birchwood has given me throughout all the research conducted during the PhD as well as his mentoring about the British lifestyle during my “Birmingham experience”.

AND Barnaby, Ashleigh and all the colleagues with whom I had the pleasure to work and to share life-experiences during my PhD.

AND Professor Paolo Fiori Nastro and Professor Paolo Girardi without whom this PhD would not exist.

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Chapter 1

Pathway to psychosis: the role of Psychotic Like Experiences

1.1 From prodrome to at risk mental state

In medicine, the prodrome is not a very useful indicator as it delivers an allusive, unclear message that is open to many interpretations. In general medicine, the disease develop when the elements that constitute the initial phase of the illness are present. Therefore the prodrome is the beginning of a disease.

Once a disease has manifested itself, it is possible to retrospectively identify those signs and symptoms, which had first appeared. However, it appears more difficult to do the contrary, that is to deduce what kind of disease will evolve from the initial symptoms. From this point of view, it seems incorrect to talk about prodromes as they are very unspecific, common to different clinical pictures, and therefore not useful to make a diagnosis. They are surely the prodromes of something, but of what?

It is almost impossible to answer this question when they first appear. In general medicine, the initial symptoms can be further explored through laboratory analyses, X-rays and other instruments that, in a high percentage of cases, help us to make a diagnosis. In psychiatry, the question seems more problematic: firstly, we do not have investigative instruments at hand, like neuroimaging or laboratory analyses, that allow us to resolve our diagnostic doubts. Moreover, the nature of mental illnesses proves to be more plastic compared to other diseases and thus the initial picture could constitute a vulnerability that must

encounter other risk factors to evolve into a frank psychosis. The dilemma of whether the initial symptoms are real and proper prodromes or a group of symptoms that characterize a "at risk population" may lie in two key elements: the diagnostic difficulty in respect to the early phases and the dynamism of mental illnesses.

The prodromes of a mental illness, in particular psychosis, emerged in all their importance and lack of specificity, too, with Kraepelin (Kraepelin 1896). Throughout the twentieth century, efforts were made towards an understanding of the precursors of psychosis both in terms of evolution and symptomatology.

The question of prodromal symptoms of psychosis already raised by Bleuler continues to be a subject of psychiatric importance even today: on one hand, emerges the importance to identify the initial signs and symptoms of the disease in order to start a treatment as soon as possible and to improve the course of such a serious illness significantly. On the other hand, the early symptoms clearly show all their lack of specificity and their difficult use as a predictive tool. Bleuler and most psychopathologists of the 20th century agreed that in the prodromal period the main symptoms of the disorder are present in their early phases. Before the out-break of the "productive" symptomatology that does not constitute the essence of schizophrenia but only the epiphenomenon, there would be the development of the core of the disease. The prodromal period would, therefore, be the time when the disease develops in its most essential components. In this respect, Bleuler thought that the initial symptoms were the beginning of the disease, but considered such symptoms not useful for an early diagnosis given their extreme variability. However, if the early symptoms were prodromes, since they are the beginning of the illness itself, from the point of view of an early diagnosis, these symptoms would not constitute reliable predictors at

all, because they were absolutely not specific and with a poor capacity to specifically predict the development of a frank psychosis.

"When speaking about initial symptoms of schizophrenia, we need to limit ourselves to those which have struck us; almost always we miss the manifestations that in reality appeared first (We aren't talking about prodromes. At the very most, it is possible to distinguish the prodromes of an acute attack and the manifestations themselves of the attack. The prodromes of an illness are inconceivable for me. This name usually describes the first symptoms that cannot be correctly interpreted yet). For all we know, all symptoms can open a clinical picture." (Bleuler, 1911)

It has only been in the last few years that researchers have been tried to identify subjects "at risk" and to intervene early in psychotic disorders (Birchwood et al., 1997).

Indeed, the poor predictability of prodromal symptoms has imposed a technique, which aims to refine diagnostic capacities and is already widely used in general medicine: the so-called "close-in" strategy (Bell 1992) that consists of identifying the co-presence of many prodromal symptoms, a state–trait model that permits us to better identify risk cases with a subsequent reduction of false positives. This type of evaluation method, first theorized and applied in Australia and UK (Phillips et al. 2000; Birchwood et al. 1997; Yung et al.1998), has also been utilized by many other research groups (Häfner et al. 2004; Miller et al. 2002, 2003a; Morrison et al. 2004) in order to be able to offer a quick and specific response to the first signs or symptoms of disease and to delay or decrease the severity of the psychotic disease, which is anticipated as the consequences and biological, psychological and socio-relational damage that ensue (Cocchi and Meneghelli, 2002; Schultze-Lutter 2004). The problem of early symptoms of psychosis is also very important

because most young people who need help do not turn spontaneously to a specialist service (Armando et al. 2009).

1.2 The close-in strategy and the ultra high-risk model

As we anticipated in previosu Paragraph, a major challenge has been to prospectively identify the prodromal phases, particularly given the non-specific nature of prodromal symptoms. Over the last decade, valid and reliable criteria have been introduced for the prospective identification of individuals at heightened risk of developing a first episode of psychosis (FEP) within a brief time period that is, as possibly being in the prodromal phase of illness.

The most commonly used method to identify help-seeking individuals in the putatively prodromal phase of psychotic disorders has been the ―ultra high risk (UHR) approach (Yung et al., 1996), which combines known trait and state risk factors for the onset of psychotic disorders, including attenuated positive psychotic symptoms, family history of psychotic disorders and functional decline, as well as brief self-limiting psychotic symptoms (Yung et al. 2003; Yung et al. 2004).

The first published study using the UHR criteria found a transition rate of 40% to threshold psychotic disorder within one year (Yung et al. 2003), despite the provision of needs-based psychosocial intervention and antidepressant treatment where indicated. This finding has subsequently been replicated by several groups internationally. Using a combination of various studies, Ruhrmann et al (2010) report an average one-year transition rate of 36.7% in UHR subjects who did not receive antipsychotic treatment.

The most recent meta-analysis on this topic (Fusar-Poli et al. 2012) report an average one-year transition rate of about 20%.

A complementary early detection strategy drawing on a different clinical tradition and symptomatology was developed in Germany (the "basic symptoms" approach). This approach found that "basic symptoms" (see Paragraph 1.3.2 for more details), which refer to subtle, self-experienced disturbances in a range of domains, accurately predicted onset of schizophrenia over a long time frame (longterm (8-12 year) transition rate of 65% and 79%, respectively, depending on the basic symptom criterion applied) within a help-seeking clinical sample from possibly earlier in the course of the illness than the UHR criteria (Klosterkotter et al. 2001). This led to a distinction between a late and early initial prodromal state (LIPS and EIPS, respectively) in the German Research Network on Schizophrenia, (Hafner et al. 2004). Further examination of the accuracy of predicting onset of psychosis within 12 months after index-assessment revealed that presenting with at least two out of nine symptoms of the "cognitive disturbances" cluster (COGDIS) resulted in a transition rate to psychosis of 23.9% within 12 months, an additional 22.4% within the second year and a further 14.9% within the third year. Thus the 12-month transition rate of the"cognitive disturbances" cluster of basic symptoms was comparable with individuals at-risk with attenuated positive symptoms (APS) from the UHR criteria (e.g., 12-month transition rate of 26.5% for APS alone (Lencz et al. 2003)).

1.3 Development of the concept of Psychotic Like Experiences

1.3.1 Definition of the concept

The prospect of a progressive improvement in the diagnostic and therapeutic capacities through the identification of early signs and symptoms is supported by a "dynamic" model of the disease itself. In this context, the psychotic disorder develops starting from a certain

vulnerability as its base along a path made up of a number of stages, in which, as a response to environmental stimuli, an improvement or worsening of the situation occurs. Passing from one stage to the next in the evolution of the clinical picture constitutes a journey through steps and plateaus, in which the difference between the single stages is exclusively quantitative. The dichotomic vision of the psychotic symptoms, evaluated as absent or present by the categorical model based on a neo Kraepelian and Jaspersian typology, is considered too rigid and incapable of responding to the fluid nature of the psychotic disorder. According to this dimensional model, there is a continuum from the starting point to the arrival point of frank psychosis whereby the disease can be staged and the different phases of an illness can be identified, thus enabling to focused interventions. The most correct definition of the proposed model is, in fact, “almost-dimensional”, in a way that continuity always is.

Is mainly for this reason that the concept of Psychotic-Like Experiences (PLEs) has been introduced. Indeed PLEs are a phenomena more easly applicable to the “almost-dimensional” model. At the same time since are present both in general and clinical population, PLEs can be investigated in terms of types, intensity and frequency, to better understand possible pathways from general population to psychotic population.

According to this and taking a step back in the trajectory that leads from healthy functioning to psychosis, many studies indicate that positive psychotic symptoms exist on a continuum, with schizophrenia at one end and non-clinical psychotic symptoms or PLEs at the other (Kendler et al.,1996; Van Os et al., 2001; Dhossche et al., 2002; Johns et al., 2004).

1.3.2 Historical background and development of the concept

In 1966, in his article entitled *The early symptoms of schizophrenia,* James Chapman reported the results of a study of changes in mental functioning subjectively perceived by 40 young schizophrenics. What emerged was that most of these phenomena would have been subjectively experienced by the patients long before the appearance of the signs of a frank disease.

The study attempted to find early signs and symptoms of schizophrenia in order to carry out the diagnosis. The prospect, however weak, shifts from a simple description of the early symptoms to the research of the reliability of such symptoms from a diagnostic point of view. Before Chapman, Gillies (1958) had proposed incomplete manifestations of the illness as identification criteria of the early forms of schizophrenia. Gillies, like his predecessors, focused on Bleuler's fundamental symptoms, on thinking, affective and volition disorders and on autistic withdrawal. He considered them to be pathognomic symptoms, but he noticed that they could fail to manifest themselves in an obvious fashion for a long time. The idea of the author was to study medical records retrospectively in relation to the first subjective malaise experienced by the schizophrenic patients and to systematize these non-specific symptoms according to their derivation from the fundamental symptoms. The initial changes included hazy thoughts, somatic preoccupations, lack of interests and a wide range of neurotic symptoms.

The research, however unsystematic, appeared very lively and intense. Classical psychopathology studies, which highlighted precursors of the real and proper onset of the illness, went along the road of a difficult as well as promising operation. Reducing the conceptual level of the search to indicators that would permit a real and concrete intervention in terms of both a diagnosis and a therapy made it possible, perhaps for the

first time, to think of a psychiatrist as a modifier of the course of psychosis. Furthermore, the idea of an developmental model of mental pathologies, which prevailed in the 20th century, was conceptualized and defined in the 60s as a continuum of the psychotic disease. The existence of a progressive and dynamic development starting from a vulnerability as a base to a frank disease was hypothesized (Meehl 1962; Strauss 1969). In this model of disease, the environmental aspect plays a crucial role, in that this situation of "proneness" to schizophrenia will evolve only in the presence of stressful stimuli. Meehl claims, in fact, that schizotaxic-schizotypal individuals (indicating with this term the fundamental vulnerability and the personality structure which it gives a first indication of this) develop a frank psychosis in low percentages. In Germany, in the 60s, Gerd Huber highlighted the existence of indefinite phenomena characterized by disturbing subjective sub-clinical sensations in the early phases of the illness. The "basic symptoms", as they were named, are cognitive, perceptual, affective, dynamic and social disturbances often recognized by the affected person years before the appearance of a frank psychosis (Huber et al. 1979; Huber 1983). Being subjective phenomena, the basic symptoms tend to remain private and are rarely noticed by others. Moreover, the individual tends to enact avoidance strategies and social withdrawal so as to hide such symptoms from others. As they are self-experiences the basic symptoms differ from Bleuler's negative symptoms, visible also to others, and from frank psychotic symptoms that the subject experiences as ego-syntonic. (Schultze-Lutter 2009). Through the transition sequences described by Klosterkötter, the basic symptoms increase in intensity to the point of transforming into Schneider's first rank symptoms: 1) delusional perceptions, 2) thought broadcasting, withdrawal and insertion 3) acoustic hallucinations, 4) delusion of control 5) somatic hallucinations (Klosterkötter 1992; Klosterkötter et al. 2008).

A change in perspective is noticeable in these model in that we pass from considering symptoms as discret and discontinued to considering them as points on a continuum function. There is a shift from the idea that there is something qualitatively different in the schizophrenic's thoughts, affects and reality to the idea that the difference is exclusively quantitative. This conception explains the intermediate degrees of psychopathological functioning of the disease, giving importance to borderline personality, to latent schizophrenias and also to the behaviour of the patient's family.

How do we include what is observed clinically into this theoretical framework, though? Are there any psychotic and non-psychotic symptoms at a prodromal level that are predictive of a subsequent psychotic development? And, even before that, are there any signs and symptoms of a more indefinite nature, which precede the prodromal phase and can act as a warning sign? What relationship exists between PLEs, attenuated sub-threshold psychotic symptoms, brief psychotic episodes, which end spontaneously, and, lastly, frank psychosis? Is it possible to construct a staging model that allows for diagnoses and phase-specific interventions?

1.3.3 Validity of the concept

At the end of the 70s, many scales were developed to investigate the possible evolution of risk factors of a frank psychosis.

With the "Wisconsin Manual for Assessing Psychotic-like experiences" (Chapman and Chapman 1980), they demonstrated the presence of PLEs in higher percentages and of a more serious nature in individuals at risk of developing psychosis compared to controls. (Chapman et al. 1984; Eckblad and Chapman 1986; Allen et al. 1987). From a longitudinal study of prodromal symptoms lasting 10 years, we can see a sensitivity and specificity of

these PLEs of at least moderate intensity of 64% and 82% respectively (90% and 69% for the group at risk of psychosis). In light of such results, the transitory nature of many PLEs emerged. In fact, the prevalence of PLEs fell from 43,5% at the first assessment to 26,4% at follow-up. This initial result had already suggested that not all PLEs had the same psychopathological value: only some ended up being indicative of developing a psychosis, while most individuals with PLEs did not develop a frank psychosis and at follow-up even showed a reduction or outright disappearance of the initial PLEs (Chapman et al. 1994).

In this, once again the central problem of an early diagnosis of psychosis shows that is built on the lack of specificity of the initial symptoms, in that it proves to be difficult to identify a specific core group among the PLEs of different psychopathological value.

The research of the predictive value of PLEs offered its first results simultaneously with the publication of an Australian study which suggested the term “at risk mental state” to define the psychopathological state prior to the development of a frank psychosis substituting the prodrome (McGorry and Singh 1995). We are dealing, in fact, with the state (and not a trait) of the individual that may and not necessarily develop psychosis.

The first research on the prevalence and effect of PLEs in the general population dates back to the 90s. The results of these studies confirmed the idea that the “prodromal” phase of psychosis is really a state of vulnerability and, therefore, a propensity towards psychosis of uncertain development. In fact, in the general population the percentage of PLEs have always occurred at high levels, failing to overlap with the data of prevalence and incidence of schizophrenia. In the United States, the life time prevalence of hallucinations amounts to 15% in women and 10% in men (Eaton et al. 1991), and, in another study carried out in Baltimore, around 10% of those interviewed presented paranoid symptoms (Tien 1991). Starting from these two works, surveys into the presence of PLEs in the general population

have been undertaken in great numbers. What emerged besides the high prevalence of PLEs, was also a significant discrepancy between the prevalence of PLEs at 28% and that of non-affective psychotic disorders at 0.7% (Kendler et al. 1996). Further studies confirmed the elevated percentage of PLEs in the general population that reached 25.2% as compared to 51.6% in psychotic patients (Peters et al. 1999) and 17.5% in the general population studied in Holland as compared to the lifetime prevalence of clinical psychotic symptoms and psychotic disorders of 4.2% and of 1.5% respectively (van Os et al. 2000). The incidence of PLEs in the general population that accounts for 2% was thus around 100 times higher than the incidence of schizophrenia (Hanssen et al. 2005). Further, the persistence of acute PLEs at two years accounted for 16.7% and the development into psychosis of 7.6%. This elevated transitory nature of such experiences (84.7%) appears to be a further confirmation of their aspecificity and their difficult utilization in a preventative key. Given that anxiety and depression are features common to the premorbid personality of schizophrenia (Davidson et al. 1999; Malmberg at al. 1998) or to prodromal symptoms (Häfner et al. 2005; Yung et al. 2007), some studies have highlighted how the interaction of PLEs with depressed mood and /or anxiety notably increases the risk of developing psychosis (Dhossche et al. 2002; Johns et al. 2004; Hanssen et al. 2005; Nishida et al. 2008).

In other studies a lifetime prevalence of PLEs was reported at 12.9% in respect to a lifetime prevalence of 4.2% of psychotic symptoms and 1.5% of psychotic disorders (van Os et al. 2000, 2001). The results of a recent meta-analysis carried out on 47 different international studies have confirmed the overall prevalence and incidence of psychotic phenomena at 5.3% and 3.1% respectively (van Os et al. 2009). This slight discrepancy between the two parameters and the data that has emerged from longitudinal studies

indicate that the nature of around 75-90% of such phenomena is substantially transitory. It is, however, true that in the presence of specific risk factors, such as genetic vulnerability, particular moments of development, stressful or traumatic life events, social adversities, use of psychoactive substances, an elevated level of urbanization or emigration from one's homeland, the same phenomena tend to persist in an anomalous way and to become more predictive of a series of mental diseases, in particular of those psychotic nature. The prevalence of PLEs, i.e. of subclinical psychotic symptoms associated to marked distress, help-seeking and to psychotic disorders, was estimated at around 8%, 4% and 3%: this data, however, was extrapolated from the minority of studies that had utilized tools capable of correctly distinguishing the different specific psychotic manifestations.

In the attempt to use PLEs in a predictive way, other authors studied themselves if it was possible to distinguish among all PLEs between those experiences with a higher probability of developing into psychosis and those with a benign development. In a study conducted on adolescents and young non-psychotic help-seekers (Yung et al. 2006), factor analysis had highlighted 3 PLEs subtypes: bizarre experiences (BE), persecutory ideas (PI) and magical thinking (MT). The BE group included sub-threshold forms of thought broadcasting and sensorial-perceptive anomalies. The PI group included suspiciousness and sub-threshold forms of other types of persecutory ideas. Lastly, the MT group included belief in the occult or telepathy. In another research carried out on a non-clinical sample of adolescents (Yung et al. 2009), number of the PLEs subtypes raised to 4 in that the first factor was differentiated into two: bizarre experiences (BE) and perceptive anomalies (PA). In the former work (Yung et al. 2006), the PLEs associated to distress, depression and poor social functioning were bizarre experiences and persecutory ideas, in the latter

(Yung et al. 2009) they were bizarre experiences, persecutory ideas and perceptive anomalies.

1.4 Unanswered questions

A central question that thus emerges is whether all PLEs are equally indicative of the risk of psychosis. We know that subthreshold PLEs confer an increased risk of developing a psychotic disorder, in both community (Poulton et al. 2000; Rossler et al. 2007) and clinical samples (Mason et al. 2004; Cannon et al. 2008). However, reports in the literature as to which PLEs are associated with an increased risk are somewhat contrasting. Clinical studies have found that unstable ideas of reference, visual and auditory perceptual disturbances (Klosterkotter et al. 2001), unusual thought content, suspiciousness, perceptual disturbance, conceptual disorganization (Aroun et al. 2006) and negative symptoms (Yung et al. 2005) are associated with an increased risk of developing severe mental disorders in clinical and community samples.

1.5 Current main question

Over recent years, a substantial body of evidence has accumulated indicating that PLEs are present in non-clinical populations (Hanssen et al, 2002; Hanssen et al, 2005). However, little as known about whether such experiences increase an individual's risk of distress, disability, or onset of full-threshold psychotic disorder. It is possible that such experiences are common, benign, and transitory developmental phenomena (Van Os et al, 1999; Van Os et al, 2003). However, some types of PLEs or their level of persistence may confer an

increased risk of future onset of psychiatric disorder, a view for which there is some recent support.

The "early intervention" paradigm in psychiatry posits that the earliest possible identification and appropriate stage-dependent intervention will result in the best outcome for the individual (McGorry et al, 2003; McGorry et al, 2007). Within this paradigm, it is important to be able to identify when PLEs indicate increased risk of future psychotic disorder. Given the reasonably high prevalence of PLEs in the general population (Hanssen et al, 2002; Hanssen et al, 2005), the best chance of identifying individuals at risk of full-threshold psychiatric disorder is through recognizing which PLEs are more significant in term of risk for psychosis onset and combining PLEs with other clinical and non-clinical features, such as distress, other psychiatric symptoms, psychosocial impairment, and help-seeking behaviour. This method will "narrow down" on individuals who may truly be at risk of future onset of psychiatric disorders, and minimise "false positive" cases.

According to these evidences, in Chapter three we will describe our studies conducted on these topics during the PhD.

Specifically, we investigated PLEs in a large community sample of adolescents and young adults aiming to determine if different subtypes of PLEs could be identified and to investigate whether some subtypes were more likely to be associated with psychosocial difficulties, such as distress, depression, poor functioning and help-seeking.

Chapter 2

22q11 microdeletion syndrome as genetic model for the study of propension to psychosis

2.1 The 22q11 microdeletion syndrome, an overview

22q11.2 microdeletion syndrome (22q11DS) is a genetic syndrome (Scambler et al. 1992) associated with a microdeletion of the chromosome 22 band q11 with an estimated prevalence of between 1:2,500 and 1:4,000 live births. 22q11DS is a complex disorder with multiple abnormalities that affect a large number of tissues and organs, many of which are derived from neural crest cells. The phenotype of this syndrome has more than 180 clinical features (Robin et al. 2005; Shprintzen et al. 2005). The diagnosis is therefore defined by the deletion of DNA from chromosome 22 at the q11.2 band spanning the region that is regarded as critical.

The physical and neurobehavioral phenotype of the syndrome includes high rates of congenital dysmorphic features (Bassett et al. 1998; Scull et al. 2001), developmental structural brain abnormalities (Chow et al. 1999), cognitive dysfunction (Swillen et al. 2000) and psychiatric disorders (Gothelf et al. 1999), particularly schizophrenia (Bassett et al. 1999; Murphy et al. 2005).

As regards the neurocognitive profile of 22q11DS, general cognitive functioning in the low borderline range is the most consistent finding, while reading decoding and spelling skills as well as auditory/verbal memory skills are areas of relative strength. By contrast,

visuospatial function, math attainment and executive function are all reported to be impaired (Anthsel et al. 2008).

Even though the brain structure in subjects with 22q11DS is not drastically different from typically developing controls, recent quantitative studies have shown a total brain volume decrease of 8.5–11% in children and adolescents with 22q11DS if compared with normal individuals (Eliez et al. 2000). Moreover, the latest imaging techniques (fMRI; DTI) have shown significant differences in brain functioning between subjects with 22q11DS and those without (Gothelf et al. 2007).

As regards psychiatric disorders, studies of school-age children have shown that individuals with 22q11DS have very high rates of psychiatric morbidity and abnormal behaviors such as attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (OPD), specific and social phobias, generalized anxiety disorder, obsessive-compulsive disorder and autism spectrum disorder (Feinstein et al. 2002; Antshel et al. 2006; Gothelf et al. 2004).

By late adolescence and early adulthood, up to one-third of patients with 22q11DS develop psychotic disorders resembling above all schizophrenia and schizoaffective disorder (Gothelf et al. 2007; Murphy et al. 1999; Bassett et al. 2003).

2.1.1 Clinical features of schizophrenia and prodromal symptoms in 22q11DS

The incidence of most psychiatric disorders, including ADHD, generalized anxiety disorder, obsessive compulsive disorder and autism spectrum disorders, is no higher among individuals with 22q11DS than in cohorts with other developmental disorders (Feinstein et al. 2002; Antshel et al. 2006). Therefore, none of these disorders, if

diagnosed, fulfill the criteria (Feinstein et al. 2002) set forth for a behavioral phenotype that is specifically associated with a syndrome.

By contrast, individuals with 22q11DS have an increased risk of developing schizophrenia (Karayiorgou et al. 1995; Xu et al. 2008): half of the adolescents affected by this syndrome report transient psychotic experiences, while as many as 30% of affected adults are diagnosed with schizophrenia (Gothelf et al. 2007; Green et al. 2009), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR), a transition rate is comparable to the highest rates observed in ultra-high risk groups (Fusar-Poli et al. 2012). This syndrome is therefore one of the highest known risk factors for schizophrenia.

Moreover, the 22q11DS is found in up to one in 50 patients with schizophrenia, with reports ranging from 0.3% to 2% (Karayiorgou et al. 1995; Arinami et al. 2006; Stefansson et al. 2008), which is significantly higher than the estimated figure of 1 in every 5,000 live births in the general population (Botto et al. 2003). The occurrence of this deletion is even higher in patients with childhood-onset schizophrenia (5.7%) (Sporn et al. 2004), and in patients with schizophrenia and additional major manifestations of 22q11DS (from 20% in patients with 1 manifestation to 53% in patients with 2 manifestations (Bassett et al. 1998).

Schizophrenic disorder associated with 22q11DS largely resembles that found in the general population as regards the core signs and symptoms, treatment response, neurocognitive profile and MRI brain anomalies (Karayiorgou et al. 2010). When Bassett et al. (2003) compared 16 adults with 22q11DS and 46 adults with schizophrenia without evidence of 22q11DS, they did not detect any significant differences in age at onset, in lifetime or cross-sectional core positive and negative schizophrenic symptoms, or in global functioning. The same authors (Bassett et al. 1998) had previously reported similar results when they studied a sample of 10 subjects with schizophrenia and 22q11DS.

Moreover, patients with 22q11DS and those with schizophrenia without 22q11DS display similar impairments in a range of cognitive functions, with patients with 22q11DS exhibiting a significant impairment in executive functions, working memory and temporal processing (Baker et al. 2005; Carroll et al. 2008). However, as no studies have, to our knowledge, yet directly compared the cognitive phenotype of schizophrenia with 22q11DS patients with that of schizophrenia patients without 22q11DS, further investigation is warranted to shed light on this specific issue.

Furthermore, few studies conducted on early signs and symptoms that are predictive of schizophrenia in patients with 22q11DS have explored patterns of psychotic and prodromal symptoms in young people with the 22q11DS. These studies have found that the incidence of major depressive disorder, attention-deficit/hyperactivity disorder, simple phobias, enuresis and impaired social adaptive skills is higher in adolescents with 22q11DS than in normal subjects (Gothelf et al. 2005; Feinstein et al. 2002; Antshel et al. 2006; Debbané et al. 2006; Antshel et al. 2010).

To our knowledge, only two studies have prospectively explored specific prodromal symptoms that are predictive of schizophrenia onset. In the first study (Gothelf et al. 2007), 32.1% of the sample developed a schizophrenic disorder during follow-up. The development of psychotic symptoms between the age of 12 years and the age of 18 years was best predicted by the presence of psychotic symptoms at the time of the baseline study (i.e. at the age of 12 years) and by the anxiety and depression scores. Baseline sub-threshold psychotic symptoms combined with both the COMT genotype and the baseline symptoms of anxiety or depression predicted 61% of the variance in the severity of psychosis at the follow-up evaluation. A low IQ at the baseline was a further predictor of

high follow-up psychosis rating-scale scores. ADHD was not found to be a predictor of psychotic outcomes.

In the second study (Antshel et al. 2010), a total of 70 children with 22q11DS, 27 siblings of children with 22q11DS and 25 community controls were followed from childhood into mid-adolescence to investigate the predictive value of prodromal symptoms of psychosis in adolescents with 22q11DS. Major depressive disorder, oppositional defiant disorder and generalized anxiety disorder diagnoses were higher in the 22q11DS sample. With very low false positive rates, the best predictor of adolescent prodromal psychotic symptoms were parent ratings of childhood odd/eccentric symptoms and child performance in an executive functioning test. (see Table 1).

2.1.2 Neuropsychological correlates of schizophrenia in 22q11DS

22q11DS is associated with a distinctive cognitive phenotype. Full-scale IQ scores for functioning commonly drop to the borderline range (IQ 70 to 75), whereas those for reading, and verbal memory tend to be spared. By contrast, mathematics learning disabilities, visuospatial deficits, attention deficits, and executive function deficits in domains such as cognitive flexibility, response inhibition and non-verbal working memory, have been reported to be areas of weakness in the 22q11DS cognitive profile (Moss et al. 1999; Sobin et al. 2005).

A number of studies have highlighted the cognitive similarities between adolescents with 22q11DS and those at high risk for schizophrenia (Gothelf et al. 1997; Antshel et al. 2010; Debbané et al. 2008; Cornblat et al. 1998). More specifically, Dabbané et al. (2008) documented source monitoring deficits in a group of adolescents with 22q11DS. The fact that source monitoring deficits constitute a characteristic memory defect in diagnosed

schizophrenia (Bentall et al. 1991) suggests that adolescents with such deficits are at very high risk for schizophrenia. Furthermore, a decrease in verbal IQ has been associated with the onset of positive symptoms in adolescents with 22q11DS (Gothelf et al. 1997; Gothelf et al. 2005; Debbané et al. 2005; Antshel et al. 2010).

Lastly, reduced executive function capacities seem to reflect a genetic risk for schizophrenia, while an executive function deficit seems to be strongly related to a high risk for schizophrenia in people with 22q11DS. Moreover, deficits in prepulse inhibition, a form of response inhibition, have been documented both in schizophrenia and in children with 22q11DS (Sobin et al. 2005). There is also evidence suggesting that deficits in verbal memory, spatial working memory and attention are indicators of genetic susceptibility to schizophrenia (Erlenmeyer et al. 2000; Lencz et al. 2006). In addition, short-term and working memory deficits, especially in the non-verbal domain, have been described as phenotypic characteristics in 22q11DS by several research groups (Moss et al. 1999; Wang et al. 2000).

From a more biological perspective, executive functions have been shown to be related to COMT activity and to cortical dopamine catabolism (Papaleo et al. 2008; Yavich et al. 2007; Weickert et al. 2008). These brain regions are implicated in the processing of long-term episodic memory. It is noteworthy that deficits in learning and memory are among the most robust correlates of schizophrenia. Indeed, findings yielded by different estimation procedures point to a deficit in recollection and increased reliance on familiarity when recognition memory judgments are made in chronic schizophrenia (van Erp et al. 2000; Lefebrve et al. 2010). Although these specific areas of memory processing have not yet been studied in 22q11DS, deficits in free recall, which primarily involves the recollection process, have been documented in people with 22q11DS (Lajiness et al. 2005).

Another type of episodic memory processing associated with executive functioning that is impaired both in patients with schizophrenia and in adolescents with 22q11DS is source monitoring. Indeed, the latest findings on source monitoring deficits in schizophrenia suggest that the process of attributing a source to internally generated material (such as thoughts, memories or voluntary actions) is prone to confuse internal and external sources (Franck et al. 2000). Source monitoring deficits have also been reported in adolescents with 22q11DS (Debbané et al. 2008), thereby reflecting a possible genetic risk for schizophrenia in this population. (see Table 1).

Table 1. Genetic, neuropsychological and psychopathological correlations between 22q11DS and Schizophrenia

Reference	Study design	Sample size	Sample age	Correlates of schizophrenia in 22q11DS
Psychopathology				
Xu et al. (2008)	Case-control	1,077	No limits	Increased risk of developing schizophrenia
Green et al. (2009)	Cohort	172	5-54	Higher rates of schizophrenia in patients with 22q11DS
Arinami (2006)	Review	-	-	Higher rates of 22q11DS in patients with schizophrenia
Stefansson et al. (2008)	Case-control	11,236	No limits	Higher rates of 22q11DS in patients with schizophrenia
Sporn et al. (2004)	Longitudinal (2- year)	75	<13	Higher rates of 22q11DS in patients with schizophrenia
Bassett et al. (2003)	Case-control	62	<50	Age of onset, positive/negative symptoms, reduced functioning
Baker et al. (2005)	Case-control	50	13-21	Cognitive impairment
Carroll et al. (2008)	Case-control	45	Adults	Cognitive impairment
Devrim et al. (2008)	Case-control	64	No limits	Cognitive impairment
Prodromal symptoms				
Gothelf et al. (2007)	Case-control (5- year)	51	Children	Sub-threshold psychotic, depressive and anxiety symptoms
Feinstein et al. (2002)	Case-control	57	6-19	Specific phobia, ADHD and oppositional defiant disorder
Antshel et al. (2006)	Between-group	154	6-15	ADHD, major depressive disorder and simple phobias
Antshel et al. (2010)	Case-control (3- year)	70	Children	Odd/eccentric symptoms
Genetics and Neuropsychology				
Karayiorgou et al. (2010)	Review	-	-	Reduced COMT activity
Debbané et al. (2008)	Case-control	52	12-17	Source monitoring deficits
Gothelf et al. (2005)	Longitudinal	24	Children	Decrease in verbal IQ
Debbane´ et al. (2006)	Cross-sectional	43	6-19	Decrease in verbal IQ
Sobin et al. (2005)	Cross-sectional	40	5-12	Deficits in prepulse inhibition
Moss et al. (1999)	Cross-sectional	33	6-27	Short-term and working memory deficits
Wang et al. (2000)	Cross-sectional	36	5-12	Short-term and working memory deficits
Lajiness-O'Neill et al. (2005)	Case-control	42	5-19	Deficits in free recall

2.2 Genetic correlates of cognitive/schizophrenia-related abnormalities in 22q11DS

22q11DS is caused by the hemizygous deletion of chromosome 22 at the q11.2 band. These deletions are believed to include between 35 and 60 known genes expressed in the brain. One of the top candidate genes for schizophrenia that has been studied in 22q11DS, is the Catechol-O-methyl transferase (COMT) which encodes an enzyme critically involved in the catabolic clearance of dopamine (Axelrod et al. 1958). This gene is located in the 1.5 Mb 22q11 microdeletion region, thus all individuals with this disorder have only one copy of this gene. The existence of a valine-to-methionine (Val-108/158-Met COMT) polymorphism which results respectively in high and low activity forms of the COMT enzyme has received empirical attention as a possible risk factor for cognitive disturbances (Karayiorgou et al. 2010), psychosis (Glatt et al. 2003; Hywel et al. 2007) and more in general as a predisposition factor to psychiatric disorders (Azzam et al. 2003; Qian et al. 2003).

Indeed, the traditional hypothesis, widely held for more than half a century, is that increased dopamine (DA) function is central to the pathophysiology of schizophrenia (Van Rossum et al. 1966; Carlsson et al. 1978). More recently, the dopamine hypothesis has been revised, with excess mesolimbic dopamine function being proposed to be secondary to low dopamine signaling in the prefrontal cortex (PFC) (Daniel et al. 1989; Davis et al. 1991). In the context of either hypothesis, COMT fine role in the regulation of dopamine trafficking in the PFC and consequently in cognitive functions [Karayorgou et al. 2010; Papaleo et al. 2008) and its hemideletion in 22q11DS make it a clear functional candidate target for cognitive dysfunctions and schizophrenia in 22q11DS.

As previously explained, COMT regulates the cortical dopamine catabolism and plays a critical role in executive functions (Papaleo et al. 2008; Yavich et al. 2007). Moreover, the

pathophysiology of schizophrenia is strongly dependent on dysregulation of dopamine levels, particularly in the prefrontal cortex (PFC) (Winterer et al. 2004). Therefore, the COMT gene represents an attractive candidate for the cognitive and psychiatric disturbances found in patients suffering from 22q11DS. However, if reduced COMT enzyme activity were the only cause of these disturbances, all individuals with 22q11DS, and not only 30%, would have these cognitive/psychiatric phenotypes. Moreover, increased COMT enzyme activity results in cognitive deficits and might constitute a weak risk factor for schizophrenia. Indeed, reduced COMT enzyme activity in healthy humans and rodents has been found to improve executive functions (Papaleo et al. 2008; Sambataro et al. 2009; Tunbridge et al. 2006). Worthy of note is the fact that functional polymorphisms and haplotypes commonly found in humans, if associated with the COMT gene, might change the latter's enzymatic activity (Chen et al. 2004). Thus, subjects with 22q11DS that carry only one copy of the COMT gene may be exposed to unusually high brain dopamine levels from an early age if they also carry COMT polymorphisms and/or haplotypes that per se result in reduced COMT enzyme activity. This hypothesis is supported by studies showing that functional COMT polymorphisms and haplotypes interact with 22q11DS in the morphology of the brain and in the susceptibility to illnesses such as ADHD and OCD (Kates et al. 2006; Michaelovsky et al. 2008; van Almenstroov et al. 2008). However, the data available regarding the effects of COMT polymorphisms and haplotypes in 22q11DS in measures of neurocognitive performance and schizophrenia have proved inconclusive. It was suggested that cognitive/schizophrenia-like abnormalities in 22q11DS may originate from a genetic interaction of COMT with other genetic loci. Indeed, 22qDS cognitive/schizophrenia abnormalities might share the characteristics of a contiguous gene syndrome. For example, the PRODH and COMT genes are both present

in the 22q11.2 locus, and PRODH-deficient mice exhibit cognitive and schizophrenia-like phenotypes only when COMT is pharmacologically blocked, thereby demonstrating the ability of COMT and PRODH to interact and compensate for one another (Paterlini et al. 2005). However, if the hemideletion of both PRODH and COMT were the only cause of cognitive/schizophrenia-like symptoms in 22q11DS, every subject with this deletion would present these abnormalities. As suggested by Paterlini and colleagues (2005), additional genes might thus be involved. It is consequently likely that cognitive/schizophrenia abnormalities associated with 22q11DS might result from an alternative epistatic interaction with other genes in the genome. Indeed, according to this hypothesis, a protective allele (i.e. which reduces COMT activity) might become an allele at risk in a different epistatic context (e.g. through synergistic mechanisms). (see Table 1).

2.2.1 Neurocognitive profiles in 22q11DS modulated by COMT

It has been suggested that haploinsufficiency of the COMT gene, within the 22q11.2 region, may contribute to the neuropsychological phenotype associated with the syndrome. Indeed, there are common single nucleotide polymorphisms and haplotypes in the COMT gene that are functional. Thus, they alter the COMT enzyme activity resulting in different levels of cortical dopamine catabolism especially in the prefrontal cortical areas (Papaleo et al. 2008; Weickert et al. 2008). This is crucial for neurocognitive profiles as dopamine levels in the PFC are critically linked to higher order cognitive abilities including executive functions, working memory and attention (Salzam et al. 2010). The most studied COMT Val/Met polymorphism has been consistently associated with prefrontal cognitive functions in children (Diamond et al. 2004) as well as adults (Goldman et al. 2009) in both normal and clinical conditions. In general, homozygosity for the Met allele is associated

with cognitive advantages (Lewandowski et al. 2007) even if several differences depending on specific conditions exist (Scheggia et al 2012).

In patients with 22q11DS, Bearden et al. (2008) documented higher executive function in the Met-hemizygous compared to the Val-hemizygous group. By contrast, Glaser et al. (2006) showed a very small effect of this COMT polymorphism on executive functions in children and young adults with 22q11DS. As previously suggested (Glaser et al. 2006), a possible explanation of these controversial results may depend on the severe nature of the overall cognitive deficits in 22q11DS thus dampening the functional effect of this COMT polymorphism with small sample sizes.

Amelsvoort et al. (2008) explored volumetric regional brain differences in adults with 22q11DS with COMT Val or Met polymorphism. What they found was that Val hemizygous subjects had a significant larger volume of frontal lobes than Met hemizygous patients as well as more grey mater density in cerebellum, brainstem, parahippocampal gyrus. These findings suggest variation in COMT activity may be implicated in the 22q11DS brain development. However, in the same study, Amelsvoort et al. (2008) failed to find an effect of COMT genotype on the subjects' neurocognitive performance.

More recently, Magnée et al. (2010) described a visual processing deficit in a group of 58 children with 22q11DS, which was moderate by the COMT Met genotype. The authors interpreted their findings in terms of dysfunctional synaptic plasticity possibly associated with deviant dopaminergic and glutamatergic transmission related to the COMT functional polymorphism.

In summary, although some evidences support the association of hemizygosity of COMT with specific 22q11DS cognitive profile, further researches are needed to better characterize it.

2.2.2 Schizophrenia in 22q11DS modulated by COMT

The strong linkage between 22q11DS and schizophrenia has led to believe that one or more of the deleted genes in this region could be a significant susceptibility gene for schizophrenia. These observations have placed COMT near the top of a rather long list of plausible candidate genes for schizophrenia (Williams et al 2007). COMT regulates the cortical dopamine catabolism and plays a critical role in executive functions (Yavich et al. 2007; Winterer et al. 2004) and the pathophysiology of schizophrenia is strongly dependent on dysregulation of dopamine levels, particularly in the PFC (Sambataro et al. 2009).

In terms of position and function then, there are probably no genes with a better a priori case for involvement in schizophrenia than COMT. This has made the Val/Met polymorphism an almost irresistible target for genetic investigation, and many thousands of cases and controls have now been studied. As would be expected for a putative risk allele of small effect, the numerous studies aimed at investigating correlation of COMT polymorphism with schizophrenia include positive and negative findings (Wiliams et al. 2007; Norton et al. 2002; Wonodi et al. 2003; Shifman et al. 2002; Glatt et al. 2003; Fan et al. 2005; Williams et al. 2005).

Focusing on 22q11DS and schizophrenia, several studies were conducted on the COMT polymorphism role in this correlation. However, findings are still not consistent.

Gothelf and Coll. (2005) in a prospective, longitudinal study of 24 subjects with 22q11DS and 23 subjects with idiopathic developmental disabilities matched for age, gender, ethnicity and IQ investigated the hypothesis that hemizygosity for COMT-Met would be a risk factor for psychotic symptoms during adolescence. At follow-up the 22q11DS COMT-

Met subgroup had significantly higher psychotic symptoms measured with BPRS than the 22q11DS COMT-Val subgroup ($p<0.05$) and the developmental disability group ($p<0.0001$), demonstrating a linkage between COMT-Met and more severe psychotic symptoms in 22q11DS.

Similar results were found in a second 5-year follow-up study (Gothelf et al. 2007) on 31 subjects with 22q11DS and 29 comparison subjects with idiopathic developmental disability matched for age and IQ. In the 22q11DS group, baseline subthreshold psychotic symptoms interacted both with the COMT genotype and with baseline symptoms of anxiety or depression to predict 61% of the variance in severity of psychosis at follow-up evaluation. In fact, individuals with 22q11DS who have the low-activity (Met) allele of the COMT gene had a more severe psychotic symptoms than those carrying the high-activity (Val) allel.

Differently, in a study (Boot et al. 2011) on 12 22q11DS subjects with schizophrenia compared to 22 22q11DS without schizophrenia, found schizophrenic patients to be more often Val hemizygous than 22q11DS subjects without schizophrenia. Significant COMT cross gender interactions were also found on dopaminergic markers, suggesting complex interactions of the COMT Val/Met polymorphism, gender and additional factors on dopamine metabolism, and its relationship with schizophrenia.

Bassett and Coll. (2007) found that lower activity Met allele was associated with higher total PANSS scores, but not significantly more prevalent than the Val allele in 33 subjects with 22q11DS and schizophrenia. Similarly, in a previous study (Murphy et al. 1999) no significant differences were found between allelic distributions of the COMT polymorphism in 40 22q11DS individuals with and without psychosis.

More recently, a 3-year follow up study (Antshel et al. 2011) investigated predictors to psychosis in 70 youth with 22q11DS, compared to 27 siblings and 25 community controls. Results did not suggest a COMT effect on psychosis: while a higher ratio of Met allele (26%) than Val allele (15%) had significant prodromal symptoms, this difference was not statistically significant (Table 2).

In summary, despite considerable research effort and a clear promising implication of COMT, it has not proved to date straightforward to demonstrate and characterise a clear relationship between genetic variation at COMT and schizophrenia in 22q11DS.

Table 2. Role of COMT genotype in 22q11DS and Schizophrenia

Reference	Study design	Sample size	Sample age	Correlates of schizophrenia in 22q11DS
COMT genotype				
Gothelf et al. (2005)	Longitudinal	24	10-17	COMT Met
Gothelf et al. (2007)	Longitudinal	60	8-16	COMT Met
Boot et al. (2011)	Case-control	34	18-43	COMT Val
Bassett et al. (2007)	Cross-sect.	73	22-43	Higher PANSS score in COMT Met
Murphy et al. (1999)	Cross-sect.	50	>17	No correlation with COMT genotype
Antshel et al. (2010)	Longitudinal	70	9-14	Higher prodromal symptoms in COMT Met

2.3 Unanswered questions

As we highlighted in this Chapter, a very significant opportunity for exploring the trajectory of psychosis onset and for investigating the efficacy of indicated preventive treatments exists in 22q11DS.

Nevertheless, several questions about the opportunity to explore 22q11DS as a genetic model for the study of schizophrenia remain unanswered.

2.3.1 First question: genetic contribution for schizophrenia in 22q11DS

The COMT gene represents an attractive candidate for schizophrenia and neurocognitive-related disorders found in patients suffering from 22q11DS. However, if reduced COMT enzyme activity were the only cause of these disturbances, all individuals with 22q11DS, and not only 30%, would have psychotic symptoms. Instead, the COMT implication for cognitive related disturbances might result more easy to disentangle and to use for future more efficient therapeutic interventions/treatments. It is interesting to note that, usually, increased but not decreased COMT enzyme activity results in cognitive deficits and might constitute a weak risk factor for schizophrenia. Indeed, reduced COMT enzyme activity in healthy humans and rodents has been found to improve executive functions (Papaleo et al. 2008; Sambataro et al. 2009; Tunbridge et al. 2005). These discrepancy might reside in the extreme situation deriving from the hemideletion present in subjects with 22q11DS. In fact, subjects with 22q11DS that carry only one copy of the COMT gene may be exposed to unusually high brain dopamine levels from an early age if they also carry COMT polymorphisms and/or haplotypes that per se result in reduced COMT enzyme activity. This hypothesis is supported by studies showing that functional COMT polymorphisms and haplotypes interact with 22q11DS in the morphology of the brain and in the

susceptibility to illnesses such as ADHD and OCD (van Amelsvoort et al. 2008; Michaelovsky et al. 2005; Kates et al. 2006). Moreover, this extreme COMT reduction might further interact with other genes microdeleted in the 22q11DS or with other yet unexplored genes impacting as well the dopaminergic system. These new epistatic interaction studies might better unravel the effects of COMT polymorphisms and haplotypes in 22q11DS in measures of neurocognitive performance and schizophrenia Indeed, 22qDS cognitive/schizophrenia abnormalities might share the characteristics of a contiguous gene syndrome. For example, the PRODH and COMT genes are both present in the 22q11.2 locus, and PRODH-deficient mice exhibit cognitive and schizophrenia-like phenotypes only when COMT is pharmacologically blocked, thereby demonstrating the ability of COMT and PRODH to interact and compensate for one another (Paterlini et al. 2005). However, if the hemideletion of both PRODH and COMT were the only cause of cognitive/schizophrenia-like symptoms in 22q11DS, every subject with this deletion would present these abnormalities. Additional genes might thus be involved. It is consequently likely that cognitive/schizophrenia abnormalities associated with 22q11DS might result from an alternative epistatic interaction with other genes in the genome. Indeed, according to this hypothesis, a normally protective allele (i.e. which reduces COMT activity) might become an allele at risk in a different epistatic context (e.g. through synergistic mechanisms).

Moreover, to date there is a lack of studies on possible gene-environment interactions in the evolution of cognitive and psychiatric symptoms in 22q11DS. As for Schizophrenia (Biederman et al. 2005), perhaps there are shared environmental exposures in schizophrenia and 22q11DS which increase the risk of schizophrenia in the latter disorder, against the background of genetic vulnerability.

Similarly, as regards other psychiatric disorders converging evidence from animal and human studies implicate the dysregulation of frontalsubcortical-cerebellar catecholaminergic circuits in the pathophysiology of ADHD, (Fallgatter et al. 2005; Pliszcka et al. 2005) and both hypo- and hyperfunctioning models of dopaminergic transmission were suggested as possible contributors (Goldman-Rakic et al. 2000). A role for the dopamine system was also proposed for the pathophysiology of OCD (in addition to the well-established serotonergic theory) and is supported by clinical and preclinical evidence (Stein et al. 2002; Buchanan et al. 2010). Nevertheless results on the COMT polymorphism role in these disorders are still controversial (Craddock et al. 2006).

In summary, although some evidences support the association of hemizygosity of COMT with specific 22q11DS psychiatric and cognitive profiles, further researches are needed to better characterize it. More complex measures of gene expression, including a broad range of neurotransmitter activity over development, will be essential for a better understanding of risk in this and other forms of schizophrenia. To further investigate the involvement of COMT variants on schizophrenia and cognitive related disturbances, it will be necessary to evaluate all of the polymorphic markers in the gene, its nearby regulatory elements and other epistatic interactions with other genes, followed by functional molecular and preclinical studies. This will clarify the COMT role in these pathologies and will move forward the use of COMT as an efficient therapeutic target.

2.3.2 Second question: are idiopathic schizophrenia and 22q11DS schizophrenia really comparable?

A central question that emerges from what has been reported is whether idiopathic schizophrenia and 22q11DS schizophrenia really comparable. Or, in other words, can 22q11DS used as a genetic model for the study of idiopathic schizophrenia?

If there are enough cross-sectional studies demonstrating that the two disorders are comparable in term of clinical features, there is still a lack of knowledge about the long-term outcome of schizophrenia in 22q11DS and treatment response.

Moreover, only few studies have investigated the features of prodromal phases in patients with 22q11DS. This topic is very important since early diagnosis and treatment in psychotic disorders is becoming the main research area in psychiatry.

Therefore it would be fundamental to demonstrate that prodromal phases (i.e. UHR state) of schizophrenia in 22q11DS are comparable to the prodromal phases in idiopathic schizophrenia.

2.4 Current main question

As regard the first question highlighted in par. 2.3.1, we are currently conducting a multisite genetic translational study. The study, which will last three years, is now at the end of the first year of recruitment. Therefore, no conclusive data are available at the moment.

This integrated preclinical and clinical study aims to provide specific genetic mechanisms and early diagnostic criteria for cognitive/schizophrenia-related abnormalities in the 22q11DS.

Our preliminary findings in mice and humans indicate that genetic reduction of the catechol-O-methyl transferase (COMT) produces cognitive deficits when combined with dysbindin (dys) genetic reduction. We aim here to address which cognitive alterations produced by COMT*dys interaction specifically relates to schizophrenia phenotypes and their neurodevelopmental mechanisms.

We are now performing behavioral and neurodevelopmental analysis in COMT*dys mice and results will be combined with behavioral and genetic studies in patients affected by 22q11DS and schizophrenia.

Based on a defined genetic risk factor, our study will be instrumental to develop early diagnosis and intervention for currently uncured cognitive and possible psychiatric disturbances in 22qDS.

This project, conducted in two Italian centers, embrace a multidisciplinary approach including behavioral, neurodevelopmental, neurophysiological, neurochemical and human genetic studies in a concerted effort to unravel specific genetic mechanisms leading to cognitive and schizophrenia-related symptoms in 22qDS.

As regard the second question highlithed in par. 2.3.2 (i.e. are idiopathic schizophrenia and 22q11DS schizophrenia really comparable), in chapter four we will describe our main study conducted on this topic during the PhD.

Specifically, we investigated differences and similarities between two samples of patients with 22q11DS and UHR (UHR+22q11DS; n=30), and with UHR alone (UHR group; n=81). We tested the hypotheses that (i) the two groups would be comparable in severity of positive symptoms, the core symptoms for a diagnosis of a psychotic disorder; (ii) the UHR+22q11DS group will have higher severity of negative symptoms and general impairment.

The main aim of this study was to demonstrate that prodromal phases (i.e. UHR state) of schizophrenia in 22q11DS are comparable to the prodromal phases in idiopathic schizophrenia.

Chapter 3

Researches on prodromal phases: Defining Psychotic Like Experiences and other clinical variables as risk factors for psychotic onset

3.1 Research 1: Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults·

3.1.1 Introduction

The identification of individuals at high risk of severe psychiatric disorders, particularly psychotic disorders, has become one of the premiere research topics in the field of psychiatry in the past decade. Increasing interest in this topic has been aroused by the view that the early identification of such disorders may improve outcome (Yung et al. 1996; Birchwood et al. 1997) and shed more light on the etiopathogenic processes involved (Birchwood et al. 1998; Parnas 2000; Klosterkotter et al. 2001; Yung et al. 2004).

The most commonly used method to identify help-seeking individuals in the putatively prodromal phase of psychotic disorders has been the "ultra high risk" (UHR) approach (Yung et al. 1996), which combines known trait and state risk factors for the onset of psychotic disorders, including attenuated positive psychotic symptoms, family history of

· This research has been published in an adapted version on Schizophrenia Research. Armando M, Nelson B, Yung AR et al. Psychotic-Like Experiences, Self- Disturbance and Depressive Symptoms in a community sample of adolescents and young adults. Schizophr Res, 2010; 119:258-265.

psychotic disorders and functional decline, as well as brief self-limiting psychotic symptoms (Yung et al. 2003; Yung et al. 2004).

Taking a step back in the trajectory that leads from healthy functioning to psychosis, many studies indicate that positive psychotic symptoms exist on a continuum, with schizophrenia at one end and PLEs at the other (Kendler et al.1996; Van Os et al 2001; Dhossche et al. 2002; Johns et al. 2004).

These studies suggest that PLEs are a frequent phenomenon in the general population and that they are not necessarily associated with distress, help-seeking or the onset of psychotic disorders (Hanssen et al. 2003; Dominguez et al. 2009; Van Os et al. 2009). Studies have yielded a prevalence rate of 5% and an incidence rate of 3% in the general population (Van Os et al 2009). Evidence also indicates that although 75-90% of developmental psychotic experiences are transient (Dominguez et al. 2009), subjects who have intense and frequent PLEs are five times more likely to be diagnosed with a psychotic disorder 4 years later (Hanssen et al. 2003).

Within this context, research is warranted to ascertain whether PLEs in the general population and the attenuated or intermittent psychotic symptoms in the UHR groups (Yung et al. 2009) are correlated with the subsequent development of severe mental disorders (Rossler et al. 2007). Indeed, such research would shed light on the mechanisms that lead to psychosis and ensure that preventive interventions are more timely and effective. For this purpose, studies need to investigate the distribution of PLEs in the general population and to identify different clusters of PLEs in order to determine which clusters are associated with a higher risk of psychosis and other severe mental disorders.

Recently has been argued that PLEs are multi-determined phenomena (see Nelson et al. 2008, Yung et al. 2007, Yung et al. 2008 for more detailed description). In this regard,

PLEs, in a given subject, might be an expression of i) a more fundamental, underlying disorder, ii) clinical noise around a non-psychotic syndrome, or iii) may simply be present in non-clinical "normal" individuals.

As the PLEs belonging to the first two categories may be considered to be those that cause the greatest concern in terms of clinical care (McCreery et al. 1996; Jackson et al. 1997), an effort is required to increase our ability to detect PLEs in these two categories, which reflect a more fundamental, underlying disturbance.

A central question that thus emerges is whether all PLEs are equally indicative of the risk of psychosis and other severe mental disorders. We know that subthreshold PLEs confer an increased risk of developing a psychotic disorder, in both community (Poulton et al. 2000; Rossler et al. 2007) and clinical samples (Mason et al. 2004; Cannon et al. 2008). However, reports in the literature as to which PLEs are associated with an increased risk are somewhat contrasting. Clinical studies have found that unstable ideas of reference, visual and auditory perceptual disturbances (Klosterkotter et al 2001), unusual thought content, suspiciousness, perceptual disturbance, conceptual disorganization (Aroun et al. 2006) and negative symptoms (Yung et al. 2005) are associated with an increased risk of developing severe mental disorders in clinical and community samples.

In a previous study, it has been investigated a clinical sample of help-seeking depressed young people who did not meet UHR criteria. Within this sample, three distinct subtypes of PLE have been found: bizarre experiences (BE), persecutory ideas (PI) and magical thinking (MT). In that sample, BE and PI were associated with distress, depression and poor functioning, while MT was not (see Yung et al. 2006 for more detail).

In another study, different types of PLE in a community sample of high school students (Yung et al., 2009) were investigated. The following subtypes of PLE were identified: BE,

PI, and MT and a fourth subtype, Perceptual Abnormalities (PA). As only BE, PI and PA were strongly associated with distress, depression and poor functioning, was speculated that not all subtypes of PLE confer the same risk of psychotic disorder.

The aim of the current study was to investigate PLEs in non-clinical population by measuring PLEs in a large community sample made up of both adolescents and young adults. This is an extension of an earlier study (Yung et al. 2009), though this study is based on a larger sample and has a wider age range (age 15-26 years) than the previous study. We adopted this age range to study PLEs because it corresponds to the age of highest risk for the onset of psychotic disorders and other mental illnesses (Patel et al. 2007).

The aims of this study were to:

- determine whether different subtypes of PLE can be identified in a large community sample of adolescents and young adults;
- to investigate whether particular subtypes of PLEs are more likely to be associated with psychosocial difficulties than other subtypes.

3.1.2 Methods

3.1.2.1 Procedures and Sample

The study was carried out on a sample of 1882 high school and university students.

The high school sample (n=848; age 15-18 years) was recruited via schools, which we approached to ask for permission to survey their Year 10 secondary students. Thirty-four of the 60 secondary schools in the Western Metropolitan Region of Melbourne that were approached consented to participate (20 government, 5 Catholic and 9 independent schools). The university student sample (n=929; age 19-26) was recruited in 3 Italian

universities (“Sapienza” University of Rome n=608, University of Latina n=101 and “G. D’Annunzio” University of Chieti n=220).

The sample comprises students who were present and voluntarily agreed to fill in the questionnaire when it was handed out during the 2008/2009 academic year. Although it cannot be considered randomized, its large size and main demographic characteristics, if compared with those found in the overall high school/university population, make it highly representative. Both the school and university student samples were assessed by means of the questionnaire during lessons. All measures were self-administered. However, trained research assistants, consisting of psychiatrists or psychologists with specific knowledge of the instruments and the background and purpose of the study, were present in the classroom at the time of assessment. The languages used were English for the Australian sample and Italian for the Italian sample. All the scales were validated in both English and Italian.

The research and ethics committees at the University of Melbourne, Victorian Department of Education, and “Sapienza” University of Rome approved the study. All participants, and/or their parent/guardian, provided written informed consent.

3.1.2.2 Instruments

The CAPE (Community Assessment of Psychic Experiences) (Stefanis et al. 2002) was used to assess PLEs and negative and depressive symptoms. This self-report scale measures the lifetime prevalence of positive (PLEs) and negative and depressive symptoms on both a frequency scale (0= never to 4= nearly always) and a distress scale (1= not distressed to 4= very distressed).

Functioning and general distress were measured by means of the GHQ-12 (General Health Questionnaire-12), a widely used screening instrument for detecting psychological strain in

the general population (Goldberg et al. 1970; Goldberg et al. 1988; Goldberg et al. 1997). The GHQ-12 was originally applied to adult populations and subsequently used and validated for younger populations (D'Arcy et al. 1984; Radovanovic et al. 1983). The level of depressive symptoms was assessed using the Depression sub-scale of the CAPE. The CAPE measures the level of distress caused by the symptoms, while the CAPE Distress scale assesses the level of distress caused by the various psychic experiences investigated.

3.1.2.3 Data Analysis

The analyses were conducted using the Statistical Package for Social Science (SPSS) Version 13 (Norusis et al. 2004). Data were screened for missing values, for the assumption of normality, linearity and homogeneity, and for outliers. Subjects for whom over 25% of the CAPE data were missing or who did not provide written informed consent were excluded from further analysis. We excluded items 20 and 15 of the CAPE-positive scale from factor analysis because these items are related more closely to cultural background and age than to psychopathology (Berenbaum et al. 2009; Jarosz et al. 1996).

The correlations matrix of the CAPE-positive items was examined. The fact that numerous correlations between items with a p value higher than 0.3 were found and that the sample comprised well over 300 subjects indicate that factor analysis was appropriate for the purposes of our study (Hinkle et al. 1998). A principal components analysis was conducted on the CAPE frequency scores to determine the number of factors. The factor structure was assessed using a principal axis factoring technique, with direct oblimin rotation. Two tests were conducted to determine whether the data set was factorable. The first test was the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy, which was used to measure the size of the partial correlations between variables. Values of at least 0.60 are required for good factor analysis (Tabachnick et al. 2007). The second test was Bartlett's test of

sphericity, which assesses whether the factor model is appropriate. Oblique rotation was chosen as it was predicted that the CAPE factors would be interrelated.

A number of methods were used to determine the optimum number of factors for the current data set**.** First, five factors had eigenvalues higher than one**.** Second, the scree plot was inspected. There was a noticeable drop-off in the second and third factors. However, as both these methods have been criticised as having shortcomings (Hayton et al. 2004), a parallel analysis using a Monte Carlo simulation method was conducted.

Once the factor structure was identified, correlations were conducted to assess the relationship between the CAPE total score, sub-scale scores and factors and measures of functioning and symptomatology both for the total and split samples (high school students vs. university students). Chi-square and t-tests were run to compare scores with variables such as age and gender.

Simple and multivariable linear regression were undertaken, using depression and functioning as dependent variables, to examine the associations between these factors. We considered p values less than .05 to be statistically significant.

3.1.3 Results

3.1.3.1 Sample characteristics

Over 25% of the CAPE data were missing in 105 (5.6 %) out of the total sample of 1882 students; following the exclusion of these 105 participants, further analysis was thus conducted on a total of 1777 participants. (see Table 3 for more detail).

Table 3: Characteristics of the Study Sample

	High school (n=848)	University (n=929)	Total sample (n=1777)
Sex			
• Male	47%	23.4%	34.7%
• Female	53%	76.6%	65.3%
Age: Mean (SD)	15 (±1.5)	21 (±2.5)	18 (±3.5)

3.1.3.2 PLEs in the sample: number of factors, distribution and psychometric properties

The 4-factor structure, which was found to represent the data most accurately, accounted for 51.5% of the explained variance. All the items loaded significantly ($r > .35$) on one of the four factors, while none had high cross loadings ($r \leq .25$) (see Table 4).

Factor 1 is related to bizarre experience (BE) and is composed of 8 items. Factor 2 is related to perceptual abnormalities (PA) and is composed of 4 items. Factor 3 is related to grandiosity (GR) and is composed of 2 items. Factor 4 is related to persecutory ideation (PI) and is composed of 5 items.

There was a significant difference between the 15-18 year age group and the 19-26 year age group, with higher scores emerging in the 15-18 year age group in the CAPE total score, BE, PA and GR ($p < .05$). There was a significant difference between males and females in the CAPE total score, PA and PI ($p < .05$), with higher scores in females (see Table 5). Correlations between factors, analyzed by means of Pearson's correlation coefficient, were positive and significant ($p < .001$) (see Table 6).

BE, PA and PI displayed good internal consistency with Cronbach's alpha ($r > .70$). GR values were lower, though this finding may be related to difficulty in achieving

convergence between a low number of items for a subscale whose content is heterogeneous. The internal consistency of the total CAPE scale was high (r = .84).

Table 4: CAPE positive items: factor loading with a 4-factor solution (only loadings ≥ .25 are displayed)

	F1	F2	F3	F4
Bizarre Experience				
26 Have you ever felt as if the thoughts in your head were not your own?	.68			
24 Have you ever felt as if the thoughts in your head are being taken away from you?	.67			
28 Have your thoughts ever been so vivid that you were worried other people would hear them?	.55			
30 Have you ever heard your thoughts being echoed back to you?	.49			
17 Have you ever felt as if electrical devices such as computers can influence the way you think?	.47			
31 Have you ever felt as if you are under the control of some force or power other than yourself?	.47			
5 Have you ever felt as if things in magazines or on TV were written especially for you?	.48			
Perceptual Abnormalities				
34 Have you ever heard voices talking to each other when you were alone?		-.83		
42 Have you ever seen objects, people or animals that other people can't see?		-.76		
33 Have you ever heard voices when you were alone?		-.76		
41 Have you ever felt as if a double has taken the place of a family member, friend or acquaintance?		-.36		
Persecutory Ideation				
2 Have you ever felt as if people seem to drop hints about you or say things with a double meaning?				.81
22 Have you ever felt that people look at you oddly because of your appearance?				.69
6 Have you ever felt as if some people are not what they seem to be?				.58
10 Have you ever felt as if there is a conspiracy against you?				.49
7 Have you ever felt that you are being persecuted in some way?				.40
Grandiosity				
11 Have you ever felt as if you are destined to be someone very important?			.82	
13 Have you ever felt that you are a very special or unusual person?			.81	

Table 5: Descriptive statistics for CAPE total and subscales. Correlation with age and sex

	Total Sample	Males	Females	P	≤ 18	>18	P
CAPE	33.4 (7.2)	32.8 (7.5)	33.8 (7.0)	0.01	34.1 (7.8)	32.7 (6.5)	<0.001
BE	9.6 (2.6)	9.5 (2.6)	9.7 (2.6)	0.18	10.0 (2.8)	9.2 (2.3)	<0.001
PA	4.8 (1.5)	5.0 (1.7)	4.8 (1.3)	0.07	5.1 (1.7)	4.6 (1.2)	<0.001
GR	4.0 (1.4)	4.1 (1.5)	4.0 (1.4)	0.24	4.0 (1.4)	4.1 (1.5)	0.039
PI	9.2 (2.3)	8.8 (2.4)	9.4 (2.3)	<0.001	9.2 (2.4)	9.1 (2.2)	0.385

Table 6: Internal consistency and inter-correlations between factors

	BE	PA	ER	PI	CAPE TOT
BE	1				
PA	.496(**)	1			
GR	.260(**)	.139(**)	1		
PI	.491(**)	.377(**)	.217(**)	1	
CAPE TOT	.840(**)	.700(**)	.468(**)	.745(**)	1

****** Correlation is significant at the $p < 0.001$.

3.1.3.3 Prevalence of PLEs

To evaluate the prevalence of PLEs, answers were recoded to 0 (never) and 1 (at least sometimes). PI had the highest prevalence, with 92.3% endorsing at least 1 item "sometimes", followed by GR (74.8%). Prevalence rates substantially decreased as the frequency rate increased (see Table 7).

Table 7: Distribution and frequency of CAPE positive items

	Never (%)	At least some-times (%)	Always/ nearly always (%)
Bizarre Experience			
26 Have you ever felt as if the thoughts in your head were not your own?	72.1	27.9	0.6
24 Have you ever felt as if the thoughts in your head are being taken away from you?	80.4	19.6	0.7
28 Have your thoughts ever been so vivid that you were worried other people would hear them?	61.0	39.0	1.2
30 Have you ever heard your thoughts being echoed back to you?	64.9	35.1	1.1
17 Have you ever felt as if electrical devices such as computers can influence the way you think?	60.2	39.8	2.4
31 Have you ever felt as if you are under the control of some force or power other than yourself?	81.4	18.6	1.5
5 Have you ever felt as if things in magazines or on TV were written especially for you?	72.4	27.6	0.6
Perceptual Abnormalities			
34 Have you ever heard voices talking to each other when you were alone?	91.3	8.7	0.9
42 Have you ever seen objects, people or animals that other people can't see?	84.7	15.3	1.0
33 Have you ever heard voices when you were alone?	75.0	25.0	1.2
41 Have you ever felt as if a double has taken the place of a family member, friend or acquaintance?	84.3	15.7	0.8
Persecutory Ideation			
2 Have you ever felt as if people seem to drop hints about you or say things with a double meaning?	20.0	80.0	3.3
22 Have you ever felt that people look at you oddly because of your appearance?	39.1	60.9	4.2
6 Have you ever felt as if some people are not what they seem to be?	7.7	92.3	5.0
10 Have you ever felt as if there is a conspiracy against you?	64.4	35.6	2.0
7 Have you ever felt that you are being persecuted in some way?	57.7	42.3	0.9
Grandiosity			
11 Have you ever felt as if you are destined to be someone very important?	34.9	65.1	6.8
13 Have you ever felt that you are a very special or unusual person?	25.2	74.8	8.7

3.1.3.4 Distress associated with PLE

To determine whether each CAPE subscale was associated with different levels of distress caused by the various psychic experiences assessed by the CAPE, the correlation between frequency and distress was analyzed. The correlation was very strong for the total CAPE-positive ($r = .85$, $p < .001$), BE ($r = .87$, $p < .001$), PA ($r = .85$, $p < .001$) and PI ($r = .82$, $p < .001$), and was strong for GR ($r = .61$, $p < .001$).

Correlations were transformed using Fisher's Z transformation to explore whether correlations were significantly different from each other. Z scores were then compared using the formula described by Hinkle et al. (1998). There was no significant difference between BE and PA ($z=0$, $p=1.0$). The correlation between BE and PA was stronger than that between BE and PI ($z=4.07$, $p<0.01$), which was in turn stronger than that between BE and GR ($z=5.11$, $p<0.001$).

3.1.3.5 Relationship between PLE and Depression

Depressive symptoms in the overall sample were significantly, though moderately, related to the total CAPE-positive ($r = .53$, $p < .001$), BE ($r = .44$, $p < .001$), PA ($r = .32$, $p < .001$) and PI ($r = .59$, $p < .001$). After the sample was split into high school students and university students, the correlation remained significant in both subsamples for CAPE-positive, BE, PA and PI.

Standard linear regression was used with depressive symptoms scores as the dependent variable. Age and gender significantly explained 3% of the variance in the CAPE-depressive scores ($R2 = 0.03$, $p < .001$). After controlling for the effects of these variables, a series of univariate regression analyses were conducted. The total CAPE score and each subscale were individually inserted in the second block to determine whether PLEs were

associated with self-reported depressive symptoms. All the CAPE scales significantly explained variance in the CAPE-depressive scores, indicating that the increase in PLEs paralleled the increase in depressive symptoms. However, BE and PI were associated with a greater increase in depression than PA and GR (see Table 8). As regards the association between distress and PLEs, correlations were transformed using Fisher's Z transformation to explore whether they were significantly different from each other. There was no significant difference between BE and PI ($z=0.1$, $p=0.52$). The correlation between PI and PA was stronger than that between PI and BE ($z=3.20$, $p<0.01$).

Table 8: Association between PLE and depressive symptoms

		B	β	t	p	C.I.	sr^2
Block 1	Age	-0.22	-.02	-.84	.21	-.073 – 0.029	.00
	Gender	3.21	.21	6.15	< .001	2.84 – 5.51	.03
Block 2	Total CAPE	0.81	.55	5.33	<.001	0.68 – 0.84	.29
	BE	1.70	.43	14.21	< .001	1.46 – 1.93	.19
	PA	2.55	.32	9.55	<.001	1.98 – 2.93	.09
	PI	2.92	.61	21.32	< .001	1.74 – 2.60	.37
	GR	0.80	.15	4.72	< .001	0.53 – 1.21	.03

Note: Depression measured by CAPE-depressive scale. CAPE = Community Assessment of Psychotic Experiences; BE = Bizarre Experiences; PA = Perceptual Abnormalities; PI = Persecutory Ideation; GR = Grandiosity. B = Beta coefficient, the unit change in depression level per unit increase in PLE. β = standardised beta coefficient. C.I. = confidence interval. sr^2 = amount of unique explained variance in depression scores for each independent variable.

3.1.3.6 Relationship between PLEs and Functioning/General Distress

Correlations between PLEs and Functioning/General Distress were significant for total CAPE-positive ($r = .25$, $p < .001$), BE ($r = .26$, $p < .001$) and PI ($r = .27$, $p < .001$). The correlation between Functioning/General Distress and GR was weaker ($r = .06$, $p < .05$). After the sample was split into high school students and university students, the correlation for total CAPE-positive, BE, PI and GR remained significant, while that for PA became significant in the university sample ($r = .11$, $p < .05$). Correlations were transformed using Fisher's Z transformation to explore whether correlations were significantly different from each other. The correlation for PI ($z=0.1$, $p=0.52$) was higher than that for BE and PA($z=3.58$, $p<0.01$).

3.1.4 Discussion

As hypothesized, this study confirms, though in a larger sample with a wider age range, previous findings (Yung et al. 2006; Yung et al. 2009), showing that different PLE subtypes emerge from a community sample and that some subtypes are more likely to be associated with psychological difficulties than other subtypes. However, if compared with the community sample analyzed previously (Yung et al. 2009), a new factor (grandiosity) is included in this cohort while another is excluded (magical thinking). The exclusion of the latter is probably due to the fact that we excluded items 20 and 15 of the CAPE-positive scale from further factor analysis because previous studies (Yung et al. 2006; Yung et al. 2009) have found that these items are related more closely to cultural background and age than to psychopathology.

BE and PI were found to be significantly associated with increased distress, depression and poor functioning, which is in keeping with the findings of Wigman et al. (2009); PA was

found to be significantly associated with increased distress; GR was found to be significantly associated with poor functioning and the distress it caused. We may hypothesise that these differences between PLEs and symptoms are ascribable to the fact that PI and BE are subjectively considered more invasive and disruptive of the self-structure, and lead to more evident symptoms than PA and GR. We may speculate that the GR is less closely related to clinical features because it may result in a feeling of being "out of the ordinary" or "fundamentally different" from other people, which is subjectively experienced as a "new and better way of life".

As regards the influence of age on the distribution of PLEs, there was a significant difference between the 15-18 year and 19-26 year age groups, with higher scores emerging in the former for the CAPE total score, BE, PA and GR, whereas no significant difference was found between PLEs and distress/general functioning. This suggests that although PLEs are more frequent in adolescents (Rossler et al. 2007; Cannon et al. 2008), their impact in terms of psychological sufferance is similar to that observed in young adults (Wigman et al. 2009).

Our findings therefore support the view that PLEs should not be regarded as a homogeneous entity. This is important for at least two reasons. Firstly, subjects who seek help and have intense and frequent PLEs are at least five times more likely to be diagnosed with a psychotic disorder 4 years later (Hanssen et al. 2003). Specific subtypes of PLEs may be more closely related to distress, poor functioning and the emergence of full-threshold disorder than other subtypes of PLEs. Secondly, identifying which subtypes of PLEs confer the highest risk of psychosis and other severe mental disorders may make an important contribution to screening activities. Moreover, it would allow non-help-seeking subjects with PLEs that are most likely to develop psychotic disorders to be recognized

(Loewy et al. 2007). These may be individuals suffering from attenuated psychotic symptoms in solitude. Indeed, many young people either actively ignore or are unable to recognize their prodromal symptoms (Armando et al. 2009) in the prodromal phases (Boydell et al. 2006).

One limitation of our study is that we relied on a self-report instrument to assess PLEs. It has been suggested that self-reporting may over-estimate the prevalence of PLEs. Kendler et al. (1996) found that 28.4% of the cohort in the US National Comorbidity Survey endorsed one or more probes for psychosis, whereas only 0.16% were diagnosed as having a narrowly defined psychotic illness. However, evidence also exists indicating that self-report instruments do yield valid estimates of PLEs. Konings et al. (2006) and Liraud et al. (2004) both found a good correlation between the CAPE and interviewer-rated psychosis. In a clinical study, Kelleher et al. (2009) found a high degree of accuracy when PLEs were screened by means of a self-report questionnaire.

A second limitation of this study is that the cross-sectional design precluded the analysis of the prediction of outcome, thus allowing only inferential speculation as regards the direction of causality and the magnitude of risk. Indeed, a longitudinal follow-up of this cohort up would shed light on the predictive validity of the different PLE subtypes.

The possibility to further "close in" on the risk factors for psychosis and other severe mental disorders by identifying phenotypic factors, other than PLEs, that are involved in the onset of such disorders remains a clinical and research challenge. The combination of PLEs with other factors, such as functional decline (Yung et al. 2003; Mason et al. 2004; Yung et al. 2006), distress (Freeman et al. 2003; Broome et al. 2005) and self-disturbance (Handest et al. 2005; Parnas et al. 2005), may place an individual at greater risk of a full-blown psychotic disorder. Moreover, particular combinations of PLEs with other factors

may result in the onset of particular types of psychotic disorder. In this regard, there is evidence suggesting that PLEs combined with self-disturbance may be predictive of conditions within the schizophrenia spectrum (Handest et al. 2005; Parnas et al. 2005; Raballo et al. 2009). The identification of PLE subtypes associated with these other factors may help predict the risk of developing full-blown, severe psychiatric disorders. It could also be used to design a screening approach aimed at identifying subjects who are at high risk of psychosis but are not included in UHR samples because that have not sought help.

To sum up, the identification of different subtypes of PLEs in this large sample confirms the findings of our previous studies. As different PLE subtypes appear to be maladaptive in different ways and to indicate varying levels of risk of psychosis and other severe mental disorders, it is, we believe, misleading to define PLEs as a homogenous entity.

3.2 Research 2: Psychotic experience subtypes, poor mental health status and help-seeking behaviour in a community sample of young adults·

3.2.1 Introduction

As we described in Chapter 1, psychotic symptoms have traditionally been considered categorical phenomena and a dichotomous approach has been taken when viewing them. However, over recent years greater attention has been paid to the meaning and role played by the transient or attenuated forms of psychotic symptoms, known as "psychotic experiences" (PEs), which have been placed on a *continuum* with full-blown symptoms, at least within the schizophrenia spectrum (Meehl et al. 1962; Strauss et al. 1969; Chapman et al. 1980; Kwapil et al. 1996).

The first longitudinal study was a 10-year follow-up study on subjects with PEs (Chapman et al. 1994), selected using a screening tool for schizotypal traits carried out on a population of university students and within a group of schizotypal subjects. 14% of the university student group with PEs subsequently developed a psychotic disorder, as opposed to 1.1% of schizotypal subjects without PEs. Studies on the prevalence and incidence of PEs in the general population date back to the early 1990s (Eaton et al. 1991; Tien et al. 1991; Kendler et al. 1996). In further studies a lifetime prevalence of PEs was reported at 12.9%, compared to lifetime prevalence rates of clinical psychotic symptoms and psychotic disorders of 4.2% and 1.5% respectively (van Os et al. 2000; van Os et al. 2001). In these studies it was noted that with an increasing number of PEs reported, the

· This research has been published in an adapted version on Early Intervention in Psychiatry. Armando M, Nelson B, Yung A. et al. Psychotic experience subtypes, poor mental health status and help-seeking behaviour in a community sample of young adults. Early Intervention in Psychiatry 2012; 6:300-308.

risk of concomitant clinical psychotic symptoms increased proportionally. Given that PEs and psychotic symptoms were similarly associated with various socio-demographic risks, the authors proposed a *continuum* model of psychosis that extends beyond the boundaries of the clinical cases to include the entire population (Claridge et al. 1962).

A 15-year-longitudinal study found that children with PEs have a 5.1 greater probability of receiving a diagnosis of schizophreniform disorder at follow-up compared to children without PEs (Poulton et al. 2000). Moreover, a 16-year longitudinal study explored the relationship between the developmental trajectory of psychopathology and its impact on the development of PEs (Scott et al. 2009). A relative worsening of psychopathology throughout childhood and adolescence increases the probability of reporting PEs at a later stage by a rate of 3.8, which increases to a rate of 4.5 in the case of continuously high levels of psychopathology throughout childhood and adolescence.

The first meta-analysis on this issue indicated that the prevalence and overall incidence of psychotic phenomena in the general population is 5.3% and at 3.1% respectively (van Os et al. 2009). This slight discrepancy between the two parameters and the data that emerged from longitudinal studies indicate that about 75-90% of these phenomena is transitory. In any case, in the presence of certain risk factors, such as particular developmental stage, stressful or traumatic life events, social adversities, drug abuse, urbanization, the same phenomena tend to persist in an abnormal way and become greatly predictive of a range of mental disorders.

Other authors have questioned whether the heterogeneity of the data gathered to date could be due to the fact that not all PEs have the same weight in terms of risk for future evolution into psychiatric disorders. To investigate this issue Yung and colleagues (2006) conducted a study on a clinical sample of young help-seekers aged between 15 and 24 years with

mood disorders. PEs were investigated using the *Community Assessment of Psychic Experiences* (CAPE) (Stefanis et al. 2002). A factor analysis identified three PEs subtypes: bizarre experiences (BE), persecutory ideas (PI) and magical thinking (MT). PI was the most prevalent of the factors, with 97.9% of participants endorsing at least 1 of the 5 items at least sometimes, compared with 73.6% reporting BE and 64.3% reporting MT. Only BE and PI were associated with distress, depression and reduced general functioning. A second study, conducted on a non-clinical sample of adolescents aged between 13 and 17 years, identified four PEs subtypes using the CAPE: BE, PI, perceptual abnormalities (PA) and MT (Yung et al. 2009). PI and MT were the most commonly experienced PEs. More than half of the sample reported they had experienced one of these PEs "at least sometimes". The prevalence rates for BE and PA were lower. In this case, only BE, PI and PA were associated with markers of poor mental health status. A third study presented in the previous Paragraph (Armando et al. 2010), conducted on a non-clinical sample of adolescents and young adults aged between 15 and 26 years using the CAPE, identified four PEs subtypes: PI, BE, PA as in the previous study, and Grandiosity (GR). PI had the highest prevalence, with 92.3% endorsing at least 1 item "sometimes", followed by GR (74.8%). Prevalence rates substantially decreased as the frequency rate increased. In this case only PI and PA were related to markers of poor mental health status.

These data suggest that PEs can be present in a given individual for a number of different reasons: as an expression of an underlying disturbance; as background clinical "noise" associated with non-psychotic disorders; or as phenomena reported by normal individuals and not associated with distress, disability or help-seeking (Nelson et al. 2009). Indeed another study conducted with a general population sample identified two different subtypes of PEs: schizophrenia nuclear symptoms, which were associated with cannabis use in

adolescence, and schizotypal signs, which were associated with childhood adversity as well as chronic physical or mental disorders in parents (Rossler et al. 2007). This research indicates that PEs do not constitute a unitary phenomenon. Instead, different types of PEs exist with different probable trajectories and different underlying causes.

In order to look more closely at the hypothesis that specific subtypes of PEs have stronger psychopathological significance than others, we decided to investigate PEs in relation to five markers of poor mental health status: distress, depressive symptoms, anxiety symptoms, reduced general functioning and help-seeking. The latter is of particular interest because it is one of the aspects of the "ultra high risk" (UHR) criteria used to identify young people at risk of a first episode of psychosis (Miller et al. 2002; Yung et al. 2003; Cannon et al. 2008). We chose to study PEs in subjects aged 19 to 26 years as the first psychotic episode typically manifests in late adolescence or in early adulthood (Patel et al. 2007).

The aims of the present study are: i) To determine whether different subtypes of PEs can be identified in a non-clinical sample of young adults; ii) To explore whether particular PE subtypes have a greater probability than others of being associated with five markers of poor mental health status: distress, depressive symptoms, anxiety symptoms, reduced general functioning and help-seeking.

3.2.2 Methods

3.2.2.1 Participants

The sample consisted of students from the Faculty of Oriental Studies and the 1st Faculty of Medicine and Surgery at the University of Rome "Sapienza", from the Faculty of Vocational Science and of Pharmacy at the University of Chieti-Pescara "G. d'Annunzio".

The sample, which consisted to a total of 997 subjects, included all students who were available at the time of distributing the questionnaires during the academic year 2009/2010. It was carried out on a voluntary basis. Although subjects were not randomly selected the large size of the sample and a control on the principal demographic variables in respect to the values found in the entire university population make it highly representative. All participants provided informed consent.

A number of trained assistants were present while subjects completed the questionnaires in order to provide assistance, if required. The entire procedure took between 50 and 60 minutes.

3.2.2.2 Instruments

We developed a Basic Data Form (BDF; available on request) designed to capture a number of sociodemographic and clinical variables. These included: resident/non resident student status, mother/father level of education, family environment, personal/familiar religious background, previous psychiatric history, previous or current psychotropic medication/psychoterapy, and drug/alcohol abuse (Armando et al. 2010).

PEs were assessed using the CAPE (Stefanis et al. 2002). The CAPE provides scores on three dimensions: positive (20 items), negative (14 items) and depressive (8 items). For each item the frequency of the experiences are indicated and the level of stress they generate. The internal consistency of the Italian version demonstrates good validity (Daneluzzo et al. 2008).

Anxiety symptoms were evaluated using the *Beck Anxiety Inventory* (BAI) (Beck et al. 1993), a 21-item self-report instrument that assesses anxiety symptoms.

Depressive symptoms were evaluated using the *Beck Depression Inventory–II* (BDI-II) (Beck et al. 1996), a 21-item self-report instrument that assesses depressive symptoms.

General functioning were assessed using the *General Health Questionnaire-12* (GHQ-12) (Goldberg et al. 1976). The validity, reliability and factorial structure of the GHQ-12 have been confirmed for the Italian version (Piccinelli et al. 1993; Politi et al. 1994). The answer to each item is given on a four point scale which is then calculated on the basis of a binary system. Different studies suggest that for the correct identification of poor general functioning the threshold value of a total score ≥4 should be used (Goldberg et al. 1976; Weich et al. 1998).

3.2.2.3 Statistical analysis

The statistical analysis of the data was carried out using central tendency indices, dispersion and quartiles for the description of numeric variables, and absolute and relative frequencies for ordinal and qualitative variables; data were screened for missing values, for the assumption of normality, linearity and homogeneity, and for outliers. The correlations matrix of the CAPE-positive items (frequency score) was examined with a similar statistical analysis of our previous study (Armando et al. 2010). There were many correlations greater than 0.3 between items and the sample was well over 300 subjects indicating that factor analysis was a meaningful technique. We applied the Principal Components Analysis (PCA) on the frequency score of positive items of the CAPE, with the application of the Varimax method for the axes rotation; only the factors with an eigenvalue >1 were considered and included in the model; the inclusion of the original variables in each factor was carried out using a cut-off value of 0.30. Factorial scores were calculated and analysis of their correlation with distress scores of the CAPE positive items, GHQ-12, BAI and BDI-II with application of the Pearson's linear correlation coefficient r were made and Bonferroni corrected. Analysis of covariance (ANCOVA) for the assessment of relations between non-help-seeking and help-seeking, in respect to factorial

scores, GHQ-12 and BAI was conducted with adjustment for depression (BDI-II total score).

For the ANCOVA, owing to the significant numeric discrepancy between the sample numbers of the non-help-seeking (n=703) and help-seeking (n=165) subjects, to balance the numeric consistencies the study was carried out on randomized (Di Giorgio et al. 1984) cases representative for clinical and socio demographic variables of the two groups. We considered p values less than .05 to be statistically significant.

3.2.3 Results

3.2.3.1 Characteristics of the sample

The sample consisted of 997 university students with a mean age of 21 years (σ=2.45), of which there were 235 males (23.8%) and 753 females (76.2%). The screening of the general level of functioning in the sample, carried out through the GHQ-12, indicated a reduced general functioning in 40.7% (n=406) of the subjects concerned. The general functioning level was significantly lower in females than males (F=7,45; p=0,006). The mean BDI-II score was 10.9 (σ=8.3) and 13.9% (n=139) of the sample showed mild to severe depressive symptoms. The mean score for the BAI turn was 11.4 (σ= 9.4) and 26.9% (n=268) of the sample showed mild to severe anxiety symptoms. 440 students (44.3%) felt, during the past year, the need to consult a psychiatrist or psychologist, but 281 of them (63.9%) did not end up actually seeing one. The causes of this high number of "unexpressed help-seeking" were the fear of stigmatization (27.5%; n=77), to economic difficulties (26.1%; n=73), to mistrust (25.4%; n=71) and finally to the lack of information (21%; n=59). Furthermore, 77.2% (n=770) of students considered the absence of an Early Intervention Service a barrier to help seeking.

3.2.3.2 PEs subtypes

The factorial analysis of frequency scores of the CAPE-positive items highlighted four factors that describe around 51% of the total variance. Factor 1, perceptual abnormalities (PA), refers to subthreshold forms of auditory and visual hallucinations. Factor 2, persecutory ideas (PI), refers to suspiciousness and other forms of subthreshold persecutory ideas. Factor 3, magical thinking (MT), refers to belief in the occult or telepathy and to subthreshold forms of grandiosity. Factor 4, bizarre experiences (BE), refers to subthreshold forms of thought pervasiveness, influence and control (table 9 and table 10).

3.2.3.3 Prevalence of the PE subtypes

Low frequency PEs (i.e., those that only occur occasionally) were very common in this sample. In particular, for PI at least one of the six items was endorsed by 98.1% (n=978) of participants, for MT at least one of the four items by 92.5% (n=922), for BE at least one of the six items by 70.8% (n=706), for PA at least one of the four items by 30.0% (n=299).

On the other hand, PEs with a higher frequency (i.e., those that are often or always manifest) were less common: for PI at least one item was identified by 60.8% (n=606) of participants, for MT by 49.7% (n=496), for BE the percentage fell to 26.0% (n=259), falling even further to 4.8% (n=48) for PA (see table 9 for single item prevalence). PI were significantly more frequent in females (F=16.67; p=0.00005) and in younger subjects (F=3.46; p=0.01). BE were significantly more frequent in females (F=16.11; p=0.00007). All other variables did not vary by sex and age.

Table 9. CAPE positive items: factor loading and frequency

Item	**Subtype of PEs**	Factor loading				Frequency (%)		
		F1	F2	F3	F4	never	at least some-times	always/nearly always
	Perceptual Abnormalities (PA)							
34	Have you ever heard voices talking to each other when you were alone?	-0.81				93.0	5.2	1.9
33	Have you ever heard voices when you were alone?	-0.70				77.3	20.0	2.7
42	Have you ever seen objects, people or animals that other people can't see?	-0.64		.32		89.6	8.7	1.7
41	Have you ever felt as if a double has taken the place of a family member, friend or acquaintance?	-0.34				92.7	5.9	1.4
	Persecutory Ideation (PI)							
2	Have you ever felt as if people seem to drop hints about you or say things with a double meaning?		-0.80			12.2	57.8	30.0
22	Have you ever felt that people look at you oddly because of your appearance?		-0.63			43.4	39.3	17.4
10	Have you ever felt as if there is a conspiracy against you?		-0.59			69.9	24.0	6.1
6	Have you ever felt as if some people are not what they seem to be?		-0.57			7.8	47.4	44.8
5	Have you ever felt as if things in magazines or on TV were written especially for you?		-0.34		0.39	83.0	14.8	2.2
7	Have you ever felt that you are being persecuted in some way?		-0.31		0.35	66.9	28.8	4.4
	Bizarre Experiences (BE)							
26	Have you ever felt as if the thoughts in your head were not your own?				0.67	75.6	19.8	4.6
28	Have your thoughts ever been so vivid that you were worried other people would hear them?				0.61	56.8	32.0	11.2
24	Have you ever felt as if the thoughts in your head are being taken away from you?	-0.34			0.57	86.5	10.3	3.2
17	Have you ever felt as if electrical devices such as computers can influence the way you think?				0.56	67.2	23.7	9.1
30	Have you ever heard your thoughts being echoed back to you?				0.40	67.9	23.5	8.6
31	Have you ever felt as if you are under the control of some force or power other than yourself?	-0.57			0.30	88.8	8.6	2.6
	Magical Thinking (MT)							
20	Have you ever believed in the power of witchcraft, voodoo or the occult?			0.82		59.0	29.9	11.1
15	Have you ever thought that people can communicate telepathically?			0.68	0.32	48.4	37.1	14.5
11	Have you ever felt as if you are destined to be someone very important?			-0.84		36.6	41.5	21.9
13	Have you ever felt that you are a very special or unusual person?			-0.84		20.0	47.9	32.1

Table 10. Correlations between subtypes of PEs distress they generate, BDI-II, BAI, total GHQ-12 score

	BDI-II	BAI	Distress	GHQ-12
PA	0.17	0.09	0.85**	0.12
PI	0.53*	0.42*	0.79**	0.26*
BE	0.39*	0.11	0.86**	0.22*
MT	0.10	0.08	0.68**	0.08

* $p<0.001$ (Bonferroni corrected) ** $p<0.0001$ (Bonferroni corrected)
Note: Distress= Distress related to PEs.

3.2.3.4 Correlation of PE subtypes with poor mental health markers

The correlations between PE subtypes and the distress level they generated were all positive and highly significant ($p<0.0001$). However, correlations between PE subtypes and reduced general functioning were positive and significant exclusively for PI ($p<0.001$), BE ($p<0.001$) and PA ($p<0.001$). Correlations between PE subtypes and depressive symptoms were positive and significant for PI ($p<0.001$) and BE ($p<0.001$). Correlations between PEs and anxiety symptoms were positive and strongly significant only for PI ($p<0.0001$).

After Bonferroni's correction to adjust for the observed significance level, all the previously reported significant correlations survived except the correlation between PA and GHQ-12 (table 10).

Also help-seeking in correlation with PE subtypes was strongly associated only with PI ($p<0.01$), with no significant depressive symptoms interaction being observed (table 11).

Table 11. Analysis of covariance, adjusted for depression: association between help-seeking and subtypes of PEs, BAI, total GHQ-12 score (Mean±S.E.)

	non-Help-seeking	Help-seeking	*p*
PA	6.87±0.16	7.18±0.20	=0.252
PI	10.64±0.23	12.50±0.29	=0.009
BE	10.73±0.29	11.22±0.36	=0.327
MT	8.26±0.25	8.57±0.31	=0.472
BAI	12.92±0.76	18.36±0.94	<0.001
GHQ-12	14.17±0.59	13.5±0.72	=0.312

3.2.4 Discussion

The results show that different subtypes of PEs can be identified in a community sample of young adults. The study confirms the results obtained by Yung et al (2006) and Armando et al (2010), which indicated that different PE subtypes are differentially correlated with mental disturbance markers of distress, depressive symptoms, anxiety symptoms, reduced general functioning and help-seeking The current study extended these previous studies by finding correlations between PE subtypes and two further markers of poor mental health status, namely help-seeking and anxiety symptoms. In contrast to the previous studies (Yung et al. 2006; Armando et al. 2010), only one PE factor, that of PI, was found to be related to all five markers of poor mental health status (table 12).

Table 12. Association between subtypes of PEs and indicators of poor mental health status

	PI	BE	PA	MT
Distress	+	+	+	+
GHQ-12	+	+	-	-
BDI-II	+	+	-	-
BAI	+	-	-	-
Help-seeking	+	-	-	-

The prevalence of low frequency PEs was high, whilst high frequency PEs were far less common, as has previously been observed in both non-psychotic clinical samples and in non-clinical samples (Yung et al. 2006; Yung et al. 2009). For example 20% (n=200) of participants claim to have sometimes heard voices, but only 2.7% (n=27) claimed to have heard them often or always. This prevalence of 20% is lower than the 28% found in adolescents, but higher than the 8% found in the general population (van Os et al. 2009). This could be due to sampling differences and to some demographic factors associated with a higher prevalence of PEs, such as urbanization and younger age. The current results also indicate that in the passage from adolescence to adult age, the prevalence of MT was bypassed by PI. This reduction of MT in the passage from childhood-adolescence to adult age was also found in previous studies (Woolley et al. 1997; Subbotsky 2007). Based on the current results and these previous studies MT does not seem to have clinical significance.

PA, PI, and BE were associated with a higher level of distress but only PI and BE were associated with a lower level of general functioning. The prevalence of reduced general functioning, defined by GHQ-12 score≥4, in our overall sample was 40.7% (n=406). This

strikingly high prevalence was consistent with a study of 7,127 adolescents, which observed a prevalence of poor functioning of 39.8% (Nishida et al. 2008), and with a study of 1,289 adolescents and young adults, which observed a prevalence of poor functioning of 36.5%.

Moreover PI and BE were both significantly associated with more severe depressive symptoms, whereas PA, in contrast to other studies (Yung et al. 2009; Armando et al. 2010), was not associated with depressive symptoms. This could be due to the fact that the current sample consisted of young adults as opposed to adolescents. Young adults may have a more "structured" identity than adolescents and be less prone to affective instability, including depressive symptoms. In any case, in so far as clinical samples are concerned, the relationship between some PE subtypes and depression has been hypothesized to be a vicious circle in which depression increases the probability of experiencing the PEs negatively, determining in this way an increase of distress, psychic malaise and secondary depressive symptoms (Yung et al. 2007).

A very high number of participants (44.3%) considered consulting a psychologist or psychiatrist. In a previous study, conducted with the same sample, we found significant correlations between perceived need for help and depressive or anxiety symptoms. Since our findings showed higher level of these symptoms than results from other studies on college students (Armando et al. 2010; Chandavarkar et al. 2007) it is probable that this accounted for the higher number of participants who considered consulting a psychologist or psychiatrist.

In addition to the above-mentioned psychosocial difficulties, this study also investigated the association between the different PE subtypes and help-seeking behaviour. Only PI was found to be more frequently reported by subjects who had consulted a psychiatrist or

psychologist, and this correlation was not influenced by the presence of an concurrent depressive symptoms. We can speculate, therefore, that experiences like suspiciousness and other subthreshold forms of persecutory ideas form a link between PEs in the general population and UHR samples, whose inclusion criteria consist of help-seeking behaviour in the context of PEs (Miller et al. 2002; Yung et al. 2003; Cannon et al. 2008).

Finally, anxiety symptoms also showed a significant positive correlation with PI. This correlation could have an important meaning if we consider that in follow-up studies (Poulton et al. 2000; Hanssen et al. 2005) PEs with incidental high level of anxiety symptoms at baseline significantly increase the risk of transition to psychosis or other severe mental disorders. It is therefore possible that subjects with PI and associated anxiety in the current sample will have a worse outcome than those who do not. Further follow up of this sample is required to investigate this possibility. The finding suggests that identifying young adults with PI may have the practical value of helping to "narrow down" our attention on people who need mental health treatment, even though we do not know exactly what disorder such symptoms are associated with.

3.2.4.1 Limitations

There are several limitations to the study. The first limitation was that it used a self-administered instrument to assess PEs. Therefore a mistaken interpretation of the questions by the participants could have led to an overestimation of the prevalence of PEs (Kendler et al. 1996). However, there is evidence of a good correlation between CAPE and the clinical interviews Liraud et al. 2004; Konings et al. 2006).

The second limitation of the study was its cross-sectional design. This did not allow us to establish the direction of causality between PEs and psychopathology or the degree of risk of developing a mental disorder which each PEs subtype confers.

The third limitation of the study concerns the sample. Being a student sample it is not random general population sample. However, the large size of the sample, the fact that it was composed of 90% (n=1108) of all the students registered in the four faculties during the academic year, the low rate of non-responders-refusers (5%; n=56) and a control on the principal demographic variables in respect to the values found in the entire university population make it highly representative.

The fourth limitation of the study is that we take only the university population into consideration, but other studies with samples of young adults of a similar age group coming both from university and not, did not show significant differences between the two sub-groups in terms of mental health status (Blanco et al. 2008).

The fifth limitation of the study is that no diagnostic interview were performed in order to explore previous or current psychiatric diagnoses. Indeed the CAPE and overall PE scores do not allow us to determine any specific psychiatric diagnosis and, least of all, to distinguish clearly between possible development of psychotic disorders as opposed to other psychopathological syndromes. Nevertheless, previous research indicates that on self-report questionnaires, subjects appear to be more likely to report psychotic symptoms and experiences than other types of symptoms (Hamera et al. 1996). Moreover, the CAPE has been widely used to assess community PEs and has been validated against interviews, there is evidence of a strong correlation between the CAPE and clinical interviews (Cannon et al. 2008; Liraud et al. 2004) and a recent paper showed that the CAPE increases the diagnostic specificity and sensitivity in schizophrenic disorders if compared with clinical evaluation alone (Boonstra et al. 2009). In addition, the fact that the presence of PEs can be considered to be predictive of future onset of severe mental disorders has been reported in several studies (Chapman et al. 1994; Poulton et al. 2000; van Os et al. 2009;

Rossler et al. 2005; Hanssen et al. 2007). Moreover the aim of the current study was not to investigate the presence of a direct correlation between PEs and specific psychiatric disorders, but rather to outline a possible framework within which some specific PEs may be considered to have a higher "specific weight" than others in terms of the evolution of the clinical pathway leading to severe mental illnesses such as psychotic disorders (Cougnard et al. 2007; Collip et al. 2008). Finally, in terms of "psychiatric diagnosis" we explored the "mental health status" using the BDI-II, BAI and GHQ-12 scales, which have been validated and widely used for these puruposes in numerous studies (Goldberg et al. 1997; Preti et al. 2007; Shean et al. 2008; Whisman et al. 2000) and which is why we chose them as indicators of poor mental health.

The final limitation of the study is the lack of data about the role of substance abuse. However in another study, conducted with the same sample, we found that 13.2% of participants used cannabis more than once a month and 2.2% used other kind of hallucinogenic drugs (Armando et al. 2010). Even though a standardized diagnostic interview screening for substance use disorders was not performed, these findings were in line with data on drug use among the Italian student population (Andersson et al. 2007). Since this previous study showed that cannabis users had higher frequency scores on MT, while other PE subtypes (i.e. PE subtypes more associated with poor mental health status) did not correlate with any kind of substance use, it is unlikely that substance abuse had a significant impact on our findings.

3.2.5 Conclusion

These results, as a whole, provide further support for the view that PEs consist of subtypes with different clinical significance. In particular, only PI was associated with all five

indicators of poor mental health status (distress, depressive symptoms, anxiety symptoms, reduced general functioning and help-seeking) and, consequently, it may be hypothesized that PI has a greater clinical significance compared to other experiences. Reports of PI should therefore be interpreted with greater clinical concern, considering furthermore that individuals with PEs of higher frequency and intensity who actually ask for help, have five times the probability of being diagnosed with a psychotic disorder four years later (Hanssen et al. 2003).

3.3 Research 3: Prevalence of Psychotic-like experiences in young adults with social anxiety disorder and correlation with affective dysregulation·

3.3.1 Introduction

Social Anxiety Disorder (SAD) is a highly prevalent comorbid disorder in patients with established schizophrenia and schizoaffective disorder, estimated to occur in over a third of patients (Huppert and Smith 2005; Pallanti et al. 2004). Patients with comorbid SAD are at greater risk for suicide attempts, greater lethality of suicide attempts, lower social adjustment and overall quality of life, and substance/alcohol abuse (Pallanti et al. 2004). The common co-occurrence of SAD and psychotic symptoms is present early in psychotic illness. It is estimated that between 28% and 33% of first-episode psychosis populations

· This research is "in press" in an adapted version on The Journal of Nervous and Mental Disease. Armando M, Girardi P, Lin A et al. Prevalence of Psychotic-like experiences in young adults with social anxiety disorder and correlation with affective dysregulation. The Journal of Nervous and Mental Disease. In press.

will have comorbid SAD (Birchwood et al. 2007; Lang and Stein 2001). Even before the onset of frank psychotic symptoms, SAD represents one of the most frequent diagnoses in the prodromal phases of psychosis (Cannon et al. 2008; Johnstone et al. 2005).

Michail and Birchwood (2009) compared the phenomenology of social anxiety disorder in first-episode psychosis with that in a non-psychotic group. They developed three possible hypotheses regarding the relationship between social anxiety and psychosis: social anxiety pre-dates the onset of persecutory beliefs and serves to trigger and/or maintain persecutory thinking; social anxiety and persecutory thinking develop concurrently in the early phase of psychosis and follow a similar course; and social anxiety develops in some as a consequence of paranoid thinking.

After examining the role of anxiety in the development of persecutory delusions, Freeman, Garety and Kuipers (2001) suggest that similar themes and processes underlie both. Anxiety is a defensive reaction to the anticipation of threat and danger (physical, social or psychological), while persecutory delusions are characterised by perceived danger or harm from others. They also argue that anxiety is inherent in paranoia and is likely to play an important role in the formation and maintenance of persecutory delusions (Freeman et al., 2001). Indeed, high levels of paranoid features correlate with higher social anxiety in populations with schizophrenia (Huppert and Smith, 2005; Lysaker et al. 2010).

Other studies highlighted the role played by the interaction of anxiety, depression and low self-esteem in the development of psychotic symptoms (Bentall and Fernyhough, 2008; Bentall et al. 2009; Thewissen et al., 2007; Yung et al. 2007). This pattern, also called “affective dysregulation”, appears to play an important role in the development and maintenance of paranoid delusions and psychotic symptoms (Smeets et al. 2010; Wigman et al. 2011).

In trying to understanding the link between anxiety, affective dysregulation and psychosis, attention has focussed on a possible cognitive/affective dysregulation related to Intolerance of Uncertainty (IU) and jumping-to-conclusions. This cognitive/affective dysregulation is conceptualized as a basic dysfunctional schema that may determinate bias in information processing and is related to the idea that uncertainty is unacceptable (Boelen and Reijntjes, 2009; Buhr and Dugas, 2006; Freeston et al. 1994). In this regard, phenomenological, cognitive and neurobiological models suggest the critical factor of "sensitization" (Collip et al. 2008) in the onset of psychosis is the faulty appraisal or interpretation of experiences or events (Blankeburg, 1971; Kapur, 2003). This may, from a phenomenological and cognitivistic point of view, be related to a pathway that starts with a weakness in self-identity, becomes an IU and subsequently leads to jumping-to-conclusions. The end result is the faulty appraisal or interpretation of experiences or events, i.e. the core of delusions (Freeman et al. 2001). Previous studies have demonstrated a correlation between psychosis, a faulty empathic process and jumping-to-conclusions (Bentall et al. 2009; Corcoran et al. 2008; Menon et al. 2008). Although IU is often described as a phenomenon that is closely related to jumping-to-conclusions, anxiety and worry (Boelen and Reijntjes, 2009; Buhr and Dugas, 2006), it has rarely been directly related to psychotic symptoms and at-risk mental state (Broome et al. 2007; White and Gumley, 2010).

While many studies have explored the presence of SAD in patients with psychosis, there has been little investigation of psychotic symptoms in patients with SAD. Investigating the association between a history of trauma and persecutory ideation and verbal hallucinations, Freeman and colleagues (2009) found that the relationship between trauma and paranoia was explained by levels of anxiety. Martin and Penn (2001) examined the linear relationship between persecutory ideation and multiple clinical and social cognitive

variables in the general population and found that higher levels of paranoid ideation were significantly associated with greater depressed mood and social anxiety. To our knowledge, only one case study has specifically investigated the presence of psychotic symptoms in three patients with SAD (Veras et al. 2011). These authors present three possible explanations for psychotic manifestations in SAD. Firstly, psychotic experiences may arise from the individual's inability to challenge the impression of being criticized by people. A second possibility is that the stressful and perpetuating nature of SAD makes some individuals more likely to present with more severe psychiatric symptoms such as delusions. Finally, it may be that in some cases, SAD is caused by a primary thought abnormality (psychotic self-reference) rather than an affective disturbance (anxious insecurity), which leads to intense concern about others' opinions.

In summary, no research has specifically investigated psychotic symptoms and their correlation with other clinical and socio-demographic variables in patients with SAD. Moreover, no study has investigated the role played by affective dysfunction in the development of Psychotic-Like Experiences (PLEs) in this group of patients. Individuals who suffer intensely and frequent PLEs are five times more likely to be diagnosed with a psychotic disorder four years later (Hanssen et al. 2003), particularly if the PLEs are of a persecutory nature (Armando et al. 2010). This highlights the importance of identifying which young people with SAD are most vulnerable to experiencing psychotic experiences.

The aims of our study were to investigate a large sample of young adults with SAD for i) the prevalence of PLEs compared with an healthy control group, and ii) the clinical (IU, anxiety, depression, general functioning, IQ, substance abuse) and sociodemographic (sex, age, cultural background, level of education) characteristics of SAD patients with and without PLEs.

We hypothesize that the prevalence of clinically relevant PLEs will be significantly higher in those with SAD than in general population. Additionally, the subsample with clinically relevant PLEs will have a different clinical picture to SAD patients without PLEs, characterised by higher levels of depression, anxiety and IU, indicative of greater affective dysregulation.

3.3.2 Methods

3.3.2.1 Procedures and Sample

The subjects in this study were 128 help-seeking young adults with SAD and 41 healthy controls. The age range was 19 to 25 years. Patients were recruited at the outpatient psychiatric unit of the Sapienza University Hospital in Rome between January 2008 and December 2010. The inclusion criteria were an Axis I diagnosis of SAD (DSM-IV-TR) (assessed on the SCID-I) and no Axis II diagnosis (assessed on the SCID-II). The exclusion criteria were a previous or current psychotic disorder (affective and/or non-affective), IQ below 85, and symptoms due to any organic etiological factor or related to drug use. The healthy controls were screened in order to exclude any psychiatric disorder using the SCID-I and SCID-II. All the participants provided written informed consent.

3.3.2.2 Instruments

Sociodemographic and clinical history. Basic information on the subjects' sociodemographic background and clinical history (i.e. familiar cultural background, level of education previous psychiatric diagnoses, previous contact with psychiatric services, substance abuse) was collected.

PLEs, negative symptoms and related distress. PLEs and negative symptoms were assessed using the positive and negative subscales of the Community Assessment of Psychic

Experiences (CAPE; Stefanis et al. 2002). This self-report scale measures the lifetime prevalence of positive (PLEs), negative and depressive symptoms on both a frequency scale (0 = never to 4 = nearly always) and a distress scale (1 = not distressed to 4 = very distressed). The latter was used to evaluate the level of distress caused by PLEs. Since has been suggested that self-reporting instruments may over-estimate the prevalence of PLEs (Kendler et al. 1996), a psychiatric clinician conducted clinical re-interviews in order to validate the self reported PLEs. Similar methodology was previously employed by Hanssen et al. (2005; 2003).

Intolerance of uncertainty. Intolerance of uncertainty was evaluated using the Intolerance to Uncertainty Scale (IUS; Freeston et al. 1994). This is a 27-item questionnaire rated on a 5-point Likert scale. The IUS has a good internal consistency (Cronbach's alpha=0.94), item-total correlations ranging from 0.36 to 0.77 and retest reliability of r=0.74 (Buhr and Dugas, 2002, 2006; Freeston et al., 1994). The scale has previously been used in studies investigating delusion formation (Broome et al., 2007), anxiety and depression (Boelen and Reijntjes, 2009; Buhr and Dugas, 2006).

Other measures. Level of anxiety and depressive symptoms were evaluated using the Beck Anxiety Inventory (BAI; Beck and Steer, 1990) and Beck Depression Inventory–II (BDI-II; Beck et al. 1996). Both are 21-item self-report instruments that assess anxiety and depressive symptoms respectively. The SCID-I for DSM-IV (First et al. 1997) was used to ascertain psychiatric diagnoses. Raters were experienced clinicians, trained in using the SCID-I. Level of general functioning was measured using the General Health Questionnaire-12 (GHQ-12; (Goldberg et al. 1997). The Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 2001) was used to assess IQ.

3.3.2.3 Data Analysis

Analyses were conducted using PASW statistics 18. As a first step, data were screened for missing values, normality, linearity, homogeneity and outliers. Eleven subjects were excluded due to missing data.

PLEs with low frequency and related low level of distress should not be considered as clinically meaningful and are not related to increased risk of further psychotic symptoms (Armando et al. 2010; Hanssen et al. 2005; Schultze-Lutter et al. 2011; van Os et al. 2009; Yung et al. 2006).

In order to reduce the risk of misclassification, a psychiatric clinician conducted clinical interview in order to validate each self-reported PLE for frequency and distress. Based on these considerations and in line with previous studies (Hanssen et al. 2003; Nishida et al. 2008; van Os et al. 2001), we defined as "clinically significant PLE" any PLE which was scored both severe and distressing (i.e. scored 3 to 4 in the severity and related distress subscales) *and* was confirmed by clinical interview. Consequently two clinical subsamples were defined. The first subsample with SAD but without clinically significant PLEs (SAD-PLEs; n=96; 74.6% of patient sample) scored 1 to 2 (never/sometimes) on any item of the CAPE positive subscale and CAPE distress subscale related to positive symptoms. The second subsample with SAD and clinically significant PLEs (SAD+PLEs; n=32; 23.7%) scored 3 to 4 on at least one item (nearly always/always) of both the positive and distress subscale.

The three groups (SAD-PLEs, SAD+PLEs and healthy control group) were compared on continuous demographic and clinical variables using ANOVA. Comparisons on categorical variables made using chi-square analysis. In order to exclude type I and type II errors because of unequal sample sizes, homogeneity of variance was confirmed using Levene's

test. A subsequent ANCOVA was conducted, covarying for demographic variables. Hochberg's GT2 was used for post hoc comparisons. Correlations were conducted within the SAD+PLEs subsample to assess the relationship between the level of PLEs and the other clinical variables. All tests were two-tailed and *p* values less than 0.05 were considered statistically significant.

3.3.3 Results

3.3.3.1 Prevalence of clinically significant PLEs in patient with SAD and healthy controls

The prevalence of clinically significant PLEs in the healthy control group was significantly lower than in the SAD group as a whole. Only two subjects (4.8%) in the control group showed clinically relevant PLEs compared to 32 subjects (23.7%) in the clinical group ($p<0.001$). All further analyses were conducted on the three defined subsamples (SAD+PLEs, SAD-PLEs, healthy controls).

3.3.3.2 Sociodemographic Characteristics

Age, gender and others sociodemographic variables were homogeneous within the three groups. There were no significant group differences for IQ or drug/alcohol abuse (see Table 13).

Table 13. Sociodemographic characteristics of the samples

Variables	SAD+PLEs (*N*=32)	SAD - PLEs (*N*=96)	Control Group (*N*=41)	*Statistics*
Age (y±*SD*)	21.1±4.7	20.7±1.7	21.8±2.9	$F_{(2)} = 2.01$, $p = .138$
Sex (*N*;%)				
M	12 (31.2)	20 (20.8)	12 (29.2)	$\chi^2_{(2)} = 4.77$, $p = .07$
F	20 (69.8)	76 (79.2)	29 (70.8)	
IQ (±*SD*)	92±8.3	94±7.1	96±10.3	$F_{(2)} = 3.16$, $p = .231$
Education level (*N*;%)				
Primary school	6(18.7)	14(14.6)	10(24.4)	$\chi^2_{(3)} = 3.52$, $p = .286$
Secondary school	19(59.3)	57(59.0)	22(53.6)	
≥ University	7(21.8)	25(26.4)	9(22.0)	
Cannabis (*N*;%)				
≤ 1/month	30 (91.0)	88 (92.1)	39 (95.1)	$\chi^2_{(2)} = 2.96$, $p = .937$
>1/month	3 (9.0)	8 (7.9)	2 (4.9)	
Alcohol (*N*;%)				
≤ 1/month	28 (89.6)	85 (89.6)	38 (92.7)	$\chi^2_{(2)} = 4.44$, $p = .816$
>1/month	5 (3.5)	11 (11.4)	3 (7.3)	
Other drugs (*N*;%)				
≤ 1/month	31 (96.0)	94 (97.7)	41 (100.0)	$\chi^2_{(2)} = 12.76$, $p = .237$
>1/month	2 (4.0)	2 (2.3)	0 (0.0)	

3.3.3.3 Comparison between SAD + PLEs, SAD – PLEs and healthy controls

We compared the three groups on clinical and functional variables. As expected, the mean scores on the CAPE intensity and distress scales were significantly different in the three subsamples [F(2) = 226; $p<.0001$], with a progressive increase from control group (23±1.4), to SAD-PLEs (30±3.4) and SAD+PLEs (40±4.5). Significant group differences ($p<.0001$) were found for all clinical and functional scores (IUS; BAI; BDI-II; CAPE-negative; GHQ-12) (see Table 14).

Post hoc analyses revealed that both the clinical groups scored significantly higher than the control group on all the clinical variables (p<.0001). Comparisons between the two clinical groups showed that the SAD+PLEs group had significantly higher scores (p<.0001) for level of intolerance of uncertainty, and depressive and negative symptoms than SAD - PLEs group (see Table 14).

Table 14. Multiple Comparison between SAD + PLEs, SAD – PLEs and healthy controls. Hochberg's GT2 post hoc

Variables	SAD+PLEs (*N*=32)	SAD-PLEs (*N*=96)	HC (*N*=41)	Statistic	(I) group	(J) group	Mean diff.	S.E.	*p*-value	95%CI
CAPE pos	40±4.5	30±3.4	23±1.4	$F_{(2)}$ =226, *p*<.0001	HC	SAD-PLEs	-6.7	.62	*p*<.0001	(-8, -5)
						SAD+PLEs	-16.7	.78	*p*<.0001	(-18, -14)
					SAD+PLEs	SAD-PLEs	9.9	.67	*p*<.0001	(8, 11)
CAPE neg	30.4±5.3	26.5±5.9	19.1±3.7	$F_{(2)}$ =43.38, *p*< .0001	HC	SAD-PLEs	-7.4	1.01	*p*<.0001	(-9, -5)
						SAD+PLEs	-11.3	1.29	*p*<.0001	(-14, -8)
					SAD+PLEs	SAD-PLEs	3.9	1.13	*p*<.05	(1, 6)
BAI	25.9±8.6	23.1±8.1	3.6±2.4	$F_{(2)}$ =125.9, *p*< .0001	HC	SAD-PLEs	-19.7	1.35	*p*<.0001	(-23, -16)
						SAD+PLEs	-22.5	1.69	*p*<.0001	(-26, -18)
					SAD+PLEs	SAD-PLEs	6.5	1.43	*p*<.0001	(-7, 6)
BDI-II	25.2±12.4	17.2±8.7	3.0±2.5	$F_{(2)}$ =61.5, *p*< .0001	HC	SAD-PLEs	-14.2	1.67	*p*<.0001	(-18, -10)
						SAD+PLEs	-22.2	2.07	*p*<.0001	(-27, -17)
					SAD+PLEs	SAD-PLEs	8.1	1.76	*p*<.0001	(3, 12)
US	81.7±16.5	71.4±13.1	49.2±12.8	$F_{(2)}$ =26.23, *p*< .0001	HC	SAD-PLEs	-22.2	3.60	*p*<.0001	(-31, -13)
						SAD+PLEs	-32.5	4.58	*p*<.0001	(-43, -21)
					SAD+PLEs	SAD-PLEs	10.3	391	*p*<.05	(1, 19)
GHQ-12	19.1±6.4	16.3±6.1	8.1±4.1	$F_{(2)}$ =37.91, *p*< .0001	HC	SAD-PLEs	-8.2	1.12	*p*<.0001	(-11, -5)
						SAD+PLEs	-10.9	1.35	*p*<.0001	(-14, 8)
					SAD+PLEs	SAD-PLEs	2.6	1.27	*p*=.079	(1, 5)

3.3.3.4 Correlation between PLEs and other clinical variables in SAD+PLEs group

Correlations between PLEs and others clinical variables were conducted within the SAD+PLEs sample in order to explore which of them was most closely related to variation in the intensity of PLEs. Correlations were significant and positive for IUS (r = .520; p<0.001) and anxiety symptoms (r = .575; p<0.001). Depressive and negative symptoms were not found to be correlated with the increasing of PLEs (Table 15).

Table 15. Correlation between PLEs and other clinical variables in SAD+PLEs subsample

	CAPE positive	CAPE negative	IUS	BAI	BDI-II
CAPE positive	1				
CAPE negative	.119	1			
IUS	.520**	.507**	1		
BAI	.575**	.215*	.593**	1	
BDI-II	.130	.560**	.619**	.230*	1

*p<.05; **p<.01

3.3.4 Discussion

The current study is, to our knowledge, the first to investigate the prevalence of PLEs in SAD and the first to examine the relationship between PLEs and other clinical variables in a sample of SAD patients compared to healthy controls. With regard to the prevalence of PLEs, 24% of the SAD patients, compared to 5% of the healthy control group, reported clinically relevant PLEs on the CAPE that were confirmed with clinical interviews. The prevalence of PLEs in our sample cannot be compared with others as no previous studies

have investigated PLEs in a similar sample. However, the rate of PLEs is significantly higher than in the general population. In a recent meta-analysis by van Os and colleagues (2009), the median prevalence of clinically significant PLEs in the general population was 1.5% (IQR 0.4–3.0%). In the largest two cohort studies where the clinical–subclinical distinction was specifically made, and a sufficiently large number of items for the assessment of psychotic experiences was used, the rates of clinically relevant symptoms were 4.2% and 3.8% respectively (Dominguez et al. 2011; van Os et al. 2001), a similar prevalence to our healthy control group.

Compared to other clinical non-psychotic groups, the mean CAPE score for the SAD group as a whole was similar to depressed patients, but the mean score of the SAD+PLEs was significantly higher (Yung et al. 2007). Conversely, Hanssen et al. (2003) compared the CAPE positive scores of four groups of patients (control group, psychotic group, anxiety group and depression group) and found that the anxiety group scored significantly higher than the control group but lower than the depression group. Nevertheless, comparisons with these previous studies are limited because no clinical interview was administered to make the distinction about clinically significant and benign PLEs, and none investigated SAD specifically.

The second aim of the study was to investigate clinical and sociodemographic differences between SAD patients with and without clinically significant PLEs. The main finding was that SAD patients who had significant PLEs show a distinct clinical pattern, characterized by higher levels of depression, intolerance of uncertainty and negative symptoms. Moreover, in the group of patients with SAD and PLEs, there was a strong relationship between higher levels of PLEs and greater anxiety and IU levels. On the other hand, the

level of PLEs was not related to socio-demographic variables, including cannabis or any other substance abuse.

The subsample with SAD+PLEs had higher levels of depression than the SAD - PLEs group. This is consistent with a number of previous studies showing a strong relationship between PLEs and depression in adolescents (Nishida et al. 2008; Scott et al. 2009; Wigman et al. 2011; Yung et al. 2007) and young adults (Wigman et al. 2011). This suggests that patients with SAD and PLEs more frequently display a combination of pessimistic thinking and low self-esteem (Bentall and Fernyhough, 2008; Bentall et al. 2009). Therefore, it appears that self-esteem and consequently affective dysregulation play an important role in paranoid delusions and psychotic symptoms (Smeets et al. 2010; Thewissen et al. 2007; Wigman et al. 2011).

Other clinical variables were found to be associated with the presence of significant psychotic experiences in SAD. In our sample, IU was significantly higher in SAD+PLEs and, within this group, there was a significant, positive correlation between the level of PLEs and IU. This finding is consistent with previous research showing that IU and related worry are associated with psychotic experiences, and that social worry predicted emotional responses over and above the intensity of psychotic experiences (Morrison and Wells, 2007; White and Gumley, 2010).

It has been argued that that this feature arises from a condition of IU caused by a loss of self identity (Freeman et al. 2008; White and Gumley, 2010), which is a typical feature of the at-risk mental state (Johnstone et al. 2005). If not resolved, this condition can lead to the development of initial positive symptoms (Colbert et al. 2006), insofar as persecutory delusion, on account of its intrinsic feature of absolute certainty, rules out the risk of *Ratlosigkeit* and *wahnstimmung* (Blankeburg, 1971; Conrad et al. 1958; Mishara, 2010).

Several studies have previously found a correlation between jumping-to-conclusions, IU and psychotic symptoms, both in clinical (Broome et al. 2007; White and Gumley, 2010) and non-clinical (Freeman et al. 2008) samples, although one recent study found no association between IU and psychotic ideation (Dudley et al. 2011).

The relationship between increasing PLEs and increasing anxiety that was found in the current SAD+PLEs subsample is consistent with previous findings of a relationship between anxiety and psychotic symptoms in clinical (Lysaker et al. 2010; Lysaker et al. 2010) and non-clinical (Nishida et al. 2008) samples. Lysaker et al. (2010) recently demonstrated that high levels of paranoid features correlated with greater social anxiety symptoms in patients with schizophrenia. Nishida et al. (2008) reported a similar association between anxiety levels and PLEs in the general population. This suggests that anxiety can contribute to the development and maintenance of psychotic experiences (Morrison et al. 2007; Freeman et al. 2009).

Interestingly, there was not a strong relationship between the level of PLEs and cannabis use in either of the two clinical groups. This finding contrasts previous studies which demonstrated this association (Fergusson et al. 2003; Henquet et al. 2005; Mackie et al. 2010; Wigman et al. 2011). Mackie and colleagues (2010) showed that among adolescents with a trajectory of increasing PLEs over two years, a rise in cannabis use preceded a sharp increase in symptoms.

Similarly, Henquet et al. (2005) found that the risk for PLEs among adolescents and young adults increased in a dose–response manner relative to the frequency of cannabis use over a 4-year period. We can hypothesize that the lack of correlation in the present study can, at least partially, be related to the low prevalence of cannabis use in our sample. In addition, it has recently been argued that the relationship between psychotic symptoms and cannabis

depends on the specific type of cannabis and the level of cannabidiol (Schubart et al. 2011), neither of which were investigated.

A strength of this study is the validation of the self-reported CAPE via clinical interview, as self-report has been shown to over-estimate the prevalence of PLEs (Kendler et al. 1996). Other studies have found a good correlation between the CAPE and interviewer-rated psychosis (Hanssen et al. 2003; Konings et al. 2006). In a clinical study, Kelleher et al. (2009) found a high degree of accuracy when PLEs were screened by means of self-report questionnaire. By using clinical interview as well as self-report, we feel confident that the data attained on the presence of PLEs is accurate. A limitation of this study is that the cross-sectional design precluded the analysis of causality and prediction of outcome. Thus, we are only able to speculate the direction of causality and the magnitude of risk.

Chapter 4

22q11 microdeletion syndrome as a possible genetic model for psychosis

4.1. Research 1: Adolescents at ultra-high risk for psychosis with and without 22q11 deletion syndrome: a comparsion of prodromal psychotic symptoms and general functioning·

4.1.1 Introduction

The identification of individuals at high risk for severe psychiatric disorders, particularly schizophrenia, has become one of the premiere research topics in psychiatry over the past decade. This has been driven by the view that the early identification of disorder may improve outcome (Yung et al. 1996; Birchwood et al. 1997) and shed light on the etiopathogenic processes involved (Birchwood et al. 1998; Parnas, 2000; Klosterkötter et al. 2001; Yung et al., 2004; Schultze-Lutter, 2009). The most commonly used method to identify help-seeking individuals in the putatively prodromal phase of psychotic disorders, specifically schizophrenia, has been the "ultra high risk" (UHR) approach (Yung et al. 1996). These criteria combine known trait and state risk factors for the onset of schizophrenia, including attenuated positive psychotic symptoms, brief self-limiting

· This research has been published in an adapted version on Schizophrenia Research. Armando M, Girardi P, Vicari S et al. Adolescents at ultra-high risk for psychosis with and without 22q11 deletion syndrome: A comparison of prodromal psychotic symptoms and general functioning. Schizophrenia Research 2012, 139: 151–156.

psychotic symptoms, trait vulnerability and functional decline (Yung et al. 2003; Yung et al. 2004).

As we introduced in Chapter 2, genetic syndromes related to schizophrenia have become increasingly important for exploring the trajectory of psychosis onset. Among these, a very significant opportunity for mapping earlier phases of this trajectory exists in 22q11DS (Karayiorgou, 2010; Insel, 2010). As we explained in Chapter 2, this syndrome associated with a microdeletion of chromosome 22 band q11 with an estimated prevalence of between 1:2,500 and 1:4,000 live births (Scambler et al. 1992). 22q11DS is a complex disorder with multiple abnormalities affecting a large number of tissues and organs, many of which are derived from neural crest cells (Robin et al. 2005; Shprintzen et al. 2005). The diagnosis is defined by the deletion of DNA from chromosome 22 at the q11.2 band spanning the region that is regarded as critical for multiple functions. The physical and neurobehavioral phenotype of the syndrome includes high rates of congenital dysmorphic features (Scutt et al. 2001), developmental structural brain abnormalities (Chow et al. 1999), and a typical cognitive phenotype (Swillen et al. 2000) characterized by general cognitive functioning in the low borderline range, while verbal memory, reading decoding and spelling skills are areas of relative strength (Antshel et al. 2008).

This syndrome is also characterized by high rates of psychiatric disorders (Gothelf et al. 2008), particularly schizophrenia (Bassett et al. 1999; Murphy et al. 2005). Studies of school-age children have shown that individuals with 22q11DS have high rates of psychiatric and behaviours disorders, such as attention deficit/hyperactivity disorder, generalised anxiety disorder and obsessive-compulsive disorder (Feinstein et al. 2002; Antshel et al. 2006; Gothelf et al. 2004). However, their incidence in 22q11DS is no higher than in other developmental disorders (Feinstein et al. 2002; Antshel et al. 2006),

suggesting that that they are not indicative of a behavioural phenotype specifically associated with this syndrome (Feinstein et al. 2002).

By contrast, as mentioned in Chapter 2, schizophrenia is specifically associated with 22q11DS (Karayiorgou et al. 1995; Xu et al. 2008). Half of the adolescents with 22q11DS report transient psychotic experiences, while up to one-third of affected adults are diagnosed with schizophrenia (Green et al. 2009; Murphy et al. 1999; Bassett et al. 2003). This rate of transition is comparable to the rates observed in UHR risk groups (Fusar-Poli et al. 2012), making 22q11DS one of the highest known risk factors for schizophrenia. Moreover, 22q11DS is found in up to one in 50 patients with schizophrenia, with reports ranging from 0.3% to 2% (Karayiorgou et al. 1995; Arinami et al. 2006; Stefansson et al. 2008). The occurrence of 22q11DS is even higher in patients with childhood-onset schizophrenia (5.7%) (Sporn et al. 2004). For this reason, 22q11DS could represent an ideal human model to explore issues related to early diagnosis and intervention for schizophrenia-related abnormalities. Identifying shared and unique features for 22q11DS and schizophrenia is critical for the understanding of genetic and neural mechanisms underlying both disorders.

Comparative studies have shown that schizophrenic illness associated with 22q11DS largely resembles the illness as it presents in the general population (Karayiorgou et al. 2010). For example, Murphy et al. (1999) found that patients with schizophrenia and 22q11DS had similar positive symptoms, less pronounced negative symptoms and an older age of onset than a demographically matched group of schizophrenia patients without 22q11DS. Other comparisons showed no significant differences in age of onset, life or cross-sectional positive or negative symptoms, or global functioning between adults with schizophrenia with and without 22q11DS (Bassett, et al. 1998; 2003).

Few studies have investigated the early signs and symptoms of schizophrenia in patients with 22q11DS. Retrospective studies have found that the incidence of major depressive disorder, attention-deficit/hyperactivity disorder, phobias, enuresis and impaired social adaptive skills is higher in adolescents with 22q11DS who developed schizophrenia than in healthy controls (Gothelf et al. 2007; Feinstein et al. 2002; Antshel et al. 2005; Debbane' et al. 2006; Antshel et al. 2010). Only two studies have prospectively explored specific prodromal symptoms that are predictive of schizophrenia onset in 22q11DS. In the first (Gothelf et al. 2007), 32% of the sample developed schizophrenic disorder during follow-up. The development of psychotic symptoms between the ages of 12 and 18 years was best predicted by the presence of attenuated psychotic symptoms, anxiety and depression at age 12. In a second study (Antshel et al. 2010), a total of 70 children with 22q11DS, 27 of their unaffected siblings and 25 community controls were followed from childhood into mid-adolescence. With very low false positive rates, the best predictor of adolescent prodromal psychotic symptoms was parent ratings of childhood odd/eccentric symptoms and child performance on a test of an executive functioning.

Even fewer studies have investigated the features of prodromal symptoms in patients with 22q11DS. In such studies, individuals with 22q11DS showed higher positive, negative (Rockers et al. 2009; Stoddard et al. 2010; Antshel et al. 2010), disorganized (Stoddard et al. 2010; Antshel et al. 2010), and general (Stoddard et al. 2010) symptoms compared to general population. A recent study compared demographically-matched groups of 23 individuals with Schizotypal Personality Disorder (SPD), 23 with 22q11DS, and 23 controls on the Structured Interview for Prodromal Syndromes (SIPS) (Shapiro et al. 2011). Both risk groups showed elevated prodromal symptoms, with approximately 60% of individuals with 22q11DS and 70% with SPD meeting symptom criteria for a prodromal

psychosis syndrome. No study has specifically explored the features of prodromal symptoms in a subsample of 22q11DS clinically defined as UHR for psychosis, and none have compared this group to UHR samples without (known) 22q11DS.

The aim of the present study was to investigate differences and similarities between two samples: patients with 22q11DS and UHR (UHR+22q11DS; n=30), and patients at UHR (UHR group; n=81). We tested the hypotheses that (i) the two groups would be comparable in severity of positive symptoms, the core symptoms for a diagnosis of a psychotic disorder; (ii) the UHR+22q11DS group will have higher severity of negative symptoms and general impairment. These hypotheses were based on literature showing that negative symptoms are related to neuroanatomical and functioning abnormalities of the ventrolateral prefrontal cortex and ventral striatum (Suzuki et al. 2005; Amodio et al. 2006; Goghari et al. 2010) which are frequently reported in patients with 22q11DS (Gothelf et al. 2005; Gothelf et al. 2007; Schaer et al. 2009). Additionally, lower general functioning can be, at least partially explained, by the close relationship between functioning and negative symptoms evidenced in a UHR group (Lin et al. 2011)

4.1.2 Methods

4.1.2.1 Participants

The study was conducted on a sample of 30 individuals with 22q11DS at UHR of psychosis (UHR+22q11DS) and 81 individuals at UHR of psychosis without 22q11DS (UHR).

UHR+22q11DS patients were recruited from the Child and Adolescent Neuropsychiatry Unit and the Clinical Genetic Unit of the Clinical and Research Hospital Bambino Gesù of Roma between 2009 and 2011. They were identified by standard cytogenetic studies using

fluorescence in situ hybridisation (FISH) and a probe from the commonly deleted 22q11.2 region. After diagnoses, individuals underwent a venous blood sample for genotypic analysis. UHR patients without 22q11DS were consecutive admissions to a specialized psychosis detection and treatment unit at the Department of Child and Adolescent Psychiatry, Medical University of Vienna, Austria, between 2004 and 2006. This group was recruited for a randomized controlled trial of omega-3 fatty acids vs placebo which is described elsewhere (Amminger et al. 2010). FISH analyses could not be performed on UHR group because the recruitment was developed for another study (Omega-3 RCT) and therefore not approved by the local Ethic Committee. However, as recently argued by Shapiro et al. (2011), individuals with 22q11.2 deletions are unlikely to be found in standard UHR samples. As previously mentioned, low base rates of the 22q11.2 deletion in the general population (1:2,500 -1:4,000), as well as in schizophrenia (0.3% - 2%) (Karayiorgou et al. 1995; Arinami et al. 2006; Stefansson et al. 2008; Hoogendoorn et al. 2008), make it very unlikely that any individual in the UHR group would have the deletion. Both UHR groups were free of antipsychotic medication.

UHR status was defined by the presence of at least one of the following well-validated criteria: attenuated positive psychotic symptoms (Group 1); brief limited intermittent psychotic symptoms (BLIPS; Group 2); and genetic risk plus a deterioration in functioning (Group 3). The presence of attenuated psychotic symptoms and BLIPS were determined by semi-structured interview applying the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) cut-off scores for symptom severity proposed by Morrison and colleagues (2004), and frequency and duration criteria of Yung et al. (1998). Detailed UHR criteria are listed in Table 16. Exclusion criteria were organic mental disorder, prior

diagnosis of psychotic disorder, mental retardation or the presence of any documented neurological condition.

Table 16. Ultra-High Risk Criteria

Group 1: Attenuated psychotic symptoms Presence of symptom scores of 3 on the PANSS delusions scale, 2-3 on the PANSS hallucinations scale, 3-4 on PANSS suspiciousness or 3-4 on PANSS conceptual disorganization scale (frequency of symptoms ≥2 times per week for a period of at least a week and not longer than 5 years, and to have occurred within the last year).
Group 2: Transient psychosis Presence of symptoms scores of ≥4 on PANSS hallucinations scale, ≥4 on PANSS delusions scale, or ≥5 on PANSS conceptual disorganization scale (symptoms not sustained beyond a week and resolve without antipsychotic medication, and have occurred within the last year).
Group 3: Trait plus state risk factors Having a schizotypal personality disorder (as defined by DSM-IV) or a first-degree relative with a DSM-IV psychotic disorder and a significant decrease in functioning from pre-morbid level, resulting in a decrease of 30% on the Global Assessment of Functioning Scale, maintained for at least a month and not longer than 5 years. The decrease in functioning needed to have occurred within the past year.

PANSS= Positive and Negative Symptoms of Schizophrenia Scale.

4.1.2.2 Procedure

The study was approved by the Ethics Committee of the Medical University of Vienna and the Ethics Committee of the Clinical and Research Hospital Bambino Gesù of Roma and was conducted in agreement with the Italian Association of 22q11.2 microdeletion syndrome (AIdel 22) within a wider project aimed at the prevention of psychopathological

disorders in patients with 22q11DS. All participants provided written informed consent and parental consent for those under 18 years of age.

4.1.2.3 Measures

The PANSS (Kay et al. 1987) was used to assess psychiatric symptoms. At both sites, raters were experienced clinicians trained in the administration of the PANSS using a standard training video. Inter-rater reliability estimates for PANSS subscales were excellent at both sites (all intra-class correlation coefficients >0·90). The SCID-P for DSM-IV (First et al. 2002) and the K-SADS-PL (Kaufman et al. 1997) were used to ascertain psychiatric diagnoses. Functioning was measured with either the Global Assessment of Functioning (GAF) (APA, 1994) or Childhood Global Assessment Scale (CGAS). Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale (MADRS) (Davidson et al. 1986). The Number-Combination Test (Oswald et al. 1987) and the Leiter-R (Roid et al. 1997) were used to assess current IQ.

4.1.2.4 Statistical Analysis

Data were analysed using statistical software PASW 18. Since sample sizes were unequal, homogeneity of variance was confirmed using Levene's test. The assumption that psychopathological (PANSS scores; MADRS score; GAF or CGAS score) variables and IQ were normally distributed in the population was confirmed using the Kolmogorov-Smirnov test (p>0.05). Therefore, groups were compared on demographic and clinical variables using chi-square analysis for categorical data. For continuous data, separated ANOVA and ANCOVA models were used covarying for IQ and MADRS scores. To control for multiple comparisons, Bonferroni correction was applied (0.05/6 psychopathological measures; critical p-value of 0.0083). Individual z-scores were considered as a measure of dispersion.

4.1.3 Results

4.1.3.1 Demographic characteristics

As shown in Table 17, the groups differed significantly on level of education, with a lower proportion of higher education in the UHR+22qDS group (p<0.001). The UHR+22qDS group also had lower current IQ (p=0.001). There was no significant group difference in age.

Table 17. Demographic characteristics and psychiatric symptoms in Ultra-High Risk and Ultra-High Risk+22qDS groups

Variable	UHR+22q11DS (n=30)	UHR (n=81)	Analyses
Male, *N* (%)	14 (46.7%)	27 (33.3%)	χ^2=1.67; p=0.142
Education, *N* (%) -Basic -Higher	 26 (86.7%) 4 (13.3%)	 37 (46.8%) 42 (53.2%)	χ^2=14.04; p<0.001
Age, *M (SD)*	16.7 (1.5)	16.5 (1.8)	F= 1.74 ; p=0.193
Current IQ, *M (SD)*	89.8 (8.9)	99.3 (15.6)	F= 10.64; p=0.001
PANSS Positive, *M (SD)*	14.3 (2.6)	14.6 (3.2)	F= 0.13; p=0.721
PANSS Negative, *M (SD)*	16.8 (3.2)	13.8 (5.8)	F= 7.28; p=0.0081
PANSS Global, *M (SD)*	32.4 (4.9)	30.1 (6.9)	F= 2.61; p=0.109
PANSS Total, *M (SD)*	63.6 (9.3)	58.5 (13.4)	F= 3.56; p=0.06
GAF/CGAS, *M (SD)*	45.2 (2.9)	60.5 (12.5)	F= 47.8; p<0.001
MADRS, *M (SD)*	21.3 (6.1)	18.2 (8.7)	F= 3.15; p=0.08
Dsym (in months), *M (SD)*	22.2 (12.1)	19.4 (14.1)	F= 0.91; p=0.34
Dpsym (in months), *M (SD)*	10.2 (8.3)	12.8 (10.8)	F= 1.47; p=0.23
AOO, *M (SD)*	16.4 (1.2)	14.8 (2.5)	F=11.14; p=0.001

Notes. Dsym: duration of any psychiatric symptom before first assessment
Dpsym: duration of any psychotic symptoms before first assessment
AOO: age of onset of UHR condition

4.1.3.2 Comparisons between groups

Table 17 summarized results on comparisons between individuals in the UHR and in UHR+22qDS groups. The age of onset of the UHR condition was significantly lower in the UHR group (14.8 years vs 16.4 years), but duration of general psychiatric and attenuated psychotic symptoms before the assessment did not differ between groups.

There was a significant group difference in the PANSS negative subscale (p=0.0081), with higher scores in the UHR+22qDS group. However, group differences in depressive symptoms were not significant (p=0.08). Since differences in PANSS negative subscale could be influenced by IQ levels and depressive symptoms, IQ and MADRS scores were introduced as covariate variables in two separated ANCOVA analyses. Also after controlling for the influence of IQ and MADRS scores, results documented difference between groups in PANSS negative subscale (respectively, F(1,108)=6.1, p=0.015; F(1,108)=4.59, p=0.034).

The UHR+22qDS group showed a significantly lower level of general functioning (GAF or CGAS score) compared with the UHR group (p<0.001). Also after controlling for the influence of IQ and MADRS scores, results showed difference between groups in level of general functioning (respectively F(1,108)=42.13, p < 0.00001; F(1,108)=49.03, p < 0.00001).

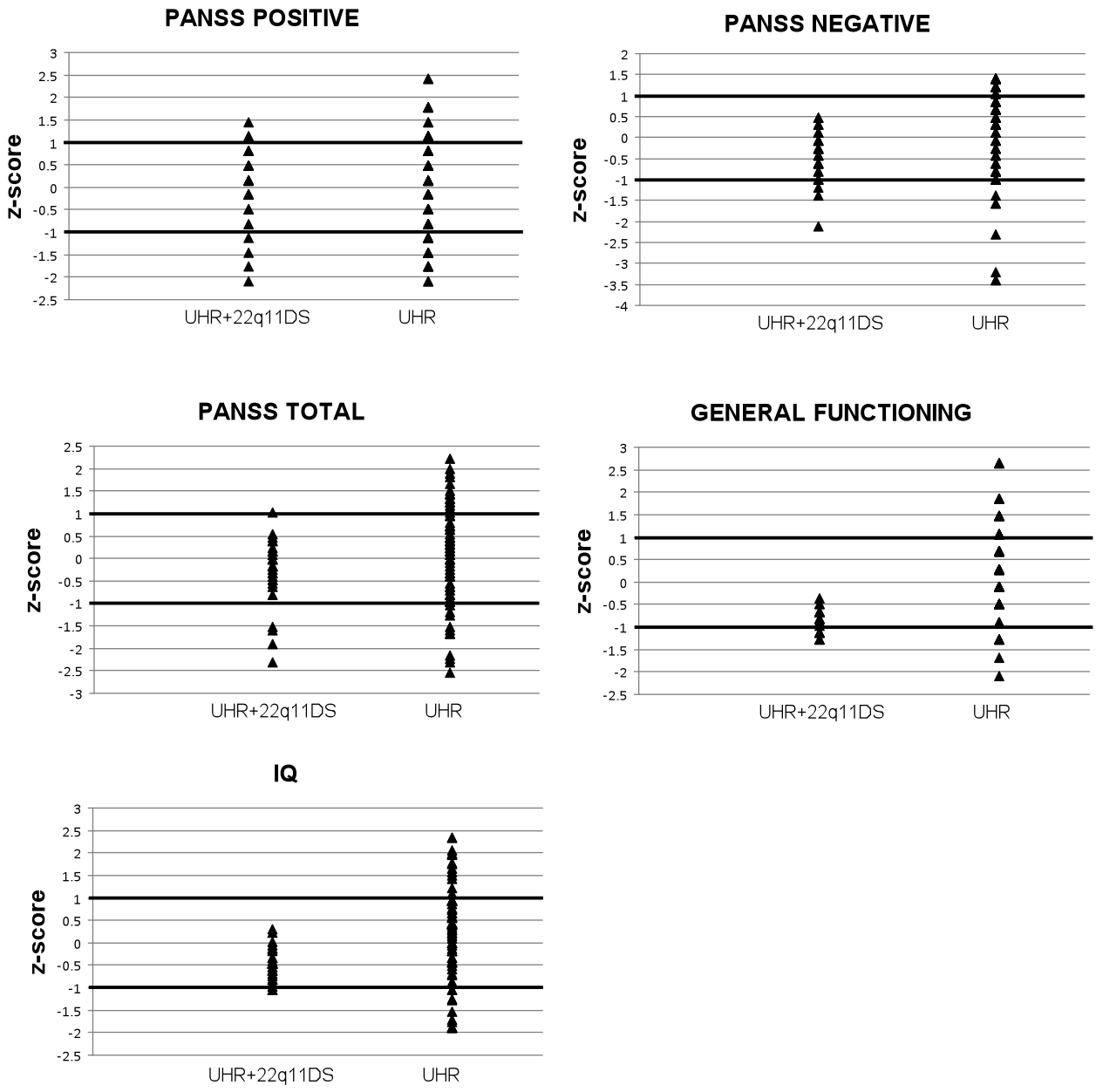
However, no significant group differences were found for the PANSS positive (p=0.72), total (p=0.06) and global (p=0.109) subscale scores. These results were confirmed also after controlling for IQ and for MADRS (after controlling for IQ, PANSS positive F(1,108)=0.11, p=0.74, PANSS total F(1,108)=3.37, p=0.07 and PANSS global F(1,108)=2.9, p=0.09); after controlling for MADRS, PANSS positive F(1,108)=1.22, p=0.27, PANSS total F(1,108)=1.02, p=0.31 and PANSS global F(1,108)=0.33, p= 0.56).

4.1.3.3 Measures of variability

Figure 1 shows, for different measures, the distribution of the scores obtained by each participant in both groups. As a measure of dispersion, we transformed the score of each participants in z-score by considering the mean score (and the standard deviation) of the two groups on each measure.

The proportion of UHR+22qDS participants who had a score below or above the mean (<1 or >1 SD) on the PANSS positive and negative subscales and total score was 37%. One the other hand, the proportion of the UHR group falling more than 1SD from the mean was 20% for the PANSS positive and negative subscales, and 16.6% for the total PANSS score. Concerning the level of general functioning, the proportion of participants in the UHR+22qDS group who had a score more than 1SD from the mean was 33.3% compared to 23.3% of the UHR group. Finally, 33.3% of participants in the UHR+22qDS group had an IQ score more than 1 SD below or above the mean, while just 6.6% of the UHR group showed IQ outside this range.

Figure 1. The distribution of the scores obtained by each participant of the UHR+22q11DS and the UHR groups. The Y-axis represents the z-score by considering the mean score (and standard deviation) of the two groups on each measure. One standard deviation limit (± 1SD) is marked on the Y-axis



4.1.4 Discussion

To our knowledge, the current study is the first to compare a group of individuals with 22q11DS who were clinically at UHR for psychosis with another clinically-defined UHR group without 22q11DS. Although positive symptom levels were similar, UHR+22q11DS showed higher negative symptoms, lower general functioning and an older age of onset of the UHR state. Investigating phenotypic similarities and differences between these UHR groups before the onset of frank psychosis is an important first step in the identification of shared and unique features underlying 22q11DS and schizophrenia. This is critical for beginning to understanding the genetic and neural mechanisms underlying both conditions.

Our first hypothesis that the two groups would be comparable in terms of the severity of positive symptoms was confirmed. This is unsurprising given that the detection of UHR status is based on the presence and severity of attenuated positive psychotic symptoms. The second hypothesis was that the UHR+22q11DS group would display greater severity of negative symptoms and general impairment. This was also confirmed. The UHR+22q11DS group showed a mean negative symptom score three points higher than the UHR group, and a mean GAF/CGAS score 15 points lower. The greater severity of negative symptoms is consistent with finding that negative symptoms are related to neuroanatomical and functioning abnormalities of the ventrolateral prefrontal cortex and ventral striatum (Suzuki et al. 2005; Amodio et al. 2006; Goghari et al. 2010) which are frequently reported in patients with 22q11DS (Gothelf et al. 2005; Gothelf et al. 2007; Schaer et al. 2009). Lower general functioning can be, at least partially explained, by the close relationship between functioning and negative symptoms evidenced in a UHR group (Lin et al. 2011) and schizophrenia samples (Herbener et al. 2005; Milev et al. 2005). Since severity of negative symptoms and general impairment are associated with worse

functional outcome following UHR (Lin et al. 2011), and a poorer long-term prognosis in schizophrenia (Tek et al. 2001; Chemerinsky et al. 2006), specific treatments approaches (Murphy et al. 2006) should be developed for UHR+22q11DS patients. For example, recent findings suggest the efficacy of Omega-3 fatty acids in reducing negative symptoms and functional impairment in UHR groups (Amminger et al. 2010; Amminger & McGorry 2012).

Interestingly, the psychopathological profile of the UHR+22q11DS group was clearly more homogeneous than the UHR group. There are two likely reasons for this. This finding may be related to the predominant genetic aetiology of UHR symptoms in 22q11DS group compared to the multi-factorial, and greater environmental-related aetiology in the UHR group. This hypothesis is an extension of the "syndrome-specific" hypothesis, derived from recent studies documenting that psychopathological risk in genetic syndromes might be specifically due to different neurobiological factors and to the abnormal brain development which may vary depending on the aetiology of genetic syndrome (Mervis & Robinson 2000; Vicari et al. 2007). Secondly, many of the UHR subjects are likely to be false positives; only a minority will go on to develop frank psychotic illness (Simon et al. 2011; Fusar-Poli et al. 2012). Given this, their symptomatic profile would be expected to be more varied than the UHR+22q11DS group.

This is the first study to compare a sample with 22q11DS thought to be in the putative prodromal period of psychotic illness with a clinical UHR group without 22q11DS. The strength of this sample is the relatively large cohort (*n*=30) of patients with UHR+22q11DS. A further strength is that all participants were neuroleptic-naive, a rare occurrence in UHR research today. Findings should be interpreted in light of the fact that the two groups were assessed at different sites, which is an important limitation of this

study. Although such practice is common, we cannot exclude the possibility that group differences may be accounted for by rater differences at the respective sites. However, this is unlikely given that i) there were only significant group differences on some measures, suggesting it is not a spurious finding, ii) the same standardized training video was used in both sites. It is also possible that findings are related to the presence of, and living with, a chronic illness, rather than specific to 22q11DS and the psychosis prodrome. While unlikely, this cannot be ruled out without a “chronic illness control group”.

Chapter 5

Discussion

5.1 Significant Findings on Psychotic Like Experiences and other clinical variables as risk factors for psychotic onset

The series of studies presented in chapter 3 has revealed a number of significant results.

Firstly, the existence of different types of PLEs with different psychopathological value has been confirmed (Armando et al. 2010; Armando et al. 2012). The PLEs subtypes highlighted in our studies overlapped with those found in previous studies (Yung et al. 2006; Yung et al. 2009) where 4 four subtypes were found: bizarre experiences (BE), persecutory ideas (PI), perceptive anomalies (PA) and magical thinking (MT). Thereby PAs, PIs and BEs brought about a higher level of distress compared to MT and , unlike the latter, ended up being significantly associated to negative psychotic symptoms and to a significant general disease. PIs and BEs were also positively correlated to depressive symptoms in contrast to MT.

In our studies presented in chapter 3, five types of PLEs were highlighted: Bizarre Experiences (BE), Perceptual Abnormalities (PA), Persecutory Ideas (PI), and Grandiosity (GR) or Magical Thinking (MT) (i.e. GR was found in Armando et al. 2010 and MT in Armando et al. 2012). Intermittent, infrequent psychotic experiences were common, while frequent experiences were not. BE and PI were strongly associated with distress, depression and poor functioning. PA and GR (or MT) were less associated with these

variables. GR (or MT) turn out to be benign PLEs, whose probable psychotic development proved to be almost non-existent.

These works indicate that PLEs have different values from a psychopathological point of view: while some prove to be potentially progressive, others appear benign and lack an underlying mental problem. Thus the same problem re-emerged for these experiences as for the symptoms that precede the onset, i.e., the necessity to distinguish the more specific and, therefore, the predictive ones from the less specific ones. Yet, it seems possible to distinguish PLEs, which are an expression of a more profound and fundamental disorder (as for example in disorders of the self), from PLEs associated to non-psychotic syndromes, which constitute a sort of clinical background noise, and, lastly, from PLEs found in normal people that are neither associated with distress, nor with a reduced social functioning, or an increased vulnerability to psychotic disorders. In substance, PLEs do not constitute a unitary phenomenon, but rather different types of PLEs exist that seem to take different trajectories and to have different underlying causes (Nelson and Yung 2009).

Secondly, our findings described in paragraph 3.3 suggest that: (i) clinically significant PLEs can be found in about one quarter of young adults with SAD; and (ii) PLEs in patients with SAD are related to other psychopathological markers, especially IU and depressive symptoms; (iii) the increase in the frequency and distress of PLEs is related to an increase of anxiety and IU levels. These findings are consistent with current hypotheses on the psychological mechanisms that underlie psychotic symptoms (Bentall et al. 2009; Morrison and Wells, 2007), in particular those that emphasize that cognitive disturbances (i.e. IU, jumping-to-conclusions), together with social anxiety, may lead to anomalous experiences. These experiences, in combination with affective dysregulation (high level of

depression and state-related anxiety) and cognitive appraisal processes may lead to the formation of clinically significant PLEs (Krabbendam and van Os. 2005; Smeets et al. 2010; Wigman et al. 2011). If the current findings are confirmed by longitudinal studies, there is clear clinical application for early intervention. In the current study, the SAD patients with PLEs did not meet diagnostic criteria for psychotic illness, but still experienced clinically relevant and distressing psychotic experiences. As such, screening for PLEs in young adults with SAD is necessary. The specific cognitive/psychopathological mechanism involved in this process should be considered in order to provide the most appropriate therapy for those patients.

5.2 Significant findings on 22q11 microdeletion syndrome as a possible genetic model for psychosis

Also the study presented in chapter 4 has revealed a number of significant results.

Indeed, if several previous studies demonstrated that schizophrenia in 22q11DS clinically and neurocognitively cannot be distinguished from the idiopathic disorder (Bassett et al. 2003; Green et al. 2009), our study is the first aimed at investigating the same issue in UHR populations.

Firstly, the two UHR groups were found to be comparable in terms of severity of positive symptoms, which are the core symptoms for a diagnosis of psychotic disorder.

Secondly, the clinical profile in the UHR+22q11DS group was clearly more homogeneous. Access to such a homogeneous population of UHR individuals as the result of a shared etiological factor provides a unique research opportunity to study the biology of the onset of schizophrenia and is ideal to trial novel treatment agents (Drew et al. 2011).

Thirdly, the groups differed on the level of negative symptoms and functioning. This has implications from a therapeutic and prognostic perspective. Given that greater negative symptoms and lower quality of life at identification as UHR are associated with poor functional outcome many years later (Lin et al. 2011), specific early intervention strategies should be implemented for young people with UHR+22q11DS. These could be psychosocial and vocational interventions that target negative symptoms and factors associated with them, such as neurocognition (Lin et al. 2011). The use of omega-3 fatty acids as an intervention also merits further investigation since these have shown efficacy in reducing negative symptoms (Amminger et al. 2010; Amminger & McGorry 2012).

From a theoretical point of view, the findings of this study contribute to our understanding of the aetiology of schizophrenia. The 22q11DS group may represent a neurodevelopmental pathway to psychotic illness (Myin-Germeys & van Os, 2007). This would differ from an affective pathway, which may be a more likely illness trajectory for individuals in the UHR group without 22q11DS that go on to develop psychosis. This is speculative and longitudinal studies designed specifically to compare the clinical, neuropsychological, genetic and neuroimaging profiles of clinical UHR groups with those of UHR+22q11DS populations are necessary. These will hopefully improve knowledge of the etiopathogenetic mechanisms involved in schizophrenia, and the detection of early signs and symptoms that are highly predictive of future psychotic onset and prognosis.

5.3 future work

A number of recommendations for future areas of research have been made in chapter 3 and 4 as well as in the discussion chapter. It is helpful to cluster these in to two groups: future work needed on PLEs and future work needed on 22q11DS.

5.3.1 future work on PLEs

Further longitudinal studies are needed for at least two reasons: 1. Identifying which PEs confer the highest risk of psychosis could help in the activity of screening of the general population (Loewy et al. 2007). It would thus be possible to accurately identify which individuals with PEs, among those who do not actually request help, have the greatest risk of developing a psychiatric disorder. 2. Distinguishing between different PE subtypes and increasing their positive predictive value would guide ethical considerations in intervention and considerations of the cost/ efficacy ratio of preventive intervention aiming to interrupt the evolution of PEs towards a full-blown illness (van Os et al. 2009).

Finally, a number of implications for health policy in favour of psychosis prevention emerge from the presented studies. Emphasis is placed on the need to restructure early intervention services so as to reduce the high level of "unexpressed help-seeking" (Armando et al. 2009), keeping in mind that it seems to be determined above all by the fear of stigmatization, by misinformation and by the absence of services exclusively dedicated to young people. These elements therefore make it necessary, on the one hand, to promote awareness and information campaigns, and on the other, to make specific reforms of existing psychiatric services.

5.3.2 future work on 22q11DS

As we anticipated in chapter 2, more complex measures of gene expression, including a broad range of neurotransmitter activity over development, will be essential for a better understanding of risk in this and other forms of schizophrenia. In general, whereas both diagnosis and drugs/treatments primarily address a late stage of schizophrenia pathology,

earlier and prodromal stages are less characterized and treated. Here, above all, is where progress is needed in the form of reliable biomarkers to identify those at risk and to allow biomedical or cognitive interventions to prevent or mitigate the development of the disorder.

Indeed, the fact that UHR+22q11DS group is clinically and etiologically more homogeneous than other UHR groups provide a strong rationale for the investigation of indicated prevention treatments in this population aimed at delaying/reducing the transition to psychosis. Indeed, as recently suggested by Karayiorgou et al. (2012), exploring the effects of an indicated prevention in a genetically and clinically homogeneous population can significantly help in identify which of the molecular, cellular and circuit deficits can serve as the best targets for the development of treatments for psychotic symptoms.

Moving from these suggestions, we are now beginning a double blind randomized controlled trial on the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) in this population. The principal aim of the this trial is to investigate the effects of 1.4g/day omega-3 PUFAs in individuals aged 12-26 years with 22q11DS at ultra-high risk for developing a first episode of psychosis.

Specifically we propose to investigate: A) The clinical effects of omega-3 PUFA supplementation in individuals with 22q11DS and UHR. B) The lipid metabolism in peripheral tissue pre/post treatment to determine biomarkers of psychosis conversion.

Our hypotheses are: A) Omega-3 PUFAs have a positive effect on clinical course and outcome in UHR+22q11DS individuals. B) Lipid metabolism characteristics described in schizophrenia will be more prevalent in individuals who make transition to psychosis. This study will contribute to the confirmation of new neuroprotective treatment strategies in the prodromal phase of psychotic disorders, in a specific syndrome where there is a strong

evidence for the high genetic load involved in the etiopatogenesis of the disorder. These will help us in better understanding the role of the genes involved in psychotic disorders and the molecular mechanisms involved in the treatment of the disorder.

At the same time, longitudinal studies on this specific UHR population can significantly improve our ability to detect which UHR patients with attenuated psychotic symptoms will go on to develop fullblown psychotic disorder. Indeed, it remains a clinical and research challenge to further **"**close in**"** on risk factors for psychosis onset by identifying phenotypic and genotypic factors that predict psychosis onset (Fusar-Poli et al. 2012).

Moreover, to date there is a lack of studies on possible gene-environment interactions in the evolution of cognitive and psychiatric symptoms in 22q11DS. As for Schizophrenia (van Os et al. 2010), perhaps there are shared environmental exposures in schizophrenia and 22q11DS which increase the risk of schizophrenia in the latter disorder, against the background of genetic vulnerability.

Despite to date research show controversial results, the 22q11DS represent indeed a powerful model for studying the role of specific genetic modifications in schizophrenia development and its correlated cognitive deficits. This is given by the clear genetic cause of this syndrome and its high risk to develop schizophrenia (Bassett et al. 2003; Insel, 2010).

In conclusion, 22q11DS is thus of considerable interest to researchers and clinicians involved in the early diagnosis, prevention and intervention/ of schizophrenia for at least three reasons:

1) From a clinical and therapeutic perspective, the study of early intervention strategies in this specific high risk group may lead to a better understanding of what therapeutic interventions most effectively reduce/delay the transition rates to psychosis. Moreover,

since 22q11DS individuals represent the risk group with the highest transition-to-psychosis rates, early intervention in the subgroup of children with sub-threshold signs of psychosis may reduce the risk of the development of psychotic disorders in adolescence.

2) Research on the role of COMT in psychotic onset and in cognitive disturbances with further longitudinal studies designed to compare the clinical, neuropsychological, genetic and neuroimaging profiles may significantly improve knowledge regarding the specific etiopathogenetic mechanisms involved in schizophrenia, and important insights into the trajectory from risk to disorder may be gained from ongoing longitudinal studies of 22q11DS childrens comparing cognitive, affective and neural development in those who do and do not develop psychosis among this cohort with a similar genomic deletion.

3) Last but not least, a synergism between preclinical and clinical studies may be achieved by cross-feeding experiments that will lead to the early detection of 22q11DS individuals who are at high risk of developing not only specific cognitive deficits and schizophrenia-related symptoms, but schizophrenia itself. Indeed, as recently highlighted in a Nature special issue on schizophrenia (Karayiourgou et al. 2010), direct translational studies that closely combine human and animal genetic studies are critically needed if preventive strategies and a cure for this debilitating neurodevelopmental disorder are to be found.

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