

PRODROMAL SYMPTOMS: A “RISK” FOR PATIENTS OR PSYCHIATRISTS?

Paolo Fiori Nastro, Elena Monducci, Elena Pappagallo, Francesca Fagioli, Riccardo Saba, Valentino Righetti, Claudia Dario, Juliana Fortes Lindau, Marco Armando, Paolo Girardi

Abstract

The question of prodromal symptoms of psychosis already raised by Bleuler, in the last years, became one of the major issues in psychiatry: 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 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. Research on psychotic-like experiences seems a good example to clarify the long standing problem of predictability of symptoms and signs present in the pre-psychotic phase of illness. Undoubtedly the elevated presence of psychotic-like experiences in the general population induces us to corroborate the idea that a psychotic illness develops along a continuum that starts from a vulnerability as a base to reach a frank disease, but only in particular conditions. Consequently, the psychotic illness should be regarded as a highly dynamic disease that develops in interaction with environmental stressors. We can speak of initial symptoms, therefore, like a syndrome at risk of psychotic development from the intrinsic point of view of the disease itself; however, we consider the continuous research into possible core symptoms, which are qualitatively specific to psychosis, to be indispensable, as it may improve our ability to better understand the psychopathological progression into the development of frank psychosis and may allow us to refine our capacity to identify subjects really at risk.

Key Words: prodromal symptoms, initial signs, early symptoms, core symptoms

Declaration of interest: none

Paolo Fiori Nastro¹, Elena Monducci¹, Elena Pappagallo¹², Francesca Fagioli¹³, Riccardo Saba⁴, Valentino Righetti⁴, Claudia Dario⁴, Juliana Fortes Lindau⁵, Marco Armando¹²⁷, Paolo Girardi⁶

1. PhD Course “Early Intervention in Psychosis”, “Sapienza” University Department of Psychiatry and Psychological Medicine, via Casal dei Pazzi 16, 00156, Rome Italy.
2. Department of Mental Health, AUSL Viterbo, Viterbo, Italy
3. ASL RME, U.O.C. Adolescence Psychiatry Unit, Rome, Italy
4. Department of Psychiatry and Psychological Medicine, “Sapienza” University of Rome, Italy.
5. Sant’Andrea Hospital and “Sapienza” University of Rome NESMOS Department Rome Italy.
6. Course of “Early Intervention in Psychosis”, Sant’Andrea Hospital and “Sapienza” University of Rome NESMOS Department, via di Grottarossa 1035,00185, Rome, Italy
7. School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

Corresponding author

Paolo Fiori Nastro MD mail: paolo.fiorinastro@uniroma1.it

Introduction

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 develops 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 aspecific, 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

SUBMITTED MARCH 2010, ACCEPTED APRIL 2010

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. In reality, 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.

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 (Phillips et al. 2000, Yung et al. 1998, Killackey et al. 2008), has also been utilized by a many other research groups

(Häfner et al. 2004; Miller et al. 2002, 2003a; Morrison et al. 2004, Compton et al. 2008; Louzã et al. 2008) 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).

Through the close-in strategy, current research has reached a predictive ability of 48% (Ruhrmann et al. 2010). The prospect of a progressive improvement in the 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 neoKraepelian 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. However, placed within the context of the disease, irrespective of its continuity to that, among others, has been conceptualised from studies on psychotic-like experiences as variations of a psychotic disorder and an incompletely expressed psychosis in the general population, the “almost-dimensional” disease model still suggests a discontinuity with the general population.

When the psychosis is not an unpredictable and fatal event, i.e. a “process” in the Jaspersian sense, but a “historical” development, the possibility of prevention takes on a concreteness and becomes a reality, making it possible to shift attention from the advanced phases of the illness – as some critics would - to the initial stages where we can observe the first signs of malaise. This latter, however, is at the cost of implying an intolerable diagnostic uncertainty and a great dilemma: Is the poor predictive ability of the initial signs and symptoms due to a scarce diagnostic capacity, or is it correlated to the very nature of these symptoms themselves, which will not necessarily develop into a psychosis? Must we, therefore, further refine our diagnostic instruments? Or must we rather consider variables of a risk phase, which may evolve further, depending on the life events that intervene? Or perhaps we should think that both components are to be taken into consideration?

Psychotic-like Experiences

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 1992a, b, Klosterkötter et al. 2008).

A change in perspective is noticeable in these model in that we pass from considering symptoms as discreet 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 psychotic-like experiences, 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?

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 (PLEs) (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. Huber and colleagues had already spoken of “outpost syndromes” for the very purpose of indicating a group of symptoms that seem pre-psychotic at the moment, but over time do not necessarily result in psychosis and can also experience a spontaneous remission before re-appearing again as a prodrome that developed in parallel to continuously progress into a frank psychosis (Huber et al. 1980; Gross 1989). Moreover, in order to assess the presence of basic symptoms the “Frankfurt Complaint Questionnaire” (FBF) was developed in parallel to “Bonn Scale for the Assessment of Basic Symptoms” (BSABS) (Süllwold and Huber 1986, Gross et al. 1987)

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 et 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 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 rose 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. The existence of different types of PLEs with different psychopathological value was confirmed by a study, which reproduced this work of the Australian group that looked into the existence of PLEs in a population of university students (Armando et al. 2009, submitted) The PLEs subtypes overlapped with those highlighted by Yung and colleagues: 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 malaise. PIs and BEs were also positively correlated to depressive symptomatology in contrast to magical thinking for that we found an inverse correlation. In a cross-sectional and multi-centric research carried out on a population of adolescents and young adults (Armando et al. 2010), slightly different 4 types of PLEs were highlighted: Bizarre Experiences (BE), Perceptual Abnormalities (PA), Persecutory Ideas (PI), and Grandiosity (GR). 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 were less associated with these variables. MT or, in the latter study, GR 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).

Conclusions

Undoubtedly, the elevated presence of PLEs in the general population implies to corroborate the idea that a psychotic illness develops along a continuum that starts from the basis of a vulnerability to finally reach a frank disease, but only in particular conditions.

The first signs of malaise are, therefore, expressions of a group of symptoms that identify a subject at risk of psychosis, and not of real and proper prodromes, because their evolution into psychosis is possible but not certain. This implicates that the illness is not a static phenomenon but plastic and develops in response to stimuli of predominantly emotional importance and against the background of a person's resilience of the subject (van Os 2009, Tait et al. 2004). The child or adolescent who has psychotic-like experiences develops a frank psychosis only if other risk factors intervene throughout his life, while he will not develop psychosis if protective factors intervene. In light of the dynamic nature of the evolution of mental illnesses, we must further improve our diagnostic capacities to reduce the number of false positives. This "close-in" strategy has produced excellent results, and it is hoped that it can produce even better ones in the light of a return of research of psychopathology. (Andreasen 2007, Parnas 2000, Cermolacce 2010,

Mishara 2010)

The observation and description of symptoms have to be integrated with assessment and psychopathological research to improve the accuracy of the psychosis trait-state risk model. In this respect, Nelson et al. (2008) proposed to integrate two different formulations, utilizing the UHR criteria as an initial screening method followed by a verification of self-disturbances. The assessment of the presence of self-disturbances can be included within the research of basic symptoms, and can be considered a phenomenological extension of the research of basic symptoms within the context of self-experiences (Vollmer-Larsen et al. 2007).

It would be possible, therefore, to understand both the central phenotype of the psychotic vulnerability and its expression in terms of attenuated or intermittent psychotic symptoms with a further reduction of the false positives and a focus on the specificity of the prediction from the body of psychic disorders to the schizophrenic spectrum in particular.

In conclusion, the early symptoms depict, in our opinion, a group of symptoms that identify a subject at risk of psychotic evolution (Carpenter 2009), in that the dynamic nature of the disease and the adolescent's personality which is still in development represent a very high level of possibility of change and a sensitivity to the positive and negative situations of life. This elevated plasticity that characterizes the human mind and, therefore, its pathology and that, on the other hand, separates psychiatry from the more static and defined organic medicine, partly clashes with the operationalistic approach, necessary for a subsequent phase of intervention.

We can speak of initial symptoms, therefore, like a syndrome of a risk of psychotic development from the intrinsic point of view of the disease itself; however, we consider the continuous research into possible core symptoms, which are qualitatively specific to psychosis to be indispensable, as they may prove highly predictive of a future development of frank psychosis and may allow us to refine our capacity to identify subjects really at risk.

Such subjective experiences observed from the basic symptoms prospect can give way to a deeper knowledge of the illness and allow us remove the idea of "madness" from the terror and impossibility of a cure (Schultze-Lutter 2009). Moreover, thinking of the prodromal phase of psychosis as something separate and not as a phase of an illness means that psychosis is no longer an inevitability but, once again, a flexible state, inside which the responsibility of the psychiatrist is great, given that an adequate psychiatric intervention in an early phase of the pathology has all the potentiality of modifying its course.

References

- Andreasen N (2007). DSM and the Death of Phenomenology in America: An Example of Unintended Consequences. *Schizophrenia Bulletin* 33, 1, 108-112.
- Allen JJ, Chapman JP, Vuketich JP, Frost LA (1987). Prediction of psychotic-like symptoms in hypothetically psychosis-prone college student. *Journal of Abnormal Psychology* 96, 83-88.

- Armando M, Fagioli F, Borra S, Carnevali R, Righetti V, Saba R, Tarsitani L, Biondi M, Fiori Nastro P (2009). Mental uneasiness, perceived stress and help-seeking in a non-resident university student sample. *Epidemiologia e Psichiatria Sociale* 18, 2, 154-60.
- Armando M, Saba R, Monducci E, Dario C, Righetti V, Girardi P, Nelson B, Yung AR, Birchwood M, Fiori Nastro P (2010). Toward a hierarchical model of Psychotic-like Experiences (PLEs): Factorial Analysis and correlation with poor mental health in a community sample of young adults, submitted
- Armando M, Nelson B, Yung AR, Ross M, Birchwood M, Girardi P, Fiori Nastro P (2010). Psychotic-Like Experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults *Schizophrenia Research* DOI: 10.1016
- Bell RQ (1992). Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses, in "Psychiatry" 55, 4, 370-381.
- Bleuler E (1911). *Dementia Praecox oder Gruppe der Schizophrenien*, F. Deuticke, Leipzig und Wien.
- Carpenter WT (2009). Anticipating DSM-V: Should psychosis risk become a diagnostic class?, *Schizophrenia Bulletin* 35, pp. 841-843.
- Cermolacce M, Sass L, Parnas J (2010). What is Bizarre in Bizarre Delusions? A Critical Review. *Schizophrenia Bulletin* 8, 1-13
- Chapman J (1966). The early symptoms of schizophrenia. *British Journal of Psychiatry* 112, 225-251.
- Chapman LJ, Chapman JP (1980). Scales for rating psychotic and psychotic-like experiences as continua. *Schizophrenia Bulletin* 6, 476-489.
- Chapman LJ, Chapman JP, Numbers JS, Edell WS, Carpenter BN, Beckfield D (1984). Impulsive nonconformity as a trait contributing to the prediction of psychotic-like and schizotypal symptoms. *Journal of Nervous and Mental Disease* 172, 681-691.
- Chapman LJ, Chapman JP, Kwapil TR, Eckblad M, Zinser M (1994). Putatively psychosis-prone subjects 10 years later. *Journal of Abnormal Psychology* 103, 171-183.
- Cocchi A, Meneghelli A (2002). Obiettivi e sviluppi di una esperienza pilota di intervento precoce nelle psicosi. *Psichiatria di Comunità* 1-2, 57-67.
- Compton MT, Goulding SM, Ramsay CE, Addington J, Corcoran C, Walker EF (2008). Early detection and intervention for psychosis: perspectives from North America. *Clinical Neuropsychiatry* 5, 6, 263-272.
- Davidson M, Reichenberg MA, Rabinowitz J, Weiser M, Kaplan Z, Mordenhay M (1999). Behavioral and intellectual makers for schizophrenia in apparently healthy male adolescents. *American Journal of Psychiatry* 156, 1328-1335.
- Dhossche D, Ferdinand R, van der Ende J, Hofstra MB, Verhulst F (2002). Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological Medicine* 32, 619-627.
- Eaton WW, Romanoski A, Anthony JC, Nestadt G (1991). Screening for psychosis in the general population with a self-report interview. *Journal of Nervous and Mental Disease* 179, 689-693.
- Eckblad M, Chapman LJ (1986). Development and validation of a scale for hypomanic personality. *Journal of Abnormal Psychology* 95, 214-222.
- Gillies H (1958). The clinical diagnosis of early schizophrenia. In Rodger TF, Mowbray KM & Roy JR (eds) *Topics in psychiatry*, Cassell, London.
- Gross G (1989). The 'basic' symptoms of schizophrenia. *British Journal of Psychiatry* 155, 7, 21-25.
- Gross G, Huber G, Klosterkötter J, Linz M (1987). *Bonner Skala für die Beurteilung von Basissymptomen*. Springer, Berlin.
- Häfner H, Maurer K, Ruhrmann S, Bechdolf A, Klosterkötter J, Wagner M, Maier W, Bottlender R, Möller HJ, Gaebel W, Wölwer W (2004) Are early detection and secondary prevention feasible? Facts and visions. *European Archives of Psychiatry and Clinical Neuroscience* 254, 117-128
- Häfner H, Maurer K, Trendler G, Heidnen W, Schmidt M, Konnecke R (2005). Schizophrenia and depression: challenging the paradigm of two separate diseases—a controlled study of schizophrenia, depression and health controls. *Schizophrenia Research* 77, 11-24.
- Hanssen M, Bak M, Bijl R, Vollebergh W, van Os J (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *British Journal of Clinical Psychology* 44, 181-191.
- Huber G, Gross G, Schüttler R, Linz M (1980). Longitudinal studies of schizophrenic patients. *Schizophrenia Bulletin* 6, 4, 592-605.
- Huber G (1983). Das Konzept substratnaher Basissymptome und seine Bedeutung für Theorie und Therapie schizophrener Erkrankungen. *Nervenarzt* 54, 23-32.
- Huber G, Gross G, Schuettler R (1979). *Schizophrenie. Verlaufs- und sozialpsychiatrische Langzeituntersuchungen an den 1945–1957 in Bonn hospitalisierten schizophrenen Kranken*. Springer, Bonn.
- Johns, LC, Cannon M, Singleton N, Murray RM, Farrell M, Brugha T, Bebbington P, Jenkins R, Meltzer H (2004). Prevalence and correlates of self-reported psychotic symptoms in the British population. *British Journal of Psychiatry* 185, 298-305.
- Kendler KS, Gallagher TJ, Abelson JM, Kessler RC (1996). Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. The National Comorbidity Survey. *Archives of General Psychiatry* 53, 1022-1031.
- Killackey E, Nelson B, Yung AR (2008). Early detection and intervention in psychosis in Australia: history, progress and potential. *Clinical Neuropsychiatry* 5, 6, 279-285.
- Klosterkötter J (1992a). The meaning of basic symptoms for the genesis of the schizophrenic nuclear syndrome. *The Japanese journal of psychiatry and neurology* 46, 3, 609-30.
- Klosterkötter J (1992b). How does the schizophrenic nuclear syndrome arise? Results of the Bonn transition series study and Anglo-American models: a comparison. *Nervenarzt* 63, 11, 675-682.
- Klosterkötter J, Schultze-Lutter F, Ruhrmann S (2008). Kraepelin and psychotic prodromal conditions. *European Archives of Psychiatry and Clinical Neuroscience* 258, suppl 2, 74-84.
- Kraepelin E (1896). *Psychiatrie: Ein Lehrbuch für Studierende und Ärzte*, 5. JA Barth, Leipzig.
- Louzã MR, Azevedo Y, Macedo G, Gattaz W (2008). An early psychosis research program in São Paulo, Brazil. Organization and implementation. *Clinical Neuropsychiatry* 5, 6, 273-278.
- Malmberg A, Lewis G, David A, Allebeck P (1998). Premorbid adjustment and personality in people with schizophrenia. *British Journal of Psychiatry* 172, 308-313.
- McGorry PD, Singh BS (1995). Schizophrenia: Risk and possibility. In Raphael B & Burrows GD (eds) *Handbook of Preventive Psychiatry*. Elsevier, New York.
- Meehl PE (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist* 17, 827-838.
- Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the structured interview for prodromal syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry* 159, 863-865.
- Miller TJ, McGlashan TH, et al. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin* 29, 4, 703-715
- Mishara AL (2010). Klaus Conrad (1905-1961): delusional mood, psychosis, and beginning schizophrenia. *Schizophrenia Bulletin* 36, 1, 9-13

- Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J, Parker S, Bentall RP (2004). A randomised controlled trial of early detection and cognitive therapy for the prevention of psychosis in people at ultra-high risk. *British Journal of Psychiatry* 185, 291-297.
- Nelson B, Yung AR, Bechdolf A, McGorry PD (2008). The phenomenological critique and self-disturbance: implications for ultra-high risk ("prodrome") research. *Schizophrenia Bulletin* 34, 381-392.
- Nelson B, Yung AR (2009). Psychotic-like experiences as overdetermined phenomena: When do they increase risk for psychotic disorder? *Schizophrenia Research* 108, 303-304.
- Nishida A, Tani H, Nishimura Y, Kajiki N, Inoue K, Okada M, Sasaki T, Okazaki Y (2008). Associations between psychotic-like experience and mental health status and other psychopathologies among Japanese early teens. *Schizophrenia Research* 99, 125-133.
- Parnas J (2000). Genetics and psychopathology of spectrum phenotypes. *Acta Psychiatrica Scandinavica* 101, 413-415.
- Peters ER, Joseph SA, Garety PA (1999). Measurement of delusion in the normal population: introducing the PDI (Peters et al. Delusions Inventory). *Schizophrenia Bulletin* 25, 553-576.
- Phillips LJ, Yung AR, McGorry PD (2000). Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. *Australian and New Zealand Journal of Psychiatry* 34, suppl, 164-169.
- Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkötter J (2010). Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Archives of General Psychiatry* 67, 3, 241-51.
- Schultze-Lutter F (2004). Prediction of psychosis is necessary and possible. In McDonald C, Schultz K, Murray R Wright P (eds) *Schizophrenia: challenging the orthodox*. Taylor & Francis, London, pp 81-90
- Schultze-Lutter F (2009). Subjective symptoms of schizophrenia in research and the clinic: The basic symptom concept. *Schizophrenia Bulletin* 35, 5-8.
- Strauss JS (1969). Hallucinations and delusions as points on continua function. *Archives of General Psychiatry* 21, 581-586.
- Süllwold L, Huber G (1986). *Schizophrene Basisstörungen*. Springer, Berlin.
- Tait L, Birchwood M, Trower P (2004). Adapting to the challenge of psychosis: personal resilience and the use of sealing-over (avoidant) coping strategies. *British Journal of Psychiatry* 185, 410-415.
- Tien AY (1991). Distributions of hallucination in the population. *Social Psychiatry and Psychiatric Epidemiology* 26, 287-292.
- van Os J, Hanssen M, Bijl RV, Ravelli A (2000). Straus (1969) revisited: a psychosis continuum in the general population?. *Schizophrenia Research* 45, 11-20.
- van Os J, Hanssen M, Bijl RV, Vollebergh W (2001). Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. *Archives of General Psychiatry* 58, 663-668.
- van Os J (2009). A salience dysregulation syndrome. *British Journal of Psychiatry* 194, 101-103.
- Vollmer-Larsen A, Handest P, Parnas J (2007). Reliability of Measuring Anomalous Experience: The Bonn Scale for the Assessment of Basic Symptoms. *Psychopathology* 40, 345-348.
- Yung AR, Phillips LJ, McGorry PD, Hallgren MA, McFarlane CA, Jackson J, Francey S, Patton GC (1998). Can we predict onset of first episode psychosis in a high risk group? *International clinical psychopharmacology* 13, suppl 1, S23-S30
- Yung AR, Buckby JA, Cotton SM, Cosgrave EM, Killackey EJ, Stanford C, Godfrey K, McGorry PD (2006). Psychotic-like experiences in non-psychotic help-seekers: Associations with distress, depression and disability. *Schizophrenia Bulletin* 32, 352-359.
- Yung AR, Buckby JA, Cosgrave EM, Killackey EJ, Baker K, Cotton SM, McGorry PD (2007). Association between psychotic experiences and depression in a clinical sample over 6 months. *Schizophrenia Research* 91, 246-253.
- Yung AR, Nelson B, Baker K, Buckby JA, Baksheev G, Cosgrave EM (2009). Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. *Australian and New Zealand Journal of Psychiatry* 43, 118-28.