Schizophrenia Research 206 (2019) 355–361

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Persistent negative symptoms in individuals at Ultra High Risk for psychosis

Alison R. Yung [a,b,c,d,*], Barnaby Nelson [c,d], Patrick D. McGorry [c,d], Stephen J. Wood [c,d,e], Ashleigh Lin [f]

[a] Division of Psychology and Mental Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[b] Greater Manchester Mental Health NHS Trust, Manchester, UK
[c] Orygen, The National Centre of Excellence in Youth Mental Health, Australia
[d] Centre for Youth Mental Health, The University of Melbourne, Australia
[e] School of Psychology, University of Birmingham, UK
[f] Telethon Kids Institute, Australia

ARTICLE INFO

Article history:
Received 21 May 2018
Received in revised form 16 October 2018
Accepted 20 October 2018
Available online 26 October 2018

Keywords:
Negative symptoms
Clinical high risk
At risk mental state
Prodrome
Neurocognition
Childhood maltreatment

ABSTRACT

Persistent negative symptoms (PNS) defined as negative symptoms that persist for at least six months in the absence of high levels of positive, depressive and extrapyramidal symptoms, are evident early in the course of schizophrenia from the first episode of psychosis. However, their presence even earlier in the illness, in those at Ultra High Risk of psychosis, has not been investigated. In this study, we examined the prevalence, baseline correlates and outcome of PNS in 363 Ultra High Risk individuals. Assessments were conducted at baseline and 2–14 years later (mean follow up time 7.4 years). Baseline assessments included demographic, clinical and neurocognitive measures, which were repeated at follow up. The prevalence of PNS in the UHR group was 6.1%. Poor premorbid social adjustment, deficits in verbal fluency and childhood maltreatment, specifically emotional neglect, were evident at baseline in the PNS group compared to the group without PNS. PNS were associated with poor psychosocial functioning and deficits in processing speed at follow up. Our findings suggest that PNS can be detected early, allowing for the identification of a subset of Ultra High Risk patients who are likely to have poor outcome. These individuals could be the target for specific intervention. Further research is needed into the pathophysiology of these PNS to develop specific interventions.

1. Introduction

Negative symptoms of schizophrenia have long been described (Bleuler, 1911; Jackson, 1885; Kraepelin, 1919) and are thought of as being fundamental to the illness (Bleuler, 1911; Strauss et al., 1974). They occur early in the illness, including in the prodromal phase preceding a first episode of psychosis (Piskulic et al., 2012). Negative symptoms are generally not responsive to antipsychotic medication (Aleman et al., 2017; Millan et al., 2014) and are associated with poor functional outcome (Lin et al., 2011; Yung et al., 2015). Although they are correlated with neurocognitive impairments (McDowd et al., 2011), their neurobiological basis remains unknown (Galderisi et al., 2015) and may be multifactorial and dependent on their nature (e.g., diminished expression versus amotivation) and chronicity (Marder and Galderisi, 2017).

Prominent negative symptoms are a central feature of the Deficit Syndrome in schizophrenia. This syndrome, first described by Carpenter and colleagues in 1988 (Carpenter et al., 1988) requires the presence of primary negative symptoms (i.e. not secondary to factors such as depression, positive symptoms or extrapyramidal features) that endure for least 12 months in the context of a diagnosis of schizophrenia. While Deficit Syndrome is a valid and useful concept, it is difficult to apply in early psychosis populations due to its requirement for a schizophrenia diagnosis and 12-month time frame.

Recently, the concept of Persistent Negative Symptoms (PNS) has been defined and acknowledged as a legitimate treatment target (Buchanan, 2007). According to the National Institute of Mental Health-MATRICS consensus report, PNS criteria require the presence of prominent negative symptoms of at least moderate severity that have not responded to the usual treatments, cause functional impairment, are present during periods of clinical stability and persist for at least six months (Buchanan, 2007; Kirkpatrick et al., 2006). The most frequent and measurable causes of secondary negative symptoms (positive, depressive and extrapyramidal symptoms) should be absent or at a low level (Buchanan, 2007; Mucci et al., 2017). Thus PNS is a useful

* Corresponding author at: Division of Psychology and Mental Health, School of Health Sciences, Faculty of Biology, Medicine and Health, Oxford Rd, Manchester M13 9PL, UK.
E-mail address: alison.yung@manchester.ac.uk (A.R. Yung).

https://doi.org/10.1016/j.schres.2018.10.019

construct in early psychosis due to its shorter time frame and absence of the requirement for a schizophrenia diagnosis (Galderisi et al., 2013).

The prevalence of PNS in first episode psychosis samples ranges from about 7% to 31%, depending on the exact PNS criteria used, length of follow up and proportion of individuals with schizophrenia included in the sample. PNS are associated with poor functional outcome in first episode psychosis (Galderisi et al., 2013) and with poor premorbid adjustment, especially in the social domain (Chang et al., 2011; Üçok and Ergül, 2014).

An association between PNS and both male gender (Chang et al., 2011) and long duration of untreated psychosis (Malla et al., 2004) has been described in first episode samples. They are more common in first episode patients with early as opposed to adult onset of illness (Puig et al., 2017). PNS have also been found to be associated with neurocognitive impairments in first episode psychosis, although findings are inconsistent across studies. One study found an association with verbal memory only (Hovington et al., 2013), another with processing speed only (Chang et al., 2016), while others have shown deficits in executive function (Puig et al., 2017; Üçok and Ergül, 2014) and attention (Üçok and Ergül, 2014). Puig et al. (2017) also found deficits in global cognition, executive functions, and verbal memory in individuals with PNS with onset of illness before age 17 compared to their counterparts with PNS but with later onset of psychosis. Taken together, these findings are consistent with PNS in early psychosis being conceptually similar to the Deficit Syndrome in schizophrenia, and suggest that PNS may be a manifestation of a neurodevelopmental process.

As PNS are evident early in the course of psychotic disorder, we aimed to determine if they could be detected even before the first psychotic episode, in individuals at Ultra High Risk (UHR) for psychosis. We hypothesised that PNS: i) could be identified in the UHR group; ii) would be associated with features typically described as 'neurodevelopmental risk factors' for schizophrenia: male gender, long duration of illness, poor premorbid adjustment and neurocognitive abnormalities (Murray and Lewis, 1987; Weinberger, 1987); and that conversely PNS would not be associated with the 'psychological risk factor' (Bentall et al., 2014; Lardinois et al., 2011) of childhood maltreatment. We further hypothesised that iii) PNS would be associated with transition to psychosis; and iv) PNS would be associated with other long-term poor outcomes at follow up such as poor functioning, low quality of life and neurocognitive dysfunction.

2. Method

2.1. Setting and patients

The PACE (Personal Assessment and Clinical Evaluation) Clinic is a specialist clinic for young people at UHR for psychosis located in Melbourne, Australia. The current data are part of a longitudinal study that aimed to reassess all individuals who took part in research at PACE between 1993 and 2006 ($N = 416$). At baseline, patients were aged 15 to 30 years and met UHR criteria rated on the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). Exclusion criteria were a previous psychotic episode (treated or untreated), organic cause for presentation or past anti-psychotic exposure equivalent to a total haloperidol dose of >50 mg. The operationalized criteria have previously been described (Yung et al., 2003; Yung et al., 2004).

A previously developed tracking system was used to relocate patients (Henry et al., 2007). The study was approved by the local Research and Ethics Committee. All patients provided written informed consent. Follow-up interviews took place between 2007 and 2009. Three hundred and sixty-three individuals had sufficient data at both baseline and follow up to enable the PNS definition to be applied. For a full description of the sample, see Nelson et al. (2013).

2.2. Assessments

In addition to the CAARMS (Yung et al., 2005), the following clinical measures were used:

Negative symptoms were assessed with the Schedule for Assessment of Negative Symptoms (SANS) (Andreasen, 1982) and general psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) at baseline and follow up. Premorbid functioning was measured with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982)(higher scores indicate lower functioning) at baseline. As in previous studies (Allen et al., 2013; Chang et al., 2016) premorbid adjustment was sub-divided into social and academic functional domains. Functioning and quality of life at follow up were assessed with the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992) and Quality of Life Scale (QLS) (Heinrichs et al., 1984) respectively.

Neurocognitive assessments were performed at baseline and follow up. Memory was assessed by Logical memory I and Visual Reproduction I from the Wechsler Memory Scale-Revised. The Verbal Memory Index was calculated from Logical memory I and Verbal Paired Associates I. The Trail Making Test Parts A and B (Reitan and Wolfson, 1985) were used. Trails A indexes psychomotor speed, while Trails B measures set-shifting. The total words generated from the letters F, A, and S on the COWAT (Benton and Hamsher, 1983) provided a measure of verbal fluency at baseline only.

History of childhood maltreatment was assessed using the brief Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), a 28-item self-report instrument that assesses childhood experiences of physical abuse and neglect, sexual abuse and emotional abuse and neglect and provides a total score for all trauma.

2.3. Definition of persistent negative symptoms

Consistent with the Buchanan criteria (Buchanan, 2007), PNS were defined as presence of at least one SANS global subscale score ≥3 at baseline and at follow up, a combined total score of 6 or less on the BPRS subscales of depression, guilt and suicidality (corresponding to an average of "very mild" or less on each item), and a combined total score of 16 or less on the BPRS psychotic subscales of conceptual disorganisation, hallucinations, suspiciousness and unusual thought content (corresponding to an average of "moderate" or less on each item). No measure of extrapyramidal symptoms was used. However, UHR individuals in the study group were not treated with antipsychotic medication at baseline.

2.4. Analyses

We compared those with PNS ("PNS") and those without PNS ("noPNS"). Categorical variables were compared using chi-squared tests. Continuous independent variables were checked for normality using visual inspection of the histograms and Q-Q plots and Kolmogorov-Smirnov test with Lilliefors correction (Peat and Barton, 2008). Skewed variables were log-transformed. Independent *t*-tests were then used to compare means. An alpha level of 0.05 was used for all statistical tests, with the Benjamini & Hochberg False Discovery Rate (B-H FDR) used to correct for multiple comparisons (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001). B-H FDR was chosen as, unlike the Bonferroni procedure, it does not assume that all tests are independent. (In this case, for example, SOFAS and QLS are highly correlated, and Trails A and Trails B are highly correlated with each other at baseline and follow up).

3. Results

Three hundred and sixty-three participants had data at both baseline and follow up that enabled the above definition of PNS to be applied.

Mean follow up time was 7.4 years for the noPNS group and 7.8 years for the PNS group ($t = -0.524$, $p = 0.601$). Of the 363 participants, 22 (6.1%) had PNS and 341 (93.9%) did not. Mean age did not differ between the groups (baseline mean age noPNS = 18.7, SD 3.3; PNS = 18.7, SD 3.1). Proportion of males in each group did not differ significantly (PNS: 54.5% male, noPNS: 42.2%, χ^2 (1) = 1.251, $p = 0.263$, adjusted $p = 0.4653$).

3.1. Premorbid and baseline correlates of PNS

Duration of illness prior to presentation to the PACE Clinic (variable log-transformed) was longer in the PNS group compared to the noPNS group, but not significantly after adjusting for multiple comparisons (see Table 1). Premorbid social adjustment was significantly worse in the PNS group compared to the noPNS group. This was evident across the premorbid developmental periods of early adolescence (aged 12–15) and late adolescence (aged 16–18). Although there was no significant difference in childhood social functioning, the effect size of premorbid social adjustment differences between the PNS and noPNS groups was consistently large across the developmental ages from childhood to late adolescence (see Table 1). The only significant difference between the groups in academic adjustment was in late adolescence, with no differences in childhood or early adolescence.

Baseline verbal fluency (COWAT score) was significantly poorer in the PNS group compared to the noPNS group. There were no differences between the groups in Trails A, Trails B, Logical Memory, Visual Reproduction or Verbal Memory Index at baseline (see Table 1). The number of participants with baseline neurocognitive data was small and insufficient to analyse the transitioned and non-transitioned groups separately. It was not possible to conduct a logistic regression to examine predictors due to the large amount of missing data. Very few UHR individuals had both PAS and neurocognitive data available.

Participants in the PNS group had a significantly higher CTQ score (log transformed) compared to those without PNS (Table 1). Post-hoc testing to examine the sub-type of childhood maltreatment revealed that the higher CTQ scores in the PNS group were due to higher emotional neglect in this group compared to the noPNS group. There were no differences between the groups in the other CTQ subscales (see Table 2).

3.2. Outcomes of participants with PNS compared to those without PNS

Ten of the 22 participants in the PNS group developed psychosis (42.9%) compared to 89 of 341 in the noPNS group (26.3%), a non-significant difference after adjusting for multiple comparisons (χ^2 (1) = 3.903, unadjusted $p = 0.046$, adjusted $p = 0.0962$).

PNS were associated with poor psychosocial functioning at follow-up, with mean SOFAS and QLS scores both significantly different between the groups with large effects sizes (see Table 3). In post-hoc testing to compare participants that transitioned to psychosis and those that did not, functioning and quality of life at follow up was significantly worse in those with PNS compared to those without PNS in both transitioned and non-transitioned groups (Table 4).

Processing speed (Trails A) at follow up was significantly slower in the PNS group compared to the noPNS group. Logical Memory, Visual Memory and Verbal Memory Index and Trails B did not differ significantly between the groups. In those who transitioned to psychosis, Trails A was also significantly slower at follow up in the PNS group compared to the noPNS group. There were no other differences in neurocognitive functioning between the PNS and noPNS in those who transitioned to psychosis. There were no significant differences in neurocognitive performance at follow up between the PNS and noPNS groups in those who did not transition to psychosis (see Tables 3 and 4).

Table 2
Post-hoc comparison of subtypes of childhood maltreatment in individuals with and without PNS.

	PNS $N = 228$	No PNS $N = 17$	t	p	Cohen's d
CTQ emotional abuse[a]	12.81 (1.54)	10.49 (1.62)	−1.750	0.082	0.44
CTQ emotional neglect[a]	15.09 (1.50)	10.57 (1.58)	−3.296	0.001	0.83
CTQ physical abuse[a]	9.17 (1.81)	7.44 (1.57)	−1.493	0.151	0.38
CTQ physical neglect[a]	8.53 (1.51)	7.26 (1.43)	−1.502	0.134	0.38
CTQ sexual abuse[a]	7.01 (1.76)	6.40 (1.62)	−0.776	0.438	0.20

Abbreviations: CTQ = Childhood Trauma Questionnaire.
[a] Natural log back transformed.

4. Discussion

4.1. Summary of findings

In this study, we showed that PNS begin even before the onset of the first psychotic episode, in the group at UHR for psychosis, with a prevalence of 6.1%. This is lower than rates found in first episode samples. This is to be expected, as not all UHR patients will develop a psychotic disorder and some may never have been truly at risk (Yung et al., 1996).

Table 1
Baseline associations for individuals with and without PNS.

	PNS	n[a]	No PNS	n[b]			
	M (95% CI)		M (95% CI)		t	Adjusted p	Cohen's d
Duration of illness, days[c]	384.8 (203.8; 726.4)	17	206.3 (174.5; 242.5)	228	−2.001	0.106	0.51
CTQ total[c]	55.47 (46.44; 66.24)	20	43.91 (41.08; 46.12)	208	−2.468	0.040	0.65
	PNS	n[a]	No PNS	n[b]			
	M (SD)		M (SD)		t	Adjusted p	Cohen's d
PAS childhood -social	2.75 (1.67)	8	1.45 (1.42)	70	−2.123	0.095	0.84
PAS childhood - academic	1.75 (1.29)	8	1.52 (1.14)	70	−0.468	0.819	0.19
PAS early adolescence – social	3.05 (1.39)	8	1.74 (1.36)	70	−2.505	0.046	0.95
PAS early adolescence – academic	2.17 (1.60)	8	2.13 (1.50)	70	−0.051	0.999	0.03
PAS late adolescence – social	3.39 (2.33)	7	1.74 (1.32)	55	−2.670	0.046	0.87
PAS late adolescence – academic	3.38 (1.80)	7	1.60 (1.19)	55	−2.771	0.046	1.09
Logical memory[d]	−0.172 (0.98)	4	0.010 (1.00)	68	0.353	0.878	0.18
Visual reproduction[d]	−0.195 (1.09)	4	0.034 (1.00)	68	0.936	0.537	0.22
Verbal memory index[d]	−0.029 (1.07)	4	0.005 (1.00)	68	0.037	0.971	0.03
Verbal fluency[d]	−1.188 (0.369)	4	0.069 (0.982)	68	2.536	0.049	1.32
Trails A time(seconds)	50.00 (45.07)	4	27.65 (8.84)	68	−0.990	0.534	0.69
Trails B time(seconds)	119.00 (45.07)	4	75.69 (33.96)	68	−1.083	0.512	1.09

Abbreviations: PNS = persistent negative symptoms, n[a] = number with PNS, n[b] = number with noPNS, PAS = Premorbid Adjustment Scale, CTQ = Childhood Trauma Questionnaire; [c]natural log back transformed; [d]reported as z scores.

Table 3
Outcomes at long-term follow-up for individuals with and without PNS.

	PNS $N = 22$	No PNS $N = 245$	*t*	Adjusted p	Cohen's d
	M (SD)	M (SD)			
SOFAS	48.32 (11.02)	69.35 (15.50)	6.221	<0.001	1.56
QLS	61.36 (20.73)	99.72 (22.27)	8.44	<0.001	1.78
Logical memory[a,b]	0.04 (1.01)	0.02 (1.00)	−0.191	0.976	0.02
Visual reproduction[a,b]	−0.20 (1.09)	0.02 (0.98)	0.946	0.575	0.21
Verbal memory index[a,b]	−0.02 (0.66)	0.01 (1.00)	0.252	0.967	0.04
Trails A time (seconds)[b]	36.40 (11.03)	28.37 (12.10)	−2.867	0.038	0.69
Trails B time (seconds)[b]	73.74 (24.86)	64.37 (21.22)	−1.825	0.132	0.41

Abbreviations: PNS = persistent negative symptoms; SOFAS = Social and Occupational Functioning Assessment Scale; QLS = Quality of Life Scale.
noPNS = 234, PNS = 20.
[a] Reported as z-score.
[b] Numbers for neurocognitive testing.

We found that individuals with PNS showed poor premorbid adjustment. This is consistent with evidence showing that people with schizophrenia frequently have poor premorbid adjustment before illness onset (e.g. see (Schmael et al., 2007) for a review) and that poor premorbid adjustment is associated with negative symptoms and poor outcome, including in first episode psychosis samples (Chang et al., 2016; Jeppesen et al., 2008; Jordan et al., 2018). Our PNS group had poor premorbid social but not academic functioning compared to the noPNS group. This is consistent with studies in first episode psychosis (Chang et al., 2016; Chang et al., 2013; Jeppesen et al., 2008), and with the finding that poor social functioning is more stable than poor role functioning in the UHR group (Cornblatt et al., 2012). The finding of reduced academic as well as social functioning in late adolescence may reflect that the UHR state was already manifest.

Of note is that the large effect size for all social PAS scores was consistent across childhood, early adolescence and late adolescence, implying chronic social impairment from an early age, consistent with a neurodevelopmental disorder. The finding of a baseline neurocognitive decrement in verbal fluency further supports this hypothesis. Against this hypothesis was the finding of no association between PNS and male gender or with long duration of illness, and that only one domain of neurocognitive function was lower in the PNS group. It is also possible that negative symptoms may influence premorbid adjustment, especially if negative symptoms have an early onset. However, we were unable to investigate the direction of causality in this study as premorbid adjustment and baseline negative symptoms were both assessed at study entry.

Further, while childhood trauma is a risk factor for psychotic illnesses including schizophrenia (Varese et al., 2012), we hypothesised that there would be no difference in rates of this between the PNS and noPNS groups. This was based on speculation that there are two pathways to developing schizophrenia, "neurodevelopmental" (Murray and Lewis, 1987; Weinberger, 1987) and "psychological" (Bentall et al., 2014; Lardinois et al., 2011), with PNS being a manifestation of the 'neurodevelopmental' pathway. However, we found higher rates of childhood maltreatment in the PNS group compared to the noPNS group. Thus dividing psychotic disorders into "neurodevelopmental" and "psychological" may be a false dichotomy. Indeed, recent thinking around the neurodevelopmental hypothesis of schizophrenia posits that genetic liability, early adverse experiences (including childhood abuse) and later stressors interact in a "Developmental Risk Factor Model of Psychosis" (Murray et al., 2017). Childhood trauma may act as a risk factor through several different mechanisms. It is thought to sensitise vulnerable individuals to stress possibly through alterations in the hypothalamic-pituitary-adrenal (HPA) axis (Ciufolini et al., 2018; Lardinois et al., 2011). Psychological reactions to history of abuse, such as enhanced threat anticipation, external attributional biases and heightened interpersonal sensitivity, can create increased stress and a vicious cycle (Reininghaus et al., 2016). Further, the detrimental effects of childhood maltreatment on the developing brain may contribute to the cognitive impairments found in psychotic disorders (Aas et al., 2012; Sheffield et al., 2013). Recently it has been suggested that childhood trauma increases proneness to psychosis through its effect on self-disturbances (anomalies in the subjective experience of the self) (Gawęda et al., 2018).

However, while there is increasing evidence about potential mechanisms by which childhood trauma increases risk of positive symptoms and cognitive dysfunction in psychotic disorders, there is a paucity of research linking childhood abuse and negative symptoms. The current study found higher rates of childhood emotional neglect, but not other forms of abuse, in the PNS group compared to the noPNS group. We could speculate that children with delayed development and unusual

Table 4
Post-hoc comparison of outcomes for individuals with and without PNS in the group that transitioned and the group that did not transition.

	No transition to psychosis				Transition to psychosis			
	PNS $N = 11$	No PNS $N = 177$	t	*p*	PNS $N = 9$	No PNS $N = 57$	t	*p*
	M (SD)	M (SD)						
SOFAS	51.00 (10.85)	72.14 (13.23)	5.410	<0.001	45.10 (10.89)	61.35 (18.58)	2.683	<0.001
QLS	55.83 (19.70)	103.63 (17.61)	9.037	<0.001	68.00 (20.94)	88.49 (29.48)	2.109	0.038
Logical memory[a,b]	0.148 (0.83)	0.071 (1.00)	−0.252	0.801	−0.076 (1.24)	−0.210 (1.06)	−0.357	0.722
Visual reproduction[a,b]	−0.256 (1.07)	0.108 (0.90)	1.283	0.201	−0.121 (1.74)	−0.248 (1.74)	−0.300	0.765
Verbal memory index[a,b]	0.205 (0.68)	0.071 (0.97)	−0.449	0.654	−0.316 (1.41)	−0.199 (1.06)	0.292	0.771
Trails A time (seconds)[b]	33.64 (6.19)	27.94 (12.50)	−4.197	0.136	39.78 (14.76)	29.70 (10.75)	−2.479	0.016
Trails B time (seconds)[b]	67.10 (12.83)	62.79 (20.27)	9.49	0.508	81.11 (33.00)	69.21 (23.43)	−1.287	0.203

Abbreviations: PNS = persistent negative symptoms; SOFAS = Social and Occupational Functioning Assessment Scale; QLS = Quality of Life Scale.
noPNS = 234, PNS = 20.
[a] Reported as z-score.
[b] Numbers for neurocognitive testing.

affect may be susceptible to this form of maltreatment, or that emotional neglect may contribute to a withdrawn, isolative state characteristic of negative symptoms. It may also be that parents with schizophrenia may be prone to emotionally neglect their children, so an underlying genetic cause and/or a gene-environment interaction may be occurring, such that the parent with negative symptoms may emotionally neglect a child who is genetically vulnerable to negative symptoms and the neglect also results in negative symptoms. This is all speculative, and further research in the area of childhood trauma and negative symptoms is needed.

As hypothesised, compared to participants without PNS, those with PNS had poorer long-term social functioning and quality of life. This was evident in both the group that did and did not develop psychosis. These results are consistent with findings in first episode psychosis populations showing that PNS predict poor functional outcome (Chang et al., 2016; Galderisi et al., 2013; Hovington et al., 2012; Jordan et al., 2018; Ventura et al., 2015).

Verbal memory, verbal fluency and processing speed have previously been found to be associated with negative symptoms and functional disability in schizophrenia (McDowd et al., 2011; Narayanan et al., 2015; Ojeda et al., 2008). While we did not find any memory dysfunction in this UHR PNS group compared to the noPNS group, our study showed that the PNS group had impaired verbal fluency at baseline and slowed processing speed at follow up, including in the subsample that developed psychosis. Previous research has suggested that processing speed is a core factor determining functional capacity in schizophrenia and mediates the relationship between verbal memory, verbal fluency and functioning (Ojeda et al., 2008), while others suggest that negative symptoms explain most of the variance in functioning (Dickinson and Coursey, 2002; Revheim et al., 2006) and influence the ability to process information. More recently it has been suggested that premorbid adjustment and verbal memory contribute to functional outcomes in first episode psychosis through both persistent positive and negative symptoms. In this model, while PNS have a greater and more prolonged effect on functioning, persistent positive symptoms significantly reduce functioning early in the course of illness (Jordan et al., 2018). We were not able to examine these associations in our study, but our findings indicate that functional disability, slower processing speed, and negative symptoms occur early in the course of illness. Individuals with these features may be at risk of non-recovery.

Half of the patients with PNS in this sample did not develop a psychotic disorder at follow up. Nonetheless they were functioning poorly. It may be that PNS are a marker of poor functional outcome, regardless of diagnosis. The PNS group that did not transition could be conceptualised as having negative schizotypy - schizotypal personality disorder without positive symptoms - or schizotaxia - a non-psychotic condition on the schizophrenia spectrum characterised by negative symptoms and neurocognitive impairment (Tsuang et al., 2002). Their presentation is also consistent with Cornblatt et al.'s "CASIS" syndrome, a constellation of cognitive deficits, affective disturbances, social isolation, neurocognitive impairment and school failure, that they view as an early "prodrome" to schizophrenia, occurring before the onset of positive psychotic experiences (Cornblatt et al., 2003). All of these constructs are conceptually similar. It may be that presence of PNS indicates a subtype of UHR patients who are closer to the neurodevelopmental type of schizophrenia than those without PNS, even in the absence of development of full threshold positive psychotic symptoms. The clinical picture may remain stable and these individuals may continue to function poorly even in the absence of transition to psychosis (Yung et al., 2010). Additionally, some of these individuals may continue to be at risk of developing a psychotic disorder.

4.2. Clinical implications

Our study has potential clinical implications. Currently individuals meeting UHR criteria are offered cognitive behavioural therapy and monitoring of mental state, regardless of presentation (National Institute of Clinical Excellence, 2014, 2015). Finding that PNS begin and are identifiable in the UHR group means that it may be possible to stratify UHR patients and target the PNS group for specific treatment, such as exercise (Firth et al., 2015; Firth et al., 2017), cognitive remediation (Bellucci et al., 2003; Javitt, 2014), and other psychosocial treatments (Lutgens et al., 2017), and for development and trialling of new interventions (Davis et al., 2014; Goff, 2017; Javitt, 2014). It also means that first episode psychosis patients should have their negative symptoms carefully assessed, as PNS may be identifiable in these individuals soon after service entry if they had a history of primary negative symptoms in the prodromal period or even prior to this. This suggests the possibility for early stratification of care pathways for these patients as well. The above treatments could be used along with early consideration of clozapine therapy – currently underused in early psychosis (Thien et al., 2018).

4.3. Limitations

PNS in this UHR study group were defined as presence of negative symptoms at baseline and follow up. The follow up period varied between 2.4 and 14.9 years. Although all had negative symptoms for at least 6 months, as specified in Buchanan's definition (Buchanan, 2007), the duration varied. Additionally, we do not know if there was any period of remission of negative symptoms between follow up points. To exclude secondary negative symptoms due to depression, we used the BPRS subscales of depression, guilt and suicidality but not anxiety. The rationale for this was that recent research applying the polygenic risk score for schizophrenia to a community sample of young people suggests that genetic risk for schizophrenia manifests itself in adolescence as negative symptoms and anxiety but not depression (Jones et al., 2016). Thus including anxiety may mask a genetic vulnerability to schizophrenia. We note also that the Calgary Depression Scale for Schizophrenia (Addington et al., 1993), which does not include any anxiety items, is recommended by Buchanan (2007), and was used by Hovington et al. (2012), to exclude depressive symptoms from the definition of PNS.

A further limitation was that there were few individuals with PNS, and the number of PNS participants in the post-hoc analysis of transitioned versus non-transitioned samples was small ($n = 9$ and 11 respectively). Missing data was also a problem. Because few participants had neurocognitive, childhood trauma and premorbid adjustment assessments, we were unable to conduct a logistic regression to examine predictors of PNS in more detail to investigate the amount of variance explained by each potential factor. Further, some of the poor functional outcome in the PNS group that developed psychosis could be due to issues other than the PNS, such as positive symptoms, substance abuse and other factors known to impact on functional outcome in early psychosis (Bertelsen et al., 2009; Jordan et al., 2018; Wade et al., 2007; White et al., 2009).

4.4. Conclusion

Our study indicates that PNS are identifiable early in the course of psychotic illness. Negative symptoms should be assessed and monitored in the UHR group. Further research using larger samples would be valuable. This may enable the examination of separate diminished expression and avolition-apathy PNS subtypes and could investigate the pathophysiology of PNS and their association with neurocognition, premorbid adjustment and childhood trauma. This could lead to hypothesis-driven intervention trials in early psychosis directed towards this important unmet therapeutic target.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to this study.

Contributors

Alison Yung designed the study and wrote drafts of the paper. Alison Yung and Ashleigh Lin conducted the analyses. All authors contributed to and have approved the final manuscript.

Funding

This work was supported by the National Health and Medical Research Council (NHMRC) Program grants 350241 and 566529 held by Drs Yung, McGorry and Wood; and the Colonial Foundation. Dr. Yung was supported by an NHMRC Senior Research Fellowship (566593) and an NHMRC Principal Research Fellowship (1136829); Dr Nelson was supported by an NHMRC Career Development Fellowship (1027532) and Senior Research Fellowship (1137687), Dr. Wood by an NHMRC Clinical Career Developmental Award (359223) and Medical Research Council grant (MR/K013599/1). Dr. Lin was supported by an NHMRC Career Development Fellowship (1148793).

The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Acknowledgements

We would like to thank all the patients involved in the PACE studies, the clinicians who managed the patients and the research assistants who collected the data.

References

Aas, M., Navari, S., Gibbs, A., Mondelli, V., Fisher, H., Morgan, C., Morgan, K., MacCabe, J., 2012. Is there a link between childhood trauma, cognition, and amygdala and hippocampus volume in first-episode psychosis? Schizophr. Res. 137, 73–79.

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. Br. J. Psychiatry 22, 39–44.

Aleman, A., Lincoln, T., Bruggeman, R., Melle, I., Arends, J., Arango, C., Knegtering, H., 2017. Treatment of negative symptoms: where do we stand, and where do we go? Schizophr. Res. 186, 55–62.

Allen, D.N., Strauss, G.P., Barchard, K., Vertinski, M., Carpenter, W.T., Buchanan, R.W., 2013. Changes in academic and social premorbid adjustment across sex and developmental period in individuals with schizophrenia. Schizophr. Res. 146, 132–137.

Andreasen, N., 1982. Scale for the Assessment of Negative Symptoms (SANS) (Iowa).

Bellucci, D., Glaberman, K., Haslam, N., 2003. Computer-assisted cognitive rehabilitation reduces negative symptoms in the severely mentally ill. Schizophr. Res. 59, 225–232.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. 57, 289–300.

Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency. Ann. Stat. 29, 1165–1188.

Bentall, R.P., de Sousa, P., Varese, F., Wickham, S., Sitko, K., Haarmans, M., Read, J., 2014. From adversity to psychosis: pathways and mechanisms from specific adversities to specific symptoms. Soc. Psychiatry Psychiatr. Epidemiol. 49, 1011–1022.

Benton, A., Hamsher, K., 1983. Multilingual Aphasia Examination. AJA Associates, Iowa City.

Bernstein, D.P., Stein, J., Newcomb, M., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl. 27, 169–190.

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlæger, J., Quach, P., Christensen, T., Krarup, G., Jørgensen, P., Nordentoft, M., 2009. Course of illness in a sample of 265 patients with first-episode psychosis—five-year follow-up of the Danish OPUS trial. Schizophr. Res. 107, 173–178.

Bleuler, E., 1911. Dementia Praecox or the Group of Schizophrenias. International Universities Press, New York.

Buchanan, R.W., 2007. Persistent negative symptoms in schizophrenia: an overview. Schizophr. Bull. 33, 1013–1022.

Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull. 8, 470–484.

Carpenter, W.T., Heinrichs, D.W., Wagman, A.M.I., 1988. Deficit and nondeficit forms of schizophrenia: the concept. Am. J. Psychiatr. 145, 578–583.

Chang, W.C., Hui, C.L., Tang, J.Y., Wong, G.H., Lam, M.M., Chan, S.K., Chen, E.Y., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr. Res. 22–28.

Chang, W.C., Tang, J.Y.M., Hui, C.L.M., Wong, G.H.Y., Chan, S., Lee, E., Chen, E.Y., 2013. The relationship of early premorbid adjustment with negative symptoms and cognitive functions in first-episode schizophrenia: a prospective three-year follow-up study. Psychiatry Res. 209, 353–360.

Chang, W.C., Lau, C.F.C., Chan, S.K., Hui, C., Chan, S., Lee, E., Lin, J., Chen, E., 2016. Premorbid, clinical and cognitive correlates of primary negative symptoms in first-episode psychosis. Psychiatry Res. 242, 144–149.

Ciufolini, S., Gayer-Anderson, C., Fisher, H., Reis Marques, T., Taylor, H., Di Forti, M., Zunszain, P., Morgan, C., Murray, R., Pariante, C., Dazzan, P., Mondelli, V., 2018. Cortisol awakening response is decreased in patients with first-episode psychosis and increased in healthy controls with a history of severe childhood abuse. Schizophr. Res. https://doi.org/10.1016/j.schres.2018.05.002.

Cornblatt, B.A., Lencz, T., Smith, C.W., Correll, C.U., Auther, A.M., Nakayama, E., 2003. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr. Bull. 29 (4), 633–651.

Cornblatt, B., Carrión, R., Addington, J., Seidman, L., Walker, E., Cannon, T., Cadenhead, K., McGlashan, T., Perkins, D., Tsuang, M., Woods, S.W., Heinssen, R., Lencz, T., 2012. Risk factors for psychosis: impaired social and role functioning. Schizophr. Bull. 38, 1247–1257.

Davis, M.C., Horan, W.P., Marder, S.R., 2014. Psychopharmacology of the negative symptoms: current status and prospects for progress. Eur. Neuropsychopharmacol. 24, 788–799.

Dickinson, D., Coursey, R.D., 2002. Independence and overlap among neurocognitive correlates of community functioning in schizophrenia. Schizophr. Res. 56, 161–170.

Firth, J., Cotter, J., Elliot, R., French, P., Yung, A.R., 2015. A systematic review and meta-analysis of exercise interventions in schizophrenia. Psychol. Med. 45 (7), 1343–1361.

Firth, J., Stubbs, B., Rosenbaum, S., Vancampfort, D., Malchow, B., Schuch, F., Elliott, R., Nuechterlein, K., Yung, A.R., 2017. Aerobic exercise improves cognitive functioning in people with schizophrenia: a systematic review and meta-analysis. Schizophr. Bull. 43, 546–556.

Galderisi, S., Mucci, A., Bitter, B., Libiger, J., Bucci, P., Fleischhacker, W., Kahn, R.S., 2013. Persistent negative symptoms in first episode patients with schizophrenia: results from the European First Episode Schizophrenia Trial. Eur. Neuropsychopharmacol. 23, 196–204.

Galderisi, S., Merlotti, E., Mucci, A., 2015. Neurobiological background of negative symptoms. Eur. Arch. Psychiatry Clin. Neurosci. 265, 543–558.

Gawęda, L., Prochwicz, K., Adamczyk, P., Frydecka, D., Misiak, B., Kotowicz, K., Szczepanowski, R., Florkowski, M., Nelson, B., 2018. The role of self-disturbances and cognitive biases in the relationship between traumatic life events and psychosis proneness in a non-clinical sample. Schizophr. Res. 193, 218–224.

Goff, D.C., 2017. D-cycloserine in schizophrenia: new strategies for improving clinical outcomes by enhancing plasticity. Curr. Neuropharmacol. 15, 21–34.

Goldman, H.H., Skodol, A.E., Lave, T., 1992. Revising Axis V for DSM-IV: a review of measures of social functioning. Am. J. Psychiatr. 149, 1148–1156.

Heinrichs, D., Hanlon, T., Carpenter, W., 1984. The Quality of Life Scale: an instrument for rating the schizophrenia deficit syndrome. Schizophr. Bull. 10, 388–398.

Henry, L.P., Harris, M.G., Amminger, G.P., Yuen, H.P., Harrigan, S.M., Lambert, M., Conus, P., Schwartz, O., Prosser, A., Farrelly, S., 2007. Early Psychosis Prevention and Intervention Centre long-term follow-up study of first-episode psychosis: methodology and baseline characteristics. Early Interv. Psychiat. 1 (1), 49–60.

Hovington, C., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2012. Identifying persistent negative symptoms in first episode psychosis. BMC Psychiatry 12, 224. https://doi.org/10.1186/1471-1244X-1112-1224.

Hovington, C., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2013. Impairment in verbal memory observed in first episode psychosis patients with persistent negative symptoms. Schizophr. Res. 147 (147), 223–229.

Jackson, J.H., 1885. On temporary mental disorders after epileptic paroxysms. West Riding Lunatic Asylum Med. Rep. 5, 105–129.

Javitt, D.C., 2014. Current and emergent treatments for symptoms and neurocognitive impairment in schizophrenia. Curr. Treat. Options Psychiatry 1, 107–120.

Jeppesen, P., Petersen, L., Thorup, A., Abel, M.B., Øhlenschlaeger, J., Christensen, T.Ø., Krarup, G., Jørgensen, P., Nordentoft, M., 2008. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. Psychol. Med. 38, 1157–1166.

Jones, H., Stergiakouli, E., Tansey, K., Hubbard, L., Heron, J., Cannon, M., Holmans, P., Lewis, G., Linden, D., Jones, P., Smith, G., O'Donovan, M., Owen, M., Walters, J., Zammit, S., 2016. Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general population. JAMA Psychiat. 73, 221–228.

Jordan, G., Veru, F., Lepage, M., Joober, R., Malla, A., Iyer, S., 2018. Pathways to functional outcomes following a first episode of psychosis: the roles of premorbid adjustment, verbal memory and symptom remission. Aust. N. Z. J. Psychiatry 52, 793–803.

Kirkpatrick, B., Fenton, W.S., Carpenter, W.T., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 32 (2), 214–219.

Kraepelin, E., 1919. Dementa Praecox and Paraphrenia. Krieger, New York.

Lardinois, M., Lataster, T., Mengelers, R., Van Os, J., Myin-Germeys, I., 2011. Childhood trauma and increased stress sensitivity in psychosis. Acta Psychiatr. Scand. 123, 28–35.

Lin, A., Wood, S.J., Nelson, B., Brewer, W.J., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Pantelis, C., Yung, A.R., 2011. Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. Schizophr. Res. 132, 1–7.

Lutgens, D., Gariepy, G., Malla, A., 2017. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis. Br. J. Psychiatry 210, 324–332.

Malla, A.K., Norman, R.M.G., Takhar, J., Manchanda, R., Townsend, L., Scholten, D., Haricharan, R., 2004. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J. Nerv. Ment. Dis. 192, 455–463.

Marder, S., Galderisi, S., 2017. The current conceptualization of negative symptoms in schizophrenia. World Psychiatry 16, 14–24.

McDowd, J., Tang, T., Tsai, P., Wang, S., Su, C., 2011. The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. Psychiatry Res. 187, 329–334.

Millan, M.J., Fone, K., Steckler, T., Horan, W.P., 2014. Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. Eur. Neuropsychopharmacol. 24, 645–692.

Mucci, A., Merlotti, E., Üçok, A., Aleman, A., Galderisi, S., 2017. Primary and persistent negative symptoms: concepts, assessments and neurobiological bases. Schizophr. Res. 186, 19–28.

Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? Br. Med. J. 295, 681–682.

Murray, R., Bhavsar, V., Tripoli, G., Howes, O., 2017. 30 years on: how the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. Schizophr. Bull. 43, 1190–1196.

Narayanan, S.S., Bhatia, T., Velligan, D., Nimgaonkar, V.L., Deshpande, S., 2015. A case control study of association between cognition and functional capacity in schizophrenia. Schizophr. Res. 169, 165–168.
National Institute of Clinical Excellence, 2014. NICE guidelines 178: psychosis and schizophrenia in adults: treatment and management. http://www.nice.org.uk/guidance/CG178.
National Institute of Clinical Excellence, 2015. NICE Quality Standard [QS80]: Psychosis and Schizophrenia in Adults.
Nelson, B., Yuen, H.P., Wood, S.J., Foley, D., Spiliotacopoulos, D., Lin, A., Bruxner, A., Simmons, M., Thompson, A., M., P., Yung, A.R., 2013. Long term follow up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. JAMA Psychiat. 70, 793–802.
Ojeda, N., Peña, J., Sánchez, P., Elizagárate, E., Ezcurra, J., 2008. Processing speed mediates the relationship between verbal memory, verbal fluency, and functional outcome in chronic schizophrenia. Schizophr. Res. 101, 225–233.
Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.
Peat, J., Barton, B., 2008. Medical Statistics: A Guide to Data Analysis and Critical Appraisal. Blackwell Publishing https://doi.org/10.1002/9780470755945.
Piskulic, D., Addington, J., Cadenhead, K., Cannon, T., Cornblatt, B., Heinssen, R., Perkins, D., Seidman, L., Tsuang, M., Walker, E., Woods, S., iMcGlashan, T.H., 2012. Negative symptoms in individuals at clinical high risk of psychosis. Psychiatry Res. 196, 220–224.
Puig, O., Baeza, I., de la Serna, E., Cabrera, B., Mezquida, G., Bioque, M., Lobo, A., González-Pinto, A., Parellada, M., Corripio, I., Vieta, E., Bobes, J., Usall, J., Contreras, F., Cuesta, M.J., Bernardo, M., Castro-Fornieles, J., 2017. Persistent negative symptoms in first-episode psychosis: early cognitive and social functioning correlates and differences between early and adult onset. J. Clin. Psychiatry https://doi.org/10.4088/JCP.16m11122 (Epub ahead of print).
Reininghaus, U., Kempton, M.J., Valmaggia, L., Craig, T.K., Garety, P., Onyejiaka, A., Gayer-Anderson, C., So, S.H., Hubbard, K., Beards, S., Dazzan, P., Pariante, C., Mondelli, V., Fisher, H.L., Mills, J.G., Viechtbauer, W., McGuire, P., van Os, J., Murray, R.M., Wykes, T., Myin-Germeys, I., Morgan, C., 2016. Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. Schizophr. Bull. 42, 712–722.
Reitan, R.M., Wolfson, D., 1985. The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and Clinical Interpretation. Neuropsychological Press, Tucson, AZ.
Revheim, N., Schechter, I., Kim, D., Silipo, G., Allingham, B., Butler, P., Javitt, D.C., 2006. Neurocognitive and symptom correlates of daily problem-solving skills in schizophrenia. Schizophr. Res. 83, 237–245.
Schmael, C., Georgi, A., Krumm, B., Buerger, C., Deschner, M., Nöthen, M.M., Schulze, T.G., Rietschel, M., 2007. Premorbid adjustment in schizophrenia–an important aspect of phenotype definition. Schizophr. Res. 92, 50–62.
Sheffield, J.M., Williams, L.E., Woodward, N., Heckers, S., 2013. Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. Schizophr. Res. 143, 185–191.
Strauss, J.S., Carpenter, W.T., Bartko, J.J., 1974. The diagnosis and understanding of schizophrenia. Part III. Speculations on the processes that underlie schizophrenic symptoms and signs. Schizophr. Bull. 11, 61–69.
Thien, K., Bowtell, M., Eaton, S., Bardell-Williams, M., Downey, L., Ratheesh, A., McGorry, P., O'Donoghue, B., 2018. Clozapine use in early psychosis. Schizophr. Res. 199, 374–379.
Tsuang, M.T., Stone, W.S., Tarbox, S.I., Faraone, S.V., 2002. An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. Schizophr. Res. 54 (1–2), 169–175.
Üçok, A., Ergül, C., 2014. Persistent negative symptoms after first episode schizophrenia: a 2-year follow-up study. Schizophr. Res. 158, 241–246.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., Bentall, R., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr. Bull. 38, 661–671.
Ventura, K.L., Gitlin, M.J., Gretchen-Doorly, D., Ered, A., Villa, K.F., Hellemann, G.S., Nuechterlein, K.H., 2015. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. Schizophr. Res. 161, 407–413.
Wade, D., Harrigan, S., McGorry, P.D., Burgess, P., Whelan, G., 2007. Impact of severity of substance use disorder on symptomatic and functional outcome in young individuals with first-episode psychosis. J. Clin. Psychiatry 68, 767–774.
Weinberger, D., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44 (7), 660–669.
White, C., Stirling, J., Hopkins, R., Morris, J., Montague, L., Tantam, D., Lewis, S., 2009. Predictors of 10-year outcome of first-episode psychosis. Psychol. Med. 39, 1447–1456.
Yung, A.R., McGorry, P.D., McFarlane, C.A., Jackson, H.J., Patton, G.C., Rakkar, A., 1996. Monitoring and care of young people at incipient risk of psychosis. Schizophr. Bull. 22 (2), 283–303.
Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S.M., McFarlane, C.A., Hallgren, M., McGorry, P.D., 2003. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr. Res. 60 (1), 21–32.
Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr. Res. 67 (2–3), 131–142.
Yung, A., Yuen, H., McGorry, P., Phillips, L., Kelly, D., Dell'Olio, M., Francey, S., Cosgrave, E., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust. N. Z. J. Psychiatry 39, 964–971.
Yung, A.R., Nelson, B., Thompson, A., Wood, S.J., 2010. The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? Schizophr. Res. 120 (1–3), 1–6.
Yung, A.R., Cotter, J., Wood, S.J., McGorry, P., Thompson, A.D., Nelson, B., Lin, A., 2015. Childhood maltreatment and transition to psychotic disorder independently predict long term functioning in young people at Ultra High Risk for psychosis. Psychol. Med. 45 (16), 3453–3465.