Long-term outcome in adolescents at ultra-high risk for psychosis: A focus on resilience

Sanne de Wit

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LONG-TERM OUTCOME IN ADOLESCENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: A FOCUS ON RESILIENCE

LANGE-TERMIJN UITKOMSTEN VAN ADOLESCENTEN
MET EEN ULTRA-HOOG RISICO OP PSYCHOSE:
EEN FOCUS OP RESILIENCE
(met een samenvatting in het Nederlands)

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“The only source of knowledge is experience.”

Albert Einstein

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Ultra-high risk for psychosis: what does it mean?

Psychosis is a syndrome that markedly interferes with an individual's functioning. It entails a significant departure from reality, often including false perceptions or beliefs and disordered thoughts and speech. Such psychotic symptoms are often accompanied by blunted or inappropriate emotional expressions and motivational deficits as well as abnormalities in mood (e.g., anxiety, depression) and sleep disturbances. It has long been recognized that, in the vast majority of cases, prodromal signs and symptoms precede the onset of psychosis. Signs and symptoms may include functional decline, subtle deviations in thought, emotion and perception, and subtreshold psychotic symptoms (1; 2), which are frequently accompanied by social decline (1; 3; 4).

Yung and McGorry were the first to set up a clinic to monitor and care for help-seeking individuals in such a prodromal phase in Australia (5). The PACE clinic selects individuals who had recently developed subsyndromal psychotic symptoms and/or had a familial risk for psychotic disorders plus a recent deterioration in functioning. These so-called 'ultra-high risk' (UHR) criteria formed a milestone in the creation of operationally defined criteria to identify individuals at risk for psychosis. The Australian program inspired the development of similar programs worldwide (e.g. 6-8) and UHR criteria were adopted and adapted by various groups internationally (for review see 5). Also, additional prodromal criteria were introduced such as basic symptoms including subjective disturbances of cognitive processing and the perception of the self and the world (9).

Soon after the introduction, several studies aimed to validate the UHR criteria. It was found that help-seeking young individuals who meet the criteria indeed have a high risk of developing psychosis with an average one-year rate of transition to psychosis of 36.7% (10). Subsequently, studies aimed to explore characteristics of UHR subjects and to facilitate application of interventions before the illness takes hold, thereby reducing or preventing the devastating effects of psychotic disorders. Schizophrenia, the most common psychotic disorder, is one of the most severe mental illnesses. Similarly to psychosis, it is often characterized by abnormal social behavior and failure to recognize what is real. Common symptoms include false beliefs, unclear of confused thinking, reduced social engagement and emotional expression, and lack of motivation. It begins at a young age, causes delay or decrease in the individual's psychosocial development, as well as great human suffering and severe stress to the ill person itself and their caring relatives. The economic losses, both direct and indirect, caused by schizophrenia are extensive (11; 12). Since the introduction of neuroleptic drugs, the proportion of those who improve has increased, but mortality among schizophrenia patients is still about twice as high as in the general population (13). Studying individuals in the prodromal phase of schizophrenia, i.e. individuals at UHR for psychosis, provides a unique opportunity for research on early treatment and interventions (14).

20 years on…

Since the introduction of UHR criteria 20 years ago, a large number of studies have investigated the mechanisms of disease onset and progression (for reviews see 15–17). Neurobiological studies have often used neuroimaging. UHR individuals have been reported to show reduced grey matter volume in the frontal and temporal lobes, anterior cingulate gyrus and hippocampal regions (18–20). Many of the brain regions identified in volumetric studies have been reported to show reduced activation in functional imaging comparisons, particularly in clusters including left inferior frontal gyrus, bilateral medial and superior frontal gyri, and left anterior cingulate (21). Longitudinal studies show volume loss in insular, temporal, parietal, and superior brain areas in individuals who develop psychosis, compared with those who do not (for review see 19). However, while it is clear that UHR individuals do show brain changes from typically developing controls (TDC), none of these changes has been able to consistently predict subsequent development of psychosis in studies.

Remarkably, transition rates from a UHR state to full-blown psychosis have been decreasing from above 50% in the initial studies using UHR criteria (22) to rates as low as 10–15% (14) in more recent reports with an average of 29% (23). This drop in transition rates raised concerns that the UHR criteria may capture a high proportion of false-positives, potentially causing fear, stigma, and leading to unnecessary treatment (24; 25). At the same time, there has been a steady increase in remission rates reported, i.e. individuals who do no longer fulfil UHR criteria at follow-up. A recent meta-analysis of eight longitudinal studies (26) reported that 73% of 773 UHR subjects did not develop psychosis over a 2-year follow-up and 46% fully remitted from their baseline symptoms. The decreasing transition rates and increasing remission rates raise the question whether the other UHR subjects continue to present with UHR symptoms and to be at risk for psychosis, or whether they actually fully remit from an initial UHR state in time. To date, this question has remained relatively unexplored, as the UHR literature has predominantly focussed on reporting transition rates to psychosis and on studying characteristics of UHR subjects that went on to develop psychosis (27).

Another concern about the UHR concept today is that the widely used focus on transition to psychosis as the main outcome of interest may be a suboptimal method for identifying individuals truly at risk of poor outcome (17; 28). The criterion of ‘transition to psychosis’ has an essentially arbitrary threshold and is based entirely on positive symptoms. There is increasing evidence that negative symptoms and the level of cognitive and social functioning are at least equally important for the long-term outcome of UHR individuals. This is supported by the finding that poor functional outcome is not entirely dependent of the development of psychosis (17; 29; 30). For these reasons, other outcomes may be more relevant and there is a call for studies focusing on functional outcomes (17; 29).

Taken together, these criticisms underscore the importance of studying remission as well as other, more comprehensive, measures of outcome. Moreover, the identification of predictors of

remission could lead to a better understanding of the heterogeneity of outcome and ultimately the disorder itself. Therefore, in this thesis, we do not focus on transition to psychosis but primarily on remission, as well as functional outcome.

The 'Dutch Prediction of Psychosis Study'

The studies presented in this thesis are part of the Dutch Prediction of Psychosis Study (DUPS), a longitudinal, naturalistic field study. It was initiated in 2002 as a collaboration between the Department of Psychiatry in Academic Medical Center (AMC) in Amsterdam and the Child and Adolescent Psychiatry Department in University Medical Center (UMC) in Utrecht. After the two-year collaboration with AMC, the UMC continued their part of the DUPS study independently, and collected follow-up data until 2012.

Participants were help-seeking adolescents referred by general practitioners or other psychiatric clinics, of which 81 individuals met UHR inclusion criteria and completed baseline assessment. Inclusion criteria were adopted from the European Prediction of Psychosis Study (EPOS), a prospective multicenter study (31). Participants were between 12 and 18 years of age at the time of recruitment and had to fulfil at least one of the UHR criteria as listed in Table 1.

Table 1. UHR criteria of the Dutch Prediction of Psychosis Study

1) **Attenuated Positive symptoms**: Reporting at least one of the following symptoms assessed with SIPS P1-P5 and D1 (score 3–5): ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, odd thinking and speech, suspiciousness or paranoid ideation, odd behaviour or appearance. Symptoms have to appear several times a week for a period of at least one week within the last three months.

2) **Brief, Limited, or Intermittent Psychotic Symptoms**: Reporting at least one of the following symptoms assessed with SIPS P1-P5 and D1 (score 6): ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, odd thinking and speech, suspiciousness or paranoid ideation, odd behaviour or appearance with a psychotic intensity with a total duration of one week or less.

3) **Familial Risk plus Reduced Functioning**: Having a schizotypal personality disorder or a first- or second degree relative with a psychotic disorder and a 30% reduction in level of social, occupational/school, and psychological functioning for at least one month in the past year.

4) **Basic Symptoms:** Reporting two or more of a selection of nine basic symptoms of the Cognitive thought disturbances scale (COGDIS). These symptoms have been present during the last three months (score ≥ 3).

The first three inclusion criteria were assessed using the Structured Interview for Prodromal Syndromes (32) and the Family Interview for Genetic Studies (33). The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (34). Exclusion criteria consisted of a past or present psychotic episode lasting more than one week, traumatic brain injury or any known neurological disorder, and verbal intellectual IQ < 75.

In addition to a cohort of UHR individuals, DUPS included a group of typically TDC. Typically developing adolescents were recruited through secondary schools in the region of Utrecht. They were excluded if they met one of the UHR-criteria, if they or any first degree relative had a history of a psychiatric illness, or if they had a second-degree relative with a psychotic disorder. A total of 83 TDC met inclusion criteria and completed baseline assessment.

The design of DUPS involves comprehensive multi-level assessment with follow-up assessments 9 months, 18 months, 2 years, and 6 years post baseline (range 3,5–8,0 years). For an overview of the assessments, see Table 2.

DUPS findings to date

Mirjam Sprong was the first to defend a thesis from the DUPS project in Utrecht. The primary aim of her dissertation was to compare potential vulnerability markers for psychosis in two groups of high-risk adolescents with different developmental pathways to psychosis: a group of UHR adolescents and a group of adolescents with Multiple Complex Developmental Disorder (MCDD). First, groups were compared on prodromal symptoms and autism traits. In addition, both high-risk groups were compared to TDC on schizotypal traits. Although the high-risk groups clearly differed in early developmental and treatment histories, as well as in autism traits, they did not differ with regard to schizotypal traits and basic symptoms, as well as disorganized and general prodromal symptoms (35). However, there were group differences in positive and negative prodromal symptoms with higher levels in the UHR group. Interestingly, 78% of the adolescents with MCDD met UHR criteria. In another study, she compared neurocognitive and behavioural impairments between the groups. Compared to nonpsychiatric controls, both groups had impairments in psychomotor speed, attentional control and verbal output generation. Both

Table 2. Overview Dutch Prediction of Psychosis Study

Measurement	Age participants	Assessment overview
T0 *(baseline)*	12–18 years	Clinical assessment
		Neuropsychological test battery (including IQ)
		EEG/ERP
		MRI
T1 *(9 months)*	13–19 years	Clinical assessment
T2 *(18 months)*	14–20 years	Clinical assessment
T3 *(24 months)*	14–21 years	Clinical assessment
		EEG/ERP
		MRI
T4 *(72 months)*	16–24 years	Clinical assessment
		IQ
		MRI
		DNA

groups also reported comparable social behavioural difficulties. Finally, Mirjam Sprong tested the impairment of facial affect processing in UHR individuals. She found that the MCDD group showed specific deficits in the accuracy of recognizing fearful expressions and an overall reduction in processing speed. No other impairments were found.

Tim Ziermans focused on neurobiological vulnerability markers in his thesis, as assessed with structural MRI and neurophysiology. At baseline, no evidence was found for gross or regional brain differences between UHR individuals and TDC (36). However, at two-year follow-up, UHR individuals showed a smaller increase in cerebral WM than TDC and more cortical thinning in the left middle temporal gyrus (37). A more pronounced decrease over time in total brain and white matter volume was found for UHR individuals who became psychotic compared to TDC and a greater decrease in total brain volume than individuals who were not psychotic. Furthermore, UHR individuals with subsequent psychosis displayed more thinning than TDC in widespread areas in the left anterior cingulate, precuneus, and temporo-parieto-occipital area. At the neurophysiological level, UHR individuals showed reduced prepulse inhibition compared to TDC, both at baseline and two-year follow-up (38; 39). Furthermore, clinical improvement in UHR individuals was associated with an increase in PPI parameters (39). In his final study (40) he tested the validity of UHR criteria for predicting the development of subsequent psychosis. He calculated both the incidence of transition and the remission rate from UHR status. Furthermore, individuals who made a transition were compared to those who did not and to those who remitted on socio-demographic and clinical characteristics. Results showed that at the end of the two-year follow-up period 15.6% of UHR adolescents had experienced a psychotic transition, 35.3% still fulfilled UHR criteria and 49.1% of UHR individuals had remitted from their original UHR status. These results indicate that early detection of UHR symptoms may identify a higher number of individuals that will never reach a clinical threshold for psychosis and that adolescents meeting UHR criteria are at least three times more likely to have remitted from their UHR status after two years than to have made a transition to psychosis. It was this last study of Tim Ziermans that inspired us to focus on remission instead of transition to psychosis in the studies presented in this thesis.

Aims and outline of this thesis

The four aims of this thesis are:

1) to investigate long-term clinical and functional outcome of UHR individuals, and to explore the course of their clinical symptoms
2) to investigate the relative value of neurocognitive and clinical variables for predicting long-term outcome
3) to explore differences in brain development of UHR individuals with different long-term outcomes
4) to explore the potential of using baseline structural MRI data to individually predict long-term clinical and functional outcome of UHR individuals, by using machine-learning techniques

In *Chapter 2* we address the first aim of this thesis. Forty-four UHR adolescents completed extensive clinical assessments at baseline and participated in long-term follow-up approximately six years later. UHR adolescents who had either converted to psychosis or who still met UHR criteria (n = 26) at follow-up were compared to individuals who had remitted from their UHR status (n = 18) on clinical and psychosocial variables.

The second aim of this thesis is addressed in *Chapter 3*. Forty-three UHR individuals and 47 controls were included who had completed an extensive clinical and neurocognitive assessment at baseline and participated in long-term follow-up. UHR adolescents who had converted to psychosis were compared to individuals who had not, as well as TDC on clinical and neurocognitive variables. Regression analyses were performed to determine which baseline measures best predicted transition to psychosis and long-term functional outcome for UHR individuals.

Chapters 4 and *5* report results from the structural MRI scans that were collected at baseline, two-year follow-up and six-year follow-up. With a total of 225 MRI scans, we investigated brain development over six years in 48 UHR individuals and 48 TDC in Chapter 4. At six-year follow-up, 35 UHR individuals were divided in resilient and non-resilient subgroups. Resilience was operationalized in two ways, as either good functioning or complete remission from UHR criteria. The main outcome measures were developmental changes in MR-based measures of cortical and subcortical anatomy. Subsequently in Chapter 5, we focused on the baseline MRI scans to explore the possibility of predicting long-term outcome from baseline MRI scans. 64 UHR individuals and 62 TDC were included for this study. At six-year follow-up, we determined resilience for 43 UHR individuals and performed Support Vector Regression analyses to predict their long-term functional and clinical outcome on a continuous scale. Complementary, we performed Support Vector Machine analyses to separate UHR individuals from TDC and resilient from non-resilient UHR individuals in a binary manner. Finally, *Chapter 6* provides a summary of these studies, as well as a discussion of the implications of the results and the limitations.

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CHAPTER 2

ADOLESCENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: LONG-TERM OUTCOME OF INDIVIDUALS WHO RECOVER FROM THEIR AT-RISK STATE

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ABSTRACT

Studies of individuals at ultra-high risk (UHR) for psychosis have mostly reported on long-term outcome of those individuals who develop psychosis compared to those who do not. However, these studies show that a large number of UHR individuals no longer meet criteria for UHR at follow-up. Therefore, this study aimed to investigate functioning at 6-year follow-up in remitted individuals, and to explore the course of their clinical symptoms. Forty-four UHR adolescents completed extensive clinical assessments at baseline and participated in long-term follow-up approximately six years later. UHR adolescents who had either converted to psychosis or who still met UHR criteria (n = 26) at follow-up were compared to individuals who had remitted from their UHR status (n = 18) on clinical and psychosocial variables. Results show that more than 40% of UHR individuals had fully remitted from their UHR status. At six-year follow-up, remitted individuals had improved clinically on most symptoms, most notably on positive symptoms. The course of their symptoms showed that the most substantial reduction in positive symptoms occurred within the first two years, while improvements in general, mood and anxiety symptoms occurred at a later stage. Baseline socio-demographic characteristics and clinical symptoms did not distinguish between remitters and non-remitters. Although remitters no longer met criteria for UHR, they did meet diagnostic criteria for a wide range of psychiatric disorders. Our findings suggest that, when related to long-term outcome, UHR criteria capture non-specific psychotic symptoms rather then risk for psychosis per se and relate more to general psychopathology.

Keywords: psychosis, ultra-high risk, remission, long-term outcome, clinical diagnosis

INTRODUCTION

The establishment of ultra-high risk (UHR) criteria for psychosis in the mid nineties by Yung and McGorry (1) has set the standard for many studies on individuals at imminent risk of developing psychosis (for a review of the criteria see 2). Early detection of imminent psychosis allows for the possibility of interventions to prevent onset, or to reduce its effects and the burden of chronic disease. It also has the potential to enhance knowledge of etiological factors of psychotic disorders and to improve accuracy of risk prediction (3–5).

Much effort has been invested in studying UHR individuals and the current widely used UHR criteria have been relatively successful in identifying individuals truly at risk of developing psychosis with initial transition rates of 35-54% within the first year (5–7). However, a recent review reported an overall decline of transition rates to an average of 18% within 6-months to 36% within 3 years (8). In addition, a recent meta-analysis of remission rates reported that 73% of 773 subjects who met initial clinical high-risk criteria did not convert to psychosis during a 2-year follow-up period. Of these, about 46% fully remitted from the prodromal psychotic symptoms, corresponding to clinical remission in 35% of the baseline sample (9).

In contrast with the many published studies that have investigated predictors of psychosis and outcome of UHR individuals who developed psychosis (8; 10), only few studies have reported on long-term outcome in UHR individuals who did not convert to psychosis or were in remission. Thus, little is known about symptomatic and functional recovery of these individuals, or whether they still have residual symptoms. Addington and colleagues (11) reported an attenuation in the severity of positive and negative symptoms in subjects clinically at high-risk (n = 303) who did not convert to psychosis at one-year follow-up. Furthermore, they found that this group improved in social and role functioning. However, they only reported on individuals who did not convert to psychosis and not on the outcome of individuals who fully remitted from their initial UHR criteria. Furthermore, the period between baseline and follow-up was relatively short (2 years). Schlosser and colleagues (12) reported on UHR individuals (n = 84) who recovered symptomatically and/or functionally within two years but focused on predictors of recovery rather than outcome. They found that lower levels of negative and mood/anxiety symptoms at baseline were related to increased likelihood of both symptomatic and functional recovery. Moreover, rapid initial improvement in positive, negative and mood/anxiety symptoms were indicators for better outcomes.

Studies investigating differences in baseline socio-demographic and clinical characteristics between remitters and non-remitters have reported mixed results (12–15). Whereas some studies did not find differences between groups, others have reported differences in psychosocial functioning. Studies comparing converters to non-converters, but not remitters, have found baseline differences on various clinical scales, particularly on scales assessing positive symptoms (16; 17). Finally, studies investigating the course of clinical symptoms in UHR individuals (11;

12; 18) have reported a rapid decrease, particularly for positive symptoms. However, of these studies, only the study of Schlosser and colleagues (12) investigated the outcome for individuals in remission separately, while the other two investigated the course of symptoms for converters versus non-converters.

Most of the studies above investigated the outcome of non-converters, a group including individuals in remission as well as individuals with sustained UHR criteria. Individuals with sustained UHR criteria represent a heterogeneous group and sometimes even have a worse outcome than converters (12; 19). As such, the discussion is ongoing whether the threshold for psychosis separating converters from non-converters is meaningful (19; 20) and there is a call for more studies examining the group who remit from their UHR status (9; 11; 21).

To better characterize the outcome of individuals who remit from an UHR state, it is important to investigate the course of clinical symptoms and outcome over long follow-up periods (9; 11; 22). In this study, we followed up a group of 44 young adolescents at UHR for a period of approximately six years and assessed clinical symptoms at 9 months, 18 months, 2 years and 6 years. Results from our two-year follow-up study were published previously (14). The aim of the current study was to 1) examine whether baseline symptom severity and psychosocial functioning were associated with six-year clinical outcome, 2) examine the course of clinical symptoms over time, and 3) assess clinical diagnosis and psychosocial functioning at six-year follow up in individuals who remitted from their UHR state (UHR-R).

METHODS

Participants

All data were collected at the Department of Psychiatry at the University Medical Center Utrecht Brain Center Rudolf Magnus in the Netherlands. Participants (both UHR individuals and healthy controls (HC)) were between 12 and 18 years of age at the time of recruitment and were included after written informed consent. After full disclosure of the study purpose and procedure, written consent was obtained from both the participants and their parents for individuals younger than 18 years of age. During follow-up assessments, individuals aged 18 years and older provided their own informed consent. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Recruitment details of this project have been described in previous publications (14; 23). Briefly, the UHR group consisted of help-seeking adolescents referred by general practitioners or other psychiatric clinics. Participants had to fulfill at least one of the following criteria: 1) attenuated positive symptoms (APS), 2) brief, limited, or intermittent psychotic symptoms (BLIPS), 3) genetic risk for psychosis, combined with a deterioration in overall level of social, occupational/school, and psychological functioning in the past year (GRD) or 4) two or more of a selection of nine

basic symptoms used to assess mild cognitive disturbances (COGDIS). The first three inclusion criteria were assessed using the Structured Interview for Prodromal Syndromes (SIPS) and the accompanying Scale of Prodromal Symptoms (SOPS) (24) and the Family Interview for Genetic Studies (25). The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P) (26). Exclusion criteria consisted of a past or present psychotic episode lasting longer than one week, traumatic brain injury or any known neurological disorder, and verbal intellectual IQ (VIQ) < 75. For one analysis, our HC group with long-term follow-up (n = 44) was included. This group consisted of typically developing adolescents recruited through secondary schools in the region of Utrecht. They were excluded if they met one of the UHR-criteria, if they or any first degree relative had a history of any psychiatric illness, or if there was a second-degree relative with a psychotic disorder.

Follow-up assessments were conducted at 9 months (T1), 18 months (T2), 2 years (T3) and approximately at six years post-baseline (T4) to determine clinical outcome. Clinical and (psychosocial) functioning measures were collected at each time point. At 6-year follow up, the UHR group was subdivided into individuals with subsequent psychotic transition (UHR-P), individuals with sustained UHR status (UHR-NP), and those who had remitted from their UHR status (UHR-R). As it was the aim of our study to investigate (clinical) outcome of individuals in remission specifically, we divided our group into two groups, i.e. remitters and non-remitters, where individuals who had converted to psychosis or who still met UHR criteria were defined as non-remitters. We followed the guidelines, and considered remission to have taken place if a subject no longer exhibited positive prodromal symptoms at the sub-psychotic level, i.e. the subject had ratings of ≤ 2 for all the SIPS/SOPS positive symptom items (24).

Global daily functioning was assessed with the modified Global Assessment of Functioning (mGAF) scale. The mGAF scale is a numeric scale (0 through 90) used by mental health clinicians and physicians to rate social, occupational and psychological functioning. It has more detailed criteria and a more structured scoring system than the original GAF (0 through 100). Because of the increased structure, the mGAF scale is more resistant to rater bias (27). Social functioning at follow-up was assessed with the Adaptive Functioning Scale "Friends" of the ASEBA Adult Self Report, a questionnaire for adults between 18 and 59 years old (28). DSM-IV diagnoses were made at consensus meetings by integrating longitudinal data of patient's medical records, clinical interviews, symptoms severity ratings, and the semi-structured Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) interview.

Data analysis

Statistical analyses were performed with IBM SPSS version 20.0. Demographic and clinical characteristics were tested for between-group differences using *t*-tests for continuous data and chi-square (Fisher's exact test) for categorical data. If assumptions of normality and/or homogeneity of variances were not met, Mann-Whitney tests were used. For these analyses, we applied a Bonferroni correction to adjust for multiple comparisons ($\alpha = 0.05 / 20 = 0.0025$).

To assess the course of clinical symptoms, a general linear model – repeated measures ANOVA design was used. When the assumption of sphericity was violated, a Huynh-Feldt correction was applied. Finally, we performed an explorative qualitative analysis of (principal) axis-I DSM-IV diagnoses at long-term follow-up. Given the explorative nature of these latter two analyses, alpha was set at 0.05.

RESULTS

Group characteristics

Baseline data were available for 70 UHR individuals. Of these individuals, 44 (63%) consented to long-term follow-up (T4, mean months between intake and follow-up 71,9 (SD = 11,3 range 41–95)). At T4 ten of these UHR individuals (22.7%) had experienced a psychotic transition. Sixteen individuals still met the UHR criteria at SIPS interview (UHR-NP; 36.4%) and eighteen individuals had remitted from their initial UHR criteria (UHR-R; 40.9%). This resulted in a total of 26 non-remitters (UHR-P + UHR-NP) and 18 remitters (UHR-R).

Baseline characteristics of socio-demographic and clinical measures

No differences at baseline between remitters and non-remitters reached the threshold for statistical significance after correction for multiple comparisons. Details of socio-demographic and clinical variables are shown in Table 1. To check for potential attrition bias, group characteristics at baseline were compared between individuals who participated in the follow-up and those who did not. Individuals with follow-up data had a significantly higher performance IQ at baseline (t_{68} = -2.22, p = 0.03) than individuals who dropped out of the study. There were no other group differences.

Six-year outcome of remitters vs. non-remitters

Remitters had fewer clinical symptoms at six-year follow-up than non-remitters (positive symptoms; t_{42} = 1.736, p < 0.001, negative symptoms; t_{42} = 3.426, p = 0.001, disorganized symptoms; t_{42} = 4.318, p < 0.001, and general symptoms; U = 77.5, p < 0.001) and on the mood and anxiety item (U = 88.5, p = 0.001). Furthermore, global daily functioning was less impaired in remitters (t_{42} = 4.057, p = < 0.001). To assess if improved functioning in the remission group was comparable to that of HC at 6 years post-baseline, the HC group with long-term follow up was included in this analysis. Although improved compared to non-remitters, we found that the remitters had poorer global functioning than HC (score of 69.7 ± 14.9 vs. 85.7 ± 5.2; U = 128.0, p = < 0.001). For psychosocial functioning, it was found that the number of individuals with a relationship was higher for remitters than non-remitters (χ^2 = 10.417, p = 0.001). Details are shown in Table 2.

The course of clinical symptoms

Figure 1 shows the trajectories of clinical symptoms from baseline (T0) to long-term follow-up (T4). The analyses showed there was a difference over time between remitters and non-remitters for total SIPS score ($F_{4,27}$ = 2.739, p = 0.05, ηp2 = 0.302). Follow-up analyses showed that this difference was due to differences in the subscales 'positive symptoms' ($F_{4,32}$ = 5.149, p = 0.003, ηp2 = 0.392) and 'general symptoms' ($F_{4,31}$ = 2.871, p = 0.04, ηp2 = 0.270). Furthermore, although not significant, the partial eta squared based effect sizes were medium to large for 'disorganized symptoms' (ηp2 = 0.198) and 'mood and anxiety' (ηp2 = 0.179) and medium for 'negative symptoms' (ηp2 = 0.079), suggesting that the lack of significant between-group differences on other subscales was mostly a consequence of relatively small group size. As such, it appears that it was symptom change/reduction in general that differed between groups, rather than one particular class of symptoms. Furthermore, within subject analyses showed an overall significant difference between the means at the different time points for positive symptoms (p = 0.001), negative symptoms (p < 0.001), and disorganized symptoms (p = 0.03). Bonferroni post-hoc tests showed that the biggest change for these subscales occurred between T3 and T4 (p < 0.001). There was only a significant interaction effect between follow-up time and group for positive symptoms.

Table 1 | Baseline characteristics of UHR individuals grouped by their clinical outcome at six-year follow-up

	Remitters	**Non-remitters**	**Statistic**	***p***
Age (mean ± SD)	14.2 ± 1.8	15.7 ± 2.3	T_{42} = 2.44	0.023*
Gender (male/female)	10/8	18/8	χ^2 = 0.860	0.525
Parental education (y, mean ± SD)				
Father	13.4 ± 2.4	14.4 ± 1.7	U = 181.0	0.186
Mother	13.2 ± 2.1	13.5 ± 2.3	U = 204.5	0.469
IQ measures (mean ± SD)				
VIQ	101.7 ± 10.7	103.9 ± 11.7	T_{42} = 0.642	0.525
PIQ	104.8 ± 17.8	98.7 ± 12.5	T_{42} = -1.324	0.193
TIQ	103.3 ± 13.1	101.5 ± 11.3	T_{42} = -0.470	0.641
SIPS/SOPS (mean ± SD)				
Total score	20.4 ± 10.3	26.6 ± 13.2	T_{42} = 1.649	0.107
Positive symptoms	6.8 ± 4.2	8.9 ± 3.8	T_{42} = 1.736	0.090
Negative symptoms	3.4 ± 3.4	5.6 ± 4.8	U = 173.0	0.142
Disorganized symptoms	4.1 ± 3.6	5.2 ± 3.6	U = 180.5	0.198
General symptoms	6.1 ± 4.7	6.9 ± 4.4	T_{42} = 0.580	0.565
Mood & anxiety[a]	2.0 ± 1.7	2.5 ± 2.1	U = 206.0	0.496
Current mGAF-score (mean ± SD)	56.8 ± 12.8	55.2 ± 16.5	T_{42} = -0.334	0.740

Table 1 | *(Continued)*

	Remitters	Non-remitters	Statistic	*p*
Cigarette smoking				
Never	15	14		
Irregular	0	2		
Regular, daily	1	9	$\chi^2 = 6.325$	0.022*
Cannabis use < 1 month				
Never, irregular	16	20		
≥ 1 consumption per week	1	4	$\chi^2 = 1.081$	0.299
Age first clinical contact				
≤ 6 years	7	7		
7-12 years	5	8		
≥ 13 years	5	11	$\chi^2 = 1.138$	0.584
1st/2nd degree relative with psychotic disorder				
No	13	19		
Yes	3	4		
Possibly	2	2	$\chi^2 = 0.356$	1.000
Psychotropic medication (any)				
No	10	15		
Yes	8	11	$\chi^2 = 0.020$	0.888
Living situation				
At home	17	24		
In institution	1	2	$\chi^2 = 0.860$	1.000
Work/school situation				
No school/work	0	1		
Fulltime work/school	17	23		
Parttime work/school	1	2	$\chi^2 = 0.805$	0.669
School level[b]				
No school	0	1		
Special education	6	4		
Elementary school	0	1		
Junior general secondary education	4	10		
Senior general secondary education	6	7		
Pre-university education	1	2	$\chi^2 = 4.003$	0.549

[a] = a single item of the SIPS was used to assess the presence and severity of mood and anxiety symptoms as was done in the study of Schlosser *et al*. (12); [b] = participants who had a job were excluded. SD = standard deviation; VIQ = verbal IQ; PIQ = performal IQ; TIQ = total IQ; SIPS/SOPS = Structured Interview for the assessment of Prodromal Syndromes/Scale of Prodromal Symptoms; mGAF = modified Global Assessment of Functioning

* = $p < 0.05$; ** = $p < 0.0025$

Table 2 | Long-term outcome of remitters and non-remitters at six-year follow-up

	Remitters	Non-remitters	Statistic	*p*
SIPS/SOPS (mean ± SD)				
Total score	13.7 ± 9.3	38.9 ± 17.5	T_{42} = 1.649	**0.000****
Positive symptoms	2.7 ± 2.6	11.4 ± 4.2	T_{41} = 6.098	**0.000****
Negative symptoms	5.5 ± 4.7	12.2 ± 8.1	T_{41} = 3.426	**0.001****
Disorganized symptoms	3.3 ± 2.8	7.8 ± 3.7	T_{41} = 4.318	**0.000****
General symptoms	2.6 ± 2.9	6.9 ± 4.7	U = 77.5	**0.000****
Mood & anxiety[a]	0.7 ± 1.1	2.8 ± 2.0	U = 88.5	**0.001****
Current mGAF-score (mean ± SD)	69.7 ± 14.9	49.4 ± 17.3	T_{42} = -4.057	**0.000****
Cigarette smoking				
Never	9	11		
Irregular	1	2		
Regular, daily	7	11	χ^2 = 0.378	0.891
Therapy				
No	13	14		
Yes	5	12	χ^2 = 1.515	0.218
Psychotropic medication (any)				
No	12	14		
Yes	6	12	χ^2 = 0.723	0.395
Antipsychotic medication				
No	15	20		
Yes	3	6	χ^2 = 0.269	0.604
Current living situation				
At home	10	14		
Independent	6	10		
In institution	2	2	χ^2 = 0.219	0.896
Current work/school situation				
No school/work	3	5		
Fulltime work/school	12	14		
Parttime work/school	3	7	χ^2 = 0.827	0.661
Relationship				
No	3	17		
Yes	13	7	χ^2 = 10.417	**0.001****
Social functioning ASEBA – ASR (mean ± SD)				
Friends (T-score)	50.0 ± 8.5	49.4 ± 8.5	T_{34} = -0.266	0.792
Family (T-score)	46.7 ± 6.4	43.9 ± 9.3	T_{34} = -1.001	0.324

[a] = a single item of the SIPS was used to assess the presence and severity of mood and anxiety symptoms as was done in the study of Schlosser *et al.* 2012. SIPS/SOPS = Structured Interview for the assessment of Prodromal Syndromes/Scale of Prodromal Symptoms; SD = standard deviation; mGAF = modified Global Assessment of Functioning; ASEBA ASR = Achenbach System of Empirically Bases Assessment – Adult Self Report

* = $p < 0.05$; ** = $p < 0.0025$

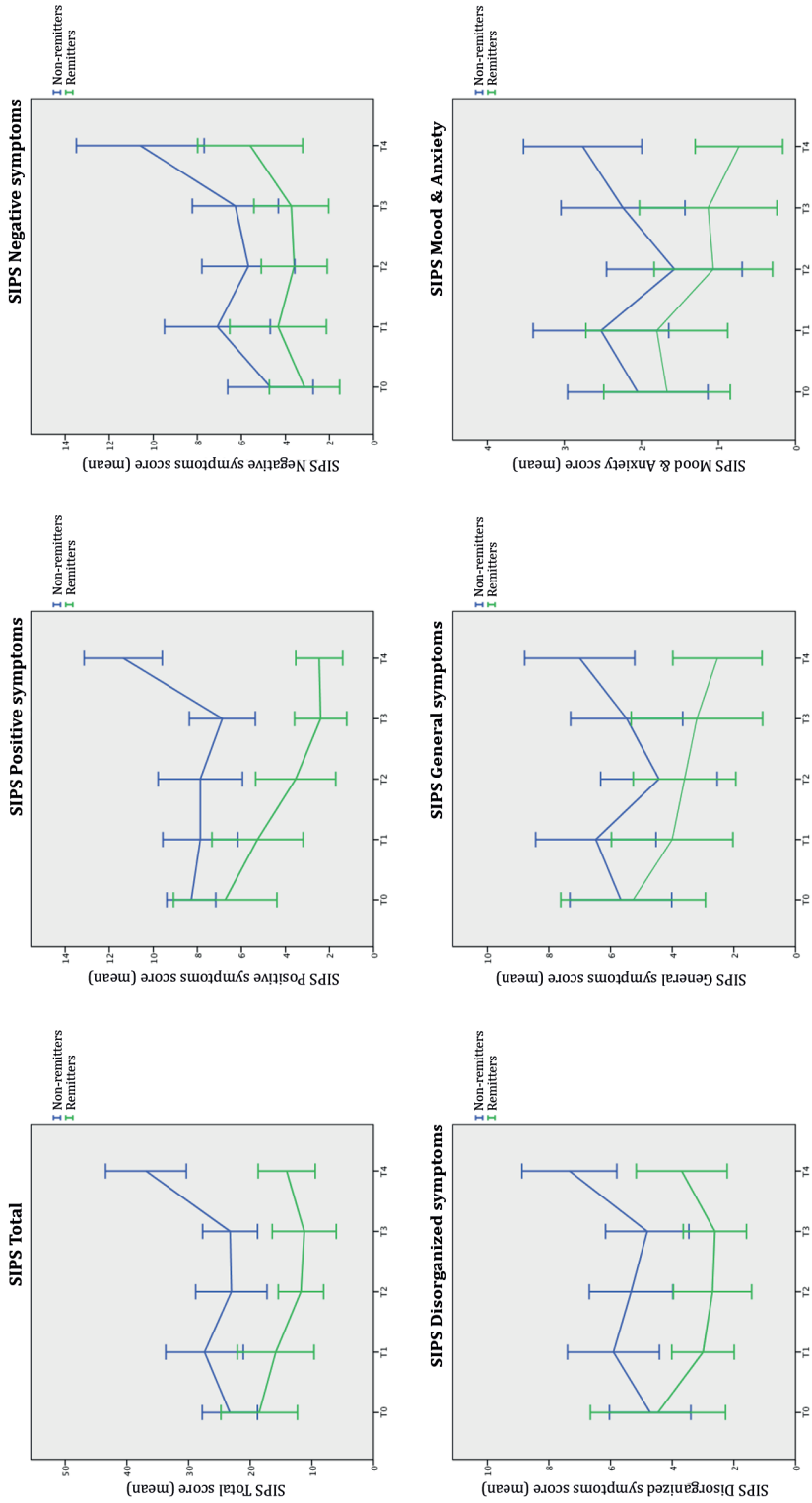

Figure 1 | Time course of clinical symptoms in remitters and non-remitters. Trajectories of SIPS Total, SIPS Positive symptoms and SIPS General symptoms showed significant group differences.

SIPS = Structured Interview for the assessment of Prodromal Syndromes; T0 = baseline; T1 = 9 months follow-up; T2 = 18 months follow-up; T3 = 2 year follow-up; T4 = 6 year follow-up. Whiskers represent standard deviation

Clinical diagnoses of remitters versus non-remitters

We performed an explorative qualitative analysis of (principal) axis-I DSM-IV diagnoses at long-term follow-up to evaluate differences between the groups (Table 3). First, the number of individuals with pervasive developmental disorders (PDD) in the remission group was high, compared to the two other groups (11 UHR-R vs. 1-UHR-P vs. 5 UHR-NP; $\chi^2 = 7.426$, $p = 0.02$). Second, there were a great variety of diagnoses in the UHR-NP group, with a relatively high number of mood- and anxiety disorders. Finally, it should be noted that a large percentage (66% excluding PDD disorders) of the subjects with an axis-I diagnosis in the remission group were in full or partial remission for that specific diagnosis. Personality disorders (DSM-IV axis-II) were only present in the UHR-NP group (2 borderline personality disorder, 1 schizotypal personality disorder). Finally, we checked if there was a similar pattern in diagnoses at baseline, but did not find it.

Table 3 | Axis I diagnoses at long-term follow-up in UHR individuals grouped by clinical outcome

	UHR-P (n = 10)	**UHR-NP (n = 16)**	**UHR-R (n = 18)**
Mood disorders	1	5	1
Depressive disorders	0	2	1
Bipolar disorders	1	3	0
Anxiety disorders	0	3	1
Pervasive developmental disorder	1	5	11
Asperger's syndrome	0	2	3
Pervasive developmental disorder, unspecified	1	3	8
Attention-deficit and disruptive behavior disorders	1	1	1
AD(H)D	0	1	1
OCD	1	0	0
Schizophrenia and psychotic disorders	6	0	0
No diagnosis	1	1	4
Axis I comorbidity	70%	56%	33%

UHR-P = UHR individuals with psychotic transition; UHR-NP = individuals with sustained UHR status; UHR-R = individuals who remitted from UHR status; AD(H)D = Attention Deficit (Hyperactive) Disorder; OCD = Obsessive Compulsive Disorder

DISCUSSION

The present study investigated whether baseline symptom severity and psychosocial functioning were associated with clinical outcome at six-year follow up in individuals initially at ultra-high risk of developing psychosis. We found that baseline characteristics did not differ between individuals who remitted from their at-risk state (40.9%) and individuals who did not. For remitters, positive

symptoms decreased more quickly than other symptoms such as depression and anxiety. The wide range of axis-I diagnoses in remitters at six year follow-up suggest that the UHR criteria may capture a wider range of risks than risk for psychosis.

Our results show that remitters did not differ from non-remitters on any baseline variables, which is in keeping with Simon and colleagues (13) and with our earlier (2-year) follow-up study (14). Because of the shorter time interval in our previous study and the young age of our cohort at baseline, we initially expected the transition rate to increase with longer follow-up periods and hence, that the clinical outcome of individuals was relatively unstable at the time of our previous study. However, this was not the case. Two other studies investigated psychosocial state and outcome at two years post-baseline (12; 15). The first found that good outcome was predicted by higher level of education and good working/studying status at baseline, the second found that better concurrent social and role functioning were associated with an increased likelihood of prodromal remission. Furthermore, Schlosser and colleagues reported that less severe negative and mood/anxiety symptoms at baseline were associated with functional recovery. However, both studies are difficult to compare with our present study, as clinical outcome was defined based on psychosocial functioning instead of the SIPS criteria we used.

At six-year follow-up we expected that remitters would have better psychosocial functioning and as such, were surprised that the only variable that differed between the groups was being in a relationship. An explanation for the negative findings could be that, in spite of having less severe psychotic symptoms and better global functioning than non-remitters, the remitters did not improve on psychosocial functioning because of symptoms related to comorbidity of other DSM-IV diagnoses (e.g. PDD).

Investigation of the time course of clinical SIPS subscales showed that the biggest improvement in positive symptoms occurred within the first two years, while a recovery from general- and mood and anxiety symptoms took longer. One other study (12) looked at the time course of clinical symptoms in remitters separately and also showed a rapid decrease in positive symptoms with the largest improvement within 1.5 years. They further reported that rapid initial improvement in negative and mood and anxiety symptoms were indicators for better outcomes, whereas we showed a gradual decline for general- and mood and anxiety symptoms over six years.

Finally, we performed an explorative analysis of (principal) axis-I DSM-IV diagnoses. Although the diagnosis PDD-NOS at baseline was not an exclusion criterion for this study (see also 23), we found a relatively high proportion of PDD-NOS in the remitters at long-term outcome. Second, we observed a great variety in diagnoses in individuals with sustained UHR criteria. Especially mood and anxiety disorders were often found in this group, as has been reported by others (16; 29). It is possible that individuals with PDD and mood or anxiety symptoms may have been mistakenly diagnosed with risk of psychosis, and, therefore experienced “symptom remission” with appropriate treatment. Conversely, there is the possibility that mood stabilizers provided neuro-

protection in the at-risk group and as such prevented the onset of psychosis (16). In either case, the use of psychotropic medication did not differ between groups in this study. Together with the high proportion of remitters, our results suggest that current UHR criteria may capture too many 'false-positive' individuals at risk, as was also stated in a recent meta-analysis (9). Considering the relatively young age of our sample (12 to 18 years) at baseline, our high number of 'false-positives' may also have been caused by individuals with a (age-related) transitory fluctuating symptomatic state.

Our study has a relatively long follow-up period of six years, and all baseline and follow-up interviews were evaluated during consensus meetings by a team of psychiatrists and psychologists with one psychiatrist (PS) involved in all evaluations. Another strong point of this study is the extensive exploration of outcome. However, there are also some limitations to our study: the attrition rate over six years was substantial (37%), probably due to our long follow-up. For some analyses, this may have resulted in diminished statistical power. Although individuals with follow-up data had a higher performance IQ at baseline than individuals who dropped out of the study, there were no clinical differences and as such, we believe that the drop-out group is unlikely to be clinically more nor less homogenous than the group of individuals that completed long-term follow-up.

In summary, our results show that more than 40% of our initial UHR-subjects fully remitted from UHR symptoms within six years. Remitted individuals not only improved in terms of their positive symptoms, but also on other symptoms. They did not differ from individuals who did not remit in terms of baseline socio-demographic characteristics and clinical symptoms. In combination with the rather broad scope of clinical diagnoses we found in remitted individuals at six years follow-up, this suggests that the currently widely used UHR criteria may capture non-specific psychotic symptoms rather then risk for psychosis per se and relate more to general psychopathology. This should be taken into account when designing early recognition services.

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CONTRIBUTORS

Authors SW, PS, TZ, SD and RK designed and wrote the protocol. Authors SW, PS and TZ contributed to the data collection. Authors SW and BO undertook the statistical analysis, and author SW wrote the first draft of the manuscript. All authors contributed and have approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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CHAPTER 3

NEUROCOGNITIVE AND CLINICAL PREDICTORS OF LONG-TERM OUTCOME IN ADOLESCENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS; A 6-YEAR FOLLOW-UP

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ABSTRACT

Background

Most studies aiming to predict transition to psychosis for individuals at ultra-high risk (UHR) have focused on either neurocognitive or clinical variables and have made little effort to combine the two. Furthermore, most have focused on a dichotomous measure of transition to psychosis rather than a continuous measure of functional outcome. We aimed to investigate the relative value of neurocognitive and clinical variables for predicting both transition to psychosis and functional outcome.

Methods

Forty-three UHR individuals and 47 controls completed an extensive clinical and neurocognitive assessment at baseline and participated in long-term follow-up approximately six years later. UHR adolescents who had converted to psychosis (UHR-P; n = 10) were compared to individuals who had not (UHR-NP; n = 33) and controls on clinical and neurocognitive variables. Regression analyses were performed to determine which baseline measures best predicted transition to psychosis and long-term functional outcome for UHR individuals.

Results

Low IQ was the single neurocognitive parameter that discriminated UHR-P individuals from UHR-NP individuals and controls. The severity of attenuated positive symptoms was the only significant predictor of a transition to psychosis and disorganized symptoms were highly predictive of functional outcome.

Conclusions

Clinical measures are currently the most important vulnerability markers for long-term outcome in adolescents at imminent risk of psychosis.

INTRODUCTION

A major aim of twenty-first century schizophrenia research is to optimize the prediction of psychosis onset to guide initiatives on early intervention. The establishment of ultra-high risk (UHR) criteria for psychosis (1; 2) has greatly enhanced our ability to study individuals relatively close temporally to the onset of psychosis and thereby our ability to improve prediction. Although many UHR studies focus on transition to psychosis as the main outcome of interest, this arbitrary threshold is arguably a suboptimal method for identifying individuals truly at risk of poor outcome (3; 4). Instead, it has been proposed that studies should focus more on functional outcomes, such as the level of cognitive impairment, psychosocial functioning and clinical status (5–8). Surprisingly, such measures have received little attention as an outcome measure until recently, despite the general recognition that functional outcome is likely to be highly associated with long-term social and occupational functioning (9; 10).

In this study we investigated the predictive power of both neurocognitive and clinical variables in predicting both transition to psychosis and functional outcome. In addition, we focused on a group of young adolescents (18 years or younger at baseline), as it is currently unclear whether predictive accuracy of neurocognitive and clinical markers is comparable between younger and older individuals with at-risk symptoms (11). A group of young adolescents at UHR and typically developing controls (TDC) were recruited at baseline and participated in a comprehensive neurocognitive assessment. Subsequently, individuals were followed up for a period of approximately six years to monitor clinical outcome. Our first aim was to determine whether neurocognitive variables could discriminate between TDC and UHR individuals at baseline and predict transition to psychosis, both by themselves and in combination with clinical parameters. Secondly, we investigated whether baseline cognitive functioning and clinical parameters could predict long-term functional outcome of UHR individuals. Based on recent meta-analytic evidence (12), we hypothesized 1) that neurocognitive functioning would be relatively impaired in UHR individuals compared to TDC, and 2) that for the UHR individuals, impairments in cognitive functioning would predict whether they later converted to psychosis (UHR-P) or not (UHR-NP), as well as long-term functional outcome (6; 7). Finally, it was expected 3) that the combination of neurocognitive and clinical parameters would provide the best prediction of long-term clinical outcome (13–15).

METHODS

Participants

All data were collected at the Department of Psychiatry at the University Medical Center Utrecht in The Netherlands. Participants were between 12 and 18 years of age at the time of recruitment and were included after informed consent was given. Participants and parents were provided with a comprehensive written and oral explanation of all procedures. After full disclosure of the

study purpose and procedure, written consent was obtained from both the participants and their parents for individuals younger than 18 years of age. During follow-up assessments, individuals aged 18 years or older provided their own informed consent. All clinical investigation has been conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Recruitment details of the project have been described in previous publications (16; 17). Briefly, the UHR group represented help-seeking adolescents referred by general practitioners or other psychiatric clinics. Participants had to fulfil at least one of the following criteria: 1) attenuated positive symptoms (APS), 2) brief, limited, or intermittent psychotic symptoms (BLIPS), 3) genetic risk for psychosis, combined with a deterioration in overall level of social, occupational/school, and psychological functioning in the past year (GRD) or 4) two or more of a selection of nine basic symptoms used to assess mild cognitive disturbances (COGDIS). The first three inclusion criteria were assessed using the Structured Interview for Prodromal Syndromes (SIPS) and the accompanying Scale of Prodromal Symptoms (SOPS) (18). The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P) (19). Exclusion criteria consisted of a past or present psychotic episode lasting longer than one week, traumatic brain injury or any known neurological disorder, and verbal intellectual functioning (VIQ) < 75. The control group consisted of TDC recruited through secondary schools in the region of Utrecht. They were excluded if they met one of the UHR-criteria, if they or any first degree relative had a history of any psychiatric illness, or if there was a second-degree relative with a psychotic disorder. History of psychiatric illness in family members of TDC was assessed with a Dutch translation of the Family Interview for Genetic Studies (20).

Follow-up assessments were conducted approximately six years post-baseline and four years after the previous clinical follow-up (17) to determine whether a psychotic transition had occurred. A psychotic syndrome was operationalized as the presence of positive symptoms that were seriously disorganizing, i.e. a score of 6 on any of the items of the SIPS Positive Symptoms subscales for a period of more than 7 days (21). Additional information on transition to psychosis was obtained by means of a customized semi-structured telephone interview or from medical record. Chart reviews were used to retrospectively confirm psychotic transition by clinical consensus (HvE, PS) and psychotic subjects were subsequently diagnosed according to DSM-IV guidelines (22). TDC subjects were re-assessed for exclusion criteria via clinical interviews and questionnaires.

Measures

Prodromal symptoms and clinical outcome

The SIPS assesses a broad spectrum of prodromal signs and symptoms, categorized in four subscales: positive, negative, disorganization and general symptoms. Symptoms are scored on a 7-point scale from 0 (absent) through 6 (extreme/psychotic intensity). The semi-structured BSABS-P interview assesses subjective disturbances that have shown to be highly predictive of psychosis (19) and are referred to as basic symptoms (BS). The items are scored on a 7-point scale

from 0 (absent) through 6 (frequent/extreme) and are summarized in three subscales: cognitive-, perceptual-, and motor disturbances. Each item on the BSABS-P corresponds to a single symptom, which differs in structure from the SIPS in which items are mostly defined by multiple symptoms. In addition, there is evidence suggesting that BS are more prominent in the initial prodromal state and symptoms measured by the SIPS are characteristic of a late prodromal phase, in closer temporal proximity of the onset of psychosis (23).

As a measure of functional outcome, the Global Assessment of Functioning (GAF) scale was used at baseline. The GAF scale is a numeric scale (0 through 100) used by mental health clinicians and physicians to rate social, occupational and psychological functioning. At follow-up, the modified GAF (mGAF) scale was used (0 through 90). It has more detailed criteria and a more structured scoring system than the original GAF. Because of the increased structure, the mGAF scale is more resistant to rater bias (24).

Neurocognitive functioning

The test battery consisted of the following measures:

1) General intelligence
   Global intellectual functioning was assessed with the Wechsler Intelligence Scales (26; 28). Full scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) were the dependent variables.
2) Verbal memory
   Verbal memory was assessed using the Dutch 15-Words Task (15WT) (25) that was based on Rey's Auditory Verbal Learning Test (29). Participants were asked to recall a list of 15 unrelated one-syllable words that was presented repeatedly verbally. Dependent variables were a) total acquisition, i.e. the total score of free recall of five trials (max. 75), and b) retention, i.e. the number of words remembered after 20 minutes delay (max. 15).
3) Psychomotor functioning
   Psychomotor functioning was assessed using a computer-administered finger tapping test (FTT) (30). Participants were asked to tap their index finger onto a mouse button as often as possible for 10 seconds. The mean number of dominant hand finger tappings over five trials was used in the analyses.
4) Executive functioning (EF)
   The developmental model of EF was adapted from Anderson (31). This model incorporates four interrelated domains that together enable executive functioning:
   a) Attentional control
      To measure sustained attention, the no distraction-fast condition of the computer-administered Continuous Performance Test-Identical Pairs version 2.0 (CPT-IP) (32) was administered. Participants were asked to respond as quickly as possible whenever two identical visual stimuli (verbal and nonverbal) were presented in a row. Dependent variable for both conditions was the sensitivity index d'. This measure is computed from the number of hits and false alarms and measures the ability to discriminate a signal from background noise by taking response bias into account.

b) Working memory and cognitive flexibility

Working memory was assessed with a computerized Spatial Working Memory Test (SWMT) (27). Participants were required to remember the spatial location of a visual stimulus, either immediately after it had disappeared or with a distraction interval of 30 seconds. Dependent variables were the mean distances between target and response in number of pixels for the two conditions separately. The number of perseverative errors on a computerized version of the Wisconsin Card Sorting Test (CST) was used as a measure of cognitive flexibility (33).

c) Goal setting and problem solving

The number of series completed on the CST (33) was used as a measure of problem solving ability and the ability to develop new concepts.

d) Information processing

A verbal fluency (VF) test was used to assess the quality and quantity of verbal output generation. Participants were first asked to name as many words as possible with the initial letter 'S' within one minute. Subsequently, they were asked to name words from the semantic category 'animals'. Dependent variables for this task were the mean numbers of acceptable words produced in each condition.

Data analysis

Statistical analyses were performed with IBM SPSS version 20.0. Demographic and clinical characteristics were checked for between-group differences (TDC vs UHR and UHR-NP vs UHR-P), using independent samples *t*-test (age), Pearson's χ^2 or, when necessary, Fisher's exact test (gender, inclusion criteria, medication use), and Mann-Whitney tests (parental education, clinical variables). Next, AN(C)OVA was used for between group comparisons of neurocognitive measures. If assumptions for normality of the data and homogeneity of variances were not met, Mann-Whitney tests were used. To reduce the chance of Type I error due to multiple comparisons, but without disproportional inflation of the chance of Type II error, a Dunn-Šidák correction of $p < 0.05$ was calculated with the formula $1 - (1 - \alpha)^{1/n}$, where n is the number of independent neurocognitive tests. Based on seven independent neurocognitive tests, this resulted in a significance threshold of $p < 0.0073$. Cohen's d was calculated for all variables to estimate effect sizes. In a series of follow-up analyses, binary logistic regression was used to test whether baseline neurocognitive and clinical variables could predict transition to psychosis within the UHR sample. After checking for assumptions and to limit the number of predictors in the model, predictive variables were selected separately for clinical subscales (SIPS and BSABS-P) and neurocognitive variables by using backward stepwise logistic regression (Likelihood ratio method), regardless of significant group differences. To maximize the number of cases in the analysis, the initial neurocognitive model included only those variables that were available for all UHR-P cases. Next, an integrated model focused only on those neurocognitive and clinical variables that were significantly related to transition to psychosis in the previous steps. Cook's distance was used to assess the influence of individual cases, participants with a score > 1 were examined and removed from analyses when necessary. Receiver Operator Curves (ROCs) were used to determine sensitivity, specificity and

variable cut-off scores. Finally, multiple regression was performed to predict long-term functional outcome for UHR individuals. Only nonredundant predictors that showed a linear relationship with functional outcome were entered into the model. Alpha for all regression analyses was set at 0.05.

RESULTS

Group characteristics

Baseline data were available for 67 UHR individuals and 72 TDC (see supplementary material for overall group characteristics). Of these individuals, 41 UHR (61%) and 47 TDC (65%) consented to long-term follow-up. Eight out of 41 UHR individuals (19.5%) had experienced a psychotic transition. Two additional UHR individuals without long-term follow-up had experienced psychotic transitions at a previous follow-up (17). As part of the goal was to predict transition to psychosis, their data from the previous follow-up were included in part of the analyses, resulting in a total of ten UHR-P (23.3%) individuals and 33 UHR-NP individuals. Mean time to transition was 1.3 years (*SD* = 1.2 y) for UHR-P individuals, with five transitions occurring in the first year post-baseline, another four within the next year and one transition at approximately 4.5 years after inclusion. DSM-IV diagnoses for UHR-P individuals were as follows: 295.30 schizophrenia, paranoid subtype (n = 7), 296.04 Bipolar I disorder, psychotic features (n = 1), 296.60 schizophrenia, residual type (n = 1), 298.9 psychosis – not otherwise specified (n = 1). Three TDC (6%) were excluded based on clinical diagnoses received since inclusion (1 epilepsy, 1 posttraumatic stress disorder, 1 affective disorder), resulting in data from 44 TDC for analysis.

There were no significant between group differences for age, gender, parental education or follow-up time. Within the UHR group the UHR-P individuals had slightly higher symptom scores at baseline than the UHR-NP individuals on all clinical variables, which reached significance for SIPS - positive (U = 258, Z = -2.69, p = 0.006) and disorganized symptoms (U = 236.5, Z = -2.07, p = 0.038), as well as BSABS-P – cognitive disturbances (U = 212.5, Z = -2.59, p = 0.008). The UHR-P group also consisted of significantly more individuals who fulfilled the GRD (Fisher's exact, p = 0.020) and COGDIS (χ^2_1 = 5.39, p < .020) criteria at baseline than the UHR-NP group. Forty percent of UHR individuals had used some form of psychotropic medication, but there were no differences in medication use between UHR-P and UHR-NP individuals. At follow-up, global daily functioning was more impaired for UHR-P individuals than for UHR-NP individuals (U = 71.5, Z = 2.00, p = .045). Details on demographic and clinical variables are shown in Table 1. To check for potential attrition bias, group characteristics were compared between TDC/UHR individuals who participated in the follow-up and those who did not (35 TDC, 24 UHR). TDC with follow-up data were older at baseline (t_{77} = -2.16, p = 0.034), reported more basic symptoms (U = 526, Z = -2.62, p = 0.009) and had lower GAF scores (U = 962, Z = 2.03, p = 0.043) than TDC who dropped out of the study. There were no such group differences for UHR individuals.

Table 1. Group characteristics long-term follow-up sample

	TDC	UHR	UHR-NP	UHR-P	TDC vs. UHR			UHR-NP vs UHR-P		
Baseline assessment	(n = 44)	(n = 43)	(n = 33)	(n = 10)	$t/\chi^2/U$	df	p	$t/\chi^2/U$	df	p
Age in years, M ± SD	15.4 ± 1.3	15.2 ± 2.2	15.0 ± 2.2	15.9 ± 2.4	t = 0.55	69	0.587	t = -1.07	14	0.302
Gender, N male (%)	23 (52)	27 (63)	19 (58)	8 (80)	χ^2 = 0.98	1	0.321	χ^2 = 1.65	1	0.199
Parental education (y)[a], M ± SD	13.7 ± 2.1	13.6 ± 1.7	13.7 ± 1.7	13.1 ± 1.7	U = 834.5		0.437	U = 125		0.314
SIPS/SOPS, M ± SD										
– Positive symptoms	0.4 ± 0.8	8.4 ± 3.9	7.5 ± 3.5	11.4 ± 3.8	U = 1854		< 0.001	U = 258		0.006
– Negative symptoms	0.1 ± 0.3	4.8 ± 4.4	4.2 ± 4.0	6.8 ± 5.0	U = 1716		< 0.001	U = 223.5		0.093
– Disorganized symptoms	0.3 ± 0.6	5.0 ± 3.6	4.3 ± 3.2	7.1 ± 4.1	U = 1747.5		< 0.001	U = 236.5		0.038
– General symptoms	0.4 ± 0.9	6.6 ± 4.3	6.2 ± 4.5	8.2 ± 3.4	U = 1776		< 0.001	U = 216.5		0.141
BSABS-P[b], M ± SD										
– Cognitive disturbances	0.5 ± 1.0	13.0 ± 8.0	11.0 ± 6.7	19.6 ± 9.0	U = 1664		< 0.001	U = 212.5		0.008
– Perceptual disturbances	0.2 ± 0.5	8.3 ± 7.8	7.5 ± 7.7	11.0 ± 8.1	U = 1754		< 0.001	U = 202		0.105
– Motor disturbances	0.0 ± 0.0	1.5 ± 2.1	1.3 ± 1.7	2.2 ± 3.4	U = 1386		< 0.001	U = 152.5		0.904
GAF, M ± SD	96 ± 6	57 ± 16	58 ± 16	56 ± 15	U = 36.5		< 0.001	U = 150.5		0.681
UHR inclusion criteria[c]										
– APS, N (%)	-	37 (86)	27 (81)	10 (100)	-			χ^2 = 2.11	1	0.146
– BLIPS, N (%)	-	1 (3)	1 (3)	0 (0)	-			χ^2 = 3.10	1	0.578
– GRD, N (%)	-	2 (0)	0 (0)	2 (25)	-			χ^2 = 6.92	1	0.009
– COGDIS, N (%)	-	23 (53)	15 (45)	8 (89)	-			χ^2 = 5.39	1	0.020
Baseline medication[d], N (%)	-	14 (42)	14 (42)	3 (30)	-			χ^2 = 0.50	1	0.481
– Antipsychotic	-	7 (21)	7 (21)	1 (10)	-			χ^2 = 0.64	1	0.425
– Antidepressant	-	6 (18)	6 (18)	2 (20)	-			χ^2 = 0.02	1	0.897
– Psychostimulant	-	1 (3)	1 (3)	0 (0)	-			χ^2 = 0.181	1	0.668
– Anxiolytic	-	2 (6)	2 (6)	1 (10)	-			χ^2 = 0.31	1	0.578
– Other	-	1 (3)	1 (3)	0 (0)	-			χ^2 = 0.31	1	0.578

Table 1. *(Continued)*

	TDC	UHR	UHR-NP	UHR-P	TDC vs. UHR			UHR-NP vs UHR-P		
Baseline assessment	(n = 44)	(n = 43)	(n = 33)	(n = 10)	$t/\chi^2/U$	df	p	$t/\chi^2/U$	df	p
Follow-up assessment										
Age in years, M ± SD	21.3 ± 1.6	21.1 ± 2.4	20.9 ± 2.3	21.5 ± 2.9	t = 0.59	72	0.555	t = -0.68	41	0.501
Follow-up time in years, M ± SD	5.8 ± 0.7	5.8 ± 1.2	5.9 ± 1.0	5.6 ± 0.9	t = 0.16	66	0.872	t = 0.51	10	0.622
range	4.8 – 7.4	2.2 – 7.9	3.4 – 7.9	2.2 – 7.8	-			-		
Days to transition, M ± SD	-	-	-	488 ± 431	-			-		
range	-	-	-	181 – 1645	-			-		
mGAF[e], M ± SD	86 ± 5	58 ± 19	61 ± 18	46 ± 23	U = 152.5		< 0.001	U = 71.5		0.045

[a] = Years of education averaged for both parents; [b] = Four BSABS-P scores (3 UHR-NP, 1 UHR-P) were incomplete; [c] = Participants fulfilling multiple criteria were added as a separate individual in each category and for one UHR-P individual the COGDIS criterium could not be evaluated due to missing values; [d] = Participants using more than one type of medication were added as a separate individual in each category; [e] = mGAF was unavailabe for two UHR-P individuals TDC = typically developing controls, UHR = Ultra-High Risk; UHR-NP = Ultra-High Risk without subsequent psychosis; UHR-P = Ultra-High Risk with subsequent psychosis; SIPS/SOPS = Structured Interview for the assessment of Prodromal Syndromes/Scale of Prodromal Symptoms; BSABS-P = Bonn Scale for the Assessment of Basic Symptoms – Prediction; GAF = Global Assessment of Functioning; APS = Attenuated Positive Symptoms; BLIPS = Brief Limited and Intermittent Psychotic Symptoms; GRD = Genetic Risk and a Deterioration in functioning; COGDIS = Cognitive Disturbances; mGAF = Modified Global Assessment of Functioning

Baseline comparison of neurocognitive measures

TDC vs UHR individuals

Test scores are presented in Table 2. Details of missing data varied per measure and details are included in the supplemental information. TDC had higher scores than UHR individuals on general intelligence measures: FSIQ ($F_{1,85}$ = 8.45, p = 0.005, d = 0.62) and VIQ ($F_{1,85}$ = 8.98, p = 0.004, d = 0.64). At a more lenient statistical threshold of $p < 0.05$ PIQ (p = 0.046) and FTT (p = 0.030) also distinguished between groups. On every other neurocognitive task, except for 15WT – delayed recall and SWMT – condition 2, the UHR group performed more poorly than TDC numerically, but these differences did not reach significance. This suggests that, compared to global intelligence measures, more specific neurocognitive skills were relatively spared in the UHR group. Comparisons of the entire baseline sample (67 UHR and 72 controls) on neurocognitive measures produced similar results: all measures of general intelligence significantly differentiated between groups with medium effect sizes ($d \approx 0.5$; see supplemental data).

UHR-NP vs. UHR-P individuals

The data showed that UHR-P had lower FSIQ and PIQ scores than UHR-NP at $p < 0.05$, but no group differences remained after correction for multiple comparisons (Table 2). However, effect sizes were large for FSIQ (d = 0.99) and PIQ (d = 0.96) and medium-to- large for VIQ (d = 0.73), suggesting that the lack of significant group differences was a consequence of low statistical power due to small group sizes. For the remaining tasks, the effect sizes were relatively small and not consistently higher or lower for either group.

Prediction of psychosis

Model based on SIPS scales

For SIPS subscales the only significant predictor variable was SIPS positive symptoms (Table 3), suggesting that higher scores on the positive symptoms subscale increased the odds of developing psychosis. The ROC curve indicated that a sensitivity of 40.0% with a specificity of 84.8% was the most optimal classification result, with a cut-off score of 11.5.

Model based on BSABS-P scales

'Cognitive disturbances' was the only subscale of the BSABS-P that was a significant predictor, with higher scores associated with increased odds of subsequent psychosis (Table 3). At an optimal cut-off score of 19 the sensitivity was 66.7% and specificity 86.7%. The subscale remained a significant predictor after removal of one influential UHR-P outlier ($p < 0.007$).

Table 2. Baseline cognitive measures for typically developing controls (TDC) and the ultra-high risk groups without (UHR-NP) and with (UHR-P) subsequent psychosis

	TDC	UHR	UHR-NP	UHR-P	TDC vs. UHR			UHR-NP vs. UHR-P		
	(n = 44)	(n = 43)	(n = 33)	(n = 10)	*F*/*U*	p	ES (*d*)	*F*/*U*	*p*	ES (*d*)
General intelligence										
– FSIQ	109.00 ± 11.04	101.72 ± 12.29	104.30 ± 11.74	93.27 ± 10.61	$F_{1,85}$ = 8.45	**0.005**	0.62	$F_{1,41}$ = 6.99	0.012	0.99
– VIQ	110.09 ± 11.58	102.70 ± 11.43	104.45 ± 11.70	96.90 ± 8.57	$F_{1,85}$ = 8.98	**0.004**	0.64	$F_{1,41}$ = 3.56	0.066	0.74
– PIQ	106.16 ± 10.85	100.40 ± 15.37	103.45 ± 15.04	90.30 ± 12.26	$F_{1,85}$ = 4.10	0.046	0.43	$F_{1,41}$ = 6.34	0.016	0.96
Verbal memory										
– 15WT direct recall	50.27 ± 9.56	50.05 ± 9.79	50.21 ± 9.48	49.44 ± 11.44	$F_{1,84}$ = 0.12	0.914	0.02	$F_{1,40}$ = 0.04	0.838	0.07
– 15WT delayed recall	10.70 ± 2.74	10.88 ± 2.62	11.00 ± 2.51	10.44 ± 3.12	$F_{1,83}$ = 0.99	0.820	-0.07	$F_{1,40}$ = 0.32	0.580	0.20
Psychomotor functioning										
– FTT dominant hand	58.54 ± 6.25	55.49 ± 6.24	55.41 ± 6.31	55.73 ± 6.38	$F_{1,81}$ = 4.86	0.030	0.49	$F_{1,37}$ = 0.19	0.891	-0.05
Executive functioning										
– CPT-IP numbers - d'	1.15 ± 0.70	0.92 ± 0.69	0.94 ± 0.71	0.87 ± 0.65	$F_{1,84}$ = 2.20	0.142	0.33	$F_{1,40}$ = 0.06	0.803	0.10
– CPT-IP symbols - d'	1.77 ± 0.69	1.56 ± 0.88	1.48 ± 0.86	1.84 ± 0.91	$F_{1,84}$ = 1.46	0.230	0.27	$F_{1,40}$ = 1.20	0.280	-0.41
– SWMT condition 1[a]	19.33 ± 8.96	19.76 ± 9.47	18.28 ± 6.90	24.56 ± 14.65	*U* = 887.5	0.386	-0.05	*U* = 163.5	0.262	-0.55
– SWMT condition 2[a]	39.00 ± 21.94	38.47 ± 13.91	39.38 ± 15.23	35.56 ± 8.36	*U* = 954	0.132	0.03	*U* = 121.5	0.761	0.31
– CST perseverations[a]	6.27 ± 4.21	6.89 ± 3.88	7.24 ± 3.93	5.43 ± 3.51	*U* = 898	0.303	-0.15	$F_{1,34}$ = 1.24	0.273	0.49
– CST series completed	2.34 ± 1.14	2.11 ± 1.26	2.21 ± 1.24	1.71 ± 1.38	*U* = 719.5	0.471	0.19	$F_{1,34}$ = 0.86	0.361	0.38
– VF words semantic	22.13 ± 4.91	20.60 ± 5.58	21.03 ± 5.08	19.20 ± 5.08	$F_{1,83}$ = 1.86	0.176	0.29	$F_{1,40}$ = 0.82	0.371	0.41
– VF words letter S	11.19 ± 4.52	10.76 ± 4.83	10.59 ± 5.10	11.30 ± 4.06	$F_{1,83}$ = 0.17	0.677	0.09	$F_{1,40}$ = 0.16	0.692	-0.15

[a] Smaller values indicate better performance; TDC = typically developing controls, UHR = Ultra-High Risk; UHR-NP = Ultra-High Risk without subsequent psychosis; UHR-P = Ultra-High Risk with subsequent psychosis; FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; 15WT = 15 Words Task; FTT = Finger Tapping Test; CPT-IP = Continuous Performance Test-Identical Pairs; SWMT = Spatial Working Memory Test; CST = Modified Card Sorting Test; VF = Verbal Fluency Test. Significant *p* values are indicated in bold letter type.

Table 3. Prediction models of transition to psychosis based on clinical or neurocognitive variables or their combination

Model[a]	B	SE	Wald	*p*	Odds ratio	95% CI	% Sensitivity	% Specificity	% PPV
SIPS									
– Constant	-4.07	0.12	9.81	0.002	0.02				
– Positive symptoms	0.31	1.30	6.21	0.013	1.36	1.07 - 1.74	40.0	84.8	44.4
BSABS-P									
– Constant	-3.62	1.17	9.55	0.002	0.03				
– Cognitive disturbances	0.16	0.06	6.06	0.014	1.17	1.03 - 1.33	66.7	86.7	60.0
Neurocognition									
– Constant	7.05	3.75	3.54	0.064	1148.18				
– FSIQ	-0.08	0.03	4.51	0.034	0.92	0.85 - 0.99	40.0	97.0	80.0
Combined									
– Constant	3.02	4.08	3.14	0.459	20.55				
– Positive symptoms	0.27	014	3.89	0.049	1.31	1.00 - 1.72	50.0	90.9	62.5
– FSIQ	-0.67	0.04	0.56	0.077	0.93	0.87 - 1.01			

[a] Logistic regression with backward stepwise elimination – final models are displayed ($p < 0.05$); SIPS = Structured Interview for the assessment of Prodromal Syndromes; BSABS-P = Bonn Scale for the Assessment of Basic Symptoms – Prediction list; FSIQ = Full Scale IQ; PPV = Positive Predictive Value

Models based on neurocognitive variables

The initial model included FSIQ, FTT and both VF variables to maximize the number of UHR-P individuals (29 UHR-NP and 10 UHR-P). In the final step, FSIQ was the only variable to remain a significant predictor, with a sensitivity of 40.0% and specificity of 97% (Table 3) and a cut-off score of 86.5. Replacing FSIQ with VIQ or PIQ did not improve the results.

Combined clinical and neurocognitive models

Two models were tested. First, SIPS positive symptoms and FSIQ were added together to maximize the number of UHR participants (33 UHR-NP and 10 UHR-P). While both predictor variables were retained in the model, only the SIPS 'positive symptoms' subscale was significant (Table 3). Next, the BSABS-P 'cognitive disturbances' subscale was entered (30 UHR-NP and 9 UHR-P). This variable was discarded after the first step and the remaining model had an overall specificity of 90.9% and a sensitivity of 50.0%. The area under the curve was highest for this model with 6 out of 9 conversions correctly predicted. ROC curves for all predictor variables and their combination are shown in Figure 1. All test variables had satisfactory areas under the curve (± 0.8, all $p < 0.05$) and the integrated model showed the highest value. In sum, SIPS positive symptoms contributed most to the prediction of psychosis, while adding FSIQ to the model slightly improved classification results.

Prediction of functional outcome

Data was available for 41 UHR individuals who completed long-term follow-up. Bivariate correlations were generated to detect linear associations between clinical and neurocognitive variables with mGAF scores at follow-up. The SIPS 'disorganization' subscale was the only variable significantly associated with mGAF at follow-up (r = -0.55, p < 0.001). When entered, the resulting model was highly significant (r^2 = 0.29, $F_{1,39}$ = 16.13, p < 0.001) and SIPS disorganization was a significant predictor (β = -0.54, t = -4.02, p < 0.001; see Figure 2), indicating that a higher score on disorganization symptoms at baseline was predictive of a poorer functional outcome. The regression was repeated with a covariate to check for the influence of time-to-follow-up, but no effect was detected.

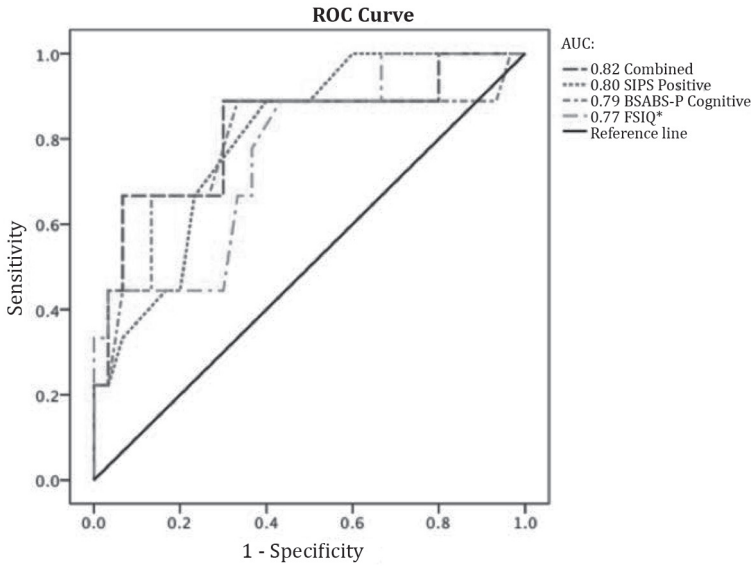

Figure 1. Receiver operating characteristics curves for Structured Interview of Prodromal Syndromes (SIPS) positive symptoms, Bonn Scale for the Assessment of Basic Symptoms – Prediction list (BSABS-P) cognitive disturbances, full-scale IQ (FSIQ) and their combination

* FSIQ scores were transformed to negative values to compare results with the clinical predictor variables

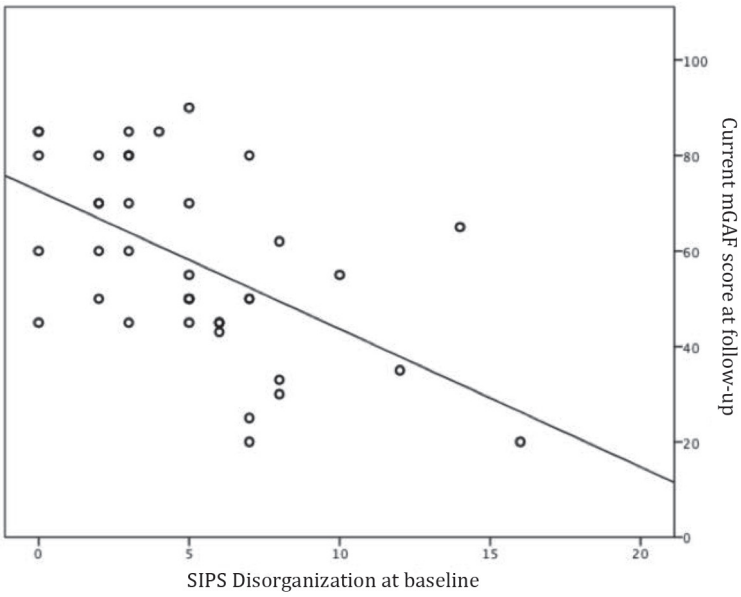

Figure 2. Scatterplot showing a significant linear association between disorganization symptoms (SIPS; X-axis) at baseline and global functioning six years later (mGAF; Y-axis)

DISCUSSION

The present study investigated whether a combination of neurocognitive parameters and clinical measures at intake could predict clinical outcome at long-term, six-year follow-up in a group of adolescents at UHR for psychosis. There were two main findings: First, we found that UHR individuals had lower IQ scores at baseline than controls and IQ significantly predicted conversion to psychosis, while no other neurocognitive variables discriminated between the groups. Second, both psychotic transition and long-term functional outcome were best predicted by clinical variables and not by neurocognitive measures: Attenuated positive symptoms contributed most to prediction of psychotic transition and global functioning was best predicted by disorganized symptoms. As such, our results suggest that clinical symptoms trump neurocognitive variables in predicting clinical outcome.

Comparison with previous studies on clinical predictors of psychosis

The added value of this study lies in its combining clinical and neurocognitive variables to predict long-term clinical outcome in adolescents at UHR for developing psychosis. Previous clinical follow-up studies have suggested that attenuated positive symptoms, low functioning and genetic risk combined with functional decline are the most reliable clinical predictors of transition to psychosis (34; 35). Our study confirms that attenuated positive symptoms at baseline are

predictive of psychosis, even at a relatively young age. The criterion of having a genetic risk in combination with functional decline was too rare among our UHR individuals (n = 2) to be included as a predictor in this study. Low functioning was not entered into prediction models of psychosis, but did not differ between UHR groups at baseline. In addition to attenuated positive symptoms, the subscale 'cognitive disturbances' of the BSABS-P also showed some predictive accuracy for psychosis. Although the small number of UHR-P individuals restricts their interpretation, our results replicate findings from a previous European multicenter study (mean age 23 at baseline) that assessed UHR symptoms with identical clinical instruments (36). Whereas our results imply that positive symptoms are a more sensitive predictor than cognitive disturbances, the classification outcome, as well as previous findings in larger samples, suggest that they may potentially be used as complementary measures (23).

Comparison with previous studies on neurocognitive predictors of psychosis

Our neurocognitive findings confirm previously established impairments of general cognition in UHR populations, but are partially at odds with studies reporting impairments in more specific cognitive domains (12; 13; 37; 38). Similarly, when we exclusively examined neurocognitive variables, psychosis was best predicted by low IQ in this study while previous studies have shown that poorer functioning in more specific (predominantly verbal) neurocognitive domains also have modest predictive capacity (for a recent overview see Lin and colleagues (14)). A number of explanations could account for these discrepancies, such as differences in sample size, neurocognitive measures and follow-up duration. For example, existent relations between cognition and clinical symptoms may have been obstructed by developmental effects, as performance on these types of tasks is highly age-dependent (39) and subclinical symptoms tend to be more frequent and transient in adolescents than in adults (40–42). Although meta-analyses have suggested there may indeed be significant neurocognitive predictors of psychosis (12; 38), results have varied widely across studies and included many negative or potential false positive findings as well (43).

To date only a few studies have considered combining neurocognitive and clinical variables in prediction models for psychosis (13–15). Their outcomes suggest that predictive accuracy of transition to psychosis could be improved by including both neurocognitive and clinical variables. In this study the highest predictive power was achieved by using clinical variables only, although global IQ measures did predict psychosis when entered as a single variable and there was some indication that IQ could contribute to a more optimal group classification when combined with symptom scores. However, a recent North-American multicenter study by Seidman and colleagues (44) also concluded that individual neurocognitive predictors did not improve predictive power beyond clinical models.

Comparison with previous studies on prediction of functional outcome

A strength of this study is that we did not only focus on transition to psychosis, but also investigated functional outcome as a perhaps more clinically relevant outcome measure of interest. Earlier studies focusing on functional outcome have suggested that negative symptoms and disorganized symptoms may be predictive of functional outcome (45) and that baseline neurocognitive functioning and the course of neurocognitive change in UHR individuals might differentiate between individuals with better or worse functional outcome (6–8). Although the use of domain-specific measures of functional outcome could have potentially been more informative, our results support the general notion that measures of functional outcome are useful assessment tools for long-term clinical prediction studies, as we were able to show that disorganized symptoms are highly predictive of global functioning six years post-baseline. However, we did not find that neurocognitive measures improved prediction of functional outcome as was suggested by the earlier studies. This discrepancy may be due to methodological differences and operationalization of functional outcome. Most previous studies used more domain-specific measures of functional outcome, while the mGAF scale in our study encompasses social, occupational and psychological functioning and thereby has the potential to better characterize global functioning. Similar arguments could provide an explanation for the lack of predictive power for baseline negative symptoms, as well the apparent clinical heterogeneity across and within UHR samples.

IQ as a vulnerability marker

The finding that low IQ is characteristic of a high-risk profile is consistent with a long history of observations that low premorbid IQ is a risk factor for schizophrenia spectrum disorders (46). However, UHR studies that investigated the predictive power of IQ have contradictory results. While two studies found that VIQ predicted transition to psychosis (44; 47), most studies have reported that intelligence measures do not predict transition to psychosis (13; 15; 48). Nevertheless, the hallmark deficit in premorbid global intellectual functioning appears robust from a very young age. Therefore, it is likely that intelligence measures are etiologically relevant, while simultaneously having negligible relevance for individual clinical trajectories. The relative lack of prediction from more specific neurocognitive measures in our adolescent sample suggests that neurocognitive deficits reported in adult UHR individuals may have limited use as early vulnerability markers for psychosis (but see Kelleher and colleagues (49)), in contrast to previously reported structural and functional brain markers (50; 51).

Methodological considerations

Several limitations of the current study need to be taken in consideration. First, our sample size and the number of UHR individuals who developed psychosis are both relatively small, and therefore the statistical analyses of the prediction of clinical outcome are somewhat underpowered. Ideally, regression analyses include 10 events per predictor variable or more, although smaller numbers can still produce robust results, albeit with a greater risk of introducing bias (52). Therefore, the results of our regression analyses, in particular for predicting psychotic transition, and ROC curves need to be interpreted with appropriate caution. By correcting for multiple comparisons

and restricting the number of predictor variables in our models, we believe we have minimized the chance of reporting on Type I error (false positive findings), with the inevitable drawback of an increased chance of Type II error. Consequently, it is possible that significant contributions of clinical and neuropsychological factors were not picked up in this study. Despite this shortcoming it is also worth noting that longitudinal follow-up studies on young UHR adolescents are rare and a great need has been voiced within the scientific community to validate findings from adult UHR studies in child and adolescent populations (53).

Second, most of the adolescents in our study were help-seeking at an early age (16), while individuals in other UHR cohorts typically do not have a history of contact with mental health services. Accordingly, a relatively high percentage (40%) of our UHR individuals was already using some form of (low-dosage) psychotropic medication at baseline. Arguably, medication may have been prescribed for individuals who were more severely affected clinically, which may in turn have helped prevent the onset of psychosis. However, there were no differences in baseline medication use between those adolescents that went on to develop psychosis and those who did not.

Third, because of the naturalistic design of the study, no systematic data was available concerning non-pharmacological interventions received by UHR participants. Consequently, treatment effects may have further influenced our results. A related limitation is that no standardized instruments were used to assess psychiatric comorbidity in this sample, while findings from a recent study indicate that especially comorbid diagnoses of anxiety and depressive disorders can have substantial impact on later global functioning (54).

In summary, our results suggest that IQ is lower in adolescents at UHR who go on to develop full-blown psychosis, but that its predictive value for transition to psychosis is limited when clinical measures are added to the equation. In this study clinical measures were a more sensitive predictor for both transition to psychosis and long-term functional outcome, in particular attenuated positive symptoms and disorganization. Consequently, these factors are important as vulnerability markers and may be considered a flag for clinical priority in help-seeking UHR adolescents. Furthermore, our results support the idea that it is useful to investigate multiple measures of clinical outcome. Although improving prediction models through long-term longitudinal follow-up is challenging, it is key to improving our understanding of the development of psychosis and associated possibilities for early intervention initiatives

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SUPPLEMENTARY INFORMATION

Table S1. Demographic and clinical characteristics for the total control and UHR samples at baseline

Total baseline sample	**TDC** (n = 79)	**UHR** (n = 67)	**Statistic**	***df***	***p***
Age in years, M ± SD	15.1 ± 1.5	15.2 ± 2.0	t = - 0.41	1, 131.6	.686
Sex, N male (%)	40 (51)	40 (60)	χ^2 = 1.20	1	.273
Handedness, N right (%)	72 (91)	60 (90)	χ^2 = 0.64	1	.801
Parental education (y), M ± SD	13.8 ± 2.0	13.5 ± 1.8	U = 2028.5		.095
Clinical variables					
– SIPS total, M ± SD	1.7 ± 2.3	24.9 ± 11.5	U = 5212.5		<.001
– BSABS total, M ± SD	1.1 ± 1.5	21.6 ± 14.3	U = 4810.5		<.001
– GAF, M ± SD	88 ± 4	56 ± 14	U = 90.0		<.001
UHR inclusion criteria[a]					
– APS, N (%)		58 (87)			
– BLIPS, N (%)		1 (1)			
– GRD, N (%)		2 (3)			
– COGDIS, N (%)		35 (54)			

[a] = years education averaged for both parents; [b] = Participants fulfilling multiple criteria were added as a separate individual in each category; TDC = typically developing controls, UHR = Ultra-High Risk; SIPS = Structured Interview for the assessment of Prodromal Syndromes; BSABS = Bonn Scale for the Assessment of Basic Symptoms; GAF = Global Assessment of Functioning; APS = Attenuated Positive Symptoms; BLIPS = Brief Limited and Intermittent Psychotic Symptoms; GRD = Genetic Risk and a Deterioration in functioning; COGDIS = Cognitive Disturbances

CHAPTER 4

BRAIN DEVELOPMENT IN ADOLESCENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: LONGITUDINAL CHANGES RELATED TO RESILIENCE

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In revision

ABSTRACT

Background

The main focus of studies of individuals at ultra-high risk for psychosis (UHR) has been on identifying brain changes in those individuals who will develop psychosis. However, longitudinal studies have shown that up to half of UHR individuals are resilient, with symptomatic remission and good functioning at follow-up. Yet little is known about brain development in resilient individuals. Therefore, the aim of this study was to investigate differences in brain development between resilient and non-resilient individuals.

Methods

A six-year longitudinal structural MRI study was performed with up to three scans per individual. The final sample consisted of 48 UHR individuals and 48 typically developing controls with a total of 225 MRI-scans, aged 12–20 years at the time of the first MRI-scan and matched for age, gender and number of follow-up scans. At six-year follow-up, 35 UHR individuals were divided in resilient and non-resilient subgroups. We operationalized resilience in two ways as either good functioning or complete remission from UHR criteria at six-year follow-up. The main outcome measures were developmental changes in MR-based measures of cortical and subcortical anatomy.

Results

We found widespread differences in volume of frontal, temporal and parietal cortex between resilient and non-resilient individuals. These were already present at baseline and remained stable over development (12–24 years). Furthermore, there were differences in the development of cortical surface area in frontal regions including cingulate gyrus.

Conclusions

Developmental differences may reflect compensatory neural mechanisms, where better functioning in resilient individuals leads to less tissue loss over development.

Keywords: ultra-high risk, psychosis, resilience, MRI, functional outcome, brain development

INTRODUCTION

Traditionally, studies of individuals at ultra-high risk (UHR) for psychosis have attempted to identify neurobiological markers to predict which UHR individuals will go on to develop psychosis (i.e. undergo a 'transition to psychosis'). Thus, the field has focused on identifying differences in the brains of those subjects who will worsen over time compared to those who will not. However, transition rates have plummeted since the earliest reports of rates of over 50% (1) to an average of 29% in more recent reports (2). At the same time, there has been a steady increase in the remission rates reported, of up to 54% (3). A recent meta-analysis of eight longitudinal studies (4) reported that 73% of 773 UHR subjects did not develop psychosis over a 2-year follow-up and 46% fully remitted from their baseline symptoms. We conducted a longer follow-up, with a mean of six years, and found that 41% of adolescents at UHR fully remitted from their at-risk state (5). Therefore, it is at least as relevant to investigate neurobiological changes in UHR subjects who show resilience and go on to function well, as it is to investigate those who undergo a transition to psychosis.

In addition, the criterion of 'transition to psychosis' has been criticized as a measure to identify which individuals will have a truly poor clinical outcome: the threshold for transition is essentially arbitrary and is based entirely on positive symptoms (6; 7). There is increasing evidence that negative symptoms and the level of cognitive and social functioning are equally important for the long-term outcome of UHR individuals (7–9).

Taken together, decreasing transition rates, high percentages of remitters and the criticism of 'transition to psychosis' as an outcome measure underscore the importance of studying remission as well as other, more comprehensive, measures of outcome. Therefore, in this study, we do both. We focus on resilience, instead of on transition to psychosis, and operationalize resilience as level of functioning. In addition, we conducted a second, more traditional operationalization of resilience as the remission of positive symptoms.

Compared to a volunteer sample of typically developing controls, UHR individuals have been reported to show reduced grey matter volume in the frontal and temporal lobes, anterior cingulate gyrus and hippocampal regions (10–12). However, most imaging studies of UHR individuals have been cross-sectional in design and have therefore been limited in their ability to show developmental differences between UHR individuals with different outcomes. The few longitudinal studies that have been conducted were only partially successful in predicting transition to psychosis and have reported many inconsistent findings (for review, see 11). This may in part be related to limited follow-up times and differences in the methods used (11), but is likely also related to the diverse clinical outcomes of UHR individuals and the relatively arbitrary criterion of transition to psychosis (5).

Therefore, we investigated brain development in resilient versus non-resilient UHR individuals over, on average, six years. We conducted a comprehensive assessment of symptoms and functioning and examined brain development, with MRI scans at three different time points. This is the first study with a long follow-up (six years) and more than two MRI scans per individual. This permits a better assessment of outcome and non-linear modelling of developmental trajectories.

METHODS

Participants

All data were collected at the Department of Psychiatry at the University Medical Center Utrecht, Brain Center Rudolf Magnus in the Netherlands. Participants were between 12 and 18 years of age at the time of recruitment and were included after written informed consent. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Recruitment details have been described previously (13; 14). Briefly, adolescents at UHR were referred by general practitioners or other psychiatry clinics. For inclusion at baseline, subjects in the UHR group had to fulfil at least one of the following criteria: 1) attenuated positive symptoms, 2) brief, limited, or intermittent psychotic symptoms, 3) genetic risk for psychosis combined with a deterioration in overall level of social, occupational/school, and psychological functioning in the past year or 4) two or more of nine basic symptoms of mild cognitive disturbances. The first three inclusion criteria were assessed using the Structured Interview for Prodromal Syndromes (15) and the Family Interview for Genetic Studies (16). The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (17). Exclusion criteria consisted of a past or present psychotic episode lasting more than one week, traumatic brain injury or any known neurological disorder, and verbal intellectual IQ < 75. The typically developing control group consisted of typically developing adolescents recruited through secondary schools in the region of Utrecht. They were excluded if they met one of the UHR-criteria, if they or any first degree relative had a history of a psychiatric illness, or if they had a second-degree relative with a psychotic disorder.

At baseline, 64 UHR individuals and 62 typically developing controls completed the clinical assessment and an MRI scan. These groups were then matched for gender, age, and number of follow-up scans, resulting in a longitudinal dataset of 48 UHR individuals and 48 typically developing controls with one, two or three scans and a total of 225 MRI scans. Participants were between 12,2 and 19,6 years of age at the time of the first MRI scan (Table 1). Follow-up assessments were conducted 9 months, 18 months, 2 years, and 6 years post baseline (range 3,5-8,0 years). The follow-ups at 9 and 18 months only included clinical assessments. For an overview of the timeline, see Figure 1.

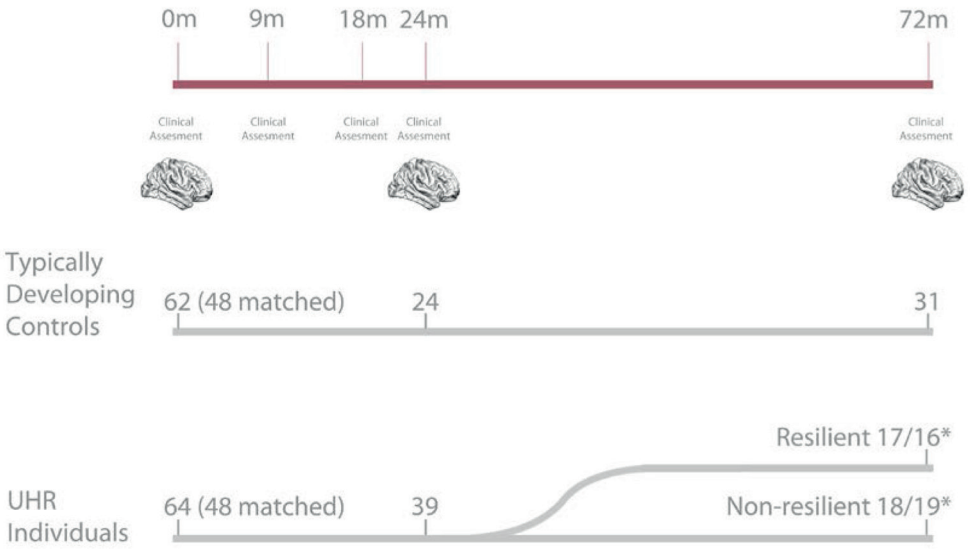

Figure 1. Timeline of the study

We split the UHR group into two groups based on the 6-year follow-up data, one 'resilient' and one 'non-resilient' subgroup. Resilience was defined one of two ways and identical analyses were run for each subgrouping. First, resilience was defined by functional outcome using the modified Global Assessment of Functioning (mGAF) scale (18). Poor functional outcome (non-resilient) was defined as an mGAF score of < 65 and good functional outcome (resilient) as an mGAF score of ≥ 65. The cut off of 65 has been used before (19) and was chosen as the 60–70 range corresponds to 'generally good function with meaningful interpersonal relationships, and some persistent mild symptoms and/or some persistent difficulty in social, occupational, or school functioning' (18). A score below 60 indicates 'moderate to severe symptoms and/or moderate to severe difficulty in social, work, or school functioning,' while scores above 70 correspond to 'some transient mild symptoms to absent or minimal symptoms and/or slight to no impairment in social, work, or school functioning'. Second, resilience was defined by complete remission from UHR criteria, as defined by McGlashan and colleagues (15). Individuals who had converted to psychosis and individuals who still met UHR criteria were classified as non-resilient individuals, whereas those individuals who no longer met UHR criteria and had never experienced psychosis were classified as resilient. Details of both subgroupings are given in supplemental information S1.

Image Acquisition

MRI scans were acquired on a single 1.5-T scanner (Philips, Best, The Netherlands). Whole brain T1-weighted three-dimensional fast field echo scans were made with 1.5-mm contiguous coronal

slices of the whole head (256 × 256 matrix, FoV = 256 mm, echo time (TE) = 4.6 ms, repetition time (TR) = 30 ms, flip angle = 30°).

Image Processing

Scans were processed and analyzed using FreeSurfer *v 5.1.0* software. Technical details of the automated reconstruction scheme of this well-validated software program are described elsewhere (20–22). We calculated average volume (mm^3), cortical thickness (mm), surface area (mm^2), and gyrification for the 34 cortical structures in each hemisphere from the Desikan-Killiany atlas (23), as well as cortical thickness and surface area for each lobe and the whole brain, and total gray and white matter volume per hemisphere and the whole brain. Gyrification could not be estimated for 7 scans, because of FreeSurfer processing errors. We also measured the volume of subcortical structures, as well as subcortical gray matter volume and gray and white matter separately for the cerebellum. In order to reduce within-subject variability between scan sessions, the longitudinal analysis processing pipeline of FreeSurfer was used for subjects with more than one scan (24; 25). Manual edits were performed as necessary by a rater blind to subject identity and group membership.

Statistical Analyses

The statistical software package R version 2.14.0 was used (1) to test for between-group differences in the demographic and clinical data and (2) to investigate the effects of age, group and their interaction on the brain measures using a linear mixed model. The mixed model procedure investigated the relationship between age, group and our measures of interest (brain measures) using a top down selection procedure to test for the best-fit growth model. We were particularly interested in two effects: (1) main effects of group, where differences between groups were present at first assessment and stable over developmental time (range 12–24 years), and (2) group*age interaction effects where the developmental trajectories differed between the groups (e.g. structure X increased over time in group A while it decreased over time in group B). Details of this model and selection procedure are provided in supplemental information S2.

RESULTS

Between-group differences in demographic and clinical characteristics

Demographic and clinical characteristics of typically developing controls and UHR individuals are provided in Table 1. Both groups were matched for age, gender and number of scans. Hand preference and intracranial volume did not differ between groups, but IQ was lower for UHR individuals than for typically developing controls.

Demographic details of subgroups defined by both operationalisations of resilience are given in Table 2. There was substantial overlap between the two operationalisations: of 17 individuals classified as resilient based on functional outcome, 12 were also classified as resilient based on

UHR remission criteria, and of 16 individuals classified as resilient based on remission, 12 were also classified as resilient based on functional outcome (Table 2). Of the five individuals classified as resilient based on functional outcome but not remission, two had had a psychosis and later remitted with high mGAF scores at 6-year follow-up. The other three still scored in the UHR range for positive symptoms, but reported good functioning (mGAF scores between 70 and 80) at 6-year follow-up. There were no statistical differences in the demographic variables between the two operationalisations of resilience ($p > .20$). In clinical terms, both definitions led to statistical improvements on symptom measures at follow-up for resilient versus non-resilient individuals, while there were few differences in symptoms at baseline. The subgroups did not differ in terms of the use of psychotropic medication for either operationalisation (Table 2). We provide results from the more comprehensive operationalisation based on functional outcome in the main paper and provide the results from the operationalisation based on remission from UHR criteria in the supplemental information.

Brain development in UHR compared to typical development

To allow comparison to earlier studies, we first tested for differences in brain development between the whole group of UHR individuals and typically developing controls. In the cortex, we found the largest differences in cortical surface area. Here, we primarily found group*age interactions, with less steep decreases over developmental time in UHR individuals in frontal and parietal areas compared to typically developing controls ($p = 0.004–0.043$). We found fewer differences in cortical volume, cortical thickness and gyrification. Furthermore, we found that UHR individuals showed stable as well as steeper decreases over developmental time in hippocampus ($p = 0.012/0.006$) and thalamus volume ($p = 0.015/0.022$), as well as smaller volume at baseline and steeper increases over developmental time in the volume of third ($p = 0.019$) and inferior lateral ventricle ($p = 0.049$) than typically developing controls. All results are listed in supplemental information S3.

Brain development in resilient versus non-resilient UHR individuals

Main effects of group and group*age interaction effects are shown in Figure 2 and listed in supplemental information S4. Results from the analyses using the other operationalisation of resilience (remission from UHR criteria) were similar to those reported in the main paper and are available in supplemental information S5.

Table 1. Demographic data for typically developing controls (TDC) and UHR individuals

	TDC	**UHR**	**UHR vs. TDC**
Number of individuals, n (males)	48 (29)	48 (29)	*n.s.*
Hand preference, n, right/non-right	40/8	44/4	*n.s.*
Parental education, years, mean (SD)			
– Mother	13.45 (2.39)	12.96 (2.16)	*n.s.*
– Father	14.22 (2.17)	13.74 (2.18)	*n.s.*
Premorbid IQ, mean (SD)	107.04 (13.12)	100.40 (11.97)	$t = 2.85$, $p = 0.01$
Age at baseline scan, years			
– Mean (SD)	15.72 (1.54)	15.43 (2.11)	*n.s.*
– Range	12.19-18.76	12.28-19.64	
Age at 6-year FU scan, years			
– Mean (SD)	21.40 (1.57)	21.16 (2.42)	*n.s.*
– Range	17.57-24.54	16.84-25.79	
Intra Cranial Volume (mm^3)	1621000 (148220)	1586000 (167740)	*n.s.*
Number of scans, n			*n.a.*
– Total number of scans, n	103	122	
– 1	48	48	
– 2	24	39	
– 3	31	35	

Notes: TDC = typically developing controls; UHR = Individuals at ultra-high risk for psychosis; IQ = intelligence quotient; SD = standard deviation; FU = follow-up

Table 2. Demographic and clinical data of resilient and non-resilient UHR individuals, based on (1) functional outcome and (2) UHR remission criteria[a]

	(1) Good functional outcome vs. Poor functional outcome			(2) Remission (R) vs. Non-remission (NON-R)		
	good outcome	**poor outcome**	**good vs. poor**	**R**	**NON-R**	**R vs. NON-R**
Number of individuals, n (males)	17 (13)	18 (10)	*n.s.*	16 (10)	19 (13)	*n.s.*
Resilient based on remission (n)	12	4		*n.a.*	*n.a.*	
Non-resilient based on remission (n)	5	14		*n.a.*	*n.a.*	
Resilient based on FO (n)	n.a.	n.a.		12	5	
Non-resilient based on FO (n)	n.a.	n.a.		4	14	
Premorbid IQ, mean (SD)	101.18 (12.89)	103.22 (10.28)	*n.s.*	101.40 (11.78)	102.90 (11.53)	*n.s.*
Age at baseline, years						
– Mean (SD)	15.42 (2.20)	15.54 (2.48)	*n.s.*	14.65 (2.00)	16.18 (2.37)	$t = 2.07$, $p = 0.05$
– Range	12.31 - 19.64	12.28 - 19.43		12.28 - 19.32	12.42 - 19.64	
Age at 6-year FU, years						
– Mean (SD)	21.34 (2.58)	20.99 (2.32)	*n.s.*	19.99 (2.41)	21.96 (2.27)	$t = 2.29$, $p = 0.03$
– Range	17.88 - 25.79	16.84-24.80		16.84-25.28	17.42 - 25.79	
SIPS/SOPS baseline, mean (SD)						
– Total score	21.35 (10.74)	25.06 (11.47)	*n.s.*	21.31 (10.58)	24.89 (11.56)	*n.s.*
– Positive symptoms	7.41 (4.53)	8.50 (3.13)	*n.s.*	6.56 (4.39)	9.16 (2.95)	$U = 89.0$, $p = 0.037$
– Negative symptoms	4.24 (4.66)	4.17 (3.67)	*n.s.*	3.62 (3.52)	4.68 (4.59)	*n.s.*
– Disorganized symptoms	3.41 (3.30)	5.89 (2.83)	$U = 68.0$, $p = 0.004$	4.50 (3.65)	4.84 (3.00)	*n.s.*
– General symptoms	6.29 (4.33)	6.50 (4.51)	*n.s.*	6.62 (4.77)	6.21 (4.10)	*n.s.*
mGAF baseline, mean (SD)	57.06 (13.57)	56.83 (17.44)	*n.s.*	54.81 (12.15)	58.74 (17.90)	*n.s.*
SIPS/SOPS 6-year FU, mean (SD)						
– Total score	11.75 (8.36)	35.11 (14.11)	$U = 20.5$, $p = < 0.001$	13.13 (9.65)	33.89 (15.35)	$U = 38.5$, $p = < 0.001$
– Positive symptoms	3.88 (3.59)	10.00 (5.54)	$U = 45.5$, $p = < 0.001$	2.44 (2.37)	11.28 (4.11)	$U = 3.5$, $p = < 0.001$
– Negative symptoms	3.88 (3.72)	11.17 (5.79)	$U = 44.0$, $p = < 0.001$	5.69 (4.85)	9.56 (6.64)	*n.s.*

Table 2. *(Continued)*

	(1) Good functional outcome vs. Poor functional outcome			(2) Remission (R) vs. Non-remission (NON-R)		
	good outcome	**poor outcome**	**good vs. poor**	**R**	**NON-R**	**R vs. NON-R**
– Disorganized symptoms	3.19 (2.74)	7.22 (3.37)	$t = 3.80$, $p = 0.001$	3.44 (2.90)	7.00 (3.52)	$U = 60.5$, $p = 0.003$
– General symptoms	1.50 (1.59)	6.72 (4.86)	$U = 42.0$, $p = < 0.001$	1.56 (1.59)	6.67 (4.92)	$U = 47.0$, $p = 0.001$
mGAF 6-year FU, mean (SD)	77.94 (7.30)	47.50 (9.94)	$t = -10.27$, $p = < 0.001$	71.87 (14.13)	54.21 (16.55)	$U = 60.0$, $p = 0.002$
Psychotropic medication baseline, any			*n.s.*			*n.s.*
– No	9	9		7	11	
– Yes	8	9		9	8	
Psychotropic medication 6-year FU, any			*n.s.*			*n.s.*
– No	13	11		11	13	
– Yes	4	7		5	6	

Notes: [a] Subgroups are based on outcome at 6-year FU; outcome was unknown for 13 UHR individuals

TDC = typically developing controls; UHR = Individuals at ultra-high risk for psychosis; R = remitter; NON-R = non-remitters; FO = functional outcome; IQ = intelligence quotient; SD = standard deviation; FU = follow-up; SIPS/SOPS = Structured Interview for Prodromal Symptoms / Scale of Prodromal Symptoms; mGAF = Modified Global Assessment of Functioning

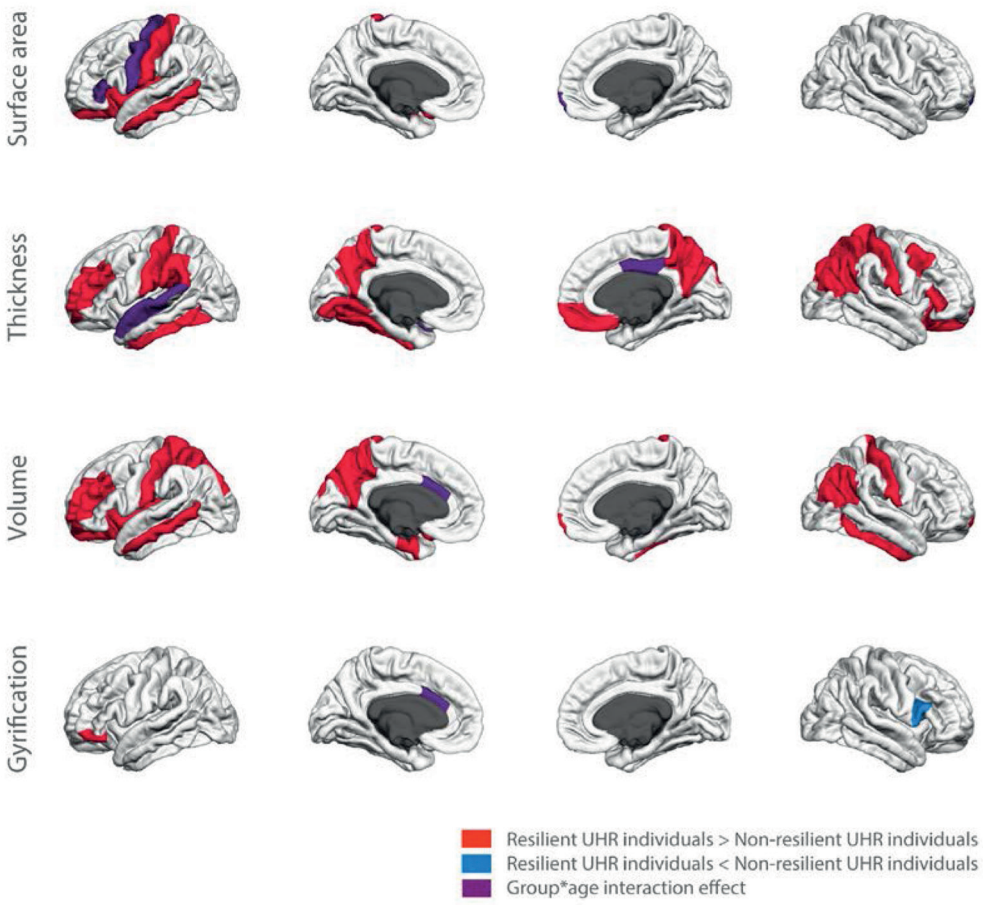

Figure 2. Differences in cortical morphology between resilient and non-resilient UHR individuals

Stable differences between groups

There were widespread differences between resilient and non-resilient UHR individuals that were stable over developmental time (i.e., main effects of group). Resilient individuals had larger volumes of frontal, temporal and parietal cortex, corpus callosum and nucleus accumbens than non-resilient individuals (p = 0.003–0.025, see supplemental information S4). Furthermore, overall cortical thickness was larger for resilient compared to non-resilient individuals, mainly due to increases in thickness in frontal, parietal and temporal lobes (p = 0.000–0.046). Cortical surface area was larger throughout the left hemisphere and there were some differences in gyrification (p = 0.003–0.042) see supplemental information S4). When we added the trajectories of typically developing controls in these areas, we found that they fell between those of resilient and non-resilient individuals. This is illustrated in the supplemental information where some of the graphs of these trajectories are provided (S6).

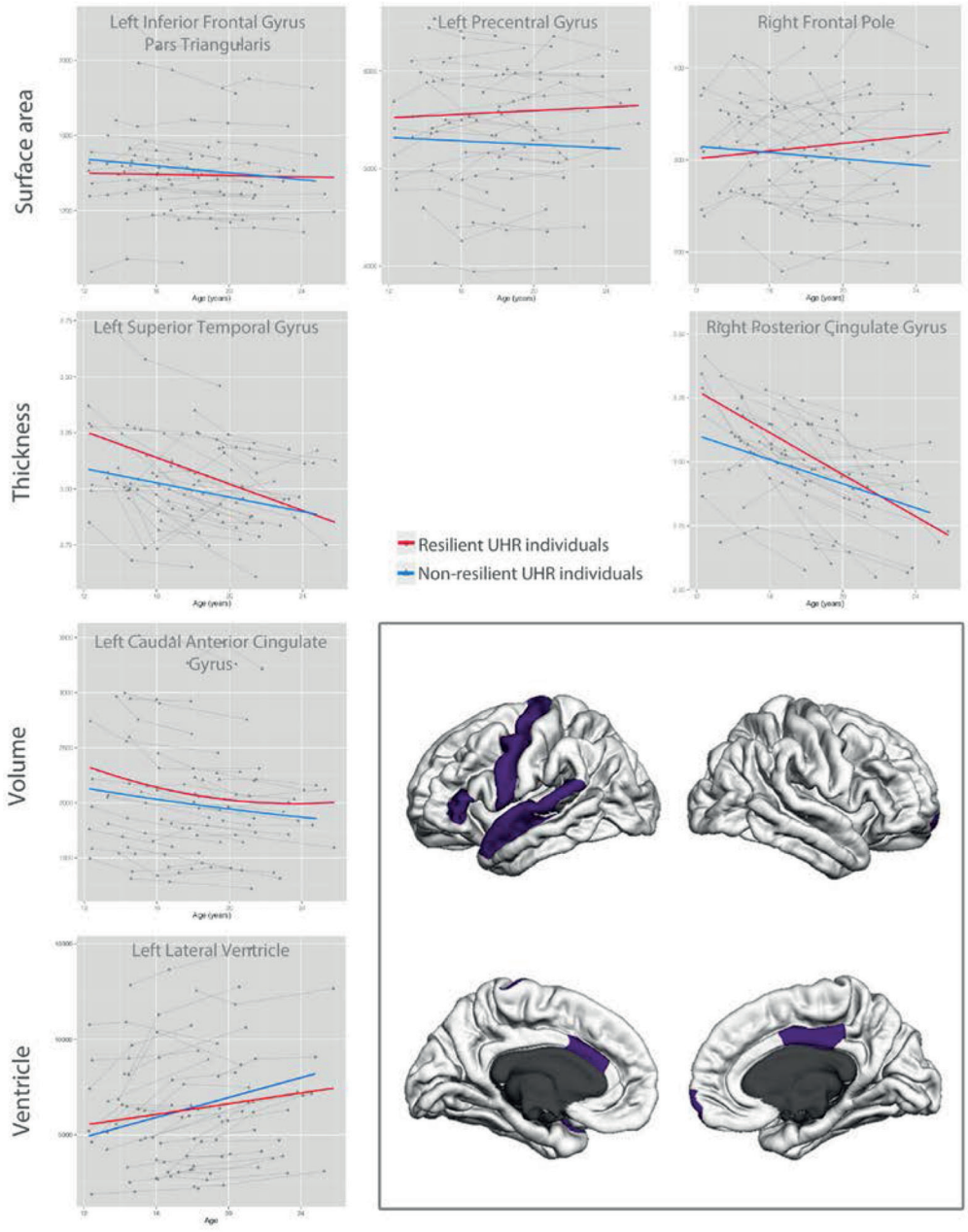

Figure 3. Distinct developmental trajectories between resilient and non-resilient UHR individuals

Developmental differences

There were some developmental differences between resilient and non-resilient UHR individuals where developmental trajectories diverged between groups over time (group*age interactions; see Figure 3). Resilient individuals showed smaller decrease in volume over developmental time in anterior cingulate gyrus (p = 0.049) and smaller increase over developmental time in lateral ventricle volume (p = 0.036). Furthermore, resilient individuals showed greater decreases in cortical thickness in superior temporal cortex (p = 0.038) and posterior cingulate gyrus (p = 0.011) than non-resilient individuals. Resilient individuals also showed increases over developmental time in cortical surface area in precentral gyrus (p = 0.037) and frontal pole (p = 0.033) compared to decreases in non-resilient individuals. Finally, resilient individuals showed decreases in gyrification in anterior cingulate gyrus over developmental time compared to increases in non-resilient individuals (p = 0.049).

DISCUSSION

We investigated brain development over six years in a matched sample of 48 adolescents at ultra-high risk for developing psychosis and 48 typically developing controls, with up to three MRI scans per individual. Our main goal was to compare brain development between resilient and non-resilient UHR individuals. We operationalized resilience two ways, as either good functioning or complete remission from UHR criteria at 6-year follow-up. We found widespread differences in the volume of frontal, temporal and parietal cortex that were already present at baseline and remained stable over development. Furthermore, there were differences between resilient and non-resilient individuals in the development of cortical surface area in multiple frontal regions including cingulate gyrus. These diverging developmental trajectories may reflect compensatory neural mechanisms, where the better functioning resilient individuals results in less tissue loss with development.

When we compared brain development between all UHR individuals and typically developing volunteers, we found diverging developmental trajectories for cortical surface area in frontal and parietal regions. Here, typically developing controls showed greater decreases over development than UHR individuals. Furthermore, we found decreases in hippocampus and thalamus volume and increases in the volume of the third and inferior lateral ventricles in UHR individuals that were already present at baseline. These findings are in keeping with other studies on psychosis and UHR (10–12; 26).

When we compared brain development between resilient and non-resilient UHR individuals, we found three types of changes: First, there were differences that were already present at baseline and that were stable over development, with the developmental trajectories parallel for both groups. These included greater cortical thickness and cortical volume and larger volume of the nucleus accumbens and corpus callosum in resilient individuals. Interestingly, when we added the

trajectories of typically developing controls in these areas, we found that they fell between those of resilient and non-resilient individuals (see supplemental information S6). As such, the volume of resilient individuals exceeded that of typically developing volunteers, suggesting that greater volume may be protective for worse outcome. Earlier longitudinal studies of development in UHR individuals have always focused on transition to psychosis. Most of these have shown differences between UHR individuals with different clinical outcomes in insular, temporal, parietal and superior frontal regions (11; 27–29). These regions overlap with our results. Our data suggest that these areas may hold promise for predicting, at a young age, which UHR individuals will get better and which will worsen over time.

A second pattern in our data is developmental trajectories that overlap at young age but diverge over developmental time. Areas showing this pattern include precentral gyrus, frontal pole, anterior cingulate gyrus and lateral ventricle (see Figure 3). The enlargement of lateral ventricles was one of the first brain findings to be reported in schizophrenia and is still one of the most consistently reported (30). In our study, the volume of lateral ventricles increased more over development for non-resilient individuals than for resilient ones. The anterior cingulate gyrus showed decreases in volume over development for both resilient and non-resilient individuals. However, its volume stabilized in early adulthood for resilient individuals, whereas it continued to decrease in the non-resilient group. This structure is important for goal-directed behavior and involved in error and conflict monitoring and has often been reported to show changes in structure and function in UHR and schizophrenia (27; 31; 32). The stabilization in the resilient group may reflect neural changes as a result of recovery in this group, whereas the continuing loss of volume in non-resilient individuals may reflect their continuing difficulties with cognitive and emotional integration (27; 32). The left precentral gyrus and right frontal pole showed developmental increases in surface area in resilient individuals compared to slight decreases in non-resilient individuals. Changes in frontal areas have often been associated with UHR and schizophrenia (for review, see 11). As such, these increases may also represent compensatory mechanisms, related to better functioning in resilience. Other structures, such as the posterior cingulate and superior temporal gyrus, showed converging trajectories, where baseline differences disappeared with development. Interestingly, both groups showed decreases over development in cortical thickness in these areas, similar to what is seen in typical development. However, the non-resilient group showed a slower rate of change than the resilient group.

Finally, there were brain areas that differed between UHR individuals and typically developing controls, but not between resilient and non-resilient UHR individuals. These included hippocampus, thalamus and frontal and parietal cortical surface area. These changes are unlikely to be useful for predicting long-term functioning in UHR individuals, as they do not differ between resilient and non-resilient individuals. Rather, they may be related to non-specific UHR risk factors, such as obstetric complications (33; 34).

We performed a second analysis where we defined resilience as complete remission from UHR criteria. The results from this analysis were similar but noisier (see supplemental information S5). We chose not to present both analyses in the main paper, as there was significant overlap between the groups defined by the two criteria. We chose to present the results from the operationalisation based on functional outcome as we felt that of the two this was the definition with the most clinical relevance. The operationalisation based on remission considers only positive symptoms, whereas the one based on functional outcome considers the whole spectrum of functioning.

There are some limitations to this study. First is the relatively modest sample size, especially for the follow-up analyses on resilience (17 versus 18 subjects for the operationalisation based on functional outcome). This is in part because it was necessary to exclude some subjects from these analyses to match subgroups for gender and age. We felt it was important to maintain this matching given the skewed distribution of gender in UHR and schizophrenia (35–37) and findings of gender differences in brain size and development (38; 39). The limited sample size means we may have been underpowered to detect subtle differences, and may be causal to the relatively small number of developmental changes found. On the other hand, longitudinal samples require far fewer participants than cross-sectional studies in order to detect small differences in brain structure. Steen and colleagues showed that the required sample to detect a 5% difference in whole brain volume is 73 patients and 73 typically developing controls in a 2-sample cross-sectional study, against just 5 patients and 5 typically developing controls in a longitudinal study design (40). Moreover, this is the first study to report results from a longitudinal UHR follow-up with more than two MRI scans per individual.

A second limitation is that a large number of UHR individuals were on medication for the duration of this study. This is often the case in UHR studies and the numbers did not differ between subgroups, neither at baseline or follow-up. This suggests that medication did not affect our results. The lack of a difference between resilient and non-resilient individuals could even be taken to suggest that medication does not play a role in individual outcome, although the sample size is too modest to permit any such definitive conclusion.

In conclusion, brain development in resilient individuals initially at UHR for psychosis differs from that of non-resilient individuals. Widespread differences in cortical thickness and volume were evident at baseline and remained stable over development, whereas various frontal areas showed diverging developmental trajectories. The stable differences that were already present at baseline may hold promise for predicting, at a young age, who will go on to recover and who will not, whereas the divergence in frontal areas may reflect neural changes related to better functioning.

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SUPPLEMENTARY INFORMATION

Supplementary Information S1: Operationalisations of resilience

At 6-year follow up, the UHR group was subdivided into 'resilient' and 'non-resilient' subgroups where resilience was operationalised using functional outcome or defined by UHR remission criteria (1).

The first operationalisation of resilience was based on functional outcome as assessed by the modified Global Assessment of Functioning (mGAF) scale. This is a numerical scale (0 through 90) that rates social, occupational and psychological functioning using a more structured scoring system than the original GAF. It is therefore more resistant to rater bias (2). Poor functional outcome was defined as an mGAF score of < 65 and good functional outcome as an mGAF score of ≥ 65. This definition of resilience resulted in subgroups of 17 resilient and 18 non-resilient individuals.

For the second operationalisation of resilience, the UHR group was split into two groups based on remission from UHR symptoms. We followed the guidelines by McGlashan and colleagues (1). As such, subjects were considered to be in remission if they no longer had positive prodromal symptoms at the sub-psychotic level (i.e., the subject had ratings of ≤ 2 for all the SIPS/SOPS positive symptom items). The group of non-remitters included (1) those individuals who had converted to psychosis (i.e., subjects with a rating of 6 for ≥ 1 SIPS/SOPS positive items for a period of more than 7 days) and individuals who still met UHR criteria (i.e., subjects with ratings of 3–5 for ≥ 1 SIPS/SOPS positive items). Chart reviews were used to retrospectively confirm psychotic transition by clinical expert consensus, and subjects were subsequently diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) guidelines (3). This definition of resilience resulted in subgroups of 16 resilient and 19 non-resilient individuals.

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Supplementary Information S2: Linear mixed models

The relationship between age, group and our measures of interest (brain measures) were tested using a linear mixed model and top down selection procedure. This procedure accounts for irregular intervals between measures, missing data and within-subject dependence (1–3). Each dependent measure of the j^{th} individual and k^{th} time-point was modeled as described previously (4). Several models including main group effects, linear age terms, quadratic age terms, cubic age terms and interaction effects were fit. The full model is represented by the following formula:

$Measurement_{jk} = Intercept + d_j + \beta_1(group) + \beta_2(age) + \beta_3(age^2) + \beta_4(age^3) + \beta_5(group * age) + \beta_6(group * age^2) + \beta_7(group * age^3) + e_{ijk}$

The e_{ijk} term represents the normally distributed residual error. Each β represents a parameter estimate; for example the quadratic age effect parameter is represented by β_3. Furthermore, interaction effects of group and age were modeled. The full model was tested against models including linear or quadratic age terms only. Intercept, group and age effects were fixed, while within-subject dependence (dj) was modeled as a random effect. All possible models were run using mean-centered age terms (age 17.8).

The choice of best model fit was determined in three steps: First, cubic, quadratic and linear age effects were fit for each region of interest (ROI). If the cubic age effect did not reach significance at $p < 0.05$, we stepped down to the quadratic developmental model, etc. Second, we investigated whether the developmental trajectories differed between groups. Hence, a full model containing both main effects of age and group, as well as interaction effects was used. We accepted the full model that allowed for differences in growth trajectories between groups if the interaction term was significant at $p < 0.05$. If that was not the case, the simpler model including main effects of age and group was tested for significance. If the main group effect term was significant, this model was selected as the model that fit best. Otherwise, the model including only age terms was selected as the best model.

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Supplementary Information S3: Table 1. Stable and developmental differences between UHR individuals and typically developing controls (TDC) [a]

Region of interest		Hemisphere	Volume			CT			SA			GI		
			Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*
Lobes	Frontal lobe	L							Linear	***Interaction***	0,047			
		R												
	Occipital lobe	L												
		R							Quadratic	UHR < TDC	0,015			
	Total (hemisphere)	L												
		R							Linear	***Interaction***	0,022			
Cortical	Caudal Anterior Cingulate Gyrus	L							Linear	UHR < TDC	0,017			
		R												
	Cuneus	L	Cubic	UHR < TDC	0,014									
		R	Quadratic	***Interaction***	0,010				Quadratic	***Interaction***	0,015			
	Entorhinal cortex	L												
		R				Linear	***Interaction***	0,029						
	Frontal Pole	L												
		R	Cubic	***Interaction***	0,042									
	Fusiform Gyrus	L												
		R							Quadratic	***Interaction***	0,017			
	Isthmus Cingulate Gyrus	L										Linear	UHR < TDC	0,010
		R												
	Lateral Occipital Gyrus	L	Cubic	***Interaction***	0,041									
		R							Cubic	UHR < TDC	0,011			
	Lingual Gyrus	L							Quadratic	Interaction	0,021	Linear	UHR < TDC	0,006
		R	Quadratic	***Interaction***	0,043				Quadratic	UHR < TDC	0,045			
	Parahippocampal Gyrus	L												
		R				Linear	UHR < TDC	0,030						
	Inferior Frontal Gyrus – Pars Orbitalis	L										Linear	***Interaction***	0,035
		R	Quadratic	UHR > TDC	0,031									

Supplementary Information S3: Table 1. *(Continued)*

Region of interest		Hemisphere	Volume			CT			SA			GI		
			Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*
	Inferior Frontal Gyrus – Pars Triangularis	L	Cubic	***Interaction***	0,021									
		R												
	Pericalcarine Cortex	L	Cubic	Interaction	0,043							Linear	UHR < TDC	0,026
		R										Linear	UHR < TDC	0,013
	Postcentral Gyrus	L												
		R							Linear	***Interaction***	0,017			
	Posterior Cingulate Gyrus	L							Linear	***Interaction***	0,023			
		R												
	Precentral Gyrus	L							Linear	***Interaction***	0,021			
		R												
	Precuneus	L										Linear	UHR < TDC	0,032
		R							Quadratic	***Interaction***	0,004			
	Rostral Anterior Cingulate Gyrus	L												
		R							Linear	***Interaction***	0,019			
	Superior Frontal Gyrus	L							Linear	***Interaction***	0,005			
		R												
Subcortical	Hippocampus	L	Quadratic	***Interaction***	0,012									
		R	Cubic	UHR < TDC	0,006									
	Thalamus	L	Quadratic	***Interaction***	0,015									
		R	Quadratic	***Interaction***	0,022									
	Inferior Lateral Ventricle	L	Linear	***Interaction***	0,049									
		R												
	3rd Ventricle	*n.a.*	Quadratic	UHR > TDC	0,019									

[a] Stable differences are indicated by "</>" whereas developmental differences are indicated by the term "interaction" in bold. CT = cortical thickness; SA = surface area; GI = gyrification index; L = left; R = right; UHR = individuals at ultra high risk for developing psychosis; TDC = typically developing controls

Supplementary Information S4: Table 2. Stable and developmental differences in brain development between resilient (R) and non resilient (NR) UHR individuals based on functional outcome

Region of interest		Hemisphere	Volume			CT			SA			GI		
			Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*
Lobes	Frontal lobe	L												
		R	Quadratic	R > NR	0,012									
	Parietal lobe	L	Quadratic	R > NR	0,003									
		R	Cubic	R > NR	0,008									
	Temporal lobe	L	Quadratic	R > NR	0,025									
		R												
	Total (hemisphere)	L	Quadratic	R > NR	0,015									
		R	Quadratic	R > NR	0,017									
Cortical	Caudal Anterior Cingulate Gyrus	L	Quadratic	***Interaction***	0,049							Linear	***Interaction***	0,049
		R												
	Caudal Middle Frontal Gyrus	L												
		R				Linear	R > NR	*0,000*						
	Entorhinal Cortex	L	Linear	R > NR	*0,005*									
		R												
	Frontal Pole	L												
		R	Linear	R > NR	*0,033*	Linear	R > NR	*0,020*	Linear	***Interaction***	0,033			
	Fusiform Gyrus	L				Cubic	R > NR	*0,011*						
		R												
	Inferior Parietal Gyrus	L												
		R	Quadratic	R > NR	*0,037*	Cubic	R > NR	*0,032*						
	Inferior Temporal Gyrus	L				Cubic	R > NR	*0,031*						
		R	Quadratic	R > NR	*0,017*									
	Insula	L	Quadratic	R > NR	*0,025*				Linear	R > NR	*0,040*			
		R												
	Lateral Orbitofrontal Cortex	L	Quadratic	R > NR	*0,026*				Linear	R > NR	*0,023*			
		R				Quadratic	R > NR	*0,026*						

Supplementary Information S4: Table 2. *(Continued)*

Region of interest	Hemisphere	Volume			CT			SA			GI		
		Growth model	Effect	*p*	Growth model	Effect	p	Growth model	Effect	*p*	Growth model	Effect	*p*
Lingual Gyrus	L				Quadratic	R > NR	*0,046*						
	R												
Medial Orbitofrontal Cortex	L												
	R				Cubic	R > NR	*0,005*						
Middle Temporal Gyrus	L	Linear	R > NR	*0,030*				Linear	R > NR	*0,042*			
	R												
Inferior Frontal Gyrus - Pars Opercularis	L												
	R										Linear	R < NR	*0,029*
Inferior Frontal Gyrus - Pars Orbitalis	L										Linear	R > NR	*0,003*
	R												
Inferior Frontal Gyrus - Pars Triangularis	L							Linear	***Interaction***	0,009			
	R				Quadratic	R > NR	*0,004*						
Postcentral Gyrus	L	Quadratic	R > NR	*0,005*	Quadratic	R > NR	*0,011*	Quadratic	R > NR	*0,041*			
	R	Quadratic	R > NR	*0,014*	Cubic	R > NR	*0,001*						
Posterior Cingulate Gyrus	L												
	R				Linear	***Interaction***	0,011						
Precentral Gyrus	L							Linear	***Interaction***	0,037			
	R												
Precuneus	L	Quadratic	R > NR	*0,003*	Quadratic	R > NR	*0,001*						
	R				Cubic	R > NR	*0,023*						
Rostral Middle Frontal Gyrus	L	Quadratic	R > NR	*0,026*	Cubic	R > NR	*0,013*						
	R												
Superior Parietal Gyrus	L	Quadratic	R > NR	*0,021*									
	R				Cubic	R > NR	*0,024*						

Supplementary Information S4: Table 2. *(Continued)*

Region of interest		Hemisphere	Volume			CT			SA			GI		
			Growth model	**Effect**	***p***	**Growth model**	**Effect**	**p**	**Growth model**	**Effect**	***p***	**Growth model**	**Effect**	***p***
	Superior Temporal Gyrus	L				Linear	***Interaction***	0,038						
		R												
	Supramarginal Gyrus	L				Quadratic	R > NR	*0,005*						
		R												
Subcortical	Nucleus Accumbens	L	Quadratic	R > NR	0,019									
		R	Linear	R > NR	0,008									
	Lateral Ventricle	L	Linear	***Interaction***	0,036									
		R												
	CC Anterior	n.a.	Linear	R > NR	0,018									
	CC Mid Anterior	n.a.	Linear	R > NR	0,006									
	CC Mid Posterior	n.a.	Linear	R > NR	0,011									

Stable differences are indicated by "</>" whereas developmental differences are indicated by the term "interaction" in bold. CT = cortical thickness; SA = surface area; GI = gyrification index; L = left; R = right; R = resilient UHR individuals; NR = non-resilient UHR individuals; CC = corpus callosum

Supplementary Information S5: Table 3. Stable and developmental differences between resilient (R) and non-resilient (NR) UHR individuals based on UHR remission criteria

Region of interest			Volume			CT			SA			GI		
		Hemisphere	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*
Lobes	Frontal lobe	L				Quadratic	R > NR	0,026						
		R				Quadratic	R > NR	0,016						
	Parietal lobe	L				Quadratic	R > NR	0,018						
		R				Cubic	R > NR	0,026						
	Temporal lobe	L				Quadratic	R > NR	0,031						
		R				Quadratic	R > NR	0,003						
	Total (hemisphere)	L				Quadratic	R > NR	0,011						
		R				Quadratic	R > NR	0,007						
Cortical	Banks of the Superior Temporal Sulcus	L				Cubic	R > NR	0,017						
		R												
	Caudal Anterior Cingulate Gyrus	L												
		R										Linear	***Interaction***	0,015
	Caudal Middle Frontal Gyrus	L				Cubic	R > NR	0,038						
		R	Linear	***Interaction***	0,027	Linear	R > NR	0,009	Linear	***Interaction***	0,001			
	Frontal Pole	L												
		R				Linear	***Interaction***	0,045						
	Fusiform Gyrus	L				Cubic	R > NR	0,007						
		R				Quadratic	R > NR	0,002						
	Inferior Parietal Gyrus	L										Linear	***Interaction***	0,026
		R												
	Inferior Temporal Gyrus	L												
		R				Quadratic	R > NR	0,006						
	Lateral Orbitofrontal Cortex	L	Quadratic	R > NR	0,015	Quadratic	R > NR	0,034						
		R												

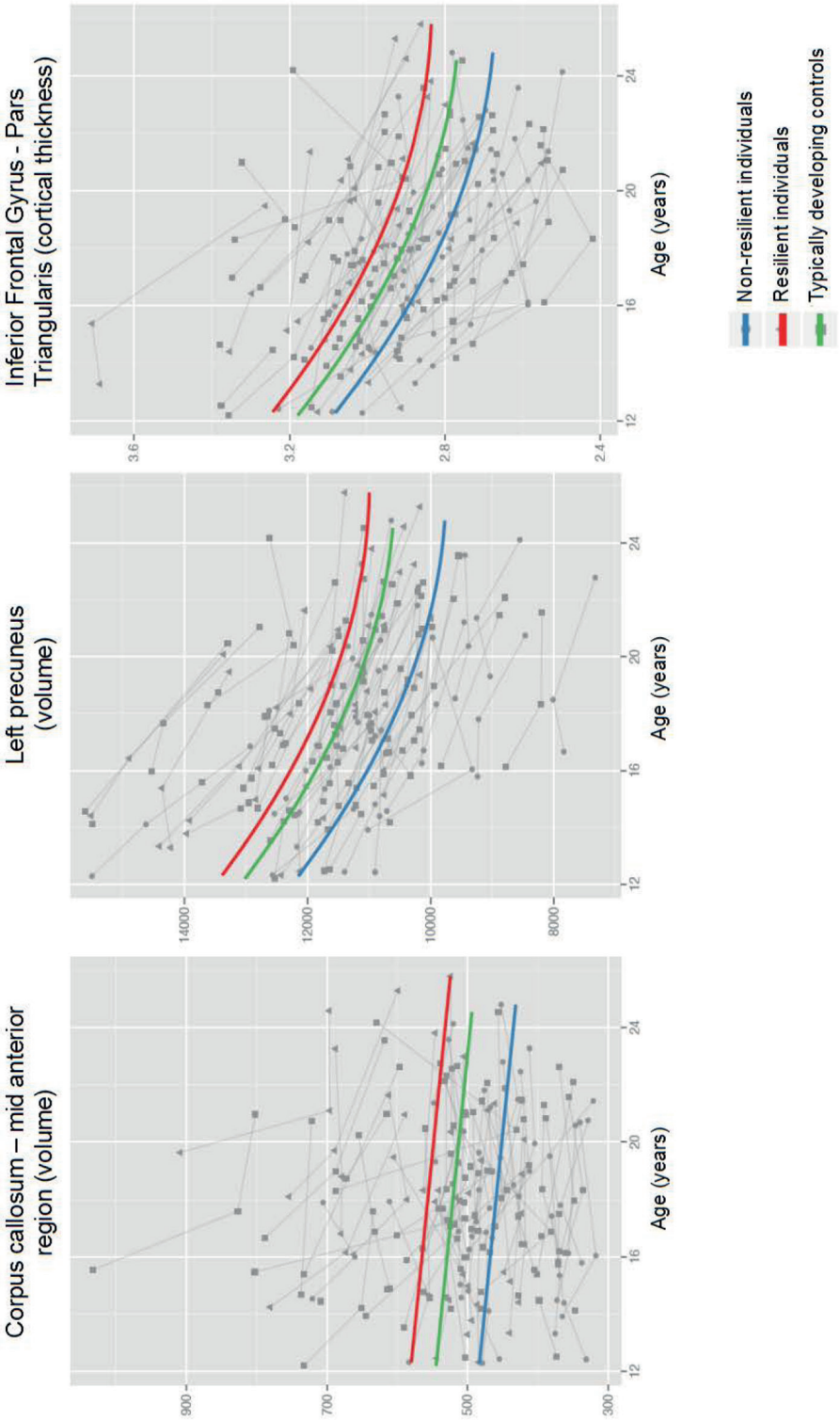
Supplementary Information S5: Table 3. *(Continued)*

Region of interest	Hemisphere	Volume			CT			SA			GI		
		Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*
Lingual Gyrus	L							Linear	R < NR	0,044			
	R												
Medial Orbitofrontal Cortex	L							Linear	R < NR	0,007			
	R				Linear	***Interaction***	0,043						
Middle Temporal Gyrus	L				Cubic	R > NR	0,046				Linear	***Interaction***	0,007
	R												
Parahippocampal Gyrus	L												
	R				Linear	R > NR	0,021	Cubic	***Interaction***	0,032			
Inferior Frontal Gyrus - Pars Orbitalis	L				Quadratic	R > NR	0,035						
	R												
Inferior Frontal Gyrus - Pars Triangularis	L												
	R	Linear	***Interaction***	0,007	Quadratic	R > NR	0,014				Linear	R < NR	0,043
Posterior Cingulate Gyrus	L	Linear	***Interaction***	0,015	Linear	***Interaction***	0,035						
	R												
Precentral Gyrus	L										Linear	***Interaction***	0,033
	R												
Precuneus	L	Quadratic	R > NR	0,049	Quadratic	R > NR	0,016						
	R												
Rostral Middle Frontal Gyrus	L				Cubic	R > NR	0,029						
	R	Linear	***Interaction***	0,022							Linear	***Interaction***	0,002
Superior Frontal Gyrus	L				Linear	R > NR	0,030						
	R				Linear	***Interaction***	0,017	Linear	***Interaction***	0,034	Linear	***Interaction***	0,010
Superior Parietal Gyrus	L				Quadratic	R > NR	0,027	Linear	R < NR	0,004			
	R							Linear	***Interaction***	0,038			
Superior Temporal Gyrus	L										Linear	***Interaction***	0,012
	R												

Supplementary Information S5: Table 3. *(Continued)*

Region of interest		Hemisphere	Volume			CT			SA			GI		
			Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*	Growth model	Effect	*p*
	Supramarginal Gyrus	L				Quadratic	R > NR	0,041						
		R	Linear	***Interaction***	0,001	Linear	***Interaction***	0,009				Linear	***Interaction***	0,011
	Temporal Pole	L												
		R				Linear	***Interaction***	0,002						
	Transverse Temporal Gyrus	L										Linear	***Interaction***	0,016
		R							Quadratic	***Interaction***	0,035			
Subcortical	Pallidum	L	Quadratic	R > NR	0,037									
		R												

Stable differences are indicated by "</>" whereas developmental differences are indicated by the term "interaction" in bold. CT = cortical thickness; SA = surface area; GI = gyrification index; L = left; R = right; R = Resilient UHR individuals; NR = Non-resilient UHR individuals



Supplementary Information S6: Figure 1. Distinct developmental trajectories between non-resilient UHR individuals, resilient UHR individuals and typically developing controls

CHAPTER 5

INDIVIDUAL PREDICTION OF LONG-TERM OUTCOME IN ADOLESCENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: APPLYING MACHINE LEARNING TECHNIQUES TO BRAIN IMAGING DATA

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In revision

ABSTRACT

An important focus of studies of individuals at ultra-high risk (UHR) for psychosis has been to identify biomarkers to predict which individuals will transition to psychosis. However, the majority of individuals will prove to be resilient and go on to experience remission of their symptoms and function well. The aim of this study was to investigate the possibility of using structural MRI measures collected in UHR adolescents at baseline to quantitatively predict their long-term clinical outcome and level of functioning. We included 64 UHR individuals and 62 typically developing adolescents (12–18 years old at recruitment). At six-year follow-up, we determined resilience for 43 UHR individuals. Support Vector Regression analyses were performed to predict long-term functional and clinical outcome from baseline MRI measures on a continuous scale, instead of the more typical binary classification. This led to predictive correlations of baseline MR measures with level of functioning, and negative and disorganization symptoms. The highest correlation (r = 0.42) was found between baseline subcortical volumes and long-term level of functioning. In conclusion, our results show that structural MRI data can be used to quantitatively predict long-term functional and clinical outcome in UHR individuals with medium effect size, suggesting that there may be scope for predicting outcome at the individual level. Moreover, we recommend classifying individual outcome on a continuous scale, enabling the assessment of different functional and clinical scales separately without the need to set a threshold.

Keywords: ultra-high risk, psychosis, long-term outcome, MRI, machine-learning, prediction

INTRODUCTION

The introduction of criteria for individuals at ultra-high risk (UHR) for developing psychosis in the mid 1990s (1) has resulted in a sizeable literature investigating the mechanisms of psychosis onset and disorder progression (for reviews see 2; 3). Besides clinical predictors, measures of brain anatomy and function have been put forward as possible neurobiological predictors for the onset of psychosis. Such potential predictors include loss of brain volume and reduced activation in insular, temporal, parietal, and superior brain areas (for review see 4). To date, such studies have focused on predicting psychosis onset. Although it is relevant to predict who will make a transition to psychosis and who will not, it is at least as important to be able to predict who will recover from their at risk state and go on to function well, i.e. who will prove to be resilient. This is particularly important as the rate of transition to psychosis reported in studies has been becoming lower in recent years, leading to a call for studies of UHR remission (5–8). Moreover, the identification of predictors of resilience could lead to a better understanding of the heterogeneity in outcome and ultimately the disorder itself.

We have previously studied remission and explored brain development in resilient and non-resilient UHR individuals, defined by long-term functional outcome (submitted for publication; 9). We found widespread differences in brain volume that were already present at young age, as well as differences that appeared later in development. The differences that were already present at young age (12 years) included reductions in volume of frontal, temporal and parietal cortex. As these differences were already present at first assessment, they may be promising for predicting who will recover from an at-risk state and who will not.

The majority of studies exploring neurobiological markers have used group-level statistical analysis, thereby limiting the clinical applicability of findings. Multivariate pattern recognition methods, such as machine learning, can be used to overcome these limitations. These methods provide the possibility to make inferences about a subject's health status at an individual level and thus are more suited for clinical decision making purposes (10). So far, machine-learning studies in UHR individuals have been scarce and classification using neuroimaging data as predictors is still in its infancy. A promising accuracy of 82% was shown in a study discriminating UHR individuals who developed psychosis from those who did not using structural MRI and four-year clinical follow-up data (11). Only one study (12) used structural brain markers to predict individual outcome based on level of functioning rather than transition to psychosis and found that cortical surface patterns predicted good versus poor outcome status at two-year follow-up with an accuracy of 82%. These studies have used Support Vector Machines (SVM) to classify groups in a binary manner. Arguably, it is clinically more relevant to predict long-term functioning on a continuous scale. By using measures on a continuous scale one does not have to make an artificial division in the sample. The threshold, which is necessary for a binary classification system, is arbitrary by definition, and there has been much discussion about the validity of the threshold for psychosis (13; 14). While some individuals may develop psychosis and go on to

recover completely, individuals who do not develop psychosis may have worse outcomes (7; 13; 14). The technique of Support Vector Regression (SVR) permits the quantitative prediction of a variable of interest (e.g. a clinical symptom score) without the need for a discrete categorical decision (e.g. affected vs. unaffected). To date, only Tognin and colleagues have attempted to predict outcome on a continuous scale (15). Using the Positive and Negative Syndrome Scale (PANSS), they found a correlation of 0.34 between two-year symptom progression and baseline cortical thickness. These results are encouraging, as they suggest brain measures may be useful for predicting later outcome in a clinically relevant manner. However, two years is not long in clinical terms and the long-term utility of such predictions needs to be assessed. Therefore, we followed up adolescents at ultra-high risk for psychosis over a six-year period and monitored clinical and functional outcome. We focused on SVR with baseline structural MRI data to individually predict long-term functional and clinical outcome on a continuous scale. To allow comparison with earlier studies, we performed complementary SVM analyses to separate UHR individuals from typically developing controls and resilient from non-resilient UHR individuals in a binary manner.

METHODS

Participants

All data were collected at the Department of Psychiatry at the University Medical Center Utrecht, Brain Center Rudolf Magnus in the Netherlands. Participants were between 12 and 18 years of age at the time of recruitment and were included after written informed consent. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Recruitment details have been previously described (16; 17). Briefly, adolescents at UHR were referred by general practitioners or other psychiatry clinics. They had to fulfill at least one of the following criteria: (1) attenuated positive symptoms, (2) brief, limited, or intermittent psychotic symptoms, (3) genetic risk for psychosis combined with a deterioration in overall level of social, occupational/school, and psychological functioning in the past year or (4) two or more of nine basic symptoms of mild cognitive disturbances. The first three inclusion criteria were assessed using the Structured Interview for Prodromal Syndromes (SIPS) (18) and the Family Interview for Genetic Studies (19). The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (20). Exclusion criteria were: a past or present psychotic episode lasting more than one week, traumatic brain injury or any known neurological disorder, and verbal intellectual IQ < 75. The typically developing control group consisted of adolescents recruited through secondary schools in the region of Utrecht. They were excluded if they met any UHR-criterion, if they or any first degree relative had a history of any psychiatric illness, or if they had a second-degree relative with a psychotic disorder.

At baseline, 64 UHR individuals and 62 typically developing controls (TDC) completed clinical assessment and an MRI scan. Clinical follow-up assessments were conducted at nine months,

18 months, 24 months, and 72 months post-baseline. Follow-up MRI scans were collected at 24 months and six years post-baseline. For the purpose of this study only baseline MRI data were used. To investigate the predictive value of neuroimaging for long-term functional and clinical outcome, the six-year follow-up data of the SIPS interview and the mGAF scale were used. For the complementary analyses of predicting outcome on a binary scale, six-year follow-up data was used to divide the UHR group into 'resilient' and 'non-resilient' subgroups. We used the outcome measure 'functional outcome' to define resilience, using the modified Global Assessment of Functioning (mGAF) scale (21). Poor functional outcome (non-resilient) was defined as an mGAF score of < 65 and good functional outcome (resilient) as an mGAF score of ≥ 65 (9). Details of this procedure have been described previously (9). Global intellectual functioning (IQ) was assessed using the Wechsler Intelligence Scales (22; 23).

Image Acquisition

MRI scans were acquired on a single 1.5-T scanner (Philips, Best, The Netherlands). Whole brain T1-weighted three-dimensional fast field echo scans were made with 1.5-mm contiguous coronal slices of the whole head (256 × 256 matrix, FoV = 256 mm, echo time (TE) = 4.6 ms, repetition time (TR) = 30 ms, flip angle = 30°).

Image Processing

Scans were processed and analyzed using FreeSurfer *v 5.1.0* software. Technical details of the automated reconstruction scheme of this well-validated software program are described elsewhere (24–26). Manual edits were performed as necessary by a rater blind to subject identity and group membership. We calculated average volume (mm^3), cortical thickness (mm), surface area (mm^2), and gyrification for the 34 cortical structures in each hemisphere from the Desikan-Killiany atlas (4 x 34 x 2 = 272 measurements) (27). For volume, extra measures included cortical volume (left, right, and total), cortical white matter volume (left, right, and total) and total gray matter volume (7 measurements). For surface area, extra measures included white surface area (left and right, 2 measurements). Gyrification could not be estimated for seven scans, because of FreeSurfer processing errors. We also measured the volume of subcortical structures (n = 25, including ventricular system), as well as total subcortical gray matter volume and gray and white matter separately for the cerebellum (left and right, 5 measurements). This resulted in a total of 311 features that were available for the SVM and SVR models. To correct for possible influences of age and gender, effects of age and gender were regressed out, and all brain imaging data were standardized by subtracting the mean and dividing by the standard deviation.

Classification models

The most frequently used machine-learning technique in psychiatric neuroimaging is the SVM classifier. SVM is a high-dimensional, pattern recognition, supervised learning algorithm (28) used to solve classification problems. The SVM model is trained to classify subjects based on their features. Full details of the modeling procedure have been described previously (29; 30). Briefly, each subject *i* is represented by features congregated into a vector x_i. These vectors exist in a high

dimensional feature space, in which a flat decision surface is constructed to separate the subjects from different classes. This is accomplished by the introduction of a decision function $y(x_i)$:

$$y(x_i) = w^T \cdot x_i - b,$$

that vanishes at the decision surface. The weight vector w is a normal vector to this surface; b is an offset. In the training phase, each subject has a label t_i (e.g., TDC -1; UHR individuals 1), and the function is optimized by requiring $y(x_i) < 0$ if $t_i = -1$, and $y(x_i) > 0$ if $t_i = 1$. When applying the model, this decision function is used to classify the test subjects according to the sign of $y(x_i)$. The weight-vector w provides information on feature importance, as well as whether it is either an increase or decrease of a particular feature's value that contributes to being classified as either 1 or -1 (in this example UHR individual or TDC).

There can be several surfaces that separate the classes. The SVM chooses the so-called optimal separating hyperplane (OSH) such that the space between the two classes, which is called the margin, is made as large as possible. The position of the OSH is determined by a subset of the subjects, the so-called support vectors. This is a necessary condition for generalization of the model to new subjects. There is a free parameter C in SVM that influences the narrowness of the margin, which was optimized as described in Nieuwenhuis *et al.*, 2012 (29).

For this study we focus on SVR. Whereas SVM classifies on a binary scale, the SVM approach has also been adapted to predict numerical values through SVR (31). Instead of constructing a hyperplane for classification, SVR derives a function on the basis of training data to predict numerical values. It uses the same principles as the SVM for classification, but with an additional parameter, ν, that controls the number of support vectors and training errors (31).

First, as a proof of principle, we built a model to separate UHR individuals from typically developing controls (model A). Next, we built models to predict clinical and functional outcome in UHR individuals at six-year follow-up: one binary model to separate resilient UHR individuals from non-resilient UHR individuals at six-year follow-up (model B, binary) to be able to compare our results to previous studies. The focus of this study is on the four continuous models (models C) that we built to predict functional outcome (model C1) and clinical outcome (models C2-4) on a continuous scale:

(A) UHR-TDC, to separate UHR individuals from typically developing controls (binary; SVM)
(B) R-NONR, to separate resilient (R) UHR individuals from non-resilient (NON-R) UHR individuals on a binary scale (binary; SVM)
(C1) mGAF score at six-year follow-up (continuous, SVR)
(C2) SIPS Positive score at six-year follow-up (continuous, SVR)
(C3) SIPS Negative score at six-year follow-up (continuous, SVR)
(C4) SIPS Disorganization score at six-year follow-up (continuous, SVR)

Features included baseline cortical volume, cortical thickness, surface area, gyrification (local gyrification index (LGI)) and subcortical volumes as described above. Features were tested separately, as well as combined, for each model. As the SIPS 'Disorganization' subscale score differed significantly between resilient and non-resilient UHR individuals at baseline, we built additional models including the baseline SIPS Disorganization score as a predictor.

Quality measures

The quality of an SVR model was assessed by the correlation coefficient (r) between true and predicted values.

The quality of a SVM model was assessed by three quantities:

- Sensitivity = TP/(TP + FP), where TP is the number of true positives (correctly classified patients), and FP is it the number of false positives.
- Specificity = TN/(TN + FN), where TN is the number of true negatives, and FN is the number of false negatives.
- Average accuracy = (sensitivity + specificity)/2.

The accuracy of the models was tested using leave-one-out (LOO) cross validation (29). In this procedure each subject is taken out once and used to test the prediction model built on the other subjects. To test the statistical significance of the corresponding accuracy, we randomly permuted the labels of the training sample and built models from these data. We repeated this process 1000 times to determine null-distributions of accuracies and weights. P-values of the accuracy and weights were calculated as the fraction of models from the permutation procedure that had a larger accuracy/weight than the accuracy/weight of our full model. To test the statistical significance of the correlation coefficient (SVR), we calculated the p-value of the Pearson correlation coefficient in the IBM Statistical Package for the Social Sciences (SPSS).

Finally, we performed a Receiver Operating Characteristic (ROC) analysis to illustrate the performance of the best binary classifier model (SVM). The curve was created by plotting the true positive rate against the false positive rate at various threshold settings.

Statistical Analyses

The statistical software package IBM SPSS version 22.0 was used (1) to test for between-group differences in the demographic and clinical data (*t*-test/Fisher's exact/Mann Whitney) and (2) to calculate the statistical significance of the correlation coefficients between the true value and predicted value from the SVR analyses (Pearson). Alpha was set at 0.05. The open source machine learning library LIBSVM (32) was integrated with our own software to carry out the SVR and SVM classifications (29).

RESULTS

Demographic and clinical characteristics

When the whole group of UHR individuals was compared to the group of typically developing controls, only IQ differed between groups, with lower IQ for UHR individuals than typically developing controls (t = 3.53, p = 0.001) (33). A full list of demographic characteristics is provided in the supplementary materials (Supplementary Table 1). There were no statistical differences in the demographic variables between resilient and non-resilient UHR individuals (Table 1). Clinically, there were few differences in baseline symptoms with only 'Disorganized symptoms' lower in resilient UHR individuals than non-resilient UHR individuals (U = 113,5, p = 0.016). At six-year follow-up, resilient UHR individuals had lower scores than non-resilient UHR individuals on all symptom scales, as well as a higher mGAF score (p < 0.001 for all comparisons; Table 1). The groups did not differ in terms of the use of psychotropic medication.

Comparison to previous literature (binary classification)

To allow comparison to earlier studies, we first built binary classification models separating UHR individuals from typically developing controls as well as resilient UHR individuals from non-resilient UHR individuals:

Separation of UHR individuals and typically developing controls (model A)

The highest average accuracy (using LOO cross validation) was achieved using subcortical volumes (64%) with a sensitivity of 59%, a specificity of 68% and significance of p = 0.018. Surface area and cortical thickness features also yielded significant models with a sensitivity of 66%, a specificity of 56%, and an average accuracy of 61% (p = 0.005) for surface area and a sensitivity of 56%, a specificity of 63%, and an average accuracy of 60% (p = 0.007) for cortical thickness. Other brain measures did not discriminate between UHR individuals and typically developing controls. Results are provided in Supplementary Table 2.

Separation of resilient UHR individuals and non-resilient UHR individuals (model B)

Models that separated resilient from non-resilient UHR individuals on a binary scale (model B, Table 2) included those using cortical volume (LOO average accuracy of 69%, p = 0.015), gyrification (LOO average accuracy of 73%, p = 0.016), and subcortical volumes (LOO average accuracy of 67%, p = 0.047). Figure 1 shows the weight-vector w from the best model (gyrification) mapped onto the brain. Warm colors indicate that increases in LGI contribute to being classified as non-resilient, while cool colors indicate that decreases in LGI contribute to being classified as non-resilient. Significant contributions to the model's discriminative pattern were found for the inferior frontal gyrus (pars orbitalis), fusiform gyrus, lateral orbitofrontal gyrus, and precentral gyrus. For subcortical volumes, substantial contributions were found for the right cerebellum, corpus callosum, amygdala, thalamus, and basal ganglia (pallidum). The binary classification model with the highest average accuracy included a combination of gyrification, subcortical volumes, and SIPS disorganization (which differed between groups at baseline) with an average

accuracy of 82% (sensitivity 69%, specificity 94%, $p = 0.003$). For the model with highest accuracy, predictive value is shown in a ROC curve in Figure 2 with an Area-Under-the-Curve of 0.753.

Table 1. Demographic and clinical data of resilient and non-resilient UHR individuals [a]

	Resilient (R)	**Non-Resilient (NON-R)**	**R vs. NON-R**
Number of individuals (n)	17	24	n.s.
Gender, M/F (n)	13/4	14/10	*n.s.*
Premorbid IQ, mean (SD)	101.18 (12.89)	101.88 (10.46)	*n.s.*
Age at baseline, years			
– Mean (SD)	15.42 (2.20)	15.86 (2.32)	*n.s.*
– Range	12.31-19.64	12.28-19.44	
Age at 6-year follow-up, years			
– Mean (SD)	21.34 (2.58)	20,96 (2,31)	n.s.
– Range	17.88 - 25.79	16.84-24.80	
SIPS/SOPS baseline, mean (SD)			
– Total score	21.35 (10.74)	26.25 (13.49)	*n.s.*
– Positive symptoms	7.41 (4.53)	8.67 (3.86)	*n.s.*
– Negative symptoms	4.24 (4.66)	4.75 (3.88)	*n.s.*
– Disorganized symptoms	3.41 (3.30)	5.79 (3.78)	*U = 113,5, p* = 0.016
– General symptoms	6.29 (4.33)	7.04 (4.81)	*n.s.*
mGAF baseline, mean (SD)	57.06 (13.57)	54.92 (16.59)	*n.s.*
SIPS/SOPS 6-year follow-up, mean (SD)			
– Total score	11.75 (8.36)	38.71 (17.09)	*U* = 22.5, *p* = <0.001
– Positive symptoms	3.88 (3.59)	10.71 (5.90)	*U = 57,0, p* = <0.001
– Negative symptoms	3.88 (3.72)	12.92 (7.47)	*U = 49.0, p* = <0.001
– Disorganized symptoms	3.19 (2.74)	7.75 (3.57)	*t = 4,33, p* = <0.001
– General symptoms	1.50 (1.59)	7.33 (4.59)	*U = 42.5, p* = <0.001
mGAF 6-year follow-up, mean (SD)	77.94 (7.30)	44.08 (11.78)	*t = 10.49, p* = <0.001
Psychotropic medication baseline, any			n.s.
– No	9	13	
– Yes	8	11	
Psychotropic medication 6-year follow-up, any			n.s.
– No	13	11	
– Yes	4	13	

Notes: [a] Subgroups are based on functional outcome at 6-year follow-up; outcome was unknown for 23 UHR individuals not included here UHR = Individuals at ultra-high risk for psychosis; IQ = intelligence quotient; SD = standard deviation; SIPS/SOPS = Structured Interview for Prodromal Symptoms / Scale of Prodromal Symptoms; mGAF = Modified Global Assessment of Functioning

Table 2. Results of baseline MRI features separating resilient from non-resilient UHR individuals (models B) and quantitative predictions of long-term functional and clinical outcome (models C)

Binary models (B)	**Sensitivity (%)**	**Specificity (%)**	**Average accuracy (%)**	***p***
Cortical Volume	71	67	69	0.015*
Surface area	47	42	44	*n.s.*
Cortical thickness	47	50	49	*n.s.*
Gyrification	69	78	73	0.016*
Subcortical volume	59	75	67	0.047*
SIPS Disorganization (all)	76	71	74	0.001**
SIPS Disorganization (gyrification subset)	75	78	76	0.002**
Gyrification + Subcortical Volume	69	78	73	0.021*
SIPS Disorganization + Gyrification	69	83	76	0.005**
SIPS Disorganization + Subcortical Volume	76	71	74	0.013*
SIPS Disorganization + Cortical Volume	59	75	67	0.002**
SIPS Disorganization + Gyrification + Subcortical Volume	69	94	82	0.003**

Continuous models (C)	***r***	***p***
Model C1: mGAF score at 6-yr follow-up		
– Gyrification	0.382	0.026*
– Subcortical Volume	0.424	0.006**
– SIPS Disorganization + Gyrification + Subcortical Volume	0.327	*n.s.*
Model C2: SIPS Positive score at 6-yr follow-up		
– Cortical thickness	0.258	*n.s.*
Model C3: SIPS Negative score at 6-yr follow-up		
– Subcortical Volume	0.349	0.028*
Model C4: SIPS Disorganization score at 6-yr follow-up		
– Gyrification	0.411	0.017*
– Subcortical Volume	0.342	0.031*
– SIPS Disorganization + Gyrification + Subcortical Volume	0.378	0.030*

Notes: [a] Subgroups are based on functional outcome at 6-year follow-up UHR = Individuals at ultra-high risk for psychosis; mGAF = Modified Global Assessment of Functioning; SIPS = Structured Interview for Prodromal Symptoms; n.s. = non-significant

* $p < 0.05$; ** $p < 0.01$

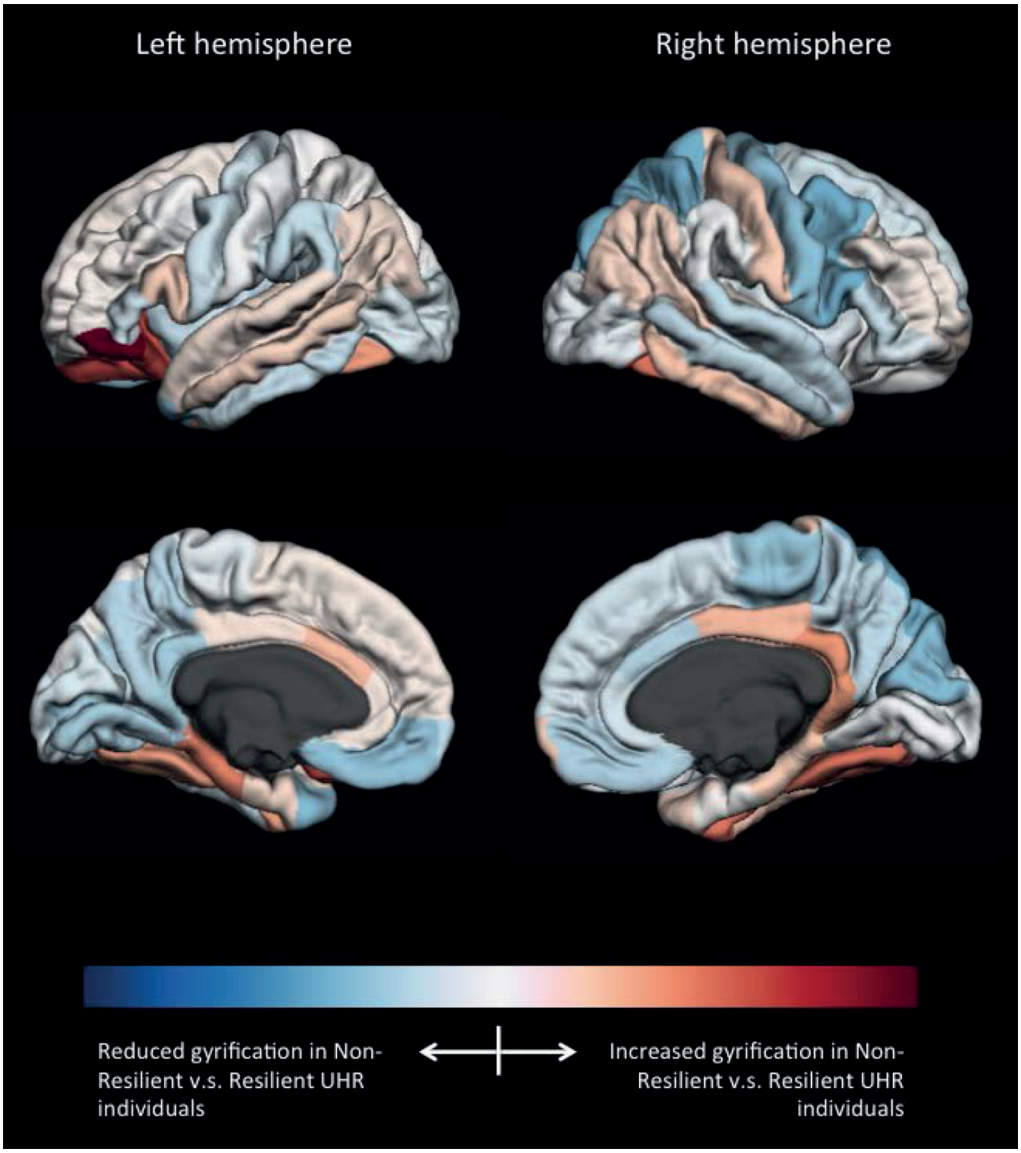

Figure 1. Weight-vector (w-map) of the model best separating resilient from non-resilient UHR individuals (gyrification)

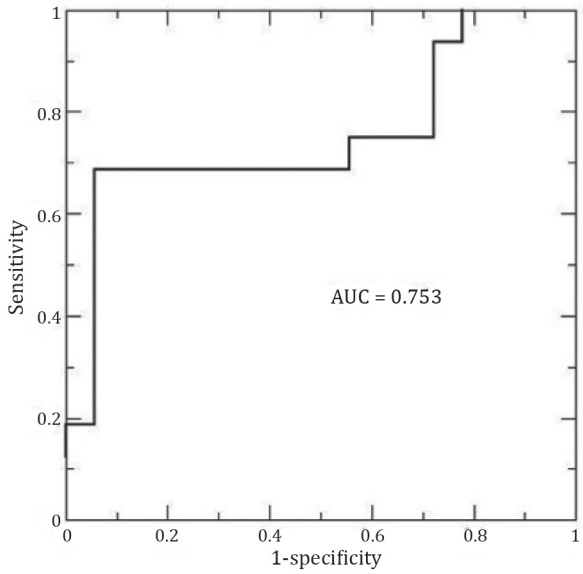

Figure 2. Receiver-Operator-Curve of the class probability values obtained from the SVM model of subcortical volume, gyrification and SIPS Disorganization

AUC = area under the curve; SVM = Support Vector Machine; SIPS = Structures Interview for Prodromal Symptoms

Long-term outcome prediction of UHR individuals on a continuous scale (models C)

Predictions of clinical and functional outcome at six-year follow-up on a continuous scale are shown in Table 2. Models with predictive correlation coefficients close to zero are not listed. Gyrification and subcortical volumes yielded significant predictive correlations with level of functioning at six-year follow-up (Model C1: $r = 0.382$, $p = 0.026$ and $r = 0.424$, $p = 0.006$ respectively), negative symptoms (Model C3: $r = 0.349$, $p = 0.028$ for subcortical volumes), and disorganization symptoms (Model C4: $r = 0.411$, $p = 0.017$ and $r = 0.342$, $p = 0.031$ respectively). Predictions and weights of the model with the highest predictive value (Model C1, baseline subcortical volumes predicting GAF score at six-year follow-up) are shown in Figure 3. Substantial contributions were primarily found for the corpus callosum, caudate nucleus, thalamus, pallidum, cerebellum, amygdala and third and lateral ventricle. Of these, only the weight of the corpus callosum (mid posterior part) reached statistical significance ($p = 0.039$). The addition of SIPS disorganization score to the brain models did not improve predictive value with correlations of 0.327 with GAF score at six-year follow up (*n.s.*) and 0.378 with SIPS Disorganization score at six-year follow-up ($p = 0.030$).

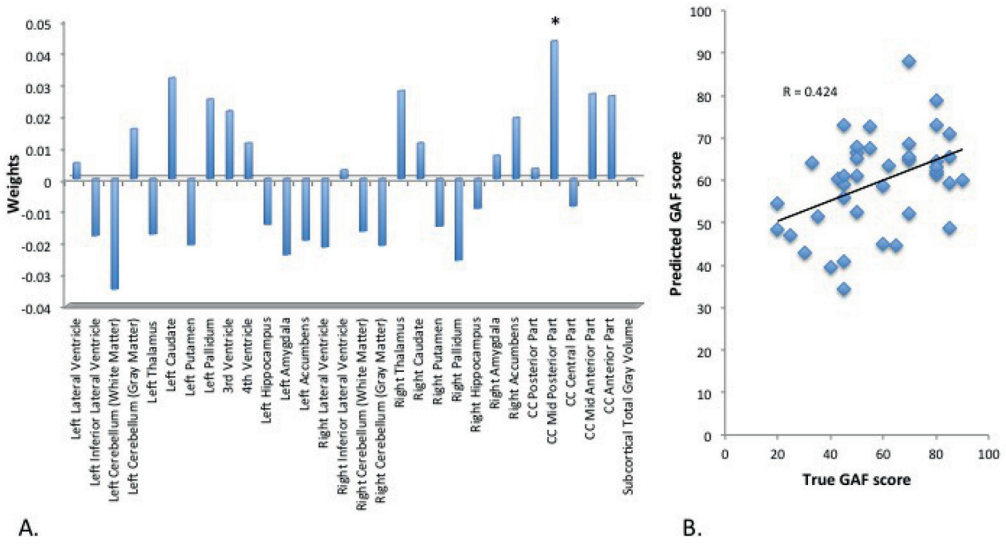

Figure 3. SVR Subcortical Volumes predicting GAF-score at 6-year follow-up

A. Weight-vector bar chart

B. Scatter plot with linear trendline

CC = corpus callosum; GAF = Global Assessment of Functioning

* = $p < 0.05$

DISCUSSION

In this paper, we set out to use baseline structural MRI data to predict long-term functional and clinical outcome in adolescents at ultra-high risk for psychosis on an individual basis. Predictions of long-term functioning on a continuous scale led to predictive correlations between baseline MRI measures and level of functioning (mGAF score), and negative and disorganization symptoms at six-year follow-up. The highest correlation (0.42) was found between baseline subcortical volumes and long-term level of functioning. Subcortical volumes with substantial contributions to this model included the corpus callosum, caudate nucleus, thalamus, pallidum, and amygdala as well as cerebellum and third and lateral ventricle.

To date, only one other study has tried to make quantitative predictions of clinical symptoms in UHR individuals at follow-up (15). Tognin and colleagues reported a predictive correlation of 0.34 between baseline cortical thickness and progression of total positive- and negative symptoms from baseline to two-year follow-up. In this study, highest prediction accuracies were found between gyrification and disorganization symptoms ($r = 0.41$) and subcortical volumes and level of functioning ($r = 0.42$). We looked at positive, negative and disorganization symptoms separately and found that it was not positive symptoms, but rather level of functioning and disorganization

symptoms that were most accurately predicted by baseline MRI data. This underscores the idea that not only positive symptoms are important for long-term outcome, but that other symptom clusters and level of functioning are equally important for the long-term outcome of UHR individuals (3; 34; 35).

Other machine-learning studies attempting to classify UHR individuals have focused on binary classification separating UHR individuals who developed psychosis from those who did not. The accuracy of their predictions based on structural MRI data range from 80 to 84% (11; 36; 37). To allow comparison to these studies we complementary separated resilient from non-resilient UHR individuals in a binary manner. We achieved accuracies ranging from 67 to 73%, based on gyrification, cortical volume and subcortical volumes. Substantial contributions to these models came from frontal (gyrification) and temporal (cortical volume) brain regions as well as corpus callosum, amygdala, thalamus, basal ganglia and cerebellum. These areas are in agreement with earlier UHR studies (see for review 4). The combination of SIPS disorganization symptom score and brain measures improved accuracy, with maximum accuracy of 82%. Interestingly, specificity was particularly high for this model, with only one non-resilient individual being misclassified as resilient at six-year follow-up. This is of great importance as this will result in the inclusion of less false-positive UHR individuals and consequently, might prevent unnecessary treatment. OneOne Only one previous study has compared good and poor functional outcome in stead of comparing individuals with and without transition to psychosis (12) and reported an accuracy of 82%. Intriguingly, their most accurate model was based on surface area data while we found that surface area did not discriminate between UHR individuals. We have previously reported that surface area did not differ between UHR groups at young age (12–18 years), but that differences appeared with development (submitted for publication; 9). As such, age differences of the samples could explain the discrepancy.

Also our subcortical findings overlap with those of earlier studies classifying UHR individuals with later transition to psychosis. Especially the thalamus and basal ganglia have been consistently reported to differ between groups (4; 11; 36; 38; 39). As our classification is based on functional outcome, this suggests that changes in subcortical structures may not be specific for the development of psychosis, but may rather be associated with general psychopathology.

Although the majority of studies have focused on binary classification, we believe it is important to predict long-term functioning on a continuous scale because of two reasons. First, it is not necessary to set a threshold, which could be of great advantage as there has been much discussion about the validity of the threshold for psychosis (13; 14). With a continuous scale it is not only possible to separate the poor functioning from good functioning UHR individuals but also to make predictions on a gradual scale within the poor and good functioning subgroups, possibly increasing accuracy. Second, it is possible to look at different clinical scales separately (e.g. positive, negative, and disorganization symptoms). This could be relevant information when choosing appropriate intervention.

Limitations of our study include medication and our relatively modest sample size. As a large number of our UHR individuals were on psychotropic medication, this could have played a role in the classification. However, the number of individuals on medication did not differ between resilient and non-resilient UHR individuals. A second possible confounder was the skewed distribution of gender between resilient and non-resilient groups, even though the difference did not reach statistical significance. However, as we were investigating brain anatomy at one time point rather than its development over time, we chose to regress gender out rather than to match groups for it. Strong points of this paper include the long follow-up period (six years) and the use of SVR models to predict outcome on a continuous scale.

In conclusion, our results show that structural MRI data can be used to quantitatively predict long-term functional and clinical outcome in UHR individuals with medium effect sizes, suggesting that there may be scope for predicting outcome at the individual level. This finding is clinically important, as individual outcome predictions on a gradual scale might allow personalized medicine. In addition, of scientific interest, it permits studying different clinical and functional scales separately.

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SUPPLEMENTARY INFORMATION

Supplementary Table 1. Demographic data for typically developing controls (TDC) and UHR individuals

	TDC	UHR	UHR vs. TDC
Number of individuals, n	62	64	*n.s.*
Gender, M/F (n)	32/30	43/21	*n.s.*
Hand preference, n, right/non-right	53/9	57/7	*n.s.*
Parental education, years, mean (SD)			
– Mother	13.25 (2.43)	12.89 (2.26)	*n.s.*
– Father	14.03 (2.21)	13.76 (2.25)	*n.s.*
Premorbid IQ, mean (SD)	107.43 (12.41)	99.52 (12.47)	$t = 3.53$, $p = 0.001$
Age at baseline scan, years			
– Mean (SD)	15.73 (1.56)	15.69 (2.12)	*n.s.*
– Range	12.19-18.76	12.09-19.64	

Notes: TDC = typically developing controls; UHR = Individuals at ultra-high risk for psychosis; M = male; F = female; IQ = intelligence quotient; SD = standard deviation

Supplementary Table 2. Support Vector Machine classification results (LOO cross validation) of baseline MRI features classifying UHR individuals from TDC

Model A (UHR-TDC)	Sensitivity (%)	Specificity (%)	Average accuracy (%)	*p*
Cortical Volume	53	56	55	*n.s.*
Surface area	66	56	61	0.005**
Cortical thickness	56	63	60	0.030*
Gyrification	70	46	58	*n.s.*
Subcortical Volume	59	68	64	0.018*

Notes: UHR = Individuals at ultra-high risk for psychosis; TDC = typically developing controls; *n.s.* = non-significant

* $p < 0.05$; ** $p < 0.01$

CHAPTER 6

GENERAL DISCUSSION (INCLUDING SUMMARY)

GENERAL DISCUSSION

Since the introduction of the UHR criteria for psychosis 20 years ago, transition rates have been becoming lower and lower, while the number of individuals remitting from UHR symptoms has increased. Together with the criticisms about the arbitrary criterion for 'transition to psychosis', this has led to a recent shift of interest from exploring the mechanism of psychosis onset to studying individuals who remit from UHR criteria (1–3). Additionally, there is a call for studies focusing on functional outcomes. Consequently, the research aims of this thesis were:

1) to investigate long-term clinical and functional outcome of UHR individuals, and to explore the course of their clinical symptoms
2) to investigate the relative value of neurocognitive and clinical variables for predicting long-term outcome
3) to explore differences in brain development of UHR individuals with different long-term outcomes
4) to explore the potential of using baseline structural MRI data to individually predict long-term clinical and functional outcome of UHR individuals, by using machine-learning techniques

Summary of results

In *Chapter 2* we aimed to investigate functioning at six-year follow-up in remitted UHR individuals, and to explore the course of their clinical symptoms. Forty-four UHR adolescents completed extensive clinical assessments at baseline and participated in long-term follow-up approximately six years later. UHR adolescents who had either converted to psychosis or who still met UHR criteria at follow-up were compared to individuals who had remitted from their UHR status on clinical and psychosocial variables. The results showed that more than 40% of UHR individuals had fully remitted from their UHR status. At six-year follow-up, remitted individuals had clinically improved on most symptoms, most notably on positive symptoms. The course of their symptoms showed that the most substantial reduction in positive symptoms occurred within the first two years, while improvements in general, mood and anxiety symptoms occurred at a later stage. Baseline socio-demographic characteristics and clinical symptoms did not distinguish remitters from non-remitters, as is in line with previous findings (4). Although remitters no longer met criteria for UHR, they did meet diagnostic criteria for a wide range of axis-I diagnoses of the DSM-IV. Especially mood and anxiety disorders were often found in this group, as has been reported by others (5; 6). The wide range of axis-I diagnoses in remitters at six year follow-up suggest that the UHR criteria may capture a wider range of risks than risk for psychosis. Furthermore, when related to long-term outcome, UHR criteria seem to capture non-specific psychotic symptoms rather then risk for psychosis per se.

In *Chapter 3* we aimed to investigate the relative value of neurocognitive and clinical variables for predicting both transition to psychosis and functional outcome in UHR individuals. Sixty-seven adolescents at UHR and 72 TDC completed an extensive clinical and neurocognitive assessment at baseline, and 43 UHR individuals and 47 TDC participated in six-year follow-up.

UHR adolescents who had converted to psychosis (UHR-P; n = 10) were compared to individuals who had not (UHR-NP, n = 33) and TDC on clinical and neurocognitive variables. There were two main findings: First, we found that UHR individuals had lower IQ scores at baseline than TDC and IQ predicted conversion to psychosis, whereas no other neurocognitive variables discriminated between the groups. Although consistent with a long history of observations that low premorbid IQ is a risk factor for schizophrenia spectrum disorders (7), UHR studies that investigated the predictive power of IQ have contradictory results (8–12). Second, we found that both psychotic transition and long-term functional outcome were best predicted by clinical variables and not by neurocognitive measures. Attenuated positive symptoms contributed most to prediction of psychotic transition, in line with other studies (13; 14). Furthermore, global functioning was best predicted by disorganized symptoms. Together, these results suggest that clinical symptoms trump neurocognitive variables in predicting clinical outcome.

In the study presented in *Chapter 4*, we investigated brain development over six years in a matched sample of 48 UHR individuals and 48 TDC, with up to three MRI scans per individual. Our main goal was to compare brain development between resilient and non-resilient UHR individuals. We operationalized resilience two ways, either by functional outcome (good versus poor) or clinical UHR symptoms (remission versus non-remission). We focused on functional outcome and found widespread differences in the volume of frontal, temporal and parietal cortex that were already present at baseline and remained stable over development. Although earlier studies focused on disease transition rather than functional outcome, most regions overlap with their results (15–18). Second, there were differences between resilient and non-resilient individuals in the development of cortical surface area in multiple frontal regions including cingulate gyrus. Similar findings have often been associated with UHR and schizophrenia (15). In conclusion, the stable differences that were already present at baseline may hold promise for predicting, at a young age, who will go on to recover and who will not, whereas the diverging developmental trajectories may reflect compensatory neural mechanisms, where the better functioning resilient individuals results in less tissue loss with development.

Chapter 5 continues where Chapter 4 ends, by further exploring the brain differences that were already present at baseline and remained stable over development. We investigated the possibility of using baseline structural MRI measures to quantitatively predict long-term clinical outcome and level of functioning in UHR individuals. For this study, we included 64 UHR individuals and 62 TDC. At six-year follow-up, we determined resilience for the remaining 43 UHR individuals. Support Vector Regression analyses were performed to predict long-term functional and clinical outcome from baseline MRI measures on a continuous scale. Complementary, we performed Support Vector Machine analyses to separate resilient from non-resilient UHR individuals in a binary manner. Predictions of long-term functioning on a continuous scale resulted in predictive correlations of MRI measures with level of functioning (mGAF score), and negative and disorganization symptoms. The highest correlation (0.42) was found between baseline subcortical volumes and long-term level of functioning. Subcortical volumes with substantial contributions

to this model included the corpus callosum, caudate nucleus, thalamus, pallidum, cerebellum, amygdala and third and lateral ventricle, areas that are in line with earlier UHR studies (15). As it was not positive symptoms but level of functioning and disorganization symptoms that yielded the highest accuracies with baseline sMRI data, results support the increasing evidence that other clinical symptoms than positive ones, and the level of functioning may be equally important for the long-term outcome of UHR individuals (19–22). Overall, our results show that structural MRI data can be used to quantitatively predict long-term functional and clinical outcome in UHR individuals with medium effect sizes, suggesting that there may be scope for predicting outcome at the individual level. This finding is clinically important, as individual outcome predictions on a gradual scale might allow personalized medicine. In addition, of scientific interest, it permits studying different clinical and functional scales separately.

Limitations

There are several limitations that recur in all chapters and that may limit the interpretation and/or generalizability of our results:

Sample size at follow-up

The DUPS study started with a decent sample size of 81 individuals who met UHR criteria and 83 TDC. As not all participants completed all baseline measures (e.g. some individuals lacked an MRI scan), baseline sample sizes were somewhat smaller for the studies included in this thesis. Unfortunately, the attrition rate over six years was substantial, probably due to our long follow-up. This resulted in a relatively modest sample size varying from 35 to 44 UHR individuals at six-year follow-up. For some analyses, this may have resulted in diminished statistical power. However, by applying techniques such as correction for multiple comparisons in chapter 3 and correcting/matching for gender and age in chapters 4 and 5, we believe we have minimized the chance of reporting false positive findings. As discussed in Chapter 3, it is also worth noting that longitudinal follow-up studies are rare, especially on young UHR adolescents, and a great need has been voiced within the scientific community to validate findings from adult UHR studies in child and adolescent populations (23). Furthermore, as discussed in Chapter 4, longitudinal samples require far fewer participants than cross-sectional studies in order to detect small differences (24).

Medication use

Most of the adolescents in our study had already sought help at an early age (25), while in other UHR studies, individuals usually do not have a history of contact with mental health services. Accordingly, a relatively high percentage (40%) of our UHR individuals was already using some form of (low-dosage) psychotropic medication at baseline. Arguably, medication may have been prescribed for individuals who were more severely affected clinically, which may in turn have helped prevent the onset of psychosis or had other influences on long-term outcome. However, there were no differences in medication use between subgroups, neither at baseline or follow-up. This suggests that medication did not affect our results. The lack of a difference between

subgroups of UHR individuals (e.g. resilient and non-resilient UHR individuals) could even be taken to suggest that medication does not play a role in individual outcome, although the sample size is too modest to permit any such definitive conclusion.

Age

Age is both a strong point and a potential limitation of our cohort. As mentioned previously, longitudinal follow-up studies on young UHR adolescents are rare and a great need has been voiced within the scientific community to validate findings from adult UHR studies in child and adolescent populations (23). As such, the relatively young age of our cohort is a strength. However, this also means that our UHR cohort was younger than other UHR cohorts. While our UHR cohort was 12 to 18 years of age at the time of recruitment, other cohorts have included UHR individuals up to 40 years of age (26). This affects the generalizability of our study results, especially for the studies concerning brain anatomy and development (Chapters 4 and 5). It is known that the relative contribution of genetic and environmental factors may vary with age for different brain regions (27–29). Furthermore, when investigating brain development, we know that adolescence is a period of significant changes in brain structure and function (30–33). It is possible that neurobiological markers discussed in this thesis cannot be generalized to older UHR populations, and our results should therefore carefully be interpreted.

Implications & future directions

The UHR state is a complex phenomenon, and one where Einstein's quote "The only source of knowledge is experience" is certainly applicable. Whereas we thought that the UHR state reflects an increased risk of developing psychosis twenty years ago, we are not so sure about the validity of the UHR criteria today (3; 5; 14; 34–37). Results of Chapter 2 support this uncertainty, where low transition rates and high remission rates suggest that current UHR criteria may capture too many 'false-positive' individuals at risk. Together with the observation of a great variety of DSM-IV diagnoses we believe UHR criteria may relate more to general psychopathology. Also at a neurobiological level, our opinion is supported. In Chapter 4, we defined 'resilient' as complete remission from UHR criteria as well as good functional outcome, and the results from the analyses were highly similar. Also in Chapter 5, where we focus on functional outcome only, we find similar brain areas as studies focusing on transition to psychosis. As transition to psychosis is solely based on positive symptoms while functional outcome also reflects other psychopathology as well as social and occupational functioning, this indicates that our MRI findings are not specific for the development of psychosis but is rather associated with general psychopathology. When designing early recognition services, this should be taken into account.

The second implication is closely related to the first. As the criterion of 'transition to psychosis' has recently been criticized as a measure to identify which UHR individuals will have a truly poor clinical outcome (19–21), we have used 'level of functioning' as a measure of long-term outcome in three of our studies. A recent review of Cotter and colleagues (22) stated that there is growing recognition that UHR individuals may function poorly regardless of whether they develop

psychosis, which is supported by our findings of Chapter 2. Combining 72 eligible studies, they found that negative and disorganised symptoms (replicated by us in Chapter 3), neurocognitive deficits and poor functioning at baseline were predictive of poor functional outcome in longitudinal studies. Strikingly, positive symptoms were unrelated to functioning in both cross-sectional and longitudinal studies. Prediction should therefore be aimed at long-term functional outcome. Moreover, there is a need for the development of novel therapies and interventions with an emphasis on improving functioning.

In conclusion, the results from this thesis show that UHR criteria are not specific to increased risk of psychosis but are rather associated with general psychopathology. This is supported by both clinical and neurobiological findings throughout this thesis. When replicated and fine-tuned in larger UHR cohorts, we believe structural imaging data may be useful for clinically relevant prediction of long-term outcome at the individual level. Second, our findings support the notion that UHR individuals may function poorly regardless of whether they develop psychosis. Prediction should therefore be aimed at long-term functional outcome and treatments aiming to improve functioning should be considered a priority for individuals in the UHR state.

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LIST OF PUBLICATIONS

CURRICULUM VITAE

NEDERLANDSE SAMENVATTING

Introductie

Het begrip "ultra-hoog risico op psychose" is geen alledaags begrip en behoeft daarom enige uitleg. Allereerst het begrip "psychose": Een psychose is een psychiatrische aandoening waarbij iemand het normale contact met de werkelijkheid kwijt is. Iemand kan erg in de war en angstig zijn, last hebben van hallucinaties of waandenkbeelden hebben. Zo kan iemand stemmen horen of bijvoorbeeld het idee hebben dat hij achtervolgd wordt. Schizofrenie is de meest voorkomende en meest uitgebreid bestudeerde psychotische stoornis. Een psychose kan echter ook eenmalig voorkomen, of optreden bij andere ziektebeelden zoals affectieve stoornissen, persoonlijkheidsstoornissen en pervasieve ontwikkelingsstoornissen. Ongeveer 4% van de volwassen bevolking heeft gedurende het leven een psychotische episode doorgemaakt. Ze ontstaan doorgaans in de adolescentie of op jong volwassen leeftijd en worden dikwijls gekenmerkt door een lange ziekteduur, een aanzienlijke belasting voor de patiënt zelf als wel zijn omgeving, hoge zorgkosten en een aanloopfase voorafgaand aan een psychose, ook wel prodromale fase genoemd. Vroege herkenning en interventie is dan ook van groot belang. Dit heeft geleid tot het ontwikkelen van onderzoeksprogramma's om psychosen in een zo'n vroeg mogelijk stadium te herkennen waarbij gebruik werd gemaakt van de zogenaamde "ultra-hoog risico" (UHR) criteria voor het ontwikkelen van een psychose. Deze criteria bestaan dikwijls uit 1) geringe positieve symptomen, 2) kortdurende en beperkte tussentijds optredende psychotische symptomen en/of 3) familiaire belasting (een eerstegraads familielid met psychose of schizotypische trekken) gecombineerd met een daling van het globaal functioneren van tenminste 30%. Veelvuldig onderzoek heeft uitgewezen dat wanneer een individu voldoet aan UHR-criteria, het risico op transitie naar psychose binnen een jaar ongeveer 35% is. Sinds de introductie van de UHR criteria twintig jaar geleden is er dan ook veelvuldig onderzoek gedaan naar (neuro)biologische kenmerken van UHR individuen en werd er, met wisselend succes, onderzocht of er (neuro)biologische predictoren zijn voor het ontwikkelen van een psychose. Echter, de percentages van individuen die een psychotische transitie ondergaan verschillen sterk per studie en het percentage is tevens afgenomen in de laatste jaren. Daarnaast hebben recente studies aangetoond dat maar liefst 45% van de UHR individuen herstelt van UHR symptomen. Onderzoek heeft zich tot op heden echter gefocust op de groep individuen die een transitie ondergingen waardoor weinig bekend is over (neurobiologische) kenmerken van de groep die herstelt, oftewel remissie laat zien. Ook wordt er steeds meer kritiek geuit op de criteria die gebruikt worden voor het vaststellen van een transitie omdat de grens arbitrair is en puur gebaseerd is op positieve symptomen. Recent onderzoek heeft aangetoond dat cognitief functioneren, sociaal functioneren en andere klinische symptomen ook van belang zijn voor iemands lange-termijn functioneren. Om deze redenen is de focus van dit proefschrift niet op transitie maar juist op remissie alsmede lange-termijn globaal functioneren. Daarbij is er gebruik gemaakt van klinische, neuropsychologische en structurele MRI maten en werden de volgende onderzoeksdoelen geformuleerd:

1) Het onderzoeken van lange-termijn klinisch- en globaal functioneren in UHR individuen, en het bestuderen van het verloop van klinische symptomen (Hoofdstuk 2)
2) Het onderzoeken van de relatieve waarde van neurocognitieve- en klinische variabelen voor het voorspellen van lange-termijn functioneren van UHR individuen (Hoofdstuk 3)
3) Het exploreren of er verschillen zijn in hersenontwikkeling tussen UHR individuen met verschillende lange-termijn uitkomsten (Hoofdstuk 4)
4) Het exploreren van de potentie om baseline structurele MRI data te gebruiken om, met behulp van machine-learning technieken, op individueel niveau lange-termijn klinisch- en globaal functioneren van UHR individuen te voorspellen (Hoofdstuk 5)

De studies opgenomen in dit proefschrift zijn allen onderdeel van het project "Dutch Prediction of Psychosis Study" (DUPS). DUPS is een longitudinaal onderzoeksproject welke is gestart in 2002. Deelnemers waren hulpzoekende adolescenten tussen de 12 en 18 jaar die verwezen werden door een huisarts of een psychiatrische kliniek. Van deze deelnemers voldeden 81 aan tenminste één UHR criterium. Daarnaast werd er een groep van 83 gezonde controle deelnemers geïncludeerd. Beide groepen zijn gedurende zes jaar gevolgd waarbij onder andere gekeken werd naar (klinisch) functioneren en tweejaarlijks een MRI scan van de hersenen werd gemaakt.

Resultaten

In *Hoofdstuk 2* werd het functioneren van UHR individuen onderzocht gedurende een follow-up periode van zes jaar. Daarnaast is onderzocht hoe het beloop van klinische symptomen er uit ziet gedurende deze tijd. Vierenveertig UHR individuen participeerden in een uitgebreide klinische evaluatie op baseline en follow-up. UHR individuen die een transitie naar psychose hadden ondergaan of nog voldeden aan UHR criteria werden vervolgens vergeleken met UHR individuen die herstelden van hun UHR status. Resultaten lieten zien dat meer dan 40% van de UHR individuen zes jaar na de eerste deelname volledig waren hersteld. Daarbij lieten zij een verbetering zien van de meeste klinische symptomen, voornamelijk positieve symptomen. De grootste afname in positieve symptomen werd gezien in de eerste twee jaar, terwijl verbetering van algemene-, stemmings- en angstsymptomen later plaatsvonden. Echter, ondanks dat zij herstelden van UHR criteria, voldeden zij wel aan diagnostische criteria voor een grote diversiteit aan as-I DSM-IV stoornissen, voornamelijk stemmings- en angststoornissen. Dit suggereert dat de UHR criteria niet specifiek een risico geven op het ontwikkelen van psychose maar eerder een risico voor algemene psychopathologie aanduiden.

In *Hoofdstuk 3* werd de relatieve waarde van neurocognitieve- en klinische variabelen voor het voorspellen van transitie naar psychose en lange-termijn globaal functioneren van UHR individuen onderzocht. Zevenenzestig UHR individuen en 72 gezonde controle deelnemers namen deel aan een uitgebreide klinische als wel neurocognitieve testbatterij. Daarvan namen 43 UHR individuen en 47 gezonde controle deelnemers ook deel aan de zes jaar follow-up. Er waren twee hoofdbevindingen: Ten eerste hadden UHR individuen een lagere IQ score op baseline dan de gezonde controles en voorspelde IQ als enige neurocognitieve maat transitie naar psychose

(n = 10). In schizofrenie studies wordt IQ dikwijls gevonden als risicofactor voor schizofrenie, in UHR studies zijn resultaten echter niet consistent als het gaat om voorspelling van psychotische transitie. Ten tweede vonden we dat zowel psychotische transitie als wel lange-termijn functioneren het beste werd voorspeld met klinische variabelen en niet met neurocognitieve maten. Voornamelijk positieve symptomen droegen hier aan bij, overeenkomstig met eerdere studies. Globaal functioneren werd het beste voorspeld met baseline desorganisatie symptomen. Dit suggereert dat klinische symptomen van grotere waarde zijn voor het voorspellen van lange-termijn uitkomsten dan neurocognitieve maten.

In de studie gepresenteerd in *Hoofdstuk 4* onderzochten we hersenontwikkeling in 48 UHR individuen en 48 gezonde controle deelnemers over een tijd van zes jaar waarbij tot 3 MRI scans per persoon werden gemaakt. Het hoofddoel was om de hersenontwikkeling te vergelijken tussen 'resilient' UHR individuen (individuen die herstelden van UHR criteria en/of goed functioneerden) en 'non-resilient' UHR individuen (individuen die nog voldeden aan UHR criteria, een psychotische transitie hadden ondergaan en/of slecht functioneerden op zes jaar follow-up). Wanneer we keken naar functionele uitkomst (globaal functioneren) vonden we verschillen in volume van meerdere gebieden in de frontale, temporale en pariëtale hersenkwab die al zichtbaar waren op baseline en stabiel bleven over de tijd heen. Daarbij was er een grote overlap in hersengebieden met eerdere UHR studies die keken naar psychotische transitie. Ten tweede vonden we verschillen tussen de groepen in de ontwikkeling in de grootte van het corticale oppervlak van meerdere frontale regio's en de cingulate gyrus, bevindingen die ook overeenkomstig zijn met eerdere UHR en schizofrenie studies. Concluderend kunnen we zeggen dat de verschillen die al zichtbaar zijn op jonge leeftijd mogelijk een voorspellende waarde hebben voor het wel of niet herstellen van de UHR status, terwijl de divergerende ontwikkelingstrajecten mogelijk neurale compensatie mechanismen aantonen, waarbij er minder weefselverlies is over tijd in 'resilient' individuen.

Hoofdstuk 5 gaat verder waar Hoofdstuk 4 eindigt door te onderzoeken of de verschillen van het brein die al zichtbaar waren op baseline inderdaad een mogelijke voorspellende waarde hebben voor het lange-termijn klinisch en globaal functioneren. Voor deze studie werden 64 UHR individuen en 62 gezonde controle deelnemers geïncludeerd en bestond de hoofdanalyse uit het uitvoeren van Support Vector Regressie analyses om kwantitatief functioneren te voorspellen met baseline MRI maten. Resultaten toonden aan dat er voorspellende correlaties waren tussen MRI maten en globaal functioneren, negatieve symptomen en desorganisatie symptomen. De hoogste correlatie van 0.42 werd gevonden tussen baseline subcorticale volumes en lange-termijn globaal functioneren. Subcorticale volumes die daar aan bijdroegen waren onder meer het corpus callosum, caudate nucleus, thalamus, pallidum en amygdala als wel het cerebellum en het ventrikelsysteem, allen regio's die eerder zijn gevonden in UHR en schizofrenie studies. De bevinding dat globaal functioneren en desorganisatie symptomen nauwkeuriger werden voorspeld dan positieve symptomen sluiten aan bij de recente bevindingen dat andere symptomen dan positieve symptomen als wel globaal functioneren minstens net zo belangrijk zijn voor iemands lange-termijn functioneren. Concluderend laten de resultaten in dit hoofdstuk zien dat

structurele MRI data gebruikt kan worden voor kwantitatieve voorspellingen van lange-termijn functioneren. Hoewel vervolgonderzoek nodig is, suggereert dit dat het potentieel mogelijk is om uitkomsten te voorspellen op individueel niveau. Daarbij raden wij aan om lange-termijn uitkomst op een continue schaal te analyseren. Het is daardoor mogelijk de klinische schalen apart te bestuderen en het is niet nodig een arbitraire grens in te stellen wat wel nodig is in een binaire uitkomst-analyse.

Conclusie

In het algemeen kunnen we concluderen dat het begrip "UHR" een complex fenomeen is waarbij de meningen omtrent de betekenis ervan divers zijn en tevens zijn veranderd gedurende de afgelopen 20 jaar. Terwijl 20 jaar geleden werd aangenomen dat de UHR status een verhoogd risico geeft op het ontwikkelen van psychose met transitie-percentages tot maar liefst 50%, zijn we de laatste jaren minder zeker over de validiteit van de UHR criteria. De lage transitie-aantallen en hoge remissie-aantallen die we vonden in Hoofdstuk 2 ondersteunen deze onzekerheid en suggereren dat de UHR criteria te veel vals-positieve individuen includeren. Samen met de bevinding dat UHR individuen een grote diversiteit aan as-I DSM-IV stoornissen laten zien, zijn wij van mening dat de UHR criteria eerder gerelateerd zijn aan algemene psychopathologie. Ook op een neurobiologisch niveau wordt deze gedachte ondersteund. Zo laten de resultaten van Hoofdstuk 4 grote gelijkenis zien wanneer we "resilience" definiëren als remissie van UHR criteria of als goede functionele uitkomst. Ook in Hoofdstuk 5, waar we focussen op functionele uitkomst, vinden we dezelfde hersengebieden als studies waarbij gekeken wordt naar psychotische transitie. Aangezien psychotische transitie puur wordt beoordeeld op basis van positieve symptomen terwijl functionele uitkomst ook andere psychopathologie en sociaal- en beroepsmatig functioneren meeneemt in de beoordeling, duiden de resultaten er op dat onze MRI bevindingen niet specifiek zijn voor het ontwikkelen van psychose maar wederom eerder algemene psychopathologie reflecteren. Wij zijn van mening dat bij het ontwikkelen van programma's voor vroege herkenning van risico-symptomen hier rekening mee gehouden moet worden.

De tweede implicatie van onze bevindingen is nauw gerelateerd aan de zojuist besproken implicatie. Vanwege de recente kritiek op de criteria die worden gebruikt voor het vaststellen van een transitie en de bevindingen dat UHR individuen die voldoen aan deze criteria niet perse een slechte klinische uitkomst hebben, hebben we door het hele proefschrift heen "globaal functioneren" als lange-termijn uitkomstmaat gebruikt. In een recente review waarbij 72 UHR studies werden gecombineerd is genoemd dat er steeds meer erkenning is voor het feit dat UHR individuen slecht functioneren ongeacht of ze wel of niet een psychotische transitie ondergaan, een gedachte die wij ondersteunen met de bevindingen in Hoofdstuk 2. De review toonde aan dat negatieve symptomen en desorganisatie symptomen (tevens door ons gevonden in Hoofdstuk 3), neurocognitieve verschillen en slecht functioneren op baseline voorspellend waren voor lange-termijn functioneren. Daarbij was het opvallend dat positieve symptomen niet gerelateerd waren aan lange-termijn functioneren, zowel niet in cross-sectionele als longitudinale studies. Wij zijn daarom van mening dat predictie moet toespitsen op lange-termijn globaal functioneren.

Daarbij is er behoefte aan nieuwe therapieën en interventie programma's met een nadruk op het verbeteren van functioneren in het algemeen.

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* Both authors contributed equally to the manuscript

CURRICULUM VITAE

Sanne de Wit was born November 22nd, 1984 in Hoofddorp. She graduated from high school (Eerste Christelijk Lyceum in Haarlem) in 2004. After that she started the Bachelor's degree program Biomedical Sciences at the VU University Amsterdam, followed by the Master's degree program Neurosience. Due to her interest in applied medical sciences and brain imaging she chose the track of Preclinical Neuroscience. Her first internship was completed at the Department of Neurology and Clinical Neuropsychology at the VU Medical Center under the supervision of Dr. Ysbrand van der Werf and Prof. Dr. Eus van Someren. For her second internship Sanne went to Canada where she worked in the lab of Dr. Rovet at the Department of Psychology of the Hospital for Sick Children in Toronto. After this internship she obtained her Master's degree in the summer of 2009. Directly after, she started her PhD project at the neuroimaging lab 'NICHE' at the Department of Psychiatry of the University Medical Center in Utrecht. She worked on the Dutch Prediction of Psychosis Study on the studies described in this thesis. On April 21st, 2016 she will defend her thesis under the supervision of Prof. Dr. Sarah Durston, Prof. Dr. René Kahn and Dr. Patricia Schothorst. After completing her PhD project, Sanne started working as a Clinical Research Associate at Julius Clinical in Zeist.

Sanne de Wit werd op 22 november 1984 geboren in Hoofddorp. In 2004 behaalde zij haar VWO diploma aan het Eerste Christelijk Lyceum in Haarlem. Daarna begon zij aan de opleiding Biomedische Wetenschappen aan de Vrije Universiteit in Amsterdam, gevolgd door de Master Neuroscience. Vanwege haar interesse in toegepast medisch wetenschappelijk onderzoek en neuroimaging koos zij daarbij voor de afstudeerrichting Preclinical Neurosience. Haar eerste onderzoeksstage volbracht zij op de afdeling Neurologie en Klinische Neuropsychologie van het VU Medisch Centrum onder begeleiding van Dr. Ysbrand van der Werf en Prof. Dr. Eus van Someren. Voor haar tweede onderzoeksstage ging zij naar Canada waar zij, onder begeleiding van Dr. Rovet, stage liep op de afdeling Psychologie van het Hospital for Sick Children in Toronto. Na deze stage behaalde zij in de zomer van 2009 haar Master diploma. Direct daarna startte Sanne haar promotietraject bij het neuroimaging lab 'NICHE' op de Afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht. Zij werkte daar op de Dutch Prediction of Psychosis Study aan de studies beschreven in dit proefschrift. Op 21 april 2016 zal zij haar proefschrift verdedigen onder supervisie van Prof. Dr. Sarah Durston, Prof. Dr. René Kahn en Dr. Patricia Schothorst. Na het afronden van haar promotietraject is Sanne in januari 2016 begonnen als Clinical Research Associate bij Julius Clinical in Zeist.