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Brain development in adolescents at ultra-high risk for psychosis: Longitudinal changes related to resilience

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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 (good functional outcome) and non-resilient (poor functional outcome) subgroups, defined by the modified Global Assessment of Functioning. 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.

1. 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% (Miller et al., 2002) to an average of 29% in more recent reports (Fusar-Poli et al., 2012a). At the same time, there has been a steady increase in the remission rates reported, of up to 54% (Simon et al., 2011). A recent meta-analysis of eight longitudinal studies (Simon et al., 2013) 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 (de Wit et al., 2014). 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 (Fusar-Poli et al., 2013; Ziermans et al., 2014). 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 (Fusar-Poli and Borgwardt, 2007; Carrión et al., 2013; Fusar-Poli et al., 2013). Moreover, some individuals may develop psychosis before going on to recover completely, while some individuals who do not develop psychosis may have worse outcomes (Yung et al., 2010; Fusar-Poli and Van Os, 2013; Cotter et al., 2014; de Wit et al., 2014). Taken together, this

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underscores the importance of studying resilience, as much as transition to psychosis. We follow the American Psychological Associate in defining resilience as *"the process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress — such as family and relationship problems, serious health problems or workplace and financial stressors. It means "bouncing back" from difficult experiences."* We therefore focus on how well individuals function at follow-up, rather than whether they have experienced a transition to psychosis and operationalise resilience as having good functional outcome. To permit comparison to the extant literature, we also perform complementary analyses using the more traditional operationalisation based on remission of positive symptoms (included as Supplemental material).

Compared to a volunteer sample of typically developing controls, UHR individuals have been reported to show reduced gray matter volume in the frontal and temporal lobes, anterior cingulate gyrus and hippocampal regions. (for reviews, see Fusar-Poli et al., 2011; Wood et al., 2013; Bois et al., 2014). However, many 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 longitudinal studies that have been conducted were only partially successful in predicting transition to psychosis and have reported many inconsistent findings (for review, see Wood et al., 2013). This may in part be related to limited follow-up times and differences in the methods used (Wood et al., 2013), but is likely also related to the diverse clinical outcomes of UHR individuals and the relatively arbitrary criterion of transition to psychosis (de Wit et al., 2014). One recent study of particular interest is that of Cropley et al. (2016): in subjects with attenuated positive symptoms, reduced gray matter volume was associated with more severe positive, negative and depressive symptoms and lower global functioning in the UHR subgroup without transition to psychosis. Unfortunately however, there is a lack of studies investigating brain development with MRI scans at different time points.

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 study includes a long follow-up of six years and more than two MRI scans per individual. This permits a better assessment of outcome and non-linear modeling of developmental trajectories.

2. Methods and materials

2.1. 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 (Sprong et al., 2008; Ziermans et al., 2011). Briefly, adolescents at UHR were referred by general practitioners or other psychiatry clinics. For inclusion at baseline, subjects in the UHR group 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 (McGlashan et al., 2001) and the Family Interview for Genetic Studies (Maxwell, 1982). The fourth inclusion criterion was assessed using the Bonn Scale for the Assessment of Basic Symptoms-Prediction List that was assessed by a clinical expert (TZ) working with child populations (Schultze-Lutter and Klosterkötter, 2002). 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, as assessed using the Wechsler Intelligence Scales by one of the co-authors (TZ) as well as fully trained research assistants. (Wechsler, 1997, 2002). 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 Fig. 1. We split the UHR group into two groups based on the 6-year clinical follow-up data, one 'resilient' and one 'non-resilient' subgroup. Clinical outcome was available for 35 UHR individuals at 6 year follow up. Resilience was defined by *functional outcome* using the modified Global Assessment of Functioning (mGAF) scale (Hall, 1995) as either a) Good functional outcome (resilient): mGAF score of ≥65 or b) Poor functional outcome (non-resilient): mGAF score of <65. The cut off of 65 has been used before (Allen et al., 2014) 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' (Hall, 1995). 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'.

To make our results comparable to the existing literature we included an extra analysis in our supplemental material, where we used the

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)	1,621,000 (148220)	1,586,000 (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.