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Altered relationships between age and functional brain activation in adolescents at clinical high risk for psychosis

Katherine H. Karlsgodt [a,b,*], Theo G.M. van Erp [c], Carrie E. Bearden [d], Tyrone D. Cannon [e]

[a] Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY 11004, USA
[b] Feinstein Institute for Medical Research, Manhasset, NY, USA
[c] Departments of Psychiatry and Human Behavior, University of California Irvine, Irvine, CA, USA
[d] Departments of Psychiatry and Psychology, University of California, Los Angeles, CA, USA
[e] Departments of Psychology and Psychiatry, Yale University, New Haven, CT, USA

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ABSTRACT

Schizophrenia is considered a neurodevelopmental disorder, but whether the adolescent period, proximal to onset, is associated with aberrant development in individuals at clinical high risk (CHR) for psychosis is incompletely understood. While abnormal gray and white matter development has been observed, alterations in functional neuroimaging (fMRI) parameters during adolescence as related to conversion to psychosis have not yet been investigated. Twenty CHR individuals and 19 typically developing controls (TDC), (ages 14–21), were recruited from the Center for Assessment and Prevention of Prodromal States (CAPPS) at UCLA. Participants performed a Sternberg-style verbal working memory (WMem) task during fMRI and data were analyzed using a cross-sectional design to test the hypothesis that there is a deviant developmental trajectory in WMem associated neural circuitry in those at risk for psychosis. Eight of the CHR adolescents converted to psychosis within 2 years of initial assessment. A voxel-wise regression examining the relationship between age and activation revealed a significant group-by-age interaction. TDC showed a negative association between age and functional activation in the WMem circuitry while CHR adolescents showed a positive association. Moreover, CHR patients who later converted to overt psychosis showed a distinct pattern of abnormal age-associated activation in the frontal cortex relative to controls, while non-converters showed a more diffuse posterior pattern. Finding that age related variation in baseline patterns of neural activity differentiate individuals who subsequently convert to psychosis from healthy subjects suggests that these differences are likely to be clinically relevant.

1. Introduction

Schizophrenia is a neurodevelopmental disorder, with cognitive, motor and social abnormalities observable many years before disease onset (Bearden et al., 2000), although overt illness onset typically does not occur until adolescence. This pattern suggests that some risk-factors that contribute to disease onset may occur very early with others occurring more proximally to disease onset. Specifying how cognitive and clinical features observed in adult patients arise over the course of development may have critical implications for intervention and ultimately, prevention.

Given that schizophrenia onset or its treatment may alter brain function, it is necessary to assess developmental trajectories before onset occurs (Karlsgodt et al., 2008), for instance by assessing clinically defined high-risk subjects (CHR) identified based on expression of sub-psychotic symptoms and changes in function. CHR adolescents who converted to psychosis have previously shown frontal lobe gray matter reductions compared with non-converters (Dazzan et al., 2012; Sun et al., 2009a) and smaller volumes in temporal regions (Mechelli et al., 2011). Further, CHR youth failed to show the typical age-associated increase in DTI measures of white matter integrity, and lower baseline integrity predicted later functioning (Karlsgodt et al., 2009a). Given these patterns, we hypothesized that, compared with healthy adolescents, CHR youth would show an altered association between age and brain physiology as assessed with functional magnetic resonance imaging (fMRI).

Patients with psychotic and schizophrenia spectrum disorders and those at genetic and clinical high-risk have deficits in a number of cognitive domains, including working memory (WMem) (Kuperberg and Heckers, 2000), and WMem has been proposed as an endophentype for this disorder (Glahn et al., 2003). Consistent with findings that the frontal lobe is relatively late to fully mature, in healthy individuals WMem processes continue to develop into

* Corresponding author at: Zucker Hillside Hospital, Department of Psychiatry, 120 Leon Lowenstein Bldg, Glen Oaks, NY 11004, USA. Tel.: +1 718 470 8184.
E-mail address: kkarlsgodt@nshs.edu (K.H. Karlsgodt).

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adulthood. The basic components of the WMem circuitry are functional by the end of childhood; even young children engage a fronto-parietal network similar to adults during WMem (Geier et al., 2009; Nelson et al., 2000). However, with increased task difficulty or complexity, children tend to activate a more diffuse, less focused and efficient network than adults (Geier et al., 2009; O'Hare et al., 2008). WMem-associated activation continues to change across adolescence (Schweinsburg et al., 2005), which suggests maturational changes that are likely to reflect refinement of the dorsolateral prefrontal cortical (DLPFC) contribution to WMem across adolescence (Geier et al., 2009). CHR individuals have shown abnormalities in fMRI activation during WMem (Broome et al., 2009; Choi et al., 2011; Fusar-Poli et al., 2010; Morey et al., 2005) but it is not clear how these differences may vary with age during adolescence.

The goals of this study were to determine whether CHR youth show a differential association between age and functional activation during adolescence compared with typically developing controls (TDC), and to clarify whether such a putative differential association is limited to adolescents who convert to psychosis. A differential association between age and functional activation between CHR and TD adolescents would suggest that an age-related developmental process may contribute to observed differences in activation between adult psychotic patients and controls. Alternatively, if the groups show similar differences in functional activation across age and differ only in mean activation, effects of an earlier risk factor provide a more likely explanation for activation differences between psychotic patients and controls.

2. Methods

2.1. Participants

Twenty CHR youth and 19 TDCs (Table 1) participated in an ongoing study at the University of California, Los Angeles. TDCs age matched to the CHR sample were recruited from the community via advertising. While the intent was also to match gender, exclusion for below chance performance, motion, and imaging artifacts resulted in proportionately more TDC females; thus all analyses were co-varied for sex. fMRI data was obtained at baseline and analyzed cross-sectionally, while clinical follow-ups over a subsequent 2 year period allowed for longitudinal determination of conversion status. CHR participants met criteria for one of three prodromal syndrome categories, as assessed by the Structured Interview for Prodromal Syndromes (SIPS (McGlashan et al., 2001)): (1) attenuated psychotic symptoms; (2) transient, recent-onset psychotic symptoms; or (3) a substantial drop in functioning in conjunction with schizotypal personality disorder or a first-degree relative with psychosis. TDC youth did not meet DSM-IV criteria for a psychiatric disorder based on SCID-I/P or K-SADS interviews, have a first-degree family history of psychosis, or meet the prodromal state criteria. Additional exclusions for all participants included: neurological disorder, drug/alcohol abuse or dependence within the past 6 months, insufficient English fluency, and/or IQ below 70. Details regarding SIPS criteria, reliability and consensus procedures are described elsewhere (Meyer et al., 2005). All participants completed informed consent or assent (parental consent was obtained for minors), approved by the UCLA Institutional Review Board, and were compensated for participation.

Table 1
Subject demographics.

	CHR ($n=20$)	TDC ($n=19$)
Age (mean ± std)	16.85 (2.06)	17.84 (2.11)
(*range*)	14–20	14–21
Gender: % female (n)	15% (3)*	47.36% (9)*
Race: percent (n)		
% Caucasian	50% (10)	42.11% (8)
% African American	10% (2)	5.2% (1)
% Asian American/Pacific Islander	15%(3)	10.5% (2)
% Latino/Hispanic	20% (4)	10.5% (2)
% Other	5% (1)	44.4% (4)
Primary SIPS diagnosis: percent (n)		
Brief Intermittent Psychotic (BIPS)	20% (4)	
Attenuated Positive Symptoms (APS)	75% (15)	
Genetic Risk & Deterioration (GRD)	5% (1)	
Medication status (n)		
Current atypical antipsychotic	4	
Current SSRI/SNRI	7	
Current mood stabilizer	2	
Current psychostimulant	2	
Current Other (cogentin, abilify, klonopin)	3	
No current medication	10	
One current medication	5	
Two current medications	4	
Three current medications	0	
Four current medications	1	

2.2. Procedures

2.2.1. Cognitive paradigm

Participants performed a Sternberg-style item recognition task during fMRI at the baseline assessment (Sternberg, 1966) as described in Karlsgodt et al. (2007, 2009b)) (Fig. 1) The experiment was run using E-Prime Software (Psychology Software Tools), images were displayed using goggles (Resonance Technologies, Inc), and responses were collected via a button box (Current Designs).

2.2.2. Clinical assessments

After the baseline scan the SIPS and SCID were re-administered at 6-month intervals, for up to 24 months with additional assessment if clinical deterioration was observed. Conversion to psychosis was defined according to SIPS criteria (Cannon et al., 2008). Briefly, the patient must exhibit psychotic symptoms of certain intensity (e.g., delusional conviction) and frequency or duration (one hour/day for four days/week during the last month) or having a severe impact (seriously disorganizing/dangerous). Psychosis is the primary defining feature of schizophrenia but may occur in other DSM-IV categories. Eight subjects converted to a psychotic disorder with diagnoses of: schizophrenia ($n=3$), schizoaffective disorder ($n=1$), schizophreniform disorder with a secondary diagnosis of depressive disorder NOS ($n=1$), mood disorder with psychotic features ($n=1$), and psychosis not otherwise specified (NOS; $n=2$). One individual with psychosis NOS also had a secondary diagnosis of depressive disorder NOS. Individuals who did not convert had diagnoses of: major depressive disorder in full or partial remission ($n=7$), pervasive developmental disorder ($n=1$), mood disorder NOS ($n=1$), ADHD ($n=1$), with one diagnosis remaining unclear at last follow-up.

2.2.3. Imaging parameters

Scans were acquired on a 3 T Siemens Allegra scanner at UCLA. A T2 weighted image with 1.5 mm in-plane resolution was taken using a set of high-resolution EPI localizers (TR/TE 5000/33 ms, 33 3-mm slices with 1 mm gap, 128 × 128 matrix, 200 mm FOV). To match any B0-related distortions, the T2 images had the same readout bandwidth along the phase encoding direction as functional scans. Functional slices matched the AC-PC aligned slices in the T2 image, and utilized an echo planar (EPI) sequence (TR/TE 3000/45 ms, 90° flip angle, 33 3 mm slices, 1 mm gap, interleaved acquisition). The voxel size was 3.125 × 3.125 × 3.99. The task consisted of 180 time points with a total duration of 9 min.

2.2.4. Image processing

A study-specific group averaged T2-weighted brain was created using Automated Image Registration (AIR) (Woods, 1998). It was used as the common space to which all subjects were registered and in which group statistics were performed. This approach minimizes misregistration of the functional data during spatial normalization and ensures similar levels of spatial transformation from individual to template space between comparison groups. To generate coordinates comparable with other data sets, statistical maps were registered to MNI-152 space.

Functional analysis was performed using FSL (FMRIB's Software Library v4.1; Smith et al., 2004). Data were motion corrected then co-registered, first the EPI to the subject's individual T2, then the T2 to the study specific common brain (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Individual subject analyses employed FEAT (FMRI Expert Analysis Tool) using a 5 mm (FWHM) Gaussian smoothing kernel and 72 s high-pass filter, with slice timing correction. Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001). Each load was

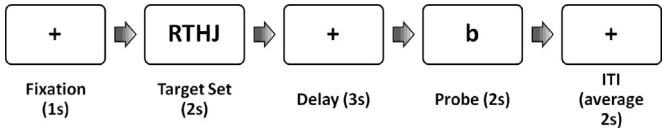

Fig. 1. Task design.