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Motor behavior reflects reduced hemispheric asymmetry in the psychosis risk period

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ABSTRACT

Background: A body of work focusing on brain connectivity, language dominance, and motor laterality research suggests that reduced hemispheric asymmetry is a core feature in schizophrenia. However, there is little consensus about whether reduced dominance is present in those at ultrahigh risk (UHR) for psychosis.
Methods: A total of 94 demonstrated right-handed neuroleptic free participants (38 UHR and 56 matched healthy controls) were assessed with structured clinical interviews and completed an innovative handwriting task using a digital tablet computer. A laterality quotient (LQ) was calculated using kinematic variables from the participant's left and right hands. A subset of the sample (26 UHR and 29 controls) returned after 12-months to complete clinical interviews in order to examine relationships between handwriting laterality and progression of psychosis risk symptoms.
Results: The UHR group showed decreased dextrality compared to healthy controls. At the 12-month follow-up, decreased dextrality accounted for 8% of the variance in worsened positive symptoms within the UHR group.
Conclusion: The current results suggest that disrupted cerebral dominance is also present in the ultrahigh risk period and that decreased dextrality may serve as a novel biomarker for the progression of psychosis risk.
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1. Introduction

Cerebral asymmetry has been proposed to be an evolutionary beneficial trait for humans. Functional specialization or dominance in one hemisphere frees the other hemisphere to accomplish varied tasks (i.e., to speak and use tools at the same time) (Vallortigara and Rogers, 2005). It has been proposed that decreased cerebral asymmetry may be a core feature of the abnormal neurodevelopment leading to the emergence of psychosis (Crow, 2004; Crow et al., 1989, 1996; Oertel-Knochel and Linden, 2011). Supportive findings from cross-sectional structural imaging studies in patients with schizophrenia note decreased volume lateralization in language and motor areas of the cortex (Barta et al., 1997; Deep-Soboslay et al., 2010; Petty et al., 1995). Functional imaging studies utilizing language tasks have described increased bilateral functional activation in schizophrenia patients compared to controls, possibly reflecting a less efficient specialization of brain areas for language function (Sommer et al., 2001; Weiss et al., 2006). Increased prevalence of non-right handedness (i.e., left handedness or mixed handedness)—characterized by decreased specialization or preference for performing manual tasks solely with the right hand—has been observed in patients with schizophrenia and proposed to be a specific sign tied to abnormal cerebral asymmetry and etiological risk factors for psychosis (Dragovic and Hammond, 2005; Satz and Green, 1999; Sommer, 2001).

Despite the strong body of work that has elucidated handedness in patients with psychosis, it remains unclear whether non-right handedness occurs in at risk individuals (Claridge et al., 1998; Erlenmeyer-Kimling et al., 2005). Archival studies of individuals who later developed schizophrenia have found evidence for mixed handedness at 7 years of age (Crow et al., 1996). However, a separate archival study found differences in eye dominance but not hand dominance (Cannon et al., 1997). In prospective and cross sectional studies involving family members who are at high genetic risk for psychosis, there has been inconclusive evidence that non-right handedness is associated with increased genetic risk (Clementz et al., 1994; Deep-Soboslay et al., 2010; Erlenmeyer-Kimling et al., 2005; Orr et al., 1999). And a very recent cross-sectional study noted that increased genetic risk for psychosis was associated with increased rather than decreased handedness lateralization during a line drawing paradigm (Manschreck et al., 2015). However, no study to date has examined handwriting lateralization in ultrahigh risk (UHR) for psychosis individuals.

One explanation for the inconclusive evidence on handedness in at risk populations may be related to the limited methodology for assessing handedness. By and large, studies in schizophrenia spectrum populations have asked participants to demonstrate manual activities that they would

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do with their left, right, or both hands. In some studies, left and right handedness is treated categorically, while in others, different cut-offs are used to differentiate right from non-right handed individuals (Satz and Green, 1999). While these methods provide excellent classification, they may miss subtle variations in handedness because they rely on self and observer reports. Recent efforts to understand movement abnormalities in psychosis and at risk populations using computer based handwriting measures may provide an objective method for assessing subtle abnormalities in handedness (Caligiuri et al., 2009, 2010; Dean and Mittal, 2015; Dean et al., 2013; Docx et al., 2012).

Decreased handedness has been associated with schizotypy and positive symptoms of psychosis (Badzakova-Trajkov et al., 2011; Barrantes-Vidal et al., 2013). This is particularly relevant as a neural diathesis stress model of psychosis suggests that early vulnerabilities (e.g., genetics, obstetric complications) lead to altered brain development, which in adolescence interacts with stressful life events, eventually leading to the development of psychotic symptoms (Cornblatt et al., 2003). Examining handedness may provide an important measure of abnormal brain development prior to the onset of the disorder, which is critical for understanding potential biomarkers and guiding preventive efforts in youth who are at risk for developing the disorder.

In order to investigate dextrality and associations to the progression of symptoms of risk in a group of right-handed UHR and healthy controls, participants completed clinical interviews at a baseline and a 12-month follow-up visit and a handwriting task on a computerized tablet at the baseline visit. We hypothesized that the UHR group would show decreased right-handed laterality (i.e., decreased dextrality) compared to the healthy controls, which would be characterized by a more equivalent laterality quotient. Furthermore, we hypothesized that decreased dextrality would be related to more severe positive symptoms at baseline and worsened progression of symptoms over a period of 12 months.

2. Materials and methods

2.1. Participants

Right handed adolescent and young adult UHR and healthy control participants (mean age = 18.31) were recruited by Craigslist, email postings, newspaper ads, and community professional referrals. Exclusion criteria consisted of head injury, the presence of a neurological disorder, and lifetime substance dependence. The presence of an Axis I psychotic disorder (e.g., schizophrenia, schizoaffective disorder, schizophreniform) and the use of any antipsychotic medication at baseline were exclusion criteria for UHR participants. The presence of any category of Axis I disorder or a psychotic disorder in a 1st degree relative was an exclusion criterion for controls. The protocol and informed consent procedures were approved by the University Institutional Review Board. See Table 1 for the demographic characteristics of the sample.

The follow-up study is ongoing, and to date, 12 months have passed for 90 individuals who have completed a baseline assessment. Each of these individuals was invited back, and 55 participants agreed to return to complete clinical interviews. Participants did not return because they could not be contacted (UHR n = 11, control n = 20) or decided not to participate (control n = 4). There were no baseline differences in age, gender, education or parent education between those who did and did not return for follow-up.

2.2. Clinical interviews

At baseline, the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 1999) was administered to both UHR and control subjects to diagnose a UHR syndrome (the SIPS was used to rule out UHR symptoms in healthy controls). A total sum score for the positive and negative symptom domain was used as an indicator of the respective dimensions of symptomatology. The Structured Clinical Interview for Axis-I DSM-IV Disorders (SCID) (First et al., 1995) was administered to rule out a psychotic disorder diagnosis.

At follow-up, the SIPS was administered to track UHR symptom changes over 12-months and the SCID was administered to assess for possible transition to psychosis. Training of advanced doctoral student interviewers was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of Kappa ≥ .80.

Table 1
UHR and healthy controls did not differ in terms of age, education, gender, and parental education. UHR participants were rated significantly higher on both positive and negative symptom domains at baseline and follow-up. UHR individuals showed significantly decreased dextrality on a measure of handwriting laterality, LQ_{FREQ}. NS indicates not significant.

	UHR	Control	Statistic	p≤
Age				
Mean (SD)	18.69 (1.85)	18.04 (2.79)	$t(92) = 1.35$	NS
Gender				
Male	21	24		
Female	17	32		
Total	38	56	$\chi^2(1, N = 94) = 1.40$	NS
Education (years)				
Mean (SD)	12.45 (1.98)	11.99 (2.72)	$t(92) = .96$	NS
Parent education				
Mean (SD)	15.65 (2.06)	15.98 (2.52)	$t(92) = -.74$	NS
Baseline symptoms				
Positive	12.21 (4.29)	.79 (1.47)	$t(42.82) = 15.56$	.001
Negative	9.85 (6.31)	.48 (1.08)	$t(38.57) = 9.05$	.001
Follow-up symptoms				
Positive	11.73 (6.27)	.24 (.58)	$t(25.38) = 9.32$	.001
Negative	9.88 (8.20)	.59 (1.50)	$t(26.50) = 5.70$	.001
Parametric stats results				
Frequency mean (SD)	−.28 (.46)	−.4 (.32)	–	–

2.3. Handedness

Right handedness was determined by requiring that participants normally write with their right hand in addition to demonstrated preference for using their right hand in all of the following manual tasks: deal a deck of cards, thread a needle, throw a ball, and use a tennis racket. These items are valid for establishing hand dominance and have been used in other investigations to assess handedness (Buchanan and Heinrichs, 1989).

2.4. Handwriting samples

Handwriting samples were acquired using Neuroscript MoveAlyzer software (http://www.neuroscript.net) installed on a Fujitsu Lifebook T901 tablet computer with a non-inking pen. Participants were instructed to draw eight concentric circles continuously in either a clockwise or counterclockwise direction within a 2 cm boundary line using one hand at a time (see Fig. 1). This stimulus has been used in previous studies that assess handedness and has been shown to be a sensitive measure of handwriting laterality (Henkel et al., 2001). Each trial consisted of 16 vertical strokes, which were segmented and processed for duration per stroke. Valid trials included at least 10 strokes. Kinematic variables were extracted from MoveAlyzer and imported into SPSS 22. The mean duration per stroke per trial (i.e., frequency of stroke) was calculated for each hand separately. A laterality quotient using mean frequency of stroke (LQ_{FREQ}) was calculated as follows:

$$LQ_{FREQ}: (R_{FREQ} - L_{FREQ}) / R_{FREQ}.$$

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