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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 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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Conflict of Interest

None.

Contributors

Authors D.J.D, J.M.O, R.E.N, and V.A.M developed the study concept. V.A.M. obtained funding for the study. All authors contributed to the study design. Testing, data collection as well as data analysis and interpretation were performed by D.J.D and R.E.N under the supervision of J.M.O and V.A.M. D.J.D drafted the paper; J.M.O, R.E.N, and V.A.M provided the critical revisions. All authors approved the final version of the paper for submission.

Keywords

Ultrahigh risk; psychosis; cerebral dominance; handwriting; laterality; dextrality

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; Crow et al., 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 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; Caligiuri et al., 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.

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 Figure 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:

$$\mathrm{LQ}_{\mathrm{FREQ}}: \left(\mathrm{R}_{\mathrm{FREQ}} - \mathrm{L}_{\mathrm{FREQ}}\right) / \mathrm{R}_{\mathrm{FREQ}}$$

Previous work suggests that this LQ can successfully classify left and right handedness (Henkel et al., 2001). More negative values on LQ_{FREQ} indicate slower duration per stroke for the left hand compared to the right hand. This would be expected given that the right hand is the preferred hand and is expected to better control pen movements. In contrast, more positive numbers (i.e., values closer to zero) indicate that the right hand was more similar to the left hand, suggesting decreased dextrality. Of note, a subset of the current participants have also completed two separate studies aimed at understanding hyperkinetic and hypokinetic movement abnormalities associated with risk for psychosis using

MoveAlyzer software (Dean and Mittal, 2015; Dean et al., 2013). These studies were not focused on laterality and did not use the same kinematic variables.

2.5. Statistical Analyses

Independent t-tests and chi-square tests were employed to examine differences between groups in continuous and categorical demographic variables, respectively. Kolmogorov-Smirnov tests revealed that the handwriting kinematic variables and laterality quotient was normally distributed; two-tailed independent t-tests were used to examine group differences for the left and right mean frequency per stroke as well as LQ_{FREQ}. The control group showed a limited range in symptom scores and Pearson correlations were run in the UHR group alone to assess the relationship between LQFREQ and symptoms. A series of 2 hierarchical regression analyses were conducted within the UHR group alone. Positive and negative symptoms at the follow-up assessment were used as the dependent variables and the respective symptom variable for the baseline assessment was entered in the first block. In the second block, LQ_{FREQ} was entered as the predictor variable. With each analysis, the magnitude of R^2 change (ΔR^2) was tested for significance. This analytic approach tests the hypotheses that while controlling for the variance explained by symptoms at baseline, decreased handwriting lateralization will be associated with respective symptoms 12 months later.

3. Results

3.1. Participants

There were no significant differences between groups on demographic characteristics including age, education, gender, and parental education. As expected, UHR participants were rated significantly higher than controls on both SIPS symptom domains positive and negative at baseline and follow-up (see Table 1 for information about the participants). Of the participants who completed the baseline handwriting task and clinical interviews, 3 developed a psychotic disorder at follow-up.

3.2. Group Differences for Kinematic Variables and Laterality Quotient

There were no significant group differences between UHR and healthy controls for any of the mean kinematic variables, including left or right frequency. The LQ_{FREQ} for the UHR group was significantly closer to zero compared to healthy controls, suggesting that the UHR group showed a similar stroke frequency for both hands and that the UHR group was significantly less lateralized to the right hand $t(92)=2.57$, $p \leq .05$.

3.3. Relationship between Baseline Symptoms and Laterality Quotient

While not significant, decreased right handedness on LQ_{FREQ} was related to elevated positive symptoms at baseline $r(36)=.19$, $p=.24$ (see Figure 2). There was not an association between LQFREQ and negative symptoms within the UHR group ($p \geq .5$).

3.4. Relationship between Follow-up Symptoms and Laterality Quotient

A hierarchical linear regression approach was used to examine the relationship between LQ_{FREQ} and the progression of positive and negative symptoms over 12-months within the

UHR group. Decreased right-handedness on LQ_{FREQ} accounted for 8% of the variance in change of positive symptoms after 12-months. While a proportion of participants improved over the follow-up period, more positive values of LQ_{FREQ} (indicating decreased dextrality) were related to worsened positive symptoms at follow-up for UHR participants who did not improve (β=.29, $p \leq .05$). There was not a significant relationship between LQ_{FREQ} and negative symptoms (see Table 2 and Figure 2).

4. Discussion

Movement abnormalities tied to aberrant neurodevelopment have been proposed to be a key sign of risk for psychosis (Callaway et al., 2014; Dean and Mittal, 2015; Dean et al., 2013; Mittal et al., 2010a; Mittal et al., 2007a; Mittal et al., 2008; Mittal et al., 2007b). However, to date, our understanding of laterality during this critical period has been limited. Importantly, this is the first study to examine handedness in UHR individuals using handwriting kinematic measurements. Altered cerebral asymmetry may be indicated by decreased dextrality, and point to early neurodevelopmental changes that are associated with risk symptoms for psychosis. In this study, we examined right-handedness using an innovative instrumental measure, which allowed us to pick up decreased laterality in the UHR group compared to healthy controls using kinematic measurements for duration of stroke. Furthermore, within the UHR group, decreased laterality was associated with the progression of more severe positive symptoms over a 12-month period. These results build on previous work with inconclusive findings regarding handedness lateralization in individuals at risk for psychosis (Cannon et al., 1997; Crow et al., 1996), suggesting that subtle differences in handwriting laterality are measured on an instrumental task, and are associated with key symptoms of risk for psychosis.

Handwriting is a highly specialized skill requiring motor coordination. Previous work in UHR samples notes that movement abnormalities typically precede the onset of psychosis and may be an early sign of abnormal brain development (Mittal et al., 2010a; Mittal et al., 2014; Mittal et al., 2011; Mittal et al., 2007a; Mittal et al., 2012; Mittal et al., 2007b; Mittal et al., 2010b; Walker et al., 1994). Archival studies suggest that early signs of abnormal fine and gross motor skill (i.e., dyspraxia) in children, also predict later development of psychosis (Schiffman et al., 2015). Handwriting analysis has emerged as an important tool for assessing movement abnormalities during the UHR period, as it is able to pick up subtle movement abnormalities that may not be visible or as severe in patients with schizophrenia (Caligiuri et al., 2010; Caligiuri et al., 2006; Docx et al., 2012; Docx et al., 2014; Morrens et al., 2014). Recent cross sectional work in UHR samples has found evidence of hyperkinetic and hypokinetic movement abnormalities using a handwriting tablet and different kinematic measurements (Dean and Mittal, 2015; Dean et al., 2013). The current study adds to this body of literature by suggesting that handwriting analysis may pick up subtle alterations in handedness in individuals identified as right-handed based on a number of demonstrated tasks, and that this is related to the progression of positive symptoms of risk for psychosis. Future work examining handwriting laterality in patients with psychosis using these instrumental measures may provide greater insight into the magnitude of these findings and further the use of instrumental measures for the assessment of movement abnormalities.

While the present results did not find a significant relationship between decreased dextrality and increased symptoms at baseline, we found a unique relationship between LQ_{FREQ} and the progression of positive symptoms over 12 months. This is in line with a large body of work in samples who may be prone to psychotic-like experiences and increased propensity for magical ideation and show increased prevalence for mixed and non-right handedness (Asai and Tanno, 2009; Barrantes-Vidal et al., 2013; Bolinskey et al., 2013; Dragovic et al., 2005; Shaw et al., 2001). In a large sample of university students, increased schizotypy is associated with decreased right-handedness (Chen and Su, 2006; van der Hoorn et al., 2010). In schizophrenia patients, first rank symptoms have been associated with increased mixed handedness using a continuous measure of hand preference on a number of different tasks (Verdoux et al., 2004). Taken together, the findings join a growing body of literature suggests that movement abnormalities may be associated with specific symptom domains in psychosis (Docx et al., 2012; Morrens et al., 2014; Morrens et al., 2008; Pappa and Dazzan, 2009; van Harten et al., 2014).

The existing understanding of the development of cerebral asymmetry and handedness is compatible with the present diathesis stress model of psychosis risk, where early genetic alterations and pre or perinatal events effect later brain development. Decreased cerebral asymmetry has been shown to be associated with genetic and epigenetic alterations as well as pre and perinatal complications (Johnston et al., 2009). The present results are in line with previous work that notes an increase prevalence of non-right-handedness in patients with psychosis (Sommer, 2001). Furthermore, these results provide support for the theory that disrupted cerebral asymmetry and altered language hemispherical dominance is a core feature of the development of psychosis (Crow, 2004; Crow et al., 1989; Crow et al., 1996; DeLisi et al., 1997). Indeed, the behavioral correlates of handedness are particularly germane to the signs and symptoms of psychosis. For example, mixed-handedness is associated with decreased cognitive abilities in several domains including arithmetic, reading and problem solving; domains also associated with risk for psychosis (Corballis et al., 2008; Wu et al., 2014). Conversely, non-right handedness is also associated with creativity in healthy individuals, an advantageous trait that has been hypothesized to promote the fitness for the genes linked to psychosis (Badzakova-Trajkov et al., 2011; Nettle and Clegg, 2006). This is particularly relevant for looking at biomarkers of risk for psychosis and the results of the present study suggest that looking at handedness lateralization may provide an easily accessible and helpful tool for assessment of risk in those showing attenuated psychotic symptoms.

The current study has several notable strengths and limitations. Neuroleptic medications have been shown to confound research involving movement abnormalities in patients with psychosis (van Harten et al., 2014); this confound was absent from the current UHR sample during the handwriting task. While the current study used an innovative technology to assess right-handedness, the handwriting results of this study are limited to a single time point. Future work examining handwriting laterality over multiple time points will be important for determining whether this is a stable marker of risk and related to eventual conversion to psychosis. We recruited participants who demonstrated strong right-handedness in order to measure the amount of decreased dextrality. This is applicable to a wide variety of other movement studies, which have focused solely on right-handed individuals (Willems et al.,

2014). However, previous research notes that there is a higher prevalence of left-handedness in schizophrenia and it will be important to examine handwriting kinematics in a group of left handed UHR individuals to get a fuller picture of handwriting laterality.

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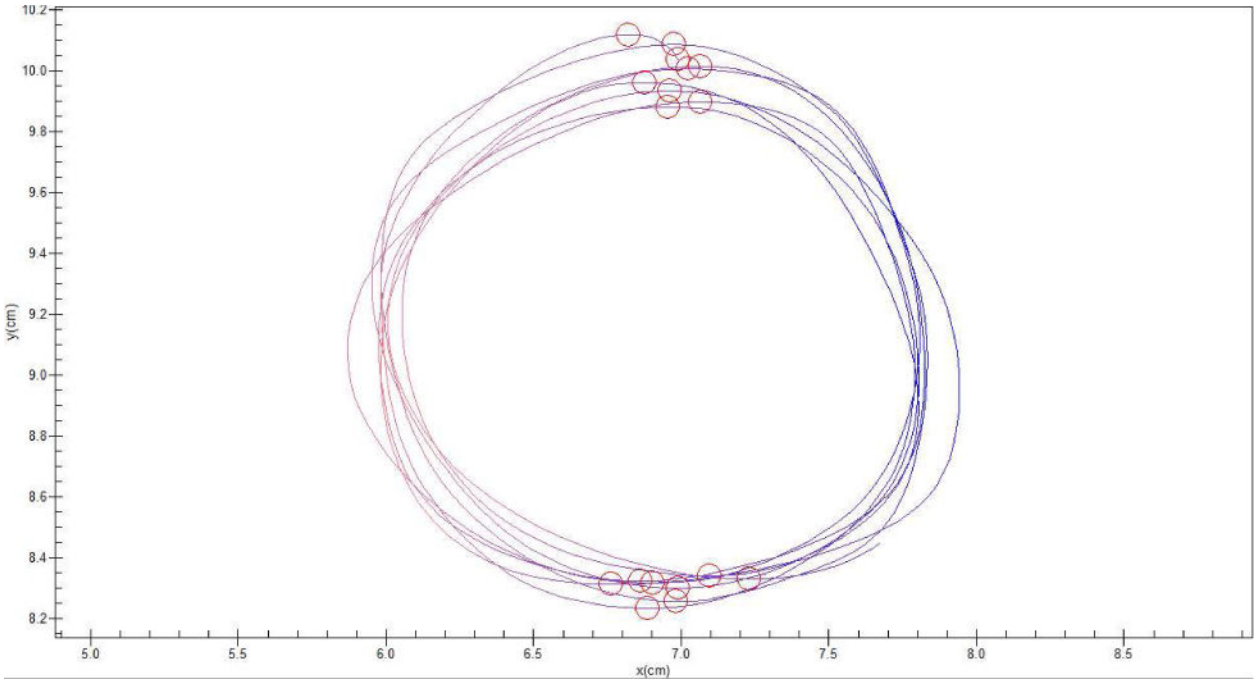

Figure 1.

An example handwriting trial. The participants draw 8 concentric circles continuously in one direction with either their left or right hand between a 2cm boundary. Strokes (red and blue lines) were segmented by MoveAlyzer. Kinematic variables for duration per stroke were extracted for all trials for both the left and right hands.

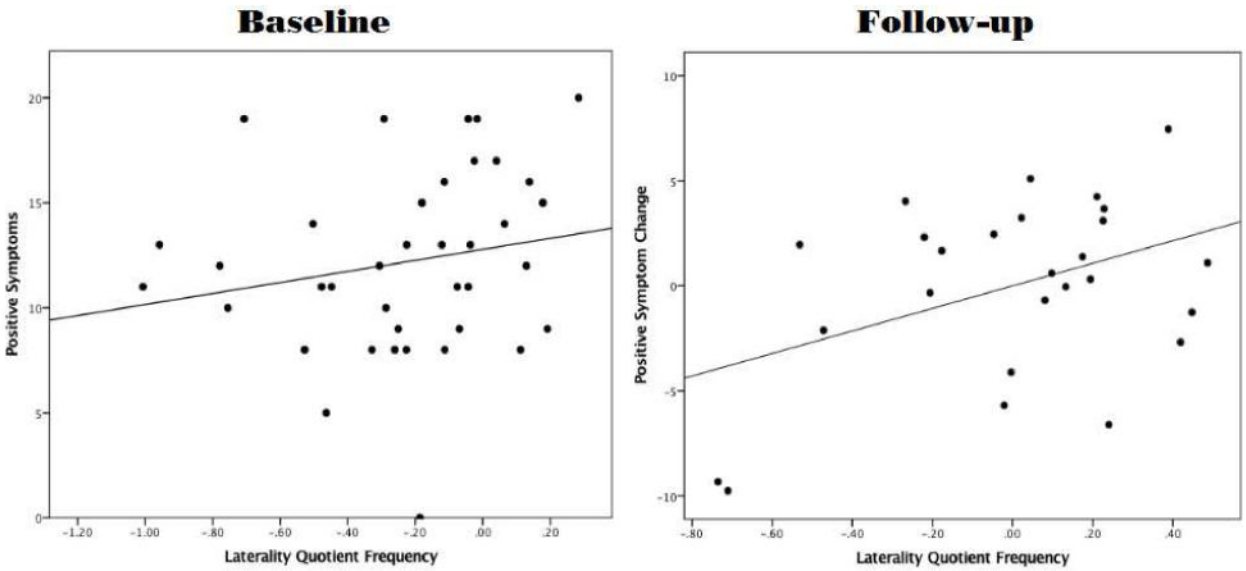

Figure 2.

The figure shows two scatter plots: the first plot shows the relationship of LQ_{FREQ} to positive symptoms at baseline. The second plot shows the relationship between LQ_{FREQ} and positive symptom change over the 12-month follow-up period. More positive numbers on LQ_{FREQ} indicate decreased dextrality. More positive numbers on the Y-axis indicate that the total SIPS positive symptom score was higher at follow-up than at baseline.

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
Laterality Quotient				
Frequency Mean Rank	55.95	42.46	U = 726	.01
Frequency Mean (SD)	−.28 (.46)	−.4 (.32)	–	–

Table 2

Linear regression was used to evaluate if decreased dextrality using LQ_{FREQ} at baseline predicted worsening positive and negative symptoms at follow-up in the UHR group alone.

Predicting 12-Month Variable	Block I- Baseline Symptoms					Block II- LQ FREQUENCY				
	R^2	df	F	β	P	ΔR^2	df	F	β	P
Positive Symptoms	.53	1, 24	27.17	.73	.0001	.08	1, 23	4.94	.29	.04
Negative Symptoms	.43	1, 24	17.90	.65	.0001	.01	1, 23	.41	.10	.53