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Impaired motor performance in adolescents at familial high-risk for schizophrenia

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ABSTRACT

Background: The Harvard Adolescent Family High Risk (FHR) Study examined multiple domains of function in young relatives of individuals diagnosed with schizophrenia to identify precursors of the illness. One such area is motor performance, which is deviant in people with schizophrenia and in children at risk for schizophrenia, usually offspring. The present study assessed accuracy of motor performance and degree of lateralization in FHR adolescents and young adults.
Methods: Subjects were 33 non-psychotic, first-degree relatives of individuals diagnosed with schizophrenia, and 30 non-psychotic comparison subjects (NpC), ranging in age from 13 to 25 who were compared using a line-drawing task.
Results: FHR individuals exhibited less precise and coordinated line drawing but greater degree of lateralization than controls. Performance on the linedrawing task was correlated with degree of genetic loading, a possible predictor of higher risk for schizophrenia in the pedigree.
Conclusions: The observation of increased motor deviance and increased lateralization in FHR can be utilized in identification and initiation of the treatment in those at high risk in order to prevent or delay the full manifestation of this devastating condition. The use of a rigorously quantified measure is likely to add to the sensitivity of measuring motor performance, especially when impairments may be subtle.

1. Introduction

While advances in identifying the molecular basis of genetic susceptibility for schizophrenia (SZ) are accelerating and have great promise (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) the best predictor of schizophrenia remains family history of psychosis. Sullivan et al. (2003) performed a meta-analysis of twin studies and calculated that as much as 80% of the probability of developing SZ or heritability can be assigned to genetic factors. Furthermore, the presence of an affected first-degree biological relative may confer an 8- to 12-fold increase in risk (Faraone et al., 1999). With more than one affected first-degree relative, the risk is even greater (Gottesman et al., 2010). The examination of unaffected, biological relatives within a high-risk family may be particularly useful for identifying evidence of neurological deviation that may represent the "forme fruste" of schizophrenia (Stone et al., 2005). Identification of a single or multiple "formes frustes" was the goal of the Harvard Adolescent Family High Risk (FHR) Study (Seidman et al., 2006a, 2006b). Using an extensive battery of neuropsychological and neuroimaging assessments, the project examined young biological relatives of individuals diagnosed with SZ and a control group of relatives of healthy individuals. Data on motor performance were collected as part of the FHR Study but not previously published.

Motor abnormalities have long been identified in SZ. They are among the earliest neurological abnormalities described in this disorder (Kraepelin, 1919; Bleuler, 1950; Manschreck et al., 1982; Manschreck, 1986; Rogers, 1992; Seidman, 1983). Prior research detected the presence of extrapyramidal system manifestations including dyskinesias in first episode, untreated SZ, and in chronic untreated SZ (Crow et al., 1982; Fenton et al., 1997; Cortese et al., 2005). Functional and anatomical impairments in brain regions (i.e., basal ganglia–cerebellum loop,

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prefrontal cortex, primary motor cortex) have been widely reported in SZ, including reduced gray matter volume (Sullivan et al., 1996; Thompson et al., 2001), left parietal cortex (Niznikiewicz et al., 2000), and bilateral anomalies in parieto-occipital cortex with SZ having predominant negative symptoms (Foong et al., 2001). Increased incidence of neurological soft signs (i.e., impairment in finger tapping, finger-thumb alternation tasks) has also been reported in SZ (Gupta et al., 1995) as well as in first-episode psychosis patients and in people identified as having a high risk for developing psychosis (Dazzan and Murray, 2002). Impaired motor performance has been associated with compromised cognitive abilities, the severity of which may predict long-term prognosis (Manschreck, 1986; Manschreck, 2003). Motor impairments include reduced fine motor control, diminished lateralization in motor performance (i.e., difference between dominant and non-dominant hand performance), elevated rates of non-right-handedness, and deviant performance accuracy (Crow et al., 1996; Manschreck et al., 2004).

Furthermore, FHR individuals may also exhibit motor abnormalities (Rossi et al., 2000). Previous studies of FHR individuals have demonstrated that significant numbers will later develop SZ and demonstrate impairment of motor control, especially fine motor coordination, prior to the onset of psychosis (Watt, 1974; Fish, 1975; Marcus et al., 1985; Manschreck, 1986; Walker et al., 1994; Rossi et al., 2000) and this can be observed as young as 8 months of age (Gamma et al., 2014). Subjective awareness of motor impairment occurs frequently among the early features of SZ (Schneider, 1959; Chapman, 1966; Mellor, 1970). More recently, Koning et al. (2011) examined dyskinesia and extrapyramidal system (EPS) signs in FHR subjects with both instrument-based and clinical measures. They found that the clinical measures detected no motor differences between the groups; on the other hand, the instrument-based measures revealed that FHR subjects had significantly more dyskinesia and EPS symptoms than controls. In addition to detecting motor abnormalities in FHR, this study also demonstrated the benefit of using more sensitive quantitative measures to assess motor performance rather than relying solely on clinical observations.

The line-drawing task is an established quantitative measure to assess motor performance developed by Maher (1993) to address the limitations of tasks previously used to assess motor deficits (e.g., mazes, pegboards, eye tracking) and provide more precise measurement of the degree of impairments that may be lateralized than those traditional tasks. Such traditional tasks are subject to one's learning ability, easily influenced by practice effects and may confound sensory and/or cognitive capacity with motor performance (i.e., eye tracking). Line-drawing is a direct measure of motor performance that is easy to administer, free of human judgment in scoring, and relies minimally on other areas of cognitive functioning. It has been utilized successfully in our laboratory and has demonstrated impaired motor performance in patients with SZ compared to non-psychotic comparison subjects (NpC) (Blyler et al., 1997). Subsequent studies using the line-drawing task demonstrated that deficient motor control, specifically movement accuracy (i.e. coordination and precision), is associated with an earlier age of diagnosis in SZ (Manschreck et al., 2004) and is a predictor of higher scores on psychometrically-estimated schizotypy in normal young adults (Lenzenweger and Maher, 2002). In addition to quantifying fine motor performance, the line-drawing task can also be used to measure the degree of lateralization as well as estimate left- or right-side dominance. Patients with SZ appear to have a subtly increased rate of left-handedness compared to controls (Goldberg and Seidman, 1991), and left-handedness has been associated with both the presence and degree of severity of thought disorder (Manoach et al., 1988). These findings suggest that lateralization (either degree or side dominance) may differ in SZ and possibly in individuals at FHR.

The present study uses the line-drawing task to measure motor performance in FHR participants and NpC without a family history of psychosis in order to determine the extent to which motor abnormalities constitute a vulnerability marker of SZ. We hypothesized that FHR subjects would demonstrate more deviance on the line-drawing task than would NpC in the (1) accuracy, (2) degree of lateralization (0–1), and (3) direction of lateralization (+ or −). Further, this study examines the effects of genetic load (an estimate of SZ heritability risk based on density of family history of psychosis) among FHR participants. In previous studies with this sample, we have found this index to be associated with more abnormalities (Glatt et al., 2006; Walder et al., 2014). We predicted that there would be an inverse correlation between degree of genetic load and line-drawing performance.

2. Methods

2.1. Participants

Thirty-three FHR subjects and 30 NpC participated in this study. While a variety of neuropsychological measures have been previously reported from the Harvard Adolescent FHR study (Seidman et al., 2006a,b; 2012; Scala et al., 2013), the line-drawing task data has not been previously reported. The FHR group consisted of the children ($n = 14$) and siblings ($n = 19$) of 25 adult probands who met DSM-IV criteria for SZ. Diagnosis was determined using the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) and the Family Interview for Genetic Studies (FIGS; Maxwell, 1996). The control group consisted of children ($n = 30$) of 18 community ascertained probands. The control probands (i.e., parents of NpC) could not have any evidence of psychosis in their first-degree relatives and could not meet DSM-IV criteria for any major mental illness. They were allowed to have past histories of nonpsychotic disorders (i.e., major depressive disorder or cannabis abuse). Inclusion criteria for the control children consist of no diagnosed mental illness. For both groups, exclusion criteria were lifetime diagnosis of psychotic illness, substance dependence, neurological disease, history of head injury or medical illness with documented cognitive sequelae, sensory impairments, current psychotropic medication use, or an IQ < 70. None were on any psychotropic medications at the time of assessment. All participants were between the ages of 13 and 25. Inclusion criteria for the control group also required the absence of biological relatives with a history of psychotic disorder. Participants provided demographic information on age, ethnicity, years of education and parental socio-economic status (SES; Hollingshead, 1975). The study was approved by the human studies committees from all recruitment sites.

2.2. Measures

2.2.1. Handedness

Handedness was determined using the Annett scale (Annett, 1970), a 12-item questionnaire of hand preference for a variety of unilateral motor tasks.

2.2.2. Line-drawing

The line-drawing task consists of participants drawing oblique straight lines from one bottom corner to the opposite upper corner of a 5.08-cm (2-in.) square (Fig. 1). Four such squares are provided: two to be completed with the right hand and two with the left hand. For each hand, one of the squares is completed with a line drawn from left to right and the other from right to left. The completed line-drawings are optically scanned, after which each line is digitized into a series of x–y coordinates. A simple linear regression is then fitted to each set of resulting coordinates. The resulting root mean square error (RMS) is a measure of departure from linearity of the drawn line. The lower the RMS value, the more accurately and precisely the line has been drawn.

Overall accuracy in performance is calculated as the sum of the four RMS values. Right and left hand performances were calculated as the sum of the two RMS values of the corresponding drawn lines; higher scores indicate poorer performance. Degree of lateralization is determined by comparing the difference in RMS values for left and

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